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contents

review

A review of tumor treating fields (TTFields): advancements in clinical applications and mechanistic insights

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Background. Tumor Treating Fields (TTFields) is a non-invasive modality for cancer treatment that utilizes a specific sinusoidal electric field ranging from 100 kHz to 300 kHz, with an intensity of 1 V/cm to 3 V/cm. Its purpose is to inhibit cancer cell proliferation and induce cell death. Despite promising outcomes from clinical trials, TTFields have received FDA approval for the treatment of glioblastoma multiforme (GBM) and malignant pleural mesothelioma (MPM). Nevertheless, global acceptance of TTFields remains limited. To enhance its clinical application in other types of cancer and gain a better understanding of its mechanisms of action, this review aims to summarize the current research status by examining existing literature on TTFields' clinical trials and mechanism studies.

Conclusions. Through this comprehensive review, we seek to stimulate novel ideas and provide physicians, patients, and researchers with a better comprehension of the development of TTFields and its potential applications in cancer treatment.

Key words: tumor treating fields; clinical applications of TTFields; mechanisms of action of TTFields

Introduction

Electromagnetic fields find various applications in medicine, including tissue ablation using thermal energy deposition at microwave and radiofrequency frequencies[1], medical imaging with electrical impedance tomography[2], nerve and muscle stimulation[3], bone regeneration[3], and more. Each of these applications employs specific electromagnetic field frequencies, intensities, and durations tailored to their purposes.

During the early 2000s, Professor Palti and his research group made an interesting discovery. They found that electric fields with low intensity (ranging from 1 V/cm to 3 V/cm, peak value) and intermediate frequency (between 100 kHz and 300 kHz) effectively inhibited the growth of tumor cells across various cell lines.[4,5] This finding led to the development of a therapeutic modality known as Tumor Treating Fields (TTFields), which utilizes these specific electric field parameters to target and suppress tumor growth.[6-8]

TTFields have demonstrated their ability to inhibit tumor cell growth through both *in vitro* and *in vivo* studies. These fields are delivered to the tumor cells or solid tumor using insulated electrodes connected to an energy source, making the entire treatment protocol safe and non-invasive.[9] For example, in the treatment of glioblastoma multiforme (GBM), a portable power supply located in the patient's backpack generates specific electric fields that are transmitted to the tumor through electrodes attached to the shaved scalp.[10] The success of preclinical trials led to the approval of TTFields treatment by the Food and Drug Administration (FDA) for recurrent GBM in

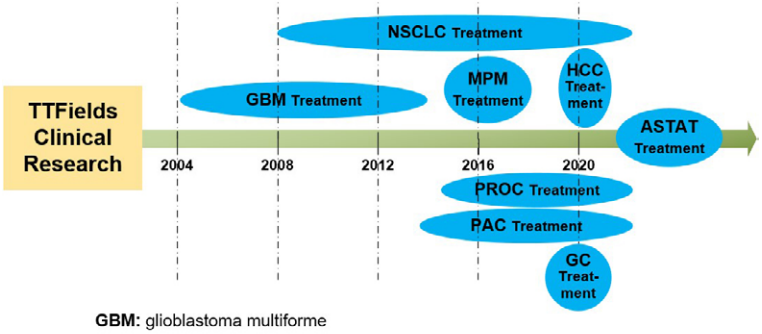

FIGURE 1. The process of TTFields clinical trials on typical tumor types.

2011, and newly diagnosed GBM in adult patients aged 22 years and older in 2015.[7,9,11] These approvals were based on the significant effect of TTFields in prolonging the survival of GBM cancer patients. As a result, clinical trials have been conducted to assess the efficacy of TTFields treatment in other types of cancer as well. These include non-small cell lung cancer (NSCLC)[12-15], platinum-resistant ovarian cancer (PROC)[16], pancreatic adenocarcinoma (PAC)[17-19], malignant pleural mesothelioma (MPM)[20-22], and hepatocellular carcinoma (HCC).[23] Additionally, clinical trials for TTFields treatment in other cancer types are currently ongoing.

Understanding the mechanism by which TTFields inhibit tumor cell growth is crucial for advancing the development of this promising technology. Previous research has suggested that TTFields exert mitotic inhibition effects on dividing cells through two main aspects. Firstly, the electric field force and torque disrupt the microtubule assembly process during prophase, leading to spindle damage.[6,19,24,25] Secondly, during telophase, the inhomogeneous electric field in the cell generates dielectrophoresis (DEP) force[26,27], driving free macromolecules and organelles towards the cleavage furrow, thereby unbalancing the intracellular microenvironment and ultimately causing the death of the dividing cell.[4,28,29]

However, while some physiological phenomena such as chromosome activity disorder[25,30] or spindle disruption have been observed through fluorescence microscopy[31], these alone cannot be considered direct evidence to support the above potential mechanisms. This is because these physiological phenomena may be related to biochemical imbalances rather than electric field mechanics. As a result, researchers are exploring the mechanism both theoretically[28,29], and experimentally[4,25] from the perspectives of biophysics and biochemistry.

This paper presents a comprehensive review of the current state of research on TTFields, focusing on the two most important aspects of this technology: clinical applications and anti-tumor mechanisms. By synthesizing the findings from a range of research works, literature, and reports, we aim to provide readers with a thorough understanding of the latest advancements in TTFields. Our review not only builds on previous research but also offers new insights that may inspire future directions for research and development. Ultimately, our goal is to contribute to the ongoing efforts to optimize the use of TTFields for cancer treatment.

Clinical developments of TTFields

Although TTFields have only been studied for less than two decades, numerous preclinical and clinical trials have been conducted to evaluate the efficacy of this therapy in treating various types of cancer. In Figure 1, we summarize the progress of TTFields clinical research on common tumor types. In the following subsections, we provide more detailed insights into the results of these studies.

TTFields treatment on GBM

GBM is the most common and aggressive form of brain tumor, has a survival rate of approximately 25% two years after diagnosis. Despite decades of research, few advances have been made in the treatment of this disease. The introduction of TTFields therapy provided a novel approach for the treatment of GBM. Clinical trials investigating the efficacy of TTFields therapy in GBM were initiated early on and are summarized as follows (Figure 2)

From 2004 to 2005, the first pilot trial was conducted to assess the safety and efficacy of TTFields therapy on GBM in humans. This trial consisted of two single arms, which involved 10 recurrent GBM patients (arm A) and 10 newly diagnosed GBM patients (arm B), respectively. In arm A, TTFields were used as the sole treatment following the failure of maintenance temozolomide (TMZ), while arm B received TTFields therapy combined with maintenance TMZ treatment.[32] Further details re-

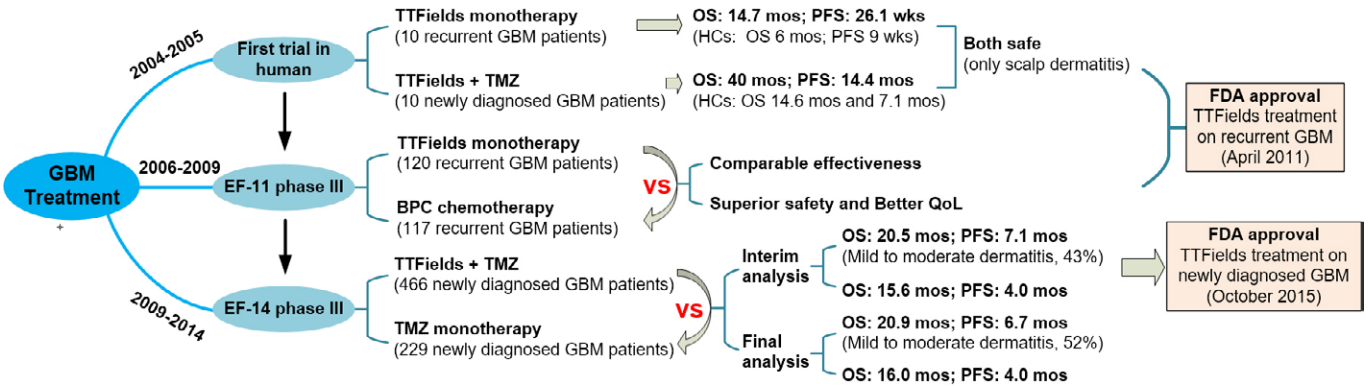

FIGURE 2. Clinical trials of TTFields treatment on glioblastoma multiforme (GBM)

EF-11= controlled randomized phase III trial EF-11; EF-14 = phase III trial EF-14; OS = overall survival; PFS = progression-free survival; TMZ = temozolomide

garding the TTFields setup and course plan can be found in.[32,33] As this was a prospective pilot study, no related randomized control group was established. Therefore, the results were analyzed by comparing them to historical data.

The clinical trial yielded promising results, as evidenced by the comparison of outcomes in arm A and arm B to those of the historical controls (HCs). In arm A, patients treated with TTFields monotherapy achieved a median overall survival (OS) of 14.7 months and a median progression-free survival (PFS) of 26.1 weeks, compared to the HC group's respective outcomes of 6 months and 9 weeks.[34] In arm B, which received TTFields combined with maintenance TMZ, had even more impressive outcomes, with a median OS and PFS exceeding 40 months and 14.4 months, respectively, compared to the HC group's median OS and PFS of 14.6 months and 7.1 months.[35] In addition, no significant side effects, such as hematological, gastrointestinal toxicities, epileptic seizures, or cardiac arrhythmias, were observed in either arm A or arm B, except for contact dermatitis on the scalp.[33] These results indicated TTFields technology is a safe and effective treatment option for GBM.

To promote the clinical advancement of TTFields, a controlled randomized phase III trial (EF-11) was conducted from 2006 to 2009, comparing the efficacy of TTFields monotherapy and best physician's choice (BPC) chemotherapy for recurrent GBM.[10] The trial involved 237 patients, randomly assigned to receive either TTFields monotherapy (120 patients) or BPC chemotherapy (117 patients).[36] Although the trial showed only comparable effectiveness between the two groups, TTFields monotherapy demonstrated superior safety and a better quality of life (QoL).

Based on the findings from the period spanning 2004 to 2009, TTFields therapy was granted FDA approval for the treatment of recurrent GBM on April 8, 2011.[11]

To further investigate the clinical application of TTFields for newly diagnosed GBM, an EF-14 phase III trial was conducted from 2009 to 2014, which enrolled about 700 patients. The patients were randomized 2:1 to receive either TTFields plus maintenance TMZ therapy (466 patients) or TMZ monotherapy (229 patients).[37] According final endpoint analysis, the TTFields + TMZ group had a median PFS of 6.7 months and a median OS of 20.9 months, compared to 4.0 months and 16.0 months, respectively, in the TMZ monotherapy group.[38] The only risk observed in TTFields + TMZ group is skin irritation beneath the electrodes (about 52% patients). Other common risks include headaches, insomnia and soft psychiatric symptoms were statistically non-significant. The significant improvement in PFS and OS by TTFields + TMZ treatment without obvious toxic side effects led to the second FDA approval of TTFields treatment on newly diagnosed GBM in October 2015.[11] To date, TTFields treatment for GBM tumors has evolved into a relatively safe and patient-friendly therapy method.

TTFields treatment on MPM and NSCLC

MPM has emerged as a leading cause of death, with incidence rates on the rise in Europe and Asia.[22] Furthermore, the majority of MPM patients are diagnosed with diffuse disease and conventional therapies always have limited efficacy in such cases. In contrast, lung cancer is the primary cause of cancer-related mortality in the US, particularly among men, and NSCLC accounts for

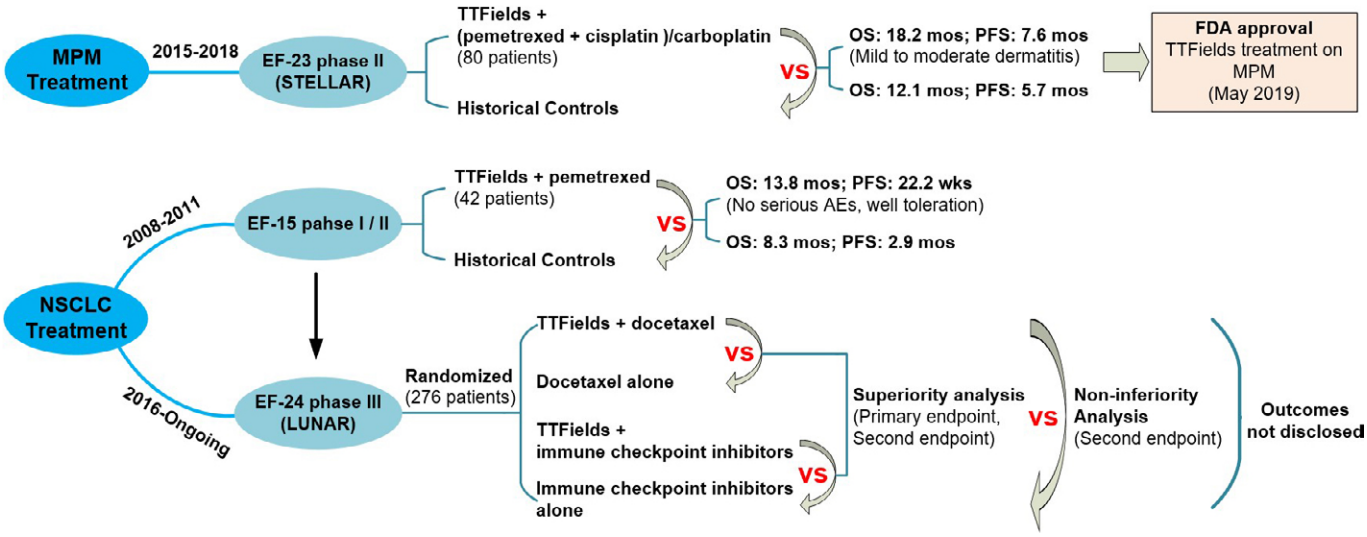

FIGURE 3. Clinical trials of TTFields treatment on malignant pleural mesothelioma and non-small cell lung cancer (NSCLC).

EF-15 phase I/II = clinical trial NCT00749346; LUNAR = clinical trial NCT02973789; OS = overall survival; PFS = progression-free survival; STELLAR = clinical trial NCT 02397928

roughly 80% to 85% of all cases of lung cancer.[39] To enhance therapeutic efficacy, researchers have postulated that TTFields could be a novel treatment modality for MPM and NSCLC, leading to the sponsorship of corresponding clinical trials. The developmental history can be succinctly summarized as follows (Figure 3).

Encouraged by the significant growth inhibition of mesothelioma cells *in vitro* treated by TTFields, the STELLAR trial (NCT 02397928) was conducted to evaluate the safety and efficacy of TTFields in combination with chemotherapy in MPM.[40] This phase II clinical trial was a prospective, single arm study that involved 80 patients and was conducted from March 2015 to April 2018.[41] The patients received standard doses of pemetrexed and cisplatin or carboplatin in combination with 150 kHz TTFields. With a minimum follow-up of 12 months, the median OS was 18.2 months compared to 12.1 months in the HCs, and median PFS was 7.6 compared to 5.7 months in HCs.[22,42] Notably, the only toxic effects related to the treatment were mild to moderate dermatitis. The results indicated a meaningful improvement in MPM treatment with TTFields and standard chemotherapy. Although the STELLAR study has the limitations of single-arm design and the results need to be confirmed by a further randomized trial, however, the FDA approved TTFields therapy on MPM under the Humanitarian Device Exemption pathway, on May 23, 2019, was based on the meaningful clinical results.[22]

The previous phase III clinical trial of TTFields as monotherapy in GBM patients demonstrated its effectiveness and improvement of quality of life. Subsequently, an open-label EF-15 phase I/II clinical trial was conducted from May 2008 to September 2011 to treat NSCLC, which included 42 patients and was registered under the identifier NCT00749346.[43] The preliminary phase I was to evaluate the adverse events (AEs) rate, while the second stage phase II continued to test feasibility and efficacy.[15] Treatment in the trial was TTFields combined with pemetrexed. During the phase I trial, no serious AEs were reported and showed a well toleration, so the safety is confirmed. The statistical analysis of phase II results[15] revealed that the median OS and median PFS of enrolled patients were 13.8 months and 22.2 weeks, respectively, compared to 8.3 months and 2.9 months in HCs reported by Hanna *et al.*[44] This study suggested that TTFields could safely improve the disease control and treatment efficacy of NSCLC. Consequently, the followed EF-24 phase III clinical trial LUNAR (NCT02973789) was initiated in December 2016.[45]

The LUNAR study was designed as randomized to test whether the addition of TTFields to immune checkpoint inhibitors or docetaxel treatment can prolong the OS.[13] This study includes a larger sample size of 276 patients and incorporates more comparative analysis. Three main comparative analysis will be reported: a) in primary endpoint, superiority analysis of OS between TTFields

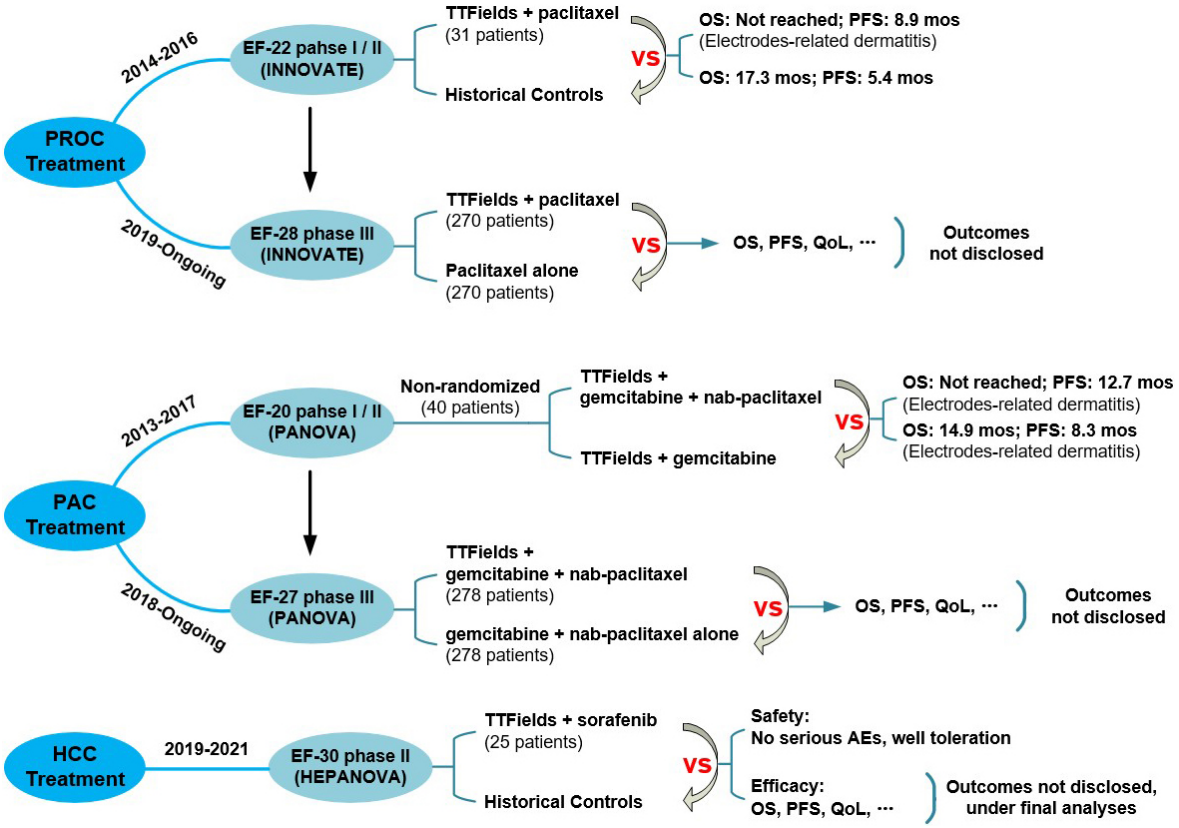

FIGURE 4. Clinical trials of TTFields treatment on platinum-resistant ovarian cancer (PROC), pancreatic adenocarcinoma (PAC) and hepatocellular carcinoma (HCC).

AEs = adverse events; INNOVATE = a phase I/II clinical trial (EF-22, NCT02244502) and a phase III randomized controlled clinical trial (EF-28, NCT03940196); OS = overall survival; QoL = quality of life (QoL); PANOVA = a phase I/II clinical trial (EF-20, NCT01971281) and a larger randomized clinical phase III (EF-27, NCT03377491); PFS = progression-free survival

+ docetaxel or immune checkpoint inhibitors vs docetaxel or immune checkpoint inhibitors alone; b) in secondary endpoint, superiority analysis of OS between TTFields + docetaxel vs docetaxel alone, and TTFields + immune checkpoint inhibitors vs immune checkpoint inhibitors alone; c) exploratory non-inferiority analysis of OS between TTFields + docetaxel vs immune checkpoint inhibitors alone. Additionally, in the second endpoint, PFS, QoL, etc. will be evaluated comprehensively. As the LUNAR study is still ongoing with an estimated completion date of September 2023, the outcome reports have not yet been disclosed.

TTFields tretament on PROC, PAC and HCC

Previous studies have provided evidence that TTFields treatment is not associated with any serious adverse events. The mitotic inhibition mechanism of TTFields has also shown potential for use in the treatment of other types of cancers in the torso. Therefore, clinical trials on PROC, PAC and HCC were initiated. The reports are presented in Figure 4.

Ovarian cancer is a frequently occurring gynecological malignancy that is responsible for a high number of female fatalities. Chemotherapy remains the standard of care in advanced ovarian cancer patients. Due to the promising results of TTFields in many different types tumor treatment, several *in vitro* and *in vivo* experiments have been conducted to assess the feasibility of TTFields can be a novel approach to treat ovarian cancer.[46,47] Furthermore, the clinical trials were also underway.[48,49] Firstly, the INNOVATE trial (EF-22, NCT02244502), a phase I/II clinical trial was conducted from September 2014 to December 2016.[50] This was a prospective, single arm, non-randomized pilot trial, designed to assess safety and preliminary efficacy of TTFields device used in PROC treatment. 31 patients were included in

the INNOVATE study and treated by TTFields in combination with weekly paclitaxel, no control group was employed in this trial. The study results showed the median PFS of patients was increased to 8.9 months compared to 5.4 months (weekly paclitaxel alone) in HCs[16,51], while the OS data was not reached in during the period, and the AEs found among patients were limited to electrodes-related dermatitis. Despite being a preliminary pilot trial, the INNOVATE study results showed promising response and survival data of PROC patients treated by TTFields. In addition to the INNOVATE trial, a phase III randomized controlled clinical trial (EF-28, NCT03940196) has been initiated to further investigate the safety and efficacy of TTFields in combination with weekly paclitaxel for PROC treatment was initiated in May 2019 and is currently ongoing (estimated completion in September 2023).[52] The sample in this study consisted of 540 participants and were randomized assigned to two arms at a 1:1 ratio. Arm A received TTFields + weekly paclitaxel treatment compared to weekly paclitaxel treatment alone in arm B. The primary endpoints for this trial include OS, PFS, and QoL, and the results will be analyzed at the endpoint. However, as the study is ongoing, no results have been reported yet.[53]

Pancreatic adenocarcinoma is another lethal malignancy for which the standard of care is combination therapy with gemcitabine and nab-paclitaxel for advanced, unresectable patients.[54] *In vitro* and *in vivo* studies have shown that TTFields can inhibit the growth of cancer cells and reduce the volume of pancreatic tumors.[19] To assess the clinical efficacy and feasibility of applying TTFields to PAC therapy, corresponding clinical trials have been conducted. PANOVA (EF-20, NCT01971281) is the first clinical trial investigating the efficacy of TTFields in PAC treatment, which was conducted from November 2013 to December 2017.[55] In this phase I/II trial, 40 patients were enrolled and non-randomly allocated into two arms. Treatments in the two arms were TTFields combined with weekly gemcitabine and TTFields in addition to gemcitabine plus nab-paclitaxel, respectively. Based on the study outcomes, the median OS and PFS of TTFields + gemcitabine group are 14.9 months and 8.3 months respectively. While TTFields + gemcitabine + nab-paclitaxel group had a PFS data of 12.7 months, but the OS was not reached at the end of follow-up period.[18] Additionally, compared to the systemic chemotherapy alone, no increase in serious AEs except contact skin reaction. The phase I/II study demonstrated that TTFields + systemic chemotherapy is safe and well-tolerated in PAC advanced patients.

After the completion of phase I/II trial, a larger randomized phase III (EF-27, NCT03377491) with a sample size of 556 patients was initiated in May 2018 to further investigate the safety and efficacy of TTFields + chemotherapy vs chemotherapy alone.[56] Therefore, in this trial, the experimental group received TTFields + gemcitabine + nab-paclitaxel treatment and the control group received gemcitabine + nab-paclitaxel alone. The study aims to analyze the results from multiple perspectives, including OS, PFS, QoL, toxicity profile and so on, but the results have not been reported yet as the trial is still ongoing and estimated to be completed in September 2024.

Liver cancer is another highly aggressive disease and is the third leading cause of cancer death globally.[57] Unfortunately, 85% patients are diagnosed at advanced stage and their only option is chemotherapy. TTFields may be a potential treatment method based on its good performance *in vitro* and *in vivo* models.[58] To assess the efficacy and safety of TTFields in combination with sorafenib to treat advanced HCC, a phase II clinical trial called HEPANOVA or EF-30 (NCT03606590) was conducted.[59] This trial was a single arm, historical control experiment including 25 participants who were treated by TTFields + sorafenib form February 2019 to September 2021. According to the objective of the trial design, the outcomes would cover overall response rate, OS (or at 1 year), PFS (or at 6 and 12 months), AEs, and so on. Although the final results of the HEPANOVA trial are currently under final analyses[60], there is a strong expectation that TTFields may emerge as a novel modality for HCC treatment.

TTFields treatment on other advanced solid tumors involving the abdomen or thorax

Since receiving FDA approval as a treatment for recurrent GBM, TTFields has garnered significant attention as a promising physical therapy modality for various types of solid tumors, particularly those that are unresectable at advanced stages.[61] Recently, a phase I clinical study (NCT05092373) has been initiated in April 2022 to evaluate the safety, AEs, and optimal dosage of TTFields therapy in combination with conventional chemotherapy, for advanced solid tumors located in the thorax or abdomen.[62] This non-randomized study has recruited 36 participants diagnosed with various

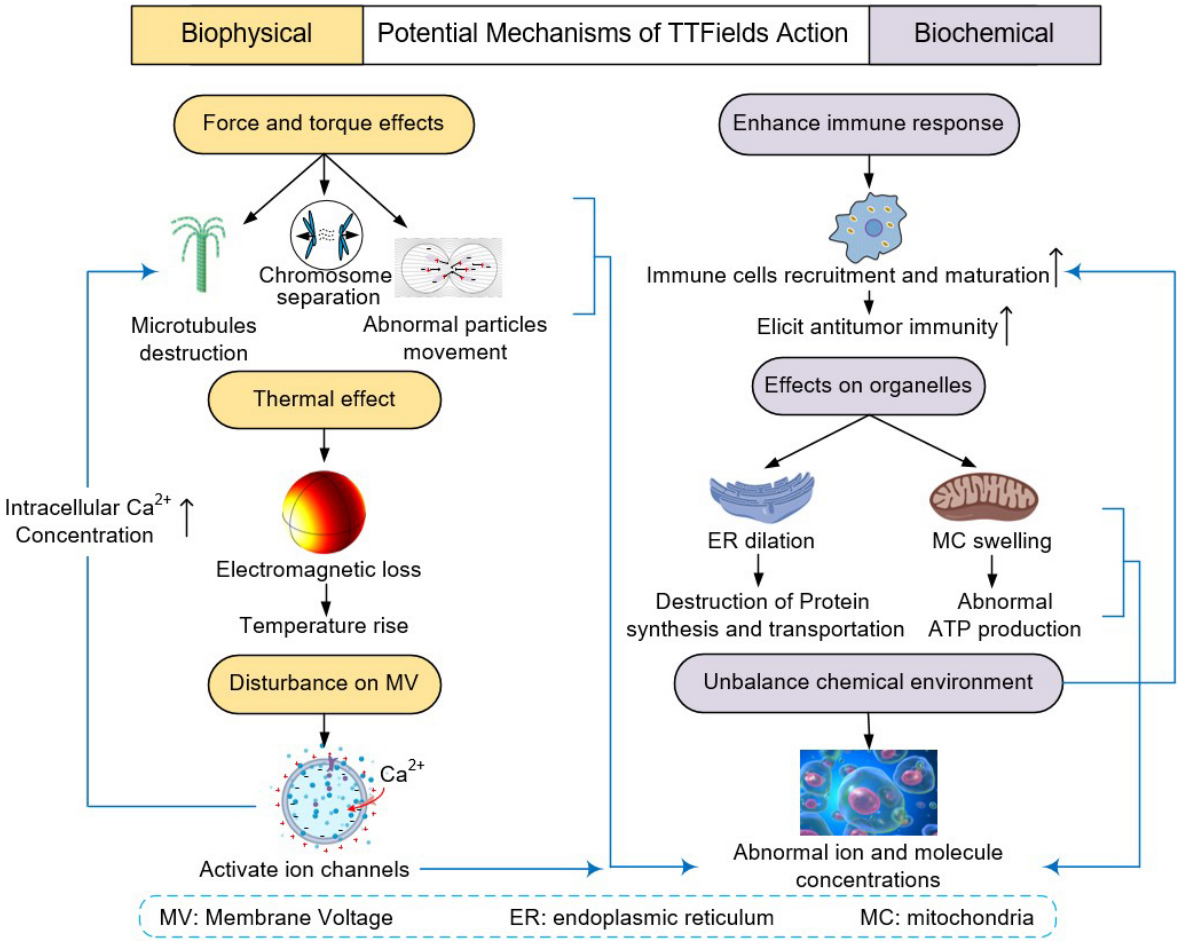

FIGURE 5. Researches on potential mechanisms of TTFields action.

types of cancer, such as breast carcinoma, endometrial carcinoma, fallopian tube carcinoma, renal cell carcinoma, malignant abdominal neoplasm, and malignant thoracic neoplasm, among others. The study comprises two experimental arms without a control group, where the first arm receives TTFields + cabozantinib, and the second arm received TTFields + atezolizumab + nab-paclitaxel. The primary outcome will assess the safety and tolerability of TTFields and ulteriorly analyze the objective response rate, median OS and PFS in the secondary outcome. The outcomes of this trial will be made public after completion, which is estimated to be in September 2026.

In summary, since the initial clinical trial of TTFields treatment on recurrent GBM, several clinical studies have been conducted to evaluate the potential of TTFields as a new therapeutic approach for cancer treatment. While some ongoing trials have yet to report results, the current evidence is promising, and there is optimism regarding the efficacy of TTFields in cancer therapy.

Progresses in revealing mechanisms of TTFields

As the development of science, researchers have an inherent curiosity to understand the underlying mechanisms that govern observed phenomena. In the case of TTFields, elucidating the mechanisms why TTFields have an inhibitory effect on cancer cells growth is an important research direction and many researchers involved in it.

Based on an overview of the existing studies, the mechanisms underlying the inhibitory effect of TTFields on cancer cell growth can be broadly categorized into two categories: biophysical and biochemical. The biophysical mechanisms pertain to the physical reactions between the electric field

and cell or subcellular structures, encompassing electric field force, torque, dielectrophoresis (DEP) force, thermal effects, membrane voltage (MV), and related phenomena. While the biochemical mechanisms mainly investigate whether TTFields interfere with intracellular and extracellular chemical environments or even intercellular communication. It should be noted that these mechanisms are often interconnected and there is no rigid boundary between them. A schematic illustration of the interplay between biophysical and biochemical mechanisms is presented in Figure 5. In this review, we will provide a detailed exploration of the mechanisms involved in both categories.

Force and torque effects on subcellular structures

Intracellular electric particles and subcellular structures are abundant in cells. When exposed to external electric fields, the resulting forces and torques can exert a range of effects on these subcellular structures, influencing their activity and morphology.

One widely accepted hypothesis for the inhibitory effect of TTFields on cancer cell growth is the cytoskeleton disruption theory. According to this theory, the electric field force and torque generated by TTFields can destroy the cytoskeleton and interfere with the cell division process, ultimately leading to cell death. This hypothesis is supported by several observations. Firstly, tubulin, the basic unit of microtubules, is a highly charged dimer protein with an electric dipole moment.[63,64] When subjected to an external electric field, the geometrical orientation of tubulin dimers is twisted by electric field torque[4,65] making it difficult for them to polymerize together, and resulting in cytoskeleton destruction. The cytoskeleton plays a crucial role in mitotic processes and maintaining proper cell shape, such as spindle formation, chromosomes traction and arrangement, and serving as a bridge for motor proteins. Therefore, cytoskeleton disruption can cause not only mitotic catastrophe, but also morphological abnormalities. This microtubule damage mechanism, initially proposed by the discoverer of TTFields, provides a plausible explanation for the observed antitumor effects of TTFields.

Although some experimental phenomena including abnormal spindle structure[19,24], chromosome aneuploidy[25,66], nuclear dysmorphologies[31,67], are observed *in vitro* in different cell lines treated by TTFields, skepticism and even contrary conclusions persist.[28,29,68,69] In fact, the proposed mechanism of cytoskeleton destruction caused by electric field force and torque has been challenged by a logical problem. It seems reasonable that the experimental results proved the above assumption, however it is possible that microtubule damage is not directly caused by force or torque, but rather by other indirect causes. In[29] researchers have attempted to address this issue by modeling single cells and intracellular substructures, and calculating electric field force and torque on the tubulin dimer or chromosome traction theoretically based on detailed electric parameters.[70,71,72,73] According to the computation results, they drew the conclusion that: a) the torque on the dimer imposed by TTFields is several orders smaller than random Brownian thermal motion energy; b) the electric field force between the microtubule terminal and kinetochore generated by TTFields is also much weaker than the natural electrostatic attraction. Therefore, the results suggesting that more rigorous scientific methods and more precise instruments are needed to further study this mechanical effects of TTFields.

Dielectrophoresis effects during mitotic telophase

In the presence of a uniform electric field, electric polar particles maintain a balance of electric field forces. However, in non-uniform electric fields, they tend to undergo dielectrophoresis (DEP) effect[27], which causes their movement. The DEP force is primarily dependent on factors such as the electric field gradient, particle size, and permittivity.[74] Biological cells contain numerous polar particles such as proteins and organelles, which can be influenced by the DEP effect when exposed to external electric fields. During the later stage of mitosis, two daughter cells will be connected by the cleavage furrow, where is very narrow with great electric field gradient. Therefore, the DEP force is much stronger in the cleavage furrow. Pushed by the DEP force, macromolecules and some free organelles will move towards the cleavage furrow, consequently, impaired cell division occurred or unhealthy daughter cells are born.[75]

It is important to highlight that the orientation of the cell division axis is a significant factor affecting the intensity of the electric fields in the cell. When the axis is aligned parallel to the external electric field, a larger number of electric field lines are concentrated in the cleavage furrow, resulting in more significant DEP effects.[75] Additionally, the duration of the telophase stage also plays a crucial

role in determining the interference effect of DEP on cell division, as the velocity of particle movement triggered by the DEP force is slow due to the viscous cytoplasm.[76] Theoretical analysis in[29] has further examined this point. The effects of cell division axis orientation and duration of the telophase stage may explain why only a subset of cells is inhibited, rather than all. Briefly, despite the DEP effect generated by TTFields should also be further confirmed, it seems to be one of the more likely mechanisms.

Thermal effect caused by electromagnetic loss

The application of electromagnetic loss thermal effect has been successfully employed in clinical treatments, such as radiofrequency ablation and microwave ablation. TTFields are low-intensity and intermediate-frequency, intuitively, the thermal effect could not be significant. To clarify this matter, Li *et al*. simulated the electromagnetic power dissipation distribution and temperature rise in the single cell.[77] Additionally, infrared camera was also employed to capture the temperature change. Expectedly, the results showed no significant temperature rise in both simulation and experiment, which suggests that TTFields may not generate a significant thermal effect. Berkelmann *et al*.[78] conducted a study to investigate the specific absorption rate (SAR), which is the standard measure to determine the safe exposure limits to electromagnetic fields. They measured the steady temperature in the cell dishes exposed to electric fields with different intensities. The results showed that only slight temperature increased (under 0.2 K) in the dish center. Moreover, in several animal experiments and clinical treatments, only a mild increase in skin temperature was monitored.[19] To further improve safety, clinical treatment devices have been designed with temperature sensors located under the electrodes. These sensors are able to detect when the temperature exceeds 41°C, at which point the power is automatically lowered.[36] Based on the combination of theoretical and experimental results, to our best knowledge, it is generally agreed upon that thermal injury can be excluded as a potential mechanism for the effects of TTFields.

Disturbance of cell membrane voltage

As the barrier between inside and outside the cell, cell membrane plays a pivotal role in maintaining the intracellular environment and keeping external interference at bay. Cell membrane possess certain voltage, which is crucial for ensuring normal ionic concentrations and performing other vital physiological functions. When the cell is exposed to an external electric field, an induced voltage will be superimposed on the natural cell membrane voltage (MV). Once the disturbance exceeds the tolerance of normal MV, the permeability of cell membrane will be affected, for example, the well-known electroporation.[79]

Whether TTFields will change the permeability of cell membrane has aroused researchers' attention, interestingly, some positive evidences has emerged in recent studies. Specifically, in a theoretical analysis conducted by Li *et al*,[29] authors calculated the TTFields induced voltage on the cancer and normal single cell membrane, and found cancer cell membranes were affected to a greater extent than healthy cell membranes. This led the authors hypothesized that TTFields can specifically increase the permeability of cancer cell membrane, particularly by impacting the function of ion channels. Moreover, experimental findings by Chang *et al*.[80] revealed that TTFields can increase the permeability of GBM cells and induce the formation of reversible pores in the cell membrane, as observed through scanning electron microscopy.

To investigate the effect of TTFields on cell membrane ion channels, Neuhaus *et al*. utilized the patch-clamp technique to record the potential change of cell membrane potential and their results indicated that TTFields activate K+ and Ca2+ ion channels on the cell membrane.[81] Disruption on the cell membrane permeability may offer a reasonable explanation for the observed improvement in therapeutic efficacy when TTFields are combined with chemotherapy. Moreover, abnormal ion channel function can cause electrolyte imbalances in cells, thereby affecting the formation and activity of subcellular structures. For instance, the concentration of Ca2+ and Mg2+ have been found to be an essential factor affecting microtubule assembly.[29,82] This founding may explain the disorder of microtubule polymerization caused by TTFields via disturbing the cell membrane permeability, but not by the direct mechanical torque on the tubulin. Although experimental evidence suggests that TTFields can increase cell membrane permeability, the relationship between TTFields frequency, pore size, and ion channel opening remains unclear and requires further investigation.

Effects on immune response

The immune system is much important for human to resist diseases. It is a common therapy method to treat diseases by stimulate the immune system and improve the immune ability with drugs or other physical means, such as cancer immunotherapy. Exploring whether TTFields activate specific immune responses to arrest tumor cell growth is an area of potential significance.

Preliminary evidence suggests that this may be the case. For example, in[83], the authors demonstrated TTFields can promote immune cells recruitment and maturation, resulting in eliciting antitumor immunity. Furthermore, they also showed the combination of TTFields with anti-PD-1 therapy resulted in a significant improvement in the antitumor effect.[83,84] Similarly, Chen *et al*.[85] reported that TTFields can be a unique activator of STING and AIM2 inflammasomes to improve antitumor immunity. This special mechanism may be generalizable and could be further explored a new avenue for antitumor immunity in other tumors. Although some preliminary findings have shown the effect of TTFields on immune responses, there is still a paucity of related studies. Further research is needed to confirm and investigate how TTFields stimulate and interact with immunity in more tumor models.

Effects on organelles' activities and morphology

Cells, the smallest units that make up most of life, are highly complex. Their normal physiological activities depend on the proper function of various organelles. Examining the mechanisms of TTFields action from the perspective of organelles may reveal unexpected findings.

Early research suggested that DEP force may be responsible for moving free organelles towards the cleavage furrow during the mitotic telophase. However, the impact of TTFields on the activities and morphology of organelles has not yet been thoroughly investigated. In recent years, some researchers have found that TTFields can trigger an increase in intracellular phagolysosome formation both *in vitro* and *in vivo* models, they believed this phenomenon may be a potential mechanism related to the cell death caused by TTFields.[86,87,88] endoplasmatic reticulum (ER) is a critical organelle involved in protein synthesis and transportation. In[83,86] the authors demonstrated they have observed abnormal morphology of ER when cells are exposed to TTFields, however, the precise relationship between TTFields and ER dysfunction in the context of induced cell death has yet to be fully elucidated. All biological activities of cells are inseparable from energy, as the energy unit, ATP is produced by a meritorious organelle called mitochondria (MC). When cancer cells are exposed TTFields, not only the direct morphological swelling change of MC was observed, but also abnormal ATP concentration was found out of the cell[83,89], which could be related to protein production disruption and cell apoptosis. Due to the fact that the tumor cells are much more aggressive to divide than healthy cells, they are more reliant on ATP energy generated by MC. Therefore, the disruption on MC structure and function by TTFields can be most likely mechanism to selectively inhibit cancer cells growth but with minimal effect on normal cells.

We believe that TTFields may affect other organelles beyond those discussed above, but the relationship between the observed experimental phenomena and the underlying mechanisms requires further clarification. Additionally, more rigorous logical analyses are needed to fully understand the effects of TTFields on organelles.

Conclusions

TTFields therapy is a remarkable discovery that employs physical means to treat cancer, offering unique advantages that have led to its FDA approvals for treating GBM and MPM, with other related approvals pending. Promising results of clinical trial investigating the TTFields therapy in GBM treatment have prompted the launch of numerous clinical trials exploring its potential in the treatment of thoracic and abdominal cancers, both with and without traditional chemotherapy. Although not all experimental data are fully disclosed, published results have revealed significant therapeutic effect enhancement and low adverse events associated with TTFields therapy. Even for trial results that have yet to be released, researchers remain confident in achieving positive outcomes. Meanwhile, the mechanisms behind the effects of TTFields therapy have received increasing attention, moving from observational studies to understanding the underlying scientific principles, this is a scientific logic from what to why. Two most popular perspectives of the mechanisms are the cytoskeleton destruction caused by electric field force and DEP effect on subcellular

structures. Besides, the mechanism studies also focus on TTFields effects on cell membrane voltage, immune response, and organelles. While some corresponding experimental phenomena have been observed *in vitro* or *in vivo*, the internal relationship between the phenomena and theory should be clarified based on more rigorous logic. Furthermore, it is plausible that the mechanism of TTFields therapy is not singular but rather a combination of multiple reasons.

To summarize, TTFields cancer treatment is a relatively novel technique that requires further development. In this paper, we reviewed two important aspects of TTFields: the clinical development and progresses in mechanism study. Many clinical trials were initiated to test the efficacy and safety of TTFields treatment, and are currently ongoing. The promising results of these studies suggest a bright future for TTFields as a cancer treatment. Nevertheless, the mechanisms of action of TTFields are still not fully revealed. Future research should focus on elucidating these mechanisms to optimize the therapeutic effect of TTFields. This can be achieved through a better understanding of the scientific mechanisms behind TTFields, and enhance its therapeutic effect through optimal combinations with traditional therapy means.

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review

Modern approach to the management of genitourinary syndrome in women with gynecological malignancies

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Background. The term genitourinary syndrome of menopause was first used in 2014 by the North American Menopause Society and the International Society for the Study of Women's Sexual Health to describe conditions previously known as atrophic vaginitis, urogenital atrophy, or vulvovaginal atrophy. It is a complex, chronic, progressive condition characterized by a wide range of signs and symptoms affecting sexual function and the tissues of the urinary and genital tracts. The main cause of genitourinary syndrome of menopause is estrogen deficiency caused by ovarian removal or dysfunction. The most bothersome symptoms are vaginal dryness, decreased vaginal lubrication, and pain during penetration and intercourse. They all have a negative impact on the quality of life.

Conclusions. The main goal of treatment is to relieve the symptoms. Treatment modalities are pharmacological or non-pharmacological. The first-line treatment for mild to moderate symptoms is the use of personal lubricants and moisturizers, but the gold standard is estrogen replacement therapy. Hormone therapy may not be an option for women with hormone-dependent cancer.

Key words: genitourinary syndrome; gynecological malignancies, therapy

Introduction

Gynecological malignancies account for approximately 10% of all cancers in women, and 40% of patients are premenopausal at the time of diagnosis.[1,2] Treatment of gynecological malignancies is often multimodal with surgery (hysterectomy with bilateral salpingo-oophorectomy), systemic therapy, and radiation leading to induced menopause. This hypoestrogenic state can lead to menopausal symptoms and can negatively affect sexual quality of life.[3]

Genitourinary syndrome of menopause (GSM) is a new term that describes conditions formerly known as vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy, all of which result from estrogen deficiency.[4] GSM is a chronic, progressive condition that causes multiple changes in the vulvar and vaginal area, pelvic floor tissues, bladder, and urethra, and impairs sexual function and libido. These changes occur in response to hypoestrogenism and do not improve with time.[5] GSM affects 27 to 84% of menopausal women.[6] Women

treated for gynecological malignancy may enter menopause earlier than healthy women.

Many survivors of gynecologic malignancies experience GSM symptoms, which impair their quality of life. Compared to healthy controls, women after surgery for early cervical cancer and endometrial cancer report sexual desire dysfunction, arousal dysfunction, entry dyspareunia and reduced intensity orgasm more often.[7,8] Fertility-sparing procedures may preserve childbearing potential, but they do not have the impact on sexual satisfaction.[9,10]

The addition of radiotherapy can additionally impair vaginal function, resulting in loss of elasticity and fibrosis of vaginal walls. After curative radiotherapy for cervical cancer, less women are sexually active compared to the time before treatment. Women report vaginal functioning problems, such as vaginal dryness, shortening and/or tightening of the vagina, which in turn correlate with diminished sexual enjoyment.[11] 45% of patients are not capable of full intercourse after curative radiotherapy for cervical cancer.[10]

Given high prevalence of GSM, it is important for physicians to address this issue. Women are often hesitant to address sexual and vaginal health issues, which are still considered taboo and are relieved when physicians bring up the topic. Because GSM is a chronic, complex condition, lifelong treatment is required to prevent recurrence of symptoms.[12]

We must keep in mind that up to 18% of endometrial carcinomas occur in women younger than 40 years. A multidisciplinary approach should be taken whether bilateral salpingo-oophorectomy is required as part of the staging procedure and when we can avoid problems with menopause.[13] Similarly, ovarian transposition should be recommended for cervical cancer in premenopausal patients undergoing pelvic irradiation to avoid premature menopause and menopausal symptoms.[14]

We will discuss treatment modalities for GSM in women with gynecological cancer, considering both hormonal and non-hormonal options.

Assessment

The clinical manifestations of GSM can be mild and nonspecific, so diagnosis may prove difficult. A careful assessment and identification of the most bothersome symptoms and their impact on quality of life should be performed before choosing a therapeutic approach. Simple and effective questionnaires are available, including the Vulvovaginal Symptoms Questionnaire (VSQ), the Sexual Symptom Checklist for Women After Cancer and EORTC QLQ CX-24, to assess symptoms, emotions, impact on life, and sexuality.[15,16] In addition, a complete medical and gynecological history and a gynecological examination are required. The examination should include inspection of the external genitalia, vaginal inspection with a speculum, and bimanual palpation to rule out other conditions that may mimic GMS, such as urinary tract infections, vulvovaginal infections, allergic reactions, and urinary incontinence.[5,17]

Symptoms and clinical manifestation

Hypoestrogenism due to bilateral oophorectomy or ovarian failure and pelvic irradiation results in anatomic and functional changes in urogenital tissue. There is loss of collagen and elastin in the vaginal epithelium, smooth muscle function is altered, and the number of small blood vessels is reduced, resulting in local tissue hypoxia. The increase in connective tissue leads to decreased elasticity, thinning of the epithelium and weakening of the vaginal mucosa.[6,18,19]

GSM presents as a wide range of signs and symptoms, the most common are summarized in Table 1. Dyspareunia and vaginal bleeding due to vaginal dryness are the most common symptoms of GSM.[12] Vaginal dryness affects up to 93% of women, and burning, itching, and pruritus affect up to 63% of women. The most common sexual complaints are decreased vaginal lubrication and dyspareunia, affecting 90% and 80% of women, respectively. Urinary symptoms, dysuria, and incontinence are less common, affecting 29% and 25% of women, respectively.[5,20]

Treatment approach

The main goal of GSM management is to relieve symptoms. The approach varies depending on the severity of symptoms. For severe and moderate symptoms, pharmacological treatment with hormone therapy (HT) is the gold standard. For mild symptoms nonhormonal therapies are subjectively effective. Nonhormonal therapies may also be used if gynecologic cancer is responsive to estrogen.[6,12] Available treatment modalities are listed in Table 2.

TABLE 1. Genital, urinary, and sexual signs and symptoms of genitourinary syndrome of menopause

Genital	Urinary	Sexual
Vaginal dryness	Dysuria	Dyspareunia
Vaginal irritation	Urgency	Decreased lubrication
Vaginal burning	Frequency	Postcoital bleeding and spotting
Vaginal itching	Reccurent urinary tract infections	Decreased arousal
Vulvar pruritus	Cystocele	Dysorgasmia
Thinning and graying pubic hair	Stress urinary incontinence	Loss of libido
Vaginal/pelvic pain and pressure	Urge urinary incontinence	Loss of arousal
Vaginal vault prolapse	Hematuria	Pelvic pain
Vaginal and introital stenosis	Nocturia	
Palor of vaginal mucosa		
Fewer vaginal rugae		
Petechiae in vaginal and cervical mucosa		
Labial shrinking and atrophia		

Pharmacological treatment

Hormone therapy

HT is the most effective therapy for GSM, but it is underutilized in women with gynecologic cancer.[6] Systemic HT is acceptable for early stage endometrial cancer (FIGO stage I–II), but is not recommended for late stage endometrial cancer (FIGO stage III–IV). Systemic HT is also not recommended for uterine sarcomas, especially leiomyosarcomas and endometrial stromal sarcomas that express estrogen and progesterone receptors.[21] According to the data, HT can be prescribed to women with epithelial ovarian cancer, but low-grade serous cancer may respond to anti-estrogen treatment, so systemic HT is not recommended in this ovarian cancer subtype. In clear cell carcinoma HT has generally been considered appropriate, but this hystological ovarian subtype itself has been associated with higher rate of venous thrombembolic events.[22] HT is also safe and acceptable in women with cervical cancer.[2,13] Recommendation for HT use in women with different gynecologic malignancy are shown in Table 3.

In women with moderate to severe GSM symptoms, the use of local estrogen might be suggested. Up to 45% of women find systemic HT insufficient to control GSM symptoms, whereas local HT is highly effective and provides symptomatic relief. The lowest dose for the shortest duration appropriate to treatment goals should be used. Estrogens and progestogens are the main hormonal preparations used in HT. Although both classes of hormones may have symptomatic benefits, progestogen is specifically added to estrogen regimens, unless the uterus has been removed to avoid endometrial hyperplasia and the increased risk of endometrial cancer. Premenopausal patients treated with curative radiotherapy with a dose of 80 Gy or more, may have symptoms of residual functional endometrium and should be advised to use estrogens in combination with a progestogen, instead of unopposed estrogens, to prevent stimulation of residual functional endometrium.[23,24]

HT is available through a variety of different routes of administration.[25] Estrogen can be administered either locally or systemically. Systemic oral, transdermal (patch and spray), intranasal, sublingual, buccal, vaginal, subcutaneous, and in-

TABLE 2. Pharmacological and non-pharmacological treatment modalities for the genitourinary syndrome of menopause

Pharmacological treatment	Non-pharmacological treatment
Hormone therapy	Lifestyle changes
SERM	Vaginal lubricants
DHEA	Vaginal moisturizers
Testosteron	Laser therapy
Lidocain	Vaginal dilatators

DHEA = dehydroepiandosterone; SERM = selective estrogen receptor modulator

TABLE 3. Recommendations for hormone therapy in women treated for gynecological malignancies

Gynecological malignancy	Recommendation	Selected articles	Level of evidence	Note
Uterine cancer				
Early stage endometrial cancer	HT acceptable	Barakat *et al.* 2006[31]	randomized control trial	1236 patients, no difference in recurrence rate with the use of HT
		Shim *et al.* 2014[32]	meta-analysis	no increased risk of recurrence
Advanced stage endometrial cancer	HT not recommended	Sinno *et al.* 2020[2]	NAMS clinical practice statement	no data supporting use of HT
Uterine sarcoma	HT not recommended	George *et al.* 2014[21]	phase 2 trial	27 patients, a potential response to anti-estrogen therapy (Letrozole)
		Sinno *et al.* 2020[2]	NAMS clinical practice statement	lack of data regarding HT safety
Ovarian cancer				
High grade serous	HT acceptable	Li *et al.* 2015[33]	meta-analysis	HT is not associated with poorer clinical outcome, epithelial ovarian cancers
Low grade serous	HT not recommended	Gershenson *et al.* 2012[34]	retrospective study	64 patients, high rate of hormone receptor expression and maintenance anti-endocrine therapy
		Sinno *et al.* 2020[2]	NAMS clinical practice statement	not sufficient safety data available
Endometrioid	HT acceptable	Power *et al.* 2016[35]	retrospective cohort data	391 patients, HT is not associated with decreased disease-free or overall survival
Clear cell	HT not recommended	Didar *et al.* 2023[22]	meta-analysis	increased risk of venous thromboembolism events
Mucinous	HT acceptable	Li *et al.* 2015[33]	meta-analysis	HT is not associated with poorer clinical outcome, epithelial ovarian cancers
Cervical cancer	HT acceptable	Ploch *et al.* 1987[36]	prospective study	120 patients, no difference in recurrence rate with the use of HT

HT = hormone therapy; NAMS = North American Menopause Society

tramuscular routes of administration of estrogen are possible, as are oral, vaginal, transdermal, intranasal, buccal, intramuscular, and intrauterine applications of progestogens.[26]

Vaginal estrogen is administered locally as a cream, gel, ring, or vaginal tablet, with minimal systemic absorption.[27,28] With vaginal application of 10 mcg of estrogen, systemic estrogen concentrations remain in the postmenopausal range.[29] There is no good evidence to support the use of a specific local estrogen product. In a retrospective cohort study of 244 women, treated for cervical, endometrial or ovarian cancer, symptom improvement was documented in one third of patients, unfortunately data on treatment efficacy is lacking for almost 60% of patients. With an incidence of 7.1%, 21.7%, and 9.7% of combined local and systemic recurrences in endometrial, ovarian, and cervical cancer, respectively, and a low incidence of other adverse outcomes, treatment was considered safe.[30] Local vaginal estrogen therapy may be considered in women with hormone-dependent cancer if symptoms persist and nonhormonal treatment has failed. This should be an informed shared decision between physician and patient.[17,27]

In a randomized double-blind trial of 1236 women surgically treated for early-stage endometrial cancer and treated with estrogen replacement therapy versus placebo for GSM, 70.1% of estrogen-treated women experienced improvement in symptoms. The recurrence rate was low at 2.1%.[31]

In a prospective cohort study of 1045 patients treated for locally advanced cervical cancer with chemoradiotherapy and brachytherapy, hormone replacement therapy was associated with less vaginal dryness (28% *vs.* 18%), less vaginal shortening (27% *vs.* 17%), and less pain during intercourse (23% *vs.* 12%).[11]

Selective estrogen receptor modulator

Ospemifene is a selective estrogen receptor modulator (SERM) and is approved for the treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy. It acts as an estrogen agonist on vaginal tissue and the endometrium, with no systemic effects on bone, breast, or cardiovascular health.[37] A meta-analysis conducted by Cui *et al.* showed that daily use of 60 mg ospemifene per os improved vaginal structure in terms of decrease in vaginal parabasal cells, increase in superficial vagi-

nal cells, and decrease in vaginal pH. The differences in endometrial thickness at weeks 12 and 52 were significant and reflected greater thickening associated with ospemifene. Endometrial thickness was also assessed, and biopsies did not show endometrial hyperplasia or carcinoma with either short- or long-term use.[38-40] However, ospemifene is not recommended for estrogen-dependent malignancies.[17]

Dehydroepiandosterone

Dehydroepiandosterone (DHEA) is a source of sex steroid hormones produced by the adrenal gland, and it is useful in treatment of vaginal dryness and dyspareunia. DHEA is metabolized to estrogens in vaginal mucosal cells and improves symptoms of vaginal irritation.[28] Studies showed that DHEA administered intravaginally for 12 weeks improves vaginal cytological environment, lowers vaginal pH, and promotes cell maturation, resulting in symptom relief. Vaginal DHEA affects serum androgen and estradiol concentrations, which increase as a result, making the safety of DHEA use in hormone-dependent cancers an issue.[27,41,42]

Testosteron

Vaginal tissue is rich in testosterone receptors, so intravaginal testosterone is sometimes used off-label for GSM treatment. The enzyme aromatase converts testosterone to estradiol, so there are legitimate concerns about the safety of elevated serum estradiol levels in response to testosterone treatment in patients with hormone-dependent cancers.[17,27] To date, hypoactive sexual desire disorder is the only evidence-based indication for the use of testosterone in postmenopausal women.[42]

Lidocain

If women suffer from penetrational dyspareunia, topical lidocaine can be used on the vaginal vestibule. In a randomized study, women who applied liquid lidocaine to the vaginal vestibule 3 minutes before intercourse reported less pain during intercourse and more comfortable penetration compared with the use of saline.[43]

Nonpharmacological treatment

Vaginal lubricants and moisturizers

Lubricants and moisturizers should be used as first-line treatment for immediate discomfort and pain relive during intercourse, especially in women with hormone-dependent cancers. Lubricants are water-, oil-, mineral oil-, plant- or silicone-based and are not absorbed by the vaginal mucosa.[27] They are applied before intercourse and have a temporary effect to reduce vaginal wall friction and relieve pain and discomfort during penetration and intercourse.[18] Moisturizers are used regularly, from daily application to once every 2–3 days. They lower vaginal pH and hydrate vaginal mucosa. They alter vaginal epithelium by absorbing and adhering to it and mimicking vaginal secretion. The effect lasts up to a few days.[5] Moisturizers are also recommended for women who are not sexually active and experience symptoms of vaginal dryness. There is a wide variety of over-the-counter lubricants and moisturizers, but women should be counseled regarding pH and osmolarity. The WHO recommends an osmolarity of no more than 380 mOsm/kg to avoid damage to the vaginal epithelium. However, most commercially available products exceed this value, so an osmolarity of up to 1200 mOsm/kg is generally accepted. In healthy women, normal vaginal pH is between 3.8 and 4.5, and lubricants or moisturizers should adhere to this range and not have a pH below 3. Additives such as parabens, microbicides and glycols should also be avoided, because they can irritate the vaginal tissue and mucosa.[44] The main limitation of using lubricants and moisturizers is short-term relief of symptoms and the fact that they do not reverse atrophy. They are suitable for mild to moderate GSM symptoms and daily wellbeing.[3] Women should be advised on which products are suitable, to avoid further damage to the vaginal epithelium.

Lifestyle changes

With regard to a conservative approach, smoking cessation is recommended as one of the GSM treatment modalities. Cigarette smoking has a negative effect on the vaginal epithelium, leading to a lack of vaginal cell maturation and increasing vaginal cell atrophy.[45] Regular sexual activity with or without a partner is recommended to maintain vaginal elasticity, blood circulation, and lubrication during arousal.[18] Regular exercise for pelvic muscle strengthening and relaxation are also advised. If available, psychosexual support should be offered.[10] Consumption of nutrients containing equol, which is produced by equol-producing bacteria from isoflavonoids, showed a beneficial effect on alleviating vaginal symptoms in GSM.[46,47]

Laser therapy

In the last 5 years, laser use has gained popularity and has become an innovative treatment method

for GSM. It is used as a minimally invasive technique that generates pulses that act on the vaginal mucosa. Epithelial cellularity and proliferation are increased, resulting in neoangiogenesis and neocolagenesis in the lamina propria of the vaginal mucosa.[48] When using lasers for GSM treatment, microablative CO2 lasers or nonablative vaginal erbium Yag lasers are an option.[17] The most common energy setting for CO2 lasers is 30–40 W and 3–10 J/cm^2 for erbium Yag lasers. In a phase I–II study, progressive increase in vaginal length and improvement in vaginal health index was achieved with laser treatment, however, this did not transfer into improvement of female sexual function index.[49] The efficacy of laser treatment for GSM caused by hormone therapy for breast cancer and in general population of postmenopausal women has been demonstrated in several retrospective series.[48]

In general, laser treatment appears to be safe and effective for GSM treatment, and no serious adverse events have been reported.[48] In women who prefer nonhormonal treatment, laser treatment may be considered, but they need to be informed about the lack of data on long-term safety and efficacy of various laser therapies for GSM symptoms.[12,17,48] In Slovenia laser treatment is not reimbursed by health insurance.

Vaginal dilators

Due to surgery and/or radiation therapy, the elasticity or length of the vagina may be compromised. In such cases, vaginal dilators can be helpful. In the early stages, dilators prevent or minimize the formation of adhesions between vaginal walls and promote elasticity and reduce fibrosis in later stages.[37] The use of vaginal dilators should begin no later than 3 months after the end of radiotherapy and should be performed at least 2 to 3 times per week for 10 to 15 minutes to achieve positive effects on vaginal stenosis.[50] It is important to educate women on how to relax the pelvic muscles and provide them with guidelines and instructions on dilators and their use.[19] In a randomized trial the women who regularly used vaginal dilators after radiotherapy had less frequent and less severe vaginal stenosis.[51]

Conclusions

Anatomic, physiologic, and sexual changes after treatment of gynecological malignancies are common and negatively impact quality of life and recovery from cancer. Physicians need to be aware of underestimated GSM symptoms and manifestations and address this issue with their patients. The treatment modality of GSM should be evaluated on an individual basis. The first-line treatment is non-homone approach, but if this fails, the use of local estrogen therapy could be used, taking into account the subtype of gynecologic malignancy.

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research article

Comparing the diagnostic efficacy of [^{18}F]FDG PET/CT and [^{18}F]FDG PET/MRI for detecting bone metastases in breast cancer: a meta-analysis

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Longjie Xia, Shenghui Qiu, Di Huang, Jianqin Lai have contributed equally as co-first author.

Background. This meta-analysis aimed to evaluate the comparative diagnostic efficacy of [^{18}F]FDG PET/CT and [^{18}F]FDG PET/MRI in detecting bone metastases in breast cancer patients.

Methods. An extensive search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases to identify available publications up to February 2023. Studies were included if they evaluated the diagnostic efficacy of [^{18}F]FDG PET/CT and [^{18}F]FDG PET/MRI in patients with breast cancer bone metastases. Sensitivity and specificity were assessed using the DerSimonian and Laird method, followed by transformation via the Freeman-Tukey double inverse sine transformation.

Results. 16 articles (including 4 head-to-head comparison articles) involving 1,261 patients were included in the meta-analysis. The overall sensitivity of [^{18}F]FDG PET/CT in patient-based analysis, lesion-based analysis, and head-to-head comparison were 0.73, 0.89, and 0.87, respectively, while the overall sensitivity of [^{18}F]FDG PET/MRI were 0.99, 0.99, and 0.99. The results indicated that [^{18}F]FDG PET/MRI appears to a higher sensitivity in comparison to [^{18}F]FDG PET/CT(all $P < 0.05$). In contrast, the overall specificity of [^{18}F]FDG PET/CT in patient-based analysis, lesion-based analysis, and head-to-head comparison were 1.00, 0.99, and 1.00, respectively, while the overall specificity of [^{18}F]FDG PET/MRI were 1.00, 0.99, and 0.98. These results suggested that [^{18}F]FDG PET/CT has a similar level of specificity compared to [^{18}F]FDG PET/MRI.

Conclusions. Our meta-analysis indicates that [^{18}F]FDG PET/MRI demonstrates superior sensitivity and similar specificity to [^{18}F]FDG PET/CT in detecting bone metastases in breast cancer patients. Further prospective research is required to confirm these findings and assess the clinical application of these techniques.

Key words: [^{18}F]FDG PET/CT; [^{18}F]FDG PET/MRI; bone metastases; breast cancer; meta-analysis

Introduction

Breast cancer is a serious global health concern and is the most prevalent malignancy affecting women.[1] Bone metastasis is a frequent complication of advanced breast cancer, with nearly 65% of patients developing bone metastases.[2] The existence of bone metastases can cause severe mor-

bidity and death, as well as reduced quality of life and an increased risk of skeletal-related events.[3] Hence, early identification of bone metastases is essential for effective treatment strategies and improved patient outcomes. For the detection of bone metastases in breast cancer, conventional imaging techniques such as X-ray, bone scintigraphy, and computed tomography (CT) have been utilized.[4] However, these modalities have limits in terms of sensitivity, specificity, and spatial resolution.[5]

With higher sensitivity and specificity, as well as the capacity to provide both metabolic and anatomical information, [18F]Fluorodeoxyglucose ([18F]FDG) positron emission tomography/computed tomography (PET/CT) and [18F]FDG positron emission tomography/magnetic resonance imaging (PET/MRI) have emerged as promising imaging modalities to identify bone metastases in breast cancer patients.[6] [18F]FDG is a radiotracer that accumulates in cancer cells and can be detected via positron emission tomography (PET). PET/CT imaging combines PET and CT imaging to provides metabolic as well as anatomical information, whereas PET/MRI imaging combines PET and magnetic resonance imaging (MRI) for a more detailed analysis of soft tissue structures.[7,8]

Numerous studies have been conducted to assess the diagnostic accuracy of [18F]FDG PET/CT and [18F]FDG PET/MRI in detecting bone metastases in breast cancer patients, with inconsistent results. Some studies have shown that [18F]FDG PET/MRI is superior to [18F]FDG PET/CT in terms of sensitivity[9,10], while others have reported similar diagnostic performance for both modalities.[11]

Therefore, a meta-analysis should be conducted to assess the diagnostic efficacy of [18F]FDG PET/CT and [18F]FDG PET/MRI for detecting bone metastases in breast cancer. The current meta-analysis would provide an overall comparison of the diagnostic efficacy of the two modalities, based on the extracted data from all available identified studies.

Methods

The meta-analysis followed the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy (PRISMA-DTA) guidelines.[12] The protocol of the current meta-analysis has been registered with PROSPERO (CRD42023402353).

Search strategy

An extensive search was conducted in the PubMed, Embase, Web of Science, and Cochrane Library databases to identify available publications up to February 2023. The search was conducted using the following keyword terms: "Positron-Emission Tomography", "Breast Neoplasms" and "Bone metastases". More details could be found in the Supplementary Table 1. The reference lists of the included studies were manually searched to find additional relevant articles.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they evaluated the diagnostic performance of [18F]FDG PET/CT and/or [18F]FDG PET/MRI in patients with breast cancer bone metastases with a sample size of more than 10 patients.

Duplicated articles, abstracts without full texts, editorial comments, letters, case reports, reviews, meta-analyses, irrelevant titles and abstracts, and non-English full-text articles were excluded. Studies with incomplete or unclear data necessary to calculate the sensitivity or specificity of the imaging modality being studied were excluded. In addition, studies using PET without CT or MRI, or using different radiotracers were excluded. For studies using the same data, only the latest studies were taken into consideration.

Retrieval of relevant articles

Two researchers independently read the titles and abstracts of retrieved articles using the predetermined selection criteria. Subsequently, full-text evaluation was conducted to ascertain each study's eligibility. The event of discrepancies between the researchers were resolved through discussion, ultimately arriving at a consensus.

Quality assessment

Two researchers independently assessed the quality of the included studies utilizing the Quality Assessment of Diagnostic Performance Studies (QUADAS-2) tool.[13] The QUADAS-2 tool encompasses four essential domains: (1) patient selection; (2) index test; (3) reference standard; and (4) flow and timing. The risk of bias was rated as "high risk," "low risk," or "unclear risk."

In assessing the risk of bias, several key aspects were evaluated. First, patient selection bias

TABLE 1. Study and patient characteristics of the included studies for [18F]FDG PET/CT

Author	Year	Type of imaging test	Study characteristics				Patient characteristics			
			Country	Study design	Analysis	Reference standard	No. of patients	Clinical indication	Mean/Median age	Previous treatment
Catalano *et al.*[15]	2015	PET/CT	Italy	Retro	PB	Pathology and/or follow-up imaging	109	Initial stage and post-treatment stage	Mean ± SD: (58.08 ± 10.7)	Surgery
Melsaether *et al.*[10]	2016	PET/CT	USA	Pro	LB	Pathology and/or follow-up imaging	51	Initial stage and post-treatment stage	Mean(range): 56 (32–76)	Chemotherapy
Botsikas *et al.*[9]	2018	PET/CT	Switzerland	Pro	PB and LB	Pathology and/or follow-up imaging	80	Initial stage and post-treatment stage	Mean ± SD: (48 ± 12.9)	NA
Sawicki *et al.*[11]	2016	PET/CT	Germany	Pro	LB	Pathology and/or follow-up imaging	21	Post-treatment stage	Mean ± SD: (59.4 ±11.5)	NA
Balci *et al.*[17]	2012	PET/CT	Turkey	Retro	PB	Pathology and/or follow-up imaging	162	Initial stage and post-treatment stage	Mean: 50.6	Surgery
Hahn *et al.*[18]	2011	PET/CT	Germany	Retro	PB and LB	Follow-up imaging	29	Initial stage	Mean (range): 57.5 (35–78)	NA
Manohar *et al.*[19]	2012	PET/CT	India	Retro	LB	Pathology and/or follow-up imaging	111	Post-treatment stage	Mean(range): 52 (22–80)	Surgery
Niikura *et al.*[25]	2011	PET/CT	Japan	Retro	LB	Pathology and/or follow-up imaging	225	Initial stage and post-treatment stage	Mean: 53.4	Chemotherapy or endocrine therapy
Riegger *et al.*[22]	2012	PET/CT	Germany	Retro	LB	Pathology and/or follow-up imaging	106	Initial stage	Mean ± SD: (57 ± 13)	NA
Rager *et al.*[23]	2018	PET/CT	Switzerland	Retro	PB and LB	Follow-up imaging	25	Initial stage and post-treatment stage	Median(range): 5 (38–82)	NA
Demir *et al.*[20]	2014	PET/CT	Turkey	Retro	LB	Pathology and/or follow-up imaging	50	Post-treatment stage	Mean ± SD: (53.9 ± 12.3)	NA
Hansen *et al.*[24]	2015	PET/CT	Denmark	Pro	LB	Pathology	18	Post-treatment stage	Mean(range): 61.5 (38–76)	Surgery
Niikura *et al.*[21]	2016	PET/CT	Japan	Pro	PB	Pathology and/or follow-up imaging	28	Initial stage and post-treatment stage	Median(range): 59 (31–76)	Surgery
Shawky *et al.*[26]	2016	PET/CT	Egypt	Pro	LB	Pathology and/or follow-up imaging	30	Post-treatment stage	Mean(range): 53.5 (33–73)	Surgery or Chemotherapy or radiotherapy
Teke *et al.*[27]	2020	PET/CT	Turkey	Retro	LB	Follow-up imaging	62	Initial stage	Median(range): 44.5 (8–81)	NO

LB = lesion-based; NA = not available; PB = patient-based; Pro = prospective; Retro = retrospective

was addressed by enrolling consecutive patients. Second, the results of the index test were evaluated independently of the outcomes of the reference standard to minimize potential bias. Third, the reference standard was evaluated without knowledge of the results of the index test to ensure objectivity. Finally, the flow and timing aspect examined the appropriateness interval (less than 3 months) between the index tests and the reference standard. Regarding applicability concerns, the analysis focused on three main questions. First, patient selection was "Are there any concerns regarding the relevance of the included patients to the scope of the review?" Second, the index test was "Are there concerns that the target condition as defined by the reference?" Third, the reference standard was "Are there concerns about the compatibility between the target condition, as established by the reference standard, and the review question?"

Data extraction

Two researchers independently extracted data from all the included articles. The gathered data included information about the author, year of publication, and the type of imaging test used in the study, study features (country, study design, analysis, and reference standard), characteristics of patients (number of patients, clinical indication, mean/median age, and previous treatment), and technical aspects (scanner modality, ligand dose, and image analysis).

In cases of disagreements, the researchers discussed the issue until a consensus was reached to ensure accuracy in the extracted data.

Outcome measures

The main outcome measure were the sensitivities and specificities of [18F]FDG PET/CT and [18F]FDG

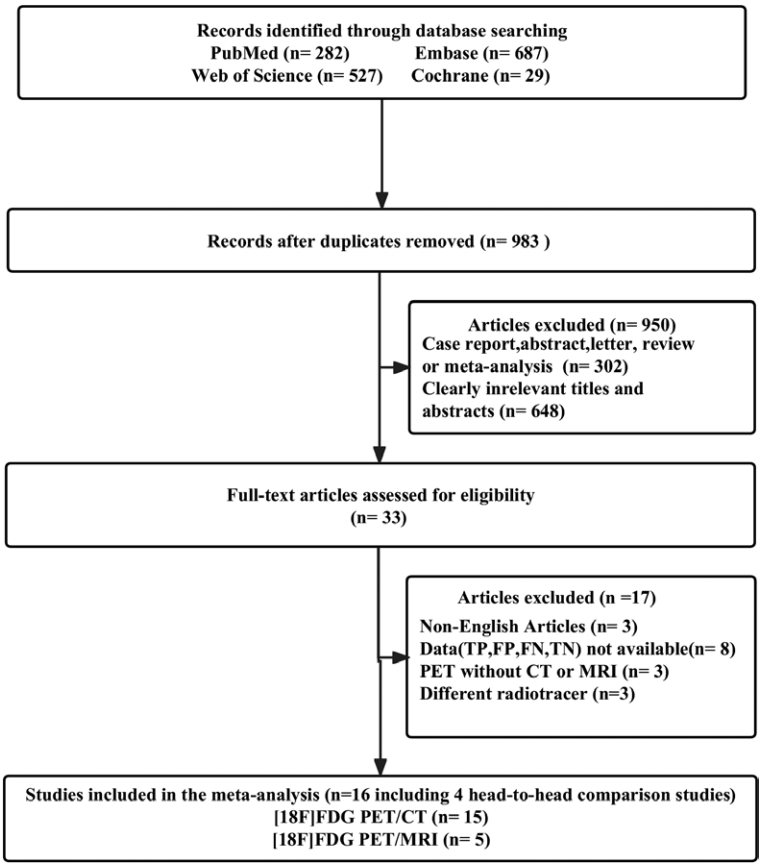

FIGURE 1. PRISMA flow diagram illustrating the study selection process.

FN = false negative; FP = false positive; TN = true negative; TP = true positive

PET/MRI in patient-based analysis, lesion-based analysis and head-to-head comparison. Sensitivity was defined as the ratio of patients or lesions with true positive (TP) scans to the sum of TP and false negative (FN) scans for either patients or lesions have been reported; Specificity was defined as the ratio of patients or lesions with true negative (TN) scans to the sum of TN scans and false negative (FN) scans have been reported.

Statistical analysis

Sensitivity and specificity were assessed using the DerSimonian and Laird method, followed by transformation via the Freeman-Tukey double inverse sine transformation. The Jackson method was used to calculate the confidence intervals. The Cochrane Q and I^2 statistics were used to assess the heterogeneity within and between groups.[14] If the heterogeneity between the studies differed significantly ($P < 0.10$ or $I^2 > 50\%$), sensitivity analysis was performed by reassessing the sensitivities or specificities following the omission of articles one by one. This was done to evaluate the robustness of the overall sensitivities or specificities and to identify single studies that may contribute to heterogeneity.

We evaluated publication bias by employing both funnel plot and Egger's test (for outcomes including over 10 studies). For all statistical tests except heterogeneity ($P < 0.10$), a significance level of $P < 0.05$ was considered statistically significant. Statistical analyses were conducted using R software version 4.1.2 for statistical computing and graphics.

Results

Search strategy and study selection

The preliminary search revealed a total of 1525 publications. However, 542 studies were considered duplicates, and another 950 did not meet the eligibility criteria and were therefore not included in the study. After a comprehensive review of the full texts of the remaining 33 articles, another 17 were deemed ineligible for the study either because data (TP, FP, FN, and TN) were not available (n = 8) or the radiotracer was different (n = 3). In addition, non-English articles (n = 2) and PET without CT or MRI articles (n = 3) were excluded. Finally, 16 articles[9-11,15-27] (including 4 head-to-head comparison articles) evaluating the diagnostic efficacy of [18F]FDG PET/CT (n = 15)[17-20,22-27], and [18F]FDG PET/MRI (n = 5)[9-11,15,16] were included in the meta-analysis. The article selection process, according to the PRISMA flow diagram, is depicted in Figure 1.

Study description and quality assessment

The 16 eligible studies included a total of 1,261 breast cancer patients (range from 18 to 225). Among the included studies, 9 articles were retrospective studies, while 7 articles were prospective studies. In terms of analysis methods, 3 articles employed patient-based analysis, 9 articles used lesion-based analysis, and 4 articles utilized both methods. 2 articles used pathology as the reference standard, 11 articles employed pathology and/or follow-up imaging as the reference standard, and 3 articles solely relied on follow-up imaging as the reference standard. Regarding clinical indications, 3 articles involved patients exclusively at the initial stage, 6 articles included patients only at the post-treatment stage, and the remaining 7 articles in-

TABLE 2. Study and patient characteristics of the included studies for [18F]FDG PET/MRI

Author	Year	Type of imaging test	Study characteristics				Patient characteristics			
			Country	Study design	Analysis	Reference standard	No. of patients	Clinical indication	Mean/Median age	Previous treatment
Catalano *et al.*[15]	2015	PET/MRI	Italy	Retro	PB	Pathology and/or follow-up imaging	109	Initial stage and post-treatment stage	Mean ± SD: (58.08 ± 10.7)	Surgery
Bruckmann *et al.*[21]	2021	PET/MRI	Germany	Pro	PB and LB	Pathology	154	Post-treatment stage	Mean ± SD: (53.8±11.9)	NO
Melsaether *et al.*[10]	2016	PET/MRI	USA	Pro	LB	Pathology and/or follow-up imaging	51	Initial stage and post-treatment stage	Mean(range): 56(32–76)	Chemotherapy
Botsikas *et al.*[9]	2018	PET/MRI	Switzerland	Pro	PB and LB	Pathology and/or follow-up imaging	80	Initial stage and post-treatment stage	Mean ± SD: (48 ± 12.9)	NA
Sawicki *et al.*[11]	2016	PET/MRI	Germany	Pro	LB	Pathology and/or follow-up imaging	21	Post-treatment stage	Mean ± SD: (59.4 ± 11.5)	NA

LB = lesion-based; NA = not available; PB = patient-based; Pro = prospective; Retro = retrospective

cluded patients at both initial and post-treatment stages. Table 1 and Table 2 summarize the study and patient characteristics of [18F]FDG PET/CT and [18F]FDG PET/MRI, while Supplementary Table 2 and Supplementary Table 3 present the technical aspects.

The risk of bias for each study according to the QUADAS-2 tool is illustrated in Figure 2. For the patient selection risk of bias assessment, we found 2 studies that graded as "high risk" since they didn't include consecutive patients. For the index test, 3 studies were graded as "high risk" since the applied cut-off values were not pre-determined. With regards to the reference standard, 2 studies were graded as "high risk" as the final diagnosis was not determined independently by two or more physicians. The flow and timing standard were graded as "high risk" in 2 studies because some participants were excluded from data analyses. There were no major concerns with the quality of the included studies based on the overall quality assessment.

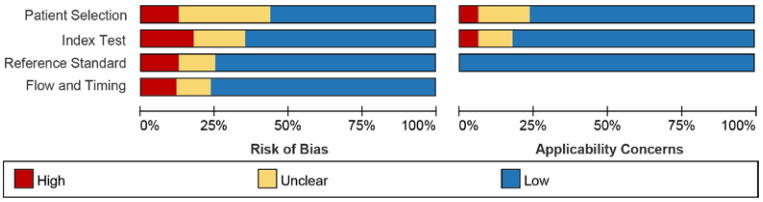

FIGURE 2. Risk of bias and applicability concerns of the included studies using the Quality Assessment of Diagnostic Performance Studies QUADAS-2 tool.

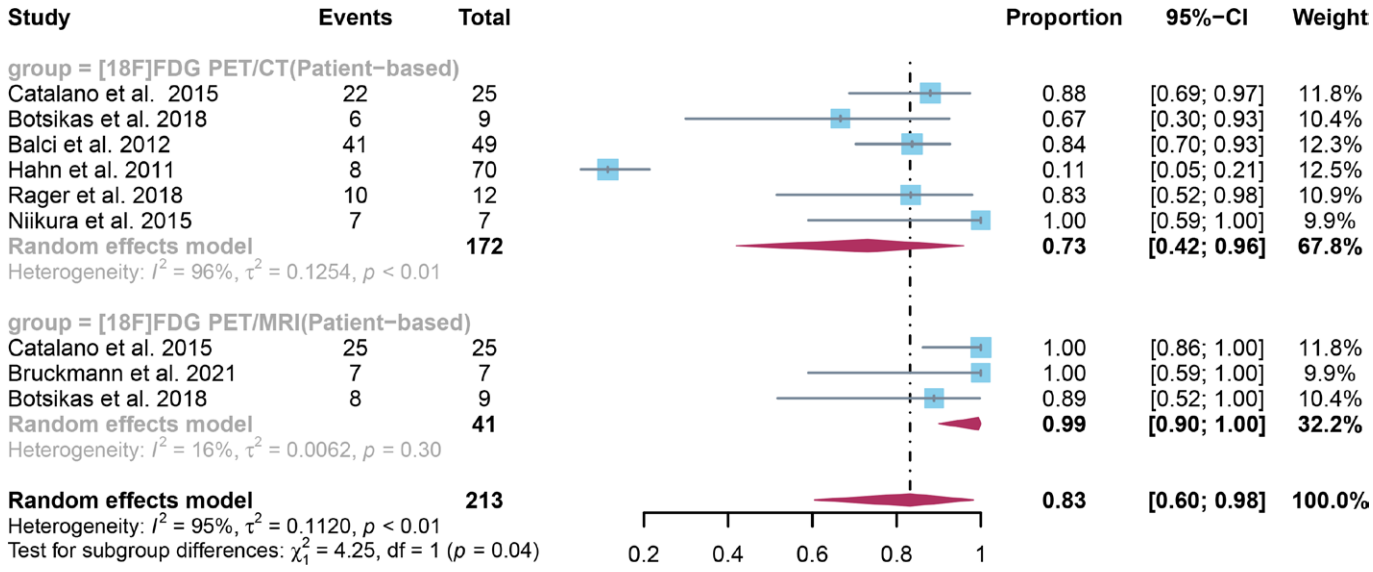

FIGURE 3. Forest plot showing the pooled sensitivities of [18F]FDG PET/CT and [18F]FDG PET/MRI in bone metastasis of breast cancer patients on a patient-based analysis. The plot displays individual study estimates (squares) with corresponding 95% confidence intervals (horizontal lines) and the pooled sensitivity estimate (diamond) for both modalities. The size of the squares represents the relative weight of each study in the meta-analysis.[9,15,17,18,21,23,25]

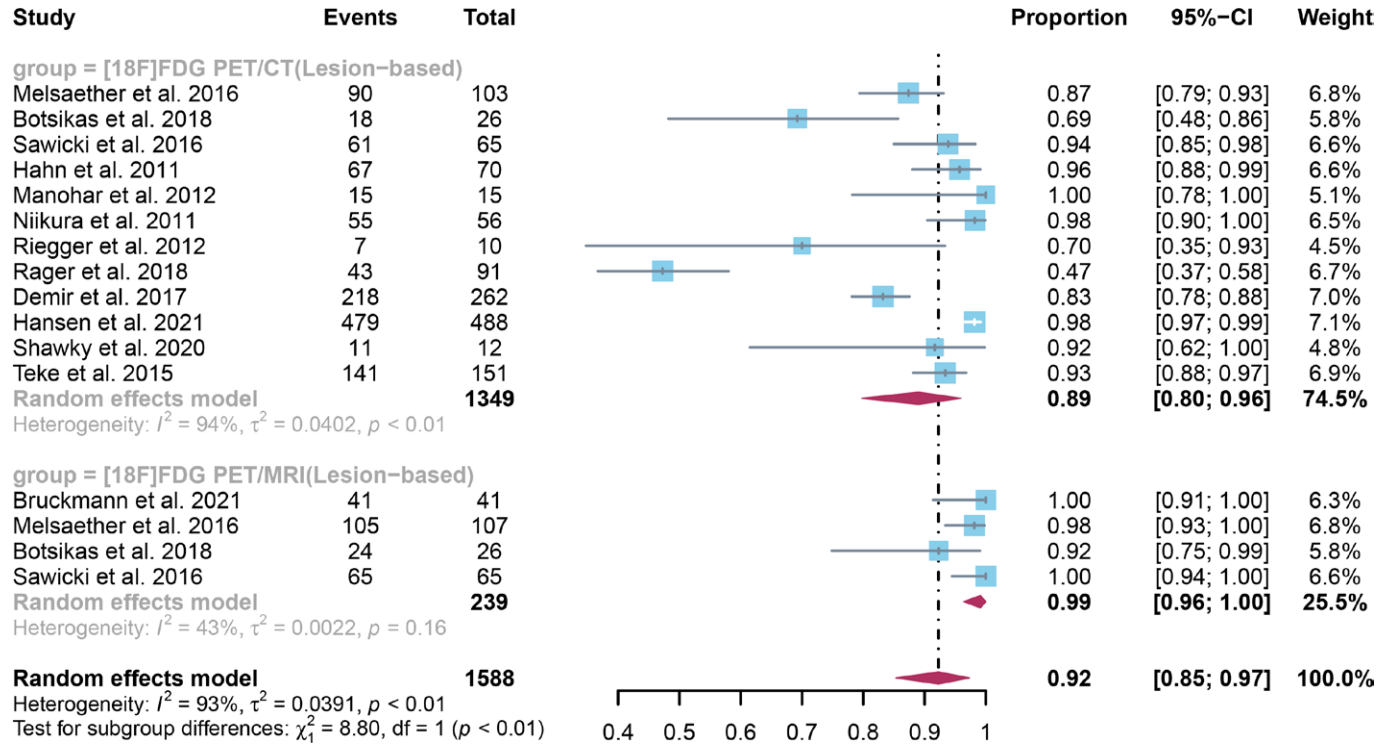

FIGURE 4. Forest plot showing the pooled sensitivities of [18F]FDG PET/CT and [18F]FDG PET/MRI in bone metastasis of breast cancer patients on a lesion-based analysis. The plot displays individual study estimates (squares) with corresponding 95% confidence intervals (horizontal lines) and the pooled sensitivity estimate (diamond) for both modalities. The size of the squares represents the relative weight of each study in the meta-analysis.[9-11,18-20,22-27]

Comparing the sensitivity of [18F] FDG PET/CT and [18F]FDG PET/MRI for detecting bone metastases in breast cancer

For patient-based analysis, a total of 8 studies with 213 patients were included in the analysis, and the pooled sensitivity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 0.73 (95% CI: 0.42–0.96), whereas [18F]FDG PET/MRI had an overall sensitivity of 0.99 (95% CI:0.90–1.00) (Figure 3). There was significant difference between [18F]FDG PET/CT and [18F]FDG PET/MRI in the sensitivity (P = 0.04) (Figure 3). After removing Hahn *et al.*'s study[18] in our sensitivity analysis, the I² value became 0%, suggesting it may be the potential source of heterogeneity. However, the results from the sensitivity analysis remained stable, with only minor variations observed, ranging from 0.66 to 0.86 (Supplementary Figure 1).

For lesion-based analysis, a total of 13 studies with 1588 lesions were included in the analysis, and the pooled sensitivity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 0.89 (95% CI: 0.80–0.96), whereas [18F]FDG PET/MRI had an overall sensitivity of 0.99 (95% CI:0.96–1.00) (Figure 4). There was significant difference between [18F]FDG PET/CT and [18F]FDG PET/MRI in the overall sensitivity (P < 0.01) (Figure 4). Regarding the pooled overall sensitivity of [18F]FDG PET/CT in lesion-based analysis, the I² was 94%. The sensitivity analysis revealed no potential source of heterogeneity. The results following sensitivity analysis remained stable, and only minor variations in the results ranging from 0.88 to 0.92 were noted (Supplementary Figure 2). The funnel plot and Egger's test revealed no evidence of publication bias for [18F]FDG PET/CT in lesion-based analysis (P = 0.30) (Supplementary Figure 3).

For head-to-head comparison, a total of 4 studies with 442 patients or lesions were included in the analysis, and the pooled sensitivity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 0.87 (95% CI: 0.77–0.94), whereas [18F]FDG PET/MRI had an overall sensitivity of 0.99 (95% CI:0.96–1.00) (Supplementary Figure 4). A significant difference was observed in the overall sensitivity between [18F]FDG PET/CT and [18F]FDG PET/MRI. (P < 0.01) (Supplementary Figure 4). Regarding the pooled overall sensitivity of [18F]

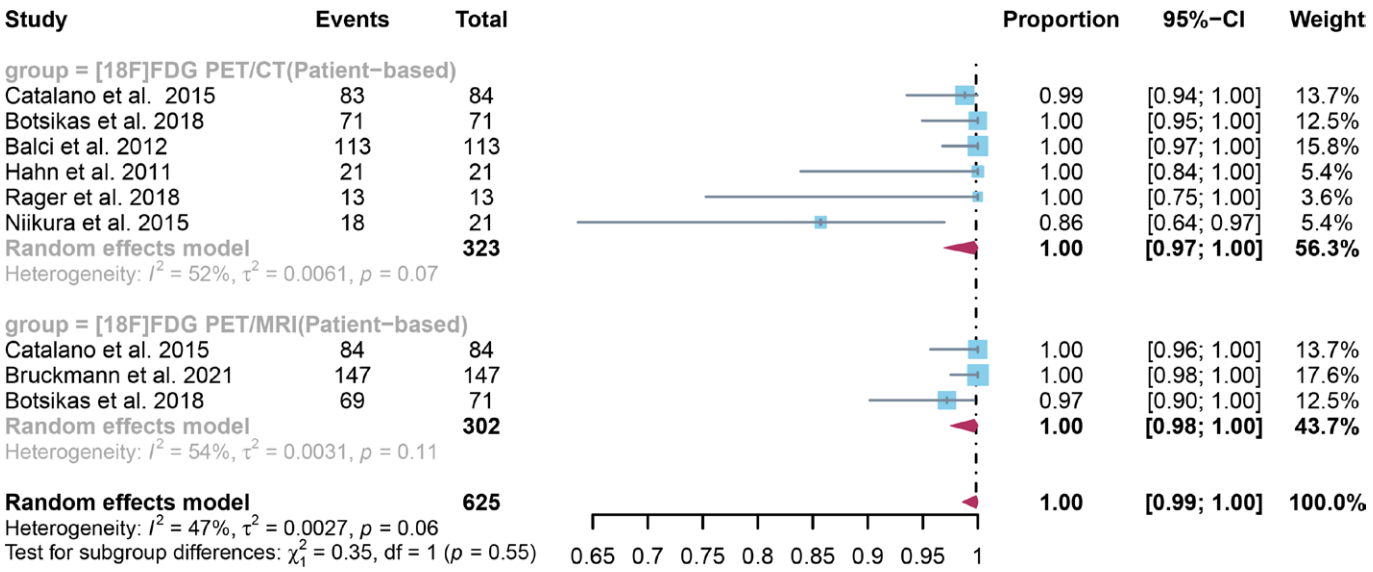

FIGURE 5. Forest plot showing the pooled specificities of [18F]FDG PET/CT and [18F]FDG PET/MRI in bone metastasis of breast cancer patients on a patient-based analysis. The plot displays individual study estimates (squares) with corresponding 95% confidence intervals (horizontal lines) and the pooled specificity estimate (diamond) for both modalities. The size of the squares represents the relative weight of each study in the meta-analysis. [9,15,17,18,21,23,25]

FDG PET/CT in lesion-based analysis, the I^2 was 64%. After removing Botsikas *et al.*'s study[9] in our sensitivity analysis, the I^2 value became 0%, suggesting it may be the potential source of heterogeneity. However, the results from the sensitivity analysis remained stable, with only minor variations observed, ranging from 0.83 to 0.90. (Supplementary Figure 5).

Comparing the specificity of [18F] FDG PET/CT and [18F]FDG PET/MRI for detecting bone metastases in breast cancer

For patient-based analysis, a total of 7 studies with 625 patients were included in the analysis, and the pooled specificity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 1.00 (95% CI: 0.97–1.00), whereas [18F]FDG PET/MRI had an overall specificity of 1.00 (95% CI:0.98–1.00) (Figure 5). There was no significant difference between [18F] FDG PET/CT and [18F]FDG PET/MRI in the overall specificity (P = 0.55) (Figure 5). The pooled overall specificity of [18F]FDG PET/CT and PET/MRI exhibited I^2 values of 52% and 54%, respectively. Sensitivity analysis revealed that removing Niikura *et al.*'s study[21] reduced PET/CT heterogeneity (I^2 = 0%), while removing Botsikas *et al.*'s study[9] had a similar effect on PET/MRI. Nonetheless, both analyses yielded stable results, with minor variations between 0.99 and 1.00 (Supplementary Figures 6 and 7).

For lesion-based analysis, a total of 9 studies with 1023 lesions were included in the analysis, and the pooled specificity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 0.99 (95% CI: 0.97–1.00), whereas [18F]FDG PET/MRI had an overall specificity of 0.99 (95% CI:0.95–1.00) (Figure 6). A significant difference was observed in the overall specificity between [18F]FDG PET/CT and [18F]FDG PET/MRI (P = 0.07) (Figure 6). Regarding the pooled overall specificity of [18F] FDG PET/CT in lesion–based analysis, the I^2 was 67%. After removing Hahn *et al.*'s study[18] in our sensitivity analysis, the I^2 value became 49%, suggesting it may be the potential source of heterogeneity. However, the results from the sensitivity analysis remained stable, with only minor variations observed, ranging from 0.99 to 1.00. (Supplementary Figure 8).

For head-to-head comparison, a total of 2 studies with 466 patients or lesions were included in the analysis, and the pooled specificity of [18F]FDG PET/CT in detecting bone metastases in breast cancer was 1.00 (95% CI: 0.98–1.00), whereas [18F]FDG PET/MRI had an overall specificity of 0.98 (95% CI:0.91–1.00) (Supplementary Figure 9). No significant difference was observed in the overall specificity between [18F]FDG PET/CT and [18F]FDG PET/MRI (P = 0.50) (Supplementary Figure 9).

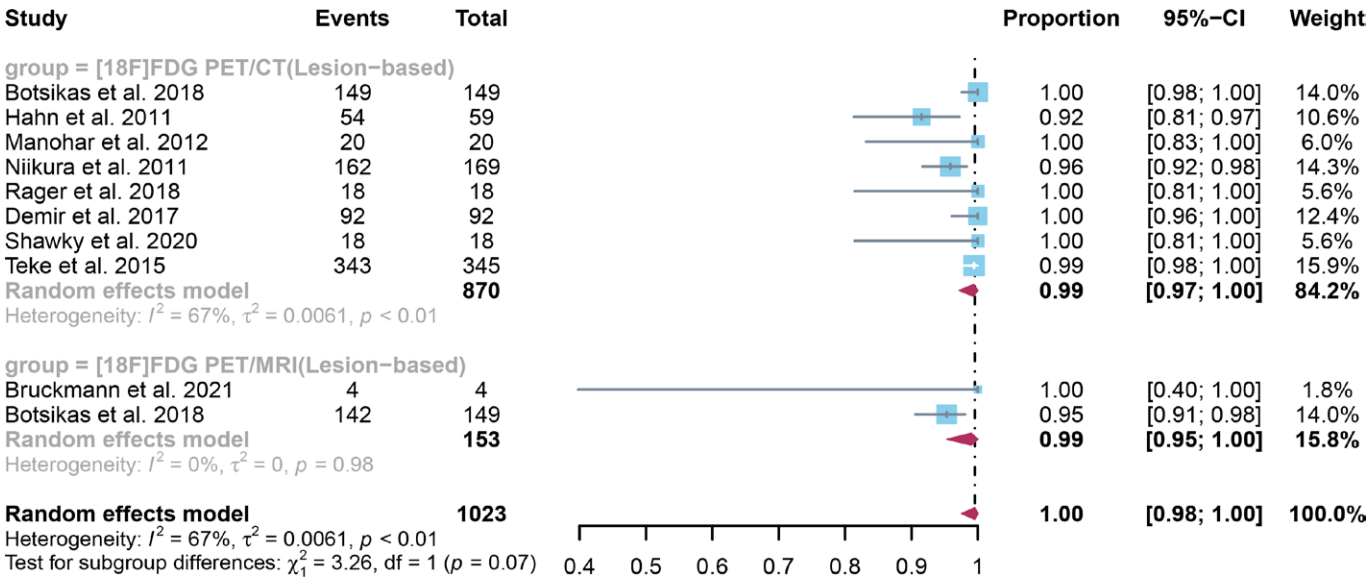

FIGURE 6. Forest plot showing the pooled specificities of [18F]FDG PET/CT and [18F]FDG PET/MRI in bone metastasis of breast cancer patients on a lesion-based analysis. The plot displays individual study estimates (squares) with corresponding 95% confidence intervals (horizontal lines) and the pooled specificity estimate (diamond) for both modalities. The size of the squares represents the relative weight of each study in the meta-analysis.[9,18-21,23,25-27]

Complementary role in identifying bone metastases of PET/CT, PET/MRI, $MRI_{(PET/MRI)}$ alone, and $CT_{(PET/CT)}$ alone for detecting bone metastases in breast cancer

In the 4 head-to-head comparison studies, one study (Melsaether *et al.*) did not provide information regarding the complementary role of PET/CT and PET/MRI in identifying bone metastases.[10] Therefore, the evaluation was from 3 studies (Supplementary Table 4). Among these studies, PET/MRI correctly identified bone metastases in 10 out of 98 patients or lesions (10.2%) with initially negative PET/CT results. Conversely, PET/CT correctly identified bone metastases in none of the 86 patients (0%) with initially negative PET/MRI results.

Furthermore, 2 studies reported information on the detection of bone metastases in breast cancer patients using $MRI_{(PET/MRI)}$ alone, while 4 studies provided data on $CT_{(PET/CT)}$ alone. The results indicate that $MRI_{(PET/MRI)}$ alone demonstrated a higher detection rate (65.5%, 180 out of 275) compared to $CT_{(PET/CT)}$ alone (51.2%, 166 out of 324) (Supplementary Table 4).

Discussion

In the field of detecting bone metastases in breast cancer, there has been uncertainty and controversy regarding the comparative diagnostic efficacy of [18F]FDG PET/CT and [18F]FDG PET/MRI.[9,15] Key issues of comparison between the two imaging modalities include differences in sensitivity and specificity, as well as potential variations in diagnostic performance across different patient populations and analysis methods. To our knowledge, this is the first meta-analysis conducted on this topic, with patient-based, lesion-based and head-to-head comparison analysis, to compare the diagnostic efficacy of [18F]FDG PET/CT and [18F]FDG PET/MRI in detection of bone metastases in breast cancer patients.

The pooled sensitivity of [18F]FDG PET/CT in patient-based analysis, lesion-based analysis and head-to-head comparison were 0.73,0.89 and 0.87, while the pooled sensitivity of [18F]FDG PET/MRI were 0.99,0.99 and 0.99. In comparison to [18F]FDG PET/CT, it was suggested that [18F]FDG PET/MRI appeared to have a higher sensitivity (all *P* 0.05). In contrast, the pooled specificity of [18F]FDG PET/CT in patient-based analysis, lesion-based analysis and head-to-head comparison were 1.00,0.99 and 1.00, while the pooled specificity of [18F]FDG PET/MRI were 1.00,0.99 and 0.98. These findings indicated that [18F]FDG PET/CT and [18F]FDG PET/MRI have comparable levels of specificity.

Our results are in line with previous researches that have also suggested that [18F]FDG PET/MRI may have a higher sensitivity for detecting bone metastases compared to [18F]FDG PET/CT.[28] In

2023, Zhang *et al*.[28] conducted a meta-analysis to compare the diagnostic accuracy of [18F]FDG PET/CT and PET/MRI for detecting distant metastases in patients with various types of cancer. In the subgroup analysis including 3 studies of breast cancer (182 patients), they found that [18F]FDG PET/MRI demonstrated higher sensitivity (0.95 versus 0.87) and specificity (0.96 versus 0.94) compared to PET/CT. Our meta-analysis included a larger number of studies (16 studies) and patients than Zhang's study, which allowed us to perform a more comprehensive and robust analysis of the diagnostic efficacy of the two imaging modalities. Despite the difference, our study also provide evidence that PET/MRI has higher sensitivity and similar specificity compared to PET/CT in detecting bone metastases of breast cancer by adding more studies.

In 2019, Evangelista *et al*.[6] conducted a head-to-head comparison study of [18F]FDG PET/CT and [18F]FDG PET/MRI for the evaluation of breast cancer. The authors included two head-to-head comparison studies that specifically focused on the detection of bone metastases in breast cancer. They reported that PET/MRI was able to detect more primary and skeletal/non-skeletal distant metastases compared to PET/CT. Our study and the study by Evangelista *et al*. are consistent in demonstrating the potential advantages of PET/MRI over PET/CT for the evaluation of bone metastasis in breast cancer. The superior sensitivity of [18F]FDG PET/MRI may be attributed to its capacity to provide both anatomical and functional information, which may be useful in cases where there is soft tissue involvement or bone marrow invasion.[29]

While the current meta-analysis found that [18F]FDG PET/MRI had a higher sensitivity than [18F]FDG PET/CT, it is important to note that [18F]FDG PET/MRI may not be available in all medical centers. The availability of [18F]FDG PET/MRI may also be affected by the medical center's location and resources. PET/CT provides high-resolution anatomical images and functional information from the PET component. In addition, it also has lower economic cost requirements compared to PET/MRI, making it a widely used imaging technique in clinical practice.[30,31] PET/CT, on the other hand, has some limitations. One of the main limitations is the exposure to ionizing radiation, especially for younger patients or those who need repeated imaging exams.[10]

Overall, [18F]FDG PET/CT and [18F]FDG PET/MRI are both useful imaging modalities for detecting bone metastases in breast cancer patients, each having their own set of benefits and limitations. The choice of which imaging modality to use will depend on various factors such as the clinical situation, the accessibility of the imaging technique, and the preferences of the physicians.

In addition, another valuable diagnostic modality, Whole-body MRI (WB-MRI), also has demonstrated it capabilities. WB-MRI provides a comprehensive evaluation of the entire body with high sensitivity and excellent soft tissue contrast.[32] On the other hand, PET/MRI combines functional and anatomical information, leading to improved specificity and simultaneous examination.[33] To make a more accurate conclusion regarding the optimal tool for detecting bone metastasis, further head-to-head studies directly comparing WB-MRI and PET/MRI are needed.

Some limitations of the current meta-analysis should be considered when interpreting the results. Firstly, the heterogeneity of the included studies may have affected the overall sensitivities or specificities of [18F]FDG PET/CT and [18F]FDG PET/MRI, which may cause by different patient populations or imaging protocols. We therefore try to find out the source of heterogeneity by performing sensitivity analysis. Secondly, the studies included in the meta-analysis were mostly retrospective (9 of 16), which may have introduced bias. Third, pathology was not available for all lesions and patients, imaging follow-up was also used as the reference standard in cases where pathological examination was unavailable. Therefore, well-designed prospective studies with standardized imaging protocols and comprehensive pathological data are needed to confirm the findings of this meta-analysis.

Conclusions

Based on the pooled results, our meta-analysis suggests that [18F]FDG PET/MRI has a higher sensitivity and similar specificity compared to [18F]FDG PET/CT in detection of bone metastases in breast cancer patients. Clinicians should consider the advantages and limitations of each imaging technique when making decisions about which method to use. Further studies with standardized imaging protocols and comprehensive pathological data are needed to confirm these findings and to explore the clinical utility of these imaging techniques.

Acknowledgements

Author Contributions: XL and CJ conceived and designed the study. XL, QS, HD, LJ, HH, and LY extracted and analyzed the data, while XL, QS, HD and LJ wrote the first version of the manuscript. All authors contributed to the manuscript and approved the final version for submission.

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research article

Central and peripheral pulmonary sclerosing pneumocytomas: multi-phase CT study and comparison with Ki-67

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Background. This study aimed to evaluate the multi-phase CT findings of central and peripheral pulmonary sclerosing pneumocytomas (PSPs) and compared them with Ki-67 to reveal their neoplastic nature.

Patients and methods. Multi-phase CT and clinical data of 33 PSPs (15 central PSPs and 18 peripheral PSPs) were retrospectively analyzed and compared their multi-phase CT features and Ki-67 levels.

Results. For quantitative indicators, central PSPs were larger than peripheral PSPs (10.39 ± 3.25 cm^3 *vs.* 4.65 ± 2.61 cm^3, P = 0.013), and tumor size was negatively correlated with acceleration index (r = -0.845, P < 0.001). The peak enhancement of central PSPs appeared in the delayed phase, with a longer time to peak enhancement (TTP, 100.81 ± 19.01 s), lower acceleration index (0.63 ± 0.17), progressive enhancement, and higher Ki-67 level. The peak enhancement of peripheral PSPs appeared in the venous phase, with the shorter TTP (62.67 ± 20.96 s, P < 0.001), higher acceleration index (0.99 ± 0.25, P < 0.001), enhancement washout, and lower Ki-67 level. For qualitative indicators, the overlying vessel sign (86.67% *vs.* 44.44%, P = 0.027), prominent pulmonary artery sign (73.33% *vs.* 27.78%, P = 0.015), and obstructive inflammation/atelectasis (26.67% *vs.* 0%, P = 0.033) were more common in central PSPs, while peripheral PSPs were more common with halo sign (38.89% *vs.* 6.67%, P = 0.046).

Conclusions. The location of PSP is a possible contributing factor to its diverse imaging-pathological findings. The tumor size, multi-phase enhancement, qualitative signs, and Ki-67 were different between central and peripheral PSPs. Combined tumor size, multi-phase findings, and Ki-67 level are helpful to reveal the nature of the borderline tumor.

Key words: pulmonary sclerosing pneumocytoma; location; multi-phase computed tomography; Ki-67

Introduction

Pulmonary sclerosing pneumocytoma (PSP), formerly known as pulmonary sclerosing hemangioma, is a rare pulmonary lesion, which was first described by Liebow and Hubbell in 1956.[1] PSP is most common in middle-aged women in East Asia, accounting for 3–5% of benign lung tumors.[2] Most patients are asymptomatic and clinically incidental. Some studies suggested that the symptoms and surgical methods of PSP were related to tumor location and its mass effect. Larger lesions near the hilum may be more likely to cause respiratory symptoms.[3] Lobectomy is often performed for central lesions, while enucleation or wedge resection is more common for peripheral lesions, without systematic lymph node dissection and subsequent radiochemotherapy.[4] However, the influence of

tumor location on PSP imaging has not been specifically evaluated. Moreover, the neoplastic nature of PSP is still controversial.[5] Although PSP is considered a benign tumor with a good prognosis, it originates from the primitive respiratory epithelium with possible metastasis and recurrence.[6,7] The intraoperative frozen biopsy of PSP is easily confused with adenocarcinoma or carcinoid, and the lower Ki-67 level has a certain discriminative effect.[8,9] As a marker of cellular proliferation and malignant potential, Ki-67 is almost not expressed in normal tissues but is significantly elevated in various malignant tumors, especially lung cancer.[9] Its expression gradually increases with the tumoral occurrence, growth, and metastasis.[10] For example, the Ki-67 index of non-small cell lung cancer is often more than 60%, indicating high malignancy, rapid progression, and poor prognosis.[11] While the Ki-67 level of adenocarcinoma is lower than other types of lung cancer, which may be related to its lower proliferation.[10] On medical imaging, PSP has the morphological characteristics of benign lesions, but with stronger enhancement on CT and higher fluorodeoxyglucose accumulation on PET/CT.[12-14] Compared with benign pulmonary tumors (hamartomas), the enhancement of PSP is more obvious, with less calcification and fat component.[12,13] Compared with malignant pulmonary tumors (adenocarcinomas or carcinoid tumors), the enhancement duration of PSP is longer, with rare lobulation and pleural invasion.[12,13] All these findings obscure its neoplastic nature. Dual-phase arteriovenous enhancement may miss some diagnostic information. While multi-phase CT can more fully show the evolution of PSP enhancement, and achieve a similar effect to dynamic enhancement with less radiation exposure. To enrich the diagnostic information of PSP, the multi-phase CT findings of central and peripheral PSPs were analyzed retrospectively, and compared with the Ki-67 to provide new insights into their neoplastic nature.

Patients and methods

Patients

This retrospective study was designed and conducted in accordance with the Declaration of Helsinki and was approved by the ethics and review board of Affiliated Yantai Yuhuangding Hospital of Qingdao University. Written informed consent was obtained from all the study participants. Thirty-three patients with PSP confirmed by pathology from 2016 to 2022 were collected, and their clinical and imaging data were retrospectively analyzed. The pathological diagnosis was determined by cell morphology and immunohistochemistry. Inclusion criteria: complete clinical data, definite pathological diagnosis, and consistent imaging protocols. Exclusion criteria: transthoracic needle aspiration biopsy before multi-phase CT examination (avoiding the influence of intratumoral hemorrhage on CT enhancement), concomitant with other pulmonary tumors, and lesions too small to measure the CT density accurately.

Imaging examinations

GE Optima CT660 (GE Healthcare, Milwaukee, USA) was used in all patients for multi-phase scanning (tube voltage = 120 kV, tube current = 10–300 mA, collimation width = 0.625 mm×128, spiral pitch = 1:1, slice thickness = 5 mm, slice interval = 5 mm), including unenhanced, arterial, venous and delayed phases. According to the different weight and cardiovascular status, the contrast medium was administrated at 3.0–3.5 mL/s and 1.5–2.0 mL/kg. After intravenous injection of a non-ionic contrast agent (Iohexol Injection, 300 mg I/mL), the arterial phase scanning was delayed for 20–25 s, the venous phase scanning was delayed for 45–65 s, and the delayed phase scanning was delayed for 95–120 s.

Imaging analysis

Imaging evaluation was performed on the Medcare AnyImage workstation (V4.5). Reconstruction was performed with a thickness of 1 mm to reduce partial volume artifact, and multiple image post-processing techniques were performed to determine the tumor locations. The tumor size was measured on lung-window images (window width, 1000 − 2000 Hu; window level, -800 − -450 Hu), and the tumor density was measured on mediastinal-window images (window width, 250 − 500 Hu; window level, 30 − 50 Hu). Based on the location of the lesion, the patients in this study were divided into central PSPs (15 cases, lesions were near the hilum and adjoined the primary or secondary bronchus) and peripheral PSPs (18 cases, lesions were near the chest wall and located distal to segmental bronchus). Imaging observation included quantitative and qualitative indicators. Quantitative indicators: tumor size (mm^3), multi-phase (unenhanced, arterial, venous, and delayed phases) CT densities (Hounsfield unit, Hu), peak enhance-

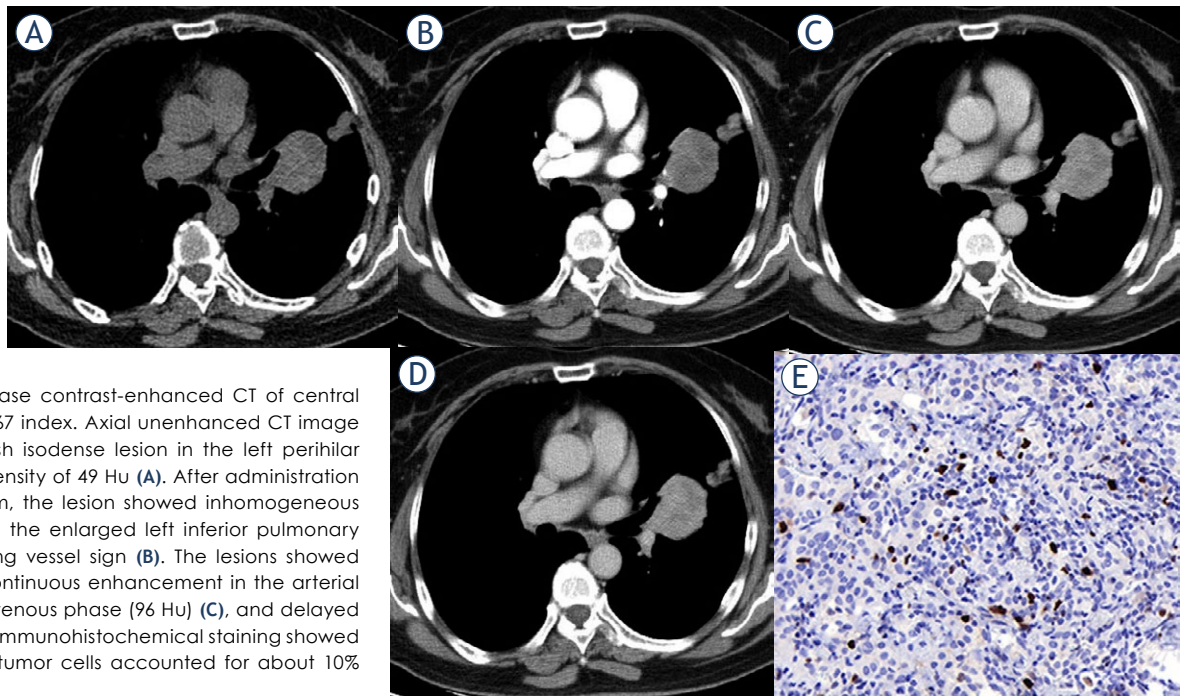

FIGURE 1. Multi-phase contrast-enhanced CT of central PSP with higher Ki-67 index. Axial unenhanced CT image revealed a roundish isodense lesion in the left perihilar region with a CT density of 49 Hu **(A)**. After administration of contrast medium, the lesion showed inhomogeneous enhancement with the enlarged left inferior pulmonary artery and overlying vessel sign **(B)**. The lesions showed progressive and continuous enhancement in the arterial phase (75 Hu) **(B)**, venous phase (96 Hu) **(C)**, and delayed phase (110 Hu) **(D)**. Immunohistochemical staining showed the Ki-67 reactive tumor cells accounted for about 10% (× 400) **(E)**.

ment value (a maximum density in the enhancement duration, Hu), net enhancement value (peak enhancement − unenhanced density, Hu), time to peak enhancement (TTP, second), enhancement washout value (peak enhancement − delayed phase density, Hu) and acceleration index (net enhancement / TTP). When measuring the CT density of each phase, the region of interest (ROI) should be set at the same slice, covering the central part of the tumor as much as possible, avoiding possible cystic change and hemorrhage, and then the average CT density of three different slices should be taken. Qualitative indicators: tumor morphology, obstructive inflammation/atelectasis, overlying vessel sign, prominent pulmonary artery sign, and halo sign. The overlying vessel sign referred to the compressed vessel around the lesion. A prominent pulmonary artery sign was defined as the obvious enlargement of the pulmonary artery adjacent to the lesion, compared with the contralateral similar pulmonary artery. The ground-glass opacity around the lesion was considered as the halo sign. All imaging data were evaluated by two chest radiologists with ten years of diagnosis experience and without knowledge of pathological findings. In case of any disagreement, it shall be settled through consultation.

Statistical analysis

In this study, descriptive statistics were processed by IBM SPSS version 22.0 (SPSS, Chicago, IL, USA). All data were presented as numbers (percentage) or mean ± SD. An independent t-test (two-tailed) or Mann-Whitney U-test was used to assess the difference between continuous variables. The Chi-square test or Fisher's exact test (two-tailed) was used for the statistical comparison of dichotomous variables. Pearson correlation was analyzed between the tumor size and acceleration index. A p-value of < 0.05 was defined as statistically significant. The inter-observer variability was examined by the interclass correlation coefficient (ICC) or Kappa value. ICC > 0.75 or Kappa ≥ 0.8 was considered a better agreement.

Results

Clinical findings

All 33 patients were female, with an average age of 54.1 ± 8.2 years. Most of them were found incidentally in healthy examinations (23 cases, 69.7%), and accompanied by non-specific respiratory symptoms (cough, expectoration, chest discomfort,

TABLE 1. Imaging and clinical comparisons between central and peripheral pulmonary sclerosing pneumocytomas (PSPs)

	Central PSPs (n = 15)	Peripheral PSPs (n = 18)	P
Age (years)	56.6 ± 8.5	51.6 ± 7.7	0.244
Size (cm^3)	10.39 ± 3.25	4.65 ± 2.61	0.013*
Respiratory symptoms n, present:absent	11:4	4:14	0.037*
Unenhanced CT density (Hu)	37.57 ± 15.61	43.64 ± 13.09	0.312
Arterial phase CT density (Hu)	67.09 ± 16.99	69.79 ± 18.67	0.767
Venous phase CT density (Hu)	91.36 ± 20.43	97.14 ± 21.38	0.373
Delayed phase CT density (Hu)	98.73 ± 26.53	74.71 ± 24.97	0.044*
Net enhancement value (Hu)	61.47 ± 12.18	57.11 ± 10.28	0.205
Peak enhancement value (Hu)	98.73 ± 26.53	97.14 ± 21.38	0.828
Enhancement washout value (Hu)	3.8 ± 8.14	20.78 ± 10.22	< 0.001*
TTP (s)	100.81 ± 19.01	62.67 ± 20.96	< 0.001*
Accelerated index	0.63 ± 0.17	0.99 ± 0.25	< 0.001*
Ki-67 index n, low:high#	9:6	17:1	0.030*
Overlying vessel sign n, present:absent	13:2	8:10	0.027*
Prominent pulmonary artery sign n, present:absent	11:4	5:13	0.015*
Obstructive inflammation/atelectasis n, present:absent	4:11	0:18	0.033*
Halo sign n, present:absent	1:14	7:11	0.046*
Peak phase n, venous phase:delayed phase	3:12	15:3	< 0.001*

Accelerated index = net enhancement/TTP; Hu = Hounsfield unit; PSP = pulmonary sclerosing pneumocytoma; TTP = time to peak enhancement;

Values are given as n (= number) or mean ± SD *Significance values; #Low = Ki-67 index ≤ 3%; High = Ki-67 index > 3%

fever, etc.). Compared with peripheral PSP, these non-specific respiratory symptoms were more common in central PSP (73.33% *vs.* 33.33%, P = 0.037). Both groups of PSP patients underwent surgical treatment, with a similar age of onset (56.6 ± 8.5 years *vs.* 51.6 ± 7.7 years, P = 0.244). Patients with central PSP were treated with lobectomy, while those with peripheral PSP underwent enucleation or wedge resection. No lymph node metastasis or surrounding structural invasion was found during the operation. Histopathologically, polygonal cells and surface cubic cells constituted hemangiomatous, papillary, sclerotic, and solid regions in different proportions. Immunohistochemically, thyroid transcription factor-1 (TTF-1, +), synapsin (Syn, -), epithelial membrane antigen, (EMA, +), and carcinoembryonic antigen (CEA, -) were shown in both tumor cell types. The Ki-67 index of all PSPs did not exceed 10%, most of them (26 cases, 78.79%) were no more than 3% and the others (7 cases, 21.21%) were 3–10%. The lower Ki-67 level (Ki-67 index ≤ 3%) was more common in peripheral PSP than in central PSP (94.44% *vs.* 60%, P = 0.030). None of the patients received any postoperative radiochemotherapy, and no recurrence or progression has been observed in the follow-up (1–7 years). See Table 1, and Figures 1–2 for details.

Imaging findings

For these quantitative and qualitative CT analyses, good inter-observer agreements were obtained between the two observers (ICC = 0.8871, Kappa = 0.8692).

A total of 33 solitary lesions were found in this study. The size of 33 PSP lesions was negatively correlated with the acceleration index (r = -0.845, P < 0.001). The central lesions were larger than the peripheral lesions (10.39 ± 3.25 cm^3 *vs.* 4.65 ± 2.61 cm^3, P = 0.013). There was no difference in CT den-

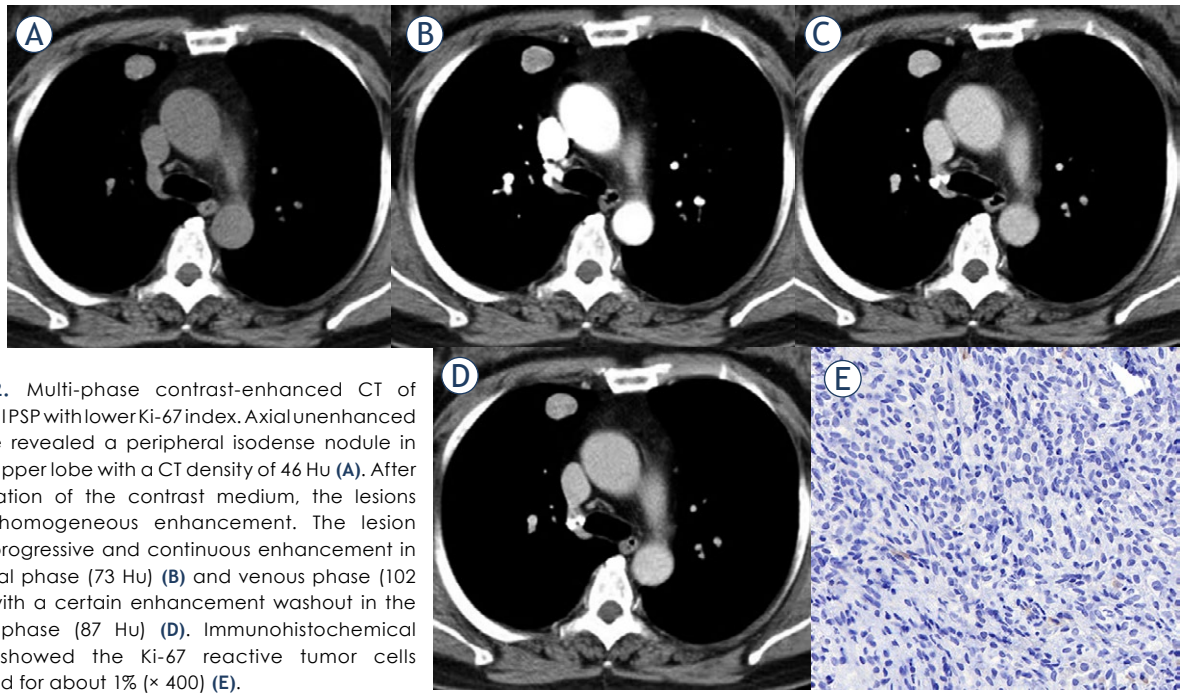

FIGURE 2. Multi-phase contrast-enhanced CT of peripheral PSP with lower Ki-67 index. Axial unenhanced CT image revealed a peripheral isodense nodule in the right upper lobe with a CT density of 46 Hu **(A)**. After administration of the contrast medium, the lesions showed homogeneous enhancement. The lesion showed progressive and continuous enhancement in the arterial phase (73 Hu) **(B)** and venous phase (102 Hu) **(C)**, with a certain enhancement washout in the delayed phase (87 Hu) **(D)**. Immunohistochemical staining showed the Ki-67 reactive tumor cells accounted for about 1% (× 400) **(E)**.

sities of unenhanced, arterial, and venous phases between the two groups, but the delayed enhancement of central PSPs was more obvious than that of peripheral PSPs (98.73 ± 26.53 Hu *vs.* 74.71 ± 24.97 Hu, P = 0.044). There was no difference in peak enhancement and net enhancement values. The peak enhancement of central PSPs appeared in the delayed phase (12/15, 80%), with a longer time to peak enhancement (TTP, 100.81 ± 19.01 s), lower acceleration index (0.63 ± 0.17), and progressive enhancement. The peak enhancement of peripheral PSPs appeared in the venous phase (15/18, 83.33%, P < 0.001), with the shorter TTP (62.67 ± 20.96 s, P < 0.001), higher acceleration index (0.99 ± 0.25, P < 0.001) and delayed enhancement washout (20.78 ± 10.22 Hu *vs.* 3.8 ± 8.14 Hu, P < 0.001).

Both types of PSP lesions were roundish with smooth edges. Compared with peripheral PSPs, obstructive inflammation/atelectasis (26.67% *vs.* 0, P = 0.033), overlying vessel sign (86.67% *vs.* 44.44%, P = 0.027), and prominent pulmonary artery sign (73.33% *vs.* 27.78%, P = 0.015) were more common in central PSPs. While peripheral PSPs were more common with a halo sign than central PSPs (38.89% *vs.* 6.67%, P = 0.046). See Table 1, and Figures 1–2 for details.

Discussion

PSP was initially considered a variant of hemangioma, with an obvious tendency of angiogenesis and sclerosis.[15] In 2015, the World Health Organization (WHO) changed its classification from "miscellaneous tumors" to "adenomas".[16] Due to the nonspecific clinical symptoms, most patients with PSP in this study were found by healthy examination, and its female susceptibility might be associated with estrogen and progesterone.[17] The larger central PSP is adjacent to the hilum, making it more likely to compress the proximal bronchi, resulting in more respiratory symptoms and obstructive inflammation/atelectasis. The mutual migration and coexistence of four histological regions make it difficult to confirm the predominant component of PSP with limited pathological sampling.[18] The ki-67 index is no more than 3% in normal cells and more than 10% in malignant tumors.[9,19] However, the Ki-67 index was 3–10% in 7 cases (21.21%) of PSP in this study. The diverse Ki-67 expression, TTF-1 (+), and EMA (+) suggested that PSP originated from the primitive alveolar epithelium and with a certain growth potential.

Because central PSPs were adjacent to the pulmonary hilar vessels, it was easier to get sufficient blood supply and tumor growth.[20] Therefore, in this study, the central PSPs were larger than the peripheral PSPs. The size of PSP was also thought to be related to Ki-67, representing tumoral proliferation. The larger PSP contains more pure malignant components with a higher KI-67 level.[21] Although the central PSPs were larger than the peripheral PSPs and with the higher Ki-67 level, there was no difference in peak enhancement and net enhancement between them. The mixture of pathological components might offset the enhancement differences.[22,23] In addition, the size of PSPs was negatively correlated with the acceleration index. With a similar net enhancement, the shorter TTP of smaller peripheral PSPs resulted in a higher perfusion efficiency and accelerated index, which were more common in malignant lesions.[22,24]

The central and peripheral PSPs had similar isodensity on unenhanced CT, which provided the comparability for subsequent contrast enhancement. The central and peripheral lesions showed continuous enhancement at the arterial and venous phases, which was consistent with the characteristic enhancement of PSP.[25] However, these PSPs showed different enhancements during the delay phase. This highlights the superiority of multi-phase CT scanning. The histological evolution of PSP might not always follow the hemangiomatous-papillary-solid-sclerotic sequence.[26,27] With the growth of PSP, its enhancement characteristics changed according to the tumor size and its pathological components.[27,28] The smaller peripheral PSPs mainly contained papillary and hemangiomatous components and were enhanced significantly in arterial and venous phases, with a peak enhancement in the venous phase.[29,30] While the enhancement washout in the delayed phase was a possible malignant sign.[22,24] The larger central PSPs contain more complex tumoral components (mainly sclerotic and solid components), resulting in continuous enhancement during the delayed phase.[29,30] This showed a progressive enhancement of benign tumors.

A comprehensive analysis of tumor size, multiphase enhancement, and Ki-67 of central and peripheral PSPs is helpful to understand their tumor nature. The Ki-67 level of larger central PSP was higher, but it showed progressive enhancement, longer TTP, and lower accelerated index (benign imaging feature). While the Ki-67 level of smaller peripheral PSP was lower, with the enhancement washout, shorter TTP, and higher accelerated index (malignant imaging feature). The inconsistency between Ki-67 and enhancement mode further revealed the nature of borderline tumors with some malignant potential. Besides, the different enhancements of central and peripheral PSPs might also be associated with the CT phase setting. Multi-phase CT (arterial, venous, and delayed phases) could extensively cover the microperfusion of PSP, which was conducive to displaying the various tumor components and avoiding the omission of diagnostic information to the greatest extent.

Overlying vessel sign is caused by the compressed blood vessels around the PSP lesions, reflecting the growing tendency of neighbor vessels to the tumors.[31] Previous studies showed that overlying vessel sign was more common in peripheral lesions.[30,31] However, similar to prominent pulmonary artery signs, the overlying vessel sign was more common in central PSPs in this study. This may be due to the larger central PSPs being closer to the pulmonary hilar vascular branches.[25,29] Compared to intratumoral microvessels, the larger extratumoral vessels are unlikely to affect the enhancement degree of PSP.[24] Therefore, there was no difference in the degree of enhancement between the central and peripheral PSPs. Peripheral PSPs were more likely to compress small airways, causing distal bronchial obstruction or local pulmonary congestion, and then the halo sign was common.[32]

Due to the limitation of sampling and irregular histological distribution, it is difficult to match the multi-phase enhancement and pathological components precisely.[14] We employ intelligent radiation dose tracking technology to minimize additional radiation exposure from multi-phase CT scans. A single-center retrospective study is difficult to avoid selection bias. The small sample size due to low incidence limited the statistical reliability. Further multi-center study with larger samples is necessary. Indeed, a single tumor marker cannot fully reflect the neoplastic essence. In clinical applications, it is important to combine Ki-67 with multi-phase CT for the evaluation of other tumors.

Conclusions

The locations of PSP may lead to differences in lesion size, multi-phase enhancement, qualitative CT signs, and Ki-67, which deepens our understanding of PSP. The central PSP is larger and has a higher Ki-67 level but with progressive enhance-

ment, longer TTP, and a lower acceleration index. The peripheral PSP is smaller and has a lower Ki-67 level but with a shorter TTP, higher acceleration index, and enhancement washout. Combining these multi-phase CT features with the Ki-67 level can clarify the borderline nature of PSP. Furthermore, when Ki-67 is further elevated, the possibility of other pulmonary malignancies should be considered.

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research article

The effects of normobaric and hyperbaric oxygenation on MRI signal intensities in T_1-weighted, T_2-weighted and FLAIR images in human brain

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Background. Dissolved oxygen has known paramagnetic effects in magnetic resonance imaging (MRI). The aim of this study was to compare the effects of normobaric oxygenation (NBO) and hyperbaric oxygenation (HBO) on human brain MRI signal intensities.

Patients and methods. Baseline brain MRI was performed in 17 healthy subjects (mean age 27.8 ± 3.2). MRI was repeated after exposure to the NBO and HBO at different time points (0 min, 25 min, 50 min). Signal intensities in T_1-weighted, T_2-weighted images and fluid attenuated inversion recovery (FLAIR) signal intensities of several intracranial structures were compared between NBO and HBO.

Results. Increased T_1-weighted signal intensities were observed in white and deep grey brain matter, cerebrospinal fluid (CSF), venous blood and vitreous body after exposure to NBO as well as to HBO compared to baseline (Dunnett's test, $p < 0.05$) without significant differences between both protocols. There was also no significant difference in T_2-weighted signal intensities between NBO and HBO. FLAIR signal intensities were increased only in the vitreous body after NBO and HBO and FLAIR signal of caudate nucleus was decreased after NBO (Dunnett's test, $p < 0.05$). The statistically significant differences in FLAIR signal intensities were found between NBO and HBO (paired t-test, $p < 0.05$) in most observed brain structures (paired t-test, $p < 0.05$).

Conclusions. Our results show that NBO and HBO alters signal intensities T_1-weighted and FLAIR images of human brain. The differences between NBO and HBO are most pronounced in FLAIR imaging.

Key words: hyperbaric oxygen; normobaric oxygen; magnetic resonance; human brain

Introduction

Magnetic resonance imaging (MRI) of brain is a superior soft-tissue contrast method that is used for the assessment of a numerous neurological conditions such as multiple sclerosis and headaches, and used to characterize strokes and space-occupying lesions. Basic MRI brain screen protocol is a simple non-contrast MRI comprising a group of basic MRI sequences when imaging the brain in cases of no particular condition is being sought (e.g. headache). The protocol is designed to obtain a good general overview of the brain. A standard screening protocol might include T_1 weighted imaging for anatomical overview, T_2 weighted imaging to evaluate basal cisterns, ventricular system and

subdural spaces, and good visualization of flow voids in vessels, fluid attenuated inversion recovery imaging (FLAIR) to assess white-matter, diffusion weighted imaging (DWI) for multiple possible purposes (from the identification of ischemic stroke to the assessment of active demyelination).

Dissolved oxygen can be used as a contrast agent in MRI due to the paramagnetic properties of the dioxygen molecule O_2[1]. Since O_2 as well as hydroxyl and superoxide radicals contain unpaired electrons, they exhibit paramagnetic effect and may shorten the spin-lattice relaxation time (T_1) in magnetic resonance imaging (MRI).[2-6] T_1 relaxation times shortening under the influence of increased partial pressure of oxygen (pO_2) in the inspired gas mixture is called tissue-oxygen-level-dependent effect (TOLD). It was observed in many tissues: arterial blood, myocardium, spleen, skeletal muscles, renal cortex, liver and fat.[4,7-9] TOLD effect was also detected in brain parenchyma (grey and white matter) and cerebrospinal fluid (CSF).[10-16] In addition, pO_2 increase also affects spin-spin relaxation time (T_2)[13,17]; however, results of available studies on the effect of pO_2 on T_2 relaxation times are controversial.[7,12] FLAIR images of healthy volunteers also showed increased CSF signal intensity during 100% oxygen breathing.[18]

Concentration of dissolved oxygen is directly proportional to its partial pressure, pO_2.[19] High pO_2 values in arterial blood as well as in brain parenchyma can be achieved with normobaric 100% oxygenation (NBO) compared to breathing normobaric air (NBA). Hyperbaric 100% oxygenation (HBO) causes a more pronounced increase of arterial and brain pO_2 compared to NBO as well as augments production of reactive oxygen species (ROS).[20-22] In few animal studies, it has been already observed that HBO had a more pronounced effect on T_1 and T_2 relaxation times compared to breathing NBO or NBA.[11,23]

To our knowledge, no human studies were performed studying the effect of HBO on MRI signal intensities. The aim of this study was to compare the effects of HBO and NBO on MRI signal intensities (e.g. T_1, T_2 and FLAIR).

Patients and methods

The study was approved by The National Ethics Committee (No. 0120-203/2019/4). Research was conducted at the Institute of Physiology (University of Ljubljana, Faculty of Medicine). Informed consent was obtained from each subject. 17 healthy volunteers (12 males and 5 females), age 20–40 years (mean age 27.8 ± 3.2), were enrolled in the study. Exclusion criteria were: history of a neurological disorder, non-MRI-compatible devices, a lung disease with FEV1/FVC < 60% and/or emphysema and/or pneumothorax, history of middle ear trauma or disease, therapy with platinum complexes, doxorubicin, bleomycin, disulfiram of mafenide acetate, pregnancy or claustrophobia.

Study protocol

MRI examination was performed before oxygen breathing protocol (baseline state), after HBO and after NBO with subsequent MRI on separate visits. NBO protocol was performed using a non-rebreather oxygen mask connected to a large reservoir supplied by 100% oxygen for 70 minutes. HBO protocol was performed in multiplace hyperbaric chamber (Kovinarska P&P, Slovenia) at 2.4 ATA with breathing of 100% oxygen for 70 minutes as shown in Figure 1. After each oxygen breathing protocol (NBO or HBO), MRI examination was repeated three times, i.e. immediately after the end of HBO or NBO, after 25 min and after 50 min.

MR image acquisition

The MRI imaging was performed on a 3T MRI system (TX Achieva Philips Netherlands) with the use of a 32-channel head coil. The MR examination consisted of:

- T_1 spin echo (SE) imaging in the transversal plane with imaging parameters: repetition time (TR) 1026 ms, echo time (TE) 10 ms, filed of view (FOV) 230 × 183 mm, matrix 256 × 163, voxel 0.9 × 1.12 mm, slice thickness 4 mm, gap 1 mm, number of slices 29, number of signals averaged (NSA) 2 with approximate duration of 5 min 38 s
- T_2 turbo spin echo (TSE) imaging in the transversal plane with imaging parameters: TR 9179 ms, TE 100 ms, FOV 230 × 185 mm, matrix 384 × 229, voxel 0.6 × 0.75 mm, slice thickness 3 mm, gap 0 mm, number of slices 50, NSA 3, sensitivity (SENS) 1.7 with approximate duration of 4 min 55 s.
- FLAIR in transversal plane: TR 11000 ms, TE 125 ms, TI 2800 ms, FOV 230 x 183 mm, matrix 328 × 185, voxel 0.7 × 0.93 mm, slice thickness 3 mm, gap 1 mm, number of slices 36, NSA 2, SPIR technique, SENS 2 with approximate duration: 3 min 51 s.

The total MRI scanning time during one MR examination was 25 min.

MR data and statistical analysis

The MRI images were analysed using ImageJ free image analysis software (National Institutes of Health, USA). Mean signal values in distinct regions of interest (ROI) on T_1-weighted, T_2-weighted and FLAIR images were obtained: frontal white matter, thalamus, caudate nucleus, putamen, hippocampus, superior sagittal sinus, vitreous body and cerebrospinal fluid (CSF).

Statistical analysis was performed using SigmaPlot 14.0 (Systat Software, Inc., USA). The signal intensities after NBO or HBO were compared to the baseline values. Shapiro-Wilk test and Brown-Forsythe were used to check for normality and equal variance. One-way repeated measurements analysis of variance (RM ANOVA) was used to test for differences between signal intensities before, immediately, 25 min and 50 min after NBO or HBO. In cases when Shapiro-Wilk or Brown-Forsythe test failed, Friedman RM ANOVA on Ranks was performed. If RM ANOVA showed statistically significant differences between groups of data, Dunnett's method for multiple comparisons was used to compare signal intensities at three time

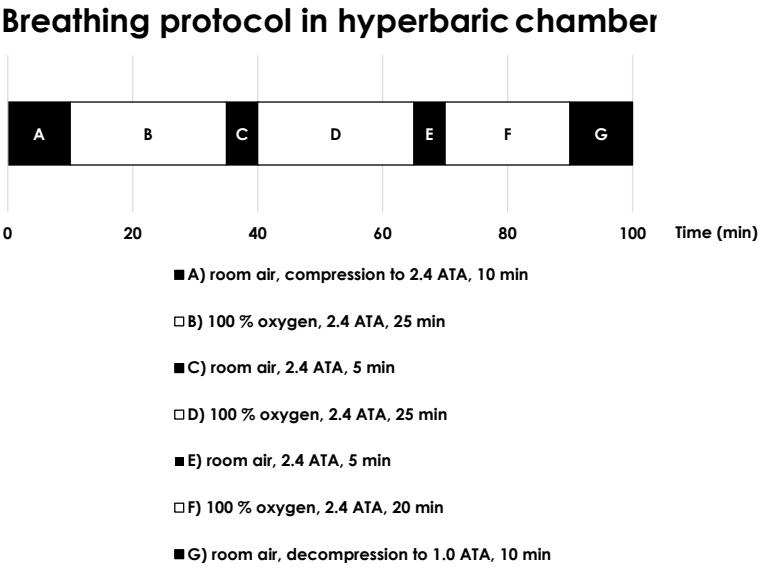

FIGURE 1. Hyperbaric oxygenation (HBO) protocol.

TABLE 1. Comparison of T_1-weighted signal intensities before, immediately, 25 min and 50 min after normobaric oxygenation (NBO) **(A)** and hyperbaric oxygenation (HBO) **(B)** (mean ± standard deviation)

A) NBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	770.1 ± 251.2	791.0 ± 238.4	837.3 ± 328.4	851.3 ± 337.7*	**0.044**
Thalamus	827.9 ± 275.6	846.7 ± 244.7	894.6 ± 338.4	914.7 ± 356.5*	**0.038**
Head of caudate nucleus	731.9 ± 238.3	753.8 ± 227.0	798.7 ± 318.8	820.9 ± 331.3*	**0.023**
Putamen	800.2 ± 257.0	814.2 ± 239.2	860.7 ± 333.8	878.1 ± 350.2	0.059
Hippocampus	701.6 ± 232.0	712.1 ± 211.3	751.8 ± 285.5	771.6 ± 303.8*	**0.038**
Superior sagittal sinus	818.0 ± 375.6	748.2 ± 252.1	778.3 ± 288.6	860.9 ± 304.8	**0.019**
Cerebrospinal fluid	356.6 ± 126.8	362.7 ± 108.5	396.6 ± 152.9*	397.7 ± 163.0*	**0.010**
Vitreous body	281.3 ± 89.6	288.0 ± 92.1	296.8 ± 115.0	302.5 ± 116.3	0.264
B) HBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	770.1 ± 251.2	834.7 ± 133.0	860.9 ± 158.9	886.6 ± 184.7*	**0.026**
Thalamus	827.9 ± 275.6	900.8 ± 147.1	933.3 ± 169.1	957.1 ± 193.9*	**0.004**
Head of caudate nucleus	731.9 ± 238.3	794.9 ± 124.4	819.9 ± 142.4	846.2 ± 173.7	**0.013**
Putamen	800.2 ± 257.0	867.1 ± 134.9	893.9 ± 154.6	922.5 ± 185.1*	**0.007**
Hippocampus	701.6 ± 232.0	764.8 ± 124.1	787.2 ± 142.1	807.5 ± 163.2	**0.044**
Superior sagittal sinus	818.0 ± 375.6	848.0 ± 227.8	911.9 ± 310.7	907.6 ± 335.0	0.127
Cerebrospinal fluid	356.6 ± 126.8	396.4 ± 60.2	400.7 ± 73.7	413.0 ± 98.9	0.256
Vitreous body	281.3 ± 89.6	361.2 ± 63.0*	335.9 ± 69.6	349.4 ± 82.8	**0.040**

*statistically significant difference compared to baseline value at $p < 0.05$; NBO = 100 % normobaric oxygen, HBO = 100 % hyperbaric oxygen

points after oxygen breathing protocol with baseline values. Additionally, RM ANOVA or Friedman RM ANOVA on Ranks was used to check for differences in signal values of each ROI in T_1-weighted, T_2-weighted and FLAIR images between baseline signal values and values after HBO/NBO at each time point (0 min, 25 min, 50 min). The signal intensity changes in T_1-weighted, T_2-weighted and FLAIR images compared to baseline in each ROI at each time point (0 min, 25 min, 50 min) after NBO and HBO were calculated. Paired t-test was used to compare the signal intensity changes at each time point between NBO and HBO. In cases when Shapiro-Wilk normality test failed, Wilcoxon signed rank test was performed. The α level was set at $p < 0.05$ for all statistical significances.

Results

The results of T_1-weighted signal intensities before, immediately, 25 min and 50 min after NBO or HBO are presented in Table 1. After NBO there was a statistically significant increase in T_1 -weighted signal intensity in all studied structures except for vitreous body and putamen (RM ANOVA, Dunnett's test, $p < 0.05$). In contrast, after HBO we observed a significant increase in T_1-weighted signal intensities except for the superior sagittal sinus and CSF (Dunnett's test, $p < 0,05$). T_1-weighted signal intensity was significantly higher immediately (0 min) as well as 25 min after the end of the HBO compared to T_1-weighted signal intensity immediately and 25 min after NBO in vitreous body (paired t-test, $p < 0.05$). In contrast, there was no difference in signal intensities in T_1-weighted images between HBO and NBO after 50 min.

The results of T_2-weighted signal intensities before, immediately, 25 min and 50 min after NBO or HBO are presented in Table 2. T_2-weighted signal intensities were increased only in frontal white matter and thalamus after NBO and in the superior sagittal sinus and vitreous body after HBO (Dunnett's test, $p < 0.05$). There was also no significant difference in T_2-weighted signal intensities between HBO and NBO.

TABLE 2. Comparison of T_2-weighted signal intensities before, immediately, 25 min and 50 min after normobaric oxygenation (NBO) **(A)** and hyperbaric oxygenation (HBO) **(B)** (mean ± standard deviation)

A) NBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	362.5 ± 33.1	367.8 ± 32.8	397.1 ± 80.4*	389.0 ± 51.3*	**0.007**
Thalamus	480.6 ± 49.6	485.1 ± 63.5	521.0 ± 114.8	508.0 ± 61.7	**0.022**
Head of caudate nucleus	621.8 ± 64.8	637.9 ± 54.0	673.6 ± 139.8	656.7 ± 91.4	0.631
Putamen	514.0 ± 57.0	527.7 ± 50.7	552.3 ± 103.4	542.2 ± 64.1	0.073
Hippocampus	694.9 ± 71.9	712.6 ± 83.5	756.9 ± 190.3	734.0 ± 98.2	0.281
Superior sagittal sinus	41.3 ± 6.8	42.7 ± 8.6	45.7 ± 12.5	45.0 ± 11.3	0.317
Cerebrospinal fluid	1996.8 ± 143.6	2059.7 ± 203.3	2171.2 ± 522.0	2107.9 ± 274.3	0.318
Vitreous body	1404.8 ± 114.8	1499.4 ± 159.1	1585.5 ± 396.5	1520.9 ± 224.1	0.080
B) HBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	362.5 ± 33.1	359.4 ± 26.7	367.0 ± 35.5	375.1 ± 44.7	0.223
Thalamus	480.6 ± 49.6	473.6 ± 34.4	479.3 ± 33.3	489.1 ± 59.1	0.365
Head of caudate nucleus	621.8 ± 64.8	617.8 ± 47.3	620.9 ± 50.0	639.5 ± 77.1	0.390
Putamen	514.0 ± 57.0	510.9 ± 37.1	514.6 ± 39.8	532.9 ± 65.4	0.256
Hippocampus	694.9 ± 71.9	695.9 ± 57.2	688.1 ± 38.4	713.4 ± 81.4	0.378
Superior sagittal sinus	41.3 ± 6.8	48.3 ± 14.0*	47.4 ± 11.8	48.0 ± 15.0	**0.047**
Cerebrospinal fluid	1996.8 ± 143.6	1972.3 ± 79.2	1984.8 ± 102.3	2027.9 ± 195.4	0.482
Vitreous body	1404.8 ± 114.8	1524.0 ± 114.7*	1529.5 ± 143.2*	1530.9 ± 189.8*	0.001

* statistically significant difference compared to baseline value at p < 0.05; NBO = 100 % normobaric oxygen; HBO = 100 % hyperbaric oxygen

The results of FLAIR signal intensities before, immediately, 25 min and 50 min after NBO or HBO are presented in Table 3. FLAIR signal intensities were increased only in the vitreous body after NBO and HBO, signal of caudate nucleus was decreased after NBO (Dunnett's test, $p < 0.05$).

The statistically significant differences in FLAIR signal intensities were found between NBO and HBO (paired t-test, $p < 0.05$) in caudate nucleus, thalamus, hippocampus and vitreous body at each time point (0 min, 25 min, 50 min). In addition, the differences were also observed between NBO in HBO in putamen and frontal white matter at 0 min and 25 min and in superior sagittal sinus at 25 min (paired t-test, $p < 0.05$).

Discussion

In the present study we observed increased signal intensity in T_1-weighted imaging in frontal white matter, thalamus, caudate nucleus and hippocampus after NBO as well as HBO, in superior sagittal sinus and CSF after NBO and in vitreous body and putamen after HBO. Additionally, signal intensity was increased in T_2-weighted imaging in frontal white matter and thalamus after NBO as well as in superior sagittal sinus and vitreous body after HBO. FLAIR signal intensities were increased only in the vitreous body after NBO and HBO. In contrast, FLAIR signal of caudate nucleus was decreased after NBO. Statistically significant differences between HBO and NBO were observed in FLAIR signal intensities of caudate nucleus, vitreous body, putamen, frontal white matter, hippocampus and thalamus and also in T_1-weighted signal intensity of vitreous body.

In our study, T_1-weighted signal intensity of brain structures increased progressively with time after NBO/HBO and was the highest 50 min after the end of both, HBO and NBO. This finding is in agreement with the paramagnetic effect of O_2. Increased level of dissolved paramagnetic molecular O_2 shortens T_1-relaxation times due to dipol-dipol interactions and increases signal intensity on T_1-weighted images.[4,7-16 23 24] Relaxation rate ($R_1 = 1/T_1$) increases proportionally with increasing pO_2 in inspired gas mixture, the increase being linear or logarithmic when in normobaric or hyperbaric conditions, respectively.[23,24] The various increase of T_1-weighted signal intensities in the observed tissues might be explained by increased microvascular pO_2 as well as by differences in tissue oxygenation.[7] The sustained increase in T_1-weighted signal intensity is further supported by a study of Rockswold *et al*. which showed significantly elevated brain tissue pO_2 30 min after the end of HBO and NBO.[25] In contrast to Rockswold *et al*., we failed to observe a peak in T_1-weighted signal intensity immediately after the end of oxygen therapy. A possible explanation is that the time delay between HBO/NBO and MRI was too long to detect the peak.

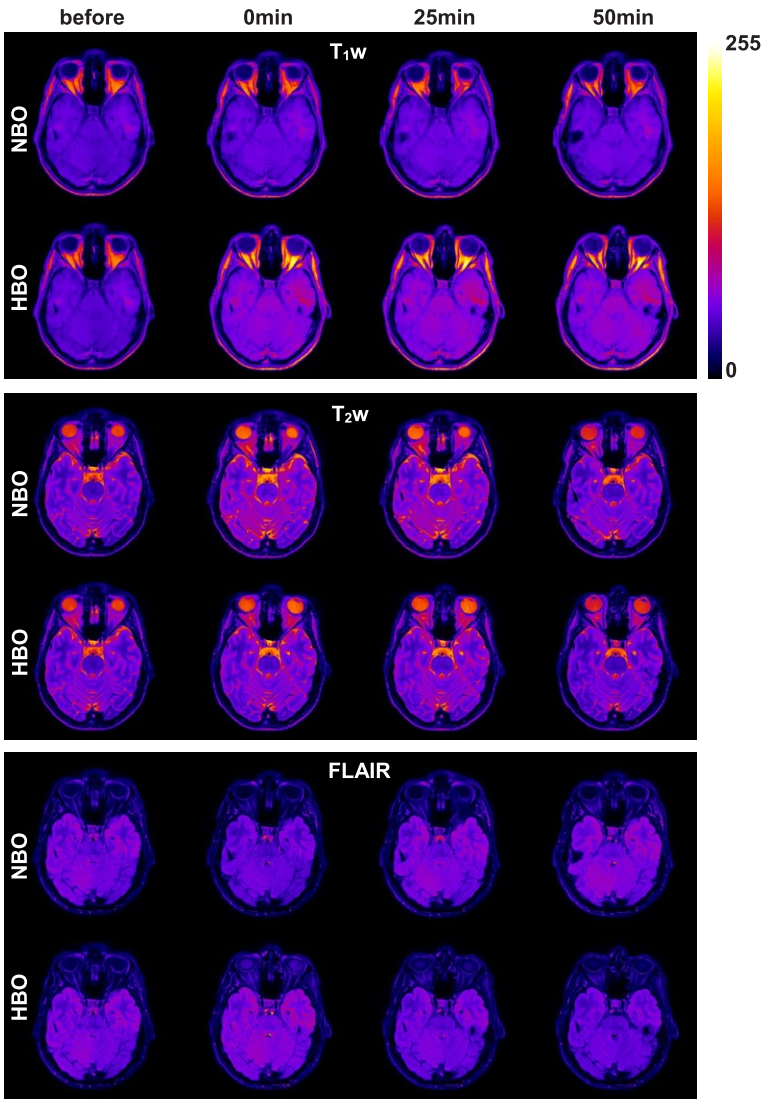

FIGURE 2. Representative MRI images in healthy subject at baseline, immediately after the end, after 25 min and after 50 min of NBO or HBO.

We observed progressive increase in T_1-weighted signal intensities after both NBO and HBO along with MRI imaging time, with the highest signal increase at the end of imaging protocol. This phenomenon could not be attributed solely to changes in pO_2, but also to the effect of ROS on

TABLE 3. Comparison of FLAIR signal intensities before, immediately, 25 min and 50 min after normobaric oxygenation (NBO) **(A)** and hyperbaric oxygenation (HBO) **(B)** (mean ± standard deviation)

A) NBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	731.7 ± 77.0	700.8 ± 89.8	713.7 ± 125.1	717.4 ± 128.7	0.615
Thalamus	897.1 ± 101.7	851.5 ± 96.7	868.6 ± 164.3	861.5 ± 153.6	0.399
Head of caudate nucleus	1119.2 ± 131.9	1083.0 ± 129.4	1070.0 ± 213.0	1030.0 ± 172.5*	**0.039**
Putamen	928.1 ± 116.5	875.8 ± 129.0	893.2 ± 184.3	893.0 ± 171.4	0.354
Hippocampus	1216.2 ± 135.7	1162.1 ± 144.8	1173.5 ± 223.0	1174.1 ± 239.1	0.490
Superior sagittal sinus	91.2 ± 23.6	84.6 ± 23.5	78.2 ± 27.2	86.0 ± 33.2	0.299
Cerebrospinal fluid	139.6 ± 33.3	140.5 ± 39.8	147.0 ± 51.8	157.8 ± 53.2	0.228
Vitreous body	127.2 ± 29.4	170.4 ± 49.1*	157.3 ± 45.0*	147.3 ± 45,9	**0.002**
B) HBO					
Structure	Baseline	0 min	25 min	50 min	p
Frontal white matter	731.7 ± 77.0	755.8 ± 113.1	794.7 ± 135.2	782.2 ± 115.3	0.508
Thalamus	897.1 ± 101.7	927.1 ± 104.6	691.3 ± 127.3	949.7 ± 110.5	0.973
Head of caudate nucleus	1119.2 ± 131.9	1180.6 ± 183.3	1208.0 ± 175.8	1190.8 ± 152.3	0.508
Putamen	928.1 ± 116.5	958.3 ± 143.4	993.0 ± 148.2	978.9 ± 133.4	0.567
Hippocampus	1216.2 ± 135.7	1269.4 ± 171.3	1294.4 ± 184.7	1286.7 ± 160.4	0.771
Superior sagittal sinus	91.2 ± 23.6	93.4 ± 25.8	105.1 ± 30.5	106.4 ± 37.0	0.193
Cerebrospinal fluid	139.6 ± 33.3	134.5 ± 27.0	139.4 ± 20.2	138.3 ± 21.8	0.909
Vitreous body	127.2 ± 29.4	691.4 ± 142.9*	523.6 ± 122.9*	378.1 ± 88.8	**< 0.001**

* statistically significant difference compared to baseline value at $p < 0.05$; NBO = 100 % normobaric oxygen; HBO = 100 % hyperbaric oxygen

T_1 and T_2-weighted images. Since ROS such as hydroxyl and superoxide radicals contain unpaired electrons, they also exhibit strong paramagnetic effect (a strong T_1 relaxation times shortening) and only a small, statistically insignificant reduction of T_2 relaxation times.[5,6] Additional point to consider is that distinct neurons respond to oxidative stress differently[26,27], which leads us to presumption that the effect of HBO-induced oxidative stress would lead to different levels of ROS and thus different effect on T_1 and T_2 weighted signal intensities in various brain regions.

The increase of T_1-weighted signal intensities was more pronounced in frontal white matter and thalamus after HBO compared to NBO. This could be explained by altered O_2 diffusion after HBO. We observed increased signal intensity in superior sagittal sinus and CSF only after NBO, but not after HBO. Longer time delay between HBO and MRI most likely lowered pO_2 in the aforementioned fluids before the beginning of MRI. We showed that T_1-weighted signal intensity of vitreous body was significantly increased immediately after the end of HBO exposure and then decreased in subsequent imaging blocks. This is in accordance with expected pO_2 dynamics in vitreous body, described by Shui *et al.*[28] Surprisingly, after the exposure to NBO, no increase in vitreous T_1-weighted signal intensity was observed. A possible explanation is that lower vitreous pO_2 (as achieved during NBO compared to HBO) dropped to baseline level before the beginning of the MRI.

In our study, there were statistical differences in T_2-weighted signal intensities between baseline and after NBO in frontal white matter and thalamus. This is in accordance with Wu *et al.* who observed significant differences in T_1 and T_2 between grey and white matter after inhalation of NBO.[12] According to Wu *et al.*, T_2 relaxation time increases in rat brain with hyperoxia. In contrast, Tadamura *et al.* did not observe this effect in human "non-brain" tissues (myocardium, spleen, liver, subcutaneous fat, skeletal muscle and bone marrow).[7] Therefore, it is possible that the effect of hyperoxia on T_2-weighted signal intensities appears to vary in different tissues. In the present study, a signifi-

cant increase in T_2-weighted signal intensities was also observed after HBO in superior sagittal sinus and vitreous body. Oxygen affects spin-spin relaxation time (T_2) by two competing mechanisms, i.e. T_2 shortening analogous to effect on T_1 (although the effect on T_2 is much smaller) and T_2 lengthening due to diffusion of water protons through field inhomogeneities induced by deoxyhemoglobin generated field gradients (blood-oxygen-level-dependent (BOLD) effect).[13,17] An increased T_2-weighted signal intensity after NBO and HBO in our study suggests that in human brain structures and vitreous body the paramagnetic effect of oxygen on T_2 relaxation times shortening prevails over BOLD effect.

Our results show statistically significant differences between HBO and NBO were observed in FLAIR signal intensities in different brain structures particularly those that are close to CSF spaces. These results are in accordance with previous studies which showed that in patients receiving 100% NBO elevated pO_2 leads to incomplete signal suppression of CSF in FLAIR imaging.[29,30] The elevated pO_2 most likely favors O_2 entry into the CSF not through the choroid plexus but directly through the walls of arteries and arterioles on the brain surface.[30] Since in HBO there is up to 2.5 times higher pO_2, this effect in FLAIR imaging is more pronounced. We observed increase in FLAIR signal of vitreous body immediately after HBO/NBO exposure and then a subsequent decrease in time – again, this is in accordance with expected pO_2 dynamics in vitreous body, as described by Shui *et al*.[28]

The results of the present study could have also some clinical implications. Namely, the prolonged intubation induces changes of signal intensities in T_1-weighted and FLAIR images of brain MRI[31] similar as those observed in our study after NBO. Knowing that prolonged oxygenation induces paramagnetic effects in brain tissues as observed in our study, it is important to take this into account when interpreting brain MRI in intubated patients or in patients after HBO therapy.

The present study has several limitations. First, we failed to show significant differences in MRI signal intensities in brain structures after HBO compared to NBO. It would be expected that brain tissue pO_2 is significantly higher after HBO compared to NBO[21] due to higher concentration of dissolved O_2 during HBO.[19] The only exception was T_1-weighted signal intensity of vitreous body immediately and 25 min after HBO compared to NBO. One possible explanation is that MRI was performed with time delay of 15 minutes after the end of HBO due to logistics. Perhaps with shorter time delay the peak in T_1-weighted signal intensities could be observed similarly as in the study of Rockswold *et al*.[25] Additionally, the present study was semiquantitative using clinical head MRI protocol and the next step would be more quantitative approach using T_1 mapping and T_2 mapping. Furthermore, we did not measure brain tissue pO_2 nor levels of ROS, which would help to explain the observed changes in signal intensities in T_1-weighted and T_2–weighted images. Since our study was performed *in vivo* in a group of volunteers measuring of brain tissue pO_2 seems rather controversial. We could only measure pO_2 in arterial blood, however these results do not reflect brain tissue pO_2 directly. However, according to the reference, at 3 ATA pO_2 in arterial blood increases to nearly 270 kPa and in tissue to above 53 kPa.[32] In contrast, in NBO conditions, partial pressure of pO_2 in the brain is expected to be only between 4 - 6.4 kPa according to study of Meixensberger *et al*.[33] These values are much lower than during HBO. Therefore, we expected similar tissue pO_2 differences between HBO and NBO in the present study protocol.

In conclusion, the increased T_1-weighted signal intensities were observed in white and grey brain tissues, brain fluids and vitreous body after NBO as well as HBO, without significant differences between both protocols. In addition, the structure limited and diverse signal intensity increase was observed in T_2-weighted imaging and FLAIR after NBO and HBO. However, the prospective quantitative studies are needed to further clarify the effects of NBO and HBO breathing on MRI in human brain.

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research article

Prominin 2 decreases cisplatin sensitivity in non-small cell lung cancer and is modulated by CTCC binding factor

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Background. Non-small cell lung cancer (NSCLC) is the major pathological type of lung cancer and accounts for the majority of lung cancer-related deaths worldwide. We investigated the molecular mechanism of prominin 2 (PROM2) involved in cisplatin resistance in NSCLC.

Patients and methods. The GEO database was analyzed to obtain differential genes to target PROM2. Immunohistochemistry and western blotting were used to detect protein expression levels. To examine the role of PROM2 in NSCLC, we overexpressed or knocked down PROM2 by transfection of plasmid or small interfering RNA. In functional experiments, CCK8 was used to detect cell viability. Cell migration and invasion and apoptosis were detected by transwell assay and flow cytometry, respectively. Mechanistically, the regulation of PROM2 by CTCF was detected by ChIP-PCR. *In vivo* experiments confirmed the role of PROM2 in NSCLC.

Results. GEO data analysis revealed that PROM2 was up-regulated in NSCLC, but its role in NSCLC remains unclear. Our clinical samples confirmed that the expression of PROM2 was markedly increased in NSCLC tissue. Functionally, Overexpression of PROM2 promotes cell proliferation, migration and invasion, and cisplatin resistance. CTCF up-regulates PROM2 expression by binding to its promoter region. *In vivo* experiments confirmed that PROM2 knockdown could inhibit tumor growth and increase the sensitivity of tumor cells to cisplatin.

Conclusions. PROM2 up-regulation in NSCLC can attenuate the sensitivity of NSCLC cells to cisplatin and promote the proliferation, migration and invasion of tumor cells. PROM2 may provide a new target for the treatment of NSCLC.

Key words: non-small cell lung cancer; PROM2; cisplatin; drug resistance; CTCF

Introduction

Non-small cell lung cancer (NSCLC), consisting of adenocarcinoma and squamous cell carcinoma, is the major pathological type of lung cancer, accounting for the majority of lung cancer-related deaths worldwide.[1,2] Despite advances in the diagnosis and treatment of patients with NSCLC, majority of the patients are diagnosed with advanced metastasis or recurrence, resulting in poor overall 5-year survival rates of patients with NSCLC.[3] So far, platinum and its derivatives are still the main choice for anticancer chemotherapy.[4] However, platinum-based chemotherapy drugs resistance is often developed during lung cancer treatment.[5] Since drug resistance mechanism is only limitedly investigated, the exact mechanisms underlying cisplatin resistance in NSCLC remain to be determined. Thus, a deeper understanding of the mechanism of cisplatin resistance will provide new ideas for discovering potential therapeutic targets and promoting therapeutic efficacy in clinic.

Prominin 2 (PROM2) is an important member of the pentaspan transmembrane family and is enriched at plasma membrane protrusions.[6] PROM2 has recently been shown to have an antiferroptosis effect. The expression of PROM2 can be rapidly induced by stimulants that increase lipid peroxidation and promote the formation of a multi-vesicular body (MVB) containing ferritin. These MVBs export as exosomes to reduce intracellular iron concentration, thereby alleviating cell ferroptosis.[7,8] PROM2 is activated by p38-mediated HSF1 transcription to antaonized 4HNE or RSL3-induced ferroptosis.[9] Notably, PROM2 can promote gemcitabine resistance by activating Akt signaling pathway in pancreatic cancer.[10] However, the role and mechanism of PROM2 in NSCLC remains unclear.

CTCC binding factor (CTCF) is a transcription factor with 11 zinc fingers that is highly conserved despite being over 700 amino acids in length.[11] As a multifunctional transcription factor, it has been reported that CTCF is involved in the occurrence of multiple cancers.[12,13] CTCF promotes colorectal cancer cell proliferation and chemotherapy resistance to 5-FU by targeting p53-hedgehog axis.[14] Notably, CTCF promotes the progression of head and neck squamous cell carcinoma and drug resistance to cisplatin and 5-FU by targeting HOXA9.[15] Nevertheless, the role of CTCF in NSCLC is extremely limited.

In this study, our results showed that PROM2 was up-regulated in NSCLC *in vivo* and *in vitro*. More importantly, ENCODE ChIP-seq data predicted the binding between CTCF and PROM2 promoter. Subsequently, the CTCF/PROM2 modulated the NSCLC cell proliferation, migration and invasion, and cisplatin resistance.

Patients and methods

The GEO microarray data GSE32863 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE32863) was analyzed to compare the expression of differential genes (DEGs) in NSCLC tissues and adjacent normal tissues. The expression level of PROM2 in lung adenocarcinoma (TCGA-LUAD) and lung squamous cell carcinoma (TCGA-LUSC) was analyzed by online platform GEPIA based on TCGA database (http://gepia.cancer-pku.cn/detail.php?gene=PROM2). Kaplan-Meier plotter was used to analyze the relationship between PROM2 expression and prognosis according to the TCGA database (https://portal.gdc.cancer.gov/). To explore the upstream regulation of PROM2, ENCODE ChIP-seq data were performed to predict the binding between PROM2 promoter and CTCF. In addition, the CTCF expression and the correlation between CTCF and PROM2 were assessed by TIMER 2.0 analysis and GEPIA platform analysis.

Clinical samples

Our study has been authorized by the Ethics Committee of the Third Affiliated Hospital of ZunYi Medical University (The First People's Hospital of ZunYi). A total of 35 NSCLC and adjacent non-tumor tissues were collected and stored in -80°C. The patient characteristics was listed in Table 2. All procedures performed in studies involving human participants were in accordance with the standards upheld by the Ethics Committee of the Third Affiliated Hospital of ZunYi Medical University (The First People's Hospital of ZunYi) and with those of the 1964 Helsinki Declaration and its later amendments for ethical research involving human subjects.

All animal experiments were approved by the Ethics Committee of the Third Affiliated Hospital of ZunYi Medical University (The First People's Hospital of ZunYi) for the use of animals and conducted in accordance with the National Institutes of Health Laboratory Animal Care and Use Guidelines.

The animal experiment complies with the ARRIVE guidelines and in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

Cell culture and transfection

Human normal lung epithelial cells (BEAS-2B) and lung cancer cells (NCI-H1650, A549, NCI-H1299, PC-9) were purchased from American Type Culture Collection (ATCC, MA, VA, USA), cultured in RPMI-1640 supplemented with 10% fetal bovine serum (FBS; Gibco, Grand Island, USA) and incubated at 37°C in 5% CO_2.

For transfection, the A549 and PC-9 cells were transfected with transfecting plasmid or Lentivirus to overexpress or knock down PROM2 using Lipofectamine®3000 (Invitrogen, Carlsbad, CA, USA) reagent.[16] For co-transfection, the A549/DPP cells were co-transfected with small interfering RNA of CTCF and/or plasmid of PROM2, and then the cell viability and proliferation were examined.

To construct cisplatin-resistant lung cancer cell lines

Resistant NSCLC cells were established by continuously exposing A549 and PC-9 cells to cisplatin in a series of concentration gradients (0.1 μM to 6 μM). Cells that survived in cell medium with 6 μM cisplatin were identified as cisplatin resistant cells (A549/DDP, PC-9/DDP). Thereafter, the parental cells or drug-resistant cells were treated with different concentrations of cisplatin (0, 1.0 μM, 10 μM, 50 μM, 100 μM, 200 μM). CCK-8 was performed to measure cell viability and calculated half maximal inhibitory concentration (IC_{50}).

Immunohistochemistry

The tissues were fixed in 4% paraformaldehyde, embedded with paraffin, sectioned at 4 μm, dewaxed in xylene, soaked in 3% hydrogen peroxide solution to eliminate endogenous catalase, and repaired in citrate solution pH 6.0 at high temperature. Primary antibody PROM2 (Abcam, Cambridge, UK; ab118492; 1:100) was added after serum blocking. After overnight at 4°C, the sections were developed by DAB, counterstained with hematoxylin for observation.

Western blotting

Clinical tissue samples or cells of each group were collected, and RIPA lysis buffer was added to extract total protein. Appropriate amounts of protein were subjected to sodium dodecyl sulfate -polyacrylamide gel electrophoresis. After electrophoresis, the protein was transferred to PVDF membrane, blocked in 5% skim milk for 1 h at 25°C, added with primary antibody, and incubated overnight at 4°C on a shaker.[17] Specific primary antibodies are as follows: PROM2 (Abcam, ab74997, 1:1000), CTCF (Abcam, ab128873), β-actin (Abcam, ab8226). After incubation with secondary antibodies, electrochemical luminescence reagent was added without light. Image J software was used to analyze the gray value of the strips.

CCK8 assay

5 × 10^3 cells/mL cells were seeded into a 96-well plate (100 μl/well) and then cultured for 0, 1, 2 and 3 days, respectively. CCK-8 solution (Beyotime, Shanghai, China; 10 μl) was added to each well, and the culture was continued for 2 h.[18] The absorbance value (OD value) at 450 nm was detected by microplate reader.

TABLE 1. Data of ENCODE ChIP-seq

TFs	Signal peak	ENCODE ID
CTCF	114.601	ENCFF797HKW
REST	94.922	ENCFF044DWW
MAFK	71.984	ENCFF757FDG
TEAD4	34.118	ENCFF186WSI

ChIP-seq = transcription factor chromatin immunoprecipitation-DNA sequencing; CTCF = transcriptional repressor 11-zinc finger protein; MAFK = bZip Maf transcription factor protein; REST = neuron-restrictive silencer factor; TEAD4 = member of the transcriptional enhancer factor family; TFs = transcription factors

Clone formation

The cells after transfection were seeded in 6-well plates and cultured for 14 days. When visible clones appeared, the colonies were stained with gentian violet (Goodbio Technology, Wuhan, China) for 30 min. The proliferation of cells was observed under a microscope.

Transwell assay

For cell migration assay, 100 μl cell suspension was added to the upper chamber, and 600 μl RPMI-1640 containing 10% FBS was added to the lower chamber. The cells were cultured for 24 h at 37°C in a 5% CO_2 incubator. For cell invasion assays, Transwell chambers coated with extracellular matrix gel were used, and the rest of the procedure was the same as for cell migration assays. At the end of culture, the upper chamber was removed and the cells on the inner surface of the filtration membrane of the chamber were wiped off. The cells were fixed with 4% paraformaldehyde, stained with 0.1% crystal violet, observed by microscope, counted and photographed. Five fields of view were randomly selected and averaged.

Flow cytometry

Cells (2 × 10^6 cells/mL) were seeded into 96-well cell culture plate and incubated at room temperature for 24, 48 and 72 h. The cells were treated according to Annexin V-FITC/PI apoptosis kit (Beyotime) instructions. The cells were resuspended in 300 μl PBS. The cells were stained with Annexin V (5 μl) and PI (5 μl) for 15 min at room temperature, and

TABLE 2. The patient characteristics had no statistical significance

Clinicopathological factor	Number of cases	PROM2 expression		P value
		High	Low	
Total Cases	35	19	16	
Gender				0.606
Male	22	13	9	
Female	13	6	7	
Age				0.814
< 60	17	9	8	
≥ 60	18	10	8	
Histological type				0.189
LSCC	12	9	3	
LAD	15	7	8	
LCLC	8	3	5	
Pathological grading				0.002
I	15	3	12	
II	11	8	3	
III	9	8	1	
TNM stage				0.006
I	13	3	10	
II	12	7	5	
III	10	9	1	
Smoking history				0.3320
yes	24	13	11	
no	11	6	5	

LAD = lung adenocarcinoma; LCLC = non-small cell lung cancer no other specified; LSCC = squamous cell lung carcinoma

the apoptosis rate was detected by flow cytometry within 4 h.[19]

Chromatin Immunoprecipitation-quantitative real-time PCR (ChIP-PCR)

A549 cells were transfected with pcDNA-CTCF or CTCF small interfering RNA and cultured in an incubator containing 5% CO_2 at 37°C for 24 h. After removal of the medium, the cells were fixed with 16% paraformaldehyde. They were divided into IgG+siNC group, CTCF+siNC group, IgG+siCTCF group and CTCF+siCTCF group. CTCF-bound DNA was captured using antibodies according to the ChIP kit (Cell signaling Technology, Boston, MA, USA) instructions. PCR was used to verify the capture of CTCF gene promoter DNA, and ChIP-PCR was used for quantitative analysis. Immunoprecipitation efficiency was calculated using input sample percentage method.

In vivo experiment

Our study was approved by the Animal Ethics Committee of the Third Affiliated Hospital of ZunYi Medical University (The First People's Hospital of ZunYi). BALB/c nude mice were subcutaneously injected with PROM2 knockdown stable A549/DDP cells (5×10^6). One week later, cisplatin (4 mg/kg) was injected into the peritoneum every 3 days. All nude mice were divided into 5 groups: control group, shNC group, cisplatin +shNC group, shPROM2#1 group and cisplatin +shPROM2#1 group, with 5 mice in each group. On the 25th day, the nude mice were sacrificed under anesthesia. The weight of the tumors was weighed and the volume of the tumors was measured. The tumors were collected for subsequent experiments.

Statistical analysis

Graphpad 7.0 software was used for data analysis. Data were expressed as mean ± standard deviation, and comparison between two groups was performed by *t* test. One-way analysis of variance analysis of variance was used to compare the differences between more than two groups. $P < 0.05$ was considered statistically significant. IC50 value was calculated by Graphpad according to the results of CCK-8 assay.

Results

PROM2 is up-regulated in NSCLC

To explore the pathogenesis of NSCLC, we analyzed the data GEO database data (GSE32863) confirmed to compare the expression of differential genes in NSCLC tissues and adjacent normal tissues and the results showed that PROM2 was up-regulated in NSCLC compared to adjacent normal tissues (Figure 1A). Interestingly, GEO microarray data GSE32863 confirmed the differential genes (DEGs) in lung cancer tissues and adjacent normal tissues. Notably, PROM2 expression was increased in lung cancer tissues (Figure 1B-1D). More importantly, online platform GEPIA data showed that both PROM2 transcript and expression levels were promoted in LUSC and LUAD patients compared to normal subjects (Figure 1E and 1F). Similarly, high expression of PROM2 predicted poor prognosis (Figure 1G). Representative images of IHC confirmed that PROM2 was highly expressed in NLCSC patient tissues compared to adjacent tissues (Figure 1H). Consistently, PROM2

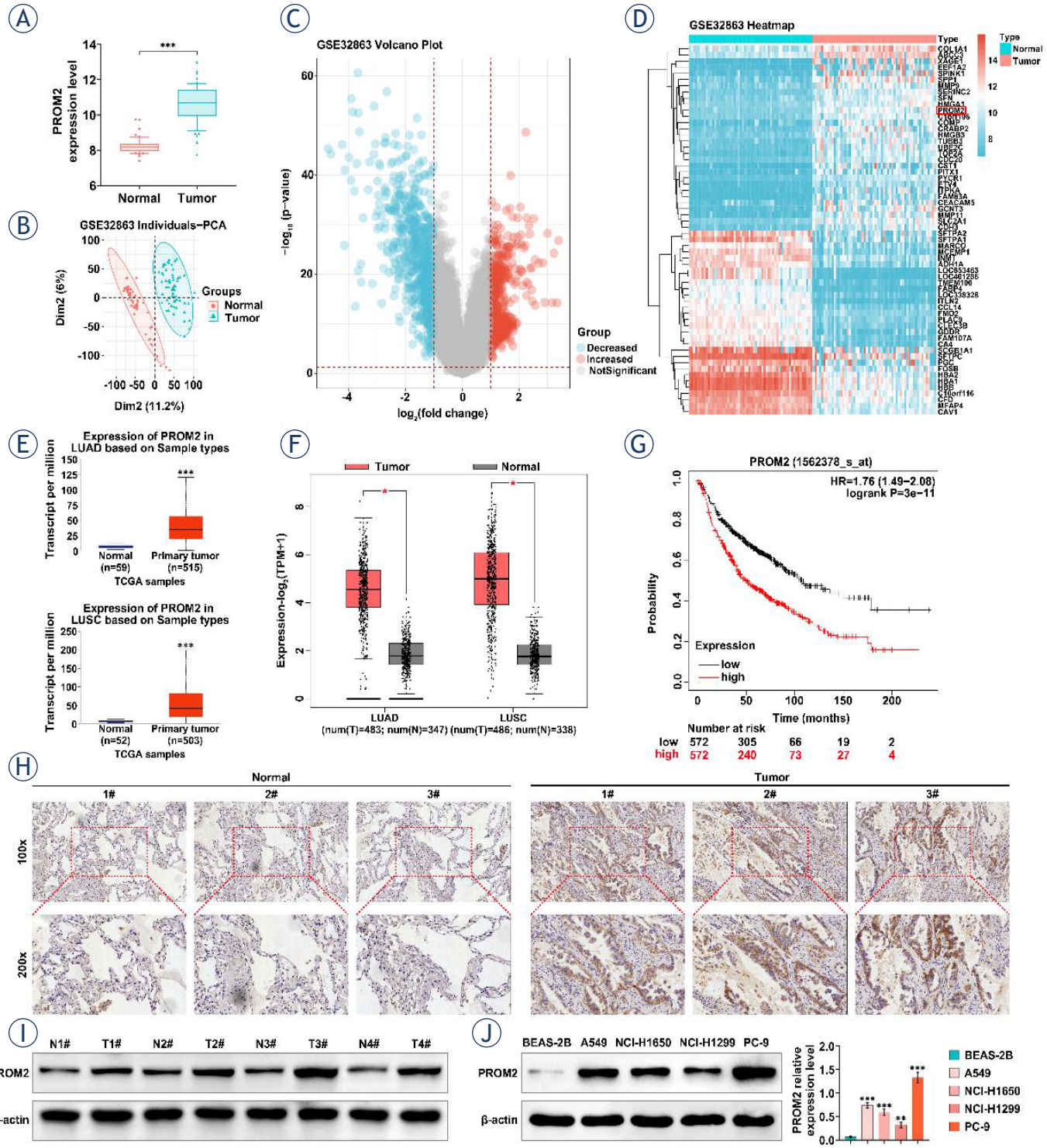

FIGURE 1. PROM2 is overexpressed in non-small cell lung cancer (NSCLC). **(A)** Expression level of PROM2 in normal group and tumor. **(B-D)** GEO microarray data GSE32863 was analyzed by LIMMA package using R language to compare the expression of differential genes (DEGs) in lung cancer tissues and adjacent normal tissues. The data were corrected and analyzed by PCA **(B)**, and the volcano map **(C)** and heat map **(D)** were drawn. **(E-F)** To analyze the expression level of PROM2 in non-small cell lung cancer (TCGA-LUAD and TCGA-LUSC) using online platform GEPIA based on TCGA database. **(G)** Kaplan-Meier plotter was used to analyze the effect of PROM2 expression on prognosis. **(H)** Representative immunohistochemical picture of PROM2 in NSCLC. **(I)** PROM2 protein level in NSCLC by Western blotting. **(J)** The protein expression of PROM2 in human normal lung epithelial cells (BEAS-2B) and lung cancer cells (NCI-H1650, A549, NCI-H1299, PC-9) was detected by western blotting.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with normal group/BEAS-2B group

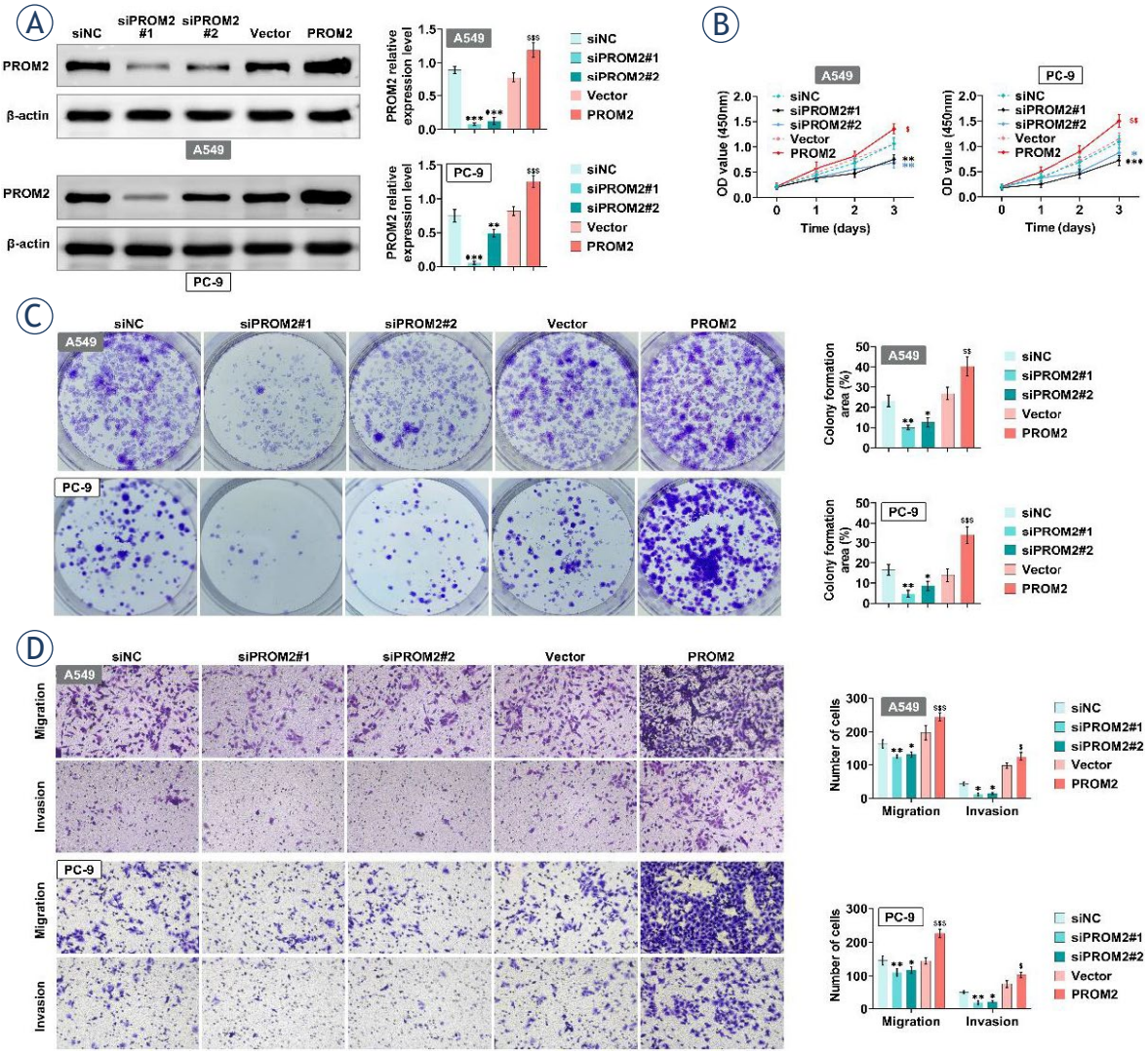

FIGURE 2. PROM2 promotes the proliferation of lung cancer cells. **(A-D)** PROM2 was overexpressed or knocked down in A549 and PC-9 cells. The protein level of PROM2 was detected by western blotting **(A)**, cell viability was detected by CCK8 **(B)**, cell proliferation was detected by clonal formation **(C)**. Transwell was used to detect cell migration and cell invasion **(D)**.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with siNC; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, $^{\$\$\$}P < 0.001$ compared with vector

expression was significantly enhanced in lung cancer cells (NCI-H1650, A549, NCI-H1299, PC-9) compared to BEAS-2B, especially in PC-9 and A549 cells (Figure 1J). Thus, the PC-9 and A549 cells was selected for subsequent experiments. These results indicated that the expression levels of PROM2 were up-regulated in NSCLC.

PROM2 promotes the proliferation of lung cancer cells

To explore the role of PROM2 in NSCLC, PROM2 was overexpressed or knocked down in A549 and PC-9 cells. As expected, PROM2 was efficiently over-expressed or knocked down (Figure 2A). Then, the effects of altered PROM2 on NSCLC viability and motility were examined. As shown in Figure 2B, A549 and PC-9 cell viability was remarkably increased after PROM2 overexpression, and was decreased by knockdown of PROM2. In addition, knockdown of PROM2 reduced the number of colonies, whereas overexpression of PROM2 exhibited opposite effect (Figure 2C). Furthermore, knockdown of PROM2 observably inhibited the number of migrated and invaded cells, while overexpression of PROM2 increased the number of migrated and invaded cells (Figure 2D). These findings indicated that PROM2 can promote the cell

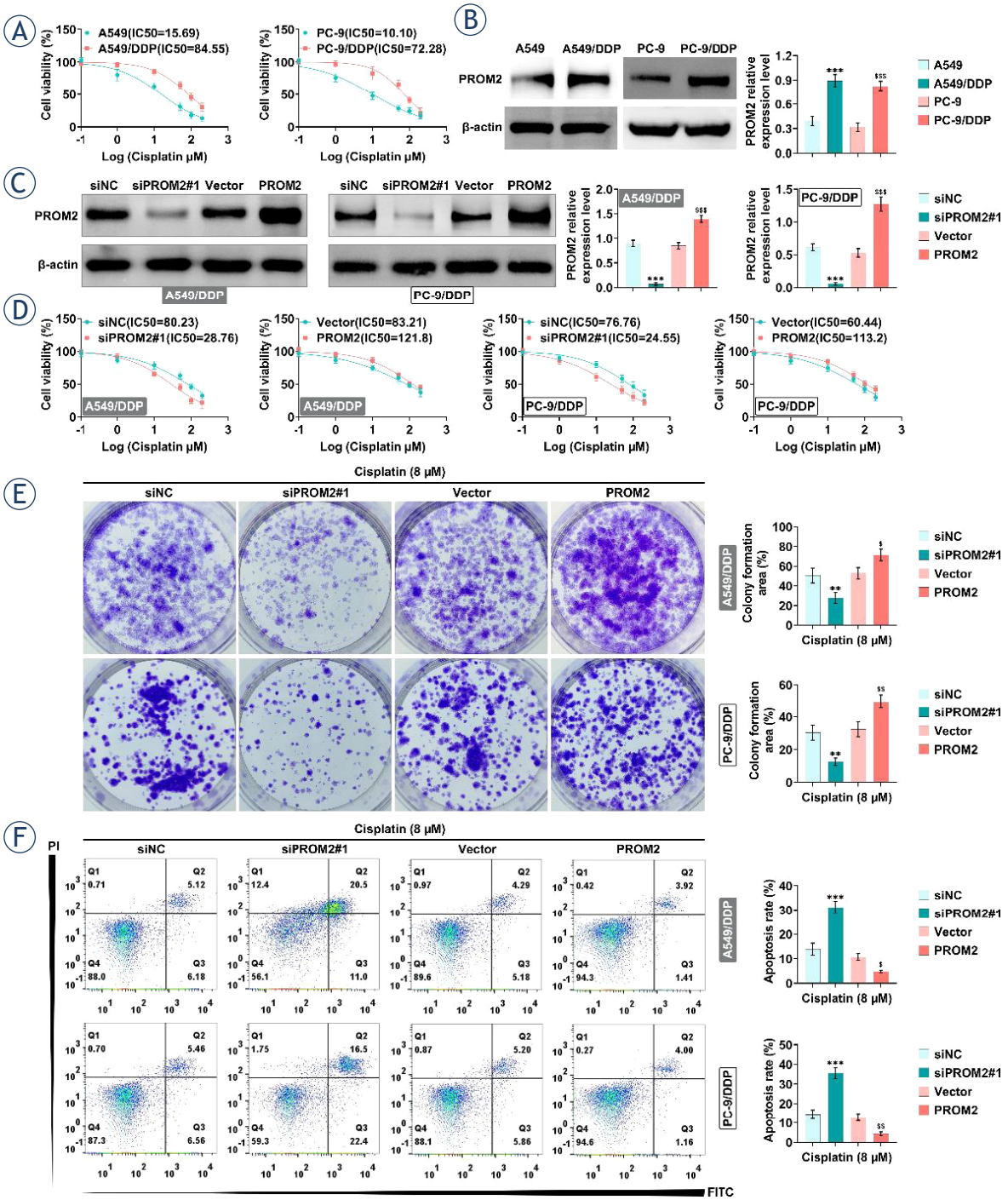

FIGURE 3. PROM2 attenuates the sensitivity of lung cancer cells to cisplatin. **(A)** Cell viability was detected by CCK8. **(B)** The expression level of PROM2 in different groups of cells was detected by western blotting. **(C-F)** PROM2 was knocked down or overexpressed in A549/DDP and PC-9/DDP, and then the protein level of PROM2 was detected by western blotting, cell viability was detected by CCK8 **(D)**, cell proliferation was detected by clone formation **(E)**, and cell apoptosis was detected by flow cytometry **(F)**.

***P* < 0.01, ****P* < 0.001 compared with A549 group; $^{\$}$*P* < 0.05, $^{\$\$}$*P* < 0.01, $^{\$\$\$}$*P* < 0.001 compared with vector

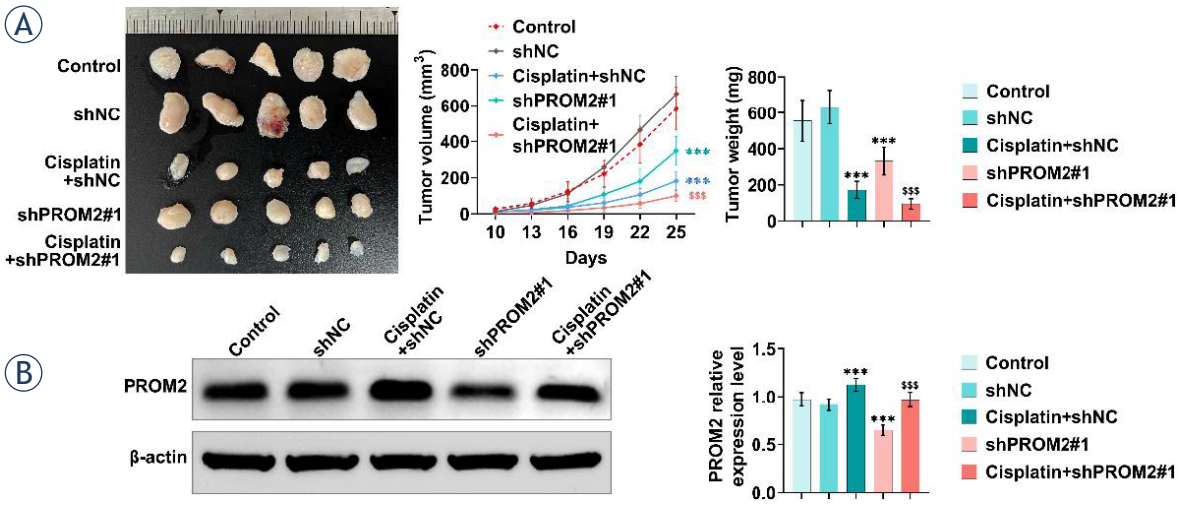

FIGURE 4. PROM2 enhances cisplatin resistance in lung cancer cells *in vivo*. BALB/c nude mice were subcutaneously injected with PROM2 knockdown stable A549/DDP cells. One week later, cisplatin (4 mg/kg) was injected into the peritoneum every 3 days. After 30 days, the cells were removed and the volume and weight were measured. **(A)** The volume and weight of tumors in different groups were detected. **(B)** The protein levels of PROM2 in different groups were detected by Western blotting.

***$P < 0.001$ compared with shNC group; $^{\$}P < 0.05$, $^{\$\$}P < 0.01$, $^{\$\$\$}P < 0.001$ compared with cisplatin+shNC

viability, proliferation, migration and invasion of lung cancer cells.

Effect of PROM2 on cisplatin sensitivity in lung cancer cells

Subsequently, to investigate the effect of PROM2 on cisplatin sensitivity in NSCLC, we constructed drug-resistant cell lines (A549/DDP and PC-9/DDP). CCK8 assay results showed that both A549/DDP and PC-9/DDP cells had a lower cisplatin sensitivity than A549 (IC_{50} 84.55 *vs*. 15.69) and PC-9 cells (IC_{50} 72.28 *vs*. 10.10) (Figure 3A). Moreover, PROM2 expression level was significantly higher in resistant cells than in parental cells (Figure 3B). To investigate the role of PROM2 in drug-resistant cells, PROM2 was down-regulated or overexpressed in A549/DDP and PC-9/DDP cells (Figure 3C). Subsequently, CCK-8 assay implied that knockdown of PROM2 enhanced cisplatin sensitivity in A549/DPP (IC_{50} 28.76 *vs*. 79.28) and PC-9/DDP (IC_{50} 27.02 *vs*. 70.43) cells, while overexpression of PROM2 inhibited cisplatin sensitivity in A549/DPP (IC_{50} 112.40 *vs*. 81.80) and PC-9/DDP (IC_{50} 98.37 *vs*. 67.66) cells (Figure 3D). Moreover, the colony formation results indicated that knockdown of PROM2 reduced cell proliferation but overexpression of PROM2 promoted cell proliferation of A549/DPP and PC-9/DDP cells (Figure 3E). Consistently, flow cytometry analysis manifested that downregulation of PROM2 increased apoptosis, while overexpression of PROM2 decreased apoptosis of A549/DPP and PC-9/DDP cells (Figure 3F). These results unfolded that PROM2 reduced cisplatin sensitivity through reducing apoptosis and promoting proliferation.

Knockdown of PROM2 enhances the sensitivity of lung cancer cells to cisplatin *in vivo*

BALB/c nude mice were subcutaneously injected with PROM2-knockdown A549/DDP cells to investigate the effect of PROM2 *in vivo*. The data indicated that cisplatin treatment reduced the volume and weight of tumors, while knockdown of PROM2 further inhibited the tumor growth (Figure 4A). More importantly, cisplatin treatment increased PROM2 expression, which was decreased by shPROM2 (Figure 4B). All these results suggested that PROM2 knockdown suppressed tumor growth through enhancing the cisplatin sensitivity.

CTCF up-regulates PROM2 expression by binding to its promoter region

By analyzing Chip ChIP-seq data, it was found that CTCF, REST, MAFK, and TEAD4 can bind to PROM2 promoter, especially CTCF (Table 1). In

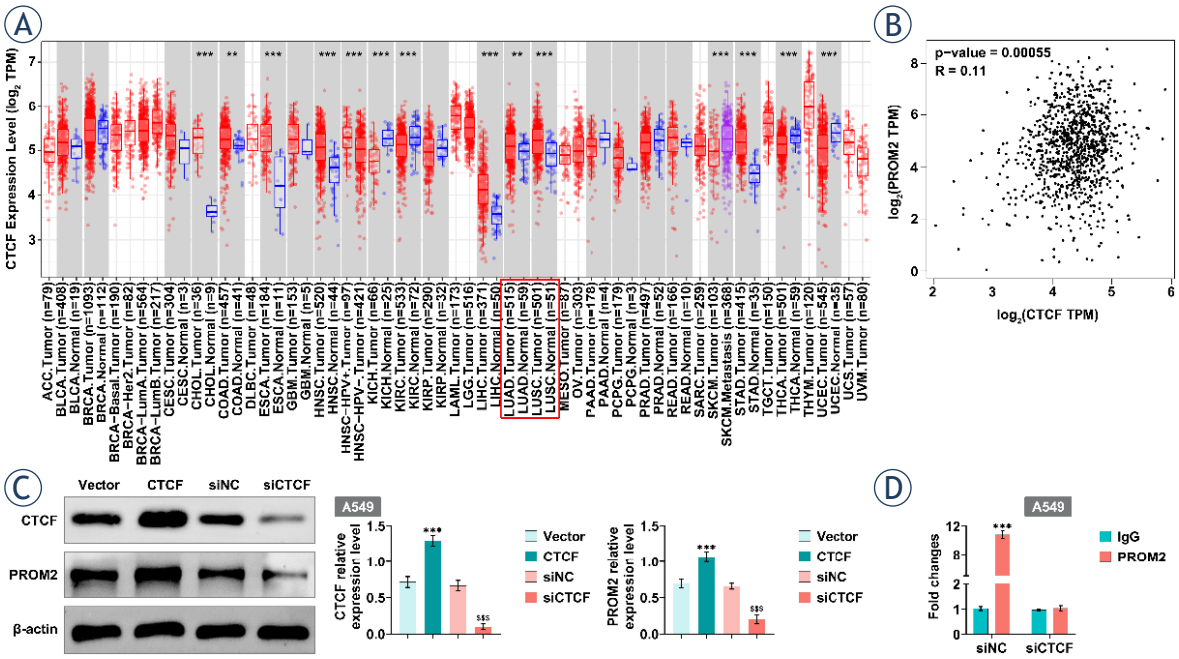

FIGURE 5. Up-regulation of PROM2 induced by CTCF. **(A)** TIMER 2.0 data analysis revealed that CTCF was overexpressed in lung cancer. **(B)** There was a positive correlation between CTCF and PROM2 in LUAD and LUSC data analyzed by GEPIA platform. **(C)** Protein levels of PROM2 and CTCF were detected by western blotting. **(D)** The expression level of PROM2 was detected by ChIP-PCR.

$^{**}P < 0.01$, $^{***}P < 0.001$ compared with vector group; $^{\$\$\$}P < 0.001$ compared with siNC

addition, TIMER 2.0 data showed that CTCF was overexpressed in lung cancer (Figure 5A). Besides, GEPIA platform analysis revealed a positive correlation between CTCF and PROM2 in LUAD and LUSC (Figure 5B). Furthermore, overexpression of CTCF significantly promoted PROM2 expression, while knockdown of CTCF reduced PROM2 expression in A549 cells (Figure 5C). Interestingly, ChIP-PCR result unfolded that the CTCF distinctly bound to PROM2 promoter (Figure 5D). These findings concluded that CTCF promoted PROM2 expression via directly binding to its promoter.

Knockdown of CTCF can increase the sensitivity of lung cancer cells to cisplatin by down-regulating PROM2

To explore the effect of CTCF on cisplatin sensitivity in NSCLC, CTCF was knocked down in A549/DDP cells. As shown in Figure 6A, siCTCF decreased PROM2 expression, which was increased by overexpression of PROM2. Moreover, CCK-8 assay showed that siCTCF promoted cisplatin sensitivity (IC_{50} 29.26 *vs*. 89.51), while overexpression of PROM2 attenuated this effect (Figure 6B). Furthermore, knockdown of CTCF reduced the number of colony formation of A549/DDP cells, which was reversed by overexpression of PROM2 (Figure 6C). Consistently, the apoptosis rate was increased by knockdown of CTCF in A549/DDP cells, which was decreased by PROM2 overexpressed (Figure 6D). Thus, these findings revealed that knockdown of CTCF can increase the sensitivity of lung cancer cells to cisplatin through down-regulating PROM2.

Discussion

Lung cancer is the most common cancer and the leading cause of cancer-related death worldwide, with NSCLC accounting for about 80% of all lung cancers in the United States.[20,21] We analyzed the database and found that PROM2 was highly expressed in NSCLC and associated with poor prognosis. More importantly, we demonstrated that PROM2 promoted the proliferation, migration and invasion of lung cancer cells, and inhibited the apoptosis, and their sensitivity to cisplatin *in vitro*. *In vivo* experiments confirmed that knockdown

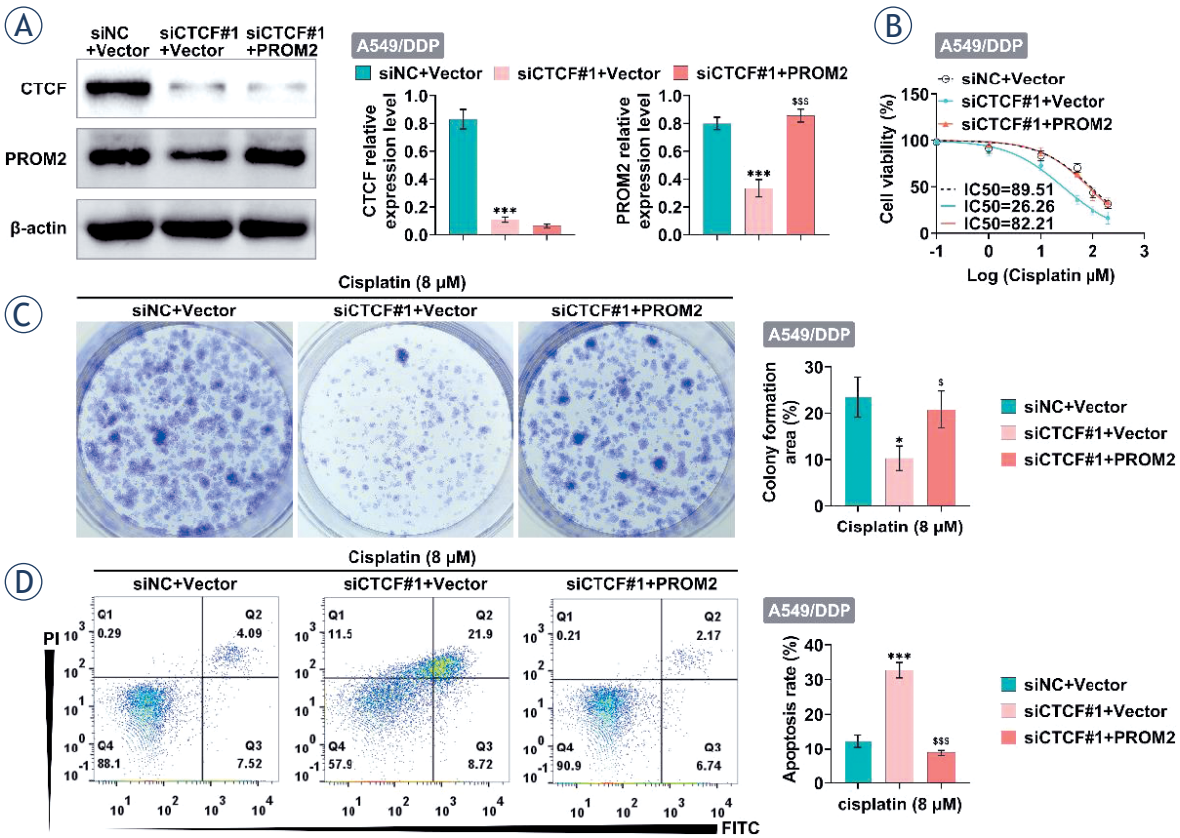

FIGURE 6. CTCF knockdown increased the sensitivity of lung cancer cells to cisplatin by down-regulating PROM2. **(A-D)** After knockdown of CTCF and/or overexpression of PROM2 in A549/DDP, the protein levels of CTCF and PROM2 were detected by western blotting **(A)**, cell viability was detected by CCK8 **(B)**, cell proliferation was detected by clone formation **(C)**, and cell apoptosis was detected by flow cytometry **(D)**.

*$P < 0.05$, ***$P < 0.001$ compared with siNC+vector; $^{\$}P < 0.05$, $^{\$\$\$}P < 0.001$ compared with siCTCF#1+vector

of PROM2 enhances the sensitivity of lung cancer cells to cisplatin, thereby inhibiting tumor growth. Furthermore, CTCF up-regulated PROM2 expression and reduced cisplatin sensitivity through directly binding to PROM2 promoter, providing a novel sight for the mechanism of the cisplatin resistance in NLCSC.

Previous studies have found that PROM2 was up-regulated in a variety of tumors, such as bladder cancer, pancreatic cancer, melanoma.[7,10,22] However, the potential role and mechanism of PROM2 in NSCLC remains unclear. In this study, the expression of PROM2 was up-regulated in NSCLC, indicating that PRMO2 was involved in the pathogenesis of NSCLC. Consistently, our clinical samples confirmed that the protein level of PROM2 was significantly increased in NSCLC tissues. Cell proliferation, migration and invasion are responsible for tumorigenesis and poor prognosis.[23] Our study found that overexpression of PROM2 promoted the proliferation, migration and invasion of lung cancer cells, which might be the first time exploring the carcinogenesis role of PROM2 in NSCLC. Fortunately, a recent report has pointed out that activated PROM2 serves as a tumorigenic regulator in bladder cancer via attenuating ferroptosis.[7]

Cisplatin-based chemotherapy remains the standard care for NSCLC patients, but many patients are prone to develop drug resistance after cisplatin treatment.[24] It has been reported that many RNAs and proteins participate in modulating cisplatin resistance in NSCLC patients.[25,26] Recently, Li *et al*. have demonstrated that PROM2 promotes gemcitabine chemoresistance via activating the Akt signaling pathway in pancreatic cancer.[10] In this study, through constructing drug-resistant cell lines (A549/DDP and PC-9/DDP), we

found that PROM2 reduced cisplatin sensitivity in lung cancer cells. Besides, reporters have confirmed that cisplatin resistance in NSCLC can result from alterations in regulation of the cell apoptosis.[27] Based on the results that high expression of PROM2 promoted the proliferation, migration and invasion, we hypothesized that PROM2 can decrease cisplatin sensitivity via enhancing NSCLC cells survival and metastasis, thereby promoting cisplatin resistance.

DNA-binding proteins can modulate proteins expression via binding to its promoter. To confirm the regulatory mechanism of PROM2 expression, CTCF was predicted to bind to PROM2 promoter. Interestingly, most gained CTCF binding events exhibit enhancer activities and are induced by oncogenic transcription factors.[28] Consistently, we demonstrated that CTCF could bind to PROM2 promoter and up-regulate PROM2 expression. Mechanically, cisplatin induces dormant and reactivated lung cancer cells, and CTCF governs the entry of cancer cells into dormant states and control the re-entry of dormant cancer cells into the cell cycle.[29] Thus, we suspected that CTCF up-regulates PROM2 expression and governs the shift of cellular dormancy and reactivation under cisplatin stimulation, subsequently promotes cell proliferation and inhibits apoptosis, thereby reducing the cisplatin sensitivity. However, the relationship between cisplatin resistance and migration phenotype is still unknown. It has been reported that the increases in cell invasion and migration abilities may be a consequence of cisplatin resistance, resulting in enhanced cancer metastasis after long-term treatment with cisplatin.[30] Therefore, we suspected that up-regulation of CTCF/PROM2 decreases cisplatin sensitivity and then enhances NSCLC cell migration and invasion. There are still some limitations in our study, and we have yet to show whether CTCF/PROM2 mechanism is the only mechanism of enhancement of cisplatin resistance in NSCLC. Other therapeutic targets of mechanism of cisplatin resistance are still unknown.

Conclusions

In conclusion, our study found that PROM2 was up-regulated in NSCLC and promoted NSCLC cells proliferation, invasion and migration, as well as the drug resistance of lung cancer cells to cisplatin, providing a theoretical target for the treatment of NSCLC, and a novel sight for therapeutic strategy for NSCLC.

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research article

Breast cancer risk assessment and risk distribution in 3,491 Slovenian women invited for screening at the age of 50; a population-based cross-sectional study

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Background. The evidence shows that risk-based strategy could be implemented to avoid unnecessary harm in mammography screening for breast cancer (BC) using age-only criterium. Our study aimed at identifying the uptake of Slovenian women to the BC risk assessment invitation and assessing the number of screening mammographies in case of risk-based screening.

Patients and methods. A cross-sectional population-based study enrolled 11,898 women at the age of 50, invited to BC screening. The data on BC risk factors, including breast density from the first 3,491 study responders was collected and BC risk was assessed using the Tyrer-Cuzick algorithm (version 8) to classify women into risk groups (low, population, moderately increased, and high risk group). The number of screening mammographies according to risk stratification was simulated.

Results. 57% (6,785) of women returned BC risk questionnaires. When stratifying 3,491 women into risk groups, 34.0% were assessed with low, 62.2% with population, 3.4% with moderately increased, and 0.4% with high 10-year BC risk. In the case of potential personalised screening, the number of screening mammographies would drop by 38.6% compared to the current screening policy.

Conclusions. The study uptake showed the feasibility of risk assessment when inviting women to regular BC screening. 3.8% of Slovenian women were recognised with higher than population 10-year BC risk. According to Slovenian BC guidelines they may be screened more often. Overall, personalised screening would decrease the number of screening mammographies in Slovenia. This information is to be considered when planning the pilot and assessing the feasibility of implementing population risk-based screening.

Key words: breast cancer screening; personalised screening; risk assessment; IBIS; Tyrer-Cuzick model; breast density

Introduction

Breast cancer (BC) is the most common cancer in women in developed countries. Globally, more than 2,200,000 women were diagnosed with BC in 2020 – 355,457 only in the European Union.[1,2] The average crude incidence rate in Slovenia has risen from 32.3/100,000 between 1965 and 1969 to

139.8/100,000 women in the period from 2015 to 2019. Between 2015 and 2019, the average annual number of new BC cases in Slovenia was 1,454 (the female population in 2019 was equal to 1,044,783).[3,4] According to estimated age-standardized incidence rate (European standard) in 2020, Slovenia ranks 18th among EU member countries.[2]

Breast cancer burden is increasing mainly due to an ageing population. Moreover, many other risk factors affect BC predisposition. The most important are reproductive risk factors (early menarche, later age at first full-term pregnancy, nulliparity and late menopause affecting the levels of endogenous hormones), hormone use (intake of exogenous hormones, hormone replacement therapy), some lifestyle factors (alcohol use, overweight and physical inactivity), a high mammographic breast density, benign breast diseases (proliferative disease without atypia and atypical hyperplasia), anthropometric characteristics (height, weight) and genetic susceptibility.[5,6]

In addition to primary prevention, secondary prevention of BC with screening can be very successful in reducing BC mortality rates in organised population–based cancer screening programmes and with an uptake over 70%.[7] BC screening programmes in the European Union member states offer standard screening for all women aged 50–69 (in certain cases 40–74) based on a single risk factor, age as an entry criterion.[8] The latest European Commission recommendations from December 2022 recommend mammography screening in women aged 50–69 and suggest screening in wider age intervals, 45–74 if feasible.[9] The evidence shows that there is high certainty that mammography screening reduces the risk of BC mortality in women aged 50–69 (138 to 483 deaths averted per 100,000 women screened). In addition, women invited to screening show a lower risk of BC being diagnosed in advanced stages, regardless of age group. However, there is also moderate certainty for undesirable effects of screening, e.g. overdiagnosis and false-positive results associated with an increased number of invasive procedures and women's distress.[10]

As already mentioned, the age is not the only risk factor and other risk factors can also contribute to the development of BC. Therefore, the one-size-fits-all approach does not take into account the heterogeneity of the BC biological subtypes nor the different BC risks in the population.[6] New scientific data suggest that a new screening strategy based on the estimation of individual BC risk may have a better harms/benefits ratio for women in comparison to the current standard age-based screening. A personalized approach can tailor screening strategies according to women's risk. In fact, the Guidelines development group of experts at European Commission Initiative on Breast Cancer (ECIBC) supports the priorities in the field of mammography screening that include identification of risk factors for stratifying women into different risk groups; to find those who should start with the screening earlier and might be screened with shorter intervals.[8] Some studies have already been conducted and some randomized controlled trials are ongoing. These studies want to test the hypothesis that an age-based BC screening strategy, where the screening policy is the same for all women in the target population, is not optimal and risk-based screening over current one-size-fits-all screening strategy should be recommended to improve the harms/benefits ratio.[11]

Various mathematical models for calculating individual BC risk are known today, to name just a few of them: the Gail model, the Breast Cancer Surveillance Consortium (BCSC) risk calculator, the Tyrer–Cuzick model, The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and an online tool enabling healthcare professionals to calculate an individual's future risks of developing breast and ovarian cancer using cancer family history, genetic and other risk factors (CanRisk model).[12-16]

In Slovenia, more than 100,000 screening mammographies are performed every year in the target population, inviting approx. 280,000 BC-free women aged 50 to 69 to the Slovenian BC screening programme every two years.[17] In addition, women at high and moderately increased risk are currently identified and assessed at the Institute of Oncology Ljubljana at the Department of Clinical Cancer Genetics. Cancer genetic counselling, genetic testing, personalised cancer screening and risk reduction strategies are offered when a woman's BC risk is more than doubled in comparison to the general population's BC risk. Since 1999, women have been selected due to positive family history, and genetic testing is offered when indicated according to the Slovenian BC diagnostic and treatment guidelines.[18] Breast cancer risk is currently assessed either by using the Tyrer-Cuzick or the CanRisk tool and personalised surveillance is offered to women at higher risk. For the general population with a lifetime risk under 15% (population risk), Slovenian guidelines recommend regular breast self-examination, early recognition of BC symptoms and signs, and participation in the Slovenian

TABLE 1. Questionnaire content used for Slovenian International Breast Cancer Intervention Study (S-IBIS) evaluation tool score calculation

Factors affecting levels of endogenous hormones (menarche, menopause, first birth age).
Exogenous hormone intake (menopause hormone replacement therapy).
Anthropometric characteristics (height, weight).
Breast biopsy (done, not done, presence of atypia, atypical hyperplasia).
Family history of breast and ovarium cancer (mother, sisters, half-sisters, daughters, grandmothers, aunts, male relatives).
Ovarian cancer of the participants.

BC screening programme. For women with moderately increased BC risk, additional yearly clinical breast examination and yearly mammography are recommended. Risk should be identified using mathematical models, e.g. Slovenian International Breast Cancer Intervention Study (S-IBIS) evaluation tool or cancer risk (CanRisk) tool based on reliable family history, which should be verified whenever possible in the cancer registry.[18,19]

No population-based cross-sectional study for assessing the BC risk in the Slovenian population invited for BC screening has been performed yet.

The aims of the study were (i) to assess the feasibility of BC risk assessment in Slovenian women when invited to the BC screening programme, (ii) to identify the distribution of women in the BC risk groups (low, population, moderately increased, and high risk) through assessing the 10-year and lifetime BC risk, by using also the information on the breast density that is not yet routinely available as a part of the standardized mammography report and (iii) to assess the number of screening mammographies in case risk-based screening would be implemented according to different screening protocols.

Patients and methods

Our study was a cross-sectional population-based study and enrolled 11,898 women at the age of 50 invited to BC screening in 2021 (birth cohort 1971). The National Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia (No. 0120-244/2018/4) approved the study. The first 3,491 questionnaires (out of 6,785 returned) were analysed for the purpose of this article. Entering all received questionnaires into the database and arranging the data was a lengthy process, so the first half of refined data was analysed preliminarily, since the sample size was already adequate (minimum sample size would be 800).

Participants recruitment and materials

Women turning 50 years are invited with a personal letter to the Slovenian BC screening programme to participate in mammography screening organized according to the EU guidelines.[17,20] All eligible women aged 50 (with no previous BC diagnosis) in 2021, were sent a self-administrated structured 5-page questionnaire via postal mail together with a screening invitation and explanatory text to sign informed consent for participating in this study. The family history questionnaire was adopted from the one used at the Department of Clinical Cancer Genetics, encompassing questions about anthropometric, reproductive and hormonal anamnesis and family history (Table 1).[21] In addition, just for the purpose of this study, breast density was assessed by the radiologist using the mediolateral oblique view of the screening mammograms, in accordance with the BI-RADS 5th edition reporting system that classifies breast density into four levels.[22]

For menopausal status, the time interval between the date of filling in the questionnaire and the date of women's last menstrual period was considered, 31 and 365 days being cut-offs for the groups (premenopausal, perimenopausal and postmenopausal).[23] For participants' description, the characteristics of study participants were grouped into categories according to the relative risk caused by the risk factors incorporated in the Tyrer-Cuzick model.[14,24] The denominator for calculating the percentage of frequencies was the sum of participants (3,491).

Risk calculation

In the Slovenian national health system, Slovenian IBIS is ready for use allowing an evidence-based assignment of an asymptomatic individual to a group of population, moderately increased and high BC risk. The S-IBIS software was developed at the Institute of Oncology Ljubljana in 2018 within

TABLE 2. Breast cancer risk categories for Slovenian women at the age of 50 and risk-based screening scenarios according to different protocols[18,24,26]

Breast cancer risk category	Lifetime risk	10-year risk	Slovenian risk-based screening guidelines[18,25]	PROCAS study protocol[27]
Low risk (%)	**	< 1.3	**	5-year mammography screening interval
Population risk (%)	< 16	1.3–3.9	2-year mammography screening interval	3-year mammography screening interval
Moderately increased risk (%)	16–30	4.0–6.5	1-year mammography screening interval	2-year mammography screening interval
High risk (%)	> 30	> 6.5	1-year mammography screening interval	1-year mammography screening interval

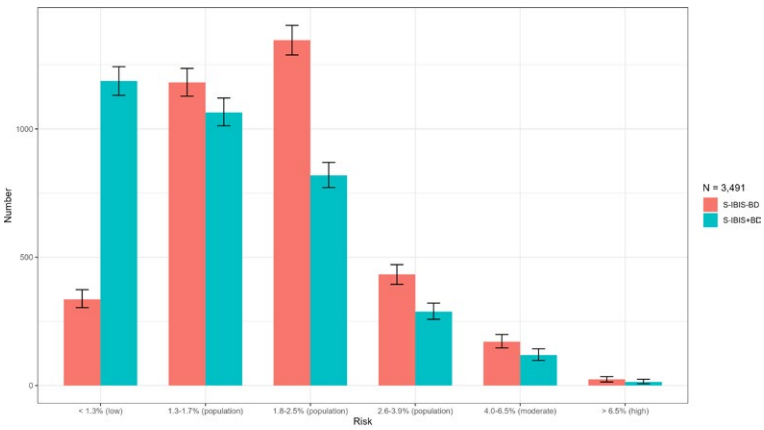
** not applicable; PROCAS = Predicting Risk of Breast Cancer at Screening

a research project.[19] It is an adjustment of the IBIS software with the Tyrer-Cuzick algorithm, where Slovenian generation-specific population BC risks were applied and it is specifically designed to calculate the individual risk of BC in Slovenian women. BC incidence and mortality rates between 2006 and 2010 were obtained from the population-based Slovenian Cancer Registry.[25] The Tyrer-Cuzick algorithm is recognized as one of the most consistent models and validated on several populations. It calculates both, a 10-year risk and a lifetime risk of BC based on the women's personal, reproductive, and family characteristics.[14] Moreover, the latest version of the model (version 8) incorporates mammographic density.[26]

After calculating the risk for each individual (first with breast density included and then without breast density), study participants were grouped into risk categories according to relative risk that was calculated with the Tyrer-Cuzick model.[14,24] The cut-offs for the distribution of individuals into the low, population, moderately increased and high risk categories for BC are shown in Table 2. Lifetime risk is defined as the risk of developing BC by the age of 85.[19,25] In case of missing or unknown data, the population reference relative risk was considered.

The number of screening mammographies was estimated for the same group of women (N = 3,491, considering all would attend the screening regularly by the age of 69) for two different risk-based scenarios/protocols according to the Slovenian BC diagnostic and treatment guidelines and English Predicting Risk of Breast Cancer at Screening (PROCAS) cohort study (Table 2).[18,25,27]

The tool SPSS, version 24 (IBM Corp., Armonk, NY, USA), R Project for Statistical Computing (v4.3.2) and RStudio (2023.03.0, R Core Team 2023) were used for the statistical analyses and risk calculations. Statistical significance was determined using the Clopper-Pearson 95% confidence intervals.



	< 1.3% (low)	1.3-1.7% (population)	1.8-2.5% (population)	2.6-3.9% (population)	4.0-6.5% (moderate)	> 6.5% (high)
S-IBIS-BD	9.6%	33.8%	38.6%	12.4%	4.9%	0.7%
S-IBIS+BD	34.0%	30.5%	23.5%	8.2%	3.4%	0.4%

S-IBIS-BD = Slovenian International Breast Cancer Intervention Study (S-IBIS) model without breast density; S-IBIS+BD = S-IBIS model including breast density

FIGURE 1. 10-year breast cancer risk distribution in Slovenian women, aged 50 years, by using S-IBIS without breast density data and with breast density data. Clopper-Pearson 95% confidence intervals are shown.

Results

In total, 57% (6,785/11,898) of women who received the Slovenian BC screening programme invitation consented to the study and filled in the questionnaire. The first 3,491 returned questionnaires were included in the BC risk assessment and analysed. The characteristics of the study participants are listed in Table 3.

The majority of women were parous (90.4%) and did not have any first (89.9%) or second-degree (83.2%) relatives affected. Further, 39.9% of women included in the study were premenopausal, 18.1% perimenopausal and 18.1% postmenopausal, 23.9% of them did not report the date of their last period. Eight-point two percent of women reported being current or previous users (in the last 5 years) of hormone replacement therapy

(HRT). More than a half (51.6%) of women were assessed with BI-RADS b score for breast density, and 40.4% with BI-RADS c score.[22] More than two-thirds of women reported their data for the risk factors, e.g. the age at menarche, the age at first childbirth, menopausal status, HRT use and breast biopsy. Moreover, breast density was assessed for 99% of participants.

Frequencies of BC risk

Table 4 shows the frequencies of BC risk in the study population; 3.4% of participating women were assessed with moderately increased 10-year BC risk, and 2.2% with moderately increased lifetime risk. Only a small proportion of women had high 10-year and lifetime risk (0.4% and 0.03%, respectively). The mean of the 10-year risk was found to be 1.7% with a standard deviation of 1.0, and the mean of the lifetime risk was 6.3% with a standard deviation of 3.2. Among 3,491 analysed study participants, 27 were diagnosed with breast cancer after first screening mammography in 2021; one of them was assessed as high risk (10 years BC risk), none as moderately increased, nine as low risk and 17 as population risk.

Breast density information

Adding breast density information to the Tyrer-Cuzick model (10-year BC risk) significantly changed the distribution of women in our study. This information moved the majority of women to lower-risk groups. The proportion of women in high, moderate and upper-population risk groups (2.6%–3.9%) was also decreased, shifting women to lower–population (1.3%-1.7%) and low risk (below 1.3%) groups (Figure 1).

Number of screening mammographies when different risk-based screening protocols are applied

Table 5 shows the change of the number of screening mammographies in the screening programme when considering different screening protocols (age-based and risk-based using the S-IBIS model including breast density [S-IBIS+BD]) applying two different risk-based protocols, described in the Slovenian guidelines and in the PROCAS study.[18,27]

When considering applying the current Slovenian risk-based screening guidelines for lifetime BC risk, 2.2% (|35,690–34,910|/34,910) more mammographies compared to the current

TABLE 3. Characteristics of study participants (n = 3,491)

	Frequency (N)	Per cent (%)
Family history: first-degree relatives with breast/ovarian cancer (mother, father, sisters, daughters)		
positive (1 relative)	326	9.3
positive (2 or more relatives)	28	0.8
negative	2,854	81.8
unknown	283	8.1
Family history: second-degree relatives with breast/ovarian cancer (aunts, uncles, grandmothers, half-sisters)		
positive (1 relative)	437	12.5
positive (2 or more relatives)	148	4.2
negative	2,552	73.1
unknown	354	10.1
Age (years) at menarche		
< 13	1,138	32.6
13	940	26.9
> 13	1,339	38.4
unknown	74	2.1
Age (years) at first birth		
< 25	1,570	45.0
25–28	736	21.1
29–34	659	18.9
35	191	5.5
nulliparous	335	9.6
unknown	0	0.0
Menopausal status		
premenopausal	1,392	39.9
perimenopausal	632	18.1
postmenopausal	631	18.1
unknown	836	23.9
HRT usage		
yes	286	8.2
no	3,123	89.5
unknown	82	2.3
Breast biopsy		
no biopsy	3,123	89.5
biopsy (hyperplasia, atypical hyperplasia, LCIS)	21	0.6
biopsy (else)	44	1.3
biopsy (unknown result)	256	7.3
unknown if biopsy done	47	1.3
Breast density		
BI-RADS a	215	6.2
BI-RADS b	1,802	51.6
BI-RADS c	1,410	40.4
BI-RADS d	34	1.0
unknown (no screening mammography)	30	0.9
BMI		
< 19	48	1.4
19–25	1,165	33.4
> 25	1,336	38.3
unknown	942	27.0

BI-RADS = breast imaging-reporting and data system[22]; BMI = body mass index; HRT = hormone replacement therapy in menopause; LCIS = lobular carcinoma in situ

TABLE 4. 10-year and lifetime breast cancer risk frequencies in the study group (risk calculated with the Slovenian International Breast Cancer Intervention Study (S-IBIS) evaluation tool, breast density information included) (N = 3,491)

Risk category	Frequency (N)	Per cent (%)
10-year breast cancer risk		
low	1,186	34.0
population	2,172	62.2
moderately increased	119	3.4
high	14	0.4
Lifetime breast cancer risk		
population	3,413	97.8
moderately increased	77	2.2
high	1	0.03

screening strategy would be performed in 20-year screening period (aged 50 to 69 years).

Considering the PROCAS protocol for 10-year BC risk, the number of screening mammographies in the risk-based screening would drop by 38.6% (|21,418–34,910|/34,910) in the 20 years compared to the current screening. It considers enhancing the screening intervals among above-average BC-risk women, but also less frequent screening intervals in the below-average risk group. An increase of 100.0% (|280–140|/140) in the number of mammographies would be observed in the high risk group and a decrease of 40.6% (|19,948–33,580|/33,580) in the low and population risk groups. In fact, even in case of risk stratification using S-IBIS with no breast density information less mammographies would be performed considering PROCAS protocols for 10-year BC risk, namely 30.5% (|24,254–34,910|/34,910) less.

Discussion

This cross-sectional population-based study enrolled 11,898 women at the age of 50 who had no previous BC diagnosis and were invited to the Slovenian BC screening programme in 2021. The first 3,491 questionnaires (out of 6,785 returned) were analysed. For each woman, risk factors data was collected and BC risk was calculated using the S-IBIS calculator. Women were classified into BC risk groups (low, population, moderately increased and high) according to Slovenian specific population-based cut-offs for distribution into risk groups (Table 2).[25]

To sum up the study objectives, (i) study uptake was satisfactory: 57% of women invited to the study returned BC risk questionnaires, proving the feasibility of BC risk assessment along with the screening participation; (ii) after individual risk calculation with breast density information included, 34.0% of responders were assessed with low, 62.2% with population, 3.4% with moderately increased and 0.4% with high 10-year BC risk and 97.8%, 2.2% and 0.03% with population, moderately increased and high lifetime risk, respectively; and finally, (iii) the number of screening mammographies would decrease for more than one third in case of PROCAS study risk-based screening protocol, as it was described in the previous and current European studies.[27,28]

Study uptake

In our study, we experienced a satisfactory uptake (57%). Our results confirm the feasibility of determining BC risk at the entry in the Slovenian BC screening programme and this result is in accordance with literature reports. The 1971 birth cohort of women eligible for screening was reached and women were offered preventive mammography screening and voluntary study participation. Therefore, no additional interventions were anticipated. The invitation to the study was part of a regular screening programme. Furthermore, the women recognized as high risk for BC will be offered genetic counselling, where BC risk factors will be reverified following the clinical pathway and BC risk will be recalculated by using verified data and genetic data where applicable.[21] As reported in the PROCAS study, the majority of women (95%) indicated they wished to receive risk information.[29] Also, the DECIDO study showed a positive attitude and a high understanding of risk-based screening.[30]

Risk stratification and comparison with other studies

According to our results, 3.4% of Slovenian women invited for mammographic screening at the age of 50 and consented to participate in our study belong to the moderately increased 10-year BC risk group and 0.4% to the high risk group and would have to be screened more often according to our guidelines. So far, these data were unavailable, since no population-based cross-sectional study has been performed to assess the BC risk in Slovenian women. Some regional and hospital/breast cen-

TABLE 5. Number of screening mammographies among 3,491 women through their whole screening period (aged 50–69 years) in case of different screening scenarios

Risk category	Lifetime breast cancer risk		10-year breast cancer risk	
	Age-based screening (current screening)[17]	Slovenian risk-based screening[18]	Age-based screening (current screening) [17]	PROCAS risk-based screening[27]
Low risk	–	–	11,860	4,744
Population risk	34,130	34,130	21,720	15,204
Moderately increased risk	770	1,540	1,190	1,190
High risk	10	20	140	280
Total	34,910	35,690	34,910	21,418

PROCAS = Predicting Risk of Breast Cancer at Screening

tres-based research have been conducted to assess women's BC risk.[19,25,31,32] Due to different subpopulations assessed and low sample volumes, the results of these studies cannot be directly compared to our study. They were all conducted among women referred to breast centres, where women with a positive family history or previous biopsies are normally assessed. Therefore, we may predict their BC risk could be higher when compared to the general population.

In 2016, a prospective cohort study among 100 asymptomatic women (aged 20–49) from one regional breast centre was conducted, testing the S-IBIS calculator (version 8) for lifetime BC risk. 18% of women were identified as moderately increased risk and none at high risk (above 30% risk). 86% of women referred for another mammography in 12 months would not need annual screening mammography. This study proved the S-IBIS is effective in decreasing the number of referrals for annual mammography.[31] In 2018, a study recruiting women from regional breast units proved that 148 (75.1%) out of 197 interviewed and examined women were assigned to the population risk category, 49 (24.9%) to the moderately increased risk category and none to the high or low risk categories.[25] For that study, the S-IBIS tool (version 8) was used and tested.[18] Another Slovenian study from 2020 was assessing the proportion of women with above average 10-year risk of BC (more than 2%) using the S-IBIS calculator version 8 (breast density not considered). All assessed women in the study were already at higher BC risk at the baseline. They were either healthy with some breast symptoms or already diagnosed with BC (for the latter, the data prior to BC diagnosis was considered); 48.7% and 39.2% of women were recognised with above average BC risk, respectively. The study concluded, that inclusion of additional risk factors into the S-IBIS is needed to reliably stratify women into the BC risk groups.[32]

As shown above, the advantage of BC risk assessment is the use of S-IBIS, a BC risk calculator in the Slovenian breast centres, which could reduce the number of unnecessary preventive mammographies for the majority of women assessed with the population risk, giving room for symptomatic women and women at moderately increased and high risk. This was proved reasonable in all aforementioned Slovenian risk studies.[25,31,32]

Furthermore, risk-based screening is already ongoing in several countries across the world, but at the moment only in study settings. The English cohort study PROCAS conducted in the UK in the period from 2009 to 2020 and recruiting 63,000 women in two large studies (aged 50–70), concluded that the Tyrer–Cuzick risk prediction model (version 6) accurately predicts BC risk.[27] However, some further improvements are still required. The study showed that 11% of women in the general population have moderately increased BC risk and 85% of women have average population risk or very low risk. It also indicated that adding breast density and genetic information improved risk precision and can be used to tailor screening. Using a combination of both predicts that 70% of the population with average or below-average risks have very low rates of advanced BC. Moreover, 3-yearly screening interval appeared effective in 70% of the population in the UK. Additionally, giving women their risk information and management feedback increased their next screening participation, and even more, it encouraged them to improve their lifestyles.[27,33] In numbers, 24% of participating women were found at low 10-year risk, 61% at average (population) risk, 11% at moderate and

4% at high with breast density information added to the Tyrer-Cuzick model (version 6).[27,33] Similar proportions were found in our study − 34%, 62%, 3%, and less than 1%, respectively. The difference, however, may be due to the age gap – only 50-year-olds in our study vs. women aged 50–70 in the PROCAS study. Furthermore, if we transpose the risk groups' distribution from our study to the PROCAS potential risk-based protocol (Table 2 and Table 5), the number of screening mammographies will decrease by more than one-third (38.6%) in 20 years of screening compared to current screening programme workload. The main reason is the longer screening interval for the majority of women with population BC risk.

At the moment, two big randomized controlled trials (RCT) are trying to answer whether personalized screening is non-inferior to the standard age-based screening protocols. WISDOM is a multicentre RCT ongoing in the USA, comparing risk-based screening to annual screening in women aged 40–74 years and determining whether risk-based screening is as safe as annual mammographic screening, which is the screening policy in that country.[34] Similarly, an European RCT ongoing in 6 countries is called MyPeBS (My Personalized Breast Screening).[28,35] Study MyPeBS is an international randomized, multicentric study assessing the effectiveness of a risk-based BC screening strategy compared to a standard screening in detecting stage 2 or higher breast cancers. It will recruit 85,000 women from Belgium, France, Israel, Italy, the United Kingdom and Spain. Each participating country has different current national guidelines − biennial or triennial mammography screening beginning from the age of 40 to 50 years and ending from 69 to 74 years.[28,35] Both RCTs are integrating polygenic risk scores (with 313 single-nucleotide polymorphisms) in the risk calculations, for which BCSC and Tyrer-Cuzick calculators are used.[34,35] Risk score 313 provides the highest level of BC risk stratification in the population, followed by mammographic breast density and other risk factors.[6] Those RCTs are aimed at investigating whether the personalised approach is at least equally or more appropriate than the standard one.[35]

Our results also show that the vast majority of women (96.2%) have low (34.0%) or population (62.2) 10-year BC risk and are thus appropriately screened every 2 years, according to Slovenian and NICE guidelines.[18,36] However, 3.8% of women at the age of 50 would need more intensive BC surveillance.

Data accuracy

Regarding the reliability of the data collected, risk feedback in PROCAS (in person or by telephone) showed that women's information on their risk factors stated in the questionnaires was not always accurate, and in some cases, women changed risk groups after consultation. The greatest proportion of changes in risk occurred in those originally assessed as having a 10-year TC risk of ≥ 8%.[27] With this in mind, the proportion of the low and population risk groups in our study may be overestimated (listed in study limitations), since the self-administrated questionnaire was quite long and demanding for an average user. Besides, it may have deterred some women from participating and entering the complete information about risk factors. Some women may have not enquired about the cancer history of their family members, especially distant relatives. However, we expect, that positive cancer diagnoses are well-known in families and that women with the highest risk were not missed.[37] Overall, risk scores should be calculated with verified data on risk factors, where more effort to obtain accurate data should be considered. The risk feedback to women (and consultation, if possible) is an example of how to improve the data accuracy for risk identification, as it is planned for our identified high risk women.

The analysed study women are representative group of the Slovenian population. In Slovenia, 10% of women at the age of 50 are nulliparous (in our study 9.6%) and 50% of women at the age of 45 to 54 are overweight or obese (body mass index higher than 25) − in our study 38.3%.[4,38] Noteworthy, 27% of study participants did not provide the data on body weight or height.

Breast density

In addition to the data collection, mammographic density is a strong independent risk factor for BC and it is not a part of standard screening mammography results.[39] For almost all women participating in our study, breast density was estimated and the majority were assessed with breast density BI-RADS b (51.6%) and BI-RADS c (40.4%). These results are in accordance with the literature reports.[40,41] However, it is known that the BI-RADS assessment method is subjective and depends on the reader, reading volume and image quality.[42] In the PROCAS study, the percentage of women in each risk category changed when density was added to the Tyrer-Cuzick risk model. Adding density

moved many women from average (population) to higher or lower risk of developing BC.[27,33,43] On the contrary, in our study, adding density mainly moved women from higher-risk groups to lower-risk groups (shift to the left) (Figure 1). We can assume that density contributes to the model to decrease the risk at the age of 50 (in the PROCAS study, women's age was 50–70, the majority of women were assessed for breast density as BI-RADS b (lower density)).

Potential risk-based screening strategies

With risk-based screening and following the Slovenian BC guidelines, the number of mammographies increased (by 2.2%) on account of women with above population risk. Less frequent screening in women with lower BC risk is not considered at this point.[18] It is clear that communicating the reduction in screening frequency in the general population is rather demanding even though more screening does not prove higher efficiency.[28,44] In reality, this is the biggest uncertainty in the risk-based screening, because it is very unlikely that less screening would be accepted in the target population. While recruiting participants for the MyPeBS study, 60% of women recognised as low risk, opted-out the intervention group due to prolonged screening intervals.[45] However, this ongoing RCT in Europe does predict less frequent screening intervals for women with population and low risk, i.e. 4 years.[28] Therefore, we can expect a smaller amount of annually performed screening mammographies in the national BC screening programme in case risk-based screening protocol that includes less frequent screening for lower-risk women is recommended. Nevertheless, at the time there is not enough evidence for such recommendation at the Europe level, since not many prospective RCTs are being conducted nor concluded.

For Slovenian situation as for the other countries, first, communicating clinical safety of less intensive screening can be an important obstacle, and secondly, the risk-based screening protocol should not be to complex to be feasible and to be able to follow-up the participants efficiently. To add, recalculation of 10-year BC risk should be considered after 10 years.

Study strengths

For the first time in Slovenia, a population-based sample of women was assessed for BC risk and it is the first time potential changes in the organised screening programme in case of introducing risk stratification have been estimated.

The mammographic density was assessed exclusively for our study (available for 99% of our participants), which made it possible to define BC risk more accurately and proved to be feasible to incorporate this information into screening data. Equally important, the IBIS software has recently been adjusted using Slovenian-specific population BC risks making it more valid.[19] Women's uptake to study participation (57%) was satisfactory when compared to other studies. In the same year, the screening participation rate of women aged 50 was 74.4%.[46] In the PROCAS study (first phase of recruitment similar to ours, where all women invited for BC screening were sent a participant invitation letter), screening uptake was 68% and study uptake 37%.[27]

Study limitations

The study questionnaires were self-administrated and data verification by enquiring with the women in person or using the health records was not performed. Furthermore, the family members' names were not collected so the family cancer history was not medically confirmed; some women did not remember all the family cancer diagnoses. In addition, some may wrongly interpret the topography of cancer (e. g. ovarium cancer instead of cervical cancer). Additionally, the health literacy of women is very variable, which can affect answering the questionnaire without explanations. Thus, some data we used might be unreliable, and probably we have under or overestimated the risk scores. To improve data quality, assistance with filling out the risk questionnaires is needed. From clinical work it is known, that majority of people cannot finish the risk tool/questionnaire without assistance. In practice for risk-based population-wide screening this means, that trained radiographers or administrative personnel should administer women at their first screening visit to gather adequate information. Besides, legal framework for data verification through other databases (like cancer registry and registry of genetically tested individuals) should be legislated.

We assume that some women did not participate in the screening programme nor in this study since they have already been regularly and thoroughly surveilled at the Institute of Oncology Ljubljana in the High risk breast clinic. After the BC risk had been assessed in the Department of Clinical Cancer Genetics, which has been operating for

more than 20 years, women with above-population BC risk were referred to the High risk breast clinic at the Institute of Oncology Ljubljana.[21] For this reason, a certain number of women with moderately increased and high risk for BC may not have been considered in our study (selection bias), thus decreasing the proportion of women in higher-risk groups.

In conclusion, assessing a personalised risk score at a woman's first screening appointment is reasonable. It can improve screening benefits for low and higher-risk groups in the target population. To plan more efficiently the BC screening and BC patients' care if the risk-based screening over the current one-size-fits-all screening strategy would be evidence-based and recommended in the future, we assessed the BC risk in a 50-year old cohort of women in Slovenia and found the majority of women belonging to the population 10-year BC risk (62.2%) and 3.4% to moderately increased BC risk group. Our evidence supports the effectiveness of the current Slovenian screening protocol for the majority of screened women. Potential future risk-based screening would change the manner of BC screening for approximately one third of Slovenian women (38% at high, moderately increased, or very low risk) with either additional screening methods at a higher frequency or with prolonged screening intervals, respectively. Risk assessment is feasible at the entry to screening. Due to the study uptake, where more than half of screened women took part, rather high risk assessment uptake among Slovenian women is expected. However, data accuracy can be improved with in-person risk assessment and risk counselling.

Still, only randomised and observational studies will answer the main question regarding personalised BC screening in the future. And this is if risk-based screening over the current one-size-fits-all strategy should be recommended.

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research article

Does tumor rupture during robot-assisted partial nephrectomy have an impact on mid-term tumor recurrences?

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Background. Intraoperative kidney tumor rupture (TR) can occur during robot-assisted partial nephrectomy (RAPN) in daily clinical practice, but there are no solid guidelines on the management and implications of it. The purpose of the study was to investigate the impact of TR on tumor recurrences, what a surgeon should do if this adverse event occurs, and how to avoid it.

Patients and methods. We retrospectively analyzed the first 100 patients who underwent RAPN at University Medical Centre Ljubljana, between 2018 and 2021. Patients were stratified into 2 groups (TR and no-TR) and were compared according to patient, tumor, pathologic, perioperative and postoperative characteristics and tumor recurrences, using the Mann-Whitney U test and chi-squared test.

Results. Of the 100 patients, 14 had TR (14%); this occurred in tumors with higher RENAL nephrometry scores (P = 0.028) and mostly with papillary renal cell carcinomas (P = 0.043). Median warm ischemia time was longer for the TR group (22 *vs.* 15 min, *P* = 0.026). In terms of studied outcomes, there were no cases of local or distant recurrence after a median observation time of 39 months (interquartile range, 31−47 months) in both groups. We observed positive surgical margins on the final oncologic report in one case in the no-TR group.

Conclusions. Tumor rupture during RAPN seems to be of no mid-term oncologic importance. According to presented results, we would recommend surgeons to proceed with tumor resection if this event occurs and abstain from conversion to radical nephrectomy or open partial nephrectomy. However, more similar cases should be studied to make more solid conclusions.

Key words: enucleation; tumor recurrence; renal cell carcinoma; robot-assisted partial nephrectomy; tumor rupture; warm ischemia time

Introduction

Partial nephrectomy (PN) is the treatment of choice for T1 renal cell carcinoma (RCC) because it provides comparable oncological safety while better preserving renal function, thus leading to a lower incidence of cardiovascular diseases.[1] Tumor enucleation is a safe procedure oncologically (perioperative, short-term, and long-term) when negative surgical margins are achieved by providing a mi-

croscopic layer of healthy kidney tissue on the surface of the tumor.[2-4]

However, decreased distance between healthy parenchyma and the tumor pseudocapsule increases the risk of slitting into the tumor (positive surgical margin) or even rupturing the tumor during excision and tumor manipulation (tumor cell spillage). There is no clear definition of TR or so-called accidental slit into the tumor with consequent spillage of tumor cells into the operative field and abdominal cavity, the frequency of which has been underestimated and the clinical impact insufficiently investigated in the literature.[5-7] One simple inattentive move with sharp instrument by surgeon or assistant could disrupt already thin layer left on the surface of the tumor. Obviously, this would happen less frequently if more of the healthy tissue is left over the tumor capsule.

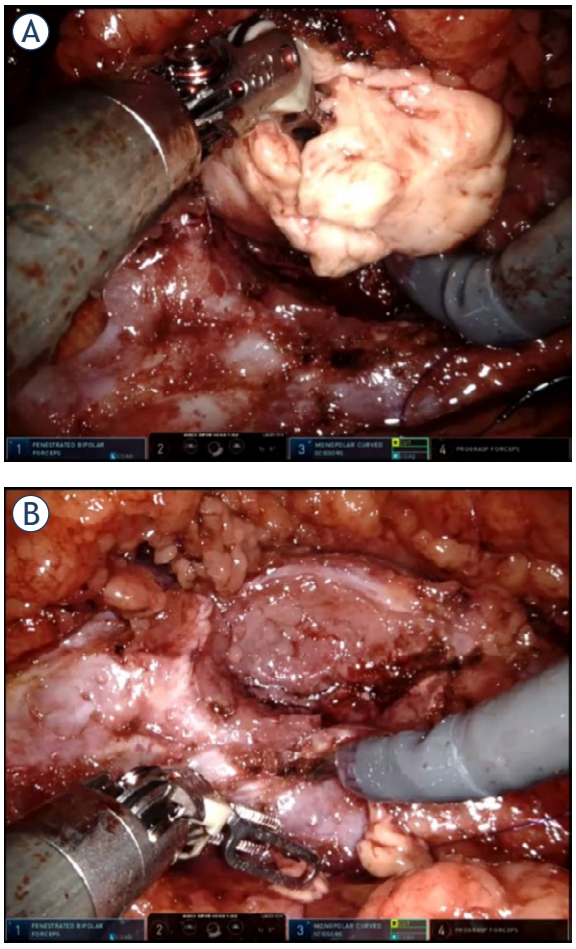

FIGURE 1. (A) Example of tumor rupture during enucleation of a renal tumor. **(B)** Tumor bed after the tumor was completely removed from healthy kidney parenchyma (intraoperative snapshots).

It has been known that a positive surgical margin in a low malignant tumor does not necessarily lead to recurrence of the disease but there is a higher chance of recurrence in tumors with higher malignant potential.[8] On the other hand, a little is known if macroscopic spillage of the tumor cells occurs.[5-7] The purpose of this study was to investigate the rate of tumor recurrences and clinical impact of tumor rupture (TR) during robot-assisted partial nephrectomy (RAPN), what a surgeon should do in the case of this undesired event and how to avoid it. The rate of tumor recurrences was measured with radiological evidence of tumor in the locoregional region and abdominal cavity.

Patients and methods

Study design and surgical technique

We conducted a retrospective study of the first 100 patients who underwent RAPN at University Medical Center (UMC) Ljubljana between June 2018 and April 2021. RAPN was performed by 2 senior surgeons, who had a previous experience in both open and laparoscopic partial nephrectomies. Our detailed technique of transabdominal RAPN has been described previously.[9] A transperitoneal approach was used in 90 procedures (90%) and a retroperitoneal approach was used in 10 procedures (10%). In 8% of cases, we removed two tumors during the same procedure. In these cases, a comprehensive standardized system for quantitating renal tumor size, location and depth (RENAL) score[10] and final histology were determined only for the larger tumor. We always try to perform enucleation of the tumor, aiming for maximal preservation of healthy renal parenchyma and renal function. No frozen sections were performed during RAPN.

Medical Ethics Committee of the Republic of Slovenia approved this study (registration number 0120-68/2023/3) and it was conducted in full compliance with the principles of the Declaration of Helsinki.

TR was defined as an intraoperative (macroscopic) slit into a tumor during tumor resection and/or tumor manipulation, which could lead to spillage of the tumor cells into the operative field and the abdominal cavity (Figure 1). Our definition is based on the definition by Khene *et al.* who defined accidental surgical incision into the tumor (ASIT) as "any accidental incision in the tumour or any accidental rupture of tumour surface during handling of the kidney and/or tumor".[5] We want to emphasize a clear distinction between TR (an

TABLE 1. Patient and tumor characteristics in the no tumor rupture group and the tumor rupture group

	No tumor rupture (*N* = 86)	Tumor rupture (*N* = 14)	*P* value
Patients, *n* (%)			
Male	59 (69)	9 (64)	0.8
Female	27 (31)	5 (36)	
Age (years), median (IQR)	60 (52–67)	60 (49–68)	0.9
Tumor size (mm), median (IQR)	30 (23–40)	37 (30–48)	0.2
RENAL nephrometry score, median (IQR)*	7 (5–8)	8 (6.25–9.75)	**0.028**
Laterality, *n* (%)			
Right kidney	40 (47)	6 (43)	0.8
Left kidney	46 (53)	8 (57)	
Tumor localization, *n* (%)			
Upper third	24 (28)	5(36)	0.8
Middle third	34 (39)	5 (36)	
Lower third	28 (33)	4 (28)	
Preoperative CT/MRI, *n* (%)			
Tumor	72 (84)	13 (93)	0.4
Cystic	14 (16)	1 (7)	

Bold indicates a significant value ($P < 0.05$).

*RENAL score was determined for 82 of 86 tumors, because 4 CT scans were not available for interpretation.

CT = computed tomography; IQR = interquartile range; MRI = magnetic resonance imaging

intraoperative, macroscopic event) and positive surgical margins (a histologic, postoperative, microscopic event).

Recurrence was defined as local recurrence at the enucleation site or atypical intraabdominal locations[2], observed on follow-up contrast-enhanced computed tomography (CT).

Patients were divided into 2 groups: tumor rupture (TR) and no tumor rupture (no-TR). Our null hypothesis was that the TR can occur independently of the radiologic, pathologic, or intraoperative variables, so all 100 patients were included in the study.

Postoperative follow-up regimen

The follow-up was performed by the urologists; the scheme depends on the tumor characteristics (size, histology, grade, resection margin, TNM classification, etc.) and the patient's life expectancy. All patients underwent regular cross sectional imaging – we followed recommendations for surveillance proposed by EAU guidelines.[1] For the purpose of the study, an additional contrast-enhanced CT was performed in all 14 cases of TR in May 2022. All CT reviews were performed by 2 abdominal radiologists (with more than 10 years of experience in kidney imaging), blinded to all clinical, biological and follow-up data.

Statistical analysis

The Mann-Whitney U test was used for analysis of continuous variables, presented as medians and interquartile ranges (IQRs). The chi-squared test was used to determine the relationship between categorical variables, presented as proportions. Both tests were two-sided and the significance level was set at $P < 0.05$.

Results

Patient and tumor characteristics

The characteristics of the patients who underwent RAPN at UMC Ljubljana between June 2018 and April 2021 are shown in Table 1. The median duration of follow-up was 39 months (IQR, 31–47 months). TR occurred in 14 cases. In the TR group, tumors tended to be larger (37 mm *vs*. 30 mm) and

TABLE 2. Pathologic characteristics and oncologic outcome in the no tumor rupture group and the tumor rupture group

	No tumor rupture (*N* = 86), *n* (%)	Tumor rupture (*N* = 14), *n* (%)	*P* value
Histology			**0.043**
Benign	8 (9)	1 (7)	
Oncocytoma	7 (8)	1 (7)	
Clear cell RCC	**44 (51)**	2 (14)	
Papillary RCC	15 (17)	**8 (57)**	
Chromophobe RCC	5 (6)	1 (7)	
Clear cell papillary RCC	4 (5)	0 (0)	
Other types of RCC	3 (3)	1 (7)	
WHO/ISUP grade (RCC)			0.6
1	21 (35)	2 (25)	
2	35 (58)	6 (75)	
3	4 (7)	0 (0)	
Pathologic stage			0.4
1a	58 (82)	9 (75)	
1b	9 (13)	2 (17)	
2a	1 (1)	1 (8)	
3	3 (4)	0 (0)	
Positive surgical margins	1 (1)	0 (0)	0.7
Local or distant recurrence	0 (0)	0 (0)	

Bold indicates a significant value ($P < 0.05$).

ISUP = International Society of Urologic Pathologists; RCC = renal cell carcinoma; WHO = World Health Organization

had a higher RENAL score (8 *vs.* 7); only the latter reached statistical significance ($P = 0.028$). Both groups were comparable in terms of sex ($P = 0.8$), median age at surgery ($P = 0.9$), tumor laterality ($P = 0.8$), and localization ($P = 0.8$).

Pathological characteristics and oncologic outcomes

Pathologic characteristics and oncologic outcomes are summarized in Table 2. RCC was identified in 83 patients, oncocytoma in 8, and benign tumors in the remaining 9 cases. The most frequent histologic type was clear cell RCC (ccRCC) (46%), followed by papillary RCC (pRCC) (23%). ccRCC was significantly more frequent in the no-TR group (51% *vs.* 14%), whereas pRCC was the most common type in the TR group (57% *vs.* 17%, $P = 0.043$). Type I pRCC was more frequent than type II pRCC in both groups (7 of 8 [88%] in the TR group *vs.* 13 of 15 [87%] in the no-TR group). There was no statistically significant difference between the groups regarding tumor grade ($P = 0.6$), pathologic stage ($P = 0.4$), and positive surgical margins ($P = 0.7$). Most of the tumors were pT1a (82% in the no-TR group *vs.* 75% in the TR group). No cases of tumor recurrences were observed.

Perioperative and postoperative outcomes

Perioperative and postoperative outcomes are summarized in Table 3. The median duration of the surgical procedure (147 min *vs.* 140 min, $P = 0.4$) and the median hospital stay after the operation (3 days *vs.* 3 days, $P = 0.8$) were not significantly different in the TR and no-TR groups. Median WIT was significantly longer in the TR group (22 *vs.* 15 min, $P = 0.026$). Median estimated blood loss was higher in the TR group (50 *vs.* 20 mL), but the result did not reach statistical significance ($P = 0.13$).

Nine percent of procedures in the no-TR group and none in TR group were performed with the no clamping method. We performed two conversions to radical nephrectomy; once due to an ipsilateral incidentaloma not seen on preoperative CT imag-

TABLE 3. Perioperative and postoperative outcomes in the no tumor rupture group and the tumor rupture group

	No tumor rupture (*N* = 86)	Tumor rupture (*N* = 14)	*P* value
Operative time (min), median (IQR)	140 (115–171)	147 (135–168)	0.4
WIT (min), median (IQR)	15 (12–19)	22 (15–25)	**0.026**
No clamping, *n* (%)	8 (9)	0 (0)	
Length of stay after surgery (days), median (IQR)	3 (2–3)	3 (2–3)	0.8
Creatinine (μmol/L), median (IQR)			
Preoperative	80 (73–94)	80 (77–87)	0.9
2 days after RAPN	80 (70–98)	80 (75–89)	0.6
Variation	1 (−7 to 7)	1 (−7 to 8)	0.7
Intraoperative EBL (mL), median (IQR)	20 (0–50)	50 (20–100)	0.13
Hemoglobin (g/L), median (IQR)			
Preoperative	148 (140–155)	148 (144–152)	0.7
2 days after RAPN	125 (119–133)	125 (122–129)	0.8
Variation	22 (14–27)	25 (20–27)	0.6
Transfusions, *n* (%)	3 (3)	0	
Major complications (Clavien-Dindo ≥ 3), *n* (%)	2 (2)	0	
Conversions to radical nephrectomy, *n* (%)	2 (2)	0 (0)	

Bold indicates a significant value (P < 0.05).

EBL = estimated blood loss; IQR = interquartile range; RAPN = robot-assisted partial nephrectomy; WIT = warm ischemia time

ing and once due to the size of the tumor, which had increased significantly since the preoperative CT. There were no conversions to open surgery.

The median creatinine level preoperatively and postoperatively and the change in creatinine were comparable between the 2 groups; it stayed near the preoperative level. Similarly, the median hemoglobin level preoperatively, postoperatively, and the median decrease in hemoglobin did not significantly differ between the groups; the median decrease was 22 g/L in the no-TR group and 25 g/L in the TR group ($P = 0.6$).

Three patients in the no-TR group needed blood transfusions after the procedure. We observed 2 major complications (defined as Clavien-Dindo classification score 3 or more[11]); one required exploration due to bleeding from the vessel at the umbilical port position and the other required superselective embolization due to active bleeding from a small renal artery branch in the tumor bed.

Discussion

To the best of our knowledge, there have been only a few papers investigating the effect of tumor rupture or cyst rupture during robotic PN.[5-7] On the other hand, a positive surgical margin is much more widely researched and discussed. It seems that a positive surgical margin in cases of RCC (especially of low grade and size) is not associated with an increased risk of recurrence or decreased survival rates as opposed to transitional cell carcinomas or adrenocortical carcinomas.[12-15] In the context of surgical margin assessment, it is debatable if only TR of the bottom border of the tumor is relevant as rupture can occur far from healthy parenchyma interface. In that case, a surgeon could make a complimentary resection of the tumor bed, so minority of TRs result in a positive surgical margin. In addition, TR can occur when a surgeon or an assistant makes a macroscopic slit into the tumor or a tumor breaks because of manipulation during excision.

In our study, we observed 14 cases of intraoperative TR (14%), which is a high number, especially for something not usually reported in the literature. After a median of 39 months (IQR, 31–47 months), we recorded no cases of tumor recurrence. Interestingly, Khene *et al.* showed the same percentage of accidental surgical incision into the tumor (ASIT) as we did and concluded it as "com-

mon event that did not appear to compromise oncological outcome".[5] They observed 9% of recurrences in the ASIT group and 6% in the control group after median follow-up 36 months, while nearly 43% of their cases were high risk tumors (pT2–3A and/or Fuhrman Grade III–IV)[5] as opposite to ours. Takagi *et al.* also showed high tumor grade along with pathological tumor upstaging from cT1 to pT3 to be risk factors for worse recurrence-free survival.[16] In addition, Grossmann *et al.* presented a case report of peritoneal carcinomatosis of the cystic papillary renal cell carcinoma following intraoperative cyst rupture during partial nephrectomy.[17] Apart from early recurrence, there is also a possibility of late recurrence (recurrence after 5 years) which occurs in around 3.5%; main predictive factors for it are higher pathological stage (≥ pT2) and age at surgery.[18,19]

Among 14 cases of TR in our study, 86% were carcinomas, 7% were oncocytomas, and 7% were benign tumors, all of them were included because we did not want to solely investigate recurrences. One multicenter cohort study reported an 18.7% rate of intraoperative cystic renal masses rupture *via* an open or robot-assisted approach, which had no influence on tumor recurrences, including no cases of local or distal recurrences.[6] Another group identified risk factors for cystic RCC rupture to be higher E (exophytic/endophytic) and N (nearness to collecting system or sinus) RENAL nephrometry scores, higher Bosniak category (specifically III), and surgeon's experience.[7] Even though recurrence-free survival and cancer-free survival were worse if cystic RCC rupture occurred, it did not seem to influence overall survival.[7]

The only study that indeed investigated the impact of tumor rupture (in their paper called "effraction") during RAPN showed the main determinants of accidental slit into the tumor to be size of the tumor and experience of the surgeon.[5] According to our results, a high RENAL nephrometry score seems to be related to TR (P = 0.028). In a TR group, tumors tended to be larger (37 mm *vs.* 30 mm), but the result did not reach statistical significance (P = 0.2). With regard to surgeon experience, we observed a decrease in the number of TRs over time. In the first 20 cases, there were 5 (25%) TRs, but the percentage decreased to 11% in the following 80 procedures. However, this result did not reach statistical significance (P = 0.11). We suggest 3 reasons that could explain this: (1) with more experience, we started operating more difficult cases; (2) TRs also occur as a consequence of tumor manipulation by an assistant and are not solely dependent on the mistakes/experience of a surgeon; (3) due to a low number of cases, the results did not show the statistical significance. Tumor enucleation is more technically demanding, therefore it could be a risk factor for TR. It is an oncologically safe surgical technique whereby the surgeon leaves a microscopic layer of healthy kidney tissue on the surface of the tumor.[1,2,4] Generally, results regarding recurrences at the enucleation site differ in the literature (ranging from 0% to 8%, depending on the size of the tumor, pT stage, RENAL nephrometry score, follow-up duration). Benign tumors and lower pT stage RCCs did not recur after the follow-ups, whereas RCCs with higher pT stage did.[20–22] For example, in sporadic follow-up of RCCs of at least 4 years, there were no recurrences at the enucleation site.[2] According to Minervini *et al.* positive surgical margins, recurrence in the ipsilateral kidney (either at the enucleation site or elsewhere), and systemic recurrence were all found in 2.4% of cases, and < 1% of patients died due to metastatic RCC after the median follow-up of 61 months.[2] Similarly, Hu *et al.* observed positive surgical margins in 3.5% of cases and less than 1% of recurrences after a median follow-up of 2.7 years.[23] We performed tumor enucleation in most cases and observed a positive surgical margin in 1 case, which is comparable with the results in the literature.[2,23]

We wanted to determine the influence of tumor type on the occurrence of tumor rupture. In our series, final pathology reports showed that most ruptured tumors were papillary RCCs, which is not surprising. Fragility is a typical feature of pRCC type I; this can be explained by its histology because its narrow papillae contain only microcapillaries without any binding and a tough pseudocapsule (specimens are described as a "minced meat" structure).[1] Some studies show the peritumoral pseudocapsule to be less developed (thinner, incomplete, or absent) in pRCCs compared with ccRCCs.[24,25] In addition, Hora *et al.* described 3 cases of spontaneous rupture of pRCCs or after minimal trauma due to extensive necrosis.[26] Moreover, pRCCs have been shown to have a substantial risk of renal tumor biopsy tract seeding (12.5%), indicating its malignant potential.[27] However, we did not observe tumor recurrence in any of the cases in the TR group.

We also wanted to determine the impact of tumor rupture on the possibility of complications during and after surgery. Pradere *et al.* showed that intraoperative cyst rupture during PN led to more postoperative complications[6],which were not observed

in our study. Our results showed that duration of the surgical procedure, duration of hospital stay, creatinine and hemoglobin levels (preoperatively and postoperatively) did not significantly differ between the TR and no-TR groups. Even though the estimated blood loss was higher in the TR group (50 *vs.* 20 mL, $P = 0.13$), the decrease in hemoglobin was not significantly different between the groups (25 *vs.* 22 g/L, $P = 0.6$). We observed 2 major complications (defined as Clavien-Dindo classification score 3 or more), but only in the no-TR group. On the other hand, WIT was significantly longer in the TR group, which could be explained in 3 ways: (1) tumor rupture with spillage of tumor tissue impairs visibility, resulting in more difficult tumor manipulation and further resection; (2) the surgeon decides to perform complementary resection of the tumor bed; (3) psychological stress experienced by the surgeon and decision making on how to proceed with the surgery. Interestingly, there was no case of tumor rupture within the no clamping group, which shows that bleeding during tumor resection alone with impaired visibility is not a sufficient reason for TR.

According to all these findings, we suggest that the surgeon should be careful to avoid TR when performing enucleation of kidney tumors. If pRCC is expected, we suggest enucleoresection instead of enucleation. The surgeon should always warn the assistant to be equally careful with any tumor manipulation (e.g., suction), especially if the tumor seems fragile. It is important that the surgeon stays focused and calm if TR occurs. Clear communication in the team is essential. The surgeon should assess the ability to control bleeding and extent of the spillage of the tumor cells, followed by the decision whether to convert to radical nephrectomy or even to open procedure for better visualization and control. If the surgeon decides to continue robot-assisted approach, sufficient irrigation of the surgical field and consequent suction are needed in order to remove spilled tumor cells. Moreover, a change in strategy (reduction of pneumoperitoneum pressure or switching to global ischemia) should also be considered. It is advisable to require the assistance of more experienced colleagues. After the procedure, patient documentation should be presented at the multidisciplinary team meetings in order to discuss potential adjuvant therapy or follow-up procedures and imaging. We believe that usage of three-dimensional models could make enucleations easier and decrease rates of surgical injury to the tumor.[28]

There are a few limitations of our study. First, the median follow-up of 39 months is relatively short to observe local recurrences, even though in the study by Khene *et al.* they observed recurrences after nearly equal follow-up.[5] Moreover, in the study by Takagi *et al.* median time from PN to recurrence was 19 months.[16] Second, the definition of TR is questionable because there is no clear pathologic-surgical agreement on what TR is, therefore we used the one available in the literature.[5] Third, due to the retrospective single-center design of the study, there is a possibility of biased interpretation of the results.

Conclusions

TR is a possible complication during RAPN, especially if tumor enucleation is performed on pRCCs with a higher RENAL nephrometry score, leading to prolonged WIT. We suggest proceeding with the resection of the tumor with a deeper resection plane and only eventually converting to radical nephrectomy or open PN, because it seems that TR has no mid-term risk of tumor recurrence or higher complication rate. The rate of long term effects of TR on tumor recurrences are still unknown.

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research article

Billroth-I anastomosis in distal subtotal gastrectomy for non-early gastric adenocarcinoma

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Background. Billroth-I (B-I) anastomosis is known as a simple and physiological reconstruction method after distal subtotal gastrectomy for early gastric cancer. Yet its role and oncological validity in non-early gastric adenocarcinoma (NEGA) remain unclear.

Patients and methods. Patients with NEGA without distant metastases operated between May 2004 and December 2020 were included. Surgical and oncologic outcomes of distal subtotal gastrectomy were studied in patients with B-I and Billroth II (B-II) anastomoses. Propensity score matching (PSM) was used to adjust for age, gender, tumor size, location, resection type, pT and pN stages.

Results. A total number of 332 patients underwent distal subtotal gastrectomy for NEGA followed by B-I and B-II anastomoses in 165 (49.7%) and 167 (50.3%) cases, respectively. B-I was applied in patients with smaller tumor size, less advanced pT stage and tumor location in the gastric antrum. The former was also associated with lower proportion of multiorgan resections and shorter operative time. After PSM, these differences became statistically non-significant, except operative time. Postoperative outcomes were similar before and after PSM. Greater lymph node yield was observed in patients with B-I anastomosis. The incidence of recurrence, specifically local recurrence was lower in patients with B-I anastomosis. However, this association was not statistically significant in the multivariable model. Median overall survival was 38 months, without significant differences between the groups.

Conclusions. The use of B-I anastomosis after distal subtotal gastrectomy for NEGA is associated with satisfactory surgical and oncologic outcomes. B-I anastomosis should be considered as a valid reconstruction method in these patients.

Key words: gastrectomy; anastomosis; Billroth-I; Billroth-II; adenocarcinoma

Introduction

The incidence of distal gastric cancer has fallen in the Western countries over the last decade.[1] However, it still prevails in Asia and other parts of the world.[2] Stomach body and pyloric antrum are the most common sites for gastric cancer among the Armenian population.

Distal subtotal gastrectomy with adequate lymphadenectomy is the cornerstone in the treatment of resectable distal gastric cancer. After resection, the continuity of gastrointestinal tract can be restored through different reconstruction methods, such as Billroth I (B-I), Billroth II (B-II) and Roux-en-Y. The two latter are based on a closure of the duodenal stump and formation of gastro-jejunal anastomosis, while B-I is performed by creating gastro-duodenal anastomosis. Thus, the main advantages of B-I over B-II and Roux-en-Y are its technical simplicity and retaining the physiological route for food passage. Several comparative studies between the above-mentioned techniques have been published to date.[3-5] In general, these focus on short-term results and/or long-term functional outcomes by examining heterogenous patient cohorts including those with early gastric cancer. While B-I is widely used in surgery for early gastric cancer, its long-term oncologic results in non-early distal gastric adenocarcinoma (NEGA) remain unclear. Furthermore, some concerns have been raised in the literature regarding its oncological safety.[6]

Current study aimed to examine the oncologic safety of performing B-I anastomosis following distal subtotal gastrectomy for NEGA.

Patients and methods

Patients underwent distal subtotal gastrectomy for gastric adenocarcinoma at Kanaker-Zeytun Medical Center and ArtMed Medical Rehabilitation Center (both in Yerevan, Armenia) between May 2004 and December 2020.

Neoadjuvant chemotherapy was utilized in a negligible number of cases (2.1%). Tumor ingrowth into adjacent major vessels (the celiac axis, the common hepatic artery, the superior mesenteric artery/vein, portal vein) was considered as a contraindication for gastrectomy. All procedures were performed by one surgeon (AMS) via laparotomy. D2 was the standard extent for lymphadenectomy in all patients with NEGA. B-I and B-II anastomoses were used for restoring the continuity of gastrointestinal tract after resection. The choice of reconstruction method was left at surgeon's discretion. The prerequisite for performing B-I was ensuring no tension between the gastric and duodenal stumps. In some cases, the gastric stump was mobilized up until the short gastric vessels to avoid tension. Although the Kocher manoeuvre was not performed routinely, the proximal section of the duodenum was mobilized sufficiently (and cut 1cm distal from the pylorus) to insure negative resection margin. If tumor extended to the upper part of the stomach or was located very close to the pylorus, B-II reconstruction was considered. The latter was performed end-to-side, approximately 40 cm distal to the ligament of Treitz via the anterocolic pathway. B-II was accompanied with Braun anastomosis created 25 cm distal to the gastrojejunostomy.

Patient follow-up included instrumental examinations and evaluation of serum tumor markers 3 and 6 months postoperatively and then every 6 months within the first 5 years after surgery. Chest and abdominal computed tomography were performed 1 year after surgery and then repeated annually.

Study design

Outcomes of distal subtotal gastrectomy for NEGA were compared between the patients who had received B-I anastomosis and those who had received B-II anastomosis. The primary endpoints of this study were long-term oncologic outcomes, namely, recurrence and survival. Secondary endpoints intra- and postoperative outcomes.

Patient demographics, clinical presentation and perioperative parameters were prospectively registered in the database throughout the study period. The long-term oncologic data were obtained from outpatient hospital visits and telephone interviews. Propensity score matching (PSM) was applied to minimize selection bias. Propensity scores were based on age, gender, tumor location, tumor size, type of resection, tumor stage and nodal stage as we believe most of these factors may influence the choice of anastomosis technique. Patients with either of these variables missing were excluded from the matching procedure.

The study protocol was considered by the accredited Institutional Review Board for Medical Ethics. The requirement for approval was waived by the ethics committee due to the retrospective nature of this study.

All patients who had undergone distal subtotal gastrectomy for NEGA within the study period met the inclusion criteria for this study. NEGA was defined as stage IB-IIIC gastric adenocarcinoma confirmed on final pathology. Patients with NEGA who had undergone surgical procedures other than distal subtotal gastrectomy, were excluded from the analysis. So were those with distant metastases or with gastric tumors other than adenocarcinoma.

TABLE 1. Perioperative data in patients with non-early gastric adenocarcinoma undergoing distal subtotal gastrectomy

Variable	Unmatched			Propensity score matched		
	B-I (n = 165)	B-II (n = 167)	p-value	B-I (n = 97)	B-II (n = 97)	p-value
Age, years, mean (SD)	60.8 (11.7)	62.6 (10.9)	0.16	60.9 (10.9)	63.2 (11.6)	0.46
Gender (female), n (%)	74 (44.8%)	59 (35.3%)	0.08	42 (43.3%)	43 (44.3%)	0.26
BMI, kg/m^2, mean (SD)	26.0 (6.5)	25.5 (5.1)	0.55	26.3 (5.9)	25.4 (5.5)	0.31
Comorbidity, n (%)	129 (78.2%)	109 (65.3%)	0.01	76 (78.3%)	63 (64.9%)	0.04
Cardiovascular disease, n (%)	88 (53.3%)	75 (44.9%)	0.13	50 (51.5%)	46 (47.4%)	0.58
Diabetes mellitus, n (%)	18 (10.9%)	16 (9.6%)	0.69	14 (14.4%)	7 (7.2%)	0.13
Number of comorbidities, mean (SD)	2.3 (1.1)	3.1 (0.9)	0.001	2.3 (1.1)	3.0 (0.8)	0.001
ASA score (III-IV), n (%)	145 (87.9%)	145 (86.8%)	0.77	87 (89.7%)	88 (90.7%)	0.81
Hemoglobin, g/dL, mean (SD)	124 (27)	119 (29)	0.09	122 (28)	119 (29)	0.42
Total protein, g/dL, mean (SD)	72 (8.4)	72 (5.9)	0.53	70.5 (9.8)	72.1 (5.8)	0.15
CEA, ng/mL, median (range) [IQR]*	1 (0.5-627.2) [1-2]	1.5 (0.5-188) [1-3]	0.02	1 (0.5-174) [1-2]	1 (0.5-100) [1-2]	0.81
Ca 19-9, U/mL, median (range) [IQR]*	8 (1-1549) [3-21]	9 (1-999) [3-29]	0.62	8.3 (1-1549) [4-25]	9 (1-999) [3-30]	0.7
Location in antrum, n (%)	160 (97%)	133 (79.6%)	0.001	93 (95.9%)	94 (96.9%)	0.65
Extended gastrectomy, n (%)	3 (1.8%)	25 (15%)	0.001	3 (3.1%)	4 (4.1%)	0.65
Operative time, min, mean (SD)	144 (28)	168 (29)	0.001	143 (27)	165 (28)	0.001
Red blood cell transfusion, n (%)	17 (10.3%)	13 (7.8%)	0.42	12 (12.4%)	7 (7.2%)	0.23
Severe complications, n (%)	8 (4.8%)	13 (7.8%)	0.27	5 (5.2%)	7 (7.2%)	0.53
Anastomotic leakage, n (%)	4 (2.4%)	5 (3%)	1.0	1 (1%)	2 (2.1%)	0.56
Relaparotomy, n (%)	7 (4.2%)	11 (6.6%)	0.35	4 (4.1%)	5 (5.2%)	0.71
30-day mortality, n (%)	1 (0.6%)	2 (1.2%)	1.0	1 (1%)	2 (2.1%)	0.56
90-day mortality, n (%)	1 (0.6%)	4 (2.4%)	0.37	1 (1%)	4 (4.1%)	0.36
Postoperative days, median (range)	11 (6-48) [9-13]	11 (5-72) [9-13]	0.51	10 (6-48) [9-13]	11 (5-72) [9-14]	0.47

ASA = American Society of Anesthesiologists; B-I = Billroth I; B-II = Billroth II; BMI = body mass index; CA 19-9 = carbohydrate antigen 19-9; CEA = *carcinoembryonic antigen*; IQR = *interquartile range; SD = standard deviation;* * = data missing in 36 patients

Definitions

Extended gastrectomy was defined as en-bloc resection of adjacent organs and structures due to clinically verified tumor invasion (cT4b stage gastric cancer) as described elsewhere.[7] Morbidity was defined according to Clavien and Dindo.[8] Grade ≥ IIIa complications were considered severe.

The 8th edition of American Joint Committee on Cancer (AJCC) staging manual for gastric cancer was used for TNM classification and disease staging.[9] Tumor size was determined by its morphometric measurement at the pathology work-up. R0 was defined as no microscopic residual cancer at the resection margins.

Tumor recurrence was diagnosed based on radiological evidence of intra-/extra-abdominal soft tissue and/or signs of peritoneal carcinomatosis. Three types of tumor recurrence were reported in this study – local recurrence, distant metastases and peritoneal carcinomatosis. Overall survival was defined as the time between the date of surgery until the date of death from any cause or the date of censoring. Data were censored at the last follow-up.

Statistics

Data were analysed using R version 4.2.2. Continuous variables are presented as mean (± standard deviation) and median (range) for normally and non-normally distributed data, respectively. The two-sample T-test was used to compare normally distributed data, while the Mann-Whitney *U* test was used for non-normally distributed data. Categorical data are presented as frequencies (percentages). The Chi-square test or Fisher's exact test, when applicable, were applied

TABLE 2. Pathology findings in patients with non-early gastric adenocarcinoma undergoing distal subtotal gastrectomy

Variable	Unmatched			Propensity score matched		
	B-I (n = 165)	B-II (n = 167)	p-value	B-I (n = 97)	B-II (n = 97)	p-value
Tumor size, cm, mean (SD)	4.5 (1.7)	6.2 (2.4)	0.001	5.1 (1.5)	5.2 (1.5)	0.52
pT stage, n (%)			0.046			0.28
T1–T2	69 (41.8%)	49 (29.3%)		32 (33%)	31 (32%)	
T3	70 (42.4%)	85 (50.9%)		44 (45.4%)	53 (54.6%)	
T4a/T4b	26 (15.8%)	33 (19.8%)		21 (21.6%)	13 (13.4%)	
pN stage, n (%)			0.089			0.62
N0	47 (28.5%)	55 (32.9%)		27 (27.8%)	32 (33%)	
N1	31 (18.8%)	17 (10.2%)		14 (14.4%)	10 (10.3%)	
N2	38 (23%)	34 (20.4%)		25 (25.8%)	23 (23.7%)	
N3a	32 (19.4%)	47 (28.1%)		19 (19.6%)	24 (24.7%)	
N3b	17 (10.3%)	14 (8.4%)		12 (12.4%)	8 (8.2%)	
Disease stage (AJCC), n (%)			0.1			0.95
I B	29 (17.6%)	26 (15.6%)		13 (13.4%)	15 (15.5%)	
II A	32 (19.4%)	26 (15.6%)		17 (17.5%)	18 (18.6%)	
II B	29 (17.6%)	16 (9.6%)		16 (16.5%)	14 (14.4%)	
III A	33 (20%)	36 (21.6%)		24 (24.7%)	21 (21.6%)	
III B	25 (15.2%)	41 (24.6%)		15 (15.5%)	20 (20.6%)	
III C	17 (10.3%)	22 (13.2%)		12 (12.4%)	9 (9.3%)	
Detected lymph nodes, mean (SD)	27 (12)	18 (9)	0.001	27 (12)	19 (10)	0.001
Positive lymph nodes, mean (SD)	6 (7)	6 (7)	0.98	6.4 (8.1)	5.6 (7.2)	0.44
Lymph node ratio, mean (SD)	0.21 (0.25)	0.28 (0.27)	0.52	0.24 (0.27)	0.28 (0.27)	0.27
R0 resection, n (%)	151 (91.5%)	120 (71.9%)	0.001	87 (89.7%)	80 (82.5%)	0.16
Tumor differentiation, n (%)			0.018			0.51
Well	30 (18.2%)	22 (13.2%)		15 (15.5%)	15 (15.5%)	
Middle	44 (26.7%)	60 (35.9%)		26 (26.8%)	33 (34%)	
Poor/non-differentiated	91 (55.1%)	85 (50.9%)		56 (57.7%)	49 (50.5%)	

ASA = American Society of Anesthesiologists; B-I = Billroth I; B-II = Billroth II; BMI = body mass index; *SD = standard deviation;*

* = data missing in 36 patients

to compare categorical variables. A two-tailed p-value < 0.05 was considered statistically significant.

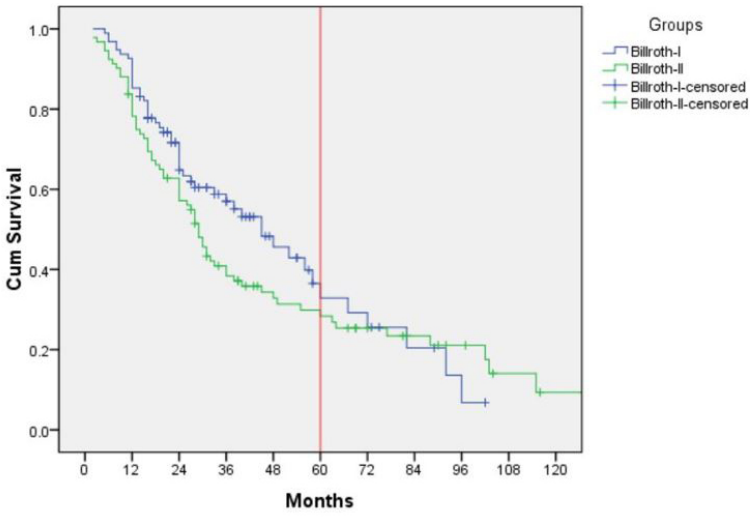
PSM was applied to achieve balanced groups with comparable baseline characteristic and potentially minimizing confounding. Logistic regression was performed to estimate the propensity to undergo two different surgical procedures for gastric cancer. The R package 'MatchIt' (version 4.5.0) was used to create the final matched cohort. The matching was done using one-to-one nearest neighbour propensity score matching without replacement within a predefined propensity score radius (ie, caliper = 0.1) with a propensity score estimated using logistic regression of the treatment on the covariates. After matching, all standardized mean differences were below 0.1, indicating adequate balance. For the propensity-score matched cohort, paired methods were used in the analysis. The paired T-test was utilized for normally distributed data, and the Wilcoxon signed-rank test was employed for non-normally distributed data. Categorical variables were analysed using McNemar's test.

A multivariable binary logistic regression model with backward selection was used to examine

TABLE 3. Long-term oncologic outcomes after distal subtotal gastrectomy with Billroth I vs Billroth II reconstruction for non-early gastric adenocarcinoma*

Variable	Unmatched			Propensity score matched		
	B-I (n = 164)	B-II (n = 165)	p-value	B-I (n = 96)	B-II (n = 95)	p-value
Adjuvant chemotherapy, n (%)¶	52 (31.7%)	44 (26.7%)	0.32	36 (37.5%)	26 (27.4%)	0.18
Recurrence, n (%)¶	34 (20.7%)	60 (36.4%)	0.002	21 (21.9%)	34 (35.8%)	0.054
Recurrence type, n (%)¶						
Local	4 (2.4%)	16 (9.7%)	0.006	3 (3.1%)	11 (11.6%)	0.022
Distant metastases	12 (7.3%)	25 (15.2%)	0.025	8 (8.3%)	12 (12.6%)	0.3
Peritoneal carcinomatosis	18 (11%)	19 (11.5%)	0.88	10 (10.4%)	11 (11.6%)	0.65
Overall survival, months, median	45 (35.4-54.6)	29 (24.3-33.7)	0.036	45 (30.9-59.1)	29 (24.9-33.1)	0.22
3-year	59%	41.1%		57%	38.4%	
5-year	34.6%	28.7%		32.9%	28.4%	

* = Patients who died after surgery (n = 3) were excluded from the analysis of long-term oncologic outcomes; ¶ = data not available in 3 patients



Parameter	Survival				p-value
	Median (95% CI)	3-year	5-year	7-year	
Billroth-I	45 (30.9 – 59.1)	57%	32.9%	20.5%	0.22
Billroth-II	29 (24.9 – 33.1)	38.4%	28.4%	23.4%	

FIGURE 1. Survival in patients with non-early non-metastatic gastric cancer undergoing subtotal distal gastrectomy with Billroth I and Billroth II reconstruction – propensity-matched analysis (1:1).

the association between disease recurrence and clinicopathological parameters significant in the univariable analysis (p-value < 0.05). Median survival was estimated by using the Kaplan-Meier method and survival curves were plotted. The log-rank test was used to compare median survival between the groups.

Results

Short-term outcomes

A total number of 332 patients underwent distal subtotal gastrectomy for NEGA. B-I and B-II reconstructions were performed in 165 (49.7%) and 167 (50.3%) patients, respectively.

After applying PSM, 97 patients were analyzed in each group. These were comparable in terms of age, gender, and body mass index (Table 1). The total number of comorbidities was greater in patients receiving B-II reconstruction. Before PSM, the use of B-I reconstruction was associated with the smaller tumor size (4.5 *vs.* 6.2 cm, p = 0.001), tumor location in gastric antrum (97% *vs.* 79.6%, p = 0.001) and multi-organ resections were less common in this group (1.8 *vs.* 15%, p = 0.001). These differences became statistically non-significant after matching. Despite PSM, operative time with B-I remained shorter in comparison to B-II (143 *vs.* 165 min, p = 0.001). Other postoperative outcomes were similar in the two matched groups.

The two matched groups were not significantly different in terms of tumor size pT, pN, AJCC stages, R0 resection rates and tumor differentiation (Table 2). Significantly greater mean lymph node yield was observed in patients who had received B-I anastomosis (27 *vs.* 19, p = 0.001). Other lymph node-related parameters such as total number of positive lymph nodes and lymph node ratio were comparable between the two methods.

TABLE 4. Uni- and multivariable analysis of prognostic factors for tumor recurrence following distal subtotal gastrectomy for non-early gastric adenocarcinoma (Propensity score matching [PSM] cohort)

Variable	Univariable		Multivariable	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age, years	0.99 (0.96–1.01)	0.33		
Gender (female)	1.34 (0.71–2.51)	0.37		
BMI, kg/m^2	0.99 (0.93–1.07)	0.89		
Comorbidity	0.74 (0.38–1.46)	0.39		
ASA score (III–IV)	0.86 (0.31–2.4)	0.78		
CEA, ng/mL	1.0 (0.99–1.02)	0.59		
Ca 19-9, U/mL	1.0 (0.99–1.001)	0.93		
Extended gastrectomy	0.99 (0.19–5.26)	0.99		
B-II reconstruction (*vs.* B-I)	1.99 (1.05–3.78)	0.035	————	–
Operative time	1.012 (1.001–1.024)	0.038	————	–
Estimated blood loss	1.001 (0.99–1.01)	0.65		
Red blood cell transfusion	0.26 (0.06–1.18)	0.082		
Severe complications	2.06 (0.53–7.96)	0.29		
Relaparotomy	2.59 (0.62–10.74)	0.19		
Tumor size	1.13 (0.92–1.38)	0.25		
pT stage				
T1–T2	reference		reference	
T3	3.86 (1.76–8.48)	0.001	3.13 (1.36–7.19)	0.007
T4a/T4b	1.04 (0.32–3.35)	0.95	0.64 (0.14–2.86)	0.56
pN stage				
N0	Reference		————	–
N1	1.82 (0.57–5.82)	0.32	————	–
N2	2.31 (0.89–5.95)	0.08	————	–
N3a	4.31 (1.69–10.94)	0.002	————	–
N3b	3.18 (0.98–10.26)	0.05	————	–
Detected lymph nodes	0.96 (0.94–0.99)	0.022	0.96 (0.93–1.01)	0.06
Lymph node ratio	1.05 (1.01–1.09)	0.025	1.01 (1.0–1.03)	0.043
R0 resection	3.2 (1.36–7.55)	0.008	2.41 (0.85–6.84)	0.1
Tumor differentiation				
Well	reference			
Middle	1.18 (0.59–2.37)	0.65		
Poor	0.63 (0.25–1.59)	0.33		
Adjuvant chemotherapy	1.28 (0.66–2.47)	0.46		

ASA = American Society of Anesthesiologists; B-I = Billroth I; B-II = Billroth II; BMI = body mass inde, CA 19-9 = carbohydrate antigen 19-9; CEA = *carcinoembryonic antigen*

Long-term outcomes

Median follow-up for the patients was 28 (2-150) months. Less than one-third (29%) of the patients received adjuvant chemotherapy overall and no significant differences were found between the groups (Table 3). The recurrence rate was lower following B-I in the unmatched cohort. The difference became statistically non-significant after applying PSM – 21.9% *vs.* 35.8%, p = 0.054. When ana-

lyzing for specific types of recurrence, local recurrence was significantly lower in patients with B-I reconstruction (3.1% *vs.* 11.6%, p = 0.022). No significant differences were found for other types of recurrence. Median survival was 38 (30-46) months, while 3- and 5-year survival rates were 52 and 32%, respectively. Overall survival was not significantly different between the groups after PSM (Figure 1).

Uni- and multivariable analyses were performed to identify prognostic factors for tumor recurrence following distal subtotal gastrectomy for NEGA (Table 4). According to the univariable analysis, operative time, reconstruction method, pT and pN stages, total number of harvested lymph nodes, lymph node ratio and R1 resection were associated with recurrence. In the multivariable analysis, reconstruction method was not associated with recurrence. pT stage and lymph node ratio were the only independent predictors for tumor recurrence.

Discussion

Our findings suggest that B-I anastomosis is a valid option in patients undergoing distal subtotal gastrectomy for NEGA. Therefore, B-I should be considered in these patients when it is technically feasible and does not compromise the oncologic outcomes. At the same time, factors such as tumor extent, its proximity to the pylorus and the size of the gastric stump should be considered when deciding on reconstruction method.

The results from this study demonstrate that oncologic outcomes after distal subtotal gastrectomy with B-I anastomosis are comparable to those after distal subtotal gastrectomy with B-II. Surprisingly though, the number of detected lymph nodes in patients with B-I anastomosis was higher compared with those with B-II. At the same time, B-I was mostly applied in the later period (2013-2020), while B-II was predominantly applied in the earlier period (2004-2012). Most likely, this represents changes in meticulousness of pathology work-up as surgical technique and the extent of lymphadenectomy did not change at our institution over time. Since the proportion of B-I was greater in the later period, we assume it has inadvertently coincided with an improved pathology work-up resulting in greater lymph node yield in this group.

Patients with B-I reconstruction were found to have lower incidence of recurrence compared to those with B-II. However, this correlation did not remain statistically significant in the PSM cohort and multivariable analysis. Low incidence of local recurrence in the B-I group demonstrates that B-I technique is oncologically justified in patients with NEGA undergoing distal subtotal gastrectomy. On the contrary, a higher rate of local recurrence after distal subtotal gastrectomy with B-II anastomosis may indicate the need for a more radical approach (ie, total gastrectomy) in some of these patients. In other words, one can assume that preserving proximal stomach in these patients to obtain better quality of life after surgery was probably not always oncologically justified.

Another important implication of this study is that it comes from a developing country with high incidence of gastric cancer, where no screening programs are utilized. As a result, most of the patients undergoing surgery for distal gastric cancer are diagnosed with NEGA. This is in contrast with the situation in the Asian countries, where about 50% of patients present with early gastric cancer.[10,12] While gastric disfunction and health-related quality of life issues are important endpoints after surgery for early gastric cancer, survival and oncologic results are central in gastrectomy for NEGA.

There are several limitations in this report worth mentioning. First and foremost, this is a retrospective study with its inherent biases. Second, no strict criteria were in place when opting for B-I or B-II anastomosis after distal subtotal gastrectomy. Thus, it was left at surgeon's discretion. Third, since this study was based on single-surgeon experience, the generalizability of our findings is limited.

B-I was associated with postoperative outcomes that were not inferior to those of B-II. Furthermore, the long-term oncologic results are not compromised when using B-I. Hence, the latter can be considered as an appropriate reconstruction method in patients with NEGA that are candidates for distal subtotal gastrectomy.

Conclusions

The use of B-I anastomosis after distal subtotal gastrectomy for NEGA is associated with satisfactory surgical and oncologic outcomes. B-I anastomosis should be considered as a valid reconstruction method in these patients.

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research article

Erector spinae plane block versus intercostal nerve block for postoperative analgesia in lung cancer surgery

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Background. A recent trend in postoperative analgesia for lung cancer surgery relies on regional nerve blocks with decreased opioid administration. Our study aims to critically assess the continuous ultrasound-guided *erector spinae* plane block (ESPB) at our institution and compare it to a standard regional anesthetic technique, the intercostal nerve block (ICNB).

Patients and methods. A prospective randomized-control study was performed to compare outcomes of patients, scheduled for video-assisted thoracoscopic (VATS) lung cancer resection, allocated to the ESPB or ICNB group. Primary outcomes were total opioid consumption and subjective pain scores at rest and cough each hour in 48 h after surgery. The secondary outcome was respiratory muscle strength, measured by maximal inspiratory and expiratory pressures (MIP/MEP) after 24 h and 48 h.

Results. 60 patients met the inclusion criteria, half ESPB. Total opioid consumption in the first 48 h was 21.64 ± 14.22 mg in the ESPB group and 38.34 ± 29.91 mg in the ICNB group ($p = 0.035$). The patients in the ESPB group had lower numerical rating scores at rest than in the ICNB group (1.19 ± 0.73 vs. 1.77 ± 1.01, $p = 0.039$). There were no significant differences in MIP/MEP decrease from baseline after 24 h (MIP $p = 0.088$, MEP $p = 0.182$) or 48 h (MIP $p = 0.110$, MEP $p = 0.645$), time to chest tube removal or hospital discharge between the two groups.

Conclusions. In the first 48 h after surgery, patients with continuous ESPB required fewer opioids and reported less pain than patients with ICNB. There were no differences regarding respiratory muscle strength, postoperative complications, and time to hospital discharge. In addition, continuous ESPB demanded more surveillance than ICNB.

Key words: erector spinae plane block; intercostal nerve block; postoperative analgesia; video-assisted thoracic surgery; thoracic anesthesia

Introduction

Post-operative analgesia is crucial for early rehabilitation in thoracic surgery, as patients are required to actively participate in respiratory physiotherapy.[1,2] Uncontrolled pain requires high doses of opioid analgesics which should be avoided according to the Early Recovery After Surgery (ERAS) guidelines.[3] An opioid-sparing analgetic regimen is used to alleviate their numerous side

effects, such as nausea, vomiting, constipation, lethargy, and respiratory depression.[4] Regional techniques have been implemented to reduce the need for opioid analgesics.[5,6]

In an attempt to find safe and less invasive methods of postoperative analgesia, new techniques of nerve blocks have emerged. Among other peripheral blocks, intercostal nerve block (ICNB) and *erector spinae* plane block (ESPB) are being introduced in recent years.[7,8] In comparison to the neuraxial blockade, they have a lower incidence of spinal cord injury, epidural hematoma, and central nervous system infection.[9-11]

The ICNB applied intrathoracically at the end of the surgery, is a regional technique currently used for video-assisted thoracoscopic (VATS) procedures at our surgical center. While fairly simple to use and applied under direct vision, there are some disadvantages of the ICNB: limited time of analgesic effect, which cannot be extended by a continuous infusion, application at the end of surgery instead of pre-incision and multiple injections that are needed to pertain a single block. The block cannot be executed in the presence of pleural infection, e.g., empyema.[12-14]

The *erector spinae* plane block (ESPB) was first described by Forero *et al*. in 2016 as a thoracolumbar interfascial plane block for treating severe neuropathic pain from the ribs.[15] This interfascial nerve block is applied under ultrasound guidance and has a large safety margin. It can also be applied to patients on anticoagulant drugs. Cadaveric studies pointed out that the local anesthetic spreads to the thoracic paravertebral space[16] or epidural space[17], whereas some stated that it spreads more lateral on the thoracic wall without passing the costotransverse foramen.[18] Its efficacy for thoracic surgeries in the first 24 hours after surgery as a single shot has been proven in previous studies and meta-analyses.[19-21]

We compared the continuous ultrasound-guided ESPB with ICNB to evaluate their analgetic efficacy in patients after lung cancer resection, representing our institution's first study of continuous ESPB in Slovenia. We present the following article in accordance with the CONSORT reporting checklist.

Patients and methods

The study was approved by the National Ethics Committee under the number 0120-372/2019/7 and the study was registered to the Clinical Trial Registry under number NCT04665531.

Patients

Sixty participants were enrolled between the 19th of February 2020 and the 14th of March 2022. Eligible patients with early-stage lung cancer were scheduled for VATS tumor resection with a three-port approach. 80% had lung lobe resection, 12% had marginal lung resection, and 8% had segmentectomy. Most of the patients had lung adenocarcinoma (72%), followed by epidermoid or squamous cell carcinoma (20%), small-cell lung carcinoma (2%), and metastasis (2%). Two tumors turned out to be benign.

Other inclusion criteria were ASA status I–III and informed written consent for participation in the study. Exclusion criteria were chronic pain syndrome, chronic opioid use, weight less than 50 kg due to risk of local anesthetic systemic toxicity (LAST), body mass index (BMI) > 35, pregnancy or breastfeeding, allergy to local anesthetics, inflammation at the catheter insertion site or inability to use the patient-controlled analgesia (PCA) pump. Patients were randomly assigned to either the intervention ESPB arm or the comparative ICNB arm. The study protocol could not be blinded because of the indiscrete intervention type.

Nerve block technique

Patients in the ICNB group received a single-shot intrathoracic ICNB after tumor extraction, approximately 30 minutes before the end of the surgery. They received 20 ml of 0.5% levobupivacaine with injections at 6 intercostal spaces, adjacent to the surgical wound. The perineural intercostal space was located under direct vision. The same surgeon performed all the surgeries and executed the ICNBs.

Patients in the ESPB group received a 20 ml bolus of 0.5% levobupivacaine through the ESPB catheter approximately 30 minutes before the end of the surgery, continued by an infusion of 5 ml/h 0.2% ropivacaine with intermittent boluses of 15 ml per 4 hours.

Two anesthesiologists, experienced in regional anesthesia, were inserting catheters to the patients before the surgery in the pre-op area. The standard monitoring and i.v. canal were applied before the intervention. The ESPB catheter insertion was performed using Samsung© ultrasound with a GE 12L-RS high-frequency linear probe. Aseptic conditions were guaranteed by using sterile drapes, sterile probe dressings, gloves, masks, and surgical gowns. The catheter insertion un-

derwent in a pronated position with the patient lightly sedated by 1–2 mcg/kg fentanyl. The insertion site was infiltrated with 2 ml of 2% lidocaine on the T4 level of the spine, approximately 3 cm ipsilateral from the midline on the transverse process. The needle was then inserted under ultrasound guidance, positioning the needle tip immediately above the periosteum. The position was confirmed by injecting approximately 10 ml of 0.9% sodium chloride solution, which caused a hydro-dissection between the *erector spinae* muscle and the underlying fascia. Then, the catheter was inserted 4–6 cm above the needle tip. (Figure 1). After needle extraction, the catheter was secured using Stat-Lock© and multiple see-through coverings (Tegaderm©). Anesthesiologists used an 18G, 80 mm BD Microlance© pointed needle and a 20G Braun© multi-orifice epidural catheter.

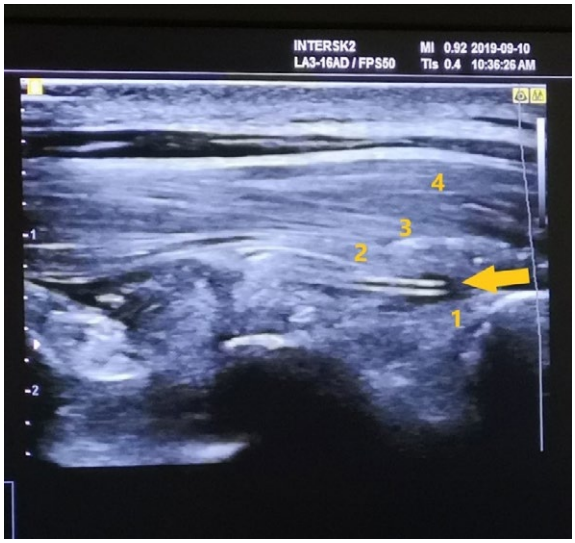

FIGURE 1. Ultrasound image of the inserted ESPB catheter (marked by an arrow) and interfascial hydro-dissection.

1 – underlying thoracic lamina, 2 – m. *erector spinae*, 3 – *m. rhomboideus*, 4 – *m. trapezius*

Peri-operative protocol

All the patients underwent the same anesthesia protocol. Induction to general anesthesia was conducted with 1.5–2 mg/kg propofol 1% and 0.75–1 mcg/kg remifentanil in a slow bolus followed by 0.6 mg/kg rocuronium. Total intravenous anesthesia was maintained with an infusion of 5 mg/kg/h propofol 1% and 0.02–0.03 mcg/kg/min remifentanil. Blood pressure was maintained with fluid administration and appropriate vasoactive drugs when needed. Reversion of neuromuscular block was performed by a bolus of 2 mg/kg sugammadex at the end of the surgery.

Patients were constantly monitored (ECG, pulse oximetry, invasive blood pressure) from admission to the pre-op area until at least 48 hours after surgery. Nurses at the intensive care unit documented the post-operative numerical rating scale for pain (NRS) every hour in the first 48 hours except when the patient was asleep. The patients expressed their current NRS on a scale from 0 to 10 with 0 meaning no pain and 10 meaning the worst pain imaginable. Nurses asked the patients about their NRS at rest and at cough in the last hour, which included spontaneous and active cough but not respiratory physiotherapy.

Every patient received a PCA pump with the protocol: demanded bolus 3 mg piritramide 1 mg/ml per 15 min with a maximum of 2 boluses per hour with no continuous infusion. If the pain reported by a patient was still higher than 3/10, a nurse applied an additional bolus of 3 mg piritramide. When a patient demanded more than 4 boluses per hour, the attending doctor initiated an infusion of 2 mg/h piritramide until the pain settled below 3/10. All the patients received regular doses of diclofenac and metamizole in terms of multimodal analgesia.

The postoperative care of the ESPB catheter followed the same protocol as for the thoracic-epidural catheter. The attending physician evaluated the catheter insertion site every day, looking for signs of infection.

All the patients performed maximal inspiratory and expiratory pressure (MIP/MEP) tests three times: on the day of the surgery prior to the surgical procedure, 24 and 48 hours later.

Statistical analysis

The statistical analyses were performed using IBM SPSS version 25, Orange data mining and visualization suite.[22] The patient and treatment characteristics were described using descriptive statistics. Demographic variables were compared with Pearson's Chi-square test. Cumulative piritramide use and NRS values are expressed as means with standard deviation. The potential differences between arms were assessed using the Kruskal-Wallis test. All the reported p-values are two-tailed with a significance level $\alpha < 0.05$. The pre-operative MIP and MEP measurements were set as baseline (100%), while the following measurements from the same patient were expressed

TABLE 1. Demographic data

	Total	ESPB	ICNB	p-value
Patients enrolled	50	25	25	
Gender (male/female)	30/20	17/8	13/12	0.25
Age (years)*	69.80 ± 8.41	69.44 ± 8.20	70.2 ± 8.76	0.53
Height (cm)*	170.20 ± 8.49	172.04 ± 8.01	168.36 ± 8.72	0.15
Weight (kg)*	76.62 ± 14.07	76.24 ± 14.36	77.00 ± 14.03	0.72
BMI (kg/m^2)*	26.37 ± 3.93	25.72 ± 4.18	27.03 ± 3.64	0.21
ASA 1/2/3	1/25/24	0/14/11	1/11/13	0.47
FEV1 before the surgery	94.78 ± 21.57	95.45 ± 21.84	94.17 ±21.77	0.88

[1] Values under age, height, weight, and BMI are given as mean and 95% confidence interval.

ASA = American Society of Anesthesiologists assessment; BMI = body mass index; ESPB = *erector spinae* plane block; FEV1 = forced expiratory volume in the first second; ICNB = intercostal block

as percentages from the baseline. Group medians were compared with the Student's t-test. Time to chest tube removal and hospital discharge were assessed by the median test.

Results

Patient allocation and follow-up are shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure 2).

There were no statistically significant demographic differences between the study groups considering gender, age, body mass index, type of surgery, ASA and forced expiratory volume in the first second (FEV1) (Table 1).

The cumulative piritramide use in the first 48 hours after surgery was 21.64 ± 14.22 mg in the ESPB group and 38.34 ± 29.91 mg in the ICNB group (p = 0.035) (Figure 3). Figure 4 shows the cumulative linear graph of piritramide use in time for each group.

The mean NRS scores at rest in the first 48 hours after surgery were 1.19 ± 0.73 in the ESPB group and 1.77 ± 1.01 in the ICNB group. The difference between groups is statistically significant (p = 0.039). The mean NRS scores at cough in the first 48 hours after surgery were 2.53 ± 1.23 for ESPB and 2.85 ± 0.98 for ICNB. The difference between groups is statistically insignificant (p = 0.432).

There were no statistically significant differences between the ESPB and ICNB groups in MIP or MEP after 24 or 48 hours (Table 2).

Time to chest tube removal was 4.13 ± 2.92 days in the ESPB group *vs.* 3.88 ± 2.26 days in the ICNB group (p = 0.41). Time to hospital discharge was 4.43 ± 2.87 days in the ESPB group *vs.* 4.08 ± 2.21 days in the ICNB group (p = 0.32).

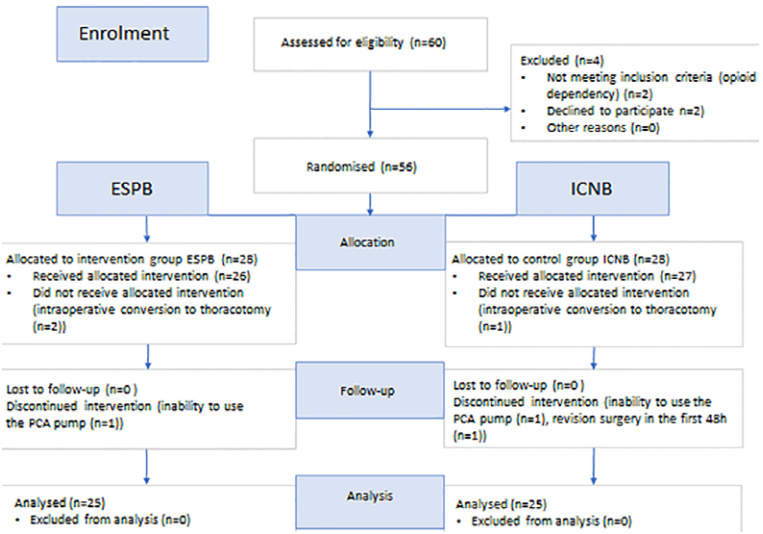

FIGURE 2. CONSORT flow diagram.

ESPB = *erector spinae* plane block; ICNB = intercostal nerve block; PCA pump = patient-controlled analgesia pump

There were no catheter-related complications such as clogging of the catheter, unintentional removal, or insertion-site infections. Attending physicians noted a few cases of minimal bleeding under the see-through coverings.

In the ESPB group, they noted one case of paroxysmal atrial fibrillation, one case of paroxysmal supraventricular tachycardia, and one case of sinus tachycardia at the time of observation. In the ICNB group, they noted 6 cases of paroxysmal

TABLE 2. Maximal inspiratory and expiratory muscle strength

Respiratory test values (%)		ESPB	ICNB	p-value
MIP	24 hours	71.58 ± 16.69	75.98 ± 24.04	0.088
	48 hours	73.42 ± 19.10	88.11 ±30.72	0.110
MEP	24 hours	73.36 ± 20.82	85.55 ± 37.35	0.182
	48 hours	74.90 ± 22.39	98.90 ± 32.29	0.645

Respiratory test values are expressed as percentages from the baseline value.

ESPB = *erector spinae* plane block; ICNB = intercostal nerve block; MEP = maximal expiratory pressure; MIP = maximal inspiratory pressure

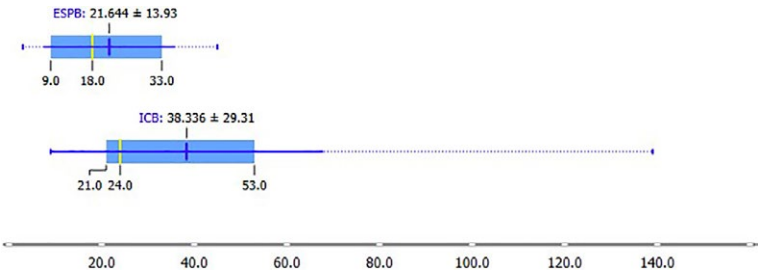

FIGURE 3. Cumulative piritramide use in the first 48 hours after surgery. The values in the graph are marked as mean (blue), median (yellow), and interquartile range.

ESPB = *erector spinae* plane block; ICNB = intercostal nerve block

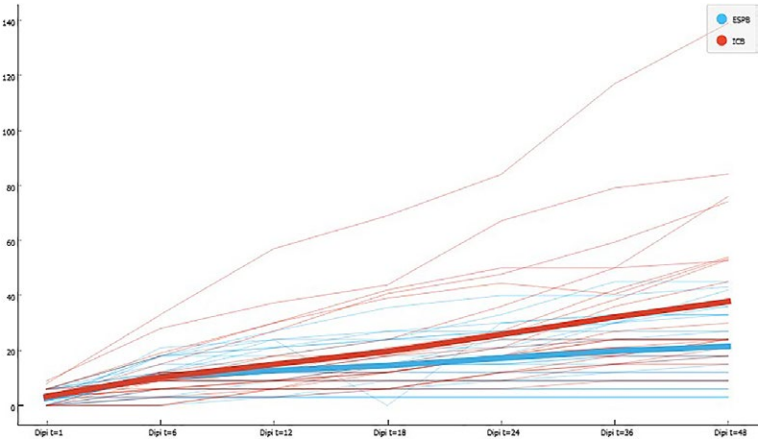

FIGURE 4. Cumulative opioid consumption in the first 48 h after surgery. The bold line shows the median values for each group.

atrial fibrillation. These arrhythmias emerged on postoperative day 1 or 2.[23] There were no other acute or sub-acute complications related to regional anesthesia.

Discussion

This study of postoperative analgesia for VATS lung cancer resection, comparing continuous ultrasound-guided ESPB versus ICNB, is the first of its kind in Slovenia. Due to the Covid-19 pandemic crisis, causing limited resources and additional healthcare concerns, the time of patient recruitment was prolonged, and only 60 patients from 200 were eligible for our study in a two-year period. The most significant findings were lower opioid demands in the ESPB group (21.64 ± 14.22 mg *vs.* 38.34 ± 29.91 mg (p = 0.035)) and lower cumulative NRS scores at rest in the first 48 hours after surgery (1.19 ± 0.73 *vs.* 1.77 ± 1.01, p = 0.039)) than in the ICNB group.

In recent years, some studies were comparing single-shot ICNB and ESPB with unclear advantages. In terms of postoperative opioid use, the ICNB was reported by some studies to be more efficient and by other studies to be less efficient than the ESPB.[24,25] A previous pilot study demonstrated the feasibility of conducting a randomized controlled trial comparing continuous ESPB versus ICNB in patients undergoing VATS.[26]

Our results are consistent with Fiorelli *et al.*[27], who reported lower opioid consumption in the first 48 hours after surgery in the ESPB group compared to the ICNB group. However, they reported higher MIP and MEP in the ESPB group. Our results are inconsistent with Turhan *et al.*, who reported significantly lower opioid consumption in the ICNB than the ESPB group, but they observed only single-shot ESPB.[24]

The mean piritramide use between the groups started to differentiate after 12 hours postoperatively, marking the time when the ICNB effect wears out. Other observed parameters, such as time to chest tube removal, hospital discharge, and complications were similar in both groups. However, continuous ESPB is more demanding from the catheter insertion procedure to regular post-operative observations.[28] The main advantages of ESPB presumably come from prolonged local anesthetic administration, enabling individual adjustments according to NRS scores.[29]

Despite the continuous neuromuscular block of the hemi-thoracic musculature, the ability to fully perform respiratory physiotherapy was not compromised by the continuous ESPB. MIP and MEP measurements decreased substantially but did not differ significantly between the two groups after 24 hours or after 48 hours. Because the absolute MIP and MEP results vary strongly in literature,

we included relative values with the patients' preoperative measurements as the baseline.[30-32]

As common complications after lung resection, cardiac arrhythmias were monitored.[33] Clinicians detected no arrhythmias as a consequence of local anesthetic administration, showing there were no cases of local anesthetic cardiotoxicity. The observed arrhythmias emerged later and were attributed to other post-operative factors.

Comparing ESPB to a placebo without regional anesthesia would be unethical considering the benefits of regional truncal blocks that have already been proven.[34] The ICNB's efficacy has been assessed in a large meta-analysis of 66 eligible studies.[35] The ICNB is reported to be superior to systemic analgesia, non-inferior to thoracic-epidural anesthesia, and marginally inferior to paravertebral block in the first 24 hours after surgery. The data suggests that the analgetic benefit of the ICNB slowly vanishes in 24 to 48 hours after surgery. Therefore, it is a reasonable comparison in 48 hours after surgery.

The main limitation of the study is the inability to double-blind the analgesic method because of the catheter. The second limitation is the number of included patients. It would be reasonable to conduct another study on a larger scale to see whether any other inter-group differences appear. The third limitation is the protocol for the continuous ESPB, which is subject to future changes regarding local anesthetic selection and administered volume. Ropivacaine is currently the best local anesthetic of choice because of its large safety profile and the lowest potential risk for cardiotoxicity[36], while new anesthetics such as liposomal bupivacaine are being researched.[37]

Conclusions

The study in our institution showed that the continuous ESPB decreases total opioid consumption and subjective pain perception at rest in the first 48 hours after VATS lung tumor resection compared to the intrathoracic ICNB. On the other hand, ESPB demands more nursing care. Regarding time to chest tube removal, hospital discharge, NRS values at cough and respiratory muscle strength, there were no observed differences between ICNB and ESPB.

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research article

Monitoring the effect of perioperative nutritional care on body composition and functional status in patients with carcinoma of gastrointestinal and hepatobiliary system and pancreas

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Background. The significance of nutritional care in the management of cancer, particularly in the surgical treatment of abdominal cancer, is increasingly acknowledged. Body composition analysis, such as the Bioelectric impedance assay (BIA), and functional tests, *e.g.,* handgrip strength, are used when assessing nutritional status alongside general and nutritional history, clinical examination, and laboratory tests. The primary approach in nutritional care is individually adjusted nutritional counselling and the use of medical nutrition, especially oral nutritional supplements. The aim of the study was to investigate the effects of perioperative nutritional care on body composition and functional status in patients with carcinoma of the gastrointestinal tract, hepatobiliary system, and pancreas.

Patients and methods. 47 patients were included, 27 received preoperative and postoperative nutritional counselling and oral nutritional supplements (Group 1), while 20, due to surgical or organisational reasons, received nutritional care only postoperatively (Group 2). The effect of nutritional therapy was measured with bioimpedance body composition and handgrip measurements.

Results. Group 2 had a higher average Nutritional Risk Screening (NRS) 2002 score upon enrolment (3 vs. 2 points); however, there was no difference when malnutrition was assessed using Global Leadership in Malnutrition (GLIM) criteria. There was a relative increase in lean body mass and fat-free mass index (FFMI) 7 days after surgery in group 1 (+4,2% vs. -2,1% in group 2). There was no difference in handgrip strength.

Conclusions. Our results indicate that combined preoperative and postoperative nutritional care is superior to only postoperative nutritional care. It seems to prevent statistically significant lean mass loss 7 days after surgery but not after 14 days or 4 weeks.

Key words: abdominal cancer; nutritional status; body composition; oral nutritional supplements; nutritional care

Introduction

Cancers of the gastrointestinal tract (colon, stomach, liver, rectum, or oesophagus) (GIT) represent about 23.2% of new cancer cases. Meanwhile, pancreatic and biliary carcinoma are less common and only account for 3.1% percent of cases but are far more lethal and together represent 5.6% of cancer deaths.[1] With the prevalence of colorectal cancer rapidly increasing around the world, the

number of patients who are undergoing surgical procedures as primary treatments is increasing proportionately.[2,3] Surgery is the mainstay treatment for cancer[4] and is complemented by chemo- and radiotherapy, both pre- and postoperatively.[5] Malnutrition is often present before the start of the cancer treatment, and its prevalence only increases after the treatment's completion.[6,7] The correlation between malnutrition, and postoperative complications and mortality has been well documented in prospective and retrospective studies.[8-10] Low muscle mass represents one of the diagnostic criteria for malnutrition. In cancer patients, its loss throughout the course of the disease is not consistent, as catabolic stress, such as surgery, accelerates proteolysis. After the disease stressor is removed, proteolysis subsides to levels before the onset of disease.[11]

The nutritional care process is the basis for the recognition of malnutrition and for the initiation of nutritional support. It starts with nutritional risk screening[12], where the recommended screening method in hospitals is the Nutritional Risk Screening (NRS) 2002 survey. Patients who are found to be at nutritional risk require a complete assessment of nutritional status in which a combination of objective and subjective parameters should be utilised.[13] For a definitive diagnosis of malnutrition, the Global Leadership in Malnutrition (GLIM) criteria are used.[14] Low muscle mass, in combination with function decline, leads to sarcopenia[15], which is linked to detrimental outcomes after surgical treatment of abdominal cancer, indicated by increased readmission rates and worse chemotherapy tolerance.[16] In clinical practice, the bedside body composition measurement with bioimpedance and the measurement of function with handgrip are frequently used for assessing patients' nutritional status. These measurements provide valuable information that contributes to the identification, diagnosis, and management of several medical conditions for which nutrition therapy is indicated.[17] The correlation of body composition with health and functional status is well established.[18,19] The hand grip strength test is among the most widely used measures of physical ability; lower hand grip strength has been proven to be a good indicator of postoperative complications, longer hospitalisations, and worse physical status. It is also an excellent prognostic factor of both short- and long-term mortality.[20]

Once a patient is found to be at risk for nutritional deficiency, treatment should be initiated. Oral nutritional supplements (ONS) are considered the first choice for nutritional treatment, along with enteral nutrition. Additionally, patients should be counselled about eating their usual diet until the night before the surgery and the correct use of ONS.[8] If an elective surgical patient is malnourished, the appropriate nutritional therapy should be implemented, and non-emergency surgeries postponed. ONS are recommended for use in all malnourished cancer patients and all high-risk patients for abdominal surgery.[8] In a recent meta-analysis, perioperative nutritional supplementation has been shown to decrease postoperative infectious and non-infectious complications and length of stay in patients undergoing gastrointestinal cancer surgery.[21]

In our pilot study, we analysed two different nutritional care approaches in our clinical practice to determine if patients receiving both preoperative and postoperative nutritional care have better body composition and functional status after surgery compared to the group that only received postoperative nutritional care. For body composition, we focused on the assessment of lean mass with fat-free mass index (FFMI), 3rd space water, and phase angle. We expected the changes in body composition to be reflected in functional status and clinical course of the treatment.

Patients and methods

Study design and population

This prospective observational study was conducted between October 2021 and May 2022 at the Department of Abdominal Surgery of University Medical Centre (UMC) Ljubljana and at the clinical nutrition unit at the outpatient clinic of UMC Ljubljana. The committee for medical ethics of the Republic of Slovenia approved the study (permit number 020-427/2021/6). The Declaration of Helsinki, The Council of Europe Oviedo Convention and its protocols were followed, and all patients signed informed consent forms. They were all treated according to the established clinical guidelines and principles of good clinical practice.

Patients with carcinoma of GIT and hepatobiliary tract and pancreas were randomly enrolled in the study during their preoperative appointment if they were above 18 years of age and were to undergo surgical treatment of carcinoma of either GIT, hepatobiliary system, or pancreas. Group 1 (G1) patients were included into the study by being invited into the clinical nutrition outpatient

TABLE 1. Baseline demographic and clinical characteristics of patients (n = 47)

Variable		All participants N = 47	G1 N = 27	G2 N = 20	P
Sex	Male, N (%)	33 (70.2)	21 (77.8)	12 (60.0)	0.214
	Female, N (%)	14 (29.8)	6 (22.2)	8 (40.0)	
Age	Years, mean ± SD	70.5 ± 11.2	70.3 ± 8.7	70.7 ± 12.9	0.477
Diagnosis	GIT tumours, N (%)	27 (57.4)	15 (55.6)	12 (60.0)	1.000
	Tumours of liver, gallbladder, biliary system and pancreas, N (%)	20 (42.6)	12 (44.4)	8 (40.0)	

GIT = gastrointestinal tract; N 0 number; SD = standard deviation

clinic after their preoperative appointment with the anaesthesiologist. It was at this point that they started taking ONS preoperatively. ONS, which are immune-modulating formulae consists of the following important components: fish oil (eicosapentaenoic acid [EPA, 0.4g] + docosahexaenoic acid [DHA]), medium chain triglycerides (MCT), vitamins D3, C, A, K, B2, 6, 12, essential elements, inulin, maltodextrin and sucrose. The patients took ONS for 7 days, after which they had their surgery. Group 2 (G2) patients were included upon admittance to the surgical ward the day before surgery, where their physical status and treatment plan allowed for immediate surgery. Therefore, the patients in G2 were called in for surgery just days after their preoperative appointment, and there was no time for preoperative nutritional preparation.

Patients were considered ineligible to participate if: they had taken ONS before being included in the study or were already being followed in another clinical nutrition unit; the carcinoma was not histologically confirmed; they withdrew their consent at any point during the study; they were taking or had previously taken illicit drugs; they had a mental health disorder that prevented them from understanding and following nutritional treatment; their participation in the study would cause them far greater harm and risk than the potential benefits (*i.e.* due to old age or numerous associated diseases).

Data collection

Data for G1 were collected at their appointment in the outpatient clinic, where general and nutritional history were assessed, body composition was measured, and handgrip strength was measured using Jamar handheld digital dynamometer (Jamar Plus Digital, Performance Health, IL, USA). In G1 no measurements were made the day before or the morning of operative procedure. The data collection for G2 started at admission to the surgical ward or the morning before the surgical procedure. Handgrip strength (kg) was not measured in the G2 at the enrolment into the study. In both groups, anthropometric data were measured, and body composition was analysed using the bioelectric impedance assay (BIA) method with

TABLE 2. Clinical characteristics of patients upon enrolment into the study

Variable		G1 N = 27	G2 N = 20	P
Body mass	kg, median (25–75%)	82.0 (70.0–98.0)	78.5 (72.3–88.3)	0.268
BMI	kg/m^2, median (25–75%)	26.2 (23.4–34.5)	27.5 (24.3–29.6)	0.569
Lean mass	kg, median (25–75%)	53.1 (47.1–64.2)	53.9 (45.0–59.6)	0.505
FFMI	median (25–75%)	17.8 (16.4–20.3)	17.6 (15.9–20.4)	0.561
Phase angle	°, median (25–75%)	4.7 (4.3–5.4)	4.6 (4.0–5.5)	0.846
3rd space water	L, median (25–75%)	-0.1 (-0.8–1.0)	0.4 (-0.4–0.9)	0.425
NRS 2002	Points, median (25–75%)	2 (0–3)	3 (3–3,8)	0.012
Malnutrition according to GLIM	No, N (%)	14 (51.9)	16 (80.0)	0.067
	Yes, N (%)	13 (48.1)	4 (20.0)	

BMI = body mass index; FFMI = fat free mass index; GLIM = Global Leadership in Malnutrition

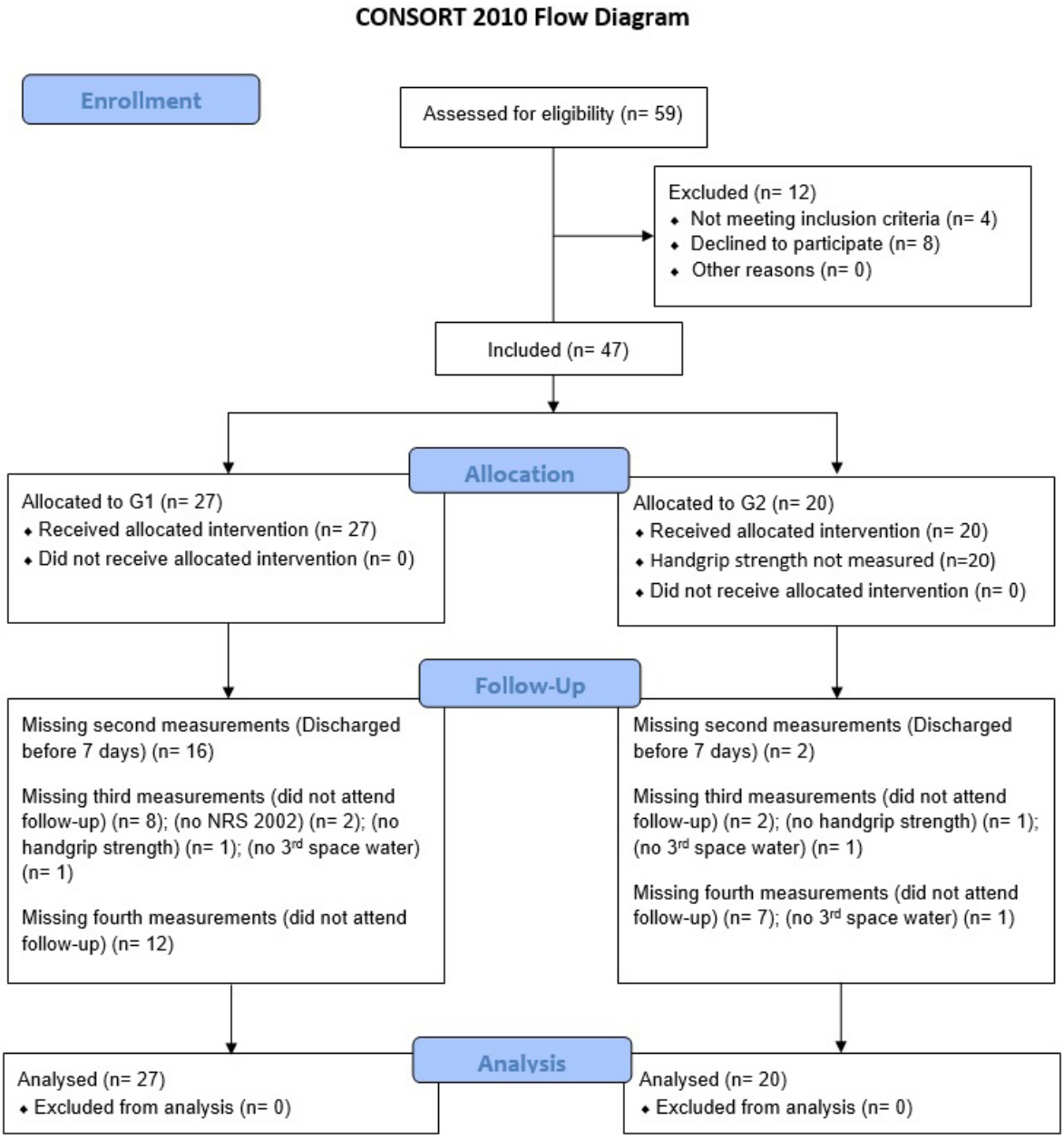

FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

BodyStat Quadscan 4000 Touch device (Bodystat, Isle of Man, UK), FFMI was calculated by BIA device using its own algorithms and nutritional risk screening was performed using the NRS 2002. We compared body mass (kg), body mass index (BMI, kg/m^2), lean mass (kg), FFMI (kg/m^2), phase angle (^{0}), 3rd space water (litres), NRS 2002 score (points), and the percentage (%) of malnourished patients according to GLIM criteria. BIA is a non-invasive and simple method for measuring body composition based on calculations from measuring the electrical conductivity of the body for one or more electric currents.[22] The body composition measurement 7 days post-surgery, while patients were still staying in the hospital, was used in the study (second measurement).

All patients were invited to two follow-up checks at the outpatient clinic. The third measurement was on the 14th day post-surgery, at which time all patients were already back home and could tolerate oral intake, including ONS. The final check-up was at 4 weeks after surgery (fourth measurement).

TABLE 3. Handgrip strength data

Variable		Upon enrolment		After 7 days	After 14 days			After 4 weeks		
		G1 N = 27	G2		G1 N = 19 [8]	G2 N = 18 [2]	P	G1 N = 15 [12]	G2 N = 13 [7]	P
Hand grip strength	kg, median (25–75%)	34.1 (28.5–41.6)	/	/	30.2 (25–35.3)	30.3 (25.8–36.8)	0.782	29.7 (23.6–32.7)	32.6 (27.3–35.6)	0.254
Hand grip strength: norm	No, N (%)	19 (70.4)	/		11 (61.1)	9 (52.9)	0.738	8 (53.3)	8 (61.5)	0.718
	Yes, N (%)	8 (29.6)	/		8 (47.1)	7 (38.9)		7 (46.7)	5 (38.5)	
Hand grip strength: deviation	median (25–75%)	0.2 (-0.1–1.2)	/		0 (-0.5–0.5)	0.3 (-0.4 –1)	0.369	0.1 (-0.7–0.3)	0.3 (-0.8–.8)	0.683

norm = patients meets the norm for hand grip strength for age and sex; **Hand grip strength: deviation = deviation of hand grip strength from the norm expressed as a multiple of standard deviation

[number of missing participants]

Nutritional monitoring was performed, ONS compliance was checked and they received nutritional counselling from a clinical dietician. A physician specializing in clinical nutrition supervised nutritional monitoring to plan an individually adjusted treatment. Patients were given verbal and written instructions about nutritional therapy.

Statistical analysis

In statistical analysis, the variables were first characterised using descriptive statistics, using frequencies for categorical variables, and median with 25%–75% range for continuous variables as not all variables were normally distributed. Data were analysed on an intention-to-treat basis, with all patients remaining in their original allocated group for all analyses. Based on our sample size and the distribution of the variables, we were able to detect a difference between groups of approximately 2.3 for FFMI and 0.74^0 for phase angle with 80% power. Power analysis was performed using Power and Sample Size Calculation version 3.0.43. For comparison between groups G1 and G2, Fisher's exact test was used for categorical variables and the Mann-Whitney test for continuous variables, including relative change between two time points. For comparison of continuous measurements obtained at different time points, Wilcoxon's test for related samples was used. The cut-off for statistical

TABLE 4. Clinical characteristics of patients at different time points

Variable		After 7 days			After 14 days			After 4 weeks		
		G1 N = 11 [16]	G2 N = 18 [2]	P	G1 N = 19 [8]	G2 N = 18 [2]	P	G1 N = 15 [12]	G2 N = 13 [7]	P
Body mass	kg median (25–75%)	72.0 (67.8–93.2)	76.4 (68.5–85.6)	0.912	73.0 (65.0–92.0)	75.5 (70–84.5)	0.869	69.4 (66–76.8)	75 (72.5–86.5)	0.130
BMI	kg/m^2 median (25–75%)	25.4 (22.7–36.1)	26.8 (24.1–29.0)	0.808	25 (22.5–34.1)	26.4 (22–28.9)	0.620	23.8 (21.7–27.2)	26 (23–29.5)	0.413
Lean mass	Kg median (25–75%)	52.0 (48.2–53.2)	52.0 (41.9–57.1)	0.842	50.1 (46.4–52.1)	53.2 (45–58)	0.707	48.4 (41.7–50.6)	55 (46.5–60.2)	0.065
FFMI	median (25–75%)	17.8 (16.5–20.8)	17.4 (15.8–19.0)	0.340	16.8 (15.8–19.4)	17.4 (15.6–19.6)	1.000	16.5 (15.1–17.5)	18.8 (15.9–19.8)	0.118
Phase angle	median (25–75%)	4.3 (3.5–4.9)	4.4 (3.3–5.1)	0.947	4.4 (4.1–5)	4.2 (3.6–4.7)	0.461	4.8 (3.7–5.3)	4.4 (3.3–4.7)	0.201
3rd space water	L median (25–75%)	0.7 (-0.3–1.6)	0.4 (-0.6–1.0)	0.642	0.5 (-0.–1.4)	0.2 (-0.1–1)	0.988	0.4 (–0.2 do 1.1)	0.4 (-0.2–1.3)	0.928
NRS 2002**	Points median (25–75%)	/			4 (3–4.3)	4 (3–4.5)	0.961	4 (3–5)	3 (3–4)	0.235

BMI = body mass index; FFMI = fat free mass index; NRS 2002 = score achieved on screening with NRS 2002 tool

[number of missing participants]

significance was considered to be $p<0.05$. All statistical analyses were performed using IBM SPSS Statistics, version 27.0 (IBM Corporation, Armonk, NY, USA).

Results

Clinical characteristics of participants at different time points in the study

During the course of our prospective study, data was collected for 47 patients. They were, on average, 72 years old and predominantly male. The distribution of cancer diagnoses among the patients shows that GIT tumours were slightly more prevalent, while the remainder of the cases consisted of various types of liver, gallbladder, biliary system, or pancreatic cancer. Table 1 describes the baseline demographic and clinical characteristics of participants.

Upon enrolment, the participants in G1 and G2 had no significant differences in any of the variables measured. Clinical characteristics of all patients are represented in Table 2.

There were no significant differences in absolute values of measured variables between G1 and G2 at any point during the study. The data is summarised in Table 3 for handgrip strength and in Table 4 for anthropometric and body composition analysis as well as NRS 2002 score. There were several missing measurements at different points during the study because the protocol was not followed, as is summarised in Figure 1.

Relative differences between the two groups when compared to the starting values

We found a significant difference in lean mass and FFMI after 7 days, where the G1 lean mass and FFMI increased, and the G2 decreased. The analysis for the third and fourth measurements showed no significant differences between measured parameters (Supplementary Tables 6, 7, and 8).

Discussion

The results of our pilot study of clinical practice in the Department of Abdominal Surgery of UMC Ljubljana indicate that the combination of pre- and postoperative nutritional care in abdominal cancer patients is superior to only postoperative nutritional care. We found that perioperative nutritional care does seem to prevent statistically significant lean mass loss 7 days after surgery but not after 14 days or 4 weeks. While there has been previous research conducted on the impact of nutritional status in cancer patients and their body composition and functional status[8-10,23], this is the first research in our clinic of patients with carcinoma of GIT, and the first Slovenian study in patients with carcinoma of hepatobiliary system and pancreas.

We checked the nutritional risk score with NRS 2002 and malnutrition according to GLIM criteria. It was crucial to check whether there were significant differences between the two groups at the beginning of the study to see if these differences could have remained present throughout the observation period and affect our findings.

The only significant difference was that patients in group 2 had a 1 point higher average NRS 2002 score, which, although statistically significant, is of questionable clinical importance as it was not reflected in body composition or functional status.

Upon enrolment, all patients were hemodynamically stable and had no clinical signs of malnutrition (*i.e.*, oedema, angular stomatitis, improper healing of the wounds, etc.), and reported no history of nutritional disorders. No participants underwent emergency surgery due to ileus or bowel perforation. This is also the case in other studies investigating nutritional care in abdominal cancers, as they are all performed on elective surgical patients.[24-27]

There were few differences between the observed groups during the course of our study. The main reason could be that the observation time was relatively short, and the number of patients was small. In a recent randomized control trial on patients with colorectal carcinoma, there was an almost 2 points higher skeletal muscle index, lower sarcopenia prevalence, and improved chemotherapy tolerance after 3 months in the intervention group.[27] Only those with a score of 3 or more points on NRS 2002 upon discharge from the hospital were included. The nutritional risk of patients in their study was estimated to be higher than in ours, which could further explain the lack of significant difference between our G1 and G2 groups, where the minimal NRS 2002 value in their study was 3. Similarly, a study conducted on patients with oesophageal carcinoma found significantly smaller relative muscle mass loss after 3 and 6 months but not after 1 month in patients that received ONS alongside disease state-specific nutrition.[28] The last check-up in our study was scheduled for 4 weeks after surgery when we ex-

pected to detect any change due to the variation in preoperative nutrition. Secondly, this was the time that some of the patients would start postoperative chemo- or radiotherapy, which could have affected the study results.[6,7] A possible conclusion could be drawn from this that the effects of nutritional care are seen in the longer term, rather than short-term (*i.e.*, 4 weeks post-surgery).

To reduce the variables in our study, all patients took the same type of ONS, EPA containing, which is considered to have an immunomodulatory effect.[29] A study published in 2019, used the same type of ONS as we did, where patients in the intervention group took ONS for the 7 consecutive days before surgery and for 21 days from when they could again tolerate oral intake.[28] The average lean mass loss in the control group was 6.74% and 6.89% in the intervention group, and the difference was neither statistically nor clinically significant. The loss was greater than in our study, even though their patients were, on average, 7 years younger. Interestingly, the effectiveness of ONS with EPA in that study was only significant when comparing the data for a subgroup of younger patients. This can be explained by either statistical error due to multiple testing or by weaker anabolic response of skeletal muscle in the elderly, which has been well documented in the medical literature.[29] Dividing participants into age groups was not reasonable in our study due to the small number of participants.

The importance of measuring body composition and muscle mass can be seen when looking at the second measurement; although there was no noteworthy distinction in body mass or BMI, a marked dissimilarity was observed in lean mass and FFMI. Rinninella *et al*.[30] found no difference in body mass between intervention and control groups 8 days and 1 month after surgery, on par with our findings based on body mass. Nevertheless, this same study found a significant increase in body mass when using ONS enriched with omega-3 fatty acids. Interestingly, three studies in the aforementioned meta-analysis that looked at muscle mass as opposed to just body mass found no significant difference in neither body mass nor muscle mass.[30] In addition, the patients received only postoperative ONS, and the control group did not receive ONS at all. Considering this, our results indicate that providing preoperative ONS on top of postoperative ONS might offer additional benefits in the first week after surgery.

When looking at hand grip strength and functional status, there is no difference between the two groups. This can partially be explained by the aforementioned anabolic muscle response as our patients were on average 72 years old. Moreover, there was no controlled exercise regime for patients in our study, although they were encouraged to exercise by the dietitian and clinical nutrition physician. It is well established that better results are achieved when treating malnourished patients and combining ONS with exercise regimens.[31] Hence, the prehabilitation should be trimodal and include nutrition, physical exercise, and a stress-reducing psychological component.[32]

It is worth highlighting that we did not observe any significant difference between the two groups at the end of the four-week period. Even though the percentage of malnourished patients in the first group was twice that in the second group, it only approached the cut-off for statistical significance. This further supports the previously proposed idea that pre-, in addition to, postoperative ONS might offer further benefits in the first week after surgery, as well as later on during the cancer treatment. This is not a definitive conclusion, but it provides outlines for further research. On top of that, the participants in the second group had a higher average NRS 2002 score but a lower relative share of malnourished patients. This demonstrates that NRS 2002 is a *screening* tool and should not be used for making definitive diagnoses, as it has been previously well established.[8,13]

It is important to address the limitations of our study. Primarily, the number of included patients was relatively low. Since there is no established clinical pathway for nutritional care, the dropout rate was relatively high. In addition to that, the patients that did not attend the follow-ups were predominantly the elderly who lived far away from the clinical nutrition unit. They had a large number of medical appointments postoperatively, and because they perceived nutritional care as less important, they decided not to attend the follow-ups so as to not burden their caretakers (*i.e.*, relatives) with transportation to and from the outpatient clinic. Secondly, the included patients were not truly randomised and this has most likely impacted the results, as the patients who were able to undergo surgery on a short notice were generally relatively fit. The final limitation is that we did not measure any clinical course parameters such as length of stay or quality of life.

In conclusion, there is an indication that combined preoperative and postoperative nutritional care could offer some advantages when compared to only postoperative nutritional care. The findings of this pilot study will be the foundation for

establishing a clinical pathway for nutritional care for abdominal cancer patients to positively affect their treatment outcomes at the UMC Ljubljana Department of Abdominal Surgery.

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research article

Treatment and outcome of patients with Graves' disease and metastatic differentiated thyroid cancer

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Background. The aim of the study was to report on the experience in a single tertiary cancer center about the treatment and outcome of patients with Graves' disease (GD) and metastatic thyroid cancer as compared with patients without GD in our country.

Patients and methods. Altogether, 28 patients (8 males, 20 females; 49–85 years of age; median 74 years) were treated because of differentiated thyroid cancer and distant metastasis at the time of diagnosis during a 10-year period (from 2010 to 2019) in the Republic of Slovenia. The subject of our retrospective study were four patients (three men, one female; 64–76 years of age, median 73 years) who had Graves' disease and metastatic thyroid cancer.

Results. The mean age of patients without GD and with GD was 74 years and 71 years, respectively (p = 0.36). There was a trend for male predominance in patients with GD (p = 0.06). There was no statistical difference in size of primary tumors, pT stage or pN stage between the group of patients without GD and with GD. The median length of follow-up was 3.33 years (range 0.04–7.83) and 5-year disease-specific survival was 51%. One of four patients with GD and 14 of 24 patients without GD died of thyroid cancer. There was no statistical difference in disease-specific survival between patients' group of without GD and with GD (p = 0.59).

Conclusions. In our country Slovenia, 14% of patients with metastatic differentiated thyroid carcinoma at the time of diagnosis had Graves' disease. There was no difference in the treatment, outcome or survival of patients with GD in comparison to those without GD.

Key words: differentiated thyroid cancer; metastases; Graves' disease; treatment

Introduction

Graves' disease (GD) is a systemic autoimmune disease directly caused by circulating antibodies against TSH receptor (anti-TSH-R) that bind to the thyrotropin receptor (TSH-R), subsequently inducing the production and release of thyroid hormone, proliferation of thyrocytes, and enlargement of the thyroid gland.[1,2] High serum anti-TSH-R antibodies were reported to stimulate the growth of thyroid cancer and metastasis.[3] A recent meta-analysis demonstrated an increased risk of distant metastasis at the time of cancer diagnosis in patients with differentiated thyroid cancer and GD in comparison to those without GD.[4]

There are only limited data in the literature about treatment of patients who have Graves' disease and metastatic thyroid cancer, probably because the prevalence of GD in patients with thyroid cancer is very low, and the present guidelines do not give specific recommendations for the treatment of patients with differentiated thyroid

cancer who have GD.[5,6] However, Pellegriti *et al*.[7] reported increased disease-specific mortality in patients with GD in comparison with matched euthyroid patients with thyroid cancer. Recently, we reported on a case report of a patient with simultaneous hormone-active metastatic Hürthle cell thyroid cancer and Graves' disease which was treated by a combined multimodal treatment, but despite treatment, the disease rapidly progressed and the patient died due to distant metastases 28 months from diagnosis.[8] The aim of the study was to report on experience in a single tertiary cancer center about the treatment and outcome of patients with Graves' disease and metastatic thyroid cancer in comparison to those without Graves' disease and metastatic thyroid cancer in our country Slovenia.

Patients and methods

Study population

There were 1524 patients (354 males and 1170 females, 11–91 years of age, median 51 years) with a differentiated thyroid carcinoma registered by The Cancer Registry of Republic of Slovenia during a 10-year period (from 2010 to 2019). During this period, altogether 28 patients (eight males, 20 females; 49–85 years of age; median 74 years) were treated because of differentiated thyroid cancer and distant metastasis at the time of diagnosis at our Institute. The subject of our retrospective study were four patients (three men, one female; 64–76 years of age, median 73 years) who had Graves' disease and metastatic thyroid cancer. The Protocol Review Board and Ethics Committee of the Institute of Oncology on 9th December 2020 (ERID-KSOPKR-0082/2020, ERIDEK-0083/2020, ERIDNPVO-0040/2020) reviewed and approved the study, which was conducted in accordance with the ethical standards prescribed in the Declaration of Helsinki. For retrospective studies, informed consent is not necessary according to the national regulations. The need for consent was waived by the Institutional Review Board and Ethics Committee of the Institute of Oncology Ljubljana.

Thyrotoxicosis with concomitant thyroid cancer was detected in 5 of 28 patients with distant metastases. Anti-TSH-R antibodies were not measured in all our patients. However, anti-TSH-R antibodies were measured in all patients with hyperfunctioning primary tumors or hyperfunctioning metastases. Elevated anti-TSH-R antibodies were detected in 4 of our 28 patients with distant metastases. All four patients with GD had a hyperfunctioning primary tumor as well as hyperfunctioning metastases.

A chart review for each patient with distant metastases was performed. All histological slides of our patients with metastatic differentiated thyroid cancer were examined by the pathologist experienced in thyroid pathomorphology. Distant metastases were diagnosed by clinical examination and additional diagnostic procedures, including lung and/or bone X-ray, ultrasonography, ultrasound guided fine-needle aspiration biopsy, radionuclide investigations with radioiodine and ^{18}F-FDG PET/CT, computed tomography, and/or nuclear magnetic resonance imaging. The tumor stage, presence of regional and/or distant metastases, as well as residual tumor after surgery were assessed by the 8th edition of TNM clinical classification according to the UICC criteria from 2017.[9] Data on patients' age, gender, disease history, presence of Graves' disease, extent of cancer, histomorphological characteristics, mode of cancer specific therapy, outcome, and survival were collected. The clinical and pathological characteristics of the tumors are presented in Table 1. The treatment of patients and their outcome are presented in Table 2.

The majority of patients received multimodal treatment. Surgery is the mainstay of the treatment of primary tumors in differentiated thyroid cancer. All surgically treated patients had primary surgery and all other cancer-specific therapies (surgery, radioiodine (RAI) ablation of thyroid remnant, RAI therapy, external beam radiotherapy (EBRT) and/or systemic therapy) at the Institute of Oncology. All patients received therapy with L-thyroxine for TSH suppression.

Follow-up

All patients had a follow-up exam at our Institute at least twice per year. This consisted of obtaining medical history, a physical examination, and determining serum Tg concentration. Imaging with radioiodine scintigraphy and/or ^{18}F-FDG PET/CT, computed tomography, and/or nuclear magnetic resonance was conducted once a year. It was also conducted whenever Tg concentration increased or clinical symptoms suggested that the disease had progressed.

Survival

Cause-specific and overall survival was defined as the period from primary cancer treatment to death or the last follow-up. The median duration of follow-up was 3.33 years (range 0.04–7.83 years).

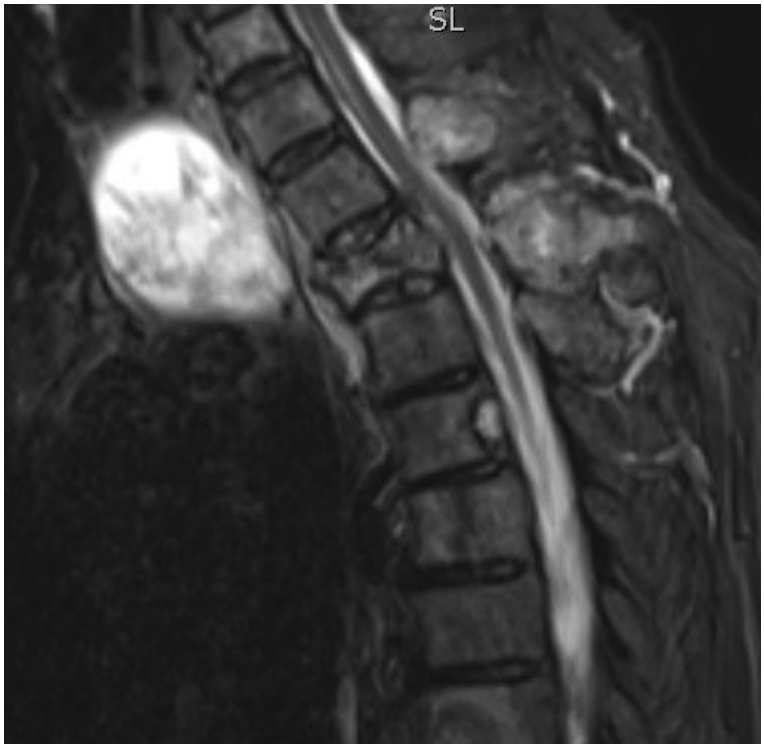

FIGURE 1. A 75-year-old patient was operated on after preparation with thiamazole for a pathological fracture of Th2. Spinal stabilization was performed.

Statistical analysis

The Student t-test or the Mann–Whitney U-test was used according to data distribution. The association between categorical variables was tested by the chi-square test or Fisher's exact test, as appropriate. All comparisons were two-sided and a p-value <0.05 was considered statistically significant. The survival curves were calculated according to the Kaplan-Meier method. A multivariate statistical analysis was not performed because of the small number of patients. The statistical package PASW 18 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

Results

Patients with Graves' disease

A 71-year-old patient with GD was presented to a surgical oncologist because of a 2.3 cm primary papillary thyroid cancer with lung metastases. He had hyperthyroidism and GD after iodine exposure, heart failure, generalized arteriosclerosis, gangrene of the lower extremity, and type 2 diabetes. He had just had a myocardial infarction with stented coronary arteries. Due to the poor general condition and accompanying diseases, we did not decide on surgical intervention or oncological treatment. He died after two months due to deterioration of heart function.

A total thyroidectomy was performed on a 76-year-old patient with hyperthyroidism due to GD and cytological suspicion of papillary thyroid cancer. Before the operation, she received thyrostatic drugs. Histologically, it was a poorly differentiated thyroid carcinoma, 6.5 cm in diameter with extensive capsular invasion, but no vascular invasion or extrathyroidal spread. The metastases were not functionally active. After hormonal withdrawal she received 150 mCi of RAI, which accumulated in the lungs, skeleton, left kidney and right paracolic area. After six months and another six months, she received 152 mCi and 145 mCi of RAI after hormonal withdrawal, which accumulated in the same places. After nine months, she received the 4th and last 152 mCi of radioiodine and accumulation was less intense. After another nine months, there was no more accumulation in the metastases on RAI whole body scan, and 18F-FDG PET-CT showed the progression in the 5th left rib and right iliac bone. The patient was still asymptomatic. The skeletal lesions with a progression of disease were treated with EBRT. Anti-TSH-R levels were elevated all the time. The Tg value fell from 11982 ng/mL before surgery to 9598 ng/mL before the first RAI therapy, and then slowly declined. Titres of anti-Tg antibodies were not increased. At the time of progression 34 months after the first treatment, Tg value was only 280 ng/mL, anti-Tg antibodies were not increased, but TPO antibodies were increasing. Because the patient was asymptomatic, the medical oncologist has not yet decided on systemic treatment and the patient has been on active surveillance for seven months since progression of the disease was diagnosed.

A 75-year-old patient was operated on after preparation with thiamazole for a pathological fracture of Th2 (Figure 1) and spinal stabilization was performed in October 2017. Postoperatively, he was irradiated in the area of the thoracic spine with sensitization with weekly low doses of vinblastine and doxorubicin. In December 2017, a total thyroidectomy was performed. Histological examination showed a 7 x 5.5 cm oncocytic tumor with regressive changes after chemotherapy. In January 2018, T3 hyperthyroidism occurred. In February 2018, the patient received 151 mCi of RAI, which accumulated in many places in the spine. In March 2018, the RAI non-avid tumor in the sternum and

TABLE 1. Clinical characteristics and pathological characteristics of tumors

Factor	Subgroup	All patients (N = 28)	Without Graves' disease (N = 24)	With Graves' disease (N =4)	p-value
Mean age of patients (year)		73.86	74.25	71.50	0.359
Mean primary tumor size (cm)		5.604	5.483	6.325	0.355
Gender	Female Male	20 8	19 5	1 3	0.058
Age (years)	54 or less 55 or more	1 27	1 23	0 4	1.00
Hyperthyreosis at presentation	No Yes	23 5	23 1	0 4	0.001
Functional metastases	No Yes	26 2	24 0	2 2	0.016
Tumor diameter (cm)	0-4 4.01 and more	9 19	8 16	1 3	1.00
pT tumor stage	pTx, pT1 or pT2 pT3 pT4	7 7 14	6 5 13	1 2 1	0.522
N stage	N0 N1 or N2	20 8	17 7	3 1	1.00
M stage	M0 M1	0 28	0 24	0 4	-
Type of metastases	Lung only Bones and others Lungs and others without bones	11 12 5	10 9 5	1 3 0	0.759
Single organ metastases	No Yes	14 14	11 13	3 1	0.596
Tumor type	Papillary Hürthle Follicular Poorly differentiated	14 6 5 3	12 4 5 3	1 2 0 1	0.279
Tumor differentiation (N = 19)	Well Moderate or poor	6 13	5 12	1 1	1.00

in the right iliac bone was treated with EBRT. Because of side effects of bisphosphonates therapy, the patient discontinued this therapy. In August 2018, he had T3 hyperthyroidism again. After preparation with thiamazole, he received 160 mCi of RAI in October 2018. It accumulated in the skeletal metastases. Due to poor accumulation of RAI in Th5, he was referred to a medical oncologist, who did not decide on systemic therapy. In March 2019, he received 161 mCi RAI, the accumulation of RAI in metastases was less intense. In February 2020, he was asymptomatic, but 18F-FDG PET-CT showed a progression of metastases, so therapy with 166 mCi of RAI was administered. Only some metastases accumulated RAI. In April 2020, MRI showed progression of metastasis in Th5 and again T3 hyperthyroidism was diagnosed, therefore therapy with sorafenib (200 mg + 400 mg) was initiated. Because of the side effects, the dose was reduced to half, which he tolerated better. But after four months, the patient stopped this therapy due to side effects. He was asymptomatic until April 2022. At that time 18F-FDG PET-CT showed new metastases in the skeleton and T3 hyperthyroidism recurred. Therapy with lenvatinib was initiated on May 2022. For the first time since the beginning of cancer treatment, anti-TSH-R levels fell to the normal level three months after initiation of treatment with lenvatinib. The level of Tg also dropped from 5838 ng/mL in May 2020 to 2360 ng/mL in August 2022.

A 64-year-old male patient had clinical signs of hyperthyroidism and a tumor measuring 9 cm in diameter of the left thyroid lobe, metastatic neck lymph node and metastases in the lungs, mediastinum, and in the 8th right rib measuring 20 x 5.6 x 4.5 cm, in the left acetabulum measuring 9 x 9 x 3 cm and in the skull measuring 5 x 4 x 2 cm.[8] The

TABLE 2. Treatment of patients and their outcome

Factor	Subgroup	All patients (N = 28)	Without Graves' disease (N = 24)	With Graves' disease (N = 4)	p-value
Thyroid surgery	No	8	7	1	1.00
	Yes	20	17	3	
Thyroid surgical procedure	Total or near-total thyroidectomy	18	15	3	1.00
	Lobectomy or less	10	9	1	
Residual tumor after surgery	No surgery	8	7	1	0.916
	R0 (without residual tumor)	11	9	2	
	R1	2	2	0	
	R2	7	6	1	
Neck dissection	No	24	21	3	0.481
	Yes	4	3	1	
Surgery of distant metastases	No	26	24	2	0.016
	Yes	2	0	2	
RAI ablation after surgery	No	10	9	1	1.00
	Yes	18	15	3	
Therapy with RAI	No	10	9	1	1.00
	Yes	18	15	3	
EBRT to the neck	No	21	17	4	0.545
	Yes	7	7	0	
EBRT (any site)	No	15	13	2	1.00
	Yes	13	11	2	
Preoperative chemotherapy	No	25	23	2	0.045
	Yes	3	1	2	
Chemotherapy	No	22	20	2	0.191
	Yes	6	4	2	
Targeted therapy	No	18	16	2	0.601
	Yes	10	8	2	
Outcome	Alive with disease	9	7	2	0.461
	Dead of disease	15	14	1	
	Dead of other causes	4	3	1	

RAI = radioiodine

region of the left hip had been irradiated with concomitant doxorubicin 20 mg once weekly. When hyperthyroidism was controlled with thiamazole, a total thyroidectomy was performed. Persistent T3 hyperthyroidism, most likely caused by anti-TSH-R stimulated T3 production in a large metastasis in the 8th right rib, was cured by rib resection. The patient was treated with three RAI therapies. But after a short interval, the disease progressed despite treatment with RAI and therapy with sorafenib. The patient died due to distant metastases 28 months from the beginning of treatment.

Histology, age of patients and type of metastases

At presentation, 5 of 28 patients had hyperthyroidism and four of them had GD. Two patients with GD had functional metastases.

Papillary carcinoma, Hürthle cell carcinoma, follicular and poorly differentiated thyroid carcinoma were diagnosed in 13, 6, 5 and 4 patients, respectively. Graves' disease was present in two patients with Hürthle cell carcinoma, one with papillary and one with poorly differentiated thyroid carcinoma (p = 0.28).

The mean age of patients without GD and with GD was 74 years and 71 years, respectively. Age of patients with and without GD was not statistically different (p = 0.36). There was a trend for male predominance in patients with GD (p = 0.06). Mean primary tumor size in patients without GD and with GD was 5.5 and 6.3 cm, respectively (p = 0.36). There was no statistical difference in pT stage (p = 0.52) or pN stage (p = 1.00) between the group of patients without GD and with GD.

Initial sites of metastases were: lungs in 24 cases, bones in 12 cases, mediastinum in eight cases,

liver in two cases and skin in one case. Single and multiple organ metastases were present in 14 and 14 patients, respectively. Lung metastases only, bone metastases only and skin metastases only were present in eleven patients, two patients and one patient, respectively. There was no statistical difference in distribution of metastases between patients without GD and with GD.

Treatment

Palliative treatment was only applied in four cases: in one due to severe comorbidities, and in three due to very advanced cancer. The data on the type of surgery for primary tumors and treatment of distant metastasis are listed in Table 2. Total or near-total thyroidectomy is considered a proper surgical procedure for thyroid cancer; however, it was performed in only 18 of 28 patients. It was not performed because of inoperable tumors (N = 8), very advanced age of the patient, severe comorbidities (N = 1), or if the patient refused surgical procedure (N = 1). Initial treatment in three patients with a locally advanced tumor was neoadjuvant chemotherapy. Tumor size decreased in all patients: by more than 30% in two patients, and by less than 30% in one patient. Metastases in regional lymph nodes were surgically treated as a part of primary surgical procedure by functional radical neck dissection in four patients. Surgical treatment of distant metastases was more common in patients with GD in comparison to those without GD (p = 0.016). Surgical therapy of bone metastases was conducted on two patients: a resection of the 8th right rib with hormone active metastases in one patient and a resection of metastasis in the 2nd thoracic vertebra due to pathological fracture and narrowing of the spinal canal in another patient.

RAI was used for the ablation of thyroid remnant tissue in 18 (64%) patients. The ablation dose was 3.4–4.8 GBq (92–129 mCi) of RAI. RAI was used also for treatment of distant metastases with empiric dose of 3.7–7.4 GBq (100–200 mCi) in 14 patients. These 18 patients received altogether 31 therapies with RAI (range 1– 4; median 2) and a dose 11.47–24.72 GBq (310–668 mCi; median 535 mCi).

Altogether, six patients were treated with chemotherapy, while kinase inhibitors were used in ten patients. EBRT was done in a total of 13 patients, of whom seven received EBRT to the neck and superior mediastinum.

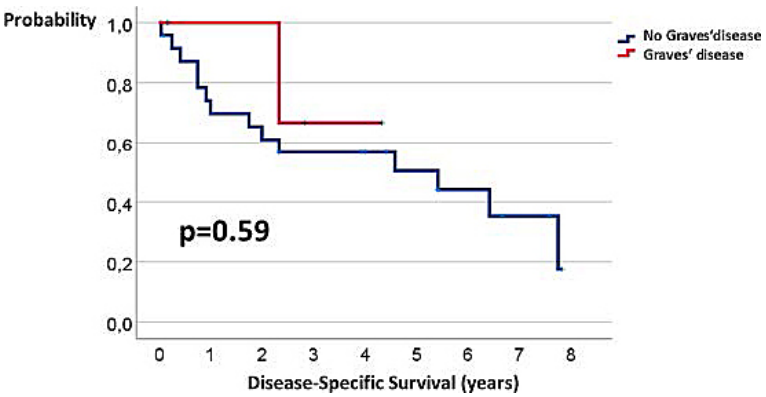

FIGURE 2. Disease-specific survival of patients with Graves' disease (GD) and without GD.

Survival

Patients were followed for 0.04–7.83 (median 3.33) years. Disease-specific survival of our 28 patients ranged from 0.04 to 7.83 years. The 5-year disease-specific and overall survival was 51% and 44%, respectively. The 3-year disease-specific survival of patients with and without Graves' disease were 67% and 57%, respectively (Figure 2). The length of disease-specific survival in patients with and without Graves' disease was not statistically different (p = 0.59). The 3-year overall survival of patients with and without Graves' disease were 50% and 54%, respectively (Figure 3). The length of overall survival in patients with and without Graves' disease was not statistically different (p=0.99).

In 18 patients who had total thyroidectomy and RAI therapy, the 5-year disease-specific and overall survival was 70% and 61%, respectively. The 3-year disease-specific survival of patients with and without Graves' disease were 66% and 81%, respectively. The length of disease-specific sur-

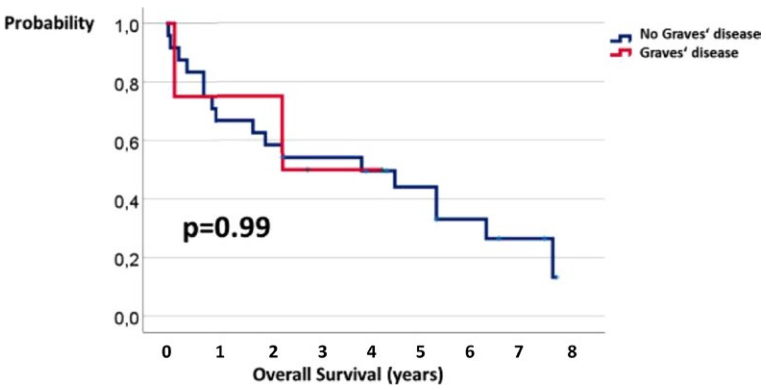

FIGURE 3. Overall survival of patients with Graves' disease (GD) and without GD.

vival in patients with and without Graves' disease was not statistically different (p = 0.66). In these 18 patients, the 3-year overall survival of patients with and without Graves' disease were 66% and 76%, respectively. The length of overall survival in patients with and without Graves' disease was not statistically different (p = 0.91).

By the end of the study, nine patients were still alive (2.3-7.83 years, median 4.42 years), four patients died of causes unrelated to primary disease, while 15 patients died of thyroid carcinoma. Of the latter, eleven patients died of distant metastases, one of uncontrolled locoregional disease, and the remaining three patients died of distant and locoregional progression of the disease. Two of four patients with Graves' disease are alive, at the time of writing for 34 and 52 months. Both have slow progression of RAI non-avid metastases; one is on systemic multikinase inhibitor therapy, while the other is still asymptomatic and on active surveillance before initiation of systemic therapy.

Discussion

The aim of our study was to report on our experience about the treatment and outcome of patients with Graves' disease and metastatic thyroid cancer in comparison to those without Graves' disease and metastatic thyroid cancer in our country. In our country, 14% of patients with metastatic differentiated thyroid carcinoma at the time of diagnosis had Graves' disease. There were no significant differences in the oncological treatment of patients with GD in comparison to those without GD. Cancer-specific and overall survival of patients with GD was not significantly shorter in comparison to those without GD.

Functioning metastatic thyroid carcinoma is a rare disease.[10] Qiu *et al*.[10] reported that the prevalence of hyperfunctioning metastases in patients with follicular thyroid carcinoma was 5/38 (13%). However, hyperfunctioning metastatic thyroid carcinoma with concomitant Graves' disease is an even rarer condition. Our data show that it was present in 7% of patients with distant metastases at the time of diagnosis.

Treatment of patients with hyperfunctioning metastases of thyroid cancer and GD is a challenging task. For the treatment of patients with hyperfunctioning thyroid carcinoma, there are two aims: to control hyperthyroidism, as well as the cancer.[11] Unfortunately, the current management guidelines for differentiated thyroid cancer does not recommend any specific management for patients with metastatic cancer and GD.[4,5]

Liu *et al*.[11] reported that total thyroidectomy may be the optimal primary treatment option for patients with functional primary tumor and metastases which are not hyperfunctioning. In such cases a total thyroidectomy reduces the dose of RAI required to treat the metastatic lesions. But in patients with hyperfunctioning metastatic lesions with non-functioning primary thyroid carcinoma, a total thyroidectomy may lead to deterioration of hyperthyroidism, as the majority of hormones are produced by metastatic lesions.[11] Such was the case in one of two of our patients with hyperfunctioning metastases. In a systematic review of the literature, Liu *et al*.[11] reported that, after total or subtotal thyroidectomy, a transient improvement of hyperthyroidism was obtained in only one of five patients, while in four patients, hyperthyroidism persisted. Furthermore, one of four patients succumbed to thyroid crisis 12 days after surgery. Likewise, Girelli *et al*.[12] reported on a case of extremely severe hyperthyroidism due to pelvic bone metastasis in which hyperthyroidism worsened after total thyroidectomy and after the first dose of RAI. But in their case, the administration of methimazole, prednisone and multiple, fractioned and small doses of radioiodine cured the hyperthyroidism and stabilized the neoplastic growth.[12] Our experience is similar to the report by Liu *et al*.[11], because after total thyroidectomy, hyperthyroidism persisted in both our patients with hyperfunctioning metastases. In one of them, therapy with thiamazole, RAI therapy, a combination of EBRT and concomitant doxorubicin chemotherapy cured hyperthyroidism caused by functional metastasis in bone metastasis in the sternum and pelvis. In the other patient, on the other hand, a surgical resection of the 8th right rib in which functional metastasis caused a T3 hyperthyroidism was needed in order to cure hyperthyroidism.[8] Our second case confirm the opinion, that in cases with a metastatic lesion which is resistant to RAI and the functioning lesion is resectable, surgery is a good treatment option.[11]

RAI is an essential part of the treatment of hyperfunctioning metastatic lesions.[10] But therapy with RAI in patients with functioning metastases may result in thyroid storm and death.[11,13] To avoid a possible thyroid storm, antithyroid medication is required before treatment with RAI.[11] In the literature review, Fu *et al*.[14] reported that activity of RAI to treat hyperfunctioning metastases varied from 13 mCi to 200 mCi.[14-17] Severe hyperthyroidism can

be improved with repeated low-dose radioiodine therapy.[16] High doses of RAI could cause a large amount of tumor cell destruction, releasing a burst of thyroid hormones and causing thyrotoxic storm if the patients are not adequately prepared before and treated after RAI.[14] Glucocorticoids and antithyroid medications should be used prior to surgery and RAI treatment to avoid the occurrence of thyrotoxic storm, as well as during RAI treatment in order to inhibit thyroid hormone synthesis and peripheral conversion of T4 to T3.[13]

Another effective evolving treatment modality for progressive metastatic thyroid cancer is systemic therapy.[8,18] Systemic therapy with a multikinase inhibitor, sorafenib, was effective in two of our patients. The effect before cancer progression lasted eight and 24 months. Furthermore, hyperthyroidism was also prevented after therapy with sorafenib in both cases. In one of them, sorafenib was stopped due to side effects after four months. After progression of the disease and recurrence of hyperthyroidism, lenvatinib effectively prevented disease progression and cured hyperthyroidism. Also, Danilovic *et al*.[18] described that targeted therapy with lenvatinib is an option for the control of hyperfunctioning metastases.

External beam radiotherapy is the treatment of choice for inoperable distant metastases and/or large functional metastases. Unfortunately, it does not always prevent hyperthyroidism.[16]

Premoli *et al*.[19] reported that there was no association between baseline anti-TSH-R levels and outcome in patients with differentiated thyroid carcinoma associated with GD. But, Valenta *et al*.[20] reported that in one of three patients with metastatic follicular thyroid cancer-causing hyperthyroidism associated with elevated anti-TSH-R, level of anti-TSH-R declined after two RAI treatments with improvement in thyrotoxicosis. Also, Basaria *et al*.[21] reported in a patient with functional metastases of papillary thyroid cancer and GD, a decline in the level of anti-TSH-R to 87% of normal range after three RAI therapies. The effect of RAI therapy was confirmed with CT investigation and with decrease of thyroglobulin level which on TSH suppression declined from 2280 ng/dL to 55 ng/dL.[21] In three of our patients with GD, levels of anti-TSH-R have not declined after therapy with RAI or with sorafenib. However, three months after initiation of therapy with lenvatinib, the level of anti-TSH-R declined dramatically in the patient.

One of the aims of our study was to compare outcome of patients with and without GD. Median survival of our patients with differentiated thyroid cancer with GD was 31 months. The 3-year disease-specific survival of patients with and without GD were 67% and 57%, respectively. The length of disease-specific survival in patients with and without GD was not statistically different ($p = 0.59$). Similar survival was reported by Als *et al*.[22] who treated five patients with functional metastatic differentiated carcinoma with median survival of 39 months. Our results are also in agreement with a systematic review and meta-analysis of 25 studies which included 987 patients with differentiated thyroid cancer with GD and 2,064 patients with differentiated thyroid cancer without GD, which showed no difference in cancer related mortality and recurrence/persistence during follow-up.[4]

Our study has several limitations. The first limitation is the retrospective nature. Another limitation is a low number of all cases with metastatic thyroid cancer. Furthermore, only two of four patients with GD had hyperfunctioning metastases. However, to our knowledge, there are no data in the literature about the national incidence of patients with metastatic thyroid cancer and concomitant GD. Furthermore, notification of cancer has been compulsory in Slovenia since the foundation of the Cancer Registry of Republic of Slovenia in 1950 and prescribed by law[23], so our data about incidences represent reliable population-based data. Additionally, all patients with thyroid cancer are treated at the Institute of Oncology in Ljubljana, so our data represent a population-based incidence of GD among patients with metastatic differentiated thyroid cancer.

Conclusions

In our country, 14% of patients with metastatic differentiated thyroid carcinoma at the time of diagnosis had GD. There was a trend for male predominance in patients with GD. Treatment of patients with metastatic differentiated thyroid carcinoma at the time of diagnosis who have GD is multidisciplinary and includes surgical therapy, RAI therapy, systemic therapy and/or EBRT. There were no significant differences in the oncological treatment of patients with GD in comparison to those without GD. Cancer-specific and overall survival of patients with GD was not significantly shorter in comparison to those without GD.

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research article

Local control and survival after stereotactic body radiation therapy of early-stage lung cancer patients in Slovenia

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Background. Stereotactic body radiation therapy (SBRT) precisely and non-invasively delivers ablative radiation dose to tumors in early-stage lung cancer patients who are not candidates for surgery or refuse it. The aim of research was to evaluate local control, overall survival (OS), local progression free survival (LPFS), distant metastases free survival (DMFS), disease free survival (DFS) and toxicity in early-stage lung cancer patients treated with SBRT in a single tertiary cancer centre.

Patients and methods. We retrospectively evaluated medical records and radiation treatment plan parameters of 228 tumors irradiated in 206 early-stage lung cancer patients between 2016 and 2021 at the Institute of Oncology Ljubljana.

Results. After 25 months of median follow up, 68 of 206 (33%) patients died. Median OS was 46 months (CI 36−56), 1-year, 2-year and 3-year OS were 87%, 74% and 62% and 5-year OS was 31%. A total of 45 disease progressions have been identified in 41 patients. Local progress only was noticed in 5 (2%) patients, systemic progress in 32 (16%) and combined systemic and local in 4 (2%) patients. Local control rate (LCR) at 1 year was 98%, at 2 and 3 years 96% and 95% at 5 years. The 1-, 2- and 3-year LPFS were 98%, 96% and 94%, respectively and 5-year LPFS was 82%. One, 2-, 3- and 5-year DFS were 89%, 81%, 72% and 49%, respectively. Among 28 toxicities recorded only one was Grade 4 (pneumonitis), all others were Grade 1 or 2. No differences in LCR, LPFS, DFS were found in univariate analysis comparing patient, tumor, and treatment characteristics. For OS the only statistically significant difference was found in patients with more than 3 comorbidities compared to those with less comorbidities.

Conclusions. Early lung cancer treated with SBRT at single tertiary cancer centre showed that LCR, LPFS, DFS, DMFS and OS were comparable to published studies. Patients with many comorbidities had significantly worse overall survival compared to those with less comorbidities. No other significant differences by patient, tumor, or treatment characteristics were found for DMFS, LPFS, and DFS. Toxicity data confirmed that treatment was well tolerated.

Key words: stereotactic body radiotherapy (SBRT); early-stage lung cancer; lung cancer; local control; survival

Introduction

Localized disease is diagnosed in up to 20% of patients with lung cancer.[1] This proportion, especially in patients with early lung cancer is increasing due to lung cancer screening programs and covid-19 pandemic's increased lung diagnostics during the last two years. Furthermore, number of inoperable or high-risk patients is growing due to an aging population. According to Slovenian national cancer registry for 2019 localized disease was reported in 18% of all newly diagnosed

lung cancer patients.[2] Standard of care for these patients is lobectomy, however due to comorbidities and old age many of them are not eligible for surgery.[3,4] Inoperable patients with small tumors and no metastases in local lymph nodes and those who refuse surgery are treated with stereotactic body radiation therapy (SBRT). SBRT is a precise technique that can deliver a very high dose (i.e., ablative dose) to the target volume in one to eight fractions.[5,6] Studies have shown that efficacy of SBRT can be compared to surgery, although no randomized phase III studies have been completed.[7] Two prospective studies, STARS and ROSEL, were closed prematurely due to poor accrual.[8] Combined data with notable limitations from these two trials suggested that SBRT could be a reasonable treatment option in medically operable patients. Recent revised STARS trial with re-accrual of the SABR arm to a larger sample size and follow-up of 5.1 years confirmed the findings.[9]

Additional prospective randomized trials on this topic that will hopefully clarify this issue are STABLE-MATES (sub-lobar resection versus SABR) and VALOR (SABR versus anatomic pulmonary resection), but results will not be ready for some years.[10,11]

The results on the effectiveness of SBRT radiation and standard radiation are contradictory. SPACE trial and LUSTRE trial (published only in abstract form) report no difference in local control and OS.[12,13] On the other hand, superior local control and OS of SBRT compared to conventional radiotherapy of the primary inoperable peripherally located stage I NSCLC was proved in phase III randomized CHISEL study.[14]

In Slovenia SBRT technique was introduced at the Institute of Oncology Ljubljana in 2016 and its use has been constantly increasing since then. It is used for the treatment of primary tumors, local recurrences and metastases. This report focuses on treatment of early lung cancer patients with SBRT and represents our first 5-year analysis.

Patients and methods

We retrospectively reviewed medical records of 206 consecutive early-stage lung cancer patients and radiation treatment plan parameters of 228 tumors irradiated with SBRT between 2016 and 2021 at Institute of Oncology Ljubljana. The cut-off date of our analysis was 6th November 2022. In our clinical practice staging investigations routinely included computed tomography (CT) of chest and abdomen, brain CT/magnetic resonance imaging, whole-body fluorodeoxyglucose positron emission tomography (FDG PET/CT), blood work, and pulmonary function tests. All patients had either biopsy-proven lung cancer or pulmonary lesions that were considered ''suspicious'' by experienced chest radiologist and showed evidence of progression on at least two serial CT imaging studies and/or increased FDG uptake on PET scan. All patients were discussed at the multidisciplinary tumor board. Any decision to proceed with radiation therapy for patients without biopsy confirmation of disease was communicated and agreed upon in multidisciplinary tumor board. Decision was typically based on the predicted probability of malignancy (i.e., enlarged lesion on serial CT scans or PET/CT-avid lesion) and weighed against risks of biopsy. Patients with more than one primary lung tumor without evidence of metastasis were carefully discussed at multidisciplinary tumor board.

SBRT procedure

All patients undergoing initial 4D-CT simulation (Siemens Somatom Definition AS® CT) required immobilization on T-bar/Wingboard with a vacuum cushion device or thermoplastic mask (for tumors in the apex of the lung). Respiratory motion for tumors in lower lobes was minimized using abdominal compression belt. First two years Novalis Tx linear accelerator (Varian) with Exact Trac verification and correction system was used for detection of patient's movement. After that TrueBeam STx and True beam linear accelerators with the external respiratory monitoring system [Real-time Position Management (RPM) System, Varian® Medical Systems, Palo Alto, CA, USA] and Optical Surface Monitoring System (OSMS) was used. Patients had pre-treatment and verification CBCT image registered to the planning CT for daily position treatment verification. All set-up errors were corrected before treatment delivery.

Internal target volume (ITV) included gross tumor volume (GTV) expended by all visible tumor motion on 4D-CT. The planning target volume (PTV) was generated using a 5 mm circumferential expansion of the ITV. Required covering of ITV was at least 99% of the prescription dose. At least 95% of the PTV volume should be covered with 100% of prescribed dose and at least 99% of PTV volume should be covered with 90% of prescribed dose. Maximum dose was prescribed between 125–150% of the prescribed dose for 1–5 fractions and 110–130% for 8 fractions. The most frequently

used energy was 6 MV. During the last two years 6 MV flattening filter free (FFF) became the preferred choice.

Dose restrictions for organ at risk (OAR) were complied according to our inhouse protocol based on AAPM Task Group 101 report, RTOG 0915 study (for 4 fractions), and LungTech study for 8 fractions.[15-17] Restrictions for spinal cord Pmax were taken after Sahgal *et al*.[18]

Statistical definitions

Local control (LC) was defined as no recurrence within the high-dose region of the primary target tumor volume. LC rate was analyzed for all treated tumors. If a patient had more than one lesion treated, progression of any treated lesions was considered a local recurrence for local progression free survival (LPFS) calculation, which was computed from the date of RT completion till date of local recurrence, last follow up or death. Disease-free survival (DFS) was defined from the date of completed RT treatment to first either systemic or local recurrence of disease, last follow up or death. Distant metastases free survival (DMFS) was calculated from the date of RT completion till date of metastatic spread, last follow up or death. Overall survival (OS) was defined from the date of completed treatment until the date of death or the last contact in months. OS was calculated for each patient regardless of solitary or multiple tumor statuses. The censored cases were defined as the patients still alive at the time of the last follow-up.

The one-, two-, three- and five-year OS, DFS, DMFS and LPFS rates were estimated from the cumulative proportion surviving at the particular time (survival table). All p values ≤ 0.05 were considered statistically significant. Data were analyzed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA).

Radiation-induced toxicity was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.[19]

The study was approved by the Institutional Ethics Committee and Review Board (ERIDNPVO-0025/2022).

Results

Patients

Between April 2016 and December 2021, 206 consecutive patients (113 males and 93 females) with 228 tumors were treated at the Institute of Oncology Ljubljana with SBRT due to primary early-stage lung cancer. Mean age of our patients was 71 years (range 53–89). ECOG performance status was mainly good (0–2, 85.4%), although many of them had multiple comorbidities, the vast majority of which were caused by smoking. Most often patients had cardiovascular diseases (ischemic heart disease, heart failure, arterial hypertension, peripheral arterial occlusive disease), lung diseases (chronic obstructive pulmonary disease, interstitial lung disease, emphysema), renal insufficiency and gastrointestinal diseases. Interestingly, almost half

TABLE 1. Patient characteristics (n = 206)

Characteristic	Number	%
Age mean in years (range)	71.2 (53–89)	
Gender		
Male	113	54.9
Female	93	45.1
Other malignancies*		
yes	96	46.6
no	110	53.4
Number of comorbidities		
0–3	125	60.7
> 3	81	39.3
Lung function (%)	mean (range)	
FVC (data available for 153 pts)	87.7 (24-152)	
FEV1 (data available for 164 pts)	61.4 (17-144)	
DLCO (data available for 140 pts)	55.6 (15-120)	
ECOG Performance status before radiotherapy		
0	17	8.3
1	78	37.9
2	81	39.2
3	30	14.6
The reason for non-surgery		
Impaired lung function	92	44.7
Comorbidity	85	41.3
Patient refused	5	2.4
Old age	4	1.9
Combined reasons	20	9.7

*synchronous or in the past

DLCO = diffusing capacity of the lungs for carbon monoxide; ECOG = Eastern Cooperative Oncology Group, FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ptc = patients

TABLE 2. Tumor characteristics (n = 228)

Characteristic	Number	%
Histology		
Adenocarcinoma	84	36.8
Squamous cell carcinoma	38	16.7
Small cell lung cancer	4	1.8
NSCLC unspecified	19	8.3
No tissue diagnosis	82	36.0
Carcinoid	1	0.4
Location		
Left upper lobe	78	34.2
Left lower lobe	31	13.6
Right upper lobe	73	32.0
Right middle lobe	11	4.8
Right lower lobe	35	15.4
T stage		
1	194	85.1
2	27	11.8
3	7	3.1

NSCLC = non-small cell lung cancer

TABLE 3. Treatment characteristics (n = 228)

Characteristic		
Number of fractions	**Number of tumors**	**%**
1	1	0.4
2	2	0.9
3	32	14.1
4	3	1.3
5	174	76.3
8	16	7.0
Treatment characteristics	**Median**	**Mean (range)**
PTV volume (cc)	22.4	30.6 (5.9-160.4)
PTV max dose %	137.5	135.5 (104.7-151.4)
ITV coverage %	100	99.7 (66.5-100)
PTV coverage (V95) %	95	90.4 (32-100)
PTV coverage (V99) %	99.8	99 (88.8-100)
BED	115.5	112.3 (59.5-151.2)
Technique	**Number of patents**	**%**
3D	62	27.2
ARC	34	14.9
VMAT	132	57.9

ARC = dynamic conformal arc therapy; BED = biological effective dose; ITV = internal target volume; PTV = planning target volume; VMAT = volumetric modulated arc therapy; 3D = conventional conformal therapy

of the patients had a concurrent or previous malignancy. We also irradiated a patient with several tumors after a heart transplant.

Patients were inoperable due to impaired lung function (44.7%), comorbidities (41.3%) or both, but 5 patients refused surgical procedure. Lung function data were not available for all patients (Table 1).

Tumors

Majority of patients (186) had radiation of a single tumor, 18 patients had 2 tumors and 2 patients 3 tumors. Table 2 shows that vast majority of patients (as per AJCC 8th edition) had T1 tumors (85.1%). Adenocarcinomas were present in 84 tumors (36.8%), but nonverified lesions were common as well (36.0%). Tumors were mainly located in upper lobes (66.2%).

Treatment

Treatment prescription dose was mostly 50–55 Gy in 5 fractions (174 patients), next most common prescription was 54 Gy in 3 fractions (32 patients) and only one patient had a single fraction with 34 Gy delivered. More centrally located tumors were treated with 60 Gy in 8 fractions (16 patients), prescription of 48 Gy in 4 fractions was rarely used (3 patients).

During the first two years only 3D or dynamic conformal arc technique (ARC) was available for SBRT. New linear accelerators made volumetric modulated arc treatment (VMAT) (57.9%) possible afterwards (Table 3).[18]

Median PTV of tumors was 22.4 cubic centimetres (cc) with wide range of size (5.9–160.4). ITV and PTV coverage as well as PTV dose maximum can be found in Table 3.

Outcomes

Out of 206 patients, 2 patients did not complete intended treatment due to deterioration of medical condition (severe coughing, pleural effusion), but their data were included in the final analysis. They both had only 2 fractions delivered out of 3 fractions planned.

After 25 months of median follow up (range 1–69), 68 of 206 (33%) patients died. Median OS was 46 months (CI 36–56), 1-year, 2-year and 3-year OS were 87%, 74% and 62% and 5-year OS was 31%.

Due to retrospective nature of the analysis cause of death could not be retrieved for 25 pa-

tients, others died due to lung cancer (24), covid-19 (6), other malignancies (6), emergencies (4) and COPD (3).

Altogether, 45 recurrences were reported in 41 (20%) patients. Progression was local only in 5 (2%) patients. In two of those local recurrence of simultaneously irradiated 2 tumors was recorded on all irradiated sites at the same time. Systemic progression was noticed in 32 (15%) patients, who had 34 tumors irradiated (2 simultaneously), while in 4 patients (2%) (4 tumors) progressions were combined. Local recurrences (local + combined) showed malignant growth within PTV in 6 tumors and at the edge of PTV within the steep dose gradient in 5 tumors.

Local control rate (LCR) at 1 year was 98%, 96% at 2 and 3 years and 95% at 5 years. Local progression free survival (LPFS) at 1-year, 2-year, 3-year and 5-year were 98%, 96%, 94% and 82%, respectively (Figure 1). Interestingly, among 4 patients with small-cell lung cancer neither had local recurrence or systemic disease during the follow up period.

Among all patients, 36 (18%) experienced systemic disease spread. Distant metastases free survival (DMFS) after 1-year, 2-year and 3-year were 90%, 84% and 74%, while 5-year DMFS was 61%. Systemic spread was noted in lung (28), mediastinal lymph nodes (12), brain (5), bone (5), liver (5), pleura (4), and adrenal gland (3). Eighteen patients with progressive disease were still alive at the cut-off date.

Outcomes showed 89%, 81%, 72% and 49% of DFS after 1-year, 2-years, 3-years and 5-years, respectively.

The following toxicities were reported in 28 patients (13.5%): chest wall pain, rib fracture, dyspnea, pneumonitis, esophagitis, cough, radiodermatitis. Except for one Grade 4 pneumonitis, toxicities were Grade 1 or 2 and of short duration.

To assess the factors affecting LPFS, DFS, DMFS and OS, several clinical and dosimetric factors were studied using univariate analysis, including age, gender, tissue diagnosis, tumor location as well as mean and median PTV size, BED, PTV95 coverage, PTV99 coverage, PTV maximum dose, treatment length and treatment technique. Non-significantly better OS was seen for patients with verified tumors compared to non-verified ones (p = 0.06) as shown in Figure 2 and those with better PS (p = 0.07). The only significant difference in median OS was found between patients with 0–3 comorbidities compared to those with 4 and more, 57 months *vs.* 43 months as shown in Figure 3 (p = 0.03).

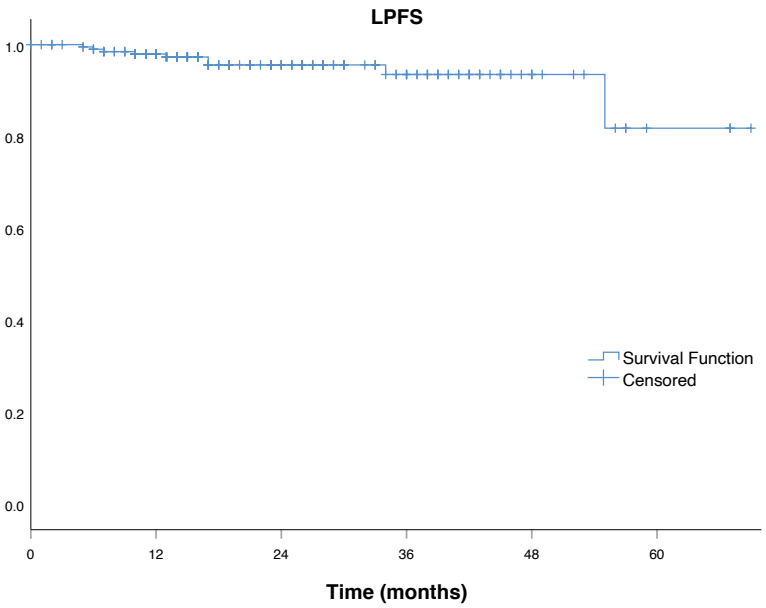

FIGURE 1. Local progression free survival (LPFS).

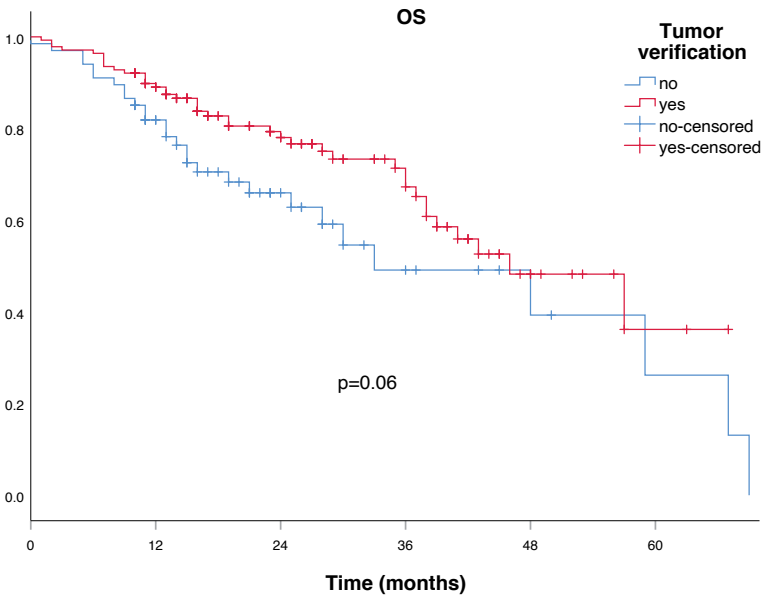

FIGURE 2. Overall survival (OS) according to tumor verification.

Discussion

SBRT, a noninvasive method of delivering a high ablative radiation dose to a small tumor volume in a few fractions, has become a standard treatment for patients with inoperable early-stage lung cancer over the past two decades.[21-24] It also offers a

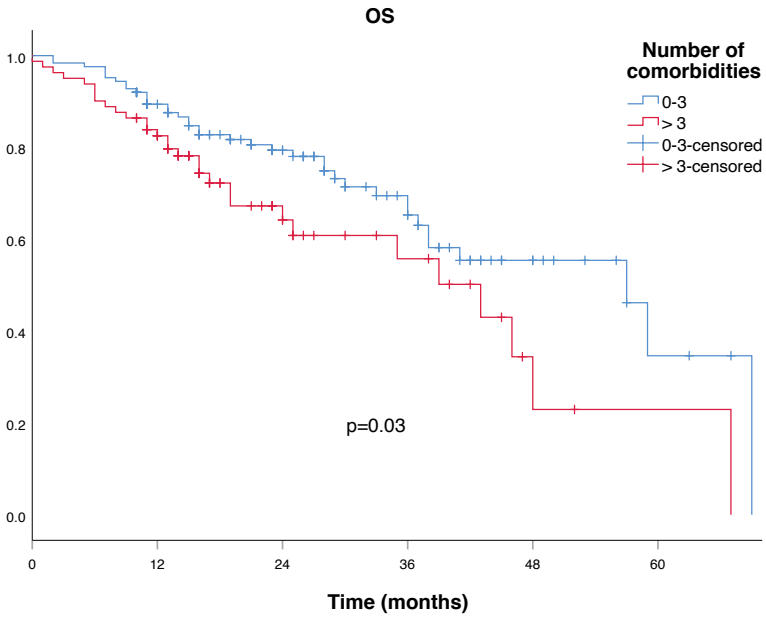

FIGURE 3. Overall survival (OS) according to number of comorbidities.

good alternative treatment option for patients who refuse surgery.

Institutions report high local control rates for patients with non-small cell lung cancer, reaching up to 95% in small peripheral tumors and negative nodes after 2–5 years. Our 1-year, 2-year, 3-year and 5-year LCR and LPFS compare favorably with published studies. One of early outcome reports in a single center showed 92% 1-year control rate and 89% at 4-year.[25] Singh *et al.* reported 1- and 2-year LC rates for all patients to be 92% and 85% respectively.[26] More recently Abreu *et al.* found 89.1% LC rate after two years.[27] Latest report from Canadian researchers, who compared 4 different treatment groups (SBRT, hypofractionation, conventional and palliative irradiation) demonstrated that SBRT offered the best local control (94% at 3-years).[28]

Overall survival showed 1-year, 2-year and 3-year after SBRT to be 87%, 74% and 62%, while 5-year OS with 31% was not so favorable, however our cohort of patients included highly comorbid individuals. In already mentioned studies other researchers report 1-year OS of 92%, 2-year 89% and 3-year 67%.[25,27,28]

Resection is the standard treatment for stage I and II lung cancer.[29] Five-year net survival of patients with localized lung cancer exceeded 60% during the period 2012–2016 in Slovenia.[30] Introduction of minimally invasive video-thoracoscopic surgery represented a revolution in surgical treatment of patients with lung cancer during that period. The latest publication from another surgical center in Slovenia showed that 5-year OS after resection was 70.2% for stage I and 60.2% for stage II.[31] Our 5-year OS with SBRT is lower, however patients in our analysis were inoperable and with many comorbidities that influenced the outcome.

Patients without treatment have 20% 5-year OS in stage I.[32] Already ten years ago, Netherland researchers reported 7% decrease in untreated non-small cell lung patients in stage I and 8-month improvement in median survival after introduction of SBRT.[33] Our OS results in inoperable patients with many comorbidities that would otherwise not be treated show that SBRT will undoubtedly contribute to increased survival rates in stage I and stage II lung cancer in Slovenia in the future.

OS data can be compared to conventional RT. We do not have local data published, but in literature 3D-RT is inferior in terms of OS.[25,28,35] Moreover, patients with many comorbidities would otherwise only be eligible for palliative radiotherapy or best supportive care. Doupnik *et al.* compared 4 different treatment groups and reported the worst 3-year survival with palliative irradiation (44%), much lower than for SBRT (67%) which is comparable to our 3-year SBRT OS (62%).[28]

We report outcomes with diversified histology of lung lesions, moreover, more than a third of patients had no tissue biopsy. The reason might be that most of our patients were treated during covid-19 epidemic when less pulmonology diagnostics was performed due to the reassignment of pulmonologists to covid wards. While biopsy confirmation remains a goal in the workup of suspected lung tumors and is recommended in all guidelines due to impaired lung function and other comorbidities, in real world situations diagnostic procedure is not possible for up to 25% of patients.[35] Different histological status of tumors (biopsy proven or not) had no influence on LPFS or DFS in our study. Patients who had verified tumors had better OS compared to non-verified ones, however the difference was not statistically significant ($p = 0.06$). The reason is probably the patient selection. More patients with poor PS, impaired lung function and other comorbidities had no tumor verification and were also not candidates for treatment after progression, especially systemic treatment. In most of the publications SBRT is presented only for NSCLC data. Retrospective data on histologically unverified early-stage NSCLC lesions treated with SBRT, as opposed to histologically verified ones, showed no significant difference regarding OS and

local control while similar rates of DFS and distant failure between pathologically confirmed and presumed NSCLC were observed.[36-38] On the other hand, a large systematic review and meta-analysis of total 43 articles showed lower 3-year overall survival and lower 2-year and 5-year cancer-specific survival for biopsy-proven disease compared to clinical disease. However, 5-year OS was the same for both groups.[39]

The recommended dose and fractionation are determined by tumor volume and location. Median BED delivered to tumors of our patients was 115.5 Gy. In fact, 91.5% of our patients received dose BED ($\alpha\beta_{10}$) 100 Gy or higher which has been associated with better outcomes for stage I/II NSCLC.[40-42] Higher dose was not associated with better survival or local tumor control in our analysis.

The optimal duration over which lung SBRT should be delivered is contradictory. Five-fraction SBRT delivered over non-consecutive days showed superior LC and similar toxicity compared to consecutive fractionation in study by Alite *et al*.[43] On the contrary, Ikawa *et al*. reported beneficial effect on tumor control for consecutive stereotactic body radiotherapy compared to non-consecutive stereotactic body radiotherapy.[44] No difference in LC was found in group of our patients who completed treatment within one week compared to those whose treatment was longer.

In our analysis, we observed no difference in LPFS or DFS by any patient, tumor, or treatment characteristic. The 5-year OS of 31% was lower than reported in comparable retrospective analyses; however, LPFS was comparable to other outcomes. Again, the reason might be patient selection. Our population of irradiated patients appears to have multiple comorbidities regardless of assessed PS. In fact, significantly better OS was found for patients with less comorbidities. Therefore, in patients with poor PS and significant comorbidities, the benefit of such treatment should carefully be discussed at multidisciplinary tumor board.

Limitation

Limitations of our study include being retrospective in nature as well as with variation in terms of tumor primary site, size, irradiation dose and histology. No strict imaging evaluation timelines were respected and varied according to clinical scenarios as well as toxicity evaluation. No data about therapy after progression was collected. Patients with more comorbidities had lower OS in our analysis, however no score system was used for calculation and due to retrospective nature of collected data, information might not be accurate.

Conclusions

Results for LC, LPFS, DFS and OS in our cohort of inoperable early-stage lung cancer patients of different histology treated with SBRT at a single tertiary cancer institution showed comparable results to published studies. Patients with many comorbidities had significantly worse survival compared to those with less comorbidities. No other significant differences by patient, tumor, or treatment characteristics were found for OS, LPFS, and DFS. Toxicity data confirmed that treatment was well tolerated.

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research article

Efficacy and safety of nintedanib and docetaxel in patients with previously treated lung non-squamous non-small cell lung cancer: a multicenter retrospective real-world analysis

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Background. The standard first-line systemic treatment for patients with non-oncogene addicted advanced non-squamous non-small cell lung cancer (NSCLC) is immunotherapy with immune checkpoint inhibitors (ICI) and/or chemotherapy (ChT). Therapy after failing ICI +/- ChT remains an open question, and docetaxel plus nintedanib represent a valid second line option.

Patients and methods. A multicenter retrospective trial of real-life treatment patterns and outcomes of patients with advanced lung adenocarcinoma treated with docetaxel plus nintedanib after the failure of ICI and/or ChT was performed. Patients from 2 Slovenian and 1 Croatian oncological center treated between June 2014 and August 2022 were enrolled. We assessed objective response (ORR), disease control rate (DCR), median progression free survival (PFS), median overall survival (OS), and safety profile of treatment.

Results. There were 96 patients included in the analysis, with ORR of 18.8%, DCR of 57.3%, median PFS of 3.0 months (95% CI: 3.0–5.0 months), and a median OS of 8.0 months (95% CI: 7.0–10.0 months). The majority of patients (n = 47,49%) received docetaxel plus nintedanib as third-line therapy. The ORR for this subset of patients was 19.1%, with a DCR of 57.4%. The highest response rate was observed in patients who received second-line docetaxel plus nintedanib after first-line combination of ChT-ICI therapy (n = 24), with an ORR of 29.2% and DCR of 66.7% and median PFS of 4.0 months (95% CI: 3.0–8.0 months). Fifty-three patients (55.2%) experienced adverse events (AEs), most frequently gastrointestinal; diarrhea (n = 29, 30.2%), and increased liver enzyme levels (n = 17, 17.7%).

Conclusions. The combination of docetaxel and nintedanib can be considered an effective therapy option with an acceptable toxicity profile for patients with advanced NSCLC after the failure of ICI +/- ChT.

Key words: advanced NSCLC; antiangiogenic therapy; docetaxel; nintedanib; real-world data

Introduction

Lung cancer remains the leading cause of cancer death, with an estimated 1.8 million deaths worldwide in 2020.[1] With the identification of oncogene drivers in non-small cell lung cancer (NSCLC), the prognosis of patients harboring specific alterations has dramatically improved. However, the propor-

tion of these patients remains low, the prevalence of targetable alterations depends on many factors, and drug resistance presents an unavoidable fact that limits the efficacy and the use of targeted drugs. For non-targetable advanced NSCLC, limited treatment options lead to worse outcomes.[2] Therefore, more therapeutic options are needed for both groups of patients with advanced NSCLC, those with driver mutations, and others without, after progression on either targeted therapy, checkpoint inhibitors (ICI) alone, or in combination with chemotherapy (ChT). Nowadays, the complexity of the tumor microenvironment is increasingly emphasized because it abounds with various pro-angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF).[3] Angiogenesis is crucial for tumor growth, maintenance, and metastasis.[4] The concept of antiangiogenic therapy is evolving and gaining attention due to its essential role in tumor development. Despite initial high expectations, antiangiogenic monotherapies have shown only modest clinical benefit, primarily due to the development of resistance. Several different mechanisms are involved, such as vessel co-option, vasculogenic mimicry, and activation of other substitute pathways.[5,6] The combination of antiangiogenic therapy with different therapeutic strategies could overcome resistance.[7]

Currently, several antiangiogenic therapies are available for the treatment of different tumor types, most of which target the VEGF signaling pathway. Bevacizumab was the first Food and Drug Administration (FDA) angiogenesis inhibitor approved in 2006 for NSCLC in combination with chemotherapy for the treatment of patients with advanced non-squamous NSCLC.[8] Ramucirumab and nintedanib are two other FDA, and European Medicines Agency (EMA) approved antiangiogenic agents for the treatment of an advanced NSCLC. In 2014, EMA approved nintedanib plus docetaxel for the treatment of patients with advanced lung adenocarcinoma following first-line ChT based on the results of LUME-Lung 1 (phase III trial), which enrolled 1,314 patients with advanced or recurrent NSCLC. In combination with docetaxel, nintedanib proved to be more effective than docetaxel alone in delaying cancer progression with median progression free survival (mPFS) of 3.5 months in the overall study population receiving docetaxel plus nintedanib, compared with 2.7 months in patients receiving docetaxel alone.[9]

While the efficacy and safety of docetaxel plus nintedanib has already been confirmed in clinical trials, we aim to provide insight into whether real-world data are comparable to those from clinical trials. We also compared the safety and tolerability of this combination with results found in the current state-of-the-art literature.

Patients and methods

This was a retrospective, non-interventional, multicenter, real-world analysis of patients with advanced/metastatic NSCLC with adenocarcinoma histology/cytology treated with a combination of docetaxel and nintedanib in different treatment lines between June 2014 and August 2022. Data were sourced from two Slovenian (University Clinic Golnik and Institute of Oncology Ljubljana, Slovenia) and one Croatian center (University Hospital Center Zagreb, Croatia). The study was performed in accordance with the Helsinki Declaration ethical standards for biomedical studies on humans and was approved by the Ethics Committee of University Hospital Center Zagreb (Decision number 02/013 AG).

Data collected from the patients' medical records included the following: sex, age, European Clinical Oncology Group (ECOG) performance status (PS) before starting docetaxel and nintedanib combination, clinical stage based on the 8th edition of the International Union Against Cancer and American Joint Committee on Cancer TNM Classification of Malignant Tumors, biomarker testing results (epidermal growth factor receptor (*EGFR*) mutation, anaplastic lymphoma kinase (*ALK*) rearrangements, ROS Proto-Oncogene 1 (*ROS1*) rearrangements, Kirsten rat sarcoma viral oncogene homolog (KRAS), mesenchymal-epithelial transition factor (MET), ret proto-oncogene (RET), fibroblast growth factor receptors (FGFR) and programmed death-ligand 1 (PD-L1) expression, smoking history, prior therapy regimen (ChT and/or iICI, tyrosine kinase inhibitors [TKI], radiotherapy), presence of brain metastases (assessed with computerized tomography [CT] and/or magnetic resonance imaging [MRI]) and adverse events associated with the use of docetaxel plus nintedanib. The response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[10] Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 criteria.[11] The cut-off date for analyzes was December 2022.

We assessed progression-free survival, objective response rate, overall survival, and the safety

profile of patients treated with docetaxel and nintedanib. PFS was defined as the time from the initiation of therapy to the time of the earliest progressive disease (PD) or study cut-off. Overall survival was assessed from the initiation of treatment until the date of death from any cause or study cut-off. A swimmer plot was applied to present the clinical outcome of patients with EGFR mutated patients. Kaplan–Meier method was used to assess the PFS and overall survival (OS). To test the difference in survival between patients with and without brain metastases and the occurrence of adverse events (AEs), the log-rank test was used.

Patients were treated and followed up as per the standard of care in a routine clinical setting in 3 centers. The response was assessed by enhanced CT until disease progression or intolerable toxicity.

Patients were treated routinely with docetaxel every 3 weeks and nintedanib 200 mg twice daily according to the summary of product characteristic (SmPC) approval. In case of adverse events, treatment was interrupted and continued at a lower dose according to the standard guidelines.

All results were obtained and plotted using R v. 3.6.2 (R Core Team, 2017).

Results

Ninety-six patients were enrolled in this study, of whom 41 were female. The median age was 59.5 years, ranging between 39 and 75. Seventy-four (77.1%) patients were current or former smokers. The most common clinical stage was IV. At the start of treatment with docetaxel plus nintedanib, 11 patients (11.4%) had ECOG PS 0, 67 (69.8%) had ECOG PS 1, and 18 (18.7%) had ECOG PS 2. Demographic data of enrolled patients are presented in Table 1.

None of the 96 patients had *ALK* or *ROS1* rearrangements, five patients had an *EGFR* mutation, one patient had *MET* exon 14 skipping mutation, three patients had *RET* rearrangement, one FGFR rearrangement was present, and *KRAS* mutation testing was positive in 7 patients.Sixteen patients had tumor PD-L1 staining ≥ 50%.

The treatment sequences were as follows: 47 patients (49.0%) received docetaxel plus nintedanib as third-line therapy after first-line platinum-based ChT and second-line monotherapy with ICI, thirteen (13.5%) patients received docetaxel plus nintedanib as third-line therapy after first-line ICI monotherapy and second-line platinum-based ChT. Second-line docetaxel plus nintedanib was given to 24 patients (25%) after the first-line combination ChT-ICI therapy. Two patients received docetaxel plus nintedanib as third-line therapy after the first-line combination ChT-ICI therapy and after second-line targeted therapy (capmatinib or pralsetinib). A subset of seven patients received docetaxel plus nintedanib after a first-line platinum-based ChT. The remaining 3 patients (3.1%) received docetaxel plus nintedanib as a fourth- or later-line therapy. These were EGFR-positive

TABLE 1. Demographic and baseline characteristics of 96 patients treated with docetaxel plus nintedanib

Variable	N = 96
Age, mean (years)	59.5 (39-75)
Sex	
Male	55 (57.3%)
Female	41 (42.7%)
ECOG performance status	
0	35 (36.4%)
1	57 (59.4%)
2	4 (4.2%)
Smoking status	
Current smokers	56 (58.3%)
Never smokers	18 (18.8%)
Former smokers	18 (18.8%)
Unknown	4 (4.2%)
Clinical stage at diagnosis	
Stage ≤ IIIB	9 (9.4%)
Stage IIIC	1 (1.0%)
Stage IV	86 (89.6%)
Brain metastases	
Yes	18 (18.7%)
No	78 (81.3%)
PD-L1 expression	
0%	35 (36.5%)
1–49%	34 (35.4%)
≥ 50%	16 (16.7%)
Unknown	11 (11.5%)
Biomarker testing	
EGFR mutation positive	5 (5.2%)
ALK rearrangement present	0 (0.0%)
ROS1 rearrangement present	0 (0.0%)
KRAS mutation present	7 (7.3%)
MET rearrangement present	1 (1.0%)
RET rearrangement present	3 (3.1%)
FGFR rearrangement present	1 (1.0%)
Docetaxel plus nintedanib line	
Second-line therapy after first line combination ChT-ICI	24 (25%)
Second-line therapy after first-line platinum-based ChT	7 (7.3%)
Third-line therapy after first-line ChT and second-line ICI	47 (49.0%)
Third-line therapy after first-line ICI and second-line ChT	13 (13.5%)
Fourth or later-lines	3 (3.1%)
Other¶	2 (2.1%)

ALK = anaplastic lymphoma kinase; ChT = chemotherapy; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptors; ICI = immune checkpoint inhibitor; KRAS = Kirsten ras oncogene homolog; MET = tyrosine-protein kinase Met; PD-L1 = programmed death-ligand 1; RET = Ret Proto-Oncogene; ROS1 = ROS Proto-Oncogene 1

Two patients received third-line docetaxel plus nintedanib after first-line combination ChT-ICI and second line targeted therapy (capmatinib or pralsetinib)

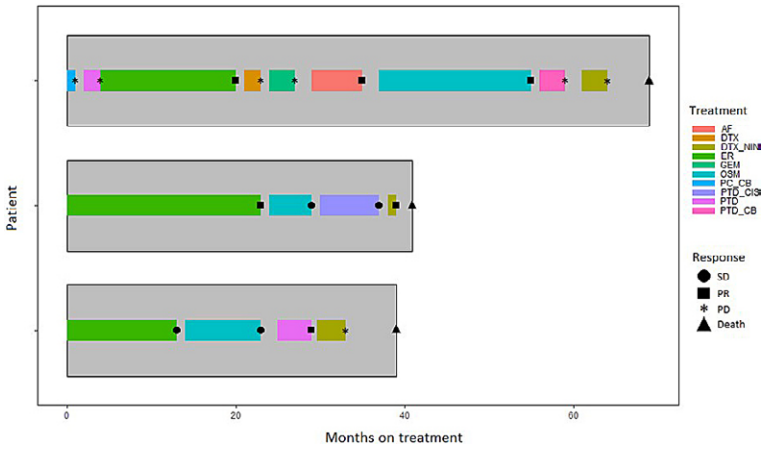

FIGURE 1. Swimmer plot of treatment duration and best treatment response in EGFR-positive patients. Different colours of the horizontal bars represent different treatment lines, while the symbols at the end of each bar represent the relevant responses.

AF = Afatinib; DTX = Docetaxel; DTX_NIN = Docetaxel plus nintedanib; EGFR = epidermal growth factor receptor; ER = Erlotinib; GEM = Gemcitabine; OSM = Osimertinib; PC_CB = Paclitaxel and carboplatin; PD = progressive disease; PR = partial response; PTD_CIS = Pemetrexed and cisplatin; PTD = Pemetrexed; PTD_CB = Pemetrexed and carboplatin; SD = stable disease

patients who had received multiple lines of targeted therapy prior to docetaxel plus nintedanib (Figure 1).

The best response to treatment with docetaxel and nintedanib in all enrolled patients is presented in Table 2. 18 patients achieved partial response (PR), corresponding to objective response (ORR) of 18.8% (complete response [CR] was not observed), while 37 (38.5%) patients had stable disease (SD) and 31 (32.2%) patients had PD. The DCR (disease control rate) was 57.3%. Response to treatment with docetaxel and nintedanib for different treatment lines is presented in Table 3. Tumor response was not evaluable for 10 patients due to early treatment discontinuation or because the evaluation was not performed.

TABLE 2. Response to treatment with docetaxel plus nintedanib in all patients

Tumor response according to RECIST version 1.1 criteria[10]	All patients N = 96
CR	0 (0.0)
PR	18 (18.8)
SD	37 (38.5)
PD	31 (32.3)
ORR (CR+PR)	18 (18.8)
DCR (CR+PR+SD)	55 (57.3)
Non-evaluable	10 (10.4)
Median PFS, months	3.0 (95% CI: 3–5)
Median OS, months	8.0 (95% CI: 7–10)

CI = confidence interval; CR = complete response; DCR = disease control rate; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease

Two patients that received third-line docetaxel plus nintedanib after a first-line combination chemotherapy-ICI regimen and second-line targeted therapy (capmatinib or pralsetinib) are not listed in the table since it was not possible to evaluate the response to therapy.

At the data cut-off, median PFS (Figure 2A) and OS (Figure 2B) across all treatment lines (n = 96) were 3.0 months (95% CI: 3–5 months) and 8.0 months (95% CI: 7–10 months), respectively.

The highest response rate was observed in patients who received docetaxel plus nintedanib as second-line therapy after first-line combination ChT-ICI therapy (n = 24), with an ORR of 29.2% and DCR of 66.7%. The median PFS for this subgroup of patients was 4.0 months (95% CI: 3.0–8.0 months) (Figure 3A).

TABLE 3. Response to treatment with docetaxel plus nintedanib in different treatment patterns

Tumor response according to RECIST version 1.1 criteria[7]	Second-line after a first-line combination ChT-ICI regimen (n = 24)	Second-line after a first-line platinum-based ChT (n = 7)	Third-line therapy following first-line ChT and second-line ICI (n = 47)	Third-line after first-line ICI and second-line ChT (n = 13)	Fourth or later-line treatment (n = 3)
CR, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR, n (%)	7 (29.2)	1 (14.3)	9 (19.1)	1 (7.7)	0 (0.0)
SD, n (%)	9 (37.5)	2 (28.6)	18 (38.3)	7 (53.8)	1(33.3)
PD, n (%)	3 (12.5)	3 (42.9)	18 (38.3)	5 (38.5)	2(66.7)
ORR, n (%)	7 (29.2)	1 (14.3)	9 (19.1)	1 (7.7)	0 (0.0)
DCR, n (%)	16 (66.7)	3 (42.9)	27 (57.4)	8 (61.5)	1(33.3)
Non-evaluable, n (%)	5 (20.8)	1 (14.3)	2 (4.3)	0 (0.0)	0 (0.0)

ChT = chemotherapy; CR = complete response; DCR = disease control rate; ICI = immune checkpoint inhibitor; ORR = objective response rate; PD = progressive disease; PR = partial reasponse; RECIST = response evaluation criteria in solid tumors; SD = stable disease

For the subset of patients receiving docetaxel plus nintedanib as third-line therapy after first-line platinum-based ChT and second-line ICI monotherapy (n = 47), the observed ORR was 19.1% and DCR 57.4%. Median PFS was 4.0 months (95% CI:3.0–8.0 months) (Figure 3B). A similar efficacy was observed in a subset of patients receiving docetaxel plus nintedanib as third-line therapy after first-line ICI monotherapy and second-line platinum-based ChT with median PFS 4.0 months (95% CI: 3-inf) (Figure 3C).

The median progression-free survival was 3.0 months (95% CI: 3.0–5.0 months) for patients with no intracranial metastases and 4.0 months (95% CI:3.0–8.0 months) for patients with intracranial metastases (Figure 2C). However, there was no statistical difference in PFS between patients with and without brain metastases ($p = 0.53$).

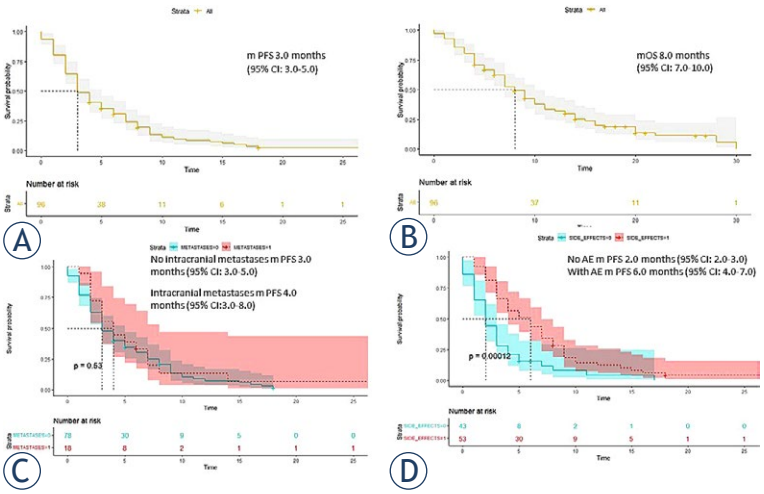

FIGURE 2. (A) Progression-free survival of all patients(PFS) (n = 96) treated with nintedanib and docetaxel combination therapy. **(B)** Overall survival (OS) of all patients treated with nintedanib and docetaxel combination therapy. **(C)** Progression-free survival (PFS) of patients with and without brain metastases. **(D)** Median progression-free survival of patients with and without adverse events.

Safety of docetaxel plus nintedanib treatment

Table 3 gives the overview of adverse events (AEs) reported with docetaxel and nintedanib treatment. Fifty-three patients (55.2%) experienced treatment related AEs. The most common were gastrointestinal; diarrhea (n = 29, 30.2%) and elevated liver enzyme levels (n = 17,17.7%), but mostly mild to moderate severity. Grade 3 AEs were observed in 8 patients (8.3%); 6 patients with elevated liver enzyme levels (6.3%), 1 patient with hypertension (1 %), and 1 with diarrhoea (1 %).

Other AEs reported were neutropenia (n = 4, 4.2%), stomatitis (n = 2), dermatitis (n = 6, 6.3%), nausea (n = 2, 2.1%), peripheral neuropathy (n = 3, 3.1%), and hypertension (n = 2, 2.1%) AEs were effectively managed by a dose reduction and did not require permanent discontinuation of treatment.

Thirty patients (31.2%) required temporary treatment discontinuation with docetaxel plus nintedanib. The main reasons were diarrhea (10.4%) and elevated liver enzymes (13.5%). Additional thirteen patients (13.5%) required a dose reduction of docetaxel mainly due to neutropenia and peripheral neuropathy, and eighteen patients (18.8%) required a dose reduction of nintedanib due to diarrhea and elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Nineteen patients (19.8%) discontinued docetaxel plus nintedanib treatment due to AEs.

There was almost no difference in the frequency of AEs between the second-line and third-line docetaxel and nintedanib combination therapy (54.8% *vs.* 55%). Adverse events were more frequent (66.6%) in a subset of patients that received fourth-line docetaxel and nintedanib combination therapy. However, this finding is considered statistically insignificant due to the small sample size.

Patients who received immunotherapy before docetaxel and nintedanib had fewer adverse events than those not treated with immunotherapy.

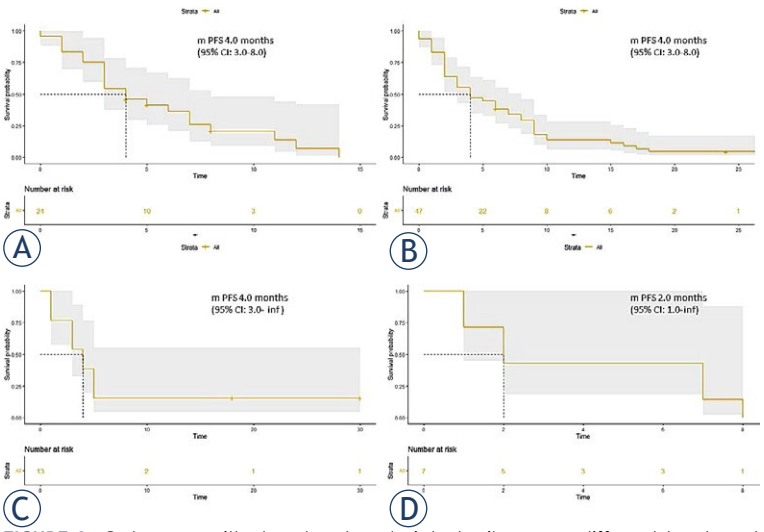

FIGURE 3. Outcomes with docetaxel and nintedanib across different treatment lines. Progression-free survival (PFS) of patients receiving docetaxel plus nintedanib as second-line treatment after first-line combination chemotherapy-checkpoint inhibitors (ChT-ICI) therapy **(A)**, third-line treatment after first-line platinum-based ChT and second-line ICI monotherapy **(B)**, third-line treatment after first-line ICI monotherapy and second-line platinum-based ChT **(C)**, and second-line treatment after first-line platinum-based ChT **(D)**.

TABLE 4. Differences in progression-free survival (PFS) and overall survival (OS) for each subset of patients according to the treatment line of docetaxel plus nintedanib

	All patients (n = 96)	Second-line after a first-line combination ChT-ICI regimen (n = 24)	Second-line after a first-line platinum-based ChT (n = 7)	Third-line therapy after first-line ChT and second-line ICI (n = 47)	Third-line after first-line ICI and second-line ChT (n = 13)	Fourth- or later-lines treatment (n = 3)
Median progression-free survival, months (95% CI)	**3** (3–5)	**4** (3–8)	**2** (1–inf)	**4** (3–8)	**4** (3–inf)	**3** (0–inf)
Median overall survival, months (95% CI)	**8** (7–10)	**9** (6–inf)	**10** (4–inf)	**10** (8–14)	**7** (3–inf)	**8** (2–inf)

Fewer than half of a group have experienced the event

ChT-ICI = chemotherapy-checkpoint inhibitors therapy; CI = confidence interval; inf = infinity

There were no treatment-related deaths due to AEs. In addition, characteristic AEs associated with VEGF pathway inhibition, such as arterial and venous thromboembolism, hemorrhage, and GI perforation, were not observed.

Discussion

Previous studies have shown that the use of ICI with or without ChT as first-line therapy in patients with advanced NSCLC improves overall survival and progression-free survival.[12,13,14] However, there is a lack of prospective, randomized controlled trials evaluating the optimal treatment for patients with advanced non-oncogene-addicted NSCLC after progression on ICI therapy with or without ChT. Despite the high initial efficacy of targeted therapies, drug resistance is inevitable, so finding new therapeutic options is also needed for patients who progress on targeted therapy. Chemotherapy has been considered as one of the standard treatments after acquiring resistance. Currently, available treatment options include single-agent chemotherapy combined with antiangiogenic drug such as nintedanib or ramucirumab.[15]

In our study, we aimed to demonstrate the multicenter experience and clinical characteristics of a cohort of patients with histologically confirmed advanced lung adenocarcinoma treated with docetaxel plus nintedanib in a real-world setting. Across all lines of treatment, median PFS was 3.0 months (95% CI: 3.0–5.0 months) and median OS 8.0 months (95% CI: 7.0–10.0 months). ORR was 18.8% and DCR was 57.3%. In a subset of patients receiving docetaxel plus nintedanib in the third-line setting, the ORR after first-line platinum-based ChT and second-line monotherapy with ICI was 19.1%. In comparison, the highest ORR (29.2%) was recorded in patients receiving docetaxel plus nintedanib as second-line therapy after first-line combination ChT-ICI therapy.

Approval of nintedanib in combination with docetaxel was based on the phase III LUME-Lung 1 trial.[9] The addition of nintedanib to docetaxel significantly prolonged PFS in the entire study population, regardless of histology (3.4 versus *vs.* 2.7 months, HR 0.79; p = 0.0019). A significant improvement in median OS (from 10.3 to 12.6 months) was observed in patients with adenocarcinoma histology, particularly in those who progressed soon, within nine months after the start of first-line treatment (from 7.9 to 10.9 months).

A significant OS benefit in adenocarcinoma patients who progressed during or shortly after the end of first-line treatment was confirmed in a subanalysis of the adenocarcinoma population of the phase III LUME-Lung 1 trial (time from the start of first-line treatment < 6 months, mOS 9.5 (nintedanib/docetaxel) *vs.* 7.5 months (placebo/docetaxel) [HR 0.73, 95% CI 0.55–0.98)).[16] A subanalysis of this trial also showed that the improvement in median OS with docetaxel plus nintedanib compared with docetaxel plus placebo was greater in the European adenocarcinoma population (4.7-month improvement in mOS).[16]

Over the past three years, several datasets about efficacy and tolerability of docetaxel plus nintedanib in the treatment of patients with advanced NSCLC after progression on platinum-based ChT followed by subsequent ICI treatment have been published. The most comprehensive retrospective real-world analysis was conducted by Metzenmacher *et al.*, and included 93 patients with NSCLC. In all evaluable patients, the ORR was 41.4%, and the DCR was 75.9%. The highest

TABLE 5. Overview of adverse events with docetaxel plus nintedanib treatment

Adverse Event*	All grades n (%)	Grade 3 n (%)
Total	53 (55.2)	8 (8.3)
Diarrhea	29(30.2)	1 (1.0)
Elevated liver enzymes	17(17.7)	6 (6.3)
Rash	6 (6.2)	
Neutropenia	4 (4.2)	
Peripheral neuropathy	3 (3.1)	
Stomatitis	2 (2.1)	
Nausea	2 (2.1)	
Hypertension	2 (2.1)	1 (1.0)

* Categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

response rate was observed in patients who were treated with docetaxel plus nintedanib following the first-line ChT and second-line ICI (ORR of 50% and DCR of 82.7%). The median OS for this group was 8.4 months (95% CI: 5.0–11.0).[17] Grohe *et al.* gave us an insight in a prospective VARGADO study by publishing the updated results for cohort B (n = 80), in which patients received docetaxel plus nintedanib after first-line ChT and second-line ICI therapy. In this study the median PFS was 6.4 months (95% CI: 4.8–7.3). At the time of analysis, the best ORR was 50% and DCR was 86%.[18]

Corral *et al.* presented the results of their smaller cohort, which consisted of eleven patients. An ORR of 36.5%, DCR of 81.8%, and PFS of 3.2 were reported.[19] Overall, we noted that the results presented in the above studies are consistent. In our subset of patients (n = 47) who received docetaxel plus nintedanib after first-line ChT and second-line ICI, response rates were lower (ORR of 19.1% and DCR of 57.4%). These outcomes, with lower DCR and PFS could have been due to the presence of poor prognostic factors of our patients included in the analysis (18.7% had brain metastases, 89.6% were found to have stage IV disease, and 64% were ECOG PS 1–2). However, more prospective studies are needed to verify these findings.

Eighteen patients included in our study already had evidence of intracranial disease progression. Most of our patients underwent whole brain radiation therapy (WBRT) due to multiple brain metastases, while in a smaller number of patients, gamma knife was performed. It is worth noting that no intracerebral complications were reported, and this group of patients responded as well to therapy as the others (Figure 2C).

Our analysis included five patients with *EGFR* mutations after failure to standard of care previous lines of therapy. Three of these patients received an EGFR-TKI before docetaxel plus nintedanib therapy. In two cases, a double mutation was found (coexistence of exon 19 deletion and exon 20 T790M). Patients received docetaxel plus nintedanib as fourth or later-line treatment. Two patients received EGFR-TKI as first-line treatment, while the remaining patient received a TKI as third-line therapy. An objective response rate and DCR were 0.0% and 33.3%, respectively. Although the LUME-Lung 1 trial did not evaluate *EGFR* mutation status, the efficacy of docetaxel and nintedanib in EGFR mutated NSCLC patients has been evaluated in recent clinical trials.[20,21]

Sixty-two patients were included in a study conducted by Hong *et al.* A median PFS of 6.5 *vs.* 3.3 months (EGFR mutated *vs.* EGFR not mutated) was considered promising, but further studies of the efficacy of docetaxel plus nintedanib in patients with EGFR-mutated NSCLC are needed.[21]

The toxicity profile was generally consistent with the known safety profile of this treatment combination, with diarrhea, elevated liver enzymes and rash beeing the most common adverse events.

Not all patients benefit from docetaxel plus nintedanib therapy, but there are currently no predictive biomarkers of response to antiangiogenic treatment. Our study demonstrated that the occurrence of AEs was associated with favourable efficacy in patients treated with this combination therapy. Median survival was two months in patients without any AEs and six months for patients with AEs. Several studies have demonstrated a correlation between the development of hypertension and longer PFS and/or OS in patients treated with antiangiogenic agents.[22,23] In contrast, data are not yet available for combination therapy with docetaxel and nintedanib. However, the correlation between therapeutic efficacy and the occurrence of AEs remains unclear.

Our study has several limitations. The first limitation is the non-comparative, retrospective design. Another limitation is radiologic evaluation; RECIST measurements were not done by an independent radiologic review board but were performed during everyday clinical practice by a radiologist on duty. This could have led to non-homogeneous reviews with differences regarding target and non-target lesions. Because of the retrospective nature of data collection, underreporting of potential side effects may have occurred.

Finally, due to the heterogeneity of the population under study (*i.e.*, different treatment lines), statistical power is decreased, resulting in nonsignificant differences between treatment groups in terms of outcome.

Our data support the use of docetaxel and nintedanib, which proved safe in 2nd and later lines, even in patients with previously treated brain metastases.

The benefit observed in ICI-pretreated patients is notable, and should be explored further to elucidate a synergistic effect between antiangiogenics and ICI.

In addition, further studies are needed to determine the best strategy to increase efficacy by modulating treatment sequences.

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research article

Effectiveness and safety of anlotinib with or without S-1 in the treatment of patients with advanced hepatocellular carcinoma in a Chinese population: a prospective, phase 2 study

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Background. The aim of the study was to observe the safety and efficacy of anlotinib (ANL) alone or combined with S-1 in the first-line treatment of advanced hepatocellular carcinoma (HCC).

Patients and methods. Fifty-four patients with untreated advanced HCC who could not be resected were randomly divided into the ANL group (n = 27) and ANL+S-1 group (n = 27). The ANL group was given 10 mg ANL orally once a day for 14 consecutive days, stopped for 1 week, and repeated every 21 days. The ANL+S-1 group was given 10 mg ANL once a day orally and 40 mg S-1 twice a day orally for 14 consecutive days, stopped for 1 week, repeated every 21 days. All patients were treated until the disease progressed or toxicity became unacceptable. For patients who could not tolerate adverse reactions, the ANL dose should be reduced to 8 mg per day. CT or MRI was reviewed every 6 weeks to evaluate the efficacy.

Results. A total of 44 patients were included in the results analysis, including 22 patients in the ANL group and 22 patients in the ANL+S-1 group. In the ANL group, the objective response rate (ORR) was 4.5% (1/22), the disease control rate (DCR) was 77.3% (17/22), the median progression-free survival (PFS) was 4.2 months (95% CI: 3.6–6.0) and the median overall survival (mOS) was 7.0 months (95% CI: 6.3–9.0). In the ANL+S-1 group, the ORR was 18.2% (4/22), the DCR was 59.1% (13/22), the median PFS was 4.0 months (95% CI: 3.6–5.4) and the mOS was 6.0 months (95% CI: 5.5–7.4). There was no significant difference in ORR ($p = 0.345$) or DCR ($p = 0.195$) between the two groups. Adverse reactions were mainly hypertension, anorexia, fatigue, liver transaminase heightened and hand and foot skin reaction.

Conclusions. ANL monotherapy was effective in the treatment of advanced HCC, and adverse reactions have been able to tolerated.

Key words: hepatocellular carcinoma (HCC); anlotinib; S-1; molecule targeted therapy; chemotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 90% of primary liver cancers. China has a high incidence of HCC, accounting for more than half of the new cases in the world each year, and ranks second only to lung cancer in tumor-related deaths.

Common treatments for HCC include tumor resection, liver transplantation, transarterial chemoembolization, radiotherapy and molecular targeted drug therapy.[1] In China, 70%–80% of patients

have advanced stage or distant metastasis at the time of clinical first diagnosis, and the opportunity for surgical resection is lost. Transarterial chemoembolization (TACE) is the most commonly used method for the treatment of advanced HCC, but it is difficult to completely block the blood supply around the tumor.[2] Therefore, drug therapy (cytotoxic drugs, multitarget antiangiogenic drugs, immune checkpoint inhibitors, etc.) has become a very important comprehensive treatment for advanced HCC.

Sorafenib is the first drug approved for the treatment of HCC, and both the SHARP study and Oriental study have confirmed that sorafenib can significantly prolong the survival of patients with advanced HCC. In the SHARP study of Westerners, the median overall survival (mOS) of sorafenib alone was 10.7 months[3], while in the Oriental study of Asians, the mOS of sorafenib alone was only 6.5 months.[4] Chinese studies have shown that the mOS of sorafenib alone in the treatment of advanced HCC is 6.0 months, which is similar to that of Oriental patients, suggesting that the efficacy of sorafenib in the treatment of HCC is poor in Asian populations. Therefore, finding more effective drugs for the treatment of HCC is of great clinical significance.

Studies have shown that anlotinib (ANL) is effective and well tolerated as a treatment for patients with advanced HCC.[5,6] The results showed that fluorouracil was effective for HCC.[7-9] Both S1 and capecitabine are fluorouracils. S-1 does not cause hand-foot syndrome and is more reasonable to combine with ANL, which has the potential to cause hand-foot syndrome, so our study design used ANL plus S-1.

The purpose of this study was to explore the safety and efficacy of ANL alone or in combination with Tigio (S-1) in the treatment of advanced HCC.

Patients and methods

Study design and participants

This is a prospective, single-center, real-world study to evaluate the efficacy and safety of ANL with or without S-1 in the first-line treatment of patients with advanced HCC. From February 2019 to August 2021, 54 HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage C (stage I–II, Child–Pugh A–B, and at least one criteria: PS1-2 or vascular invasion/extrahepatic spread)[10] confirmed by histopathological examination or in accordance with the clinical diagnostic criteria of primary liver cancer were included. This study was conducted in accordance with the Helsinki Declaration and approved by the Review Committee of the Ethics Committee of the affiliated Hospital of Guilin Medical University.

The main inclusion criteria were as follows: (1) Age ≥ 18 years old, BCLC stage C. (2) Eastern Cooperative Oncology Group (ECOG) physical status score: 0–2, and the estimated survival time was at least 3 months. (3) At least one measurable lesion evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST1·1). (4) Hemoglobin ≥ 95 g/L, leukocytes ≥ 4.0×10^9/L and platelets ≥ 100×10^9/L. Serum creatinine was normal, and ALT and AST were less than 2.5 times the normal upper limit. (5) There was no hypertension. (6) The patient signed the informed consent form. The main exclusion criteria were as follows: (1) A history of gastrointestinal bleeding or a clear tendency of gastrointestinal bleeding in the past 6 months, such as esophageal varices with the risk of bleeding, local active ulcer lesions, and fecal occult blood ≥ +. (2) Routine urine tests showed urinary protein ≥ + + or confirmed that 24-hour urinary protein was more than 1.0 g. (3) Patients with hypertension who could not be reduced to the normal range by antihypertensive drugs (systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg).

Procedures

The patients were randomly divided into the ANL group (n = 27) and the ANL+S-1 group (n = 27). Patients in the ANL group were treated with 10 mg of ANL once a day for 14 days. The ANL+S-1 group was treated with 10 mg of ANL once a day and 40 mg of S-1 twice a day. Both drugs were taken continuously for 14 days, discontinued for one week and repeated every 21 days. The two groups were treated with drugs until the disease progressed or could not tolerate adverse reactions. For patients who could not tolerate adverse reactions, the dose of ANL was reduced to 8 mg daily. The curative effect was evaluated by magnetic resonance imaging (MRI) or computed tomography (CT) every 6 weeks.

Statistical analysis

The chi-square test was used to compare the counting data of the two groups, the Kaplan–Meier method was used to generate a survival curve, and the log-rank test was used to compare the dif-

ference in PFS and OS between the two groups. We used SPSS software (version 25.0) to perform all the statistical analyses. All statistical tests were bilateral tests, and $p < 0.05$ was statistically significant. This study was registered at the Chinese Clinical Trial Registry (chictr.org.cn), registration number: ChiCTR1900022129.

Results

Patient characteristics

Table 1 summarizes the baseline characteristics of the participants.

Antitumor activity

A total of 44 patients were involved in the efficacy analysis (efficacy-evaluable population), with 22 cases in the ANL group and 22 cases in the ANL+S-1 group. In the ANL group, 1 (4.5%) patient achieved a PR, but none achieved a CR. The ORR was 4.5% (1/22), and the DCR was 77.3% (17/22). The median PFS was 4.2 months (95% CI, 3.6–6.0) (Figure 1, 2). The median OS was 7.0 months (95% CI, 6.3–9.0). In the ANL+S-1 group, 4 (18.2%) patients achieved a PR, but none achieved a CR. The ORR was 18.2% (4/22), and the DCR was 59.1% (13/22). The median PFS was 4.0 months (95% CI, 3.6–5.4) (Figure 1, 2). The median OS was 6.0 months (95% CI, 5.5–7.4). There was no significant difference in ORR (p = 0.345) or DCR (p = 0.195) between the two groups. The longest observation time in this study was 30 months, and the 1- and 2-year survival rates were 22.7% and 4.5% (ANL group) and 4.5% and 0.0% (ANL+S-1 group), respectively. Fisher's accuracy test revealed no significant difference in the 1-year and 2-year survival rates between the two groups. ($P > 0.05$).

Safety

The most frequent adverse effects (AEs) were hypertension and fatigue. Hypertension, hand-foot skin, and diarrhea were among the grade 3 treatment-related AEs that occurred in 7 (15.9%) of the patients. Most of these events can be reversed by adjusting the dose of ANL or by taking other drugs (such as antihypertensive drugs). In the ANL group, 4 patients reduced the dose of ANL due to grade 3 or 4 adverse reactions. In the ANL+S-1 group, 3 patients reduced the dose of ANL due to grade 3 or 4 adverse reactions. There were no treatment-related fatalities. The treatment-related AEs

TABLE 1. Baseline characteristics of the ANL group and ANL+S-1 group were compared

	Group ANL n=27	Group ANL+S-1 n=27	x^2	*P*
Gender n %				
Male	23(85.2)	22(81.5)	0.133	0.715
Female	4(14.8)	5(18.5)		
Age median	54	56		
ECOG PS n %			0.912	0.340
1	8(29.6)	5(18.5)		
2	19(70.4)	22(81.5)		
Child-Pugh, n %			0.078	0.780
A grade	10(37.0)	11(40.7)		
B grade ≤ 7	17(63.0)	16(59.3)		
Stages (BCLC), n %				
C	27(100.0)	27(100.0)		
AFP n %			0.318	0.573
AFP ≥ 400 ng/mL	16(59.3)	18(66.7)		
AFP < 400 ng/mL	11(40.7)	9(33.3)		
HBV DNA n %			1.421	0.233
≥ 1.0×10^3 IU/mL	6(22.2)	10(37.0)		
< 1.0×10^3 IU/mL	21(77.8)	17(63.0)		
PVTT n %			0.092	0.761
PV1–3	18(66.7)	16(59.3)		
PV4	2(7.4)	3(11.1)		
EHS n %	9(33.3)	7(25.9)	0.355	0.551

AFP = alfafetoprotein; ANL = anlotinib; BCLC = BCLC staging system; ECOG PS = Eastern Cooperative Oncology Group performance status; EHS = extrahepatic spread; HPV = hepatitis B virus; PVTT = portal vein tumor thrombosis; VP1 = PVTT extending distal to the second portal branch; VP2 = PVTT extending to the second portal branch; VP3 = PVTT extending to the first portal branch; VP4 = PVTT extending to the main portal trunk or opposite-side portal branch

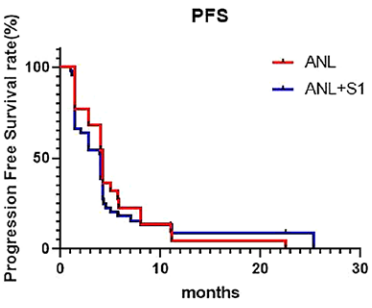

FIGURE 1. Comparison of progression-free survival (PFS) between the anlotinib (ANL) group and ANL+S1 group.

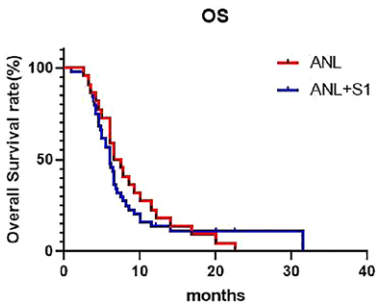

FIGURE 2. Comparison of overall survival (OS) between the anlotinib (ANL) group and the ANL+ S1 group.

TABLE 2. Incidence and grade of major adverse reactions in the ANL group and ANL+ S-1 group

Adverse reactions	Group ANL (n=22)				Group ANL+S-1 (n=22)				x^2	P
	Any level	1	2	3/4	Any level	1	2	3/4		
Hypertension	11(50.0%)	7	2	2	12(54.5%)	6	3	3	0.910	0.763
Anorexia	5(22.7%)	4	1	0	8(36.4%)	5	3	0	0.983	0.322
Fatigue	16(72.7%)	14	2	0	18(81.8%)	16	2	0	0.518	0.472
Hand-foot-skin reaction	5(22.7%)	3	1	1	7(31.8%)	4	3	0	0.458	0.498
Leucopenia	3(13.6%)	2	1	0	4(18.2%)	3	1	0	0.170	0.680
Bleeding	1(4.5%)	0	1	0	0(0.0%)	0	0	0	0.410	0.235
ALT abnormal	6(27.3%)	6	0	0	8(36.4%)	7	1	0	0.419	0.517
Oral mucositis	3(13.6%)	1	2	0	5(22.7%)	3	2	0	0.617	0.432
Hypothyroidism	6(27.3%)	4	2	0	6(27.3%)	5	1	0	0.000	1.000
Diarrhea	1(4.5%)	0	0	1	2(9.1%)	1	1	0	0.364	0.546

The comparison of adverse reactions was the comparison of any grade data between the ANL and ANL+S-1 groups.

ALT = alanine transaminase; ANL = anlotinib

did not interrupt the study. Table 2 shows all AEs, whether treatment-related or not.

Discussion

In this phase II prospective clinical trial, we observed the efficacy and safety of ANL alone or in combination with S-1 in patients with advanced HCC. To the best of our knowledge, this is the first controlled study to evaluate ANL alone or in combination with S-1 in patients with advanced HCC. The results showed that ANL had certain antitumor activity in the treatment of advanced HCC and that adverse reactions could be controlled. However, it would be necessary to compare ANL with standard treatment in a randomized trial with more patients included before this drug appears in standard practice for HCC.

Anlotinib is a novel multitarget tyrosine kinase inhibitor that mainly inhibits vascular endothelial growth factor receptor 2 and 3 (VEGFR2/3), fibroblast growth factor 1–4 (FGFR1-4), platelet-derived growth factor receptor α and β (PDGFR α/β), C-Kit and Ret.[11] VEGFR, FGFR and PDGFR are related to tumor angiogenesis and growth. C-Kit and Ret are important members of the tyrosine kinase receptor protein family and receptors of stem cell factors. Their products are tyrosine kinase type ◎, which makes tumor cells proliferate. Therefore, ANL could inhibit tumor cell and tumor vascular growth at the same time. Pharmacokinetic evaluation showed that ANL had a long elimination half-life (116 ± 47 hours) and significant accumulation after multiple oral administrations. In basic research on lung cancer, ANL induced apoptosis and protective autophagy in lung cancer cell lines. Autophagy inhibition further enhanced the cytotoxicity of ANL and enhanced the antiangiogenic effect of ANL through JAK2/STAT3/VEGFA signaling.[13] ANL could inhibit the proliferation, migration and invasion of small cell lung cancer H446 cells by inhibiting the c-Met pathway and activating the ERK1/2 pathway.[14] ANL can also induce apoptosis and inhibit proliferation of hepatocellular carcinoma cells through Erk and Akt pathways.[15] The above studies showed that ANL inhibits tumor angiogenesis and promotes tumor cell apoptosis through multiple signal transduction pathways. Other studies have found that ANL overcomes the multidrug resistance of colorectal cancer cells to cytotoxic drugs by inhibiting the PI3K/AKT pathway[16], suggesting that after treatment, patients are resistant to multiple cytotoxic drugs, and the combined use of ANL may be beneficial again.

The mechanism of action of ANL is similar to that of apatinib.[17] Some studies have confirmed that the ORR of apatinib in the first-line treatment of HCC was 16%, the DCR was 60%, the PFS was 5 months and the OS was 13 months.[18] From clinical practice, it was observed that the adverse reactions of ANL were lighter than those of apatinib, so we chose to use ANL in this study. S1 is fluorouracil. The results showed that fluorouracil was effective for HCC.[7-9] S-1 has no adverse reaction to hand-foot syndrome, and it was more reasonable to combine

with ANL, which may have hand-foot syndrome. Therefore, to achieve a better tumor control rate, longer survival time and better quality of life, we used ANL combined with S-1 for advanced HCC. Some studies have shown that the combination of ANL and the S-1 regimen was beneficial in the third-line treatment of non-small cell lung cancer, the OS of patients in the combination group was longer than that in the S-1 group[19,20], and the ORR in the combined group was higher than that in the ANL group.[21] However, the results of this study show that there is no significant difference in ORR, DCR, PFS and OS between the ANL group and the ANL plus S-1 group, indicating that there was no significant clinical benefit from the combination of ANL and S-1 in the treatment of advanced HCC, and whether it is related to the lower dose of S-1 needs further study. The results of this study showed that the mPFS and mOS of patients treated with ANL alone were 4.2 months and 7.0 months, respectively, of which 1 patient still had no progress after 22.5 months. For patients with BCLC stage C, the clinical benefits are positive. Clinical studies have shown that HCC patients with portal vein tumor thrombus (PVTT) can be treated with hepatic arterial infusion chemotherapy (HAIC) or sorafenib. Compared with VP4 (PVTT extending to the main portal trunk or opposite-side portal branch) patients, the OS of VP2 (PVTT extending to the second portal branch) – 3 (PVTT extending to the first portal branch) patients was 7.1 months and 5.5 months, respectively.[22] Most of the patients in this study were PVTT patients, most of whom were VP1 (PVTT extending distal to the second portal branch)-3 type. The mOS of ANL alone was 7.0 months in our study, which was similar to that of sorafenib. In our study, there was no significant difference in the 1-year and 2-year survival rates between the two groups, suggesting that ANL combined with S-1 was no better than ANL alone.

In this study, the main adverse reactions included hypertension, loss of appetite, fatigue, increased liver transaminase and hand and foot skin reactions, most of which were grade 1–2, and only a few patients with grade 3–4 adverse reactions needed to reduce the dose of ANL, indicating that the side effects of ANL were tolerable. Adverse reactions in NSCLC patients treated with ANL included hypertension (67.4%), hand and foot syndrome (43.9%), hemoptysis (14.0%), elevated thyroid stimulating hormone (TSH) (46.6%) and corrected QT interval (26.2%).[23] Our study showed that the incidence of the above adverse reactions was lower than that reported in the literature, which was related to the use of medium-dose ANL. The results of the ALTER-0303 study of ANL in the treatment of NSCLC showed that a total of 57.8% of patients received antihypertensive drugs for hypertension, 18.0% of patients received levothyroxine for hypothyroidism, 8.2% of patients received beta ester for high triglycerides, 3.7% of patients received cortisone cream for hand and foot syndrome, and 12.9% of patients received antidiarrheal drugs. In the ANL group, 8.16% and 10.54% of the patients needed to reduce the dose and stop taking drugs, respectively.[24] Most small molecular inhibitors showed greater side effects due to the low selectivity of VEGFR2 tyrosine kinase, while ANL was a highly selective VEGFR2 inhibitor with fewer side effects. In this study, there were more patients with leukopenia in the ANL+S-1 group than in the ANL group, but there was no significant difference between the two groups, which may be related to the small sample size or low myelosuppression with a low dose of S-1. Studies have shown that grade 3 or more adverse events of daily 12 mg ANL treatment for liver cancer include hypertension (12.73%), decreased white blood cell count (3.64%), decreased absolute neutrophil count (1.82%), decreased platelet count (9.09%), fatigue (3.64%), decreased hemoglobin (1.82%) and diarrhea (1.82%). There were also phase II clinical studies that showed that the grade 3–5 adverse events of daily 12 mg ANL in the treatment of liver cancer were hypertension (8%), diarrhea (8%) and hand and foot syndrome (6%).[26] In our study, the adverse reactions above grade 3 in the ANL group were hypertension (9.10%), diarrhea (4.55%) and hand and foot skin reactions (4.55%). There were no other adverse reactions above grade 3, and there were fewer adverse reactions above grade 3, which was considered to be related to the daily dose of 10 mg in this study.

The study has some limitations. First, this was a single-center study. Second, the study had a small sample size, with only 22 patients per cohort. The study is not powered enough to compare the ANL and ANL+S1 groups and to conclude that S1 does not add to efficacy.

Conclusions

In conclusion, ANL monotherapy is effective in the treatment of advanced HCC, and adverse reactions can be tolerated. However, ANL combined with S-1 did not improve ORR and DCR or prolong PFS and OS in advanced HCC patients.

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Polja za zdravljenje tumorjev (TTFields). Napredek pri klinični uporabi in mehanizmi delovanja

Li X, Liu K, Xing L, Rubinsky B

Izhodišča. Polja za zdravljenje tumorjev (*angl. tumor treating fields*, TTFields) so neinvazivna metoda zdravljenja raka, pri kateri uporabljamo specifično sinusno električno polje s frekvenco od 100 kHz do 300 kHz in jakostjo od 1 V/cm do 4 V/cm. S takšnimi električnimi polji želimo zavirati razmnoževanje rakavih celic in povzročiti njihovo smrt. Kljub obetavnim rezultatom kliničnih preskušanj je do sedaj Uprava za hrano in zdravila (angl. Food and Drug Administration, FDA) odobrila polja TTFields le za zdravljenje multiformnega glioblastoma in malignantnega plevralnega mezotelioma. Tako je globalno sprejetje polj TTFields še vedno omejeno. Da bi izboljšali klinično uporabo TTFields pri drugih vrstah raka in bolje razumeli mehanizme delovanja, je namen pričujočega pregleda povzeti trenutno stanje raziskav s pregledom obstoječe literature o kliničnih preskušanjih in o raziskavah mehanizmov TTFields.

Zaključki. S tem izčrpnim pregledom želimo spodbuditi nove zamisli ter zdravnikom, bolnikom in raziskovalcem omogočiti boljše razumevanje razvoja TTFields ter njihove možne uporabe pri zdravljenju raka.

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Sodobna obravnava genitourinarnega sindroma pri bolnicah z ginekološkim rakom

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Izhodišča. Izraz genitourinarni sindrom v menopavzi so prvič uporabili leta 2014 v Severnoameriškem združenju za menopavzo in Mednarodnem združenju za preučevanje spolnega zdravja žensk. Genitourinarni sindrom v menopavzi opisuje stanja, ki smo jih poznali kot atrofični vaginitis, urogenitalna atrofija ali vulvovaginalna atrofija. To je zapleteno, kronično, napredujoče stanje, za katerega je značilen širok spekter znakov in simptomov, ki vplivajo na spolno funkcijo ter tkivo sečil in genitalij. Pomanjkanje estrogena, zaradi odstranitve ali nedelovanja jajčnikov, je glavni vzrok genitourinarnega sindroma v menopavzi. Najbolj moteči simptomi, ki tudi negativno vplivajo na kakovost življenja, so suha nožnica, zmanjšano vlaženje nožnice ter bolečina med penetracijo in spolnim odnosom.

Zaključki. Glavni cilj zdravljenja je lajšanje simptomov. Možni pristopi zdravljenja so farmakološki ali nefarmakološki. Prva izbira pri zdravljenju blagih do zmernih simptomov je uporaba lubrikantov in vlažilcev. Za bolj izrazite težave je zlati standard nadomestno zdravljenje z estrogenom. Vendar pa hormonska terapija ni vedno možna izbira pri ženskah s hormonsko odvisnim rakom.

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Primerjava diagnostične učinkovitosti [^{18}F] FDG PET/CT in [^{18}F]FDG PET/MRI za odkrivanje kostnih zasevkov pri bolnikih z rakom dojke. Metaanaliza

Xia L, Lai J, Huang D, Qiu S, Hu H, Luo Y, Cao J

Izhodišča. Namen metaanalize je bil oceniti primerjalno diagnostično učinkovitost [18F]FDG PET/CT in [18F]FDG PET/MRI ob odkrivanju kostnih zasevkov pri bolnicah z rakom dojke.

Metode. Obsežno smo poizvedovali v podatkovnih zbirkah *PubMed*, *Embase*, *Web of Science* in *Cochrane Library*, da bi ugotovili, katere objavljene raziskave so dosegljive do leta 2023. V analizo smo vključili tiste raziskave, ki so ocenjevale diagnostično učinkovitost [18F]FDG PET/CT in [18F]FDG PET/MRI pri bolnicah s kostnimi zasevki raka dojke. Občutljivost in specifičnost smo ocenjevali z metodo *DerSimonian* in *Laird*, nato pa naredili prevedbo prek dvojne inverzne transformacije *Freeman-Tukey*.

Rezultati. V metaanalizo smo vključili 16 člankov (vključno s 4 primerjalnimi članki), ki so obravnavali 1.261 bolnikov. Celokupna občutljivost [18F]FDG PET/CT, ki je temeljila na analizi bolnikov in lezij ter primerjalnih člankih, je bila 0,73; 0,89 in 0,8; celokupna občutljivost [18F]FDG PET/MRI pa je bila 0,99; 0,99 in 0,99. Rezultati so pokazali, da se pri [18F]FDG PET/MRI kaže večja občutljivost v primerjavi z [18F]FDG PET/CT (vsi $P < 0,05$). Nasprotno z občutljivostjo, je bila celokupna specifičnost [18F]FDG PET/CT, ki je temeljila na analizi bolnikov in lezij ter primerjalnih člankih, 1,00, 0,99, in 1,00; celokupna specifičnost pa [^{18}F]FDG PET/MRI 1.00, 0.99 in 0,98. To kaže, da sta imeli preiskavi 18F]FDG PET/CT in [18F]FDG PET/MRI podobno stopnjo specifičnosti.

Zaključki. Metaanaliza je pokazala, da je [18F]FDG PET/MRI imela boljšo občutljivost in podobno specifičnost kot [18F]FDG PET/CT ob odkrivanju kostnih zasevkov pri bolnicah z rakom dojk. Za potrditev teh ugotovitev in oceno klinične uporabe so potrebne nadaljnje prospektivne klinične raziskave.

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Centralni in periferni pljučni sklerozirajoči pnevmocitomi. Večfazna preiskava CT in primerjava s Ki-67

Zhang Y, Ran C, Li W

Izhodišča. Namen raziskave je bil ovrednotiti rezultate večfazne računalniške tomografije (CT) centralnih in perifernih pljučnih sklerozirajočih pnevmocitomov in jih primerjati s Ki-67, da bi razkrili njihovo morebitno neoplastično naravo.

Bolniki in metode. Retrospektivno smo analizirali večfazne CT in klinične podatke pri 33 pljučnih sklerozirajočih pnevmocitomih (15 centralnih in 18 perifernih). Primerjali smo njihove lastnosti z večfaznim CT in ravnmi Ki-67.

Rezultati. Centralni pljučni sklerozirajoči pnevmocitomi so bili večji od perifernih (10,39 ± 3,25 cm^3 v primerjavi s 4,65 ± 2,61 cm^3; P = 0,013), velikost tumorja pa je bila v negativni korelaciji z indeksom pospeška (r = -0,845; P< 0,001). Največja ojačitev centralnih pljučnih sklerozirajočih pnevmocitomov se je pojavila v zapozneli fazi, z daljšim časom do največje ojačitve (*angl. time to peak enhancement, TTP*) (100,81 ± 19,01 s), nižjim indeksom pospeška (0,63 ± 0,17) in progresivno ojačitvijo ter višjo ravnjo Ki-67. Največja ojačitev perifernih pljučnih sklerozirajočih pnevmocitomov se je pojavila v venski fazi, s krajšim TTP (62,67 ± 20,96 s; P < 0,001), višjim indeksom pospeška (0,99 ± 0,25; P < 0,001) in izpiranjem ojačitve ter nižjo ravnijo Ki-67. Znak prekrivajočih žil (86,67 % proti 44,44 %; P = 0,027), izrazit znak pljučne arterije (73,33 % proti 27,78 %; P = 0,015) in obstruktivno vnetje/atelektaza (26,67 % proti 0 %; P = 0,033) so bili pogostejši pri centralnih pljučnih sklerozirajočih pnevmocitomih, medtem ko je bil pri perifernih pogostejši znak halo (38,89 % proti 6,67 %; P = 0,046).

Zaključki. Lokacija pljučnih sklerozirajočih pnevmocitomov je možen dejavnik, ki prispeva k njihovim raznolikim slikovno-patološkim izvidom. Velikost tumorja, večfazne CT ojačitve, kvalitativni znaki in Ki-67 so bili različni med centralnimi in perifernimi pljučnimi sklerozirajočimi pnevmocitomi. Kombinacija velikosti tumorja, večfazna CT preiskava in raven Ki-67 pomagajo razkriti naravo mejnega tumorja.

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Učinki dihanja normobaričnega in hiperbaričnega kisika na intenziteto signalov T_1-utežene, T_2-utežene in FLAIR slike pri magnetnoresonančnem slikanju človeških možganov

Velej V, Cankar K, Vidmar J

Izhodišča. Raztopljeni kisik ima znane paramagnetne učinke pri slikanju z magnetno resonanco (MRI). Namen raziskave je bil primerjati učinke normobarične oksigenacije in hiperbarične oksigenacije na intenziteto signala MRI v človeških možganih.

Bolniki in metode. Izhodiščno MRI je bila narejeno na 17 zdravih preiskovancih (povprečna starost je bila 27,8 ± 3,2 let). MRI smo nato ponovili po izpostavljenosti normobarični in hiperbarični oksigenaciji v različnih časovnih intervalih (0 min, 25 min, 50 min). Primerjali smo intenzitete signala na T_1 in T_2 obteženem slikanju ter pri slikanju z metodo supresije tekočine (*angl. fluid attenuated inversion recovery*, FLAIR) na različnih intrakranialnih strukturah po izpostavljenosti normobarični in hiperbarični oksigenaciji.

Rezultati. V beli in globoki sivi možganovini, v likvorju in venski krvi ter v steklovini smo po izpostavljenosti normobarični in hiperbarični oksigenaciji opazili povečano intenzivnost signala T_1-utežene slike v primerjavi z izhodiščem (Dunnettov test, $p < 0,05$) brez pomembnih razlik med obema načinoma oksigenacije. Prav tako nismo ugotovili pomembne razlike v intenzivnosti signala T_2-utežene slike med normobarično in hiperbarično oksigenacijo. Intenzivnost signala FLAIR je bila povečana samo v steklovini po normobarični in hiperbarični oksigenaciji, intenziteta signala kavdatnega jedra pa je bila po normobarični oksigenaciji zmanjšana (Dunnettov test, $p < 0,05$). Med normobarično in hiperbarično oksigenacijo (parni t-test, $p < 0,05$) so bile statistično značilne razlike v intenziteti FLAIR signala na večini opazovanih možganskih struktur (parni t-test, $p < 0,05$).

Zaključki. Rezultati raziskave kažejo, da se po izpostavljenosti normobarični in hiperbarični oksigenaciji spremenita intenzivnost signala T_1-utežene slike in FLAIR v človeških možganih. Razlike med normobarično in hiperbarično oksigenaciji so najbolj izrazite pri slikanju z metodo FLAIR.

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Prominin 2 zmanjša občutljivost za cisplatin pri nedrobnoceličnem pljučnem raku in ga uravnava z veznim faktorjem CTCC

Tang J, Shu D, Fang Z, Yang G

Izhodišča. Nedrobnocelični pljučni rak (NSCLC) je najpogostejša oblika pljučnega raka in predstavlja po vsem svetu večino smrti povezanih z rakom. Namen raziskave je bil ugotoviti molekularne mehanizme prominina 2 (PROM2), ki sodeluje pri odpornosti NSCLC na cisplatin.

Bolniki in metode. Analizirali smo bazo podatkov GEO, da bi pridobili diferencialne gene, ki so povezani s PROM2. Za odkrivanje ravni izražanja beljakovin smo uporabili imunohistokemične teste in test *Western blot*. Da bi preučili vlogo PROM2 pri NSCLC, smo prekomerno izrazili ali utišali PROM2 s transfekcijo plazmida ali s pomočjo sRNA. V funkcionalnih poskusih smo uporabili CCK8 za odkrivanje viabilnosti celic. Celično migracijo in invazijo ter apoptozo smo ugotavljali s testom migracije (*angl. Transwell*) oziroma s pretočno citometrijo. Mehansko smo regulacija PROM2 s CTCC vezivnim proteinom (CTCF) analizirali s pomočjo kromatin imunoprecipitacijo kvantitativno v realnem času (*angl. Chromatin Immunoprecipitation-quantitative real-time*) PCR (ChIP-PCR). S poskusi *in vivo* smo potrdili vlogo PROM2 pri NSCLC.

Rezultati. Analiza podatkov GEO je pokazala, da je izražanje PROM2 pri NSCLC povečano, vendar njegova vloga pri NSCLC ostaja nejasna. Klinični vzorci so potrdili, da je bilo izražanje PROM2 izrazito povečano v tkivu NSCLC. Funkcionalno prekomerno izražanje PROM2 spodbuja celično proliferacijo, migracijo in invazijo ter odpornost na cisplatin. Transkripcijski represor protein CTCF poveča izražanje PROM2 tako, da se veže na njegovo promocijsko regijo. S poskusi *in vivo* smo ugotovili, da utišanje PROM2 zavira rast tumorja in poveča občutljivost tumorskih celic na cisplatin.

Zaključki. Povečano izražanje PROM2 pri NSCLC zmanjša občutljivost celic NSCLC na cisplatin in spodbuja proliferacijo, migracijo in invazijo tumorskih celic. PROM2 bi tako lahko predstavljal novo tarčo za zdravljenje NSCLC.

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Ocena ogroženosti z rakom dojk in razporeditev glede na ogroženost pri 3.491-ih Slovenkah, povabljenih v presejalni program v starosti 50 let. Populacijska presečna raziskava

Jarm K, Zadnik V, Birk M, Vrhovec M, Hertl K, Klaneček Ž, Studen A, Šval C, Krajc M

Izhodišča. Nepotrebnim slabostim mamografskega presejanja za raka dojk bi se lahko izognili z individualiziranim pristopom, ki temelji na ogroženosti žensk z rakom dojk. Namen raziskave je bil preveriti udeležbo slovenskih žensk pri ocenjevanju ogroženosti z rakom dojk in oceniti število presejalnih mamografij v primeru presejanja na podlagi ogroženosti.

Bolniki in metode. Presečna populacijska raziskava je vključila 11.898 žensk v starosti 50 let, ki smo jih povabili v presejalni program za raka dojk. V analizo smo vključili prvih 3.491 odzivnic in na podlagi zbranih podatkov o nevarnostnih dejavnikih, vključno z gostoto dojk, s pomočjo Tyrer-Cuzickovega algoritma (8. različica) ženske razporedili v skupine glede na njihovo ogroženost (majhna ogroženost, populacijska, zmerna in velika). Ocenili smo število mamografij glede na različne individualizirane protokole presejanja.

Rezultati. Vprašalnike o nevarnostnih dejavnikih za raka dojk je izpolnilo 57 % (6.785) žensk. Po izračunu ogroženosti smo jih 34,0 % razporedili v skupino z majhno 10-letno ogroženostjo, 62,2 % s populacijsko, 3,4 % z zmerno in 0,4 % z veliko ogroženostjo. Če bi izvajali individualizirano presejanje, bi se število presejalnih mamografij v primerjavi s trenutno politiko presejanja zmanjšalo za 38,6 %.

Zaključki. Ocena ogroženosti z rakom dojk pri ženskah, ki vstopajo v presejalni program, je izvedljiva. Za 3,8 % žensk smo ugotovili, da so ogrožene bolj kot splošna populacija. Po priporočilih slovenskih smernic za raka dojk bi te lahko presejali bolj pogosto, v celoti pa bi individualizirano presejanje zmanjšalo število presejalnih mamografij na državni ravni. Ta ugotovitev bi lahko pripomogla k preizkušanju izvajanja populacijskega individualiziranega presejanja v Sloveniji na podlagi tveganja.

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Ali ima razpok tumorja med robotsko asistirano delno nefrektomijo vpliv na ponovitve tumorja v srednjeročnem časovnem obdobju?

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Izhodišča. V vsakodnevni klinični praksi lahko med robotsko asistirano delno nefrektomijo (*angl. robot-assisted partial nephrectomy*, RAPN) pride do razpoka ledvičnega tumorja, vendar nimamo trdnih smernic o ravnanju in posledicah tega neželenega dogodka. Namen raziskave je bil oceniti vpliv razpoka tumorja na ponovitve tumorja, kako ravnati v takšnem primeru in kako se mu izogniti.

Bolniki in metode. Retrospektivno smo analizirali prvih 100 bolnikov, ki smo jim v Univerzitetnem kliničnem centru Ljubljana med leti 2018 do 2021 opravili RAPN. Bolnike smo razdelili v dve skupini (skupino z razpokom in brez razpoka tumorja) in ju primerjali glede na značilnosti bolnika in tumorja, patološke, perioperativne in pooperativne značilnosti ter ponovitve tumorja z uporabo testa Mann-Whitney U in testa hi-kvadrat.

Rezultati. Pri 14 od 100 bolnikov je prišlo do razpoka tumorja (14 %); to se je zgodilo pri tumorjih z višjimi vrednostmi točkovnika RENAL (P = 0,028) in pogosteje pri papilarnem karcinomu ledvičnih celic (P = 0,043). Srednji čas tople ishemije je bil daljši v skupini z razpokom tumorja (22 proti 15 min, P = 0,026). Po srednjem času opazovanja 39 mesecev (interkvartilni razpon 31−47 mesecev) ni bilo primerov lokalne ali oddaljene ponovitve bolezni v obeh skupinah. Pozitivni kirurški rob na končnem patohistološkem izvidu smo ugotovili pri enem bolniku v skupini brez razpoka tumorja.

Zaključki. Zdi se, da razpok tumorja med RAPN nima srednjeročnega onkološkega pomena. Glede na rezultate raziskave svetujemo, da kirurgi nadaljujejo z resekcijo tumorja ob nastanku tega neželenega dogodka, in se vzdržijo prehoda na radikalno nefrektomijo ali odprto delno nefrektomijo. Za trdnejše zaključke bo potrebno preučiti več podobnih primerov.

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Anastomoza Billroth-I pri distalni subtotalni gastrektomiji zaradi žleznega raka želodca, ki ni v začetnem stadiju

Shahbazyan SS, Sahakyan MA, Gabrielyan A, Lai X, Martirosyan A, Petrosyan H, Yesayan S, Sahakyan AM

Izhodišča. Anastomoza Billroth-I (B-I) je preprosta in fiziološka metoda rekonstrukcije po distalni subtotalni gastrektomiji zaradi začetne oblike raka želodca. Njena vloga in onkološki pomen pri žleznem raku želodca, ki ni ni začetne oblike, pa ostajata nejasna.

Bolniki in metode. V raziskavo smo vključeni bolniki z nezačetnim stadijem bolezni, vendar brez oddaljenih metastaz, ki smo jih operirali med majem 2004 in decembrom 2020. Kirurški in onkološki potek bolezni po distalni subtotalni gastrektomije smo analizirali pri bolnikih z anastomozami B-I in Billroth II (B-II). Uporabili smo metodo ujemanja na podlagi ocene nagnjenosti (*angl. propensity score matching,* PSM) za prilagoditev glede na starost, spol, velikost tumorja, lokalizacijo, vrsto resekcije ter stadijev pT in pN.

Rezultati. Pri 332 bolnikih smo naredili distalno subtotalno gastrektomijo zaradi žleznega raka želodca, nato pa anastomozo B-I pri 165 (49,7 %) in B-II pri 167 (50,3 %) primerih. B-I smo opravili pri bolnikih z manjšo velikostjo tumorja, manj napredovalim stadijem pT in lokacijo tumorja v želodčnem antrumu. Resekcija B-I je bila povezana z manjšim deležem večorganskih resekcij in krajšim operativnim časom. Po PSM te razlike niso bile več statistično značilne, razen pri operativnem času. Postoperativni potek bolezni je bil podoben ne glede na uporabo PSM. Pri bolnikih z anastomozo B-I smo odstranili več bezgavk in zasledili smo manj recidivov bolezni, zlasti lokalnih, vendar slednja povezava ni bila statistično značilna v multivariatnem modelu. Srednja vrednost celokupnega preživetja je bila 38 mesecev. Med skupinama ni bilo statistično značilnih razlik.

Zaključki. Uporaba anastomoze B-I po distalni subtotalni gastrektomiji zaradi žleznega raka želodca, ki ni ni začetne oblike, je povezana z zadovoljivimi kirurškimi in onkološkimi rezultati. Anastomozo B-I bi lahko uporabljali kot primerno metodo rekonstrukcije pri teh bolnikih.

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Primerjava analgetične učinkovitosti blokade pod mišico erector spinae z interkostalnim blokom pri operacijah pljučnega raka

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Izhodišča. V sodobni peri-operativni analgeziji pri operacijah pljučnega raka uporabljamo tehnike regionalne anestezije za zmanjševanje uporabe opioidnih analgetikov. Namen raziskave je bil kritično oceniti kontinuirani ultrazvočno vodeni blok pod mišico *erector spinae* (*angl. erector spinae plane block*, ESPB) v naši ustanovi in ga primerjati s standardno regionalno anestetično tehniko, interkostalnim živčnim blokom (*angl. intercostal nerve block*, ICNB).

Bolniki in metode. Prospektivno, randomizirano in kontrolirano raziskavo smo izvedli pri bolnikih, ki smo jih predvideli za videotorakoskopsko operacijo pljučnega raka. Bolnike smo razvrstili v skupino z ESPB ali ICNB. Primarna cilja raziskave sta bila: ugotoviti skupno porabo opioidov in subjektivno oceno bolečine v mirovanju ter pri kašlju vsako uro v 48 urah po operaciji. Sekundarni cilj pa je bil merjenje moči dihalnih mišic s testom maksimalnega inspiratornega in ekspiratornega tlaka pri ustih (MIP/MEP) po 24 in 48 urah.

Rezultati. Vključili smo 60 bolnikov, pol v interventno skupino ESPB. Skupna poraba opioidnih analgetikov v 48 urah je bila 21,64 ± 14,22 mg v skupini ESPB in 38,34 ± 29,91 mg v skupini ICNB (p = 0.035). Bolniki v skupini ESPB so imeli manj bolečine v mirovanju kot skupina ICNB (1,19 ± 0,3 proti 1,77 ± 1,01; p = 0,039). Ni bilo statistično značilnih razlik med skupinama pri meritvah MIP/MEP po 24 urah (MIP p = 0,088; MEP p = 0,182) ali 48 urah (MIP p = 0,110; MEP p = 0;645), času do odstranitve torakalnega drena ali času hospitalizacije.

Zaključki. V prvih 48 urah po operaciji so bolniki s kontinuiranim ESPB porabili manj opioidnih analgetikov in navajali manj bolečine kot bolniki z ICNB. Med skupinama ni bilo razlik glede moči dihalnih mišic, pooperativnih zapletov in časa hospitalizacije. Dodatno, kontinuirani ESPB je zahteval več pooperativne nege kot ICNB.

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Spremljanje učinka perioperativne prehranske oskrbe na telesno sestavo in funkcionalno stanje pri bolnikih s karcinomom gastrointestinalnega in hepatobiliarnega sistema ter trebušne slinavke

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Izhodišča. Prehranska oskrba je vse bolj uveljavljen in pomemben del zdravljenja bolnikov z rakom prebavil. Poleg anamneze in kliničnega pregleda uporabljamo pri prehranski obravnavi tudi meritev telesne sestave s testom bioelektrične impedance (*angl. bioelectric impedance assay*, BIA) in funkcionalnimi testi, kot je meritev moči stiska roke. Pri izvajanju prehranske podpore najprej bolniku individualno prehransko svetujemo in predpišemo medicinsko prehrano, predvsem oralne prehranske dodatke. Namen raziskave je bil opredeliti vpliv perioperativne prehranske oskrbe pri bolnikih z rakom prebavil.

Bolniki in metode. V raziskavo je bilo vključenih 47 bolnikov, od katerih jih je 27 prehransko svetovanje in oralne prehranske dodatke prejelo predoperativno in po operaciji (skupina 1), 20 pa le po operaciji (skupina 2), saj so bili zaradi kirurških ali organizacijskih razlogov operirani preden bi lahko izvedli prehransko oskrbo.

Rezultati. Skupina 2 je imela v povprečju višje število točk pri presejanju z orodjem za presejanje prehranske ogroženosti 2002 (*angl. Nutritional Risk Screening*, NRS 2002) ob vključitvi v raziskavo, vendar ni bilo razlike, ko smo podhranjenost ocenili po merilih Globalne pobude za opredelitev podhranjenosti (*angl. Global Leadership in Malnutrition*, GLIM). Skupina 1 je imela po 7 dneh relativno povečanje puste telesne mase in indeksa puste mase (+4,2 %) v primerjavi z bolniki skupine 2, kjer smo beležili upad (-2,1 %). Pri testu stiska roke razlik ni bilo.

Zaključki. Raziskava nakazuje, da je kombinacija pred- in po- operativne prehranske oskrbe bolj učinkovita kot le po operaciji. To se kaže v statistično značilno manjšem zmanjšanju puste mase po 7 dneh po operaciji, ne pa po 14 dneh in po 4 tednih.

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Zdravljenje in potek bolezni bolnikov z Gravesovo boleznijo in metastatskim diferenciranim rakom ščitnice

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Izhodišča. Namen raziskave je bil poročati o izkušnjah terciarnega onkološkega centra z zdravljenjem in potekom bolezni bolnikov z Gravesovo boleznijo (GD) in metastatskim rakom ščitnice v primerjavi z bolniki brez GD v državi Sloveniji.

Bolniki in metode. Skupno smo zaradi diferenciranega raka ščitnice in ob postavitvi diagnoze oddaljenih metastaz v 10-letnem obdobju (od 2010 do 2019) v Republiki Sloveniji zdravili 28 bolnikov (8 moških, 20 žensk; starost 49−85 let; srednja vrednost 74 let). V retrospektivni raziskavi smo analizirali štiri bolnike (tri moške, eno žensko; starost 64−76 let, srednja vrednost 73 let), ki so imeli Gravesovo bolezen in metastatski rak ščitnice.

Rezultati. Povprečna starost bolnikov brez GD in z GD je bila 74 oziroma 71 let (p = 0,36). Pri bolnikih z GD smo videli težnjo prevlade moških (p = 0,06). Med skupino bolnikov brez GD in z GD ni bilo statistično pomembne razlike v velikosti primarnih tumorjev, stopnji pT ali stopnji pN. Srednja dolžina spremljanja bolnikov je bila 3,33 leta (razpon 0,04–7,83), 5-letno preživetje, specifično za bolezen, pa 51 %. Eden od štirih bolnikov z GD in 14 od 24 bolnikov brez GD je umrl zaradi raka ščitnice. Med skupinama bolnikov brez GD in z GD ni bilo statistično pomembne razlike v bolezensko specifičnem preživetju (p = 0,59).

Zaključki. V Sloveniji je imelo 14 % bolnikov z metastatskim diferenciranim karcinomom ščitnice ob postavitvi diagnoze Gravesovo bolezen. Razlik v zdravljenju, poteku bolezni ali preživetju bolnikov z GD v primerjavi z bolniki brez GD ni bilo.

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Lokalna kontrola in preživetje po stereotaktičnem obsevanju bolnikov z zgodnjim rakom pljuč v Sloveniji

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Izhodišča. Stereotaktična telesna radioterapija (SBRT) je natančno in neinvazivno obsevanje tumorjev z ablativno dozo pri bolnikih z zgodnjim stadijem pljučnega raka, ki ni operabilen, ali pa bolniki operacijo zavračajo. Cilj raziskave je bil ovrednotiti lokalni nadzor bolezni, celokupno preživetje, preživetje brez lokalnega napredovanja bolezni, preživetje brez oddaljenih zasevkov, preživetje brez bolezni in toksičnost pri bolnikih z zgodnjim stadijem pljučnega raka, zdravljenih s SBRT v terciarnem onkološkem centru.

Bolniki in metode. Retrospektivno smo ovrednotili podatke iz zdravstvene dokumentacije in parametre načrtov obsevanja 228 tumorjev pri 206 bolnikih z zgodnjim stadijem pljučnega raka, ki smo jih zdravili med letoma 2016 in 2021 na Onkološkem inštitutu v Ljubljani.

Rezultati. Po 25 mesecih srednjega spremljanja je umrlo 68 od 206 (33 %) bolnikov. Srednje celokupno preživetje je bilo 46 mesecev (interval zaupanja [CI] 36–56 mesecev), 1-letno, 2-letno in 3-letno preživetje je bilo 87 %, 74 % in 62 %, 5-letno pa 31 %. Skupno smo ugotovili 45 napredovanj bolezni pri 41 bolnikih. Samo lokalno napredovanje smo zaznali pri 5 (2 %) bolnikih, sistemsko pri 32 (16 %) ter kombinirano sistemsko in lokalno napredovanje pri 4 (2 %) bolnikih. Stopnja lokalne kontrole po 1 letu je bila 98 %, po 2 in 3 letih 96 % in 95 % po 5 letih. 1-, 2- in 3-letno preživetje brez lokalnega napredovanja bolezni je bilo 98 %, 96 % oziroma 94 %, 5-letno pa 82 %. Eno, 2-, 3- in 5-letno preživetje brez bolezni je bilo 89 %, 81 %, 72 % oziroma 49 %. Med 28 zabeleženimi neželenimi učinki je bila samo ena toksičnost stopnje 4 (pnevmonitis), vse ostale pa so bile stopnje 1 ali 2. Pri univariatni analizi primerjave značilnosti bolnikov, tumorja in zdravljenja ni bilo ugotovljenih razlik v preživetju brez lokalnega napredovanja bolezni, preživetju brez oddaljenih metastaz in preživetju brez bolezni. Celokupno preživetje se je statistično značilno razlikovalo samo pri bolnikih z več kot tremi komorbidnostmi v primerjavi s tistimi, ki so jih imeli manj.

Zaključki. Pri zgodnjem pljučnem raku, ki smo ga zdravili s SBRT v terciarnem onkološkem centru, smo dosegli primerljiv lokalni nadzor, celokupno preživetje, preživetje brez lokalnega napredovanja bolezni, preživetje brez oddaljenih metastaz, preživetje brez bolezni in toksičnost glede na objavljene raziskave. Bolniki s številnimi komorbidnostmi so imeli znatno slabše skupno preživetje v primerjavi s tistimi z manj komorbidnostmi. Nismo pa našli nobenih pomembnih razlik glede na značilnosti bolnikov, tumorje ali zdravljenja. Podatki o toksičnosti so potrdili, da so bolniki zdravljenje dobro prenašali.

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Učinkovitost in varnost nintedaniba in docetaksela pri predhodno zdravljenih bolnikih z napredovalim neploščatoceličnim nedrobnoceličnim rakom pljuč. Multicentrična retrospektivna raziskava

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Izhodišča. Standardni prvi red zdravljenja bolnikov z napredovalim neploščatoceličnim nedrobnoceličnim rakom pljuč (NDRP) brez molekularnih alteracij je imunoterapija z zaviralci imunskih nadzornih točk (ZINT) in/ali kemoterapija (KT). Optimalno zdravljenje po napredovanju bolezni ostaja odprto vprašanje, ena od ustreznih možnosti zdravljenja je kombinacija docetaksela z nintedanibom.

Bolniki in metode. V multicentrični retrospektivni raziskavi smo zbrali podatke o dnevni klinični praksi pri bolnikih, ki so prejeli docetaksel in nintedanib ob napredovanju bolezni po predhodnem zdravljenju z ZINT+/-KT med januarjem 2014 in avgustom 2022 v dveh Slovenskih in enem Hrvaškem onkološkem centru. Ovrednotili smo objektivni delež odgovorov (*angl. objective response rate*, ORR), delež nadzora nad boleznijo *(angl. disease control rate,* DCR), srednje preživetje brez napredovanja bolezni (*angl. median progression free survival*, PFS), in srednje celokupno preživetje (*angl. median overall survival*, OS), ob tem pa tudi najpogostejše neželene učinke (NU).

Rezultati. V raziskavo smo vključili 96 bolnikov, ORR je bil 18,8 %, DCR 57,3 %, srednji PFS 3,0 mesecev (95 % interval zaupanja [CI]: 3,0–5,0) in srednji OS 8,0 mesecev (95 % CI: 7,0–10,0). Večina bolnikov (n = 47; 49 %) je prejela kombinacijo docetaksela in nintedaniba kot tretji red zdravljenja, pri teh je bil ORR 19,1 % in DCR 57,4 %. Najvišji delež odgovorov pa je bil dosežen pri drugem redu zdravljenja po napredovanju bolezni predhodno zdravljenih bolnikov s KT-ZINT (n = 24): ORR 29,2 %, DCR 66,7 % in srednji PFS 4,0 mesecev (95 % CI: 3,0–8,0). NU je imelo 53 bolnikov (55,2 %), najpogosteje gastrointestinalne (drisko 29 bolnikov; 30,2 %) in povišane jetrne transaminaze (17 bolnikov; 17,7 %).

Zaključki. Zdravljenje z docetakselom in nintedanibom se je v dnevni klinični praksi pokazalo učinkovito s sprejemljivim toksičnim profilom pri bolnikih z napredovalim neploščatoceličnim NDRP ob napredovanju bolezni po predhodnem zdravljenju z ZINT +/- KT.

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Učinkovitost in varnost anlotiniba z ali brez S-1 pri zdravljenju bolnikov z napredovalim hepatocelularnim karcinomom v kitajski populaciji. Prospektivna raziskava druge faze

Kang M, Xue F, Xu S, Shi J, Mo Y

Izhodišča. Namen raziskave je bil opazovanje varnosti in učinkovitosti anlotiniba kot edinega zdravljenja prvega reda ali v kombinaciji s S-1 pri bolnikih z napredovaleim hepatocelularnim karcinomom (HCC).

Bolniki in metode. 54 bolnikov z nezdravljenim napredovalim HCC, ki je bil neresektibilen, smo naključno razdelili v skupino anlotinib (n = 27) in skupino anlotinib+S-1 (n = 27). V skupini anlotinib so bolniki 14 zaporednih dni enkrat na dan peroralno prejemali 10 mg anlotiniba, nato so ga za en teden prenehali prejemati in to ponovili vsakih 21 dni. Skupina anlotinib+S-1 je je imela enak režim zdravljenja, le ob anlotinibu je prejemala še S-1. Vse bolnike smo zdravili, dokler bolezen ni napredovala ali dokler toksičnost ni postala nesprejemljiva. Pri bolnikih, ki niso prenašali neželenih učinkov, je bilo potrebno odmerek anlotiniba zmanjšati na 8 mg na dan. Vsakih 6 tednov smo naredili preiskavo CT ali MRI, da bi ocenili učinkovitost zdravljenja.

Rezultati. V analizo smo vključili 44 bolnikov, v skupini anlotinib 22 in v skupini anlotinib+S-1 22 bolnikov. V skupini anlotinib je bila stopnja objektivnega odgovora na zdravljenje (*angl. objective response rate*, ORR) 4,5 % (1/22), stopnja nadzora bolezni (*angl. disease control rate*, DCR) 77,3 % (17/22), srednja vrednost časa do napredovanja bolezni (*angl. progression-free survival*, PFS) 4,2 meseca (95 % interval zaupanja [CI]: 3,6–6,0) in srednja vrednost celokupnega preživetja (*angl. overall survival*, OS) 7,0 meseca (95 %CI: 6,3–9,0). V skupini anlotinib+S-1 je bil ORR 18,2 % (4/22), DCR 59,1 % (13/22), srednja vrednost PFS 4,0 meseca (95 %CI: 3,6–5,4), srednja vrednost OS pa 6,0 meseca (95 %CI: 5,5–7,4). Med obema skupinama ni bilo pomembnih statističnih razlik v ORR (p = 0,345) in DCR (p = 0,195). Neželeni učinki so bili predvsem hipertenzija, anoreksija, utrujenost, povišana jetrna transaminaza ter kožna reakcija rok in nog.

Zaključki. Monoterapija z anlotinibom je bila učinkovita pri zdravljenju napredovalega HCC, neželene učinke pa je bilo mogoče prenašati.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

IME ZDRAVILA: Verzenios 50 mg/100 mg/150 mg filmsko obložene tablete **KAKOVOSTNA IN KOLIČINSKA SESTAVA:** Ena filmsko obložena tableta vsebuje 50 mg/100 mg/150 mg abemaciklib. Ena filmsko obložena tableta vsebuje 14 mg/28 mg/42 mg laktoze (v obliki monohidrata). **Terapevtske indikacije:** Zgodnji rak dojk: Zdravilo Verzenios je v kombinaciji z endokrinim zdravljenjem indicirano za adjuvantno zdravljenje odraslih bolnikov z na hormonske receptorje (HR) pozitivnim, na receptorje humanega epidermalnega rastnega faktorja 2 (HER2) negativnim zgodnjim rakom dojk s pozitivnimi bezgavkami, pri katerih obstaja veliko tveganje za ponovitev. Pri ženskah v pred- ali perimenopavzi je treba endokrino zdravljenje z zaviralcem aromataze kombinirati z agonistom gonadoliberina (LHRH – luteinizing hormone–releasing hormone). Napredovali ali metastatski rak dojk: Zdravilo Verzenios je indicirano za zdravljenje žensk z lokalno napredovalim ali metastatskim, na hormonske receptorje (HR) pozitivnim in na receptorje humanega epidermalnega rastnega faktorja 2 (HER2) negativnim rakom dojk v kombinaciji z zaviralcem aromataze ali s fulvestrantom kot začetnim endokrinim zdravljenjem ali pri ženskah, ki so prejele predhodno endokrino zdravljenje. Pri ženskah v pred- ali perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom LHRH. **Odmerjanje in način uporabe:** Zdravljenje z zdravilom Verzenios mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek abemaciklib je 150 mg dvakrat na dan, kadar se uporablja v kombinaciji z endokrinim zdravljenjem. *Zgodnji rak dojk:* Zdravilo Verzenios je treba jemati neprekinjeno dve leti, ali do ponovitve bolezni ali pojava nesprejemljive toksičnosti. *Napredovali ali metastatski rak dojk:* Zdravilo Verzenios je treba jemati, dokler ima bolnica od zdravljenja klinično korist ali do pojava nesprejemljive toksičnosti. Če bolnica bruha ali izpusti odmerek zdravila Verzenios, ji je treba naročiti, da naj naslednji odmerek vzame ob predvidenem času; dodatnega odmerka ne sme vzeti. Obvladovanje nekaterih neželenih učinkov lahko zahteva prekinitev in/ali zmanjšanje odmerka. Zdravljenje z abemaciklibom prekinite v primeru povišanja vrednosti AST in/ali ALT >3 x ZMN SKUPAJ s celokupnim bilirubinom > 2,0 x ZMN v odsotnosti holestaze ter pri bolnicah z intersticijsko pljučno boleznijo (ILD)/pnevmonitis stopnje 3 ali 4. Sočasni uporabi močnih zaviralcev CYP3A4 se je treba izogibati. Če se uporabi močnih zaviralcev CYP3A4 ni mogoče izogniti, je treba odmerek abemaciklib znižati na 100 mg dvakrat na dan. Pri bolnicah, pri katerih je bil odmerek znižan na 100 mg abemaciklib dvakrat na dan in pri katerih se sočasnemu dajanju močnega zaviralca CYP3A4 ni mogoče izogniti, je treba odmerek abemaciklib dodatno znižati na 50 mg dvakrat na dan. Pri bolnicah, pri katerih je bil odmerek znižan na 50 mg abemaciklib dvakrat na dan in pri katerih se sočasnemu dajanju močnega zaviralca CYP3A4 ni mogoče izogniti, je mogoče z odmerkom abemaciklib nadaljevati ob natančnem spremljanju znakov toksičnosti. Alternativno je mogoče odmerek abemaciklib znižati na 50 mg enkrat na dan ali prekiniti dajanje abemaciklib. Če je uporaba zaviralca CYP3A4 prekinjena, je treba odmerek abemaciklib povečati na odmerek, kakršen je bil pred uvedbo zaviralca CYP3A4 (po 3–5 razpolovnih časih zaviralca CYP3A4). Prilagajanje odmerka glede na starost in pri bolnicah z blago ali zmerno ledvično okvaro ter z blago (Child Pugh A) ali zmerno (Child Pugh B) jetrno okvaro ni potrebno. Pri dajanju abemaciklib bolnicam s hudo ledvično okvaro sta potrebna previdnost in skrbno spremljanje glede znakov toksičnosti. Način uporabe: Zdravilo Verzenios je namenjeno za peroralno uporabo. Odmerek se lahko vzame s hrano ali brez nje. Zdravila se ne sme jemati z grenivko ali grenivkinim sokom. Bolnice naj odmerke vzamejo vsak dan ob približno istem času. Tableto je treba pogoltniti celo (bolnice tablet pred zaužitjem ne smejo gristi, drobiti ali deliti). **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri bolnicah, ki so prejemale abemaciklib, so poročali o nevtropeniji, o večji pogostnosti okužb kot pri bolnicah, zdravljenih s placebom in endokrinim zdravljenjem, o povečanih vrednostih ALT in AST. Pri bolnicah, pri katerih se pojavi nevtropenija stopnje 3 ali 4, je priporočljivo prilagoditi odmerek. Do primerov nevtropenične sepse s smrtnim izidom je prišlo pri < 1 % bolnic z metastatskim rakom dojk. Bolnicam je treba naročiti, naj o vsaki epizodi povišane telesne temperature poročajo zdravstvenemu delavcu. Bolnice je treba spremljati za znake in simptome globoke venske tromboze (VTE) in pljučne embolije ter jih zdraviti, kot je medicinsko utemeljeno. Glede na stopnjo VTE bo morda treba spremeniti odmerek abemaciklib. Glede na povečanje vrednosti ALT ali AST je mogoče potrebna prilagoditev odmerka. Driska je najpogostejši neželeni učinek. Bolnice je treba ob prvem znaku tekočega blata začeti zdraviti z antidiaroiki, kot je loperamid, povečati vnos peroralnih tekočin in obvestiti zdravnika. Sočasni uporabi induktorjev CYP3A4 se je treba izogibati zaradi tveganja za zmanjšano učinkovitost abemaciklib. Bolnice z redkimi dednimi motnjami, kot so intoleranca za galaktozo, popolno pomanjkanje laktaze ali malapsorpcija glukoze/galaktoze, tega zdravila ne smejo jemati. Bolnice je treba spremljati glede pljučnih simptomov, ki kažejo na ILD/pnevmonitis, in jih ustrezno zdraviti. Glede na stopnjo ILD/pnevmonitisa je morda potrebno prilagajanje odmerka abemaciklib. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Abemaciklib se primarno presnavlja s CYP3A4. Sočasna uporaba abema-cikliba in zaviralcev CYP3A4 lahko poveča plazemsko koncentracijo abemaciklib. Uporabi močnih zaviralcev CYP3A4 sočasno z abe-maciklibom se je treba izogibati. Če je močne zaviralce CYP3A4 treba dajati sočasno, je treba odmerek abemaciklib zmanjšati, nato pa bolnico skrbno spremljati glede toksičnosti. Pri bolnicah, zdravljenih z zmernimi ali šibkimi zaviralci CYP3A4, ni potrebno prilagajanje odmerka, vendar jih je treba skrbno spremljati za znake toksičnosti. Sočasni uporabi močnih induktorjev CYP3A4 (vključno, vendar ne omejeno na: karbamazepin, fenitoin, rifampicin in šentjanževko) se je treba izogibati zaradi tveganja za zmanjšano učinkovitost abema-cikliba. Abemaciklib in njegovi glavni aktivni presnovki zavirajo prenašalce v ledvicah, in sicer kationski organski prenašalec 2 (OCT2) ter prenašalca MATE1. In vivo lahko pride do medsebojnega delovanja abemaciklib in klinično pomembnih substratov teh prenašalcev, kot je dofelitid ali kreatinin. Trenutno ni znano, ali lahko abemaciklib zmanjša učinkovitost sistemskih hormonskih kontraceptivov, zato se ženskam, ki uporabljajo sistemske hormonske kontraceptive, svetuje, da hkrati uporabljajo tudi mehansko metodo. **Neželeni učinki:** *Najpogostejši* neželeni učinki so driska, okužbe, nevtropenija, levkopenija, anemija, utrujenost, navzea, bruhanje in zmanjšanje apetita. *Zelo pogosti:* okužbe, nevtropenija, levkopenija, anemija, trombocitopenija, limfopenija, zmanjšanje apetita, glavobol, disgevzija, omotica, driska, bruhanje, navzea, stomatitis, alopecija, pruritus, izpuščaj, pireksija, utrujenost, povečana vrednost alanin-aminotransferaze, pove-čana vrednost aspartat-aminotransferaze. *Pogosti:* povečano solzenje, venska trombembolija, ILD/pnevmonitis, dispepsija, spremembe na nohtih, suha koža, mišična šibkost. Občasni: febrilna nevtropenija. **Rok uporabnosti** 3 leta. **Posebna navodila za shranjevanje** Za shranjevanje zdravila niso potrebna posebna navodila. I**metnik dovoljenja za promet z zdravilom:** Eli Lilly Nederland B.V., Papendorp-seweg 83, 3528BJ, Utrecht, Nizozemska. Datum prve odobritve dovoljenja za promet: 27. september 2018. Datum zadnjega podaljšanja: 23. junij 2023 **Datum zadnje revizije besedila:** 23.6.2023. **Režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika.

Reference: 1. Povzetek glavnih značilnosti zdravila Verzenios, zadnja odobrena verzija.
Pomembno: Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. Pred predpisovan-jem zdravila Verzenios si preberite zadnji veljavni Povzetek glavnih značilnosti zdravil. Podrobne informacije o zdravilu so objavljene na spletni strani Evropske agencije za zdravila http://www.ema.europa.eu

Eli Lilly farmacevtska družba, d.o.o., Dunajska cesta 167, 1000 Ljubljana, telefon 01 / 580 00 10, faks 01 / 569 17 05
PP-AL-SI-0228, 17.8.2023, Samo za strokovno javnost.

PR/BSI/BEN/2022/017

TANTUM VERDE®

benzidaminijev klorid

Za lajšanje bolečine in oteklin v ustni in žrelu, ki so posledica radiomukozitisa

Bistvene informacije iz Povzetka glavnih značilnosti zdravila

Tantum Verde 1,5 mg/ml oralno pršilo, raztopina
Tantum Verde 3 mg/ml oralno pršilo, raztopina

Sestava: 1,5 mg/ml: 1 ml raztopine vsebuje 1,5 mg benzidaminijevega klorida, kar ustreza 1,34 mg benzidamina. V enem razpršku je 0,17 ml raztopine. En razpršek vsebuje 0,255 mg benzidaminijevega klorida, kar ustreza 0,2278 mg benzidamina. **Sestava 3 mg/ml:** 1 ml raztopine vsebuje 3 mg benzidaminijevega klorida, kar ustreza 2,68 mg benzidamina. V enem razpršku je 0,17 ml raztopine. En razpršek vsebuje 0,51 mg benzidaminijevega klorida, kar ustreza 0,4556 mg benzidamina. **Terapevtske indikacije:** Samozdravljenje: Lajšanje bolečine in oteklin pri vnetju v ustni votlini in žrelu, ki so lahko posledica okužb in stanj po operaciji. Po nasvetu in navodilu zdravnika: Lajšanje bolečine in oteklin v ustni votlini in žrelu, ki so posledica radiomukozitisa. **Odmerjanje in način uporabe:** Uporaba: 2- do 6-krat na dan (vsake 1,5 do 3 ure). Odmerjanje 1,5 mg/ml: Odrasli: 4 do 8 razprškov 2- do 6-krat na dan. Pediatrična populacija: Mladostniki, stari od 12 do 18 let: 4-8 razprškov 2- do 6-krat na dan. Otroci od 6 do 12 let: 4 razprški 2- do 6-krat na dan. Otroci, mlajši od 6 let: 1 razpršek na 4 kg telesne mase; do največ 4 razprške 2- do 6-krat na dan. Odmerjanje 3 mg/ml: Odrasli: 2 do 4 razprški 2- do 6-krat na dan. Pediatrična populacija: Mladostniki, stari od 12 do 18 let: 2 do 4 razprški 2- do 6-krat na dan. Otroci od 6 do 12 let: 2 razprška 2- do 6-krat na dan. Otroci, mlajši od 6 let: 1 razpršek na 8 kg telesne mase; do največ 2 razprška 2- do 6-krat na dan. Starejši bolniki, bolniki z jetrno okvaro in bolniki z ledvično okvaro: niso potrebni posebni previdnostni ukrepi. Trajanje zdravljenja ne sme biti daljše od 7 dni. Način uporabe: Za orofaringealno uporabo. Zdravilo se razprši v usta in žrelo. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Pri nekaterih bolnikih lahko resne bolezni povzročijo ustne/žrelne ulceracije. Če se simptomi v treh dneh ne izboljšajo, se mora bolnik posvetovati z zdravnikom ali zobozdravnikom, kot je primerno. Uporaba benzidamina ni priporočljiva za bolnike s preobčutljivostjo na salicilno kislino ali druga nesteroidna protivnetna zdravila. Pri bolnikih, ki imajo ali so imeli bronhialno astmo, lahko pride do bronhospazma. Pri takih bolnikih je potrebna previdnost. To zdravilo vsebuje 13,6 mg alkohola (etanola) v enem razpršku (0,17 ml), kar ustreza manj kot 0,34 ml piva oziroma 0,14 ml vina. Majhna količina alkohola v zdravilu ne bo imela nobenih opaznih učinkov. To zdravilo vsebuje metilparahidroksibenzoat (E218). Lahko povzroči alergijske reakcije (lahko zapoznele). To zdravilo vsebuje manj kot 1 mmol (23 mg) natrija v enem razpršku (0,17 ml), kar v bistvu pomeni 'brez natrija'. Zdravilo vsebuje aromo poprove mete z benzilalkoholom, cinamilalkoholom, citralom, citronelolom, geraniolom, izoevgenolom, linalolom, evgenolom in D-limonen, ki lahko povzročijo alergijske reakcije. Zdravilo z jakostjo 3 mg/ml vsebuje makrogolglicerol hidroksistearat 40. Lahko povzroči želodčne težave in drisko. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Študij medsebojnega delovanja niso izvedli. **Nosečnost in dojenje:** O uporabi benzidamina pri nosečnicah in doječih ženskah ni zadostnih podatkov. Uporaba zdravila med nosečnostjo in dojenjem ni priporočljiva. **Vpliv na sposobnost vožnje in upravljanja strojev:** Zdravilo v priporočenem odmerku nima vpliva na sposobnost vožnje in upravljanja strojev. **Neželeni učinki:** Neznana pogostnost (ni mogoče oceniti iz razpoložljivih podatkov): anafilaktične reakcije, preobčutljivostne reakcije, odrevenelost, laringospazem, suha usta, navzea in bruhanje, oralna hipestezija, angioedem, fotosenzitivnost, pekoč občutek v ustih. Neposredno po uporabi se lahko pojavi občutek odrevenelosti v ustih in v žrelu. Ta učinek se pojavi zaradi načina delovanja zdravila in po kratkem času izgine. **Način in režim izdaje zdravila:** BRp-Izdaja zdravila je brez recepta v lekarnah in specializiranih prodajalnah. **Imetnik dovoljenja za promet:** Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A., Viale Amelia 70, 00181 Rim, Italija **Datum zadnje revizije besedila:** 05. 04. 2022

Pred svetovanjem ali izdajo preberite celoten Povzetek glavnih značilnosti zdravila.

Samo za strokovno javnost.

Datum priprave informacije: april 2022

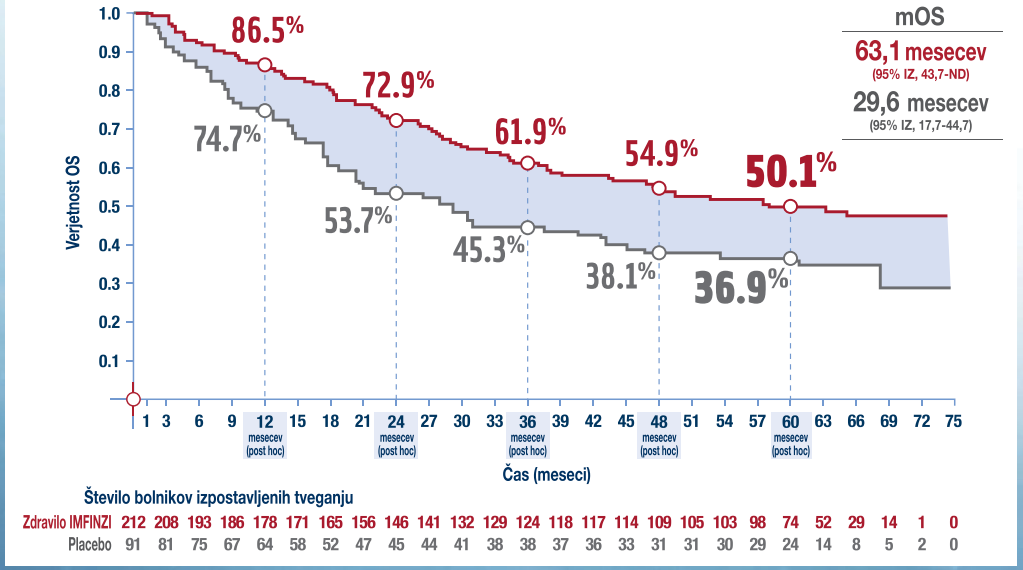
ANGELINI

Odgovoren za trženje: Bonifar d.o.o.

IMFINZI™
durvalumab
50 mg/ml koncentrat za raztopino za infundiranje

AKTIVIRA IMUNSKI SISTEM.
PREPOZNA. **REAGIRA.**

5-LETNO CELOKUPNO PREŽIVETJE BOLNIKOV Z LOKALNO NAPREDOVALIM, NEOPERABILNIM NSCLC S PDL-1 ≥ 1%[1]



Po petih letih je bilo živih še 50% bolnikov zdravljenih z zdravilom Imfinzi po zaključeni sočasni kemoradioterapiji na osnovi platine.

NSCLC... nedrobnocelični rak pljuč (non small cell lung cancer), mOS...mediano celokupno preživetje

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Imfinzi 50 mg/ml koncentrat za raztopino za infundiranje

SESTAVA: 1 ml koncentrata za raztopino za infundiranje vsebuje 50 mg durvalumaba. Ena viala z 2,4 ml koncentrata vsebuje 120 mg durvalumaba. Ena viala z 10 ml koncentrata vsebuje 500 mg durvalumaba. **INDIKACIJE:** Neoperabilni nedrobnocelični rak pljuč (NSCLC). Zdravilo IMFINZI je kot samostojno zdravljenje indicirano za zdravljenje lokalno napredovalega, neoperabilnega nedrobnoceličnega raka pljuč (NSCLC – non small cell lung cancer) pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD L1 na tumorskih celicah in pri katerih bolezen ni napredovala po kemoradioterapiji na osnovi platine. Zdravilo IMFINZI je v kombinaciji s tremelimumabom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja odraslih z metastatskim NSCLC brez senzibilizirajočih mutacij EGFR ali pozitivnih mutacij ALK. Drobnocelični rak pljuč (SCLC). Zdravilo IMFINZI je v kombinaciji z etopozidom in bodisi karboplatinom bodisi cisplatinom indicirano za prvo linijo zdravljenja odraslih z razsejanim drobnoceličnim rakom pljuč (ES SCLC – extensive stage small cell lung cancer). Rak biliarnega trakta (RBT). Zdravilo IMFINZI je v kombinaciji z gemcitabinom in cisplatinom indicirano za prvo linijo zdravljenja odraslih z neoperabilnim ali metastatskim rakom biliarnega trakta (RBT). Hepatocelularni karcinom (HCK). Zdravilo IMFINZI je v kombinaciji s tremelimumabom indicirano za prvo linijo zdravljenja odraslih z napredovalim ali neoperabilnim karcinomom jetrnih celic (hepatocelularnim karcinomom – HCK). **ODMERJANJE IN NAČIN UPORABE:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje na področju zdravljenja raka. Bolnike z lokalno napredovalim nedrobnoceličnim rakom pljuč je treba za zdravljenje izbrati na podlagi izraženosti PD-L1, ugotovljene z validirano testno metodo. Odmerjanje: Priporočeni odmerek zdravila Imfinzi pri samostojnem zdravljenju pri lokalno napredovalem NSCLC je 10 mg/kg na 2 tedna ali 1500 mg na 4 tedne do napredovanja bolezni, nesprejemljivih toksičnih učinkov ali največ 12 mesecev. Priporočeni odmerek zdravila Imfinzi pri kombiniranem zdravljenju pri metastatskem NSCLC je med kemoterapijo s platino: 1500 mg v kombinaciji s 75 mg tremelimumaba in kemoterapijo na osnovi platine na 3 tedne (21 dni) 4 cikle (12 tednov), po kemoterapiji s platino: 1500 mg na 4 tedne kot monoterapija in vzdrževalno zdravljenje s pemetreksedom (na podlagi histologije) na 4 tedne, peti odmerek 75 mg tremelimumaba je treba dati 16. teden skupaj z zdravilom Imfinzi, do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri ES-SCLC je priporočeni odmerek zdravila Imfinzi 1500 mg v kombinaciji s kemoterapijo na 3 tedne (21 dni) 4 cikluse in nato 1500 mg na 4 tedne kot samostojno zdravljenje do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri RBT je priporočeni odmerek zdravila Imfinzi 1500 mg v kombinaciji s kemoterapijo na 3 tedne (21 dni) do 8 ciklusov, nato po 1500 mg na 4 tedne kot samostojno zdravljenje do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Pri HCK je priporočeni odmerek 1500 mg zdravila IMFINZI v kombinaciji s 300 mg tremelimumaba v enem odmerku 1. dan 1. cikla, nato zdravilo Imfinzi kot monoterapija na 4 tedne do napredovanja bolezni ali nesprejemljivih toksičnih učinkov. Povečevanje ali zmanjševanje odmerka ni priporočljivo. Glede na individualno varnost in prenašanje je lahko potrebna odložitev zdravljenja ali trajno prenehanje uporabe zdravila. V primeru domnevnih imunsko pogojenih neželenih učinkov je treba opraviti ustrezno ovrednotenje za potrditev etiologije oziroma izključitev druge etiologije. Glede na resnost neželenega učinka je treba prenehati uporabljati zdravilo Imfinzi in/ali tremelimumab in pričeti z dajanjem kortikosteroidov. Če se stanje ne izboljša ali se poslabša, pride v poštev povečanje odmerka kortikosteroidov in/ali dodatna uporaba sistemskih imunosupresivov. Po izboljšanju na ≤ 1. stopnjo je treba začeti s postopnim zmanjševanjem kortikosteroida in ga zmanjševati v obdobju vsaj 1 meseca. Po odložitvi uporabe je mogoče zdravilo Imfinzi in/ali tremelimumab znova začeti uporabljati v času 12 tednov, če se neželeni učinki izboljšajo na ≤ 1. stopnjo in je odmerek kortikosteroida zmanjšan na ≤ 10 mg prednizona ali ekvivalenta na dan. Zdravilo Imfinzi in tremelimumab je treba dokončno ukiniti, če se imunsko pogojeni neželeni učinki 3. stopnje (močno izraženi) ponavljajo in pri katerih koli imunsko pogojenih neželenih učinkih 4. stopnje (življenjsko nevarni), razen pri endokrinopatijah, ki jih nadziramo z nadomestnimi hormoni. Način uporabe: Zdravilo Imfinzi je namenjeno za intravensko uporabo. Dati ga je treba kot raztopino za intravensko infundiranje v obdobju 1 ure. Če je zdravilo Imfinzi uporabljeno v kombinaciji s kemoterapijo, je treba dati zdravilo Imfinzi pred kemoterapijo na isti dan. Če je zdravilo Imfinzi uporabljeno v kombinaciji s tremelimumabom in kemoterapijo na osnovi platine, je treba najprej dati tremelimumab, ki mu v istem dnevu sledita zdravilo Imfinzi in nato kemoterapija na osnovi platine. Če je zdravilo Imfinzi uporabljeno v kombinaciji s petim odmerkom tremelimumaba in vzdrževalnim zdravljenjem s pemetreksedom 16. teden, je treba najprej dati tremelimumab, ki mu v istem dnevu sledita zdravilo Imfinzi in potem vzdrževalno zdravljenje s pemetreksedom. Zdravilo Imfinzi, tremelimumab in kemoterapijo na osnovi platine je treba dati v ločenih intravenskih infuzijah. Dajanje zdravila Imfinzi in tremelimumaba vsako traja po 1 uro. Če je zdravilo Imfinzi uporabljeno v kombinaciji s tremelimumabom, je treba dati tremelimumab pred zdravilom Imfinzi na isti dan. Zdravilo Imfinzi in tremelimumab je treba dati v ločenih intravenskih infuzijah.**KONTRAINDIKACIJE:** Preobčutljivost na učinkovino (učinkovine) ali katero koli pomožno snov. **OPOZORILA IN PREVIDNOSTNI UKREPI:** Za izboljšanje sledljivosti bioloških zdravil je treba jasno zabeležiti lastniško ime in številko serije uporabljenega zdravila. Imunsko pogojeni pnevmonitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, sta se pojavila imunsko pogojeni pnevmonitis ali intersticijska bolezen pljuč, opredeljeno kot potreba po uporabi sistemskih kortikosteroidov in brez jasne druge etiologije. Pnevmonitis in radiacijski pnevmonitis: Pri bolnikih, zdravljenih z radioterapijo pljuč, je pogost radiacijski pnevmonitis in klinična slika pnevmonitisa in radiacijskega pnevmonitisa je zelo podobna. V študiji PACIFIC sta se pri bolnikih, ki so opravili zdravljenje z najmanj 2 cikloma sočasne kemoradioterapije od 1 do 42 dni pred začetkom preskušanja, pnevmonitis ali radiacijski pnevmonitis pojavila pri 161 (33,9 %) bolnikih v skupini z zdravilom Imfinzi in pri 58 (24,8 %) bolnikih v skupini s placebom, vključno s 3. stopnjo (3,4 % in 3,0 %) in 5. stopnjo (1,1 % in 1,7 %). Bolnike je treba spremljati glede znakov in simptomov pnevmonitisa ali radiacijskega pnevmonitisa. Imunsko pogojeni hepatitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavil imunsko pogojeni hepatitis, opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Alanin-aminotransferazo, aspartat-aminotransferazo, celokupni bilirubin in alkalno fosfatazo kontrolirajte pred začetkom zdravljenja in pred vsako nadaljnjo infuzijo. Dodaten nadzor pride v poštev na podlagi kliničnega ocene. Imunsko pogojeni kolitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, sta se pojavila imunsko pogojeni kolitis ali driska, opredeljeno kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Pri bolnikih, ki so prejemali zdravilo Imfinzi v kombinaciji s tremelimumabom, so poročali o neželenih učinkih perforacije črevesa in perforacije debelega črevesa. Imunsko pogojene endokrinopatije: Imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, so se pojavili imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis; hipertiroidizmu lahko sledi hipotiroidizem. Bolnike je treba spremljati glede nenormalnih izvidov delovanje ščitnice pred zdravljenjem in redno med zdravljenjem ter kot je potrebno glede na klinično oceno. Imunsko pogojena adrenalna insuficienca: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavila imunsko pogojena adrenalna insuficienca. Bolnike je treba spremljati glede kliničnih znakov in simptomov adrenalne insuficience. Imunsko pogojena sladkorna bolezen tipa 1: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavila imunsko pogojena sladkorna bolezen tipa 1, ki se lahko najprej kaže kot diabetična ketoacidoza, ki je lahko smrtno nevarna, če je dovolj zgodaj ne odkrijemo. Bolnike je treba spremljati glede kliničnih znakov in simptomov sladkorne bolezni tipa 1. Imunsko pogojeni hipofizitis/hipopituitarizem: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, sta se pojavila imunsko pogojena hipofizitis ali hipopituitarizem. Bolnike je treba spremljati glede kliničnih znakov in simptomov hipofizitisa ali hipopituitarizma. Imunsko pogojeni nefritis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavil imunsko pogojeni nefritis, opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojeni izpuščaj: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavil imunsko pogojeni izpuščaj ali dermatitis (vključno s pemfigoidom), opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Pri bolnikih, ki so bili zdravljeni z zaviralci PD-1, so poročali o pojavljanju Stevens-Johnsonovega sindroma ali toksične epidermalne nekrolize. Imunsko pogojeni miokarditis: Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, se je pojavil imunsko pogojeni miokarditis, ki je lahko usoden. Imunsko pogojeni pankreatitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi v kombinaciji s tremelimumabom in kemoterapijo, se je pojavil imunsko pogojeni pankreatitis. Drugi imunsko pogojeni neželeni učinki: Glede na mehanizem delovanja zdravila Imfinzi ali zdravila Imfinzi v kombinaciji s tremelimumabom se lahko pojavijo še drugi potencialno imunsko pogojeni učinki. Naslednji imunsko pogojeni neželeni učinki so bili opaženi pri bolnikih, ki so prejemali samostojno zdravljenje z zdravilom Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom: miastenija gravis, transverzni mielitis, miozitis, polimiozitis, meningitis, encefalitis, Guillain Barréjev sindrom, imunska trombocitopenija, neinfektivni cistitis. Z infundiranjem povezane reakcije: Bolnike je treba spremljati glede znakov in simptomov z infundiranjem povezanih reakcij. Pri bolnikih, ki so prejemali zdravilo Imfinzi ali zdravilo Imfinzi v kombinaciji s tremelimumabom, so bile opisane hude z infundiranjem povezane reakcije. Za bolezen specifični previdnostni ukrepi (RBT): Holangitis in okužbe biliarnega trakta pri bolnikih z napredovalim RBT niso redke. V študiji TOPAZ-1 so o primerih holangitisa poročali v obeh terapevtskih skupinah (14,5 % v skupini z zdravilom Imfinzi + kemoterapijo, 8,2 % v skupini s placebom + kemoterapijo); ti primeri so bili večinoma povezani z biliarnimi opornicami in niso imeli imunsko posredovane etiologije. Bolnike z RBT (zlasti tiste z biliarno opornico) je treba natančno nadzorovati glede holangitisa ali okužb biliarnega trakta tako pred uvedbo zdravljenja kot redno med zdravljenjem. Metastatski NSCLC: Podatkov o starejših bolnikih (≥ 75 let), zdravljenih z zdravilom Imfinzi v kombinaciji s tremelimumabom in kemoterapijo na osnovi platine, je malo. Morebitno korist/tveganje te sheme je priporočljivo skrbno pretehtati za vsakega bolnika posebej. Bolniki, ki niso bili vključeni v klinične študije: V klinične študije niso bili vključeni bolniki z naslednjimi značilnostmi: izhodiščno oceno zmogljivosti ECOG ≥ 2; aktivno ali predhodno dokumentirano avtoimunsko boleznijo v 2 letih pred začetkom študije; anamnezo imunske pomanjkljivosti; anamnezo hudih imunsko pogojenih neželenih učinkov; boleznimi, ki so zahtevale sistemsko imunosupresijo, razen fiziološkega odmerka sistemskih kortikosteroidov (≤ 10 mg na dan prednizona ali ekvivalenta); neobvladanimi sočasnimi boleznimi; aktivno tuberkulozo ali okužbo s hepatitisom B ali C ali HIV; bolniki, ki so prejeli živo oslabljeno cepivo v 30 dneh pred začetkom zdravljenja z zdravilom Imfinzi ali v 30 dneh po začetku. Dokler takšnih podatkov ni, je treba durvalumab v teh skupinah bolnikov uporabljati previdno ter po skrbnem individualnem pretehtanju možnih koristi in tveganj za posameznega bolnika. Varnost sočasnega profilaktičnega kranialnega obsevanja obenem z zdravilom Imfinzi pri bolnikih z ES SCLC ni znana. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI:** Razen fizioloških odmerkov sistemskih kortikosteroidov (≤ 10 mg na dan prednizona ali ekvivalenta) pred uvedbo durvalumaba ni priporočljivo uporabljati sistemskih kortikosteroidov ali imunosupresivov, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost durvalumaba. Vendar pa je mogoče kortikosteroide ali druge imunosupresive uporabiti po začetku zdravljenja z durvalumabom za zdravljenje imunsko pogojenih neželenih učinkov. Z durvalumabom niso izvedli formalnih farmakokinetičnih (PK) študij medsebojnega delovanja zdravil. Primarni poti odstranjevanja durvalumaba sta katabolizem beljakovin preko retikuloendotelijskega sistema oziroma tarčno posredovano odstranjevanje, zato ni pričakovati presnovnih medsebojnih delovanj med zdravili. Farmakokinetična medsebojna delovanja med durvalumabom in kemoterapijo so ocenjevali v študiji CASPIAN; izkazalo se je, da sočasno zdravljenje z durvalumabom ne vpliva na farmakokinetiko etopozida, karboplatina ali cisplatina. Poleg tega populacijska farmakokinetična analiza kaže, da sočasno zdravljenje s kemoterapijo ne vpliva pomembno na farmakokinetiko durvalumaba. Farmakokinetična medsebojna delovanja med durvalumabom v kombinaciji s tremelimumabom in kemoterapijo na osnovi platine so ocenili v študiji POSEIDON. Izkazalo se je, da med sočasnim zdravljenjem ni bilo klinično pomembnih farmakokinetičnih medsebojnih delovanj med tremelimumabom, durvalumabom, nab-paklitakselom, gemcitabinom, pemetreksedom, karboplatinom ali cisplatinom. **PLODNOST, NOSEČNOST IN DOJENJE:** Ženske v rodni dobi morajo med zdravljenjem z durvalumabom in vsaj še 3 mesece po zadnjem odmerku durvalumaba uporabljati učinkovito kontracepcijo. Podatkov o uporabi durvalumaba pri noseničnah ni. Glede na mehanizem delovanja durvalumab lahko vpliva na vzdrževanje nosečnosti; v alogenskem modelu nosečnosti pri miših je bilo ugotovljeno, da moteno signaliziranje PD-L1 poveča izgubo plodov. Pri nosečnici uporabljeni durvalumab lahko škoduje plodu in ga ni priporočljivo uporabljati med nosečnostjo in pri ženskah v rodni dobi, ki ne uporabljajo učinkovite kontracepcije med zdravljenjem in vsaj še 3 mesece po zadnjem odmerku. Ni znano, ali se durvalumab pri človeku izloča v materinem mleku. Pri človeku protitelesa lahko prehajajo v materino mleko, a možnost absorpcije in škode za novorojenčka ni znana. Toda možnega tveganja za dojenega otroka ni mogoče izključiti. Odločiti se je treba, ali naj ženska prekine z dojenjem ali naj prekine zdravljenje z durvalumabom oziroma sploh ne začne zdravljenja z njim, pri čemer je treba upoštevati koristi dojenja za otroka in koristi zdravljenja za žensko. Podatkov o možnih vplivih durvalumaba na plodnost pri človeku ali živalih ni. **NEŽELENI UČINKI:** Ugotovitve o varnosti zdravila Imfinzi pri samostojnem zdravljenju temeljijo na kumulativnih podatkih 3006 bolnikov z več vrstami tumorjev. Zdravilo Imfinzi so uporabljali v odmerku 10 mg/kg na 2 tedna ali v odmerku 20 mg/kg na 4 tedne. Najpogostejši neželeni učinki (> 10 %) so bili kašelj/produktiven kašelj (21,5 %), driska (16,3 %), izpuščaj (16,0 %), zvišana telesna temperatura (13,8 %), okužbe zgornjih dihal (13,5 %), bolečine v trebuhu (12,7 %), srbenje (10,8 %) in hipotiroidizem (10,1 %). Podatki o varnosti zdravila Imfinzi v kombinaciji s kemoterapijo temeljijo na kumulativnih podatkih 603 bolnikov iz 2 študij (TOPAZ-1 in CASPIAN). Najpogostejši (> 10 %) neželeni učinki so bili nevtropenija (53,1 %), anemija (43,9 %), navzea (37,5 %), utrujenost (36.8 %), trombocitopenija (28,0 %), zaprtje (25,4 %), zmanjšan apetit (22,6 %), bolečine v trebuhu (18,4 %), alopecija (18,4 %), levkopenija (17,2 %), bruhanje (16,9 %), zvišana telesna temperatura (15,1 %), izpuščaj (14,8 %), driska (13,8 %), zvišana aspartat-aminotransferaza ali zvišana alanin-aminotransferaza (10,9 %), kašelj/produktiven kašelj (10,8 %) in srbenje (10,4 %). Izsledki o varnosti zdravila Imfinzi v kombinaciji s 75 mg tremelimumaba in kemoterapijo temeljijo na podatkih 330 bolnikov z metastatskim NSCLC. Najpogostejši (> 20 %) neželeni učinki so bili anemija (49,7 %), navzea (41,5 %), nevtropenija (41,2 %), utrujenost (36,1 %), izpuščaj (25,8 %), trombocitopenija (24,5 %) in driska (21,5 %). Izsledki o varnosti zdravila Imfinzi v kombinaciji z enkratnim odmerkom 300 mg tremelimumaba temljijo na združenih podatkih 462 bolnikov s HCK iz študije HIMALAYA in še ene študije pri bolnikih s HCK, študija 22. Najpogostejši neželeni učinki (> 10 %) so bili izpuščaj (32,5 %), srbenje (25,5 %), driska (25,3 %), bolečine v trebuhu (19,7 %), zvišana aspartat aminotransferaza/zvišana alanin aminotransferaza (18,0 %), zvišana telesna temperatura (13,9 %), hipotiroidizem (13,0 %), kašelj/produktiven kašelj (10,8 %), periferni edemi (10,4 %) in zvišana lipaza (10,0 %). **VRSTA IN VSEBINA OVOJNINE:** 2,4 ml (skupno 120 mg durvalumaba) koncentrata v stekleni viali iz stekla tipa 1 z elastomernim zamaškom in sivo snemno aluminijsko zaporo. Pakiranje vsebuje 1 vialo. 10 ml (skupno 500 mg durvalumaba) koncentrata v stekleni viali iz stekla tipa 1 z elastomernim zamaškom in belo snemno aluminijsko zaporo. Pakiranje vsebuje 1 vialo. **NAČIN IZDAJANJA ZDRAVILA:** H - Predpisovanje in izdaja zdravila je le na recept. **DATUM REVIZIJA BESEDILA:** 24.4.2023 (SI-3078) **IMETNIK DOVOLJENJA ZA PROMET:** AstraZeneca AB, S-151 85, Sodertalje, Švedska **Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.** Dodatne informacije so na voljo pri družbi AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, Ljubljana, telefon +386 1 51 35 600.

Samo za strokovno javnost. Informacija pripravljena avgusta 2023.

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***Prvi in edini zaviralec PARP odobren za 4 različne lokalizacije tumorjev*[1-5]**

RAK JAJČNIKOV

Prvi zaviralec PARP odobren za vzdrževalno zdravljenje napredovalega raka jajčnikov v monoterapiji (v 1L pri bolnicah z mutacijo *gena BRCA1/2* in 2L) ali kombinaciji z bevacizumabom (pri bolnicah s HRD).[1-3, 5]

RAK DOJK

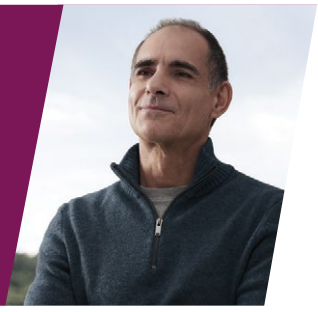
Prvi zaviralec PARP odobren za zdravljenje, pri bolnikih z zarodno mutacijo gena *BRCA1/2*, ki imajo HER2-negativni zgodnji, lokalno napredovali ali razsejan rak dojk.*,[1-2, 4]

RAK TREBUŠNE SLINAVKE

Edini zaviralec PARP odobren za vzdrževalno zdravljenje bolnikov z zarodno mutacijo gena *BRCA1/2*, ki imajo razsejani adenokarcinom trebušne slinavke in jim bolezen ni napredovala po najmanj 16 tednih prvega reda zdravljenja s kemoterapijo na osnovi platine.[1-4]

RAK PROSTATE

Edini zaviralec PARP odobren za zdravljenje bolnikov z razsejanim KORP v monoterapiji za bolnike z mutacijami gena *BRCA1/2*, ki jim je bolezen napredovala po zdravljenju z novim hormonskim zdravilom, in v kombinaciji z abirateronom ne glede na status mutacij.*,[1-4]



* Zdravilo Lynparza še ni razvrščeno na listo zdravil za naslednje indikacije: zgodnji rak dojk in v kombinaciji z abirateronom za zdravljenje raka prostate.

PARP – poli (ADP-riboza) polimeraza, **1L** – v prvem redu zdravljenja, **2L** – v drugem redu zdravljenja, **HRD** – pomanjkanje homologne rekombinacije, **KORP** – na kastracijo odporen rak prostate

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

LYNPARZA 100 mg filmsko obložene tablete, LYNPARZA 150 mg filmsko obložene tablete

SESTAVA: Ena filmsko obložena tableta vsebuje 100 mg olapariba ali 150 mg olapariba.

INDIKACIJE: Rak jajčnikov: 1) *zdravilo Lynparza je indicirano kot monoterapija za*:
- vzdrževalno zdravljenje odraslih bolnic z napredovalim (stadij III in IV po FIGO) epitelijskim rakom visokega gradusa jajčnikov, jajcevodov ali primarnim peritonealnim rakom z mutacijo gena BRCA1/2 (germinalno in/ali somatsko), ki so v odzivu (popolnem ali delnem) po zaključeni prvi liniji kemoterapije na osnovi platine.
- vzdrževalno zdravljenje odraslih bolnic, pri katerih je prišlo do ponovitve epitelijskega raka visokega gradusa jajčnikov, jajcevodov ali primarnega peritonealnega raka, občutljivega na platino, ki so v popolnem ali delnem odzivu na kemoterapijo na osnovi platine.

2) *zdravilo Lynparza je v kombinaciji z bevacizumabom indicirano za*:
- vzdrževalno zdravljenje odraslih bolnic z napredovalim (stadij III in IV po FIGO) epitelijskim rakom visokega gradusa jajčnikov, jajcevodov ali primarnim peritonealnim rakom, ki so v popolnem ali delnem odzivu po zaključeni prvi liniji kemoterapije na osnovi platine v kombinaciji z bevacizumabom, pri katerih je rak povezan s pozitivnim stanjem pomanjkanja homologne rekombinacije (HRD – homologous recombination deficiency), opredeljenim z mutacijo gena BRCA1/2 in/ali genomsko nestabilnostjo.

Rak dojk: *zdravilo Lynparza je indicirano kot*:
- monoterapija ali v kombinaciji z endokrinim zdravljenjem za adjuvantno zdravljenje odraslih bolnikov z germinalnimi mutacijami gena BRCA1/2, ki imajo HER2-negativnega zgodnjega raka dojk z velikim tveganjem in so bili predhodno zdravljeni z neoadjuvantno ali adjuvantno kemoterapijo.
- monoterapija za zdravljenje odraslih bolnikov z germinalno mutacijo gena BRCA1/2, ki imajo HER2-negativnega lokalno napredovalega ali metastatskega raka dojk. Bolniki morajo biti predhodno zdravljeni z antraciklinom in taksanom v okviru (neo)adjuvantnega zdravljenja ali zdravljenja metastatske bolezni, razen če za ti zdravljenji niso primerni. Pri bolnikih, ki imajo raka dojk s pozitivnimi hormonskimi receptorji (HR), je morala bolezen prav tako napredovati med predhodnim hormonskim zdravljenjem ali po njem, ali morajo bolniki veljati za neprimerne za hormonsko zdravljenje.

Adenokarcinom trebušne slinavke: zdravilo Lynparza je kot monoterapija indicirano za vzdrževalno zdravljenje odraslih bolnikov z germinalno mutacijo gena BRCA1/2, ki imajo metastatski adenokarcinom trebušne slinavke in njihova bolezen ni napredovala po najmanj 16 tednih zdravljenja s platino v shemi prve linije kemoterapije.

Rak prostate: *zdravilo Lynparza je indicirano*:
- kot monoterapija za zdravljenje odraslih bolnikov z metastatskim, na kastracijo odpornim rakom prostate (mKORP) in mutacijami gena BRCA1/2 (germinalnimi in/ali somatskimi), pri katerih je bolezen napredovala po predhodni terapiji, ki je vsebovala novo hormonsko zdravilo.
- v kombinaciji z abirateronom in prednizonom ali prednizolonom za zdravljenje odraslih bolnikov z mKORP, pri katerih kemoterapija ni klinično indicirana

ODMERJANJE IN NAČIN UPORABE: Priporočeni odmerek zdravila Lynparza pri monoterapiji ali v kombinaciji z bevacizumabom pri raku jajčnikov ali v kombinaciji z abirateronom in prednizonom ali prednizolonom pri raku prostate ali z endokrinim zdravljenjem je 300 mg dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 600 mg). 100-mg tablete so na voljo za zmanjšanje odmerka. Bolnice s ponovitvijo raka jajčnikov morajo začeti zdravljenje z zdravilom Lynparza najpozneje v 8 tednih po zadnjem odmerku sheme zdravljenja na osnovi platine. Če je zdravilo Lynparza uporabljeno v kombinaciji z bevacizumabom za prvo linijo vzdrževalnega zdravljenja po dokončanju prve linije zdravljenja na osnovi platine in z bevacizumabom, je odmerek bevacizumaba 15 mg/kg enkrat na 3 tedne. Glejte celotne informacije o zdravilu za bevacizumab. Za priporočeno odmerjanje partnerskega zdravila/partnerskih zdravil (zaviralec aromataze/antiestrogen in/ali LHRH) v kombinaciji endokrinega zdravljenja glejte celotne informacije o zadevnem zdravilu. Če je zdravilo Lynparza uporabljeno v kombinaciji z abirateronom za zdravljenje bolnikov z mKORP, je odmerek abirateron 1000 mg peroralno enkrat na dan. Abirateron je treba dajati s 5 mg prednizona ali prednizolona peroralno dvakrat na dan. Glejte celotne informacije o zdravilu za abirateron.Prvo linijo vzdrževalnega zdravljenja napredovalega raka jajčnikov z mutacijo gena BRCA in prvo linijo vzdrževalnega zdravljenja HRD-pozitivnega napredovalega raka jajčnikov v kombinaciji z bevacizumabom je priporočljivo nadaljevati do radiološkega napredovanja bolezni ali nesprejemljive toksičnosti ali do največ 2 leti, če po 2 letih ni radioloških znakov bolezni. V primeru znakov bolezni po 2 letih, se lahko zdravljenje nadaljuje, če bi le to po mnenju zdravnika bilo koristno za bolnico. Glejte informacije o zdravilu bevacizumab za priporočeno celotno trajanje zdravljenja največ 15 mesecev, vključno z obdobji v kombinaciji s kemoterapijo in kot vzdrževalno zdravljenje. Pri adjuvantnem zdravljenju zgodnjega raka dojk je prporočljivo, da bolniki prejemajo zdravljenje do 1 leto ali do ponovitve bolezni ali do nesprejemljive toksičnosti, kar od tega se zgodi najprej. Zdravljenje ponovitve raka jajčnikov, raka dojk, adenokarcinoma trebušne slinavke in raka prostate je priporočljivo nadaljevati do napredovanja osnovne bolezni ali nesprejemljive toksičnosti. Učinkovitost in varnost ponovnega vzdrževalnega zdravljenja z zdravilom Lynparza po prvi ali poznejši ponovitvi bolezni pri bolnicah z rakom jajčnikov nista bili dokazani. Podatkov o učinkovitosti in varnosti ponovnega zdravljenja pri bolnicah z rakom dojk ni. Pri raku prostate je treba pri bolnikih, ki niso bili kirurško kastrirani, nadaljevati z medicinsko kastracijo z analogom luteinizirajočega hormona sproščajočega hormona. Če je zdravilo Lynparza uporabljeno v kombinaciji z abirateronom in prednizonom ali prednizolonom, je zdravljenje priporočljivo nadaljevati do napredovanja osnovne bolezni ali do nesprejemljivih toksičnih učinkov. Pri vseh bolnikih je treba med zdravljenjem še naprej uporabljati analoge GnRH (gonadotropin sproščajočega hormona) ali pa morajo bolniki pred tem opraviti obojestransko orhidektomijo. Glejte informacije o zdravilu za abirateron. Podatkov o učinkovitosti ali varnosti ponovnega zdravljenja z zdravilom Lynparza pri bolnikih z rakom prostate ni. V primeru potrebe po zmanjšanju odmerka zaradi neželenih učinkov je priporočeno zmanjšanje odmerka na 250 mg dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 500 mg). Če je potrebno še dodatno zmanjšanje odmerka, je priporočljivo zmanjšanje odmerka na 200 mg dvakrat na dan (to ustreza celotnemu dnevnemu odmerku 400 mg). Zdravljenje z zdravilom Lynparza mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil proti raku. Mutacijsko stanje *BRCA* in/ali genomsko nestabilnost morajo imeti bolniki potrjeno z validiranim testom. Pred uporabo zdravila Lynparza v kombinaciji z abirateronom in prednizonom ali prednizolonom za zdravljenje bolnikov z mKORP genomsko testiranje ni potrebno. Genetsko svetovanje bolnikom z mutacijami *BRCA* je treba opraviti v skladu z lokalnimi predpisi. Zdravilo Lynparza se lahko pri bolnikih z blago okvaro ledvic (očistek kreatinina 51 do 80 ml/min) uporablja brez prilagoditve odmerka. Pri bolnikih z zmerno okvaro ledvic (očistek kreatinina 31 do 50 ml/min) je priporočen odmerek 200 mg dvakrat na dan. Uporaba zdravila se pri bolnikih s hudo okvaro ali končno odpovedjo ledvic (očistek kreatinina ≤ 30 ml/min) ne priporoča, ker varnost in farmakokinetika pri tej skupini bolnikov nista bili raziskani. Zdravilo Lynparza se lahko daje bolnikom z blago ali zmerno okvaro jeter (klasifikacija Child-Pugh A ali B) brez prilagoditve odmerka. Uporabe zdravila Lynparza se ne priporoča pri bolnikih s hudo okvaro jeter (klasifikacija Child-Pugh C), ker varnost in farmakokinetika pri tej skupini bolnikov nista bili raziskani. Zdravilo Lynparza je za peroralno uporabo. Tablete zdravila Lynparza je treba pogoltniti cele in se jih ne sme gristi, drobiti, raztapljati ali lomiti. Lahko se jih jemlje ne glede na obroke. **KONTRAINDIKACIJE:** Preobčutljivost na učinkovino ali katero koli pomožno snov. Dojenje med zdravljenjem in en mesec po zadnjem odmerku. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** *Hematološki toksični učinki:* Pri bolnikih, zdravljenih z zdravilom Lynparza, so bili opisani hematološki toksični učinki, vključno s klinično diagnozo in/ali laboratorijskimi izsledki, na splošno blage ali zmerne (stopnja 1 ali 2 po CTCAE) anemije, nevtropenije, trombocitopenije in limfopenije. Bolniki ne smejo začeti zdravljenja z zdravilom Lynparza, dokler ne okrevajo po hematoloških toksičnih učinkih predhodnega zdravljenja proti raku. Preiskava celotne krvne slike je priporočljiva na začetku zdravljenja, potem vsak mesec prvih 12 mesecev zdravljenja in pozneje redno. Če se pri bolniku pojavijo hudi hematološki toksični učinki ali je odvisen od transfuzij krvi, je treba zdravljenje z zdravilom Lynparza prekiniti in uvesti ustrezno hematološko testiranje. Če krvne vrednosti ostanejo klinično nenormalne še 4 tedne po prekinitvi uporabe zdravila Lynparza, je priporočljivo opraviti preiskavo kostnega mozga in/ali krvno citogenetsko analizo. *Mielodisplastični sindrom/akutna mieloična levkemija (MDS/AML):* Celokupna pojavnost MDS/AML je bila pri bolnikih, ki so v kliničnih preizkušanjih prejemali monoterapijo z zdravilom Lynparza, vključno v obdobju dolgoročnega spremljanja preživetja, < 1,5 %, z večjo pojavnostjo pri bolnicah z *BRCA*m, pri katerih je prišlo do ponovitve na platino občutljivega raka jajčnikov, ki so predhodno prejele vsaj dve liniji kemoterapije s platino in so jih spremljali 5 let. Večina teh primerov je bila s smrtnim izidom. Če obstaja sum na MDS/AML, je potrebno bolnico napotiti na nadaljnje preiskave k hematologu, vključno z analizo kostnega mozga in odvzemom krvi za citogenetiko. Če se po preiskavi dolgotrajne hematološke toksičnosti potrdi MDS/AML, je treba uporabo zdravila Lynparza prekiniti in bolnico ustrezno zdraviti. *Venski trombembolični dogodki:* Med zdravljenjem z zdravilom Lynparza so poročali o venskih trombemboličnih dogodkih, predvsem o pljučni emboliji, vendar ti dogodki niso imeli kakšnega doslednega kliničnega vzorca. V primerjavi z drugimi odobrenimi indikacijami so opažali večjo pojavnost pri bolnikih z metastatskim, na kastracijo odpornim rakom prostate, ki so prejemali tudi androgeno deprivacijsko zdravljenje. Bolnike spremljajte glede kliničnih znakov in simptomov venske tromboze in pljučne embolije, ter jih zdravite kot je medicinsko ustrezno. Bolniki z anamnezo VTE imajo morda večje tveganje za njeno ponovitev in jih je treba ustrezno spremljati. *Pnevmonitis:* V kliničnih študijah je bil pnevmonitis, vključno s smrtnim izidom, opisan pri < 1,0 % bolnikov, ki so prejemali zdravilo Lynparza, spremljali pa so jih številni predispozicijski dejavniki. Če se pri bolniku pojavijo novi ali poslabšajo obstoječi dihalni simptomi, npr. dispneja, kašelj in zvišana telesna temperatura, ali je ugotovljen nenormalen radiološki izvid prsnih organov, je treba zdravljenje z zdravilom Lynparza prekiniti in takoj opraviti preiskave. Če je pnevmonitis potrjen, je treba zdravljenje z zdravilom Lynparza prekiniti in bolnika ustrezno zdraviti. **MEDSEBOJNO DELOVANJE Z DRUGIMI ZDRAVILI IN DRUGE OBLIKE INTERAKCIJ:** Zdravilo Lynparza se uporablja kot monoterapija in ni primerno za uporabo v kombinaciji z mielosupresivnimi zdravili proti raku, vključno z zdravili, ki poškodujejo DNA. Sočasna uporaba olapariba s cepivi ali imunosupresivnimi zdravili ni raziskana. Za presnovni očistek olapariba so pretežno odgovorni izoencimi CYP3A4/5. Sočasna uporaba zdravila Lynparza z znanimi močnimi ali zmernimi zaviralci tega izoencima ni priporočljiva. Če je treba sočasno uporabiti močne ali zmerne zaviralce CYP3A, je treba odmerek zdravila Lynparza zmanjšati. Prav tako med zdravljenjem z zdravilom Lynparza ni priporočljivo pitje grenivkinega soka. Prav tako olapariba ni priporočljivo uporabljati z znanimi močnimi ali zmernimi do močnimi induktorji tega izoencima, ker obstaja možnost, da se učinkovitost zdravila Lynparza bistveno zmanjša. Olaparib *in vitro* zavira CYP3A4 ter *in vivo* predvidoma blago zavira CYP3A. Zato je potrebna previdnost pri sočasni uporabi olapariba z občutljivimi substrati CYP3A4 ali substrati, ki imajo ozko terapevtsko okno. Bolnike, ki sočasno z olaparibom prejemajo substrate CYP3A z ozkim terapevtskim oknom, je priporočljivo ustrezno klinično spremljati. *In vitro* so ugotovili indukcijo CYP1A2, 2B6 in 3A4, prav tako ni mogoče izključiti možnosti, da olaparib inducira CYP2C9, CYP2C19 in P-gp, zato lahko olaparib po sočasni uporabi zmanjša izpostavljenost substratom teh presnovnih encimov in prenašalne beljakovine. Učinkovitost nekaterih hormonskih kontraceptivov se lahko zmanjša, če so uporabljeni sočasno z olaparibom. *In vitro* olaparib zavira efluksni prenašaleca P-gp, zato je potrebno bolnike, ki sočasno prejemajo substrate P-gp, ustrezno klinično spremljati. *In vitro* olaparib zavira BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 in MATE2K. Ni mogoče izključiti možnosti, da olaparib poveča izpostavljenost BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 in MATE2K. Še zlasti je previdnost potrebna, če se olaparib uporablja v kombinaciji s katerim koli statinom. Izvedli so klinično študijo za oceno kombinacije olapariba z anastrozolom, letrozolom in tamoksifenom, vendar klinično pomembnih medsebojnih delovanj niso opazili. **NEŽELENI UČINKI:** Zdravilo Lynparza je bilo povezano z neželenimi učinki, ki so bili na splošno blage ali zmerne resnosti (stopnja po CTCAE 1 ali 2) in na splošno niso zahtevali prekinitve zdravljenja. Če je zdravilo Lynparza uporabljeno v kombinaciji z bevacizumabom pri raku jajčnikov ali v kombinaciji z abirateronom in prednizonom ali prednizolonom pri raku prostate, se varnostni profil na splošno sklada z varnostnim profilom vsakega posameznega zdravila. Varnostni profil temelji na kumulativnih podatkih 4499 bolnikov s solidnimi tumorji, ki so bili v kliničnih preskušanjih zdravljeni z monoterapijo z zdravilom Lynparza v priporočenem odmerku. *Zelo pogosti neželeni učinki:* anemija, nevtropenija, levkopenija, zmanjšanje apetita, omotica, glavobol, spremenjen okus, kašelj, dispneja, bruhanje, driska, navzea, dispepsija in utrujenost (vključno z astenijo). *Pogosti neželeni učinki:* limfopenija, trombocitopenija, stomatitis, bolečine v zgornjem delu trebuha, izpuščaj, zvišanje kreatinina v krvi in venska trombembolija. **PLODNOST, NOSEČNOST IN DOJENJE:** Ženske v rodni dobi ne smejo biti noseče na začetku zdravljenja z zdravilom Lynparza in ne smejo zanositi med zdravljenjem in še 6 mesecev po prejetju zadnjega odmerka. Pri vseh ženskah v rodni dobi je potrebno pred zdravljenjem opraviti test nosečnosti in ga redno izvajati med celotnim zdravljenjem. Priporočljivi sta dve visoko učinkoviti in komplementarni obliki kontracepcije. Zaradi možnega medsebojnega delovanja olapariba s hormonsko kontracepcijo je treba razmisliti o dodatni nehormonski kontracepciji. Pri ženskah s hormonsko odvisnim rakom je treba razmisliti o dveh nehormonskih načinih kontracepcije. Zdravilo Lynparza je kontraindicirano med obdobjem dojenja in še en mesec po prejetju zadnjega odmerka. Moški bolniki morajo med zdravljenjem in še 3 mesece po prejetju zadnjega odmerka zdravila Lynparza med spolnimi odnosi z nosečo žensko ali žensko v rodni dobi uporabljati kondom. Tudi partnerke moških bolnikov morajo uporabljati visoko učinkovito kontracepcijo, če so v rodni dobi. Moški bolniki med zdravljenjem z zdravilom Lynparza in še 3 mesece po zadnjem odmerku tega zdravila ne smejo darovati sperme. **REŽIM PREDPISOVANJA IN IZDAJE ZDRAVILA:** Rp/Spec. **DATUM ZADNJE REVIZIJE BESEDILA:** 30. 3. 2023 (SI-3066). **IMETNIK DOVOLJENJA ZA PROMET**: AstraZeneca AB, SE-151 85 Södertälje , Švedska. Dodatne informacije so na voljo pri podjetju AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, 1000 Ljubljana, telefon: 01/51 35 600. **Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila.**

Literatura: 1. Povzetek glavnih značilnosti zdravila Lynparza, 30. 3. 2023, **2.** https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca, dostopano 25. 7. 2023, **3.** https://www.ema.europa.eu/en/medicines/human/EPAR/zejula, dostopano 25. 7. 2023, **4.** https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna, dostopano 25. 7. 2023, **5.** https://www.ema.europa.eu/en/news/lynparza-recommended-approval-ovarian-cancer, dostopano 25. 7. 2023

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KLJUČ ZA VEČ PRILOŽNOSTI PRI ZDRAVLJENJU VAŠIH BOLNIKOV

KEYTRUDA®
(pembrolizumab, MSD)

KEYTRUDA je odobrena za zdravljenje 21 indikacij rakavih obolenj[1]

Referenca: 1. Keytruda EU SmPC

Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab. Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: odraslih in mladostnikov, starih 12 let ali več, z napredovalim (neoperabilnim ali metastatskim) melanomom; za adjuvantno zdravljenje odraslih in mladostnikov, starih 12 let ali več, z melanomom v stadiju IIB, IIC ali III, in sicer po popolni kirurški odstranitvi; metastatskega nedrobnoceličnega pljučnega raka (NSCLC) v prvi liniji zdravljenja pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS) in brez pozitivnih tumorskih mutacij EGFR ali ALK; lokalno napredovalega ali metastatskega NSCLC pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 (TPS) in so bili predhodno zdravljeni z vsaj eno shemo kemoterapije, bolniki s pozitivnimi tumorskimi mutacijami EGFR ali ALK so pred prejemom zdravila KEYTRUDA morali prejeti tudi tarčno zdravljenje; odraslih in pediatričnih bolnikov, starih 3 leta ali več, s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) ni bila uspešna, ali po najmanj dveh predhodnih zdravljenjih kadar ASCT ne pride v poštev kot možnost zdravljenja; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, predhodno zdravljenih s kemoterapijo, ki je vključevala platino; lokalno napredovalega ali metastatskega urotelijskega raka pri odraslih, ki niso primerni za zdravljenje s kemoterapijo, ki vsebuje cisplatin in imajo tumorje z izraženostjo PD-L1 ≥ 10, ocenjeno s kombinirano pozitivno oceno (CPS); ponovljenega ali metastatskega ploščatoceličnega raka glave in vratu (HNSCC) pri odraslih, ki imajo tumorje z ≥ 50 % izraženostjo PD-L1 (TPS), in pri katerih je bolezen napredovala med zdravljenjem ali po zdravljenju s kemoterapijo, ki je vključevala platino; za adjuvantno zdravljenje odraslih z rakom ledvičnih celic s povišanim tveganjem za ponovitev bolezni po nefrektomiji, ali po nefrektomiji in kirurški odstranitvi metastatskih lezij, za zdravljenje odraslih z MSI-H (microsatellite instability-high) ali dMMR (mismatch repair deficient) kolorektalnim rakom v naslednjih terapevtskih okoliščinah: prva linija zdravljenja metastatskega kolorektalnega raka; zdravljenje neoperabilnega ali metastatskega kolorektalnega raka po predhodnem kombiniranem zdravljenju, ki je temeljilo na fluoropirimidinu; in za zdravljenje MSI-H ali dMMR tumorjev pri odraslih z: napredovalim ali ponovljenim rakom endometrija, pri katerih je bolezen napredovala med ali po predhodnem zdravljenju, ki je vključevalo platino, v katerih koli terapevtskih okoliščinah, in ki niso kandidati za kurativno operacijo ali obsevanje; neoperabilnim ali metastatskim rakom želodca, tankega črevesa ali žolčnika in žolčnih vodov, pri katerih je bolezen napredovala med ali po vsaj enem predhodnem zdravljenju. Zdravilo KEYTRUDA je kot samostojno zdravljenje ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) indicirano za prvo linijo zdravljenja metastatskega ali neoperabilnega ponovljenega ploščatoceličnega raka glave in vratu pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. Zdravilo KEYTRUDA je v kombinaciji s pemetreksedom in kemoterapijo na osnovi platine indicirano za prvo linijo zdravljenja metastatskega neploščatoceličnega NSCLC pri odraslih, pri katerih tumorji nimajo pozitivnih mutacij EGFR ali ALK; v kombinaciji s karboplatinom in bodisi paklitakselom bodisi nab-paklitakselom je indicirano za prvo linijo zdravljenja metastatskega ploščatoceličnega NSCLC pri odraslih; v kombinaciji z aksitinibom ali v kombinaciji z lenvatinibom je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih; v kombinaciji s kemoterapijo s platino in fluoropirimidinom je indicirano za prvo linijo zdravljenja lokalno napredovalega neoperabilnega ali metastatskega raka požiralnika ali HER-2 negativnega adenokarcinoma gastroezofagealnega prehoda pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10; v kombinaciji s kemoterapijo za neoadjuvantno zdravljenje, in v nadaljevanju kot samostojno adjuvantno zdravljenje po kirurškem posegu, je indicirano za zdravljenje odraslih z lokalno napredovalim trojno negativnim rakom dojk ali trojno negativnim rakom dojk v zgodnjem stadiju z visokim tveganjem za ponovitev bolezni; v kombinaciji s kemoterapijo je indicirano za zdravljenje lokalno ponovljenega neoperabilnega ali metastatskega trojno negativnega raka dojk pri odraslih, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 10 in predhodno niso prejeli kemoterapije za metastatsko bolezen; v kombinaciji z lenvatinibom je indicirano za zdravljenje napredovalega ali ponovljenega raka endometrija (EC) pri odraslih z napredovalo boleznijo med ali po predhodnem zdravljenju s kemoterapijo, ki je vključevala platino, v katerih koli terapevtskih okoliščinah, in ki niso kandidati za kurativno operacijo ali obsevanje; v kombinaciji s kemoterapijo, z bevacizumabom ali brez njega, je indicirano za zdravljenje persistentnega, ponovljenega ali metastatskega raka materničnega vratu pri odraslih bolnicah, ki imajo tumorje z izraženostjo PD-L1 s CPS ≥ 1. **Odmerjanje in način uporabe:** Testiranje PD-L1: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi izraženosti PD-L1 tumorja potrditi z validirano preiskavo. Testiranje MSI/MMR: Če je navedeno v indikaciji, je treba izbiro bolnika za zdravljenje z zdravilom KEYTRUDA na podlagi MSI-H/dMMR statusa tumorja potrditi z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA pri odraslih je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje pri pediatričnih bolnikih s cHL, starih 3 leta ali več, ali bolnikih z melanomom, starih 12 let ali več, je 2 mg/kg telesne mase (do največ 200 mg) na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti zdravil sočasno uporabljenih zdravil. Če se uporablja kot del kombiniranega zdravljenja skupaj z intravensko kemoterapijo, je treba zdravilo KEYTRUDA aplicirati prvo. Bolnike je treba zdraviti do napredovanja bolezni ali nesprejemljivih toksičnih učinkov (in do maksimalnega trajanja zdravljenja, če je le to določeno za indikacijo). Pri adjuvantnem zdravljenju melanoma ali RCC je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. Za neoadjuvantno in adjuvantno zdravljenje TNBC morajo bolniki neoadjuvantno prejeti zdravilo KEYTRUDA v kombinaciji s kemoterapijo, in sicer 8 odmerkov po 200 mg na 3 tedne ali 4 odmerke po 400 mg na 6 tednov, ali do napredovanja bolezni, ki izključuje definitivni kirurški poseg, ali do pojava nesprejemljivih toksičnih učinkov, čemur sledi adjuvantno zdravljenje z zdravilom KEYTRUDA kot samostojnim zdravljenjem, in sicer 9 odmerkov po 200 mg na 3 tedne ali 5 odmerkov po 400 mg na 6 tednov ali do ponovitve bolezni ali pojava nesprejemljivih toksičnih učinkov. Bolniki, pri katerih pride do napredovanja bolezni, ki izključuje definitivni kirurški poseg, ali do nesprejemljivih toksičnih učinkov povezanih z zdravilom KEYTRUDA kot neoadjuvantnim zdravljenjem v kombinaciji s kemoterapijo, ne smejo prejeti zdravila KEYTRUDA kot samostojnega zdravljenja za adjuvantno zdravljenje. Če je aksitinib uporabljen v kombinaciji s pembrolizumabom, se lahko razmisli o povečanju odmerka aksitiniba nad začetnih 5 mg v presledkih šest tednov ali več. V primeru uporabe v kombinaciji z lenvatinibom je treba zdravljenje z enim ali obema zdraviloma prekiniti, kot je primerno. Uporabo lenvatiniba je treba zadržati, odmerek zmanjšati ali prenehati z uporabo, v skladu z navodili v povzetku glavnih značilnosti zdravila za lenvatinib, in sicer za kombinacijo s pembrolizumabom. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago ali zmerno okvaro jeter prilagoditev odmerka ni potrebna. Odložitev odmerka ali ukinitev zdravljenja: Zmanjšanje odmerka zdravila KEYTRUDA ni priporočljivo. Za obvladovanje neželenih učinkov je treba uporabo zdravila KEYTRUDA zadržati ali ukiniti, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Povzetek posebnih opozoril, previdnostnih ukrepov, interakcij in neželenih učinkov:** Imunsko pogojeni neželeni učinki (pnevmonitis, kolitis, hepatitis, nefritis, endokrinopatije, neželeni učinki na kožo in drugi): Pri bolnikih, ki so prejemali pembrolizumab, so se pojavili imunsko pogojeni neželeni učinki, vključno s hudimi in smrtnimi primeri. Večina imunsko pogojenih neželenih učinkov, ki so se pojavili med zdravljenjem s pembrolizumabom, je bila reverzibilnih in so jih obvladali s prekinitvami uporabe pembrolizumaba, uporabo kortikosteroidov in/ali podporno oskrbo. Pojavijo se lahko tudi po zadnjem odmerku pembrolizumaba in hkrati prizadanejo več organskih sistemov. V primeru suma na imunsko pogojene neželene učinke je treba poskrbeti za ustrezno oceno za potrditev etiologije oziroma izključitev drugih vzrokov. Glede na izrazitost neželenega učinka je treba zadržati uporabo pembrolizumaba in uporabiti kortikosteroide – za natančna navodila, prosimo, glejte Povzetek glavnih značilnosti zdravila Keytruda. Zdravljenje s pembrolizumabom lahko poveča tveganje za zavrnitev pri prejemnikih presadkov čvrstih organov. Pri bolnikih, ki so prejemali pembrolizumab, so poročali o hudih z infuzijo povezanih reakcijah, vključno s preobčutljivostjo in anafilaksijo. Pembrolizumab se iz obtoka odstrani s katabolizmom, zato presnovnih medsebojnih delovanj zdravil ni pričakovati. Uporabi sistemskih kortikosteroidov ali imunosupresivov pred uvedbo pembrolizumaba se je treba izogibati, ker lahko vplivajo na farmakodinamično aktivnost in učinkovitost pembrolizumaba. Vendar pa je kortikosteroide ali druge imunosupresive mogoče uporabiti za zdravljenje imunsko pogojenih neželenih učinkov. Kortikosteroide je mogoče uporabiti tudi kot premedikacijo, če je pembrolizumab uporabljen v kombinaciji s kemoterapijo, kot antiemetično profilakso in/ali za ublažitev neželenih učinkov, povezanih s kemoterapijo. Ženske v rodni dobi morajo med zdravljenjem s pembrolizumabom in vsaj še 4 mesece po zadnjem odmerku pembrolizumaba uporabljati učinkovito kontracepcijo, med nosečnostjo in dojenjem se ga ne sme uporabljati. Varnost pembrolizumaba pri samostojnem zdravljenju so v kliničnih študijah ocenili pri 7.631 bolnikih, ki so imeli različne vrste raka, s štirimi odmerki (2 mg/kg telesne mase na 3 tedne, 200 mg na 3 tedne in 10 mg/kg telesne mase na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 8,5 meseca (v razponu od 1 dneva do 39 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom pa so bili utrujenost (31 %), diareja (22 %) in navzea (20 %). Večina poročanih neželenih učinkov pri samostojnem zdravljenju je bila po izrazitosti 1. ali 2. stopnje. Najresnejši neželeni učinki so bili imunsko pogojeni neželeni učinki in hude z infuzijo povezane reakcije. Pojavnost imunsko pogojenih neželenih učinkov pri uporabi pembrolizumaba samega za adjuvantno zdravljenje (n = 1.480) je znašala 36,1 % za vse stopnje in 8,9 % od 3. do 5. stopnje, pri metastatski bolezni (n = 5.375) pa 24,2 % za vse stopnje in 6,4 % od 3. do 5. stopnje. Pri adjuvantnem zdravljenju niso zaznali nobenih novih imunsko pogojenih neželenih učinkov. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 3.123 bolnikih z različnimi vrstami raka, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg telesne mase ali 10 mg/kg telesne mase na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (55 %), navzea (54 %), utrujenost (38 %), nevtropenija (36 %), zaprtost (35 %), alopecija (35 %), diareja (34 %), bruhanje (28 %) in zmanjšanje apetita (27 %). Pojavnost neželenih učinkov 3. do 5. stopnje je pri bolnikih z NSCLC pri kombiniranem zdravljenju s pembrolizumabom znašala 67 % in pri zdravljenju samo s kemoterapijo 66 %, pri bolnikih s HNSCC pri kombiniranem zdravljenju s pembrolizumabom 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %, pri bolnikih z rakom požiralnika pri kombiniranem zdravljenju s pembrolizumabom 86 % in pri zdravljenju samo s kemoterapijo 83 %, pri bolnikih s TNBC pri kombiniranem zdravljenju s pembrolizumabom 80 % in pri zdravljenju samo s kemoterapijo 77 % in pri bolnicah z rakom materničnega vratu pri kombiniranem zdravljenju s pembrolizumabom 82 % in pri zdravljenju samo s kemoterapijo 75 %. Varnost pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom pri napredovalem RCC in v kombinaciji z lenvatinibom pri napredovalem EC so ocenili pri skupno 1.456 bolnikih z napredovalim RCC ali napredovalim EC, ki so v kliničnih študijah prejemali 200 mg pembrolizumaba na 3 tedne skupaj s 5 mg aksitiniba dvakrat na dan ali z 20 mg lenvatiniba enkrat na dan, kot je bilo ustrezno. V teh populacijah bolnikov so bili najpogostejši neželeni učinki diareja (58 %), hipertenzija (54 %), hipotiroidizem (46 %), utrujenost (41 %), zmanjšan apetit (40 %), navzea (40 %), artralgija (30 %), bruhanje (28 %), zmanjšanje telesne mase (28 %), disfonija (28 %), bolečine v trebuhu (28 %), proteinurija (27 %), sindrom palmarno-plantarne eritrodizestezije (26 %), izpuščaj (26 %), stomatitis (25 %), zaprtost (25 %), mišično-skeletna bolečina (23 %), glavobol (23 %) in kašelj (21 %). Neželenih učinkov od 3. do 5. stopnje je bilo pri bolnikih z RCC med uporabo pembrolizumaba v kombinaciji z aksitinibom ali lenvatinibom 80 % in med uporabo sunitiniba samega 71 %. Pri bolnicah z EC je bilo neželenih učinkov od 3. do 5. stopnje med uporabo pembrolizumaba v kombinaciji z lenvatinibom 89 % in med uporabo kemoterapije same 73 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila. Za dodatne informacije o varnosti v primeru uporabe pembrolizumaba v kombinaciji glejte povzetke glavnih značilnosti zdravila za posamezne komponente kombiniranega zdravljenja. **Način in režim izdaje zdravila:** H – Predpisovanje in izdaja zdravila je le na recept, zdravilo se uporablja samo v bolnišnicah. **Imetnik dovoljenja za promet z zdravilom:** Merck Sharp & Dohme B.V. , Waarderweg 39, 2031 BN Haarlem, Nizozems

MSD
Merck Sharp & Dohme inovativna zdravila d.o.o.,
Ameriška ulica 2, 1000 Ljubljana,
tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50;
Pripravljeno v Sloveniji, 11/2022; SI-KEY-00492 EXP: 11/2024

Samo za strokovno javnost.

H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

25 LET | *kliničnih raziskav v Sloveniji*

V 25 letih smo sponzorirali ali podprli 57 intervencijskih kliničnih raziskav, ki so gonilo razvoja in napredka v medicini, in s tem je več kot 780 bolnikov dobilo možnost inovativnega zdravljenja.

M-SI-00000814 (V2.0)
Informacija pripravljena v marcu 2023.

Zdravilo Lonsurf je indicirano v monoterapiji za zdravljenje odraslih bolnikov z metastatskim kolorektalnim rakom (KRR), ki so bili predhodno že zdravljeni ali niso primerni za zdravljenja, ki so na voljo. Ta vključujejo kemoterapijo na osnovi fluoropirimidina, oksaliplatina in irinotekana, zdravljenje z zaviralci žilnega endotelijskega rastnega dejavnika (VEGF – Vascular Endothelial Growth Factor) in zaviralci receptorjev za epidermalni rastni dejavnik (EGFR – Epidermal Growth Factor Receptor).[1]

Zdravilo Lonsurf je indicirano v monoterapiji za zdravljenje odraslih bolnikov z metastatskim rakom želodca vključno z adenokarcinomom gastro-ezofagealnega prehoda, ki so bili predhodno že zdravljeni z najmanj dvema sistemskima režimoma zdravljenja za napredovalo bolezen.[1]

VEČ ČASA

za več trenutkov, ki štejejo

Podaljša celokupno preživetje

v 3. liniji zdravljenja bolnikov z mCRC in mGC[2,3]

Literatura: 1. Povzetek glavnih značilnosti zdravila Lonsurf, december 2020.
2. Mayer R et al. N Engl J Med. 2015;372:1909-19. 3. Shitara K et al.
Lancet Oncol. 2018;19:1437-1448.

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Pri globalnem razvoju zdravila sodelujeta obe družbi
in ga tržita na svojih določenih področjih.

Lonsurf®
trifluridin/tipiracil

Skrajšan povzetek glavnih značilnosti zdravila: Lonsurf 15 mg/6,14 mg filmsko obložene tablete in Lonsurf 20 mg/8,19 mg filmsko obložene tablete
SESTAVA*: Lonsurf 15 mg/6,14 mg: Ena filmsko obložena tableta vsebuje 15 mg trifluridina in 6,14 mg tipiracila (v obliki klorida). **Lonsurf 20 mg/8,19 mg**: Ena filmsko obložena tableta vsebuje 20 mg trifluridina in 8,19 mg tipiracila (v obliki klorida). **TERAPEVTSKE INDIKACIJE*:** Kolorektalni rak - v monoterapiji za zdravljenje odraslih bolnikov z metastatskim kolorektalnim rakom, ki so bili predhodno že zdravljeni ali niso primerni za zdravljenja, ki so na voljo. Ta vključujejo kemoterapijo na osnovi fluoropirimidina, oksaliplatina in irinotekana, zdravljenje z zaviralci žilnega endotelijskega rastnega dejavnika (VEGF - Vascular Endothelial Growth Factor) in zaviralci receptorjev za epidermalni rastni dejavnik (EGFR - Epidermal Growth Factor Receptor). Rak želodca - v monoterapiji za zdravljenje odraslih bolnikov z metastatskim rakom želodca vključno z adenokarcinomom gastro-ezofagealnega prehoda, ki so bili predhodno že zdravljeni z najmanj dvema sistemskima režimoma zdravljenja za napredovalo bolezen. **ODMERJANJE IN NAČIN UPORABE*:** Priporočeni začetni odmerek zdravila Lonsurf pri odraslih je 35 mg/m^2/odmerek peroralno dvakrat dnevno na 1. do 5. dan in 8. do 12. dan vsakega 28-dnevnega cikla zdravljenja, najpozneje 1 uro po zaključku jutranjega in večernega obroka (20 mg/m^2/odmerek dvakrat dnevno pri bolnikih s hudo ledvično okvaro). Odmerek, izračunan glede na telesno površino, ne sme preseči 80 mg/odmerek. Možne prilagoditve odmerka glede na varnost in prenašanje zdravila: dovoljena so zmanjšanja odmerka na najmanjši odmerek 20 mg/m^2 dvakrat dnevno (oz. 15 mg/m^2 dvakrat dnevno pri bolnikih s hudo ledvično okvaro). Potem ko je bil odmerek zmanjšan, povečanje ni dovoljeno. **KONTRAINDIKACIJE*:** Preobčutljivost na učinkovini ali katero koli pomožno snov. **OPOZORILA IN PREVIDNOSTNI UKREPI*:** Supresija kostnega mozga: Pred uvedbo zdravljenja in po potrebi za spremljanje toksičnosti zdravila, najmanj pred vsakim ciklom zdravljenja, je treba pregledati celotno krvno sliko. Zdravljenja ne smete začeti, če je absolutno število nevtrofilcev < 1,5 x 10^9/l, če je število trombocitov < 75 x 10^9/l ali če se je pri bolniku zaradi predhodnih zdravljenj pojavila klinično pomembna nehematološka toksičnost 3. ali 4. stopnje, ki še traja. Bolnike je treba skrbno spremljati zaradi morebitnih okužb, uvesti je treba ustrezne ukrepe, kot je klinično indicirano. Toksičnost za prebavila: Potrebna je uporaba antiemetikov, antidiarikov ter drugih ukrepov, kot je klinično indicirano. Če je potrebno, prilagodite odmerke. Ledvična okvara: Uporaba zdravila ni priporočljiva pri bolnikih s končno stopnjo ledvične okvare. Bolnike z ledvično okvaro je potrebno med zdravljenjem skrbno spremljati; bolnike z zmerno ali hudo ledvično okvaro je treba zaradi hematološke toksičnosti bolj pogosto spremljati. Jetrna okvara: Uporaba zdravila Lonsurf pri bolnikih z obstoječo zmerno ali hudo jetrno okvaro ni priporočljiva. Proteinurija: Pred začetkom zdravljenja in med njim je priporočljivo spremljanje proteinurije z urinskimi testnimi lističi. Pomožne snovi: Zdravilo vsebuje laktozo. **INTERAKCIJE*:** Previdnost: Zdravila, ki medsebojno delujejo z nukleozidnimi prenašalci CNT1, ENT1 in ENT2, zaviralci OCT2 ali MATE1, substrati humane timidin-kinaze (npr. zidovudin), hormonski kontraceptivi. **PLODNOST*. NOSEČNOST IN DOJENJE*:** Ni priporočljivo. **KONTRACEPCIJA*:** Ženske in moški morajo uporabljati zelo učinkovite metode kontracepcije med zdravljenjem in do 6 mesecev po zaključku zdravljenja. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA STROJEV*:** Med zdravljenjem se lahko pojavijo utrujenost, omotica ali splošno slabo počutje. **NEŽELENI UČINKI*:** Zelo pogosti: nevtropenija, levkopenija, anemija, trombocitopenija, zmanjšan apetit, diareja, navzea, bruhanje, utrujenost. Pogosti: okužba spodnjih dihal, febrilna nevtropenija, limfopenija, hipoalbuminemija, disgevzija, periferna nevropatija, dispneja, bolečina v trebuhu, zaprtje, stomatitis, bolezni ustne votline, hiperbilirubinemija, sindrom palmarne plantarne eritrodisestezije, izpuščaj, alopecija, pruritus, suha koža, proteinurija, pireksija, edem, vnetje sluznice, splošno slabo počutje, zvišanje jetrnih encimov, zvišanje alkalne fosfataze v krvi, zmanjšanje telesne mase. Občasni: septični šok, infekcijski enteritis, pljučnica, okužba žolčevoda, gripa, okužba sečil, gingivitis, herpes zoster, tinea pedis, okužba s kandido, bakterijska okužba, okužba, nevtropenična sepsa, okužba zgornjih dihal, konjunktivitis, bolečina zaradi raka, pancitopenija, granulocitopenija, monocitopenija, eritropenija, levkocitoza, monocitoza, dehidracija, hiperglikemija, hiperkaliemija, hipokaliemija, hipofosfatemija, hipernatriemija, hiponatriemija, hipokalciemija, protin, anksioznost, nespečnost, nevrotoksičnost, disestezija, hiperestezija, hipoestezija, sinkopa, parestezija, pekoč občutek, letargija, omotica, glavobol, zmanjšana ostrina vida, zamegljen vid, diplopija, katarakta, suho oko, vrtoglavica, neugodje v ušesu, angina pektoris, aritmija, palpitacije, embolija, hipertenzija, hipotenzija, vročinski oblivi, pljučna embolija, plevralni izliv, izcedek iz nosu, disfonija, orofaringealna bolečina, epistaksa, kašelj, hemoragični enterokolitis, krvavitev v prebavilih, akutni pankreatitis, ascites, ileus, subileus, kolitis, gastritis, refluksni gastritis, ezofagitis, moteno praznjenje želodca, abdominalna distenzija, analno vnetje, razjede v ustih, dispepsija, gastroezofagealna refluksna bolezen, proktalgija, bukalni polip, krvavitev dlesni, glositis, parodontalna bolezen, bolezen zob, siljenje na bruhanje, flatulenca, slab zadah, hepatotoksičnost, razširitev žolčnih vodov, luščenje kože, urtikarija, preobčutljivostne reakcije na svetlobo, eritem, akne, hiperhidroza, žulj, bolezni nohtov, otekanje sklepov, artralgija, bolečina v kosteh, mialgija, mišično-skeletna bolečina, mišična oslabelost, mišični krči, bolečina v okončinah, ledvična odpoved, neinfektivni cistitis, motnje mikcije, hematurija, levkociturija, motnje menstruacije, poslabšanje splošnega zdravstvenega stanja, bolečina, občutek spremembe telesne temperature, kseroza, nelagodje, zvišanje kreatinina v krvi, podaljšanje intervala QT na elektrokardiogramu, povečanje mednarodnega umerjenega razmerja (INR), podaljšanje aktiviranega parcialnega tromboplastinskega časa (aPTČ), zvišanje sečnine v krvi, zvišanje laktatne dehidrogenaze v krvi, znižanje celokupnih proteinov, zvišanje C-reaktivnega proteina, zmanjšan hematokrit. Post-marketinške izkušnje: intersticijska bolezen pljuč. **PREVELIKO ODMERJANJE*:** Neželeni učinki, o katerih so poročali v povezavi s prevelikim odmerjanjem, so bili v skladu z uveljavljenim varnostnim profilom. Glavni pričakovani zaplet prevelikega odmerjanja je supresija kostnega mozga. **FARMAKODINAMIČNE LASTNOSTI*:** *Farmakoterapevtska skupina:* zdravila z delovanjem na novotvorbe, antimetaboliti, oznaka ATC: L01BC59. Zdravilo Lonsurf sestavljata antineoplastični timidinski nukleozidni analog, trifluridin, in zaviralec timidin-fosforilaze (TPaze), tipiracilijev klorid. Po privzemu v rakave celice timidin-kinaza fosforilira trifluridin. Ta se v celicah nato presnovi v substrat deoksiribonukleinske kisline (DNA), ki se vgradi neposredno v DNA ter tako preprečuje celično proliferacijo. TPaza hitro razgradi trifluridin in njegova presnova po peroralni uporabi je hitra zaradi učinka prvega prehoda, zato je v zdravilo vključen zaviralec TPaze, tipiracilijev klorid. **PAKIRANJE*:** 20 filmsko obloženih tablet. **NAČIN PREDPISOVANJA IN IZDAJE ZDRAVILA:** Rp/Spec. **Imetnik dovoljenja za promet:** Les Laboratoires Servier, 50, rue Carnot, 92284 Suresnes cedex, Francija. Številka dovoljenja za promet z zdravilom: EU/1/16/1096/001 (Lonsurf 15 mg/6,14 mg), EU/1/16/1096/004 (Lonsurf 20 mg/8,19 mg). **Datum zadnje revizije besedila: december 2020. *Pred predpisovanjem preberite celoten povzetek glavnih značilnosti zdravila. Celoten povzetek glavnih značilnosti zdravila in podrobnejše informacije so na voljo pri: Servier Pharma d.o.o., Podmilščakova ulica 24, 1000 Ljubljana, tel: 01 563 48 11, www.servier.si.**

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Dent RAG, Cole P. In vitro maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95. doi: 10.1038/bjc.1981.71

Chapman S, Nakielny R. *A guide to radiological procedures*. London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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Zdravilo **LORVIQUA** v monoterapiji je indicirano za zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim rakom pljuč (NSCLC), ki je ALK pozitiven, in se predhodno niso zdravili z zaviralcem ALK.[1]

Zdravilo **LORVIQUA** v monoterapiji je indicirano za zdravljenje odraslih bolnikov z napredovalim NSCLC, ki je ALK-pozitiven, pri katerih je bolezen napredovala po:

- zdravljenju z alektinibom ali ceritinibom kot prvim ALK zaviralcem tirozin kinaze (TKI); ali
- zdravljenju s krizotinibom in vsaj še 1 drugim ALK TKI.[1]

BISTVENI PODATKI IZ POVZETKA GLAVNIH ZNAČILNOSTI ZDRAVILA

Lorviqua 25 mg, 100 mg filmsko obložene tablete
▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o kateremkoli domnevnem neželenem učinku zdravila. Glejte poglavje 4.8 povzetka glavnih značilnosti zdravila, kako poročati o neželenih učinkih. **Sestava in oblika zdravila:** Ena filmsko obložena tableta vsebuje 25 mg ali 100 mg lorlatiniba in 1,58 mg oz. 4,20 mg laktoze monohidrata. **Indikacije:** Zdravljenje odraslih bolnikov z napredovalim nedrobnoceličnim rakom pljuč (NSCLC – *Non-Small Cell Lung Cancer*), ki je ALK (anaplastična limfomska kinaza) pozitiven in se predhodno niso zdravili z zaviralcem ALK, ter pri bolnikih, pri katerih je bolezen napredovala po: zdravljenju z alektinibom ali ceritinibom kot prvim ALK zaviralcem tirozin kinaze (TKI – *Tyrosine Kinase Inhibitor*) ali zdravljenju s krizotinibom in vsaj še 1 drugim ALK TKI. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Odkrivanje ALK-pozitivnega NSCLC je potrebno pri izbiri bolnikov, saj so to edini bolniki, pri katerih so dokazali korist. Priporočeni odmerek je 100 mg peroralno enkrat na dan. Zdravljenje je treba nadaljevati do napredovanja bolezni ali nesprejemljive toksičnosti. Če bolnik izpusti odmerek, ga mora vzeti takoj, ko se spomni, razen če do naslednjega odmerka manjka manj kot 4 ure. Bolniki ne smejo vzeti 2 odmerkov hkrati, da bi nadomestili izpuščeni odmerek. Prilagajanje odmerkov: Ravni zmanjšanja odmerka: *prvo zmanjšanje odmerka*: 75 mg peroralno enkrat na dan; *drugo zmanjšanje odmerka*: 50 mg peroralno enkrat na dan. Zdravljenje je treba atrajno prekiniti, če bolnik ne prenaša odmerka 50 mg peroralno enkrat na dan. Za prilagajanje odmerkov zaradi neželenih učinkov glejte preglednico 1 v SmPC-ju. Posebne populacije: *Starejši bolniki (≥ 65 let):* Zaradi omejenih podatkov priporočil o odmerjanju ni mogoče dati. *Okvara ledvic*: Prilagajanje odmerkov pri bolnikih z normalnim delovanjem in blago ali zmerno okvaro [absolutna ocena hitrosti glomerulne filtracije (eGFR – estimated Glomerular Filtration Rate): ≥ 30 ml/min] ni potrebno. Pri bolnikih s hudo okvaro ledvic (absolutna vrednost eGFR < 30 ml/min) je priporočljiv zmanjšan odmerek lorlatiniba, npr. začetni odmerek 75 mg peroralno enkrat na dan. Podatkov pri bolnikih na ledvični dializi ni na voljo. *Okvara jeter*: Pri bolnikih z blago okvaro ni potrebno prilagajanje odmerkov. Podatkov o uporabi pri zmerni ali hudi okvari ni, zato uporaba ni priporočljiva. *Pediatrična populacija*: Varnost in učinkovitost pri otrocih in mladostnikih, starih < 18 let, nista bili dokazani. Način uporabe: Peroralna uporaba, vsak dan ob približno istem času, s hrano ali brez nje. Tablete je treba pogoltniti cele. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. Uporaba močnih induktorjev CYP3A4/5. **Posebna opozorila in previdnostni ukrepi:** Hiperlipidemija: Uporaba je povezana z zvečanji vrednosti holesterola in trigliceridov v serumu – morda bo treba uvesti ali povečati odmerek zdravil za zniževanje ravni lipidov. Učinki na osrednje živčevje: Opazili so učinke na osrednje živčevje, vključno s psihotičnimi učinki in spremembami v kognitivni funkciji, razpoloženju, duševnem stanju ali govoru – morda bo treba prilagoditi odmerek ali prekiniti zdravljenje. Atrioventrikularni blok: Pri bolnikih, ki so prejemali lorlatinib, so poročali o podaljšanju intervala PR in AVbloku. Potrebno je spremljanje EKG in morda bo treba prilagoditi odmerek. Zmanjšanje iztisnega deleža levega prekata: Pri bolnikih, ki so prejemali lorlatinib in pri katerih so opravili izhodiščno in še vsaj eno nadaljnjo oceno iztisnega deleža levega prekata (LVEF – *Left Ventricular Ejection Fraction*), so poročali o zmanjšanju LVEF. Če imajo bolniki dejavnike tveganja za srce ali stanja, ki vplivajo na LVEF, ali se jim med zdravljenjem pojavijo pomembni srčni znaki/simptomi, je treba razmisliti o spremljanju srca, vključno z oceno LVEF. Zvečanje vrednosti lipaze in amilaze: Pri bolnikih, ki so prejemali lorlatinib, se je pojavilo zvečanje vrednosti lipaze in/ali amilaze. Zaradi sočasne hipertrigliceridemije in/ali morebitnega intrinzičnega mehanizma je treba upoštevati tveganje za pankreatitis. Bolnike je treba spremljati glede zvečanja vrednosti lipaze in amilaze. Intersticijska bolezen pljuč (ILD – *Interstitial Lung Disease*)/pnevmonitis: Pri uporabi lorlatiniba so se pojavili hudi ali življenjsko ogrožajoči pljučni neželeni učinki, skladni z ILD/pnevmonitisom. Vse bolnike, pri katerih pride do poslabšanja respiratornih simptomov, ki kažejo na ILD/pnevmonitis, je treba takoj pregledati glede ILD/pnevmonitisa. Hipertenzija: Pri bolnikih, ki so prejemali loratinib, so poročali o hipertenziji. Pred uvedbo lorlatiniba mora biti krvni tlak pod nadzorom. Med zdravljenjem je treba krvni tlak preveriti po 2 tednih in nato najmanj enkrat na mesec ter glede na stopnjo resnosti zdravljenje prekiniti in nato nadaljevati z zmanjšanim odmerkom ali trajno prekiniti. Hiperglikemija: Pri bolnikih, ki so prejemali loratinib, se je pojavila hiperglikemija. Pred uvedbo je treba oceniti koncentracijo glukoze v serumu na tešče in jo nato redno spremljati v skladu z nacionalnimi smernicami ter glede na stopnjo resnosti zdravljenje prekiniti in nato nadaljevati z zmanjšanim odmerkom ali trajno prekiniti. Laktoza: Vsebuje laktozo. Bolniki z redko dedno intoleranco za galaktozo, odsotnostjo encima laktaze ali malabsorpcijo glukoze/galaktoze ne smejo jemati tega zdravila. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Učinek zdravil na lorlatinib: *Induktorji CYP3A4/5:* Sočasna uporaba močnih induktorjev CYP3A4/5 (npr. rifampicin, karbamazepin, enzalutamid, mitotan, fenitoin in šentjanževka) je kontraindicirana. *Zaviralci CYP3A4/5:* Sočasni uporabi močnih zaviralcev CYP3A4/5 (npr. boceprevir, kobicistat, itrakonazol, ketokonazol, posakonazol, troleandomicin, vorikonazol, ritonavir, paritaprevir v kombinaciji z ritonavirom in ombitasvirom in/ali dasabuvirom ter ritonavir v kombinaciji z elvitegravirom, indinavirom, lopinavirom ali tipranavirom in grenivka ali grenivkin sok), se je treba izogibati, saj lahko pride do zvečanja koncentracij lorlatiniba v plazmi (če je sočasna uporaba nujna, je priporočljivo zmanjšati odmerek lorlatiniba). Učinek lorlatiniba na druga zdravila: *Substrati CYP3A4/5:* Izogibati se je treba sočasnemu dajanju lorlatiniba in substratov CYP3A4/5 z ozkimi terapevtskimi indeksi (npr. alfentanil, ciklosporin, dihidroergotamin, ergotamin, fentanil, hormonski kontraceptivi, pimozid, kinidin, sirolimus in takrolimus), saj lahko lorlatinib zmanjša koncentracije teh zdravil. *Substrati P-glikoproteina:* Substrate P-gp, ki imajo ozke terapevtske indekse (npr. digoksin, dabigatraneteksilat), je treba v kombinaciji z lorlatinibom uporabljati previdno, saj obstaja verjetnost, da se koncentracija teh substratov v plazmi zmanjša. *Študije in vitro s prenašalci zdravil, ki niso P-gp:* Lorlatinib je treba v kombinaciji s substrati BCRP, OATP1B1, OATP1B3, OCT1, MATE1 in OAT3 uporabljati previdno, saj klinično pomembnih sprememb v plazemski izpostavljenosti teh substratov ni mogoče izključiti. **Plodnost, nosečnost in dojenje:** Ženskam v rodni dobi je treba svetovati, naj se med zdravljenjem z lorlatinibom izogibajo zanositvi in naj med zdravljenjem uporabljajo visoko učinkovito nehormonsko metodo kontracepcije, saj lahko lorlatinib povzroči, da hormonski kontraceptivi postanejo neučinkoviti. Učinkovito kontracepcijo je treba uporabljati še vsaj 35 dni po zaključku zdravljenja. Med zdravljenjem in še vsaj 14 tednov po zadnjem odmerku morajo bolniki, ki imajo partnerice v rodni dobi, uporabljati učinkovito kontracepcijo. Nosečnost: Študije na živalih so pokazale embriofetalno toksičnost, zato uporaba med nosečnostjo ali pri ženskah v rodni dobi, ki ne uporabljajo kontracepcije, ni priporočljiva. Dojenje: Med zdravljenjem in še 7 dni po zadnjem odmerku je treba prenehati z dojenjem. Plodnost: Zdravljenje lahko ogrozi plodnost pri moških. **Vpliv na sposobnost vožnje in upravljanja strojev:** Ima zmeren vpliv na sposobnost vožnje in upravljanja strojev. Potrebna je previdnost, saj se pri bolnikih lahko pojavijo učinki na osrednje živčevje. **Neželeni učinki:** Zelo pogosti: anemija, hiperholesterolemija, hipertrigliceridemija, učinki na razpoloženje, učinki na kognitivne funkcije, periferna nevropatija, glavobol, motnja vida, hipertenzija, diareja, navzea, zaprtje, izpuščaj, artralgija, mialgija, edem, utrujenost, zvečanje telesne mase, zvečanje vrednosti lipaze, zvečanje vrednosti amilaze. **Način in režim izdaje:** Rp/Spec - Predpisovanje in izdaja zdravila je le na recept zdravnika specialista ustreznega področja medicine ali od njega pooblaščenega zdravnika. **Imetnik dovoljenja za promet:** Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgija. **Datum zadnje revizije besedila:** 04.04.2023

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

Literatura: 1. Povzetek glavnih značilnosti zdravila Lorviqua, 04.04.2023.

ALK = anaplastična limfomska kinaza, **CŽS** = centralni živčni sistem, **mNSCLC** = (Metastatic Non-Small Cell Lung Cancer) metastatski nedrobnocelični rak pljuč, **NSCLC** = (Non-Small Cell Lung Cancer) nedrobnocelični rak pljuč, **TKI** = (Tyrosine Kinase Inhibitor) zaviralec tirozin kinaze.

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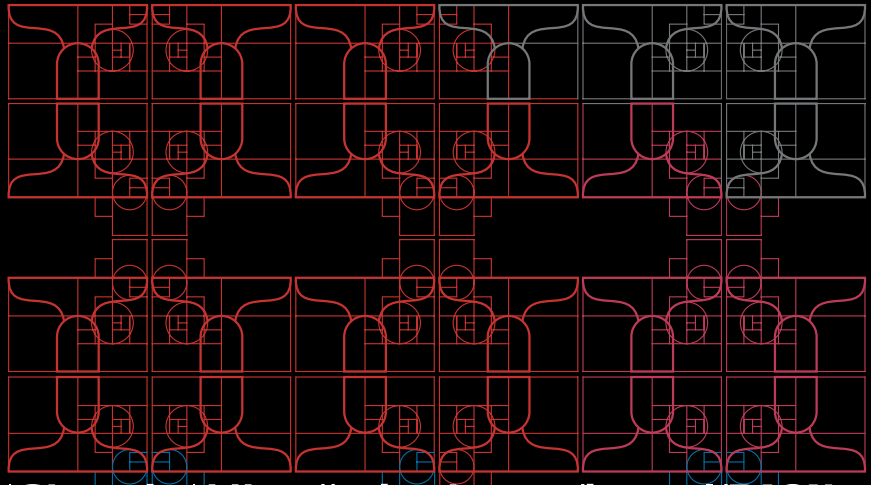

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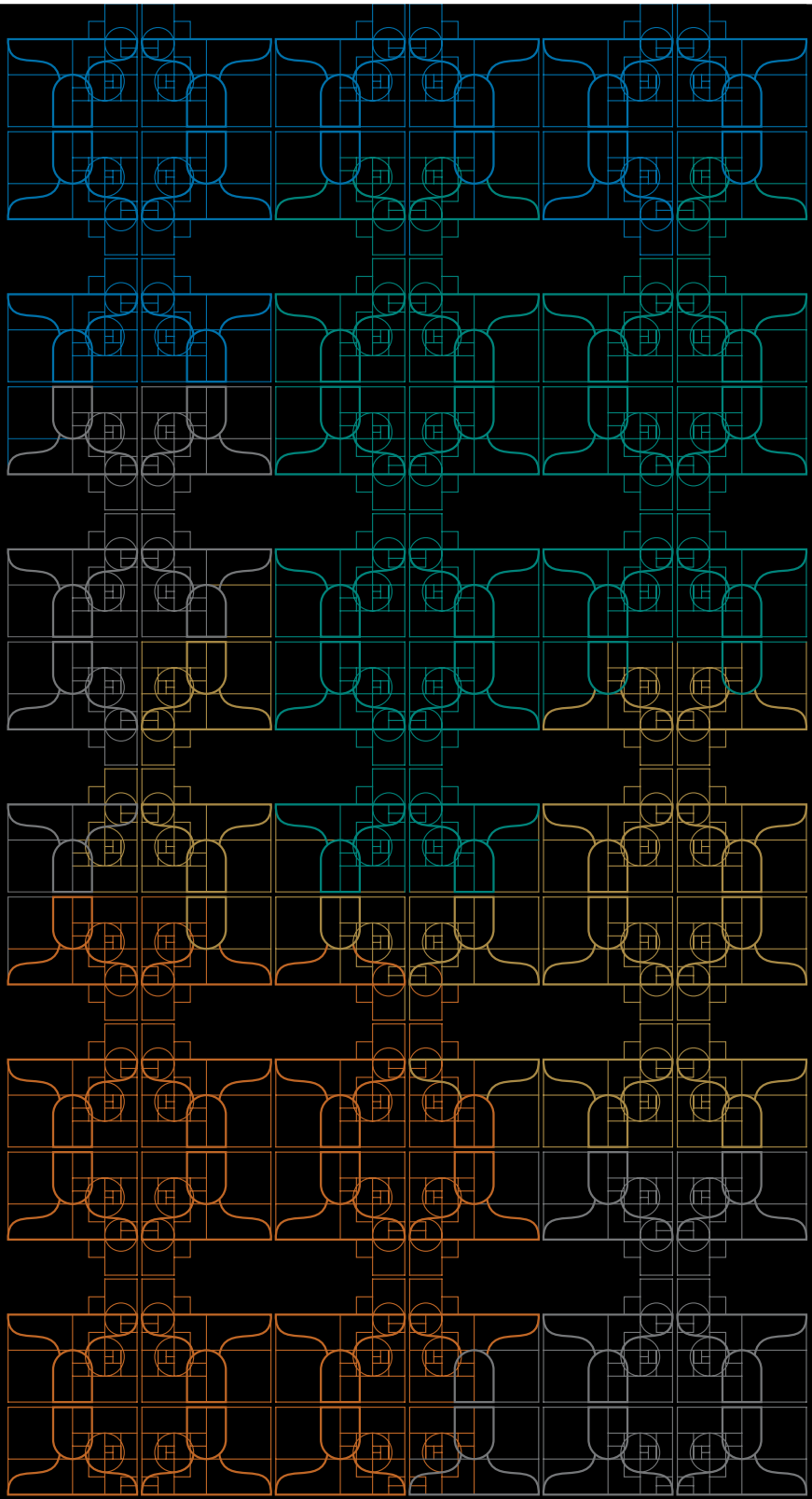

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