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Editorial office

Radiology and Oncology
Zaloška cesta 2
P. O. Box 2217
SI-1000 Ljubljana
Slovenia
Phone: +386 1 5879 369
Phone/Fax: +386 1 5879 434
E-mail: gsersa@onko-i.si

Reader for English
Vida Kološa

Secretary
Mira Klemenčič
Zvezdana Vukmirović

Design
Monika Fink-Serša, Samo Rovan, Ivana Ljubanović

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contents

review

Artificial intelligence in musculoskeletal oncological radiology

Matjaz Vogrin[1,2], Teodor Trojner[1], Robi Kelc[1,2]

[1] Department of Orthopaedic Surgery, University Medical Center Maribor, Slovenia
[2] Faculty of Medicine, University of Maribor, Slovenia

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Correspondence to: Assist. Prof. Robi Kelc, M.D., Ph.D., Department of Orthopaedic Surgery, University Medical Centre Maribor, Ljubljanska ulica 5; SI-2000 Maribor. E-mail: robi.kelc @gmail.com

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Background. Due to the rarity of primary bone tumors, precise radiologic diagnosis often requires an experienced musculoskeletal radiologist. In order to make the diagnosis more precise and to prevent the overlooking of potentially dangerous conditions, artificial intelligence has been continuously incorporated into medical practice in recent decades. This paper reviews some of the most promising systems developed, including those for diagnosis of primary and secondary bone tumors, breast, lung and colon neoplasms.

Conclusions. Although there is still a shortage of long-term studies confirming its benefits, there is probably a considerable potential for further development of computer-based expert systems aiming at a more efficient diagnosis of bone and soft tissue tumors.

Key words: artificial intelligence; deep learning; tumor recognition; cancer imaging; image segmentation

Introduction

Primary bone and soft tissue neoplasms present a minority among neoplastic lesions. Due to their rarity, precise radiologic diagnosis often requires an experienced radiologist with special interests in musculoskeletal oncology. To surmount the challenge of making precise diagnoses, and more importantly, to prevent overlooking potentially fatal conditions, attempts to incorporate artificial intelligence and its related techniques into medical practice have occurred in the last decades (Figure 1).

Being first introduced by McCarthy in the 1950s, artificial intelligence (AI) is a general term that describes computer machines that imitate human intelligence.[1] Machine learning, a subset of AI, uses computational algorithms, which learn with experience and therefore improve the performance of tasks.[2] The rapid progress of computational power and big data availability allowed the emergence of an even more specialized subfield of machine learning, called deep learning. It is a promising method capable of processing raw data to perform detection or classification tasks.[3] Deep learning algorithms, implemented as artificial neural networks, mimic biological nervous systems.[4] The network is organized in layers composed of interconnected nodes imitating architecture in a biologic brain.[2,5] Nodes are weighted individually for the purpose of increasing data extraction. In order to classify data, weights are automatically and dynamically optimized during the training phase.[5,6] Regarding the layers, three different kinds are present in each neural network. It begins with an input layer, which receives input data, followed by numerous hidden layers extracting the pattern within the data. It terminates with the output layer, which produces results or output data (Figure 2).[5]

Among the different types of artificial neural networks, convolutional neural networks, in particular, gained attention in radiology due to their high performance in recognizing images.[7] By calculating the intensity of each pixel or voxel, together with evaluating complex patterns in each image, they provide reliable quantitative image

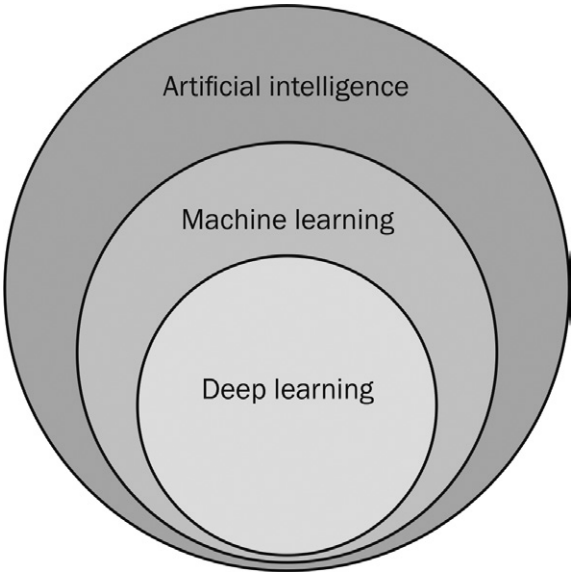

FIGURE 1. Schematic illustration of the hierarchy of artificial intelligence and its machine learning and deep learning subfields.

interpretations, eventually surpassing human performance.[8]

However, to build an intelligent machine a training phase is required, which requires sufficient computational power and large datasets. The latter is obtained from radiological images, which is in the domain of radiomics. Radiomics is a process of quantitative extraction of a high number of semantic and agnostic features from diagnostic images.[9] Its approaches, like feature extraction and feature engineering techniques, are essential in the formation of AI applications.[10]

Artificial intelligence in cancer imaging (oncologic radiology)

Until recently, radiologists' decisions were based predominantly on his or her experience of recognizing patterns and appreciating various features of each tumor including size, location, intensity, and surface characteristics, all combined with patients' demographic data. However, after many consecutive image interpretations, they were consciously or subconsciously faced with fatigue[11], which could lead to errors and potentially jeopardize patients' health and own credibility.[12]

AI's potentials are developing exponentially. Instead of qualitative and subjective image interpretations, it allows quantifiable and objective data extraction with the ability to reproduce the same results.[13] Furthermore, by quantifying information otherwise not detectable to humans, AI may complement clinical decision-making.[5,13]

Computer-aided detection (CADe) and computer-aided diagnosis (CADx) algorithms have been used for the last two decades[14] predominantly in mammography[15], detection of lung[16], and colon[17] malignancies. In contrast to CAD algorithms, which only highlight the features they have been exactly trained for, actual AI systems continue to learn and improve in time. By focusing on the specific diagnosis, systems learn to discover new typical patterns that have not been linked with the disease before.[18] For example, Beck *et al*. developed a machine learning-based computer program named "Computational Pathologist (C-Path)" to automatically analyze breast cancer and predict its prognosis.[19] Importantly, regardless of all well-known histological characteristics that were implemented into the program, C-Path recognized surrounding stroma as another important prognostic factor.[19] Convolutional neural networks have also given optimistic results in automated detection.[6] It has been used for automated detection of liver tumors on CT scans with high detection accuracy and precision of 93% and 67%, respectively.[20] Similarly, a deep learning-based CADe for detection of brain metastasis on magnetic resonance imaging (MRI) has been developed and achieved a sensitivity of 96% and reasonable specificity.[21]

In general, characterization is composed of segmentation, diagnosis, and staging of tumors.[13] Image segmentation is the process used in cancer imaging to outline pathological area and distinguish it from non-pathological adjacent tissue. It can range from planar measurements to advanced 3-dimensional assessment of tumor volume.[13] Tumors have traditionally been manually labelled by radiologists, which is indeed time-consuming, as well as a subject of interobserver variability.[13,22] Thus, implementation of AI into automated image segmentation could potentially take over, increase the quality and reproducibility of measurements, and also save time.[5,13] For example, machine learning has been used for breast density segmentation on mammography, which turns out to be as accurate as manual ones.[23] Ye *et al*. successfully proposed and verified a fully automatic nasopharyngeal carcinoma segmentation method based on dual-sequence MRI and convolutional neural network.[24] The mean dice similarity coefficient (DSC) of the models with only T1 sequence, only T2 sequence, and dual sequence were 0.620 ± 0.0642,

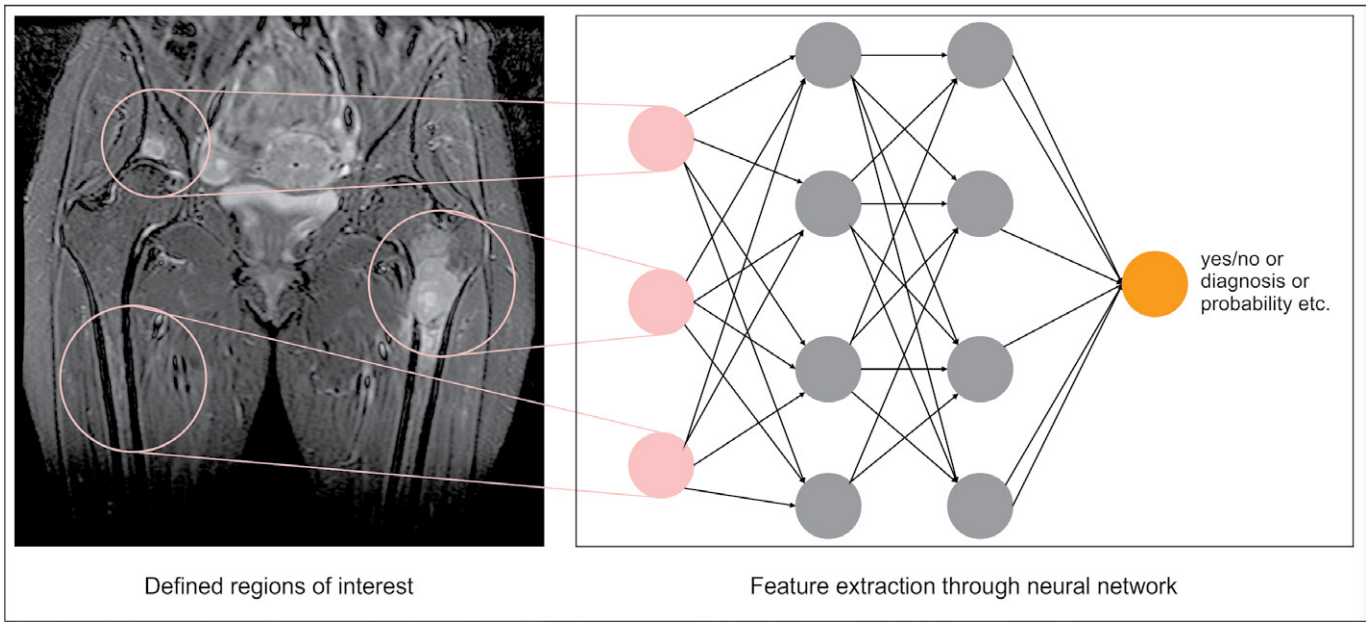

FIGURE 2. Schematic presentation of a neural network. Regions of interests (ROI) are defined, either by user or by an automated computer process. These present the input cells (in pink) a neural network. For each ROI the neural network extracts and compute features within the hidden layers (in grey) by using pre-trained data sets. Finally, the output cell offers the final results in different possible forms (yes/no, final diagnosis, probability of malignancy etc.).

0.642 ± 0.118, and 0.721 ± 0.036, respectively. The combination of different features acquired from T1 and T2 sequences significantly improved the segmentation accuracy.[24]

Ability to quantitatively extract tumor features has great potential in the process of making diagnosis. With machine learning, Liu *et al*. quantitatively represented radiological traits characteristics of lung nodules and showed improved accuracy of cancer diagnosis in pulmonary nodules.[25] Convolutional neural network has also shown to be an effective and objective method that provides an accurate diagnosis of pancreatic cancer.[26]

Another important aspect of tumor characterization includes staging. Mainly, TNM classification is used to assess the extent of primary tumor, lymph nodes, and metastases and therefore classify the lesion in a specific stage. However, attempts to extend the TNM cancer staging system have been made. For instance, CAD has shown to be a promising method of evaluation of tumor extent and multifocality in invasive breast cancer patients and therefore expanding the staging algorithms.[27]

In tumor response monitoring, many AI approaches have shown some potential. For example, AI and machine learning have been successfully implemented into the pre-procedural prediction of trans-arterial chemoembolization treatment outcomes in patients with hepatocellular carcinoma using clinical and imaging features.[28] Ha *et al*. demonstrated promising results in the utilization of convolutional neural network to predict neoadjuvant chemotherapy response prior to the first cycle of therapy in breast carcinoma using baseline MRI tumor datasets.[29] Positive response to chemotherapy led to decreased tumor metabolism, opening a potential opportunity to detect lower accumulation rates of a radiotracer.[30] Differentiating between responders and non-responders based on low-dose ^{18}F-FDG PET/MRI scans might, therefore, be another opportunity of the implementation of convolutional neural networks.[6]

Complementary to radiologic diagnosis, additional advanced methods have been proposed, promising even further advances in cancer management. Liquid biopsy based on circular tumor DNA (ctDNA) analysis may importantly improve early tumor detection, diagnosis, monitoring therapy, and progression in time.[31] Contrary to standard tissue biopsies, liquid biopsies taken from blood may provide us with detailed biochemical characteristics of the neoplastic lesion and detect potential metastasis.[32] What is more, a combination of liquid biopsies and radiomics, supervised by deep learning may significantly improve cancer management in the future.

Artificial intelligence in skeletal tumors

The first attempts to introduce computational power into diagnostic procedures of primary bone tumors date back to the 1960s.[33] Based on Bayes' formula, a computer program accurately predicted a bone tumor diagnosis in 77.9% of cases. Later in 1980, the same author set a milestone by publishing an article about computed-based radiographic grading of bone tumor destruction.[34] This was a cornerstone for further research and implementation of neural networks into the diagnosis of focal bone lesions.[35,36]

A scarce number of articles regarding AI and primary bone tumors have been published so far, while considerably more has been done on the detection and segmentation of bone metastasis. For example, Burns *et al*. successfully identified and segmented sclerotic lesions in the thoracolumbar spine using CADe techniques. The sensitivity for lesions detection was 79%.[37] What is more, Wang *et al*. developed a Siamese convolutional neural network to research the potential of automated spinal metastasis detection in MRI. The proposed approach accurately detected all spinal metastatic lesions with a false-positive rate of 0.4 per case.[38] Another research proposed a machine learning-based whole-body automatic disease classification tool to distinguish benign processes and malignant bone lesions in ^{18}F-NaF PET/CT images.[39]

Healthy and tumorous bone differs in numerous characteristics. Unlike healthy osseous tissue, which consists of cortical and trabecular part, primary bone malignancies may penetrate cortex and spread into adjacent soft tissue, as well as cause swelling around the bone or even weaken the bone architecture and lead to pathological fracture.[40] Radiologically, they differ in absorption rate, which can be quantitatively evaluated. For example, CADx has been used to detect and classify primary bone tumors into benign and malignant lesions using x-ray images. In their study, Ping *et al*. an overall greater intensity of pixels for malignant bone tumors compared to benign bone tumors.[41] Another study by Bandyopadhyay *et al*. proposed a CADx method to automatically analyze bone x-ray images. By integrating several classifiers, the method achieved accurate decisions regarding a bone-destruction pattern, stage, and grade of cancer in 85% of cases.[42]

When describing sarcomas, diagnosed on MRI, features like tumor size, shape, and enhancement pattern are estimated and taken into consideration along with patient's demographic data.[2] Machine learning and artificial neural network excel in quantifying and extracting supplementary features, which can correlate with clinical characteristics, diagnosis, and outcomes. Most of these are out of human visual perception and include intervoxel relationships, image intensity analysis, and filtered images analysis.[43] Deep learning-based algorithm has also been developed to predict survival rates in patients with synovial sarcoma.[44] Its prediction was more precise compared to the Cox proportional hazard model, which is a commonly used regression model in medical research.

In primary bone tumors, bone tumor matrix, its density, and zone of transition represent suitable characteristics than may be classified through deep learning techniques. In fact, recurrent convolutional neural network outshined experienced musculoskeletal radiologists in bone tumor matrix classification with 86% vs. 72%, respectively.[45] Li *et al*. proposed a super label guided convolutional neural network to classify CT images of bone tumors.[46] In comparison, results exceeded the classic convolutional neural network. However, the classification included only nine types of the most common skeletal tumors.

Limitations and future directions

There are indeed some limitations of AI. First, it could potentially still be a subject of interobserver variability, due to different algorithms used in a neural networks of different AI systems or unequal learning stages in which the systems process a specific task. Standardization is mandatory to establish a large database. Data also needs to be accessible in order to integrate them into large sets. Prior to that quality check, labelling, classification, and segmentation need to be done manually by experts, making the process expensive and time-consuming.[13] However, introducing deep learning-based techniques to the extensive quality ground-truth training datasets is essential for the development of accurate algorithms.[47,48] Also, ethical dilemmas should be taken into consideration. When dealing with systems that operate with enormous amounts of data, patients' privacy as well as human dignity may be jeopardized, unless meticulous safety mechanisms are implemented. There are also no long-term follow-up studies available thus far. On the contrary, the appreciating results

of the already published studies and the presentation of a commercially available application is only a matter of time.

Undoubtedly, all kinds of artificial intelligence are persistently being integrated into the complex management of musculoskeletal tumors and tumors of other sites. Deep learning-based techniques are expected to minimalize false positive rates as well as assure accurate decisions and diagnoses.[49] Further automatization of radiological tasks is expected to take place in the future. Among physicians, radiologists in particular are required to perform many time-consuming tasks, like image segmentation, delineation of regions of interest, and image annotation. AI techniques have an enormous potential to transform their workflow, which will allow them to focus on more meaningful tasks.[11]

On the other hand, "imaging is not an isolated measure of disease."[13] Neoplastic lesions are complex conditions, following DNA mutations that cause abnormal cellular proliferation.[50] Despite many mutations being discovered and related to specific malignancies, intertumoural and intratumoural heterogeneity exist.[51] Undoubtedly, molecular approaches, like genetic biomarkers and molecular imaging have already significantly contributed to a better understanding of cancer management. Finally, combining radiomics with other aspects of a broad family of "-omics", including genomics, proteomics, and metabolomics, and therefore drastically expanding datasets available for advanced AI modalities, might move us closer to the precision medicine.[52]

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review

Physical activity and cancer risk. Actual knowledge and possible biological mechanisms

Mihaela Jurdana

Faculty of Health Sciences, University of Primorska, Izola, Slovenia

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Correspondence to: Mihaela Jurdana, Ph.D., Faculty of Health Sciences, University of Primorska, Polje 42, SI-6310 Izola, Slovenija.
Phone: +386 5 662 64 69; Fax.: +386 5 662 64 80

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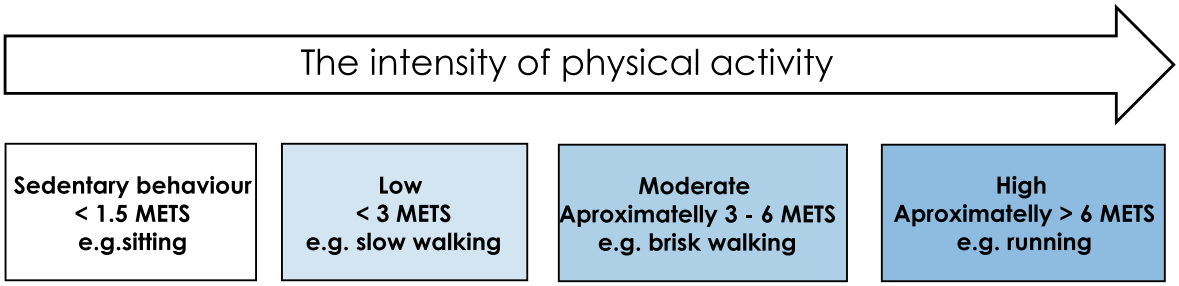
Background. Scientific evidence has shown that an increase in regular physical activity is associated with a decrease in the development of many types of cancer. Potential mechanisms that link physical activity to reduced cancer risk include a decrease in systemic inflammation, hyperinsulinemia, insulin-like growth factor (IGF-I), sex hormones, pro-inflammatory leptin and other obesity-related cytokines, and a significant increase in anti-inflammatory adiponectin levels. In addition, physical activity improves immune function and the composition and diversity of the gastrointestinal microbiota. Moderate physical activity is important for cancer protection, but the most significant changes in the inflammatory profile are conferred by physical activity performed at higher intensities. Thus, there is a need for further investigation into the type, intensity, and duration of physical activity for the prevention of some types of cancer and the development of effective recommendations.

Conclusions. There is a strong evidence that physical activity of moderate to vigorous intensity protects against colon and breast cancer, and probably against cancer at all other sites.

Key words: physical activity; cancer; pro-inflammatory and anti-inflammatory cytokines; biological mechanisms

Introduction

The International Agency for Research on Cancer (IARC) reports that 25% of all cancer cases worldwide are caused by obesity and sedentary lifestyle.[1] The idea of physical activity as a means for preventing cancer was explored in the early 20th century when two studies were published, suggesting that cancer mortality rates among men with different occupations decreased with increased physical activity.[2,3] To date, the evidence of "skeletal muscle contraction effect" has been growing rapidly and many epidemiological studies on the role of physical activity in cancer prevention have been published. There is substantial evidence that greater physical activity levels lower the risk of some cancers.[4] Recently gathered data has revealed that physical activity is associated with various site-specific cancers in many ways. In addition, preclinical studies have indicated that physical activity may similarly reduce cancer progression, its recurrence and have an impact on better survival rates.[5] Furthermore, physical activity could decrease breast and colon cancer incidence with a linear dose response relationship indicating that engaging in longer exercise sessions or exercising with higher intensity will result in a greater reduction in cancer risk.[4,6] New evidence suggests that a comparable association might exist for other cancers, but for a complete evaluation, physical activity type, frequency and intensity need to be assessed.[7] The World Cancer Research Fund's first report indicated a strong positive impact of physical activity in relation to colorectal and breast cancer.[8,9] Furthermore, cancer risk varies within population subgroups such as a gender, age, race, body mass index, and physical fitness level. The effects of physical activity on the cancer outcome are associated with these parameters.[6] The recent data of a multi-ethnic cohort study confirm the association



METs = metabolic equivalents

FIGURE 1. Levels of physical activity intensity (sedentary behaviour, low, moderate and vigorous or high).

between physical activity and colon cancer risk, and suggest possible differences in the strength of the association according to race and ethnicity.[10]

Several acceptable biological mechanisms link physical activity with cancer, including changes in sex hormones and other metabolic hormones, decrease in body fat mass and central adiposity, an increase in anti-inflammatory myokines exerting anti-inflammatory responses, and recently demonstrated changes in microbiota composition.

This review provides data from epidemiological studies on physical activity and cancer, and biological mechanisms to explain the association between physical activity and cancer.

Physical activity recommendations

Significant decreases in cancer incidence have been demonstrated among those who take into account the physical activity recommendations.[11] The American Cancer Society (ACS), the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and the World Health Organization (WHO) have published recommendations considered to reduce the risk of various diseases including cancer.[12] In summary, the recommendations for adults of 150 minutes (2.5h) to 300 minutes (5h) of moderate physical activity, or at least 75 minutes (1.25 hours) to 150 minutes (2.5h) of vigorous physical activity per week, can reduce cancer risk. For additional health benefits, muscle-strengthening activities involving major muscle groups should be conducted on two or more days a week. [12,13]

To express the intensity level of physical activity, the rate of energy expenditure expressed as metabolic equivalents (METs) are commonly used.[13] One MET is the rate of energy expenditure while sitting at rest, which for most people approximates an oxygen uptake of 3.5 millilitres per kilogram of body weight per minute. The energy expenditure of other activities is expressed in multiples of METs. A 3 MET activity expends 3 times the energy used at rest. The MET model is used in epidemiological studies and provides general medical thresholds and guidelines for a population.[4]

Based on the MET hours/week (MET h/w) model, physical activity can be classified as occupational physical activity (OPA) or leisure time physical activity (LTPA). OPA is low for sitting work, moderate for standing and walking work and high for manual work. LTPA is low for activities < 3MET, moderate for activities approximately 3–6 MET and vigorous or high intensity for activities > 6 MET.[13] (Figure 1). A recent study by Matthews *et al.*, provides strong evidence that current recommendation levels of LTPA, both moderate to vigorous (7.5–15 MET h/w or 150–300 minutes/week) provide cancer (colon, breast, endometrial, kidney, myeloma, liver, non-Hodgkin lymphoma) protection in a dose dependent manner.[4] Minor incidence of some cancer types seems to be correlated with vigorous LTPA. [4]

Actual knowledge on the association between physical activity and cancer

Several studies have been performed to assess the effect of LTPA in lowering cancer risk. There is convincing evidence of the beneficial effect of physical activity on the risk of colon and breast cancer and probable evidence for other cancers.[4,6,7] Original scientific articles and systematic reviews (based largely on epidemiological studies consisting of large cohorts and case controls) have demonstrat-

ed a dose–response relationship between physical activity and cancer risk.[4,14]

Breast cancer

In 1980 it was hypothesized that physical activity protects against breast cancer and many studies have confirmed this association risk.[15]

Physical activity is associated with a reduced risk of breast cancer incidence and better survival rates among women with breast cancer diagnosis.[16] Physically active women had up to 20% lower risk incidence of breast cancer in comparison to inactive women, providing evidence that physical activity influences sex hormones, insulin resistance, and inflammatory adipokines.[17,18] Another early case control study demonstrated a clear reduction of breast cancer in younger women during the reproductive period, who engaged in the recommended level of physical activity (3–6 MET h/w).[19] Similarly, observational evidence suggests that regular physical activity reduces the risk of breast cancer incidence and mortality among obese menopausal and postmenopausal women.[20-23]

The Nurses' Health Study collected information over 29 years and reported that moderate or vigorous physical activity for 7 or more hours per week (> 6 MET h/w) compared to those who reported less than 1 hour per week (< 3 MET h/w) resulted in a 20 % reduction in developing breast cancer. The association was similar in both premenopausal and postmenopausal women.[24,25]

Campbell *et al.* state that regular exercise in association with weight reduction decreases the levels of sex hormones, as well as reducing breast cancer risk.[26] In this study, more than 400 overweight to obese sedentary women, aged 50–75 years, were assigned to one of the following groups: a) moderate to vigorous intensity aerobic exercise only, b) diet only, c) moderate to vigorous intensity aerobic exercise and diet, and d) control. They found that physical activity among postmenopausal women might lower breast cancer risk by reducing fat mass, alongside a significantly greater decrease of estrogen and significantly increased sex hormone–binding globulin (SHBG)[27] which regulates the availability of free estrogen to hormone sensitive tissue by binding biologically active estrogen.

Taken together, these findings suggest that weight loss is the key factor linking alterations in diet or exercise to sex hormone changes. In the study conducted by Niehoff *et al.* 2019 the association between physical activity and breast cancer risk was examined in a large population of women with a family history of breast cancer. This demonstrated that physical activity was associated with reduced postmenopausal, but not premenopausal, breast cancer risk.[28] The diversity of available data of physical activity and cancer association is due to population heterogeneity and the influence of breast cancer modifiable and non-modifiable factors, such as genetics, early age menarche, nulliparity, older age at first childbirth and breastfeeding.[29] Although there is a proven link between physical activity and breast cancer, the type and dose of physical activity may have a varied effect. Physical activity can reduce the risk of breast cancer in women who engaged with moderate intensity levels. In addition, a greater decreased risk was found for vigorous intensity levels of physical activity with a stronger association in postmenopausal women.[4] Risk reduction was observed among women who participated in physical activity during all periods in their lives.

Colon and rectal cancer

To date, the most definitive epidemiological studies have provided consistent evidence that physical activity is associated with a lower risk of colon cancer.[8,30,31]

A meta-analysis of numerous prospective studies, examining the association between physical activity of various intensity levels and the risk of developing colon and rectal cancer have been evaluated, showing that increased levels of physical activity considerably decreases the colon and rectal cancer risk.[32] Moreover, others reported that higher levels of physical activity in colon cancer survivors have a minor possibility of cancer recurrence and improved survival compared to inactive survivors.[33]

Risk reduction for colon cancer in physically active individuals was greater in case control studies (24%) in comparison with cohort studies (17%). Similar results were found for OPA (22%) and LTPA (23%).[34]

The association between colon cancer and physical activity in case control studies showed an equally significant risk reduction for men and women (24%) while in cohort studies this association was greater for men than for women.[4,35,36] The effects of physical activity on colon and rectal cancer may be influenced by different parameters; physical activity type, intensity, frequency and duration, as well as vary by sex and race/ethnicity.[37] The large multiethnic cohort study conducted by Park *et al.*, demonstrated an inverse association be-

tween moderate/vigorous activity and colorectal cancer risk, which appears to be stronger in men, especially among men with longer sitting time.[10] A possible explanation of the diverse benefits between the sexes may reflect hormonal differences.[10]

The case–control study of Boyle considered 870 colorectal cancers cases (proximal colon, distal colon and rectal), compared 996 age and sex matched healthy controls, and analysed the timing and intensity of physical activity on sub site specific colorectal cancer risk, showing a strong reduction of distal colon cancer risk.[38] Authors of this study demonstrated that physical activity with more than 6 MET h/w was associated with a lower distal colon cancer risk by about 40%, while an increase of physical activity to 18 MET h/w further increased the percentage of cancer risk reduction. An association between physical activity and rectal cancer in participants exercising 6 MET h/w or more was also observed. In general, the overall data show no association between the total physical activity level and recreational physical activity and rectal cancer. Recently, it was found that LTPA was associated with a lower risk of both, colon and rectal cancer.[22] A health initiative observational study found an inverse association between leisure time physical activity and rectal cancer, particularly, in postmenopausal women.[39]

Another case control study revealed that participants who spent more than ten years in sedentary work presented a greater risk of distal colon cancer and rectal cancer compared to those who never held sedentary work.[40] However, the risk was significantly reduced in participants who performed jobs requiring heavy activity.[40]

The health benefits of moderate to vigorous physical activity have been recently proposed to prevent colorectal cancer among people with longer sitting times.[10] In addition, others confirm the protective role of moderate physical activity with the risk of the polyp's development and adenomas.[41]

Other cancer sites

Many studies reported on the association between physical activity and lower risk of several other site-specific types of cancer.[9,42] Evidence is less consistent than for breast and colorectal cancer and can be classified as probable or possible. Regardless, patient data from nine cohort studies (US, European and Australian cohorts) including adult engagement in the recommended amounts of LTPA (moderate to intense activity) demonstrate, in addition to colon and breast cancer, also lower risk levels for endometrial and kidney cancer, liver cancer, lung, gastric and non-Hodgkin lymphoma (women only).[4,42]

Endometrial cancer

Previous meta-analysis studies of endometrial cancers found evidence of a decreased risk in moderately to vigorously physically active women.[43] Many other studies investigated the influence of physical activity and body mass, since obesity is a strong risk factor for endometrial cancer as it is related to physical inactivity.[44]

Bladder cancer

The meta-analysis of many cohort studies and several case-control studies reported lower rates of bladder cancer for individuals with the highest level of recreational or OPA than those who were the least physically active.[45] The LTPA of over one million individuals was associated with a reduced risk of bladder and kidney cancer.[22]

Lung cancer

Lung cancer has been less well studied than the cancers described above, but some epidemiological studies have revealed an association between physical activity and reduced cancer risk among former and current smokers.[46]

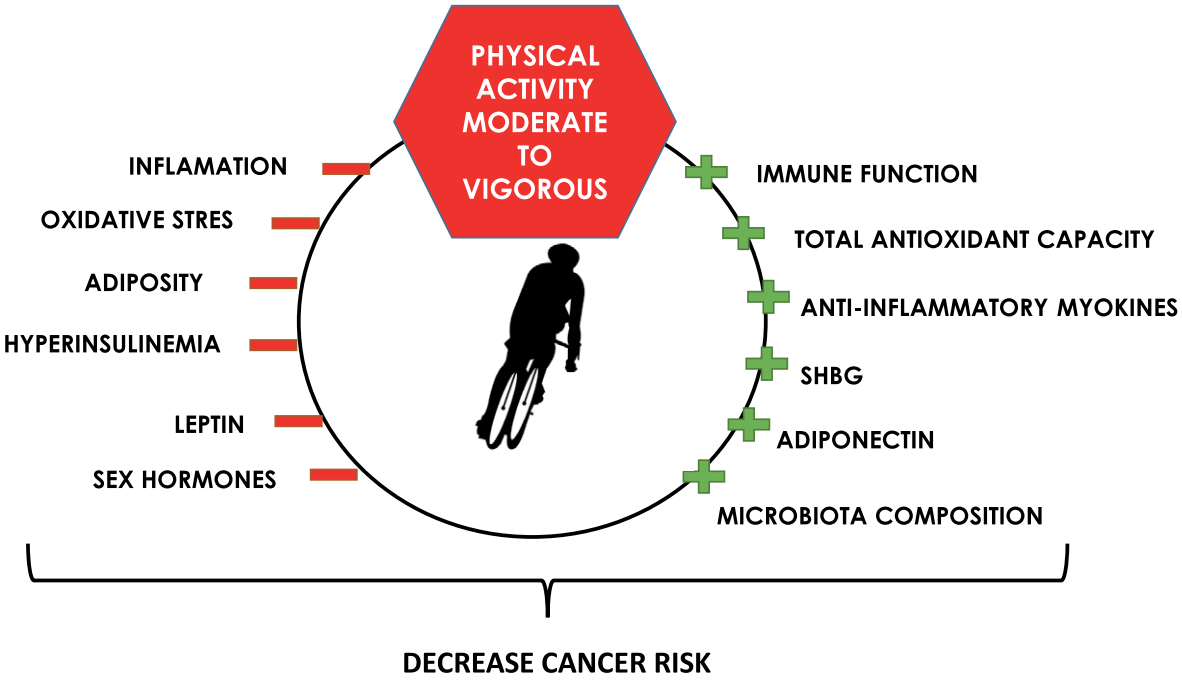
Prostate cancer

Evidence suggesting that physical activity can reduce prostate cancer risk is on the increase. Although rigorous physical activity may be needed to influence hormone levels involved in the etiology of this cancer.[47]

The data for several other cancers are limited and further research is needed in order to strengthen the hypothesis that physical activity reduces the development of cancer.[22] Preliminary evidence suggests that higher levels of physical activity may influence cancer risk at several of these sites.[22]

Potential biological mechanisms in the relation between physical activity and cancer risk

The most commonly hypothesized mechanisms proposed for physical activity and reduced cancer



SHBG = sex hormone–binding globulin

FIGURE 2. The effects of physical activity on cancer prevention.

Moderate to vigorous physical activity improves immune function, total antioxidant capacity, increases SHBG production and anti-inflammatory plasma adiponectin and improves gut microbiota composition. In addition, moderate to vigorous physical activity decreases systemic inflammation, oxidative stress, reduces adipose tissue and hyperinsulinemia, decreases inflammatory hormone leptin and regulates sex hormone levels.

risk are presented below. Moreover, the association between physical activity and gut microbiota composition in relation to cancer is described. The effects of physical activity on cancer prevention are summarized in Figure 2.

Anti-inflammatory action of muscle derived myokines

Skeletal muscle plays an important role in counteracting pro-inflammatory effects. During the past decade, it was identified as a secretory organ.[48] Cytokines or other peptides that are produced, expressed and released by skeletal muscle and exert autocrine, paracrine or endocrine effects should be classified as 'myokines'. It has been suggested that myokines may contribute to exercise-induced protection against several chronic diseases.[48] Inflammation is a normal component of host defence; however, chronic low-grade inflammation is a key contributor in a range of chronic diseases and plays a critical role in cancer development and is crucial for the sustenance of the processes of tumorigenesis.[49] Interleukin-1 (IL-1), tumor necrosis factor α (TNF-α), and interleukin-6 (IL-6) are inflammatory cytokines that have been measured in relation to cancer.[49] Increased levels of pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines have been linked to increased cancer risk and a permanent presence of inflammatory cytokines also maintains an environment in which cancer cells can proliferate.[49] Evidence suggests that regularly performed LTPA, moderate to vigorous may reduce markers of systemic inflammation.[50] However, there is a substantial body of evidence that high-intensity or prolonged endurance training leads to increased oxidative stress that may result in a pro-inflammatory response from the immune system to protect the host tissue.[51] In addition, an increase in the expression of pro-inflammatory cytokines can be crucial for long-term adaptive responses to exercise training.[52] Although high-intensity endurance training can increase antioxidant enzyme activity and reduce markers of training-induced oxidative stress, very high training loads of elite and non-elite athletes participating in ultra-endurance competitions are associated with an acute reduction in antioxidant capacity and an increase in markers of oxidative stress.[53]

Skeletal muscle is an important source of anti-inflammatory myokines, including muscle derived interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 15 (IL-15), and interleukin 1 receptor antagonist (IL-1ra), which act as antagonists to the generally pro-inflammatory cytokines.[54]

The pro-inflammatory TNF-α plays an important role in cancer promotion.[55] TNF-α was originally identified as a factor that caused tumor necrosis in high concentrations; its activity at moderate levels can promote tumor growth. One of the key functions for TNF-α is to activate the pro-inflammatory transcription factor (NFκB), involved in cancer pathogenesis.[56]

Interestingly, IL-6 produced by monocytes or macrophages acts as a pro-inflammatory response, whereas skeletal muscle derived IL-6 acts as an anti-inflammatory response by reducing TNF-α concentration or NFκB activation.[57]

It turns out that regenerative or anti-inflammatory activities of interleukin-6 are mediated by classic signalling, whereas pro-inflammatory responses of interleukin-6 are rather mediated by trans signaling.[58] In classic signaling, interleukin-6 stimulates target cells via a membrane bound interleukin-6 receptor (IL-6R), which upon ligand binding associates with the signalling receptor protein gp130 and trigger the activation of the JAK/STAT signalling pathway. In cells that express only gp130 but not IL-6R, IL-6 binds to the soluble IL-6R (sIL-6R) and the complex in turn binds to gp130 to trigger activation of intracellular signalling, known as trans signaling.[58]

Skeletal muscle IL-6 was the first identified myokine and, to date, the most studied myokine which is produced and released by contracting skeletal muscle fibres, exerting extensive anti-inflammatory effects in other organs via an inflammatory (TNF-α) independent pathway.[59] IL-6 was discovered as a myokine because of the observation that IL-6 increases up to 100-fold in the circulation during and after physical activity.[59] Therefore, the exercise release of IL-6 induces an increase in anti-inflammatory IL-1ra and IL-10. In most exercise-related studies, TNF-α does not change and is likely to be suppressed by the muscle derived IL-6, as demonstrated by a modest decrease of TNF-α after exercise.[48] This confirms that anti-inflammatory effects of regular exercise can protect against systemic low-grade inflammation. The anti-inflammatory effects can be mediated by a reduction in visceral fat and body fat as well as by an anti-inflammatory environment through the release of myokines.[59,60]

Another skeletal muscle myokine, IL-15, has been identified as an anabolic factor in muscle growth and it appears to play an important role in fat metabolism.[60] Interestingly, a negative association between plasma IL-15 concentration and abdominal fat mass was established, which supports the idea that muscle-expressed IL-15 may be involved in the reduction of visceral fat mass and may play an important role in the decrease of many cancer risks.[57]

Skeletal muscle is an endocrine organ, which, in addition to releasing myokines, also produces and secretes microRNAs into circulation.[61] Loss of function microRNA experiments demonstrated that microRNAs have significant roles in the regulation of protein function in cancer, cancer cell proliferation and survival.[61]

Immune function

It has been demonstrated that moderate physical activity may enhance the immune function by increasing the number and activity of immune function cells such as neutrophils, eosinophils, monocytes and lymphocytes, and stimulate an increase in natural killer cells which have an important role in tumor suppression.[5,62] Interestingly, regular moderate physical activity can increase the total antioxidant capacity of defence and be responsible for the elimination of reactive oxygen species (ROS).[5] These highly reactive species are responsible for oxidative stress and play an important role in the progression of various types of human cancer.[63] Moderate to vigorous physical activity can also provide a higher number of mitochondria in skeletal muscles that consequently provide a greater capacity to reduce oxidative stress.[64] Indeed, each mitochondrion has a reduced oxidative load, and, as such, more electrons are directed to cytochrome oxidase instead of producing reactive oxygen species.[65]

Hormones

Regular moderate to vigorous intensities of physical activity influences the levels of biologically available sex hormones and decreases the incidence of hormone-related cancers, including breast cancer, endometrium, ovaries, and prostate cancer.[66,67] Many studies have concluded that physical activity modifies metabolic hormone levels by lowering circulating fat, which produces the sex hormones responsible for the stimulatory effect on mammary glands and increases SHBG production, reducing

their ability to influence target tissue. During menopause, the concentration of estrogens declines, but adipose tissue in obese women still produces estrogens after menopause.[68] Physical activity responsible for reducing body fat mass, counteracts adipose tissue and is crucial for the reduction of breast cancer risk.[68] Another study performed on premenopausal women demonstrated that regular physical activity and high LTPA reduce the concentration of estradiol and increase SHBG independent of obesity, thus indicating that the protective effect of exercise is not completely mediated by the changes in adiposity.[69] Furthermore, excess levels of some androgens in men have been suggested to increase the risk of prostate cancer. Increased production of SHBG during physical activity may prevent prostate cancer development by decreasing the levels of biologically available testosterone.[47]

Regular moderate to vigorous physical activity affects cancer risk by reducing the levels of insulin and insulin growth factor-1 (IGF-1).[70] High levels of (IGF-1) and insulin resistance have been responsible for an increased risk of various cancer types.[70] The epidemiological evidence between insulin levels and cancer risk is associated with hyperinsulinemia. Insulin is a powerful mitogen and is involved in glucose metabolism enhancing tumor development. Hyperinsulinemia promotes the synthesis and activity of (IGF-1), a mitogen that increases cellular proliferation, differentiation and transformation and inhibits apoptosis.[71] Intervention strategies including regular physical activity reduce insulin levels, fasting glucose levels, decrease hepatic and muscle insulin resistance, and total IGF-1, increase glucose transporter protein and mRNA, increase activity of glycogen synthase and hexokinase, decrease release and increase clearance of free fatty acids, increase muscle glucose delivery because of increased muscle capillary density, and effect changes in muscle composition to increase glucose disposal.[72] This proves that the mechanism involved is directly associated with skeletal muscle contraction during exercise.

Adiposity

Chronic low-grade inflammation in adiposity is associated with a higher risk of several cancer types.[73-75] Adipose tissue as an endocrine organ which produces and releases a variety of pro-inflammatory cytokines such as (IL- 6), (TNF-α), (CRP), leptin, and anti-inflammatory adiponectin. During exercise, in particular resistance training, skeletal muscle cells produce and express anti-inflammatory myokines, belonging to distinctly different families, responsible for reducing pro-inflammatory leptin, (IL-6) and (TNF-α) secretion and significantly increase the adiponectin level.[76] Some pro-inflammatory cytokines, such as the obesity hormone leptin, have a potential role in the development of a large variety of malignancies and are currently at the centre of the obesity-cancer link.[77] In humans, excessive adipose tissue is directly associated with elevated levels of leptin, which is significantly higher in women than in men, even after the adjustment for total body fat mass.[78,79] One explanation for this tendency is a differential regulation of leptin expression by sex hormones; estrogens were observed to increase leptin levels, while testosterone was observed to decrease leptin levels.[80] Leptin, in addition, can act as a mitogen and can increase the expression of anti-apoptotic proteins, inflammatory (TNF-α and IL-6), and angiogenic factors (VEGF). Interestingly, the effects of exercise, and particularly resistance exercise, can reduce leptin concertation, exerting an anti-inflammatory response.[76, 81-83] To date, the evidence that leptin can indeed be involved in the neoplastic processes has been provided by studies on breast and colorectal cancer, while limited studies are available for other cancer types.[84]

Moreover, adipose tissue adiponectin levels have been shown to exert anti-inflammatory actions and may thus counteract the increased cancer risk seen in obesity-induced inflammation.[85] Plasma adiponectin levels are known to be associated with insulin sensitivity and the risk of developing metabolic disorders and malignancy.[86] As exercise training improves insulin sensitivity and prevents the development of obesity related diseases, it has been proposed that exercise-induced improvement in insulin sensitivity is mediated through the regulation of plasma adiponectin levels. In addition, low serum adiponectin levels and high serum leptin levels are independent risks for cancer metastasis.[87] Since physical inactivity is strongly linked with excess weight/obesity, and both are important risk factors for cancer development, regular physical activity appears to be important for the prevention of cancer development through reduction adiposity, in particular the metabolically active abdominal fat both of which are known to contribute to systemic inflammation.[83]

The role of microbiota composition

The human gastrointestinal tract (GIT) is colonized by trillions of microbial cells, and numerous studies

have shown the importance of gut microbiota composition in several physiological and pathological processes, including local gastrointestinal cancer, as well as others such as distal cancer (head and neck, breast, oesophageal, pancreatic, and prostate cancer).[88] A microbial imbalance or dysbiosis can be caused by several risk factors, such as aging, smoking, having an unhealthy diet, and inflammation that increases the host's risk for neoplastic transformation.[89] Gut microbiota provides nutrients, regulates epithelial development, and affects the immune system. Additionally, an augmented microbial diversity is associated with improvement in the health status and the immune system.[90] It has been demonstrated that gut microbiota can be modulated by different factors. Recently, human and animal studies have revealed that aerobic exercise increases microbiota diversity, altering the bacterial composition and influencing the production of important metabolites of gut bacteria.[91]

Regular aerobic physical activity affects colon motility, provides a positive effect on the gut by reducing transient stool time and contact time between pathogens and the gastrointestinal mucosa layer.[92] Physical activity may reduce prostaglandine production and inflammation and protect the integrity of the intestine. In this manner, physical activity prevents the risk of many diseases such as colon cancer, diverticulosis and other inflammatory diseases.[93] Other possible positive effects of exercise include elevated short-chain fatty acids (SCFAs) and immunoglobulin production and an increase in butyrate concentration. The increase of fecal butyrate has anti-carcinogenic and anti-inflammatory properties.[94] In addition, exercise can prevent obesity and induce changes in microbiota composition and diversity, and potentially contribute to reducing weight and obesity-associated pathologies.[95] Recently, it has been demonstrated that aerobic exercise training alters the gut microbiota and microbial-derived SCFA in sedentary lean and obese adults without any changes to dietary patterns.[96] This evidence supports the idea that regular physical activity appears to be an important environmental factor that induces changes in microbial composition benefits for the host, and stimulates gut bacteria to produce substrates that protect against GIT disorders and colon cancer.

Conclusions

The epidemiological data for the beneficial effects of physical activity and cancer risk are being gathered rapidly and several possible mechanisms have been proposed to explain the link between physical activity and cancer. Physical activity can reduce the risk of various types of cancers by mechanisms including: decreasing markers of systemic inflammation by releasing anti-inflammatory myokines, improving insulin resistance, reducing leptin levels and hyperinsulinemia, increasing adiponectin levels and function of immune cells, decreasing circulating estrogen and androgen levels, and decreasing transient stool time and contact time between pathogens and the gastrointestinal mucosa layer. Discovering that skeletal muscle is an endocrine organ elucidated some of the proposed mechanisms.

Based on the current level of knowledge, some unexplained factors remain: existing evidence is limited to be able to support a specific dose of physical activity among a specific population subgroup, tailored for site-specific cancer reduction; how to measure precise physical activity; and how different type, dose and intensities of exercise are attributed to lowering certain cancer risks. General guidelines recommend 150 minutes of moderate physical activity or at least 75 of vigorous physical activity per week.[11, 97] The second report by the World Cancer Research Fund (WRCF) states that "more physical activity is better". Although any dose of physical activity is important for the reduction of cancer risk; to date, data from numerous studies have reported that higher levels of physical activity (150–300 minutes per week or 7–15 MET h/w) in particular, making vigorous is important for cancer prevention.[4]

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research article

Clinical relevance of ^{18}F-FDG PET/CT in the postoperative follow-up of patients with history of medullary thyroid cancer

Jelena Saponjski[1], Djuro Macut[2], Dragana Sobic Saranovic[3], Branislava Radovic[1], Vera Artiko[3]

[1] Center for Nuclear Medicine, Clinical Center of Serbia, Belgrade, Serbia
[2] Clinic for Endocrinology, Diabetes and Metabolic Diseases, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[3] Center for Nuclear Medicine, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

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Correspondence to: Prof. Vera Artiko, M.D., Ph.D., Director, Center for Nuclear Medicine, Clinical Center of Serbia, Visegradska 26, 11 000 Belgrade, Serbia. E-mail: vera.artiko@gmail.com

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Background. The aim of the study was evaluation of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography with computed tomography (PET/CT) in the detection of active disease in the patients with suspected recurrence of the medullary thyroid carcinoma (MTC).

Patients and methods. ^{18}F-FDG PET/CT investigation was performed in 67 patients, investigated from 2010 to 2019. Follow up was performed from 6 to 116 months after surgery (median 16.5 months, $\bar{x} \pm SD$ = 29±28.9 months). Twenty five of 67 patients underwent ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) scintigraphy, 11 underwent somatostatin receptor scintigraphy (SRS) with ^{99m}Tc-HYNIC TOC while 11 ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy.

Results. From 67 patients, 35 (52.2%) had true positive ^{18}F-FDG PET/CT findings (TP). Average maximal standardized uptake value (SUVmax) for all TP lesions was 5.01+3.6. In 25 (37.3%) patients findings were true negative (TN). Four (6%) patients had false positive (FP) findings while three (4.5%) were false negative (FN). Thus, sensitivity of the ^{18}F-FDG PET/CT was 92.11%, specificity 86.21%, positive predictive value 89.74%, negative predictive value 89.29% and accuracy 89.55%. In 27 patients (40%) ^{18}F-FDG PET/CT finding influenced further management of the patient.

Conclusions. ^{18}F-FDG PET/CT has high accuracy in the detection of metastases/recurrences of MTC in patients after thyroidectomy as well as in evaluation and the appropriate choice of the therapy.

Key words: ^{18}F-FDG PET/CT; medullary thyroid carcinoma; follow up; postoperative

Introduction

Medullary carcinoma of thyroid gland (MTC) is a malignant neuroendocrine tumor originated from the para-follicular C cells. The incidence is 1 to 2% of thyroid malignancies. It may occur as sporadic or hereditary form as a part of type 2 multiple endocrine neoplasia (MEN2) syndromes with surgery representing the primary therapeutic modality.[1,2] C cells secrete specifically calcitonin and procalcitonin which are considered as specific tumor markers.[3] Carcinoembryonic antigen (CEA) is not specific marker for this tumor but is useful in follow up of the treatment. Both calcitonin and CEA doubling times are considered as prognostic predictors in patients with persistent disease after surgery.[4]

Diagnosis of MTC during management of thyroid nodular disease could be established by fine needle aspiration cytology, immunocytochemical staining against calcitonin and/or its measurement in the needle washouts or additional immunostaining against specific biomarkers such as calcitonin, CEA, chromogranin A. Elevated basal values of serum calcitonin especially when greater than 100 pg/ml, or calcitonin levels obtained during calcium stimulation test are used for diagnosis of MTC.[5]

Total thyroidectomy and neck dissection is considered as the first line and curative treatment. In the treatment of progressive MTC, surgery, imaging-guided local treatments and tyrosine kinase inhibitors can be used and combined.[1] In the diagnosis of MTC, different anatomical and functional imaging procedures may be used. Ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) are used in staging of the disease before primary surgery. The role of nuclear medicine methods is reserved for detection and localization of recurrent disease when serum tumor marker levels are elevated and when the findings of morphologic imaging methods are inconclusive.[6,7]

The most frequently used radiopharmaceuticals for the diagnosis and follow up of MTC, labelled with γ emitting radionuclides, are metaiodobenzylguanidine (MIBG) labelled either with ^{131}I or ^{123}I, ^{99m}Tc-pentavalent dimercaptosuccinic acid (^{99m}Tc(V)-DMSA), ^{111}In-pentetreotide (Octreoscan) and ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide (Tektrotyd).[8-13] The radiopharmaceuticals labelled with a positron-emitting radionuclides suitable for positron emission tomography with computed tomography (PET/CT) are ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA), and ^{68}Ga-labelled somatostatin analogues (^{68}Ga- DOTATATE or DOTATOC). According to the literature, overall sensitivity of conventional nuclear medicine methods γ emitting radionuclides is lower in comparison to conventional anatomic imaging (*i.e.* US, CT, MRI) and positron emission tomography/computed tomography.[7,8] However, still, application of PET/CT in the nuclear medicine worldwide is limited. Radiopharmaceuticals track different metabolic pathways or receptor expression/functioning, and proved to be useful in detecting MTC recurrences/metastasis. Nuclear medicine methods may help guiding the appropriate choice of the therapy but also offer possibility of radionuclide therapy with radiolabeled somatostatin analogues or metaiodobenzylguanidine.

The aim of our study was to examine specificity and sensitivity of ^{18}F-FDG PET/CT in comparison to other available nuclear imaging methods used for the follow-up of MTC patients treated with the first-line radical thyroidectomy.

Patients and methods

In this cohort retrospective study, ^{18}F-FDG PET/CT investigation was performed in 67 consecutive patients (32 males and 35 females, 52.2±16.2 years of age) in a period from 2010 to 2019. Follow up was performed from 6 to 116 months after surgery (median 16.5 months, $\bar{x} \pm SD$ = 29±28.9 months), in order to detect active disease after total thyroidectomy and estimate the effect of adjuvant medical or radiotherapy. The majority of patients (56) had increased serum concentration of calcitonin (45-8526 pg/ml) while 16/67 had increased concentration of CEA. All the patients underwent radiological imaging methods (CT, NMR, US). In addition to ^{18}F-FDG PET/CT investigation, 25 patients underwent ^{99m}Tc-DMSA scintigraphy, 11 somatostatin receptor scintigraphy (SRS) with ^{99m}Tc- HYNIC TOC and 11 ^{99m}Tc-MIBG scintigraphy.

The patients underwent ^{18}F-FDG PET/CT examination on a 64-slice PET/CT scanner (Biograph, TruePoint64, Siemens Medical Solutions Inc. USA). Radiopharmaceutical (5.5MBq/kg) was injected to the patient after fasting for at least 6 hours. Afterwards, patients rested in a quiet and darkened room for 60 min, after which images of PET/CT were obtained. Low-dose non-enhanced CT scans (120 kV with automatic, real-time dose modulation amperage, slice thickness of 5 mm, pitch of 1.5 and a rotation time of 0.5 s) and 3-dimensional PET scans (6-7 fields of view, 3 min/field) were acquired from the base of the skull to the mid-thigh. Non-corrected and attenuation-corrected CT, PET and fused PET/CT images were displayed for analysis on a Syngo Multimodality workplace (Siemens AG). The FDG uptake was analyzed visually and quantitatively using SUVmax index. FDG PET/CT findings were considered positive in the case of higher accumulation FDG in comparison to surrounding parenchyma, mediastinal blood vessels and the liver. For assessment of glucose metabolism level in metastasis, SUVmax was used. Tumor lesions were defined by volume of interest placed around every suspected focus of intense FDG uptake, with 50% threshold. The measurements of SUVmax, were done on reconstructed images, after using ordered subsets expectation maximization as statistical reconstruction method, but no absolute cut-off value of SUVmax was used for the diagnosis. Images were interpreted separately by two nuclear medicine physicians, unaware of results of other imaging modalities. In cases of discrepancy, images were presented to multidisciplinary team and experts' opinion was adopted.

In addition to ^{18}F-FDG PET/CT investigation, when required, whole body scintigraphy, single photon emission computed tomography (SPECT) imaging and, if necessary spot views were per-

TABLE 1. ^{18}F-FDG PET/CT findings in medullary thyroid carcinoma patients with calcitonin levels

Findings	Number	%	Increased calcitonin levels	Calcitonin levels above 1000 pg/ml
TP	35/67	52.2	35/35 (100%)	18/35 (51%)
TN	25/67	37.3	18/25 (72%)	0
FP	4/67	6	2/4 (50%)	0
FN	3/67	4.5	2/3 (66%)	2/3 (66%)
Sensitivity	92.11% (95% CI 78.62% to 98.34%)			
Specificity	86.21% (95% CI 68.34% to 96.11%)			
Positive predictive value	89.74% (95% CI 77.81% to 95.62%			
Negative predictive value	89.29% (95% CI 73.59% to 96.14%)			
Accuracy	89.55% (95% CI 79.65% to 95.70%)			

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

formed with ^{99m}Tc(V)-DMSA, ^{99m}Tc-HYNIC-TOC), and ^{123}I-MIBG using ECAM gamma camera and computer (ESOFT).

The patient underwent an intravenous injection of 740 MBq ^{99m}Tc(V)--DMSA and after 2 h 30 min, a whole body scintigraphy was performed (scanning speed 10 cm/min).

Somatostatin receptor scintigraphy (SRS) of the whole body was performed 2 h and 24 h after i.v. administration of 740 MBq ^{99m}Tc-HYNIC-TOC. Before study therapy with somatostatin analogs was withdrawn, mild laxatives were introduced, patients were fasting and were well hydrated. Scintigraphy with ^{123}I-MIBG was performed 24 h after slow intravenous injection of no less than 80 MBq. Whole-body planar images were acquired at scanning speeds of 5cm/min. Each spot view was acquired for a maximum of 10 min (about 500 kcounts).

Investigation was followed by SPECT of particular region. It was performed using 360º orbit, step and shoot mode, at 30 sec per view. The acquired data were collected in a 128 x 128 computer matrix and reconstructed using filtered back-projections with a Butterworth filter (cut-off 0.6 cycles/pixel, order 5) and iterative reconstruction.

Whole body and SPECT images were first evaluated visually by two experienced nuclear medicine physicians. Visual appearance of an increased focal uptake of tracer in the suspected tumor site was considered a positive finding.

Reference standards for active disease were surgery, biopsy and follow up of 5 years.

Descriptive statistical methods were used such as mean value, standard deviation, sensitivity, specificity, positive predictive value, negative predictive value and accuracy, as well as the percentage. Progression- free survival was assessed by Kaplan Meier survival analyses.

Ethical consideration

All the patients gave the informed consent for the investigation and the study was approved by Ethical Committee of Clinical Center of Serbia (668/6/2018) and Ethical Committee of Faculty of Medicine University of Belgrade (1550/V-9/2019).

Results

The results of PET/CT findings are shown in the Table 1. From 67 patients 35 (52.2%) had positive ^{18}F-FDG PET/CT findings (TP): 15 in the neck lymph nodes (42.9%), 13 in mediastinal lymph nodes (37.1%), 2 (5.7%) in mediastinal and abdominal lymph nodes and lungs, 2 (5.7%) in thyroid neck region and 3 on multiple localizations in bones, lungs and mediastinum (8.6%), with SUVmax 5.01+3.6. In 25 (37.3%) patients accumulation of FDG was physiological (TN). Four (6%) patients were false positive (FP), 3 with enlarged jugular lymph nodes and negative pathohistological finding and one with hilar lymphadenopathy which has not been visualized on control PET/CT scans. Three (4.5%) were false negative (FN), two of which with increased calcitonin levels (above 1000 pg/ml) and one because of the recently finished chemotherapy and slight accumulation in the neck lymph node which was considered as reactive (4.7%). In 27 patients (40%) FDG PET/CT finding influenced further therapeutic management of the patient.

The results of ^{99m}Tc(V)-DMSA scintigraphy are shown in the Table 2. In the patients who underwent ^{99m}Tc-DMSA scintigraphy, there were 4 TP, 13 TN, 3 FP (after surgery) and 5 FN (small lesions). In 11/14 (78.6%) TN patients ^{18}F-FDG PET/CT and ^{99m}Tc-DMSA findings were concordant.

Concordance of the ^{18}F-FDG PET/CT findings with the results of other radionuclide methods in selected number of MTC patients are shown in Table 3 and Figures 1–3. When patients were FDG PET true negative, they were also negative (TN) or FP with other modalities which emphasized the value of FDG PET in comparison to other methods. However, sometimes, additional information was obtained by other methods. Thus, in one TP patient with FDG PET/CT, because of lymph node metastases and suspicious but not obvious liver metastases, scintigraphy with ^{123}I-MIBG showed obvious liver metastases, *i.e.* accomplished the PET/CT finding, while scintigraphy with two other methods (DMSA, Tektrotyd) was FN. In another two TP patients on FDG PET/CT, expression of somatostatin receptors was very high, so the corresponding therapy was ordered.

Kaplan Meier progression-free survival analysis in FDG TP patients showed median survival of 15 months (95% CI 11.14+18.85 months), while median survival in TN (disease free patients) at the moment of investigation was 30 months (95% CI 1.08+58.92 months) (Figure 4).

TABLE 2. ^{99m}Tc-DMSA scintigraphy findings in medullary thyroid carcinoma patients

Findings	Number	%
TP	4	
TN	13	
FP	3	
FN	5	
Sensitivity		44.44% (95% CI 13.70% to 78.80%)
Specificity		81.25% (95% CI 54.35% to 95.95%)
Positive predictive value		57.14% (95% CI 27.55% to 82.38%)
Negative predictive value		72.22% (95% CI 58.07% to 83.00%)
Accuracy		68.00% (95% CI 46.50% to 85.05%)

^{99m}Tc(V)-DMSA = ^{99m}Tc-pentavalent dimercaptosuccinic acid; CI = confidence interval; FN = false negative; FP = false positive; TN = true negative; TP = true positive

TABLE 3. Concordance of the ^{18}F-FDG PET/CT findings with the results of other radionuclide methods in selected number of medullary thyroid carcinoma patients

^{18}F-FDG PET/CT	^{99m}Tc(V)-DMSA	^{99m}Tc-HYNIC-TOC	^{123}I-MIBG
14 TP (100%)	4 TP (28.6%) 4 FN (28.6%)	5 TP (35.7%) 3 FN (21.4%)	3 TP (21.4%) 2 FN (14.3%)
14 TN (100%)	**11 TN (78.6%)** 2 FP (14.3%)	1 FP (7%) 1 TN (7%)	3 TN (21.4%) 2 FP (14.3%)
4 FP (100%)	1 FP (25%) 2 TN (50%)	1 FP (7%)	
1 FN (100%)	**1 FN (100%)**		**1 FN (100%)**

^{123}I-MIBG = metaiodobenzylguanidine; ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; ^{99m}Tc(V)-DMSA = ^{99m}Tc-pentavalent dimercaptosuccinic acid; FN = false negative; FP = false positive; PET/CT = positron emission tomography with computed tomography; Tektrotyd = ^{99m}Tc-EDDA/HYNIC-Tyr3-octreotide; TN = true negative; TP = true positive

Discussion

Our results point out very high sensitivity (92. 11%) of ^{18}F-FDG PET/CT in the detection of recurrence or metastases of MTC, relatively high positive (89.74%) and negative predictive value (89.29%) as well as accuracy (89.55%). Specificity was 86.21%. The main reason for FP and FN results was subjective assessment of the size and the uptake in the lymph nodes after the therapy, which emphasized the importance of follow up in order to avoid FP and FN results. According to our results, ^{18}F-FDG PET/CT can be used in the follow-up period of patients with elevated plasma calcitonin in order to detect recurrence and residual disease after the primary operation.

The results of other investigators for sensitivity vary from 47 to 93% while specificity ranged from 67-92%.[14-18] Like in our study, where ^{18}F-FDG PET/CT contributed significantly in 40% of the cases, other authors revealed that ^{18}F-FDG PET/CT provides additional information important for the further management of the patients in a significant number of cases (up to 54%).[19-21] Other studies also showed that ^{18}F-FDG PET/CT positive finding may influence the management of recurrent MTC when hypermetabolic lesions are detected. [22-24] In all our TP patients serum calcitonin levels were increased, and in 51% of them were higher than 1000 pg/ml, while 72% of TN had increased calcitonin levels but none of them higher than 1000 pg/ml. However, in 2/3 FN findings calcitonin level was increased above 1000 pg/ml. This is in accordance with the data of other investigators who proved that there is a positive relationship between serum levels of calcitonin and CEA and the sensitivity of ^{18}F-FDG PET/CT. Moreover, it was shown that sensitivity of ^{18}F-FDG PET/CT improves in patients with shorter serum calcitonin and CEA doubling times. This is confirming the usefulness of ^{18}F-FDG PET/CT method in patients with more aggressive forms

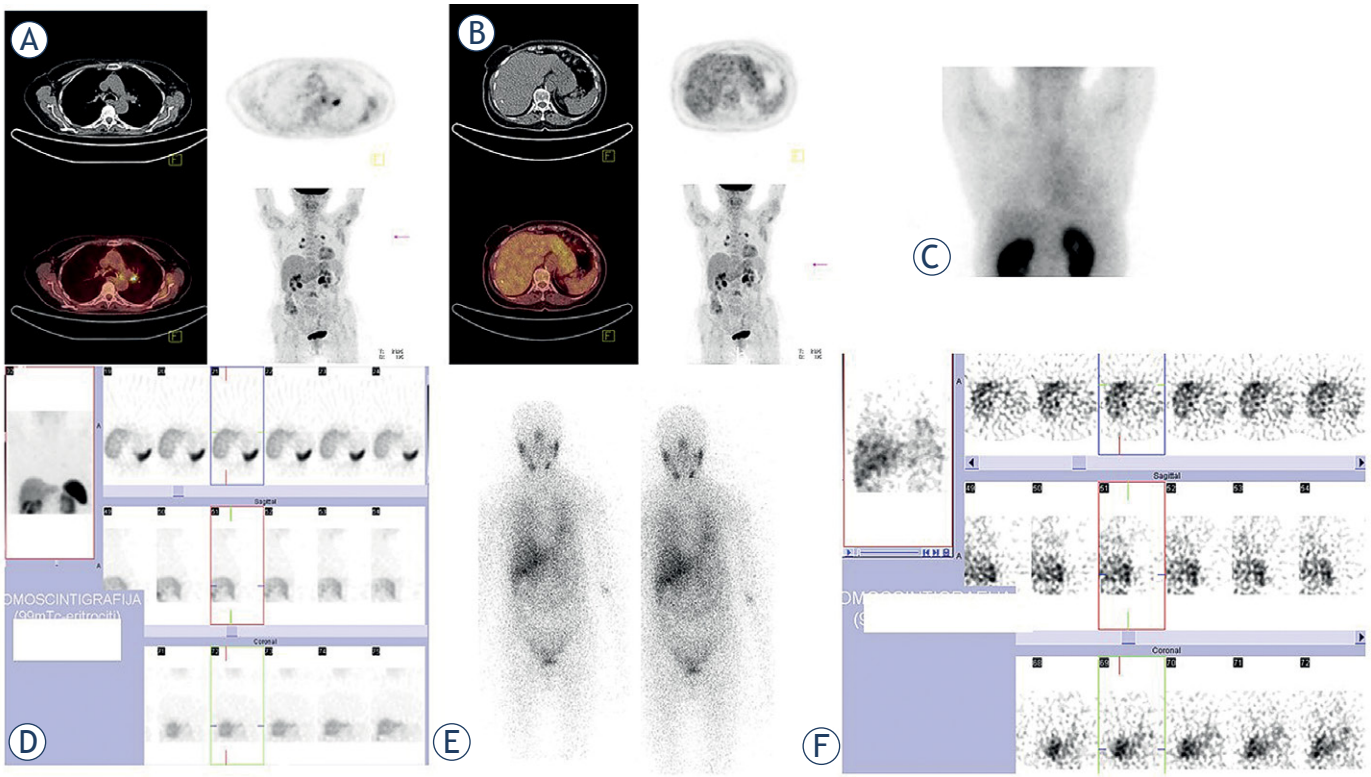

FIGURE 1. Patient with diagnosis of MTC after total thyroidectomy. **(A, B)** FDG PET/CT confirmed high uptake metastases in the mediastinal lymph nodes and uneven distribution of FDG in the liver. **(C)** ^{99m}Tc-DMSA spot view scintigraphy finding is negative. **(D)** ^{99m}Tc - tektrotyd SPECT finding is negative. **(E)** ^{123}I – MIBG WB finding showed high uptake in multiple liver metastases. **(F)** ^{123}I – MIBG SPECT finding showed high uptake in multiple liver metastases.

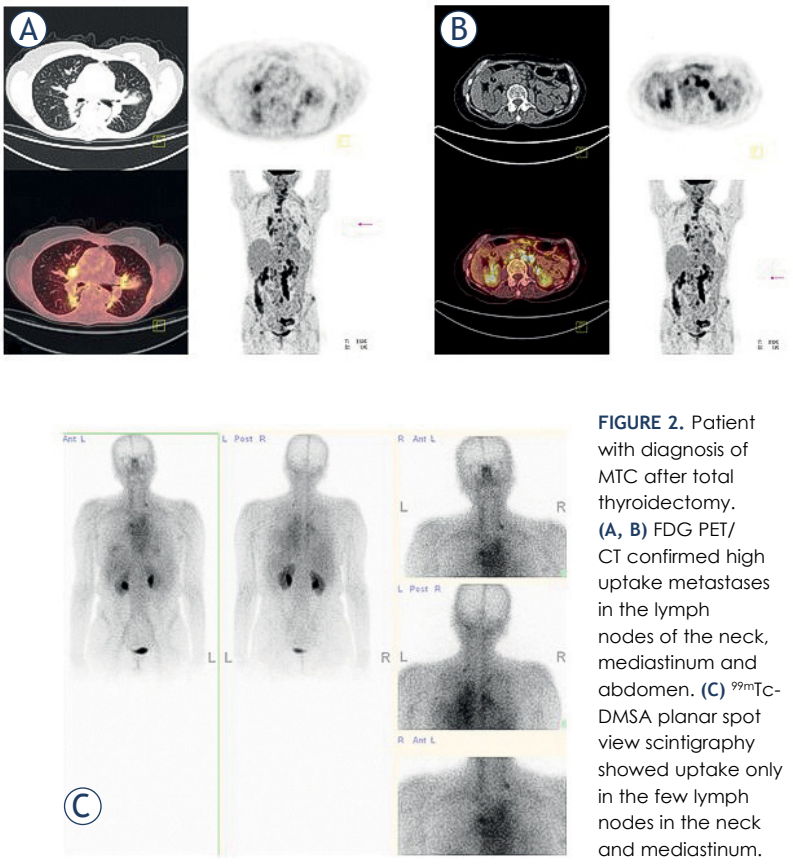

FIGURE 2. Patient with diagnosis of MTC after total thyroidectomy. **(A, B)** FDG PET/CT confirmed high uptake metastases in the lymph nodes of the neck, mediastinum and abdomen. **(C)** ^{99m}Tc-DMSA planar spot view scintigraphy showed uptake only in the few lymph nodes in the neck and mediastinum.

of disease in comparison to those with slowly progressive disease.[4,25-26] Furthermore, ^{18}F-FDG PET/CT is able to accurately identify MTC patients with poor prognosis and life expectancy, and to evaluate response to targeted therapies in patients with advanced metastatic disease.[27]

Our investigation showed that progression-free survival in FDG TP patients showed median survival of 15 months in the patients with recurrences and metastases, while median progression-free survival in disease free patients at the moment of investigation was 30 months. This is in accordance with the results of other authors. Thus, Fox *et al.* obtained that progression free survival was 19.2 months, while Elisei *et al.* obtained that progression free survival was, in dependence of the therapy 11.2 vs 4.0 months.[28,29]

Our results obtained with ^{99m}Tc(V)-DMSA showed in general slightly lower sensitivity in the detection of metastatic or recurrent disease (44.4%) in comparison to majority of other others authors. Thus Verga *et al.* reported a sensitivity rate of 50%, Ugur *et al.* even 95%, while the study of Adams *et al.*, revealed 65% and Howe *et al.* 71.4%.[30-33] However, relatively large number of TN patients in

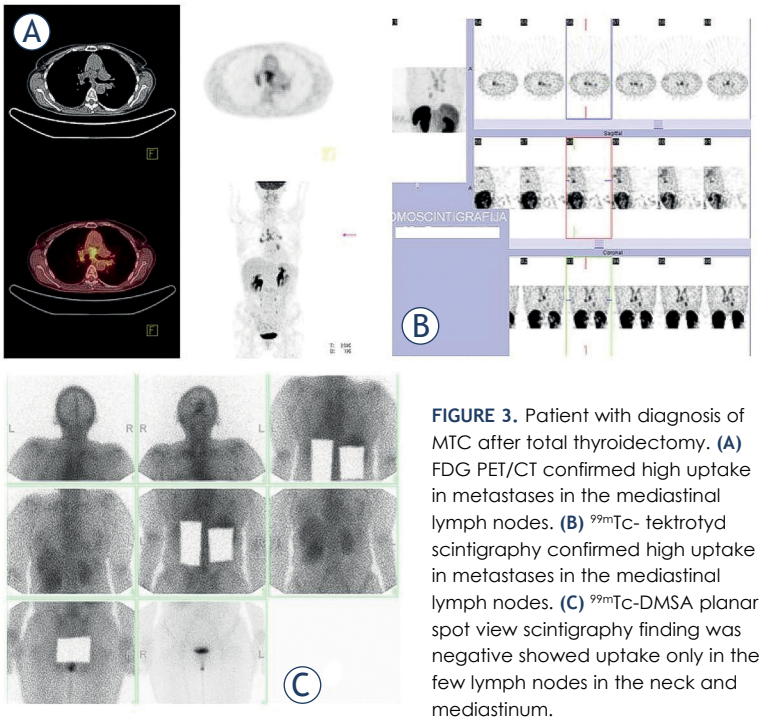

FIGURE 3. Patient with diagnosis of MTC after total thyroidectomy. **(A)** FDG PET/CT confirmed high uptake in metastases in the mediastinal lymph nodes. **(B)** ^{99m}Tc- tektrotyd scintigraphy confirmed high uptake in metastases in the mediastinal lymph nodes. **(C)** ^{99m}Tc-DMSA planar spot view scintigraphy finding was negative showed uptake only in the few lymph nodes in the neck and mediastinum.

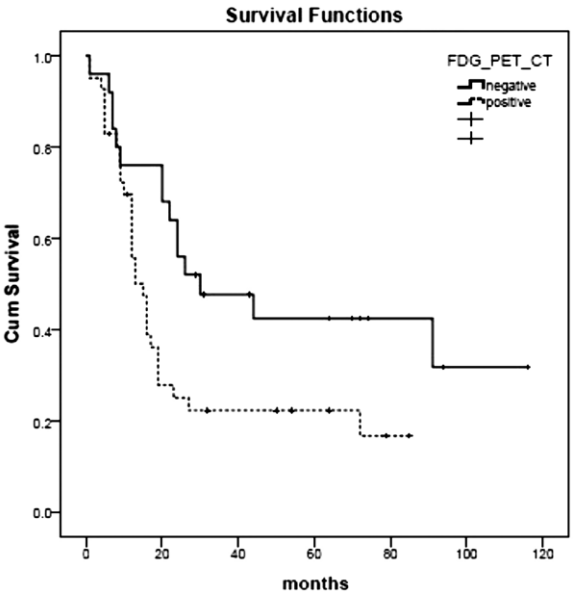

FIGURE 4. Kaplan Meier progression-free survival curve in positive FDG patients with median survival of 15 months (95% CI 11.14 ± 18.85 months), while median survival in disease free patients was 30 months (95% CI 1.08+58.92 months).

our study leads us to conclusion that DMSA scintigraphy could be used together with ^{18}F-FDG PET/CT to rule out residual or metastatic disease. A wide range of sensitivity could be explained by different commercial kits used, with different stability of the isomeric composition.[34] Taking this into consideration, DMSA scintigraphy should not be the best option in preoperative setting in comparison to postoperative detection of residual disease presumably when calcitonin level starts to increase.[7,34]

Taking into consideration our results and those of other investigators, ^{18}F-FDG PET/CT showed higher sensitivity in patients with MTC when compared to single photon emission tracers.[18-20] In our group of MTC patients who had both ^{18}F-FDG PET/CT and DMSA just a small number underwent MIBG and SRS scintigraphy, and statistical analysis could not be made. However, a small number of cases on the management of recurrent and metastatic MTC implicated that the sensitivity of ^{123}I/^{131}I-MIBG and Octreoscan used for this indication is low and ranged between 30% and 71%.[7] However, the advantage of MIBG and SRS scintigraphy is the possibility of radionuclide therapy in the cases with high uptake. Similar to our findings, Rubello *et al.* concluded that ^{18}F-FDG PET had the highest sensitivity in localizing metastatic disease in comparison to ^{99m}Tc(V)-DMSA scintigraphy, ^{111}In-DTPA-octreotide, US, CT and MRI.[21] Szakall *et al.* showed that ^{18}F-FDG PET was superior with better sensitivity than CT, MRI, and ^{131}I-MIBG in localizing lymph node involvement in patients with known MTC and postoperatively elevated calcitonin levels.[34] These authors also found that while FDG PET was superior in comparison to anatomic modalities in the lesions in neck, supraclavicular and mediastinal, CT had advantage in detection of liver and lung metastases, while FDG PET and MR were similar.[34]

Although there is no single imaging method sensitive enough to reveal all MTC recurrences, our results confirmed an advantage of ^{18}F-FDG PET/CT in comparison to gamma emitting radiopharmaceuticals. Positron emitting radiopharmaceuticals beyond FDG, such as fluorine-18 dihydroxyphenylalanine (^{18}F-FDOPA) and somatostatin analogues labelled with gallium-68 (^{68}Ga-SSA) tracks different metabolic pathways or receptor expression/functioning, and proved to be useful in detecting MTC recurrences/metastasis. According to the literature data, PET/CT imaging with available radiopharmaceuticals is suggested when serum calcitonin exceed 150 pg/mL or calcitonin doubling time is shortened (*i.e.* < 24 months).[36-38] If available, ^{18}F-FDOPA PET/CT is preferred, but if the finding is negative or this radiopharmaceutical unavailable, ^{18}F-FDG PET/CT should be performed, in particular if calcitonin and CEA levels are rapidly rising (*i.e.* doubling time <

1 year) or an aggressive behavior of the disease is expected (*e.g.* CEA levels disproportionately high compared with calcitonin levels).[27,39] According to Kushchayev *et al.*, functional imaging, primarily PET/CT with ^{18}F-FDOPA and ^{18}F-FDG, plays a crucial role in the evaluation and management of MTC and has proven to be an efficient tool for the detection of metastases in patients with elevated calcitonin levels.[40] Furthermore, ^{68}Ga-SSA PET/CT could be considered in the cases with inconclusive anatomic imaging, ^{18}F-FDOPA and ^{18}F-FDG PET/CT results as well to assess the feasibility of peptide receptor radionuclide therapy.[27]

^{18}F-FDG PET/CT is a useful method with high diagnostic accuracy in the detection of secondary deposits of MTC in patients after radical thyroid surgery. It can be used alone or in line with other nuclear medicine methods as it is ^{99m}Tc(V)-DMSA especially in the cases when other position emitting radiopharmaceuticals are not available (^{18}F-FDOPA and ^{68}Ga-SSA).

Conclusions

^{18}F-FDG PET/CT has high accuracy in the detection of metastases/recurrences of MTC in patients with elevated calcitonin level after thyroidectomy and is superior to radionuclide single photon imaging modalities for identifying true positive disease.

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research article

Radiological evaluation of ex novo high grade glioma: velocity of diametric expansion and acceleration time study

Roberto Altieri[1,2,3], Francesco Certo[2], Giuseppe La Rocca[4], Antonio Melcarne[5], Diego Garbossa[5], Alberto Bianchi[6], Salvatore Crimi[6], Alessandro Pluchino[7], Simone Peschillo[1], Giuseppe M.V. Barbagallo[1,2]

[1] Division of Neurosurgery, Department of Neurosciences, Policlinico "G. Rodolico", University Hospital, Catania, Italy
[2] Multidisciplinary Research Center on Brain Tumors Diagnosis and Treatment, University of Catania, Catania, Italy
[3] PhD program at Department of Neuroscience, University of Turin, Turin, Italy
[4] Division of Neurosurgery, Catholic University School of Medicine, Rome, Italy
[5] Department of Neuroscience, University of Turin, Turin, Italy
[6] Department of General Surgery and Medical Surgery Specialties, University of Catania, Catania, Italy
[7] Department of Physics and Astronomy "E. Maiorana", University of Catania, Catania, Italy

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Correspondence to: Roberto Altieri, M.D., Department of Neurosurgery, Policlinico "G. Rodolico" University Hospital, Via Santa Sofia, 78, 95125 Catania, Italy. Phone: +39 953 781 143; E-mail: roberto.altieri.87@gmail.com

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Background. One of the greatest neuro-oncological concern remains the lack of knowledge about the etiopathogenesis and physiopathology of gliomas. Several studies reported a strict correlation between radiological features and biological behaviour of gliomas; in this way the velocity of diametric expansion (VDE) correlate with lower grade glioma aggressiveness. However, there are no the same strong evidences for high grade gliomas (HGG) because of the lack of several preoperative MRI.

Patients and methods. We describe a series of 4 patients affected by HGG followed from 2014 to January 2019. Two patients are male and two female; two had a pathological diagnosis of glioblastoma (GBM), one of anaplastic astrocytoma (AA) and one had a neuroradiological diagnosis of GBM. The VDE and the acceleration time (AT) was calculated for fluid attenuated inversion recovery (FLAIR) volume and for the enhancing nodule (EN). Every patients underwent sequential MRI study along a mean period of 413 days.

Results. Mean VDE evaluated on FLAIR volume was 39.91 mm/year. Mean percentage ratio between peak values and mean value of acceleration was 282.7%. Median appearance time of EN after first MRI scan was 432 days. Mean VDE was 45.02 mm/year. Mean percentage ratio between peak values and mean value of acceleration was 257.52%.

Conclusions. To our knowledge, this is the first report on VDE and acceleration growth in HGG confirming their strong aggressiveness. In a case in which we need to repeat an MRI, time between consecutive scans should be reduced to a maximum of 15–20 days and surgery should be executed as soon as possible.

Key words: acceleration time; glioblastoma; anaplastic astrocytoma; high grade glioma; radiological growth; velocity of diametric expansion

Introduction

High grade glioma (HGG) still represent a challenge for the medical community worldwide.[1-4] Currently, average survival rates reported for anaplastic astrocytoma (AA) and glioblastoma (GBM) are 3–4 years and 10–16 months, respectively.[5] One of the greatest concerns remains the lack of knowledge about the etiopathogenesis and pathophysiology of gliomas. The new WHO classification tried

to explain the biological behavior of these tumors, analyzing their metabolic and genetic pathways.[5] However, such classification has determined further fragmentation of our knowledge, in a time when we need a minimum common denominator to solve this terrible puzzle.[6,7] In recent years, research focused on glioma neuroradiological features trying to relate these with their biological behavior.[8-15] As a consequence, many preoperative information about low grade gliomas (LGG) came from analysis of velocity of diametric expansion (VDE). Pallud and Mandonnet[16-19] reported a strict correlation between VDE and glioma aggressiveness: growth values under 4 mm between two consecutive MRI studies suggest a low invasiveness rate and thus lower malignancy.[20,21] However, the same evidences are not available for HGG because of the lack of several preoperative MRI and no growth patterns have been standardized for HGG. We report a series of four patients in whom HGG growth and evolution were radiologically analyzed thanks to a long preoperative follow-up since tumor diagnosis until treatment.

Patients and methods

We describe a series of 4 patients followed by the first author from 2014 to January 2019. Two patients are male, two are female, two had a pathological diagnosis of GBM, one of AA and one received a neuroradiological diagnosis of GBM. Every patient was radiologically followed through almost three pre-operative MRI scans, focusing on T1 with gadolinium and T2/*fluid attenuated* inversion recovery (FLAIR) sequences. Tumor volume was calculated by neurosurgeons with experience in neuro-oncological field, using Horos software for MacOs for manual segmentation of T1 and FLAIR 3D volumetric images in each MRI scan.[22] For each patient's MRI scans mean tumor diameter (MTD)[20] was calculated through the following formula, starting from FLAIR-altered region's and enhancing nodule's (EN) volume (V), and expressed in millimeters (mm):

$$MTD = \sqrt[3]{2 * V} \qquad \text{[eq. 1].}$$

It represents the reverse formula of ellipsoid volume formula calculation: $\frac{D1 * D2 * D3}{2}$ assuming the three diameters as equivalent.

Variation of MTD (ΔMTD) between two consecutive MRI scans of each patient, was calculated as follows:

$$\Delta MTD = MTD_{(n+1)} - MTD_{(n)} \cup n \neq 0 \qquad \text{[eq. 2]}$$

Where n is the ordinal number of MRI scan for each patient.

Velocity of diametric expansion (VDE)[18,20], or MTD difference over time (days) between two consecutive MRI scans, was calculated as:

$$\text{VDE} = \frac{\Delta MTD}{\Delta T} \qquad \text{[eq. 3]}$$

where ΔT is the number of days between two consecutive MRI scans. VDE is reported as millimeters on days (mm/dd). Assuming a linear VDE growth, VDE for each interval of time was then calculated respect to 1-solar-year, as follow:

$$\text{Annual VDE} = \text{VDE} \times 365 \qquad \text{[eq. 4]}$$

For each patient, mean acceleration (Acc) or VDE variation over time, was calculated as follows:

$$\text{Acc} = \frac{VDE(n+1) - VDE\,(n)}{\Delta T} \qquad \text{[eq. 5]}$$

Where n is the ordinal number of MRI scan for each patient; ΔT is the number of days between two consecutive MRI scans. VDE is expressed in mm/dd, thus Acc results as mm/dd^2.

In order to evaluate variation of VDE and Acc along observation time, further analysis were conducted for any patient. In particular, we observed peak of VDE and Acc values in all patients.

About VDE, we quantified these peaks highest value of VDE /mean VDE value ratio (listed in Table 3) in every patient along observation period, expressed as percentage [eq. 6]:

$$\text{VDE peak} = \left(\frac{v_{max} \times n}{\sum_i^n v_i}\right) \times 100 \qquad \text{[eq. 6].}$$

Where v is the VDE value; v_{max} is the highest value of VDE recorded for any patient along all observation period; n total number of MRI scans for each patient; i the ordinal number of MRI scan.

In Acc peak analysis, we evaluated ratio between highest Acc value and mean Acc value for any patient (listed in table 4), expressed as percentage, as follows:

$$\text{Acc peak} = \left(\frac{\alpha_{max} \times n}{\sum_i^n \alpha_i}\right) \times 100 \qquad \text{[eq. 7].}$$

Where α is the Acc value; α_{max} is the highest value of Acc recorded for any patient along all observation period; n total number of MRI scans for each patient, i the ordinal number of MRI scan.

Further analysis evaluated EN/FLAIR volumes ratio (EFVR) (eq. 8), EN/FLAIR MTD ratio (EFMR) and their evolution over observation time (eq. 10 and 11), as follows:

$$EFVR = \frac{EN\ volume_{(n)}}{FLAIR\ volume_{(n)}} \quad \text{[eq. 8];}$$

$$EFMR = \frac{EN\ MTD_{(n)}}{FLAIR\ MTD_{(n)}} \quad \text{[eq. 9];}$$

EFVR on single interval of time between consequent MRI scan = $EFVR/[T_{(n+1)} - T_{(n)}]$ [eq. 10];

EFVR on total interval of time between first and last MRI scan of each patient = $EFVR/[T_{(n_f)} - T_{(n_0)}]$ [eq. 11];

EFMR on single interval of time between consequent MRI scan = $EFMR/[T_{(n+1)} - T_{(n)}]$ [eq. 12];

EFMR on total interval of time between first and last MRI scan of each patient = $EFMR/[T_{(n_f)} - T_{(n_0)}]$ [eq. 13];

Where n is the ordinal number of MRI scan for each patient; n_0 and n_f are the first and last MRI scan for each patient, respectively.

Every analysis was conducted for whole-tumor FLAIR volume and for single EN. The analysis and graphic representation were carried out with Microsoft Office Excel® software.

In addition, a literature review was performed using PubMed MEDLINE database and searching for "radiological glioma growth", "glioma radiologic follow-up", "glioma volume growth".

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

Case 1

A 39 y.o. male patient was under radiological follow-up since 5 years after meningioma resection. MRI scan was obtained once a year. After 5 years of negative post-operative MRI, the exam showed hyperintensity in the right hippocampal and parahippocampal areas on T2/FLAIR sequences, without enhancement after gadolinium infusion. MTD was 35.5 mm. For the sake of a closer follow-up, a new MRI scan with spectroscopy was scheduled 3 months later. In this second MRI scan, the FLAIR hyperintense lesion MTD was 39.7 mm, with no enhancement after gadolinium injection. Spectroscopy showed a peak in N-acetyl-aspartate (NAA), choline (Cho) and Creatinine (Cr) values. Both data suggested a likely diagnosis of ex novo HGG. Despite strong recommendation to undergo surgery, the patient delayed surgical treatment by 3 months. The new MRI scan, obtained the day before surgery for surgical planning, showed a MTD of 45 mm and contrast enhancement on T1-weighted sequences. The post-operative MRI showed a complete resection of the enhancing tumor. After resection, histopathologic diagnosis revealed AA, wild-type (WT) for IDH1. All values of ΔMTD, VDE and Acc calculated according to equations [2], [4,] [5], [6], [7] are listed in Table 1. After tumor gross total resection, the patient underwent the Stupp regimen for adjuvant treatment and died 16 months later.

Case 2

A 37 y.o. male patient, after an episode of dysarthria, underwent a neuroradiological workout. MRI images showed a left fronto-parieto-insular enhancing lesion suspicious for ex novo GBM. FLAIR and EN MTD were respectively 56.59 mm and 42.02 mm. After a week, he repeated the MRI with spectroscopy showing elevation of Cho and reduction of NAA values, elevation of Cho/NAA ratio, mild elevation of lactate signal. At the same time, central necrosis was visible. A diagnosis of GBM was made. FLAIR and EN MTD were 59.83 cc and 48 cc respectively. VDE was 169.23 mm/year for FLAIR tumor volume, whilst for EN was 311.81 mm/year. Due to poor neurological condition and tumor location, surgery was avoided. Following further neurological deterioration, he underwent a new MRI scan 2 weeks later. FLAIR tumor MTD was 72.60 mm, EN MTD was 52.16 mm. At this point, chemotherapy with temozolmide (TMZ) started. About two months later, a repeat MRI study showed good response. MTD was 67.37 mm for FLAIR tumor volume and 43.80 mm for EN, in which TMZ effect was higher (Figure 1). In fact, ΔMTD was - 5.22 mm and - 9.36 on FLAIR and EN nodule volume, respectively. Values of ΔMTD, VDE and Acc calculated according to equations [2], [4,] [5], [6], [7] for every

TABLE 1. Data about patient #1, #2, #3, #4

#Patient	#MRI	Days after previous MRI	V FLAIR (cc)	MTD (mm)	ΔMTD (mm)	VDE (mm/ day)	VDE (mm/ year)	Acc (VDE/ dd)	V EN	MTD (mm)	ΔMTD (mm)	VDE (mm/ day)	VDE (mm/ year)	Acc (VDE/ dd)
1	1	0	0	0	0	0	0.00	0.0000						
	2	365	22.53	35.5	35.5	0.0973	35.50	0.0003						
	3	90	31.47	39.7	4.2	0.0467	17.03	0.0005						
	4	60	45.65	45	5.3	0.0883	32.24	0.0015						
2	1	0	90.6	56.59	0.00	0.00	0.00	0.0000	37.1	42.02	0.00	0.00	0.00	0.0000
	2	7	107.1	59.83	3.25	0.46	169.23	0.0662	55.3	48.00	5.98	0.85	311.81	0.1220
	3	18	191.3	72.60	12.76	0.71	258.82	0.0394	75.1	53.16	5.16	0.29	104.54	0.0159
	4	36	152.9	67.37	-5.22	-0.15	-52.97	-0.0040	42	43.80	-9.36	-0.26	-94.91	-0.0072
3	1	0	0	0	0	0.000	0	0.0000	0	0	0	0	0	0
	2	465	4.8	21.25	21.25	0.046	16.68	0.0001	0	0	0	0.00	0	0
	3	277	9.1	26.30	5.05	0.018	6.66	0.0001	0	0	0	0.00	0	0
	4	48	16.4	32.01	5.71	0.119	43.39	0.0025	0.3	8.43	8.43	0.18	64.14	0.0037
	5	21	22.8	35.73	3.72	0.177	64.59	0.0084	0.7	11.19	2.75	0.13	47.84	0.0062
	6	14	36.2	41.68	5.95	0.425	155.18	0.0304	2.7	17.54	6.36	0.45	165.74	0.0324
	7	29	36.2	41.68	0.00	0.000	0.00	0.0000	4.9	21.40	3.86	0.13	48.53	0.0046
4	1	0	0.2	7.37	0.00	0.00	0.00	0.0000	0	0	0	0	0	0
	2	160	1	12.60	5.23	0.03	11.93	0.0002	0.2	7.37	7.37	0.05	16.81	0.0003
	3	36	1	12.60	0.00	0.00	0.00	0.0000	0.3	8.43	1.07	0.03	10.81	0.0008
	4	27	1	12.60	0.00	0.00	0.00	0.0000	0.3	8.43	0.00	0.00	0.00	0.0000
Mean values					5.405		39.91	0.0077			2.11		45.02	0.0119

Acc = acceleration; MRI = magnetic resonance imaging; MTD = mean tumor diameter; ΔMTD = variation of MTD respect to previous value; VDE = velocity of diameter expansion; V EN = volume of enhancing nodule post gadolinium; V FLAIR = volume of fluid attenuated inversion recovery altered regions

MRI scan are listed in Table 1, divided for FLAIR and EN volumes. 6 months after initial diagnosis the patient remains alive.

Case 3

A 72 y.o. female patient, after a seizure, underwent MRI workout without pathological findings. She repeated a MRI scan after 15 months and a FLAIR alteration in the left motor areas was seen. MTD was 21.25 mm. She refused any treatment. MRI scan was repeated further 9 months later showing a bilateral alteration of FLAIR signal in the frontal lobes. MTD was 26.30 mm. However, the patient chose to undergo neuroradiological follow-up rather than surgery. After two months, a new MRI scan showed an EN in the right frontal lobe. MTD of EN was 8.43 mm, MTD of FLAIR altered regions was 32.01 mm. Neurosurgeons suggested excision of the EN, but the patient refused again. Further MRI scans at 2, 6 and 10 weeks were obtained. MTD of EN were 11.19, 17.54 and 21.40 mm, respectively. MTD of FLAIR-altered regions were 35.73, 41.68 and 41.68 mm, respectively (Figure 2). At the end complete resection of EN was obtained; histopathological diagnosis was compatible with GBM, IDH1 WT. She underwent adjuvant therapy according to the Stupp regimen and remains alive 31 months after the index surgery. All values of ΔMTD, VDE and Acc calculated according to equations [2], [4,] [5], [6], [7] for every MRI scan are listed in Table 1, divided for FLAIR and EN volumes.

TABLE 2. Data on fluid attenuated inversion recovery (FLAIR) tumor and enhancing nodule (EN) volume velocity of diameter expansion (VDE). Reported as mm/year

#Patient	Mean FLAIR VDE	DS FLAIR VDE	Mean EN VDE	DS EN VDE
1	21.19	16.26		
2	93.77	145.21	80.36	174.48
3	40.93	55.88	46.61	59.19
4	2.98	5.97	6.90	8.34
Total mean value	39.9		45.02	

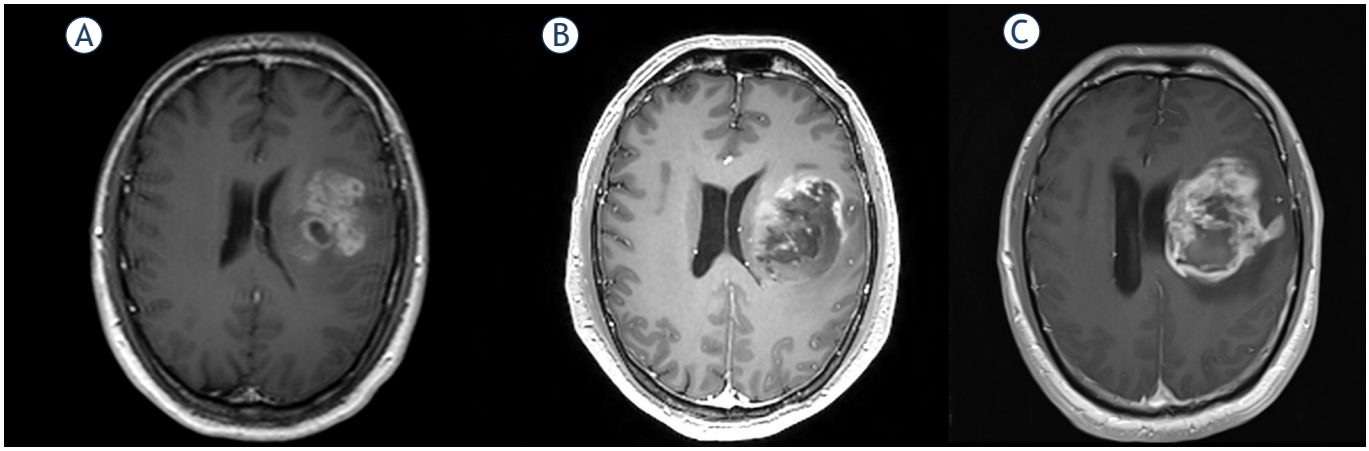

FIGURE 1. MRI scans in Patient 2 at 0 **(A)**, 18 **(B)** and 54 **(C)** days. (T1 with gadolinium sequences).

Case 4

A 56 y.o. female patient underwent MRI for persisting headache. An incidental slight alteration of FLAIR signal in the left gyrus rectus was discovered. MTD was 7.37 mm. She repeated an MRI 5 months later to evaluate tumor evolution and an EN appeared in the previously FLAIR-altered area. MTD of the EN was 7.37 mm, whereas MTD of FLAIR-altered area was 12.6 mm and there were no further changes in the next MRIs. An MRI with spectroscopy was obtained one month later and this suggested a GBM. The new MTD of the EN was 8.43 mm. Surgical treatment was then proposed. She underwent preoperative MRI for neuronavigation one month later. MTD of the EN was 8.43 mm (Figure 3). Complete resection of EN was carried out and histopathological diagnosis revealed GBM IDH1 WT. She underwent adjuvant therapy with Stupp regimen and is still alive 12 months after surgery. All values of ΔMTD, VDE and Acc calculated according to equations [2], [4,] [5], [6], [7] for every MRI scan are listed in Table 1, divided for FLAIR and EN volumes.

General evaluations

Each patient underwent sequential MRI studies, with an average number of 4 scans along a mean period of 413 days. ENs were evident only in patient 2 on the first MRI study, whereas appeared at fourth, fourth and second MRI scan in patients n. 1, 3 and 4, respectively. No common time correlation between evidence of first FLAIR alteration and EN appearance was found. Median appearance time after first MRI scan was 432 days.

Final mean tumor volume, evaluated on each patient's last T2/FLAIR MRI sequences, was 59 cc, with a median volume variation along sequential MRIs of 6.4 cc.

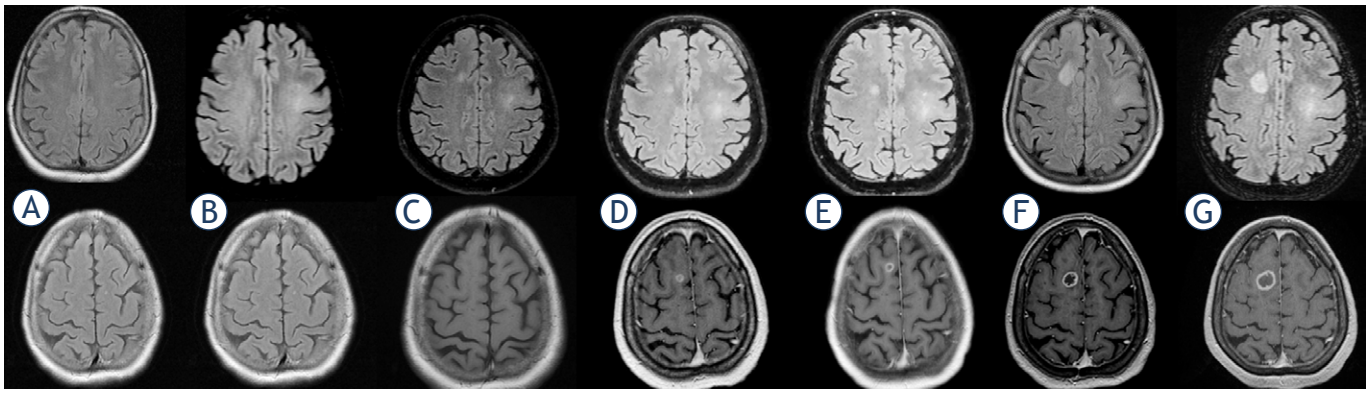

FIGURE 2. MRI scans in Patient 3 at 0 **(A)**, 465 **(B)**, 742 **(C)**, 790 **(D)**, 811 **(E)**, 825 **(F)** and 854 **(G)** days (fluid attenuated inversion recovery [FLAIR] and T1 with gadolinium sequences).

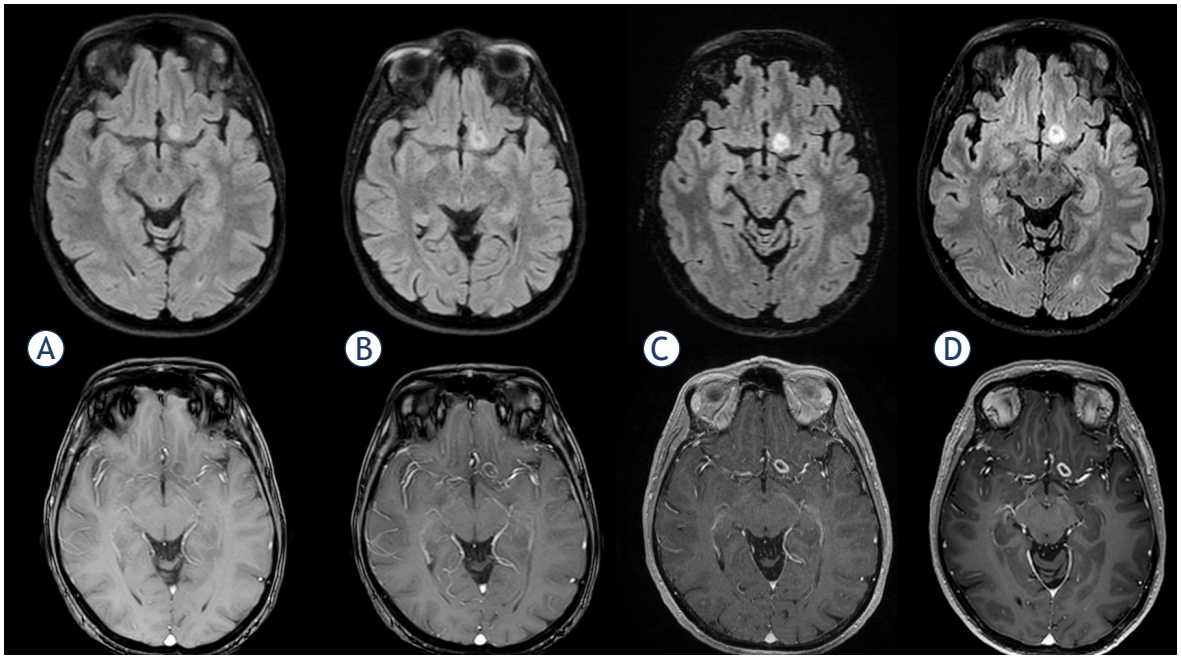

FIGURE 3. MRI scans in Patient 4 at 0 **(A)**, 160 **(B)**, 196 **(C)** and 223 **(D)** days (fluid attenuated inversion recovery [FLAIR] and T1 with gadolinium sequences).

Mean MTD at last MRI was 41,66 mm and 24.54 mm for FLAIR and EN volume, respectively, whilst median ΔMTD along the observation period was 5.4 mm and 2.11 mm, for FLAIR and EN volume, respectively (Table 1).

Mean VDE was 39.9 mm/year and 45.2 mm/year for FLAIR volume and EN, respectively (Table 1, 2).

VDE analysis revealed peak in variation along time. Mean percentage maximal VDE/mean VDE ratio, calculated according to eq. 6, was 221.49% and 259.47% for FLAIR and EN volumes, respectively (Table 3).

Acceleration analysis according to [eq. 5] revealed a mean value of 0.0077 mm/dd^2 and 0.0119 mm/days^2 for FLAIR and EN volume, respectively. Mean percentage ratio between peak values and mean value of acceleration was 282.7% for FLAIR volume and 257.52% for EN, respectively (table 4). In patient n. 1 late occurrence of the EN didn't allow complete evaluation of MTD variation, VDE and Acc (Figure 4).

Analysis of EFVR and EFMR, according to eq. 8–13 did not show significant results.

Discussion

Ex novo HGG diagnosis usually becomes evident when the tumor mass is wide and resection must be carried out as soon as possible. Thus, for each patient no many preoperative MRI scans are available for mathematical analysis of tumor growth. In the past decades, imaging studies on LGG evolution[23,24] let neurosurgeons to change their mind on treatment: from a "wait-and-see" approach to an early resection one, due to the understanding of malignant transformation risk.[17,18] Indeed, Mandonnet *et al*. published in 2008[19] a pioneering

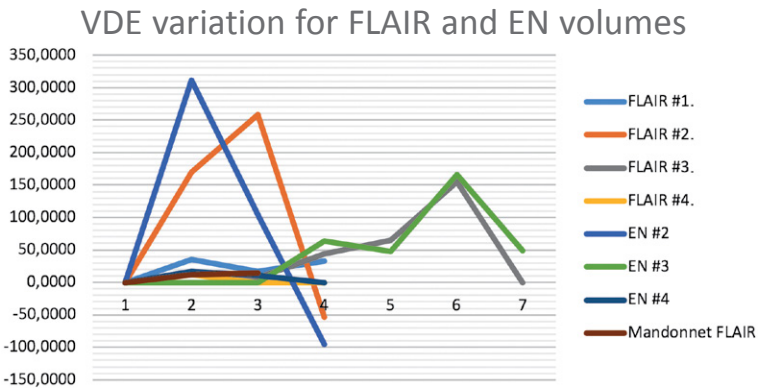

FIGURE 4. Velocity of diameter expansion (VDE) variation of mean tumor diameter (MTD) for fluid attenuated inversion recovery [FLAIR] and enhancing nodule (EN) volumes for each patient. Plus the case reported by Mandonnet *et al.* as specified in Discussion paragraph. Graphic shows variation of acceleration (Acc) based on VDE (mm/days^2) for FLAIR tumor volume and EN volume along time. Except obvious similar variation for two types of volume considered, peaks are easily notable. VDE of patient #1 is covered by patient #4.

TABLE 3. Raw data about velocity of diameter expansion (VDE) of fluid attenuated inversion recovery (FLAIR) and enhancing nodule (EN) volume. Mean percentage maximal VDE/mean VDE ratio could help in early high grade gliomas (HGG) diagnosis

Interval of consecutive MRI	VDE Pt #1 FLAIR	VDE Pt #2 FLAIR	VDE Pt #2 EN	VDE Pt #3 FLAIR	VDE Pt #3 EN	VDE Pt #4 FLAIR	VDE Pt #4 EN	Mean Values
1	35.50	169.23	311.81	16.68	0.00	11.93	16.81	
2	17.03	258.82	104.54	6.66	0.00	0.00	10.81	
3	32.24	-52.97	-94.91	43.39	64.14	0.00	0.00	
4				64.59	47.84			
5				155.18	165.74			
6				0.00	48.53			
Mean Values	28.26	125.03	107.15	47.75	54.37	3.98	9.21	
FLAIR VDE Peak/ VDE mean value ratio (percentage)	125.63	135.36		324.99		300.00		221.49
EN VDE Peak/ VDE mean value ratio (percentage)			291.02		304.81		182.57	259.47
Mean Values								240.48

TABLE 4. Raw data of mean acceleration (Acc) based on velocity of diameter expansion (VDE) of fluid attenuated inversion recovery (FLAIR) and enhancing nodule (EN) volume. Mean percentage maximal Acc/mean Acc ratio of each patient could help in early high grade gliomas (HGG) diagnosis

Interval of consecutive MRI	Acc Pt #1 FLAIR	Acc Pt #2 FLAIR	Acc Pt #2 EN	Acc Pt #3 FLAIR	Acc Pt #3 EN	Acc Pt #4 FLAIR	Acc Pt #4 EN	Mean Values
1	0.0003	0.0662	0.1220	0.00010	0	0.0002	0.0003	
2	0.0005	0.0394	0.0159	0.00007	0	0.0000	0.0008	
3	0.0015	-0.0040	-0.0072	0.00248	0.0037	0.0000	0.0000	
4				0.00843	0.0062			
5				0.03037	0.0324			
6				0.00000	0.0046			
Mean Values	0.0008	0.0339	0.0436	0.0069	0.0078	0.0001	0.0004	
FLAIR Acc Peak/ Acc mean value ratio (percentage)	195.6695	195.5808		439.7477		300		282.7495
EN Acc Peak/ Acc mean value ratio (percentage)			280.0617		414.7516		77.74935	257.5209
Mean Values								270.1352

paper on the role of VDE in LGG and Pallud, few years later, reported that a VDE over 8 mm/year is an independent negative prognostic factor for survival in LGG patients.[20] In the past, few studies reported mathematical models of growth based on simple exponential growth of Volume Doubling Time (VDT)[25,26] or linear growth of tumor radius.[27] In 2015 Stensjoen *et al.* analyzed tumor's growth curve in 106 patients, considering two consecutive MRI scans, and reported the Gompertzian growth to be the most reliable mathematical model to predict tumor mass evolution; and this had already been reported by previous studies.[9,28,29] As seen in LGG, valuable evaluations of malignancy and evolutions could come from MTD analysis and its variation among sequential MRI studies. Mandonnet *et al.* reported an incidental insular tumor, followed for 9 months: VDE was 12 and 14 mm/year at 5 and 9 months, respectively. Histopathologic analysis then revealed an AA.[21] Cochereau *et al.* reported a secondary GBM, in which VDE after evolution was 13 mm/year.[30] In such cases, authors suggest that an annual VDE value over 8 mm/year should represent an alarm for HGG suspect. Our experience with ex novo HGG, shows even higher mean values for annual VDE: 39.91 and 45.02 mm/year for FLAIR and

EN volume, respectively, enforcing previous findings and suggesting a more aggressive behaviour of an ex novo HGG respect the secondary ones. Wide differences in VDE values between our cases and cases reported by other authors, might come from different pathogenisis (primary versus secondary HGG), different observation times and biological features of the brain tumors. However, we want to underline how the VDE variate along the observation time. FLAIR VDE shows peaks, particularly in patients n.3 and n.4, with a ratio between peak and mean VDE value of 324.99% (n = 3.25 mm/dd) and 300% (n = 3 mm/dd), respectively. As shown in Figure 1, VDE variations follow a similar pattern in FLAIR and EN volume: progressive growth reach the highest value and then a rapid decrease is registered. Even if such peaks happen in different moments for each patients, such difference may be caused by different starting observation time. Speculating the possibility to follow growth curves of different HGG, all with the same onset time, peaks and following decrease could all happen in the same interval of time. Similar pattern, as in our cohort, could be found even in Mandonnet *et al.* case report.[21] Moreover the reported mean VDE of the EN is higher than FLAIR volume VDE suggesting the higher biological aggressiveness of the enhancing regions. In addition, not yet reported to our knowledge, mean Acc values show different peaks along tumor life. In our experience mean percentage ratio between peak and mean Acc values was 270.13%. Last data could improve early diagnosis of suspected primary or secondary HGG, even if a consensus about MRI timing doesn't exist. Follow-up MRI scans could be proposed every 4 months[31] to patients with early-detected LGG. Pallud *et al.* proposed a timing between 6 weeks and 3 months according to Chang score.[16] However, the wait and see policy in suspected HGG can let tumors grow and induce deficits. Thus, 3 months interval between two consecutive MRIs could be proposed when tumors could be misdiagnosed. Conversely, if strong suspect for HGG exists, observation could be carried out monthly. Indeed, Acc peak over 270% or VDE peak over 240% in comparison to mean values, for both FLAIR and EN volume, could help in diagnosis. Moreover, no long interval time is needed between MRIs: in our experience Acc variation could be seen even after 15–20 days. Obviously, at least three consecutive MRI scans are needed for VDE and Acc analysis. In summary, even if large series should confirm these data, we strongly propose surgical treatment in case of Acc peak and rapid VDE evolution, due to the high probability that MRI alterations refer to HGG. Such analysis could be helpful as prognostic factor and evolution parameter in case of surgical untreatable patients, *i.e.* due to poor general conditions or patient refusing surgery. However, sudden changes in VDE and Acc values do not have known causes. A clue could come from evolution of secondary gliomas, in which a previous LGG has been reported. By now, accumulation of mutation in LGG genes, particularly on chromatin modelling system, let a more aggressive phenotype acquisition. Maybe, as no long observation time has been obtained for HGG, our data could report a crucial moment of HGG evolution. Such peaks could refer to gain of mutation in high percentage of proliferating cells. Thus, MTD could increase in EN and FLAIR due to peripheral disposition of viable glioma cells. Such an expansion would not be compensated by core necrosis. However, too many different factors, *i.e.* mechanical, growth-factors-related, neo-angiogenesis, supervene in HGG infiltration and evolution. This could also explain our different results in time of peak presentation since first diagnosis, associated with the unknown time of tumor onset. It would be interesting to analyze such variation in animal models, even if inoculation of glioma cells is an important bias in infiltration pattern study. A sudden increase in MTD as reported by VDE and Acc analysis, a biopsy and genetic analysis could be investigated and related if possible.

Conclusions

To our knowledge, this is the first study describing parameters of acceleration and VDE peak in a retrospective series of ex novo HGG. Through sequential MRIs and evaluation of these parameters, an early diagnosis of HGG could be done. In addition, time between consecutive MRI scans could be reduced to 15–20 days. This work represent a pilot study on new findings of HGG growth curve, never investigated, due to short observation time in case of HGG suspect. Despite limitations in number of patients and observation time, if our data are confirmed in larger series, such values could be helpful as prognostic factors in non-surgical patient. In an attempt to obtain further confirmations, a multicenter register could be create, where all data about long-preoperative-follow-up of HGG could be reported. Moreover, studies on in-vivo and in-vitro models could associate genome mutations with such phenotypical variation, looking for new biological tumor pathways of interest.

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research article

Tumoral volume measured preoperatively by magnetic resonance imaging is related to survival in endometrial cancer

Pluvio J. Coronado[1], Javier de Santiago-López[1], Javier de Santiago-García[2], Ramiro Méndez[3], Maria Fasero[4], Miguel A. Herraiz[1]

[1] Women's Health Institute José Botella Llusiá, Hospital Clínico San Carlos, Fundación de Investigación del Hospital Clínico San Carlos (IdISSC), Universidad Complutense, Madrid, Spain
[2] Service of Gynecology Oncology. MD Anderson Cancer Center Madrid, Spain
[3] Service of Radiology. Hospital Clínico San Carlos, Madrid, Spain
[4] Service of Obstetrics and Gynecology, Hospital Sanitas La Zarzuela, Universidad Francisco de Vitoria, Madrid, Spain

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Correspondence to: Pluvio J. Coronado, M.D., Ph.D., Instituto de Salud de la Mujer, Hospital Clinico San Carlos, C/Martín Lagos s/n, 28040, Madrid, Spain. E-mail: pcoronadom@sego.es

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Background. The aim of the study was to determine if the endometrial tumor volume (TV) measured by magnetic resonance imaging (MRI-TV) is associated with survival in endometrial cancer and lymph nodes metastases (LN+).

Patients and methods. We evaluated the MRI imaging and records of 341 women with endometrial cancer and preoperative MRI from 2008 to 2018. The MRI-TV was calculated using the ellipsoid formula measuring three perpendicular tumor diameters. Tumor myometrial invasion was also analyzed.

Results. Higher MRI-TV was associated with age ≥ 65y, non-endometrioid tumors, grade-3, deep-myometrial invasion, LN+ and advanced FIGO stage. There were 37 patients with LN+ (8.8%). Non-endometrioid tumors, deep-myometrial invasion, grade-3 and MRI-TV ≥ 10 cm^3 were the factors associated with LN+. Using a receiver operating characteristic [ROC] curve, the MRI-TV cut-off for survival was 10 cm^3 (area under curve [AUC] = 0.70; 95% CI: 0.61–0.73). 5 years disease-free (DFS) and overall survival (OS) was significantly lower in MRI-TV ≥ 10 cm^3 (69.3% *vs.* 84.5%, and 75.4% *vs.* 96.1%, respectively). MRI-TV was considered an independent factor of DFS (HR: 2.20, 95% CI: 1.09–4.45, p = 0.029) and OS (HR: 3.88, 95% CI: 1.34–11.24, p = 0.012) in multivariate analysis.

Conclusions. MRI-TV was associated with LN+, and MRI-TV ≥ 10 cm^3 was an independent prognostic factor of lower DFS and OS. The MRI-TV can be auxiliary information to plan the surgery strategy and predict the adjuvant treatment in women with endometrial cancer.

Key words: tumoral volume; magnetic resonance image; endometrial cancer; recurrence; survival

Introduction

Endometrial cancer (EC) is the most common malignant tumor of the female reproductive tract in developed countries. Its prevalence has increased worldwide in the last years.[1,2,3] In Spain, EC is the third most common cancer in women and the most common tumor of the female genital tract.[4]

Patient prognosis depends on different factors, including stage, depth of myometrial invasion (DMI), lymphovascular space invasion, grade, and nodal status. Besides molecular alterations, DMI is one of the most important morphologic prognostic factors, correlating with tumor grade, presence of lymph node (LN) metastases and survival.[5,6] Preoperatively, magnetic resonance imaging (MRI) can accurately assess the DMI[4], whereas histologic type and grade only can be determined with endometrial tumor sampling.

Standard surgical therapy for localized EC includes hysterectomy with bilateral salpingo-oophorectomy (HT & BSO); however, the criteria for selecting patients for lymphadenectomy (LND) are still controversial.[7,8] During the last two decades many authors have attempted to identify prognostic factors for stratifying women with EC into risk categories, in order to tailor the surgical and adjuvant treatment on the basis of estimated risk of tumor dissemination and recurrence.[7] Different investigators have defined low-risk groups consistent with disease confined to the uterine corpus, histologic grade 1 or 2, endometriod histologic subtype, less than 50% DMI and tumor diameter of 2 cm or less to avoid LND.[7,9,10] The LN evaluation is recommended in intermediate and high-risk EC.[8] However, recent matched-pair studies have observed a lack of survival benefit of the systematic LND in those types of EC.[11,12]

Although tumor size is a factor that determines the stage of disease in many types of cancer (head and neck, breast, lung, renal, uterine cervix, vulva, uterine sarcoma, melanoma and soft tissue sarcoma), it is not involved in defining the stage of EC.[13] Different authors have been trying to demonstrate the relationship between tumor diameter in resected uterine specimens and prognosis in EC.[9,10] Naturally, postoperative assessment is not suitable for taking decisions of the better surgical approach and for selecting patients for neoadjuvant therapies. Therefore, preoperative assessment impacts the planning for surgery.[14] Hence, some recent Japanese studies measured preoperatively tumor volumes by MRI, concluding that it is effective for predicting LN metastases and planning the LND.[15,16] However, there is no good evidence about the role of tumor volume (TV) measured by MRI in the patient's prognosis.

The aim of this study was to determine if the tumor volume measured in the preoperative MRI study (MRI-TV) has a relationship with disease-free survival (DFS) as a primary objective and with overall survival (OS) and LN involvement as secondary goals.

Patients and methods

A historical cohort of women diagnosed of EC between 2008 and 2018 was analyzed in Hospital Clinico San Carlos in Madrid, Spain. We included all women diagnosed of EC who underwent a presurgical MRI. All the patients had undergone HT & BSO. Pelvic or pelvic and para-aortic LND were always performed by the same oncological team. Women diagnosed with uterine sarcomas or concomitant neoplasm, those who had been treated with primary chemo and/or radiotherapy or had been operated without presurgical MRI were excluded. The study was approved by the local Institutional Review Boards (No. 16/443-E). All patients were managed according to the guidelines approved by the Spanish Society of Gynecology and Obstetrics and all of them signed a specific consent form.[17]

All MRI studies were performed in 1.5T magnets (Signa Excite and Signa HDx, General Electric Medical Systems) using a standard protocol. High-resolution T2 weighted images were acquired in three perpendicular planes and then contrast enhanced T1 fat suppressed series were acquired in two or three different planes. Diffusion weighted sequences (b ≥ 800 s/mm2) were acquired in most, but not in all the cases. All MR images were analyzed in the Radiology Service of the center by expert radiologists. The maximum tumor diameters were measured in three perpendicular axes, on the images that showed better the tumor-to-myometrium contrast (usually on the gadolinium enhanced series, having the T2 and diffusion images as references). The tumoral volume was calculated using the ellipsoid volume formula (length × height × width × [π/6]).

In addition, DMI was assessed following the standardized criteria using unenhanced T2 and gadolinium enhanced T1 series. DMI was defined as the distance between the myometrial interface and the deeper invasion point. Deep myometrial invasion was considered when the tumor affected 50% or more of the myometrial thickness.

In 237 cases in which it was the retrieved ultrasound reports, there was information about the DMI that was recorded and included. DMI was assessed during a real-time two-dimensional examination, and deep myometrial invasion was measured as the distance between endometrium-myometrium junction and maximum tumor depth.

In our center, intraoperative frozen section evaluation (FSE) of DMI is routinely performed. This information was available and recorded in 189 cases. Two pathologists with wide experience in gynecological cancers where the ones that performed the intraoperative assessment of myometrial invasion and histological grade in all of the samples.

Continuous variables were described as median and interquartile range [p25-p75] and were compared using the T-test in normal distributions or the Mann-Whitney test in non-parametrical dis-

tributions. Discrete variables were represented with absolute frequencies and percentages, and they were compared by the Chi-squared test or the Fisher's exact test in case of small cell comparisons. The McNemar test was used to assess the differences among the techniques evaluating the deep myometrial invasion. Receiver operating characteristic (ROC) curve was calculated to analyze the relation between the tumoral volume measured by MRI and the recurrence in order to identify the tumoral volume cut-off predicting the relapse. For survival analysis, Cox's method was used in order to assess which factors were directly associated with survival. Multivariate modeling using Cox's proportional hazard models, including the significant variables in univariate analysis, was performed to obtain a subset of independent predictors of DFS and OS. Hazard ratio (HR) with a 95% confidence interval (CI) was calculated. The Kaplan-Meier method was used to estimate the survival distribution depending on the tumoral volume using the cut-off chosen. The Log-Rank (Mantel-Cox) test was used to calculate the statistical signification between the groups in relation to disease recurrence and death. All statistical tests were 2-sided and statistical significance was defined as a *p*-value lower than 0.05. All computations were performed using IBM SPSS Statistic version 22.0 for Windows.

Results

The series baseline is shown in the Table 1. The highest accuracy for detecting DMI was the intraoperative FSE (sensitivity 94%, 95% CI: 88–100%) The MRI had sensitivity of 75%, 95% CI: 66–84% and transvaginal ultrasound 58%, 95% CI: 47–69 %, respectively. FSE was significantly more sensitive in detecting deep myometrial invasion than MRI (p = 0.049).

The median of MRI-TV was 8.2 cm^3 (interquartile range [IQR]: 1.9–20.4). We found that higher MRI-TV was associated with advanced age, the highest histological grade 3, deep myometrial invasion, advanced International Federation of Gynecology and Obstetrics (FIGO) stage, LN involvement, disease recurrence and death (Table 2).

In order to identify a MRI-TV cut-off that could be considered a risk factor in EC, we performed a ROC curve. The more efficient cut-off in detection of tumor recurrence was a TV = 10 cm^3, showing a 72.5% sensitivity and 59.8% specificity detecting the tumor recurrence (area under curve [AUC] = 0.70; 95% CI: 0.61–0.73).

TABLE 1. Baseline patient´s characteristics

Variable	N=341
Age (years)	65.7 [58.0–74.0]
< 65y	186 (54.5%)
≥ 65y	155 (45.5%)
BMI (kg/m2)	29.3 [24.8–33.0]
< 30	200 (58.7%)
≥ 30	141 (41.3%)
Histologic subtype	
Endometrioid	278 (81.5%)
Mucinous	5 (1.5)
Squamous	6 (1.8%)
Serous Papillary	23 (6.7%)
Clear cells	13 (3.8%)
Mixed mesodermal tumors	12 (3.5%)
Undifferenced	1 (0.3%)
Histological Grade	
G1	159 (46.6%)
G2	86 (25.2%)
G3	96 (28.25%)
Myometrial invasion	
< 50%	207 (60.7%)
≥ 50%	134 (39.3%)
FIGO stage	
I	270 (79.2%)
II	15 (4.4%)
III	45 (13.2%)
IV	11 (3.2%)
Surgical treatment	
HT & BSO alone	96 (37.4%)
With pelvic lymphadenectomy	74 (28.8%)
With pelvic & paraaortic lymphadenectomy	87 (33.9%)
Lymph nodes status (N = 216)	
Negatives	179 (82.9%)
Positives	37 (17.1%)
Adjuvant treatment	
None	150 (44.0%)
Irradiation	146 (42.8%)
Chemotherapy	9 (2.6%)
Irradiation and Chemotherapy	36 (10.6%)
Follow-up (months)	30.5 (18.5–46.2)
Recurrence	51 (15.0%)
Decrease	29 (8.5%)

Data are given as median and [interquartile range, p25-p75] or number (percentage).

BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics; HT & BSO = hysterectomy with bilateral salpingo-oophorectomy

Analyzing only the 216 cases in which LND was performed, we found that the LN involvement was associated with the histological subtype, grade 3 and DMI. MRI-TV ≥ 10 cm^3 was significantly associated with LN metastases (Table 3).

After a median follow-up of 30.5 months (IQR 18.5-46.2), 51 (15.0%) women presented a relapse and 29 (8.5%) deceased. Among the relapsed patients, 8 were alive and free of disease, 22 were alive with disease, and 21 died. Among the deceased patients, 21 women had disease-related death, and 8 died due to other causes.

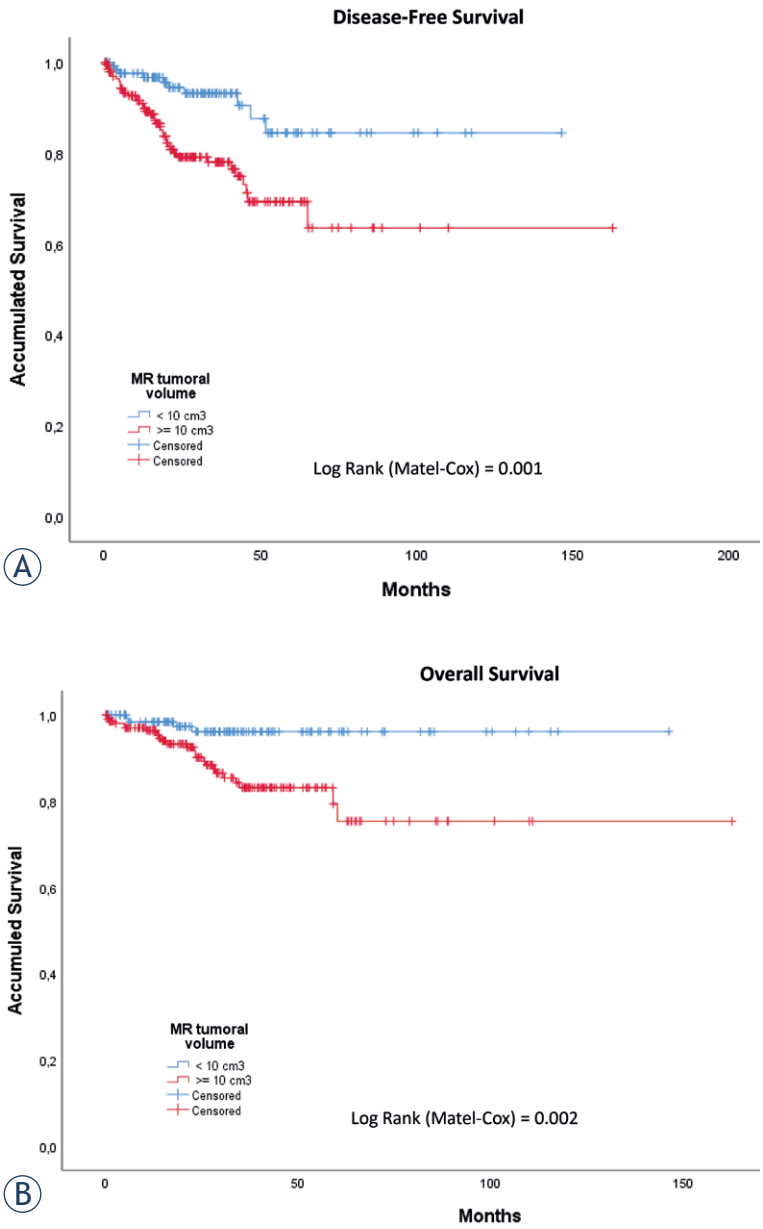

FIGURE 1. Kaplan Meier curves representing the survival in relation of tumoral volume measured by magnetic resonance. **(A)** Disease-free survival; **(B)** Overall Survival.

TABLE 2. Relation between tumor volume measured by magnetic resonance and pathological factors in 341 endometrial cancer

Variables	MR tumor volume cm3	p value*
Tumoral volume	8.2 (1.9–20.4)	-
Age (years)		
< 65	5.4 (1.5–15.4)	0.001
≥ 65	11.0 (2.8–30.0)	
BMI (kg/m2)		
< 30	9.1 (2.3–22.3)	0.525
≥ 30	7.5 (1.6–23.6)	
Histologic subtype		
Endometrioid	7.9 (1.8–20.4)	0.859
Non endometrioid	12.4 (3.3–40.1)	
Histological Grade		
G1–G2	6.7 (1.3–17.2)	< 0.001
G3	13.8 (4.6–41.0)	
Myometrial invasion		
< 50%	4.6 (1.2–15.4)	< 0.001
≥ 50%	14.1 (5.7–35.1)	
FIGO stage		
I–II	7.6 (1.5–19.6)	< 0.001
III–IV	15.6 (6.5–44.7)	
Lymph node status (N = 216)		
Negatives	9.3 (3.3–20.9)	0.008
Positives	15.6 (6.3–40.7)	
Recurrence		
No	7.6 (1.7–17.4)	< 0.001
Yes	22.4 (5.6–49.2)	
Overall Survival		
Alive	8.0 (1.8–18.6)	< 0.001
Death	30.5 (9.6–56.4)	

Data are gives as median (p25–p75).

* = Mann-Whitney U independent sample test; BMI = body mass index; FIGO = International Federation of Gynecology and Obstetrics

Survival analysis showed a 5-year DFS of 69.3% in tumors ≥ 10 cm³, which was significantly lower than in tumors of < 10 cm³ (84.5%, Log Rank test: 0.001) (Figure 1A). In relation to OS, 5-year OS survival was lower in tumors ≥ 10 cm³ in comparison with tumors < 10 cm³ (75.4% *vs.* 96.1%, Log Rank test: 0.002) (Figure 1B). Cox's univariate analysis identified the age (p < 0.001), MRI-TV (p = 0.001), non-endometrioid tumors (p = 0.006), grade-3 (p < 0.001), myometrial invasion (p = 0.009) and advanced stage (p < 0.001) as predicting factors of recurrence (Table 4). MRI-TV (p = 0.029), grade 3 (p < 0.001) and advanced stage (III–IV) (p = 0.047) were the independent factors of recurrence in the multivariate analysis (Table 5). In relation with OS, the age (p < 0.001), MRI-TV (p = 0.005), grade-3 (p = 0.001) and advanced stage (p = 0.001) were the predictor factors of mortality (Table 4). In multivariant analysis, MRI-TV (p = 0.012) and grade-3 (p = 0.011) were the independent factors of OS.

Discussion

In woman with EC, the preoperative MRI-TV correlates with the LN involvement and is an independent prognostic factor for DFS and OS in this series. A cut-off of 10 cm³ determines properly the cases that might present with positive LN and should undergo LND. It also adds information about poor prognosis and the need for adjuvant treatment. The relation between relapse and MRI-

TV in EC has been described by other studies. A Japanese study in 667 women with EC and using a volume index defined as the product of the maximum diameter in the 3 planes (longitudinal, anteroposterior and horizontal), found a MRI-TV ≥ 36 cm^3 as an independent prognostic factor of OS (HR 2.0; 95% CI:1.3–3.1).[18] This study used as cut-off a fixed value of MRI-TV based on other study from the same group[16], and considered the volume of the endometrial cavity as a single measure of three measures. In our study, the endometrial cavity was considered as ellipsoid, more like the real shape of the endometrial tumor. However, both studies have similar outcomes, suggesting the MRI-TV is an independent prognostic factor to take in consideration in the preoperative assessment of women diagnosed of EC. In addition, the MRI-TV in the Japanese study was significantly associated with LN involvement, especially when TV was ≥ 125 cm^3. Similar finding was also found in our study when we analyzed the MRI-TV both as continuous variable and as qualitative using 10 cm^3 as cut-off value. The differences in the cut-off may be because of the different method to measure the endometrial cavity. A Japan-Korea cooperative study with the same methodology, found similar results in 327 cases, showing a MRI-TV > 36 cm^3 as an independent prognostic factor of LN metastases.[19] Other studies analyzing the preoperative metabolic volume by PET/CT and MRI found the tumor volume as an independent prognostic factor for DFS and it was significantly associated with recurrence in patients with endometrioid EC.[20]

MRI has been considered as the best technique to diagnose deep myometrial invasion. However, in our series, the best option was FSE. A recent study found a higher performance using fusion of T2-weighted magnetic with diffusion-weighted MR images, with a sensitivity of 92.3% and specificity of 95.5% for deep myometrial invasion detection.[21] In relation to ultrasound, we obtained a poor result in order to detect the deep myometrial invasion. A recent study analyzing 210 women with proven EC found that both subjective assessment and objective ratios were significant predictors of the myometrial invasion, but subjective assessment was confirmed as the most reliable method to assess myometrial invasion (sensitivity 79% and specificity 73%).[22] A meta-analysis of 35 studies with 6387 women diagnosed of EC found that FSE had a significantly better diagnostic performance than intraoperative gross evaluation (sensitivity 84% *vs*. 71%) for the intraoperative diagnosis of deep myometrial invasion.

TABLE 3. Predictor factors of lymph node metastases in 216 cases of endometrial cancer with known lymph node status

Variables	No lymph node metastases N = 179	Lymph node metastases N = 37	*p* value
Age (years)			
< 65	78 (43.6%)	12 (32.4%)	0.211
≥ 65	101 (56.4%)	25 (67.6%)	
Histologic subtype			
Endometrioid	147 (82.1%)	23 (62.2%)	0.007
Non endometrioid	32 (17.9%)	14 (37.8%)	
Histological Grade			
G1–G2	118 (56.9%)	13 (35.1%)	< 0.001
G3	61 (43.1%)	24 (64.9%)	
Myometrial invasion			
< 50%	90 (50.3%)	8 (21.6%)	0.001
≥ 50%	89 (49.7%)	29 (78.4%)	
Maximum tumor size			0.390
< 2 cm	43 (24.0%)	6 (16.2%)	
≥ 2 cm	136 (76.0%)	31 (83.8%)	
MR tumor volume			
< 10 cm^3	61 (34.1%)	5 (13.5%)	0.013
≥ 10 cm^3	118 (65.9%)	32 (86.5%)	

TABLE 4. Analysis of disease-free and overall survival using Cox regression model

Variables	Disease-free	p value	overall	p value
Age (continue, years)	1.06 (1.03–1.09)	< 0.001	1.09 (1.05–1.13)	< 0.001
MRI tumor volume				
< 10 cm^3	1		1	
≥ 10 cm^3	2.99 (1.50–5.99)	0.001	4.50 (1.56–12.93)	0.005
Histologic subtype				
Endometrioid	1		1	
Non endometrioid	2.55 (1.30–5.01)	0.006	2.40 (0.97–5.95)	0.052
Histological Grade				
G1–G2	1		1	
G3	4.02 (2.31–6.98)	< 0.001	3.55 (1.71–7.37)	0.001
Myometrial invasion				
< 50%	1		1	
≥ 50%	2.10 (1.20–3.64)	0.009	1.89 (0.91–3.93)	0.088
FIGO stage				
I–II	1		1	
III–IV	6.70 (3.83–11.72)	< 0.001	3.94 (1.79–8.68)	0.001

Data are given in Hazard Ratio (95% confidence interval).

FIGO = International Federation of Gynecology and Obstetrics; MRI = magnetic resonance image

The tumoral size has been associated with several classic prognostic factors and it has been considered as a prognostic factor in many human tumors, including gynecological tumors such as cervix, vulva and breast, but not in ovarian and EC.[13] The Mayo clinic criteria in EC[9], suggested the tumoral size > 2 cm as high risk of LN metastases. In our series, the MRI-TV was associated with the classical prognostic factors in the EC. This finding was also found by other authors.[18,19] High-risk clinico-

TABLE 5. Multivariant analysis of disease-free and overall survival using Cox regression model with the classic histological prognostic factors

Variables	Disease-free survival	p value	Overall survival	p value
MRI tumor volume				
< 10 cm^3	1		1	
≥ 10 cm^3	2.20 (1.09–4.45)	0.029	3.88 (1.34–11.24)	0.012
Histologic subtype				
Endometrioid	1		1	
Non endometrioid	1.06 (0.50–2.24)	0.873	1.16 (0.43–3.16)	0.766
Histological Grade				
G1–G2	1		1	
G3	3.60 (1.95–6.66)	< 0.001	3.07 (1.47–6.41)	0.003
Myometrial invasion				
< 50%	1		1	
≥ 50%	1.77 (1.01–4.46)	0.047	1.51 (0.72–3.17)	0.279

Data are given in Hazard Ratio (95% confidence interval).

MRI = magnetic resonance image

pathological features (such as deep myometrial invasion, histological grade and non-endometrioid subtypes), LN involvement and advanced FIGO stages were increased with higher MRI-TV, suggesting a positive correlation between it and the adverse outcomes.

Sentinel node biopsy is a good way to have LN status information and to avoid the complete LND.[23] However, this procedure is not free of complications and a preoperative information predicting the LN involvement could help in the process of making the decision of whether or not to perform the LN assessment. Based on our results, we suggest performing a LN assessment in EC with large TV. Nevertheless, we cannot set the best TV cut-off from which assess the LN status.

In our study, the TV was measured by different radiologist, and even though we used the same criteria, it could be a limitation because of the inter-observer variability that can alter the endometrial measures. On the other hand, the type of adjuvant treatment and the type of surgery could differ between the cases and this could have influenced the patients' survival. The main strength of this study, with respect to others that also analyzed the TV, is the use of an ellipsoid to measure the TV, because is the shape more similar to endometrial cavity, and the result of the product of three single measures results on a cubic shape.

Conclusions

In conclusion, the TV measured by MRI is a predictor of high-risk pathological factors, and it is positively associated with LN involvement. The TV higher than 10 cm^3 is related with poor prognosis in univariate and multivariate analysis. The preoperative measure of TV by MRI can therefore be a good tool to determine the best surgery strategy in EC.

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research article

Trends in population-based cancer survival in Slovenia

Vesna Zadnik[1], Tina Zagar[1], Katarina Lokar[1], Sonja Tomsic[1], Amela Duratovic Konjevic[2], Branko Zakotnik[1]

[1] Epidemiology and Cancer Registry, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Institute of Oncology Ljubljana, Ljubljana, Slovenia

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Correspondence to: Prof. Vesna Zadnik, M.D., Ph.D., Zaloška 2, SI-1000 Ljubljana, Slovenia. E-mail: vzadnik@onko-i.si

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Background. The aim of our study was to describe the survival of Slovenian cancer patients diagnosed in the last twenty years. An insight is given into the improvement made in different cancer types, population groups and prognostic factors.

Materials and methods. The principal data source was the population-based Slovenian Cancer Registry. The survival analysis included patients diagnosed with cancer in twenty years period from 1997 to 2016, which has been divided into four consecutive five-year periods. In addition, the analysis was stratified by cancer type, gender, age and stage. The survival was estimated using net survival calculated by the Pohar-Perme method and the complete approach has been applied.

Results. The survival of Slovenian cancer patients has been increasing over time. During the 20 years observed, five-year net survival increased by 11 percentage points. Significantly higher growth was observed in men. Age and stage at diagnosis are still crucial for the survival of cancer patients. Five-year net survival is lowest in those over 75 years of age at diagnosis but has also improved by seven percentage points over the past 20 years. The five-year net survival of patients in the localized stage increased by ten percentage points over the 20 years under observation. Survival of patients in the distant stage has not been improving. In both sexes, survival for melanoma, colorectal and lung cancers have increased significantly over the last 20 years. Progress has also been made in the two most common gender specific cancers: breast cancer in women and prostate cancer in men. Still, the significant progress in prostate cancer is probably mostly due to lead-time bias as during the study period, Slovenia used indiscriminate PSA testing, which probably artificially prolonged survival.

Conclusions. The survival of Slovenian cancer patients has been increasing over time, which gives us a basis and an incentive for future improvements. To monitor the effectiveness of managing the cancer epidemic, the cancer burden needs to be monitored also in the future, using quality data and scientifically justified methodological approaches. In this process a well organised population-based cancer registries should play a key role.

Key words: cancer burden; cancer survival; time trend; Slovenian Cancer Registry

Introduction

Global health indicators show that cancer is an epidemic of modern times. Epidemiological indicators from Slovenian Cancer Registry confirm similar situation also in Slovenia. Among all causes of death, it ranks 1st in men and 2nd in women. In recent years, 15,000 Slovenes per year have developed cancer, and slightly over 6,000 have died of cancer. There are more than 120,000 people living in Slovenia who had ever been diagnosed with cancer. Since cancer is more common among the elderly (only a third of patients are younger than 65 years at the time of diagnosis), and the Slovenian

population is ageing, it is expected that the burden of this disease will increase, even if the level of risk factors remains the same as today.[1,2]

Continuous and systematic collection, storage and analysis of data on all cancer patients in a defined population is the basis for controlling this major public health problem – a key role is played by population-based cancer registries. One of their main purpose is to collect accurate and complete cancer data that can be used to plan and evaluate the National Cancer Control Programmes, specifically in the fields of primary and secondary prevention, diagnostics, treatment and rehabilitation and palliative care, to plan the capacities and resources needed to manage cancer (staff, medical equipment, hospital and rehabilitation facilities).[3] Incidence, mortality and survival are the main cancer burden indicators that are reported by the population-based cancer registries. Cancer mortality is the primary indicator of the cancer burden worldwide, since it is available for the largest number of countries. Mortality depends on the number of new patients (incidence) on one hand and on their survival on the other. Survival itself does not depend on the incidence, as it considers only those who have already fallen ill, so it indirectly indicates the success of diagnosis and treatment (in patients with earlier diagnosed disease and prompt treatment according to guidelines, a better survival is expected) and is considered as the most powerful indicator. The population survival of cancer patients, as shown by cancer registries is, therefore, a composite indicator. It reflects the characteristics of patients as well as the organization, accessibility, quality, and efficiency of the healthcare system. Clinical studies usually present the results of survival of groups of patients with a specific disease and for specific well-defined treatment, where strict entry criteria for the study group are defined, such as stage, performance status 0 or 1, normal organ function, age under 70 years etc. Population data on survival significantly differs from that. Population survival is affected, for example, by the disease stage at diagnosis, which depends on the time length from the first signs to the visit of general practitioner and further to the time of diagnosis. This time may be reduced through informing the population about when to visit a physician in case of health problems and the ability of general practitioners to consider the possibility of a serious disease, through increasing the availability of diagnostic tests, and minimising waiting times. The availability of screening programmes with proved benefit further increases the chances of cure or at least better survival, as they detect precancerous lesions or early-stage of the disease. Once diagnosed, the success of treatment depends on the type of cancer, the patient's characteristics (age, comorbidities, general physical performance, etc.) and also on the availability of multidisciplinary treatment and the qualifications of the medical team. All of these diverse factors that determine population survival must be considered by the researcher or clinician who interprets the results of population survival studies, and even more so when comparing survival between countries.[4]

In this study we are presenting the survival of Slovenian cancer patients diagnosed in the last twenty years. An insight is given into the improvement that was made in different cancer types, different population groups (gender and age) and stage at diagnosis. The survival improvements support reported ongoing progress achieved by Slovenian oncology and Slovenian healthcare system. The results of survival analysis are further discussed in the comprehensive report, which contains also insights from clinical experts who are involved in specific treatment of cancer patients in Slovenia.[5]

Materials and methods

The principal data source for the analysis is the population-based Slovenian Cancer Registry (SCR). Thus, the data refer to all cancer patients, residents of Republic of Slovenia at the time of diagnosis, irrespective of where they have been diagnosed, treated or where they have died. The SCR's quality and completeness indices prove that cancer registration in Slovenia adequately covers the entire population.[6] To assure completeness and to obtain additional information on registered cancer cases, SCR is linked with several governmental and health databases. Synchronisation of data between different sources is based on unique personal identification number, which is assigned to every resident in Slovenia and recorded in every state registry including SCR. Using unique personal identification number guaranties data integrity, data quality and prevents duplication. SCR is linked with the Central Register of Population through secure on-line connection (24/7 availability) and daily updates information on vital status and address for each person registered by SCR. The electronic linkage to the national Mortality Database and to the breast, colorectal and cervical screening registries is performed at least once per year.[6,7]

The data on gender, date of diagnosis, age at diagnosis, code of primary site according to the International classification of Diseases (10th edition), stage at diagnosis (general categorization into localized, regional or distant stage) and vital status with the date of end of follow-up (date of death, date of lost to follow-up or date of the end of study) were extracted from the SCR's database for all cancer cases. The survival analysis included patients who were diagnosed with cancer in the years from 1997 to 2016. The entire observed period has been divided into four consecutive five-year periods. The patients older than 95 years of age were excluded from survival analysis. Separate analyses were made for children (0–14 years), adolescents (15–19 years) and adults (20–94 years).

All analyses were performed on data registered in the SCR database on 1st September 2019 and 234,827 cases of cancer were extracted from the database. Among them, there were 37,917 non-melanoma skin cancer patients. Because this is a frequent but almost completely curable disease, we excluded these patients from the analysis. Further, we excluded 1,711 cases of cancer being registered by death certificate only, since the date of diagnosis is unknown, 4,470 cases in which the date of registration was the same as the date of death (mostly they are diagnosed at autopsy), and 668 cases in which the person was 95 years of age or older. The vital status of patients was last checked on 31st August 2019. At the end of the observation period, the person can be alive, dead or lost from the vital statistics records. Between 1997 and 2001, 26 persons with no follow-up data in the Central Register of Population were registered in the SCR (0.06% of 45,390 new cancer cases during this period) and only 3 persons with no follow-up data between 2002 and 2016 (0.002% of 189,437).

In the group of patients, the survival is interpreted as the proportion of patients who are still alive after a certain time from the diagnosis. Survival time is defined as the time between the date of cancer diagnosis and the date of the end of follow-up. The survival was estimated using net survival calculated by the Pohar-Perme method. Net survival is the survival that would be observed if the only cause of death was the disease we are studying, i.e. causal specific survival. For example, a net survival of 30% over five years tells us that in a hypothetical case where patients would die only from cancer and no other causes, 70% of those patients would die within five years from diagnosis.[8,9] Because all the included patients were not followed-up for five years we have applied the complete approach in the survival calculation.[10] For the calculation, we used the *relsurv* library for the R software environment.[11]

Results and discussion

There were 191,154 patients aged 20 to 94 years diagnosed between 1997 and 2016 with any cancer (non-melanoma skin cancer excluded). Throughout the observed period, slightly more men than women were diagnosed, of which most were aged from 50 to 74 years. In solid tumours, the disease was mostly detected in the localized stage. The five most frequent cancers in Slovenia – non-melanoma skin, prostate, colorectal, breast and lung cancer – account for 60% of all new cancer cases.[1]

Survival of cancer gradually increased in relation to the year of diagnosis. Over the 20-year period, five-year net survival increased by slightly less than 11 percentage points (Figure 1). The rise is in concordance to observed in our last three reports on survival of Slovenian cancer patients diagnosed with cancer between 1963–1990, 1983–1997 and 1995–2005.[12,13,14] According to the CONCORD-3 study which compared the five-year net survivals of adult patients with 15 different cancers between 2010 and 2014 in 26 European countries, in most cases the survivals of Slovenian cancer patients are below the European average.[14]

As presented in Table 1, in the first observed period, between 1997 and 2001, the net five-year survival for all cancers combined was much better for women than for men, with a difference of 16 percentage points. In the 20-year period significantly higher growth was observed in men, where five-year net survival increased by 17 percentage points (from 38% to 56%). In women, five-year net survival increased by six percentage points (from 54% to 60%). At a first glance, it seems that men have started to take better care of their health and that the 'macho' male population (refusing to see a doctor) is disappearing. Undoubtedly, breast and prostate cancer, which represent as many as a fifth of all cancer patients in men and women, contribute the most to reducing the gap between the genders. A large proportion of the increase in survival in men can be attributed to the survival of patients with prostate cancer, where it rose by as much as 21 percentage points (Table 1). However, this significant progress in prostate cancer survival is probably mostly artificial (lead time bias), since we used indiscriminate PSA testing in Slovenia quite uncritically during the study period, with which we also detected those prostate cancers that devel-

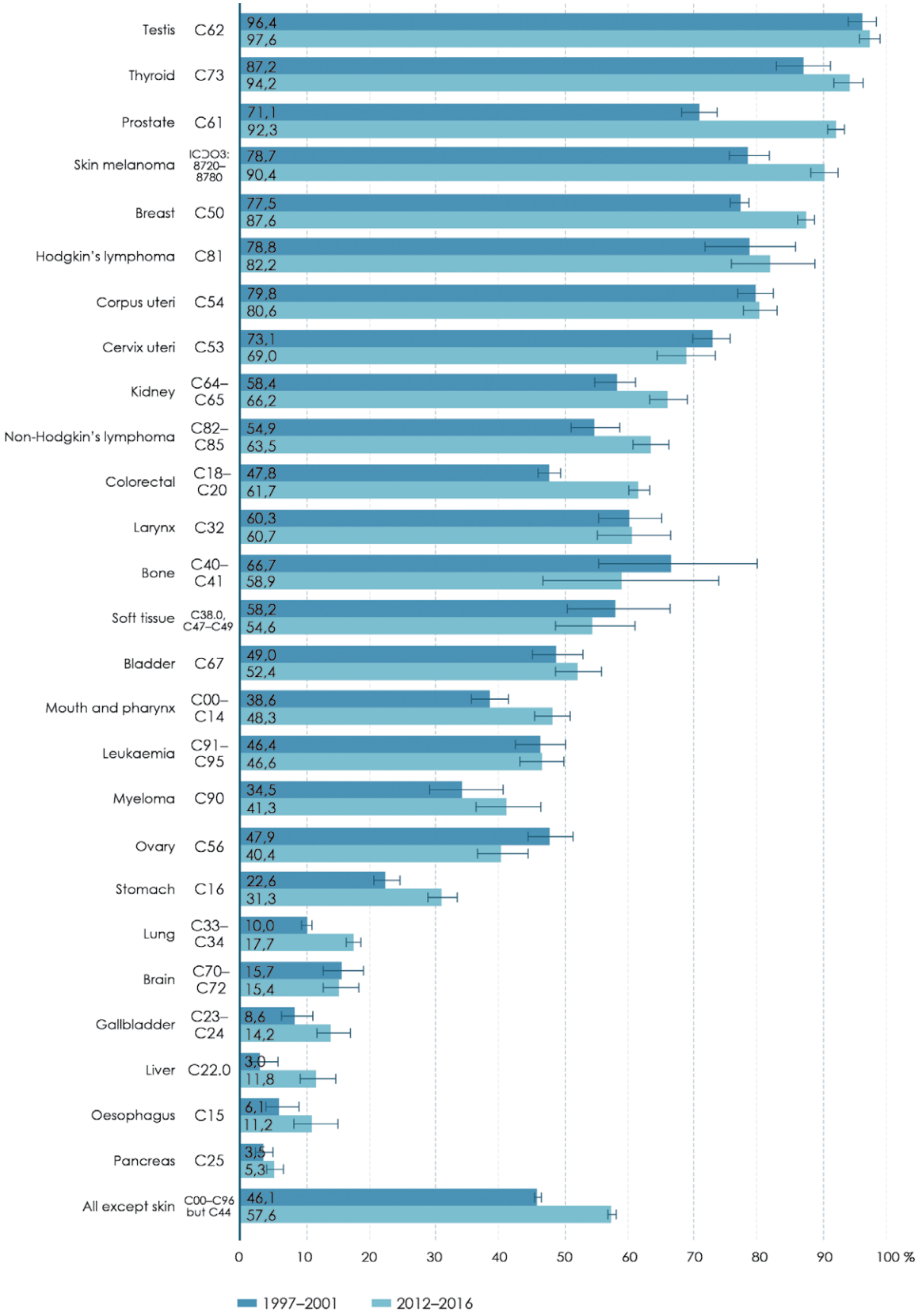

FIGURE 1. Five-year net survival (with a 95% confidence interval) of adult patients (20–94 years) with selected cancers, Slovenia 1997–2001 and 2012–2016.

TABLE 1. Five-year net survival (with a 95% confidence interval) of adult patients (20–94 years) with selected cancers by sex, Slovenia 1997–2001 and 2012–2016

Cancer type	Male				Female			
	1997–2001		2012–2016		1997–2001		2012–2016	
	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval	Five-year net survival	95% confidence interval
C00-C14 Mouth and pharynx	34.4	31.6-37.3	43.6	40.6-46.8	61.1	53.8-69.4	65.2	58.5-72.8
C32 Larynx	59.4	54.4-64.9	62.1	56.3-68.4	67.9	55.2-83.5	51.5	38.6-68.5
C15 Oesophagus	5.1	3.2-8.1	10.5	7.5-14.9	8.2	3.7-18.3	14.2	8.0-25.1
C16 Stomach	20.7	18.4-23.4	31.6	28.8-34.7	25.4	22.4-28.9	30.7	27.3-34.7
C18-C20 Colon and rectum	47.1	44.9-49.5	63.1	61.1-65.2	48.7	46.3-51.2	59.7	57.4-62.1
C22 Liver and intrahepatic bile ducts	2.9	1.3-6.4	12.3	9.5-15.9	3.4	1.0-11.6	9.1	4.8-17.1
C23-C24 Gallbladder and billiary tract	11.9	8.0-17.5	14.7	11.2-19.3	6.5	4.3-9.9	13.7	10.6-17.8
C25 Pancreas	4.3	2.7-4.8	4.7	3.4-6.6	2.8	1.7-4.8	6.0	4.5-8.0
C33-C34 Trachea, bronchus and lung	9.6	8.6-10.7	15.5	14.3-16.8	11.4	9.5-13.6	22.1	20.2-24.1
C38.0, C47-C49 Connective and soft tissue	61.3	51.1-73.7	58.0	48.9-68.7	55.0	45.1-67.0	52.0	44.8-60.3
C40-C41 Bone	66.7	52.3-85.1	65.7	48.9-88.3	66.0	50.7-86.1	51.8	36.5-73.3
C43 Malignant melanoma of skin	75.4	70.9-80.3	90.0	87.0-93.2	81.8	77.9-85.8	90.8	88.0-93.7
C50 Breast	-	-	-	-	77.5	76.0-79.0	87.6	86.3-88.9
C53 Cervix uteri	-	-	-	-	73.1	70.2-76	69.0	64.7-73.7
C54 Corpus uteri	-	-	-	-	79.8	77.1-82.6	80.6	78.0-83.3
C56 Ovary	-	-	-	-	47.9	44.5-51.6	40.4	36.7-44.5
C61 Prostate	71.1	68.4-73.8	92.3	91.0-93.7	-	-	-	-
C62 Testis	96.4	94.2-98.7	97.6	95.9-99.3	-	-	-	-
C64-C65 Kidney with renal pelvis	56.5	52.1-61.3	64.6	61.1-68.3	61.4	56-67.4	69.3	64.8-74.1
C67 Bladder	48.5	44.1-53.2	55.3	51.3-59.6	50.5	42.9-59.4	44.4	38.4-51.3
C70-C72 Central and autonomic nervous system	13.2	9.8-17.9	15.8	12.4-20.1	18.7	14.2-24.7	15.0	11.4-19.7
C73 Thyroid gland	88.1	79.5-97.7	90.6	85.1-96.4	86.6	82.1-91.4	95.3	92.7-97.9
C81 Hodgkin's lymphoma	78.3	69.3-88.5	78.3	69.2-88.5	79.0	69.5-89.7	85.7	77.3-95.1
C82-C85 non-Hodgkin's lymphoma	55.1	49.8-60.9	65.7	61.9-69.8	54.7	49.8-60.1	61.3	57.6-65.2
C90 Multiple myeloma and malignant plasma cell neoplasms	36.8	28.9-46.9	38.9	32.6-46.4	32.8	26.4-40.7	44.0	37.5-51.5
C91-C95 Leukaemias	49.8	44.7-55.4	46.0	41.8-50.6	41.6	36.2-47.9	47.2	41.9-53.0
C00-C96 (but C44) All sites, but skin	38.4	37.6-39.2	55.8	55.0-56.5	54.3	53.4-55.1	59.9	59.1-60.6

op slowly and would not cause health problems for men during their lifetime. This artificially prolongs survival, as the disease is detected earlier, but the course of the disease is not changed.[15] However, the most common cancer in women, breast cancer, has not seen such a large improvement in survival (Table 1). The breast cancer screening programme was introduced across the whole country only in 2018, so it could not make a significant contribution to the results of our current analysis.[16]

In both sexes, survival for other three common cancers have increased significantly over the last 20 years: colorectal cancer (by 14 percentage points, from 48% to 62%), cutaneous melanoma (by 11 percentage points, from 79% to 90%), and lung cancer (by 8 percentage points, from 10% to 18%) (Figure 1). These results reflect earlier diagnostics and advances in systemic treatment. Despite treatment progress, the survival of lung cancer patients remains low. There are some other cancers where almost no progress over time was observed and in which survival remains low including pancreatic, oesophageal, gallbladder and bile duct, liver and brain cancers.

Age and stage at diagnosis are prognostic factors for disease development and treatment outcome and also for the survival of cancer patients. The survival of persons aged 20 to 49 was better in the last two periods compared to other age groups and improved by 15 percentage points in period 2012 to 2016 compared to the period 1997 to 2001 (Figure 2). Five-year net survival is lowest in those over 75 years of age but also in this age group has improved by seven percentage points over the last 20 years. The number of older patients with cancer is increasing in Slovenia, for example, the number of patients aged over 75 has more than doubled in the analysed period.[17] It is precisely these patients who most frequently have comorbidities that can severely limit attainability of specific oncological treatment, which explains why the proportion of patients without specific oncological treatment remained roughly the same through time despite the increasingly complex treatments available - around 20% according to the last SCR's report on cancer patient's survival.[5] We can conclude that doctors equally often decide to treat elderly patients, although more complex treatments are often accompanied by many more side effects. Consequently, as seen from our analysis in the last three time periods, the five-year net survival of the oldest group of patients still remained almost the same, while in the younger groups it increases steadily and significantly. Apparently, the age and concomitant diseases are a wall that we cannot scale with today's treatments.

The importance of the stage at diagnosis cannot be overemphasised. The five-year net survival of patients diagnosed with solid tumours in localized stage increased by 10 percentage points over the 20 years of observation and reached 85% in the last period. Five-year net survival of patients diagnosed with cancer in regional stage approaches 55%, whereas in patients diagnosed with cancer in distant stage it is only slightly below 25% and does not improve statistically significantly through time (Figure 3). Despite a number of new insights into prognostic and predictive factors and with the advancement of molecular biology which enabled more effective treatments, the classical stage of TNM remains the basic predictor of disease progression and survival (together with the age of cancer patient). Reporting the stage in cancer registries is historically simplified into three groups: localized, regional, and distant disease. Results show, that nowadays the disease is more frequently diagnosed in the localized stage and less often in the regional stage; the percentage of patients with distant disease remains the same. This is partly due to more accurate and accessible diagnostic methods that allow detecting more and smaller distant lesions despite on a whole the diagnostic is done earlier.

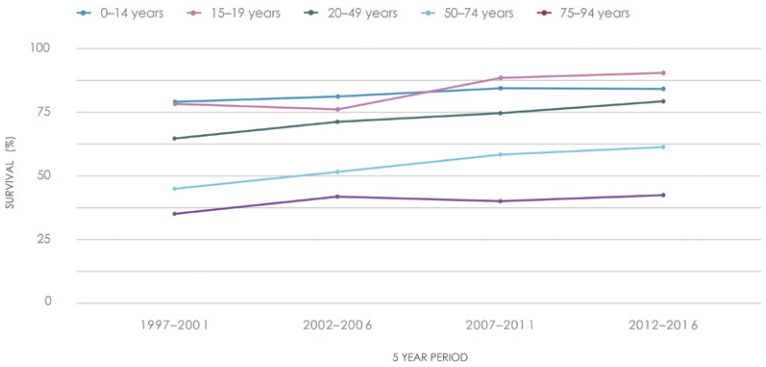

FIGURE 2. Five-year net survival of patients with cancer (all sites but non-melanoma skin cancer) by age group, Slovenia 1997–2016.

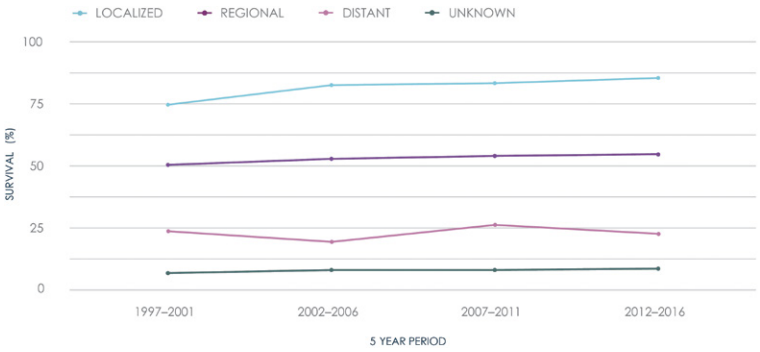

FIGURE 3. Five-year net survival of patients with cancer (all solid tumours but non-melanoma skin cancer) by stage at diagnosis, Slovenia 1997–2016.

From our analysis, we can conclude that the improvement in survival can be explained by the disease being diagnosed at an earlier stage and is not just the consequence of the stage-shift described above. This is certainly the case for the last period for colorectal and breast cancers. For all patients who respond to the screening invitation, the five-year risk of death is four to five times lower than for those who do not respond to the invitation, due to the disease being diagnosed at a lower stage.[18] Of course, survival is not a measure of the success of a screening programme (it's biased due to time advantage), but treatment of the disease at an earlier stage undoubtedly affects recovery and consequently cause specific mortality. Successful screening programmes and high population responsiveness are therefore improving survival.

Although rarely, cancer is diagnosed in children as well. In the present survival analysis, we included

TABLE 2. Five-year net survival of children (0–14 years) and adolescences (15–19 years) with cancer by period of diagnosis, sex, age group and stage at diagnosis for solid tumours, Slovenia 1997–2016

Period of diagnosis	Gender		Age at diagnosis				Stage (C00-C80)			All
	Male	Female	0–4 year	5–9 year	10–14 year	15–19 year	Localized	Regional	Distant	
1997 – 2001	205	146	93	48	78	132	116	59	20	351
2002 – 2006	180	149	96	49	51	133	114	52	21	329
2007 – 2011	170	161	89	53	69	120	126	33	18	331
2012 – 2016	200	168	104	74	56	134	144	53	27	368

1,379 children and adolescents (aged 0 to 19 years) diagnosed in Slovenia in the target period 1997 to 2016. The net survival has been gradually increasing with respect to the year of diagnosis. For example, the five-year net survival for all childhood cancers combined increased by almost 8 percentage points and exceeded 85% in the last period 2012–2016 compared to the first period 1997–2001 and being less than 30% fifty years ago.[12,19] There is a significant difference in the survival among patients with different cancer sites: patients with malignant brain tumours survived five years in 70%, those diagnosed with leukaemia in 88%, but all of those diagnosed with lymphomas survived five years in 98%. The 20-year improvement was the highest in lymphomas – for 12 percentage points. Clearly, the malignant diseases in children are heterogeneous group and a retrospective analysis of factors contributing to the observed improvement in survival is difficult. In Slovenia, all children suspected of having cancer undergo a diagnostic workup and treatment in a single national paediatric centre, which positively affects their survival along with developments in diagnostics and treatment.[19,20]

Similarly, as in adults, boys achieve slightly lower survivals than girls, but the gap between the sexes has been narrowing over time (Table 2). Five-year net survival was similar in children and in adolescents in all observed periods (Figure 2, Table 2). In the first two observed periods, between 1997 and 2006, it was slightly better in the 0 to 14 years age group, and in the last two periods, between 2007 and 2016, it was reversed being better in the 15–19 age group. In the last observed period, from 2012 to 2016, it reached 85 and 91% for children and adolescents, respectively. The five-year net survival of children and adolescents with solid tumours with localized and regional stage disease exceeds 85% in the last ten years. In children and adolescents with distant disease at diagnosis, the five-year net survival approaches 70% (Table 2).

Conclusions

Population-based cancer survival is a composite indicator reflecting the characteristics of patients as well as the organisation, accessibility, quality, and efficiency of the healthcare system. This analysis is the starting point of our fourth comprehensive report on the survival of Slovenian cancer patients[5] and shows the progress of Slovenian oncology and healthcare, as well as Slovenian general attitude towards cancer over the last twenty-year period. As we determined, the survival of Slovenian cancer patients has been increasing over time, which gives us a basis and an incentive for future improvements. In addition, the lag in survival of Slovenian cancer patients in comparison with the patients from other European health systems identified in some cancers in the CONCORD-3 study[14] and in the last EUROCARE study[21]provides us with a legitimate basis for considering improvements in the future.

The National Cancer Control Programme delivers a comprehensive set of activities in the fields of primary and secondary prevention, diagnostics, treatment and rehabilitation, as well as palliative care. Therefore, in order to reduce the cancer burden and improve the quality of life and economic sustainability, all evidence-based primary and secondary prevention programmes must be established and used, and evidence-based treatment implemented in scientifically acceptable time frames. The development of medical science, oncology and molecular biology in the last 20 years has brought many revolutionary insights into the field of oncology, which undoubtedly have had an impact and will have an even more significant impact on the survival of cancer patients in the future. To monitor the effectiveness of managing the cancer epidemic of today, also in the future the burden of cancer will need to be monitored based on quality data and scientifically justified methodological approaches both provided by established cancer

registries. Further on, cooperation between oncological epidemiologists and clinical specialists is crucial for a comprehensive review and preparation of proposals for improvement.

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research article

Completely resected stage III melanoma controversy - 15 years of national tertiary centre experience

Barbara Peric[1,2], Sara Milicevic[1], Andraz Perhavec[1,2], Marko Hocevar[1,2,3], Janez Zgajnar[1,2]

[1] Department of Surgery, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] Faculty of Medicine, University of Maribor, Maribor, Slovenia

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Correspondence to: Assist. Prof. Barbara Perić, M.D., Ph.D., Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia. E-mail: bperic@onko-i.si

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Background. Two prospective randomized studies analysing cutaneous melanoma (CM) patients with sentinel lymph node (SLN) metastases and rapid development of systemic adjuvant therapy have changed our approach to stage III CM treatment. The aim of this study was to compare results of retrospective survival analysis of stage III CM patients' treatment from Slovenian national CM register to leading international clinical guidelines.

Patients and methods. Since 2000, all Slovenian CM patients with primary tumour ≥ TIb are treated at the Institute of Oncology Ljubljana and data are prospectively collected into a national CM registry. A retrospective analysis of 2426 sentinel lymph node (SLN) biopsies and 789 lymphadenectomies performed until 2015 was conducted using Kaplan-Meier survival curves and log-rank tests.

Results. Positive SLN was found in 519/2426 (21.4%) of patients and completion dissection (CLND) was performed in 455 patients. The 5-year overall survival (OS) of CLND group was 58% *vs.* 47% of metachronous metastases group (MLNM) (p = 0.003). The 5-year OS of patients with lymph node (LN) metastases and unknown primary site (UPM) was 45% *vs.* 21% of patients with synchronous LN metastasis. Patients with SLN tumour burden < 0.3 mm had 5-year OS similar to SLN negative patients (86% *vs.* 85%; p = 0.926). The 5-year OS of patients with burden > 1.0 mm was similar to the MLNM group (49% *vs.* 47%; p = 0.280).

Conclusions. Stage III melanoma patients is a heterogeneous group with significant OS differences. CLND after positive SLNB might still remain a method of treatment for selected patients with stage III.

Key words: cutaneous melanoma; sentinel node biopsy; completion lymph node dissection; overall survival

Introduction

Since Morton has introduced the concept of sentinel lymph node (SLN) biopsy, the procedure had been a central part of cutaneous melanoma (CM) treatment. The information about SLN metastases is considered as one of the most important indicators of recurrence and survival of CM patients.[1,2] Completion lymph nodes dissection (CLND) was offered to patients with positive SLN despite significant morbidity which is only slightly lower in case of CLND compared to therapeutic lymphadenectomy.[3] Common belief was that at least 20% of patients with positive non-SLN would benefit from that kind of treatment.[4]

Despite all attempts to prove otherwise, two prospective randomised studies conducted in recent years have shown that CLND does not improve survival of patients with positive SLN compared to follow up of the nodal basin with ultrasound (US).[5,6]

Although there was no significant improvement of overall survival (OS), the MSLT-2 study did indicate, that immediate CLND offers better regional

control and that non-SLN burden is an independent prognostic indicator for recurrence (hazard ratio [HR]: 1.78; p = 0.005).[5]

In years to follow, studies comparing systemic adjuvant treatment of CM to those receiving placebo after surgical treatment have shown improved regional relapse free survival (RFS) and OS in patients with targeted therapy.[7-9] That knowledge combined with results of MSLT-II and DeCOG led clinicians to belief, that CLND in patients with positive SLN is no longer warranted.[10]

But group of stage III patients is one of the most heterogeneous groups with expected 5-year OS ranging from 30–60% and adjuvant systemic therapy is potentially toxic and costly.[11,12] In case of first reported adjuvant systemic therapy trial, 43% of patients receiving ipilimumab had grade 3 or 4 side effects but in later studies, the percentage has dropped to approximately 14%.[7,8] Toxicity rates have dropped and at the same time 1-year RFS has increased to 70.5% in completely resected stage III CM patients treated with anti-PD-1 agent nivolumab and 75.4% in case of adjuvant pembrolizumab.[13] But one has to keep in mind that individual costs of adjuvant immunotherapy treatment in our country can reach up to 67.000 Euros per year. How to make adjuvant systemic treatment combined with suitable follow up of regional lymph node basin available to all patients are nowadays concerns of many clinicians.

Perhaps additional piece of information is hiding in the SLN burden. Studies in the past have associated SLN burden of > 1 mm with significantly worse outcome and a need for adjuvant systemic treatment. On the other hand different studies were not able to confirm the minimal SLN burden as reproducible factor for excellent survival at all sites. Despite that it seems, that burden of < 0.1 mm is associated with 5-year survival of 83–91%, with non-SLN positivity rates between 0 and 12%.[14]

The aim of our study was to compare survival based on retrospective analyse of stage III CM from national CM base to current understanding of lymph node surgery.

Patients and methods

Data of CM patients treated at the Institute of Oncology Ljubljana (OI) were prospectively collected into clinical melanoma registry. Data of SLN biopsy procedures were collected since January 2000, the year of the SLN biopsy introduction in Slovenia. Complete lymph node dissection data were registered since 2003. In Slovenia all CM surgical procedures (with exclusion of skin biopsy) are performed at the OI. Clinical melanoma registry of the OI serves as a substitute of the national CM database.

Data of 2426 patients with CM (CM ≥ TIb based on confirmed histology) undergoing SLN biopsy at the OI between 2000 and 2015 were analysed. The SLN biopsy procedure was performed according to established recommendations.[15] During described period, gross and microscopic examination of SLN was performed by 4 dedicated pathologists at the institute using SLN protocol that has been adopted by the EORTC as the standard procedure for pathological handling of SLN for CM.[16] The false negative rate (FNR) was defined as false negative/true positive combined with false negative. All patients with positive SLN and performance status ECOG 0–2, who agreed to further surgical treatment, underwent CLND. Altogether there were 455 patients with positive SLN and CLND.

To that number we added the analysis of 149 patients with synchronous primary CM and clinically detected regional lymph node metastasis (SLNM), 121 patients with metachronous primary CM and regional lymph node metastasis (MLNM), and 64 patients with melanoma of unknown primary site (UPM). Synchronous metastases were defined as metastases detected clinically prior to surgery or occurring within 6 months of the initial CM diagnosis. Patients with first recurrence of the disease in the regional lymph node basin later in course of the disease were classified to the MLNM group. UPM was defined as clinically detected and histologically confirmed nodal melanoma metastases with no evidence of primary lesion. Patients with synchronous nodal and in-transit metastases were excluded from the study as were patients with previously excised pigmented skin lesion without proper histological evaluation. Finally, data of 789 patients after complete lymph node dissection divided in four groups (CLND, SLNM, MLNM and UPM) operated between 2003 and 2015 were retrospectively analysed.

The date of study closure was January 15th 2019. Data were summarized as mean ± SD, unless otherwise specified. Chi-square test was used for categorical variables while quantitative variables were compared using Kruskal-Wallis test. Overall survival (OS) time was calculated from the date of the excision of primary lesion (or the date of lymph node dissection in the case of UPM) to the date of death and censored at the closing date for survivors. Survival analyses were performed

TABLE 1. Demographics of sentinel lymph node biopsy (SLNB) group

	Negative SLN No. (%)	Positive SLN No. (%)	Unfound SLN No. (%)	All SLNB No. (%)
Number of patients	1837(75.7)	519 (21.4)	70 (2.9)	2426 (100.0)
Tumour site				
Head	174 (9.5)	34 (6.6)	21 (30.0)	229 (9.4)
Neck	30 (1.6)	6 (1.2)	7 (10.0)	43 (1.8)
Trunk	857 (46.7)	268 (51.6)	30 (42.9)	1155 (47.6)
Limbs	776 (42.2)	211 (40.7)	12 (17.1)	999 (41.2)
Breslow thickness (mm)				
< 1.5	757 (41.2)	67 (12.7)	24 (32.9)	848 (34.8)
1.5–3.5	735 (40.0)	226 (43.5)	26 (37.1)	987 (40.7)
3.5	323 (17.6)	224 (43.2)	20 (28.6)	567 (23.4)
Unknown	20 (1.1)	3 (0.6)	1 (1.4)	24 (1.0)
Ulceration				
Yes	554 (30.2)	234 (45.1)	40 (57.1)	828 (34.1)
No	1054 (57.4)	232 (44.7)	22 (31.4)	1308 (53.9)
Unknown	229 (12.5)	53 (10.2)	8 (11.4)	290 (12.0)
Tumour subtype				
SSM	260 (14.2)	62 (11.9)	9 (12.9)	331 (13.6)
NM	277 (15.1)	129 (24.9)	10 (14.3)	416 (17.1)
LMM	14 (0.8)	1 (0.2)	1 (1.4)	16 (0.7)
ALM	29 (1.6)	10 (1.9)	0 (0.0)	39 (1.6)
Other	105 (5.7)	25 (4.8)	2 (2.9)	132 (5.4)
Unknown	1152 (62.7)	292 (56.3)	48 (68.6)	1492 (61.5)

ALM = acral lentiginous melanoma; LMM = lentigo malignant melanoma; NM = nodular melanoma; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; SSM = superficial spreading melanoma

by constructing Kaplan-Meier survival curves and compared using log-rank tests. Comparisons between groups of patients undergoing complete lymph node dissection (CLND, MLNM, SLNM and UPM) for each parameter were calculated using $\chi 2$ or nonparametric Kruskal-Wallis analysis as indicated. Statistical analysis was performed using SPSS for Windows, version 22.0. A p-value < 0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Institutional Review Board Committee and was conducted in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

Results

Between 2000 and 2015, 2426 CM patients had SLN biopsy procedures at the OI. Positive SLN was found in 519 (21.4%) patients, of these 13 (2.5%) had metastatic lymph nodes in two nodal basins. The size of SLN metastasis was recorded (in mm) in 91.7% of cases.

SLN biopsy procedure was unsuccessfully performed in 70 patients (70/2426, 2.9%). Preoperative lymphoscintigraphy failed to detect the SLN in 23/2426 (0.9%) patients. Unsuccessful surgical retrieval was recorded in 47/2426 (1.9%) patients. Lymph node basin with the highest percentage of unsuccessful surgery was neck 24/310 (7.7%), followed by interval lymph nodes 6/115 (5.2%), axilla 13/1238 (1.1%) and groin 4/693 (0.6%).

In 455 patients with positive SLN, CLND was performed. Patients with unsuccessfully retrieved SLN or negative SLN and lymph node recurrence discovered during follow up (88/1837; 4.7%) were considered as false negative (FN). According to that the FNR was 14.5%. In addition, there were 33 patients with only wide local excision who developed nodal recurrence. Since there was no statistically significant difference in OS between the two subgroups of patients (p = 0.373) they were in further analysis merged together as MLNM. Demographics of patients undergoing SLN biopsy are depicted in Table 1.

Demographics of four groups of patients undergoing complete lymph node dissection (CLND, SLNM, MLNM, UPM) are summarized in Table 2.

Median follow-up of patients after lymphadenectomy was 47 months (range 20 days - 198 months). At the time of data cut-off, 60.1% of patients died. The 5-year OS of CLND group was 58%, MLNM 47%, SLNM 21% and UPM 45%, while 10-year OS was as follows: 45% for CLND, 29% for MLNM, 19% for SLNM and 40% for UPM group (Figure 1).

The 5-year OS of MLNM group was significantly worse than survival of CLND group (47% *vs.* 58%; p = 0.003). However, the 5-year OS of CLND group was heterogeneous based on different tumour burden in SLN: < 0.3 mm 86%, 0.3–0.69 mm 72%, 0.7–1.0 mm 61% and > 1.0 mm 49% (Figure 2). Patients with SLN tumour burden < 0.3 mm had the 5-year OS similar to SLN negative group (86% *vs.* 85%; p = 0.926). The 5-year OS of patients with SLN tumour burden > 1.0 mm was comparable to the MLNM group (49% *vs.* 47%; p = 0.280).

The percentage of positive non-SLN differed according to the size of the SLN tumour burden;

3.2% (2/63) of patients with SLN metastasis < 0.3 mm, 7.4% (5/68) of patients with SLN metastasis 0.3–0.69 mm, 11.9% (7/59) of patients with SLN metastasis 0.7–1.0 mm, 23.0% (51/222) of patients with SLN metastasis > 1 mm and 32.6% (14/43) of patients with SLN metastasis of unknown size had positive non-SLN.

Discussion

Data of 2426 patients with CM undergoing SLN biopsy and 789 patients after CLND treated at the Institute of Oncology Ljubljana during 15-year period were retrospectively analysed. The results have shown that 5-year OS of patients with SLN tumour burden < 0.3 mm is comparable to OS of patients with negative SLN (p = 0.926). On the other end of spectrum were patients with SLN tumour burden of > 1 mm with survival comparable to patients with metachronous regional lymph node metastasis (5-year OS 49% *vs*. 47%, p = 0.280). Patients with CLND after positive SLN had significantly improved survival compared to those with dissection after delayed dissection (p = 0.003).

In last two decades three prospective randomized studies have addressed the management of regional lymph nodes in CM patients.[2,5,6] The result of the first, MSLT-I, confirmed the critical role of the SLN biopsy although it did not demonstrate the melanoma specific survival (MSS) benefit. Despite that, the results did show that early removal of lymph node metastases in intermediate thickness CM could improve survival. 10-year distant disease free survival was 54.8% in the group with intermediate thickness CM following CLND after positive SLN biopsy and 35.6% in the case of observation and nodal recurrence. According to our analysis 10-year OS was 45% in CLND group compared to the 29% OS of the MLNM group which had the characteristics similar to the true observational group. The survival difference was slightly smaller in our population in comparison to MSLT-1 trial which can be explained by population differences. MSLT-I included 81.6% of patients with intermediate thickness CM with median thickness of 1.8 mm in biopsy group, while median thickness in our population was 3 mm. One third of patients had SLN tumour burden > 1 mm.[2,11] In our population the percentage was 48.8%. The observed differences in survival indicate that the benefit of the CLND is not limited only to patients with intermediate thickness CM.

TABLE 2. Demographics of the four groups with lymph node dissection

	CLND No. (%)	MLNM No. (%)	SLNM No. (%)	UPM No. (%)	p
Number of patients	455 (57.7)	121 (15.3)	149 (18.9)	64 (8.1)	
Age (years)					**0.005**
Mean	56	60	59	58	
Median	56	64	61	61	
Gender					**0.198**
F	206 (45.3)	63 (52.1)	65 (43.6)	23 (36.0)	
M	249 (54.7)	58 (47.9)	84 (56.4)	41 (64.0)	
Primary tumour site					**0.254**
Head	29 (6.4)	16 (13.2)	25 (16.8)	-	
Neck	5 (1.1)	4 (3.3)	2 (1.3)	-	
Trunk	235 (51.6)	48 (39.7)	64 (43.0)	-	
Limbs	186 (40.9)	53 (43.8)	58 (39.0)	-	
Breslow thickness (mm)					**< 0.001**
Mean ± SD	3.9 ± 0.1	3.5 ± 0.3	8.5 ± 0.8	-	
Median	3.0	2.6	6.0	-	
< 1.5	60 (13.2)	28 (23.1)	12 (8.1)	-	
1.5–3.5	202 (44.4)	54 (44.6)	21 (14.1)	-	
> 3.5	190 (41.8)	35 (28.9)	105 (70.5)	-	
Unknown	3 (0.7)	4 (3.3)	11 (7.4)	-	
Clark level					**< 0.001**
II	2 (0.4)	1 (0.8)	1 (0.7)	-	
III	87 (19.1)	32 (26.4)	16 (10.7)	-	
IV	234 (51.4)	50 (41.3)	63 (42.3)	-	
V	41 (9.0)	7 (5.8)	33 (22.1)	-	
Unknown	91 (20.0)	31 (25.6)	36 (24.2)	-	
Ulceration					
Present	197 (43.4)	47 (38.8)	91 (61.1)	-	**< 0.001**
Absent	213 (46.8)	52 (43.0)	18 (12.1)	-	
Unknown	45 (9.9)	22 (18.2)	40 (26.8)	-	
Number of positive nodes					**< 0.001**
Mean ± S.D.	1.6 ± 1.8	3.3 ± 4.0	4.3 ± 5.4	4.5 ± 7.0	
Median	1	2	2	2	
Diameter of the largest lymph node metastases (mm)					**< 0.001**
Mean ± S.D.	3.5 ± 5.7	35.3 ± 30.7	20.8 ± 14.2	46.0 ± 27.2	
Median	1.4	28	16	47	

CLND = completion lymph nodes dissection; MLNM = metachronous lymph node metastasis; SLNM = synchronous lymph node metastasis; UPM = unknown primary site metastases

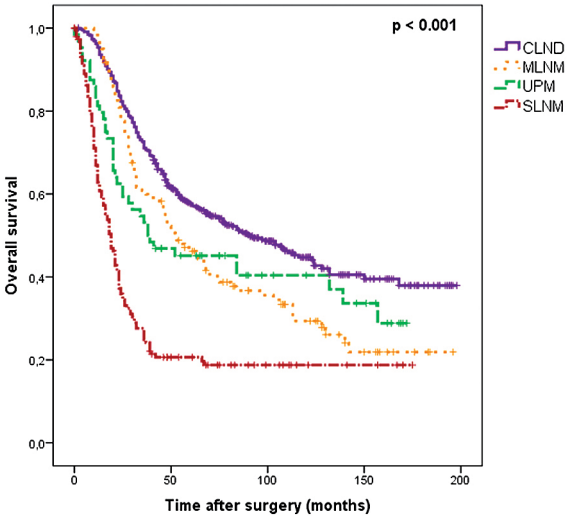

FIGURE 1. Overall survival (OS) of groups with completion lymph nodes dissection (CLND), synchronous lymph node metastasis (SLNM), metachronous lymph node metastasis (MLNM), unknown primary site metastases (UPM).

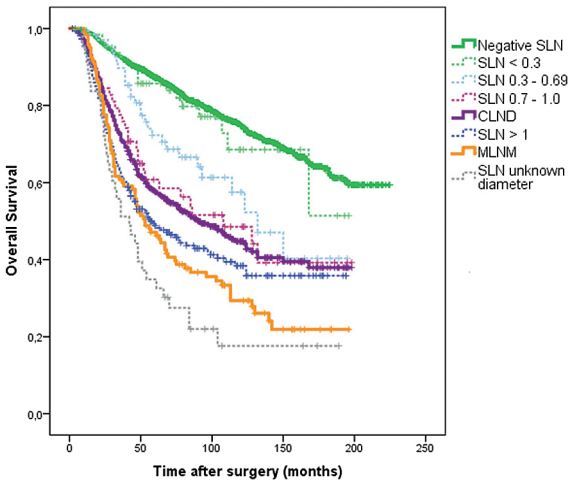

FIGURE 2. Overall survival (OS) according to sentinel lymph node (SLN) tumour burden.

Studies following MSLT-I and addressing the question of improved OS survival after the CLND included small proportion of patients with SLN tumour burden > 1 mm (two thirds of patients in each DeCOG study arm had SLN tumour burden ≤ 1 mm) which would, together with exclusion of patients with head and neck CM and those with extracapsular extension, indicate selection bias during study accrual.[5,6,11] One interesting notion comparing our results to the results of the MSLT-II is, that they have include approximately 6% less patients with ulceration (37.0% of CLND compared to our 43.3%) and 20% less patients with thick melanoma (21.8% MSLT-II *vs*. 41.8%). The percentage of patients with SLN tumour burden > 1 mm was 21.7% in MSLT-II CLND group and 48.8% in our study respectively. The comparison imposes a question whether one can rely on the prospective randomized trials while facing a specific real life population? Differences in our national results indicate that direct implementation of the conclusions of randomised trials may not always be suitable. Results of DeCOG and MSLT-II studies failed to prove the OS survival benefit of the CLND. In case of our cohort the 5-year OS of patients following CLND was improved by 11% compared to the MLNM group (58% *vs*. 47%, p = 0.003) with no signifficant difference in the Breslow thicknes or presence of ulceration between the two groups.

Intriguing relationship between Breslow thickness and nodal burden was observed. In our study the worst OS survival was associated with SLNM group with only 21% alive after 5 years. The group of SLNM patients had substantially thicker CM yet their nodal burden was smaller compared to MLNM group (35.3 ± 30.7 mm MLNM *vs*. 20.8 ± 14.2 mm) indicating different primary tumour biology but also indicating the effect of the delayed lymphadenectomy on the size of the nodal burden. If the timing of lymphadenectomy is a vital part of treatment the concern about possible loss of regional control during observation after SLN biopsy is raised. Many clinicians are aware that unresectable regional disease is a serious clinical problem in CM. At the moment it is not known in how many cases observation and sequential regional relapse would actually cause loss of regional control.[11] But not only regional control, other results could also be influenced by timing, as indicated in the Delgado meta-analysis. They concluded that there appears to be a time-dependent disease specific survival advantage related to early or immediate surgery regardless of the extent of the procedure compared to delayed or none in the case of nodal metastases.[17]

Can we reassure our patient that it is safe to leave the possible CM metastases in lymph node basin in cases where SLN biopsy is not followed by CLND? Many would argue that in the case of high risk for disease progression, small tumour burden in lymph node basin makes no change.[6,11] Interestingly that is in contrast to some basic research showing that especially in CM models stem-like tumour cells have been found to reside in the vessels in the vicinity of lymphatic nodes, suggest-

ing that there is a kind of 'lymphovascular' stem cell niche which is not removed without CLND. It is speculated that these stem-like tumour cells might 'hibernate' for a long time span within the lymphovascular niche, and may form new tumours even years after surgical removal of the primary tumour. Similarly, the persistence of metastatic tumour cells in non-SLN subcapsular sinuses might also relate to a tumour cell survival supporting function of lymphatic vessels, which could play a role in premetastatic lymphatic niches as well.[18] On the other hand, lymphatic endothelial cells (LEC) are expressing PD-L1 surface receptors that directly interface with leukocytes and causes dysfunctional T cell activation, so one would speculate that the risk of tumour progression can be minimized with adjuvant immunotherapy. Studies aimed at adjuvant therapy in CM patients did show less relapses compared to placebo group and indicated that adjuvant systemic therapy can lead to sustained and durable survival benefit. However additional validation of this approach with extended follow-up in patients receiving adjuvant systemic therapy for CM is warranted, including correlation with OS data.[19] It is important to note that trials that influenced our understanding of stage III melanoma treatment (MSLT-1, MSLT-2, DeCOG) included patients with completely resected CM and SLN burden > 1 mm.[11]

With results of MSLT-II and underpowered DeCOG trial indicating no benefit from CLND after positive SLN we can expect, that only a small number of patients will be advised to have CLND in the future. It will be up to clinicians to decide, who with stage III disease should receive adjuvant systemic therapy and the decision will be based only on information gathered from SLN biopsy instead on information gathered from CLND available for adjuvant trials. Unfortunately, until new conclusions are available, results from previous adjuvant trials cannot simply be extrapolated to patients who only had SLN biopsy. The information about the non-SLN status might be lacking.[20] Our own results show that 17.4% of patients (79/455) had positive non-SLN and with that possible decision influencing information.

The issue of additional information gained from CLND was addressed by Verver and colleagues. They used a retrospective cohort of SN-positive patients previously collected and described to construct a model of risk stratification based solely on primary CM and SLN biopsy information. Their model is based on presence or absence of the ulceration and SLN burden of > 1 mm or ≤ 1 mm. They concluded that CLND upstaged 19% of patients in the N-category and 5% of patients in AJCC stage 8Th edition (6% AJCC stage upstaging in the 7th edition). The survival analysis showed significant difference between low risk group (absent ulceration and SLN burden ≤ 1 mm) with 5-year MSS of 82.4% and intermediate risk (ulceration present and SLN ≤ 1 mm or ulceration absent and SLN > 1 mm) with survival around 67.6% and substantial gap between intermediate and high risk group (ulceration present and SLN > 1 mm) with 44% 5-year MSS in the later.[20] Verver's model is a significant step to understanding the stage III survival heterogeneity but if tumor burden is an important prognostic indicator, four group prognostication sounds somehow crude. In our analysis we defined groups according to SLN burden. The OS survival analysis done according to the four group stratification caused previously described CLND curve to fan out. The analysis proved that group of patients with SLN burden > 1 mm are high risk patients with 5-year OS of 49%. In fact, their survival did not differ statistically from the MLNM group. On the other side of the spectrum are patients with SLN burden < 0.3 mm with excellent prognosis and 5-year OS of 86% similar to the group with negative SLN. In the middle are those with SLN burden > 0.3 mm and ≤ 1 mm with 60–70% 5-year OS. Additional analysis showed that 9.4% of these patients had metastases in non-SLN. Based on current recommendations those patients would not receive any additional adjuvant treatment. For those CM patents not receiving adjuvant systemic treatment and not being able to undergo regular nodal basin US, surgery remains a treatment option, which should be taken under consideration.

Conclusions

Stage III melanoma patients are extremely heterogeneous group with significant survival differences. Since not all of them can be treated with systemic adjuvant therapy, CLND after positive SLNB may be offered to selected CM patients. Considering adjuvant treatment, CLND provides independent prognostic information that at the moment cannot be replaced satisfactorily by other variables.

Authors' contribution

BP contributed to the conception of the study, drafted the work and interpretated the data. SM

performed data acquisition, analysis and contributed to data interpretation. AP contributed to interpretation of data and substantively revised the manuscript. MH made substantial contributions to the conception and design of the work and added critical remarks to the revised version. JZ contributed to the conception, interpretation of data and substantively revised the manuscript.

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research article

Surgical resection of synchronous liver metastases in gastric cancer patients. A propensity score-matched study

Tomaz Jagric[1], Matjaz Horvat[2]

[1] Department of General and Abdominal Surgery, University Medical Centre Maribor, Slovenia
[2] Faculty of Medicine, University of Maribor, Slovenia

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Correspondence to: Assist. Prof. Tomaž Jagrič, M.D., Ph.D., Department of General and Abdominal Surgery, University Medical Centre Maribor; Ljubljanska ulica 5; 2000 Maribor. E-mail: tomaz.jagric@gmail.com

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Background. The aim of the study was to determine the value of synchronous liver resection in patients with oligometastatic gastric cancer and the prognostic factors in these patients.

Patients and methods. We compared the results of 21 gastric patients with liver metastases and synchronous liver resection (LMR) to 21 propensity score-matched patients with gastric cancer and liver metastases in whom liver resection was not performed (LM0) and to a propensity score-matched control group of 21 patients without liver metastases and stage III and IV resectable gastric cancer (CG).

Results. The overall 5-year survival of LMR, LM0 and CG were 14.3%, 0%, and 19%, respectively (p = 0.002). Five-year survival was 47.5% for well-differentiated tumour compared to 0% in patients with moderate or poor tumour differentiation ($p = 0.006$). In addition, patients with R0 resection and TNM stage N0–1 had a significantly better survival compared to patients with TNM N stage N2–3 (5-year survival: 60% for N0–1 *vs*. 7.7% for N2–3; $p = 0.007$).

Conclusions. The results presented in the study support synchronous liver resections in gastric patients and provide additional criteria for patient selection.

Key words: gastric cancer; liver metastases; synchronous resection; propensity score

Introduction

Liver metastases occur in 3.5–14% of gastric cancer patients.[1-8,12,15-17] Surgical resection has been shown to be a viable option in selected cases of gastric cancer patients with liver metastases. Since no randomised controlled trials are yet available regarding the treatment of liver metastases in gastric cancer[1-8], no clear-cut recommendations exist as to which patient could benefit the most from such treatment. The aim of our study was to determine the value of synchronous liver resection in patients with oligometastatic gastric cancer and to determine the prognostic factors in these patients. We compared the results of propensity score-matched gastric cancer patients with and without liver resections as well as with a control group of stage III and IV patients without liver metastases.

Patients and methods

Patients

Patient and tumour characteristics, preoperative diagnostics and laboratory data, types of operations, perioperative complications and mortality from 1546 patient data has been included in our database since 1991. Histopathological descriptions were handled in accordance with the International Union Against Cancer 8th TNM classification of gastric cancer.[11] Postoperative complications were defined according to the Clavien–Dindo classification.[9]

Chemotherapy schemes varied during the study period. The administered preoperative and postoperative regimens included: epirubicin + oxaliplatin, capecitabine + fluorouracil, capecitabine + oxaliplatin, or 5-fluorouracil + leucovorin. For our analysis, only the patients who had synchronous liver metastases and gastric resection with curative intent (LMR) were selected. The results of these operations were compared to propensity score-matched (PSM) patients with liver metastases who had gastric cancer resection, in whom the surgeon did not opt for additional liver resection (LM0). The decision regarding liver metastasis resection was obtained on the preoperative tumour board and during the operation at surgeon's discretion. Patients were selected for liver resection, if they met the following criteria: (i) three or less metastases (oligometastatic gastric cancer); (ii) no distant metastases; (iii) resectable primary tumour; (iv) good general health. The nomenclature of hepatic anatomy and resection was used according to the Brisbane 2000 system.[10] Since we could not determine retrospectively whether patients' general state or advanced disease precluded liver metastases resection in LM0 group, we selected an additional PSM control group (CG). For CG, the propensity score-matched stage III and IV gastric cancer patients without having liver metastases resected with curative intent were used for estimation of treatment benefit. Follow-up was carried out by surgeons and oncologists. Informed consent was obtained from all individual participants included in the study. The study was approved by the local ethics committee of the University Medical Centre Maribor in Slovenia (UKC-MB-KME-58/20).

Propensity score-matching

The data from 1546 patients prospectively stored in our database was used for PSM. Patients were matched using the propensity score method as described by Rosenbaum and Rubin.[18,19] The propensity score for an individual was calculated on the given covariates of preoperative haemoglobin levels, age, American Society for Anaesthesiology (ASA) score and the International Union against Cancer (UICC) stage using the multivariate logistic regression model. With this method three groups of PSM patients containing 21 patients each was formed: (i) Patients with liver metastases and no liver resection (LM0); (ii) Patients with liver metastases and liver resection (LMR); (iii) Patients with stage III and IV gastric cancer and no liver resection (CG). In all patients a gastrectomy with local curative intent was performed.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage. Continuous variables were compared with Student's t-test for normally distributed variables; nonparametric variables were tested with Mann-Whitney's U-test. The cut-off levels of continuous variables were determined by means of receiver operator curves with cut-off value of AUC above 0.75 and p value of less than 0.05. Variables above the threshold p value of 0.1 were included for multivariate analysis. The Cox regression model was used for primary analysis. Estimates of treatment effect were expressed as hazard ratios with 95% confidence interval. Kaplan-Meier curves were constructed to determine time-to-event endpoints. Differences in survivals between groups were determined with the Log-rank and Breslow tests. P value of >0.05 was selected as the level of significance. All statistical analyses were performed on SPSS for Windows 10 v. 22 (IBM).

Results

Patients

In the final analysis 63 patients resected for gastric cancer were included. The characteristics of these patients, their tumours, and operations are provided in Table 1. All three groups were balanced according to age, gender, tumour location, operations, UICC and TNM stage and number of resected lymph nodes. In the LM0 group, significantly less patients received chemotherapy compared to LMR and CG group (4.8% *vs.* 42.9% *vs.* 42.9%; p = 0.004). A D2 lymphadenectomy was performed significantly more often in the LMR and CG compared to patients in the LM0 group (LM0: 19%, LMR: 76.2% and CG: 81%; $p < 0.0001$). The number of harvested lymph nodes (LNs) per operation was significantly higher in LMR and CG compared to LM0 group (LM0: 18 ± 9 LNs, LMR: 27.6 ± 14.6 LNs; CG: 26 ± 17 LNs; $p = 0.028$). All patients in LM0 had locally microscopically negative resection margins. In LMR patients a R0 resection could be obtained in 85.7% compared to 100% in the CG (p = 0.076). LM0 patients had significantly more liver metastases compared to LMR patients (p < 0.0001). Most of LM0 patients had more than three metastases (71.4%) compared to one liver metastasis usually present in LMR patients (90.5%). Patients with liver metastases (LM0 and LMR) had a tumour location almost exclusively in the middle and lower third

TABLE 1. Patients', tumour and operations characteristics of the included patients

	All patients	PSM groups			p
		LM0	LMR	CG	
Age [years ± SD]	64.43 ± 9.9	64.9 ± 6.9	65.5 ± 10	62.7 ± 12.5	NS
Gender [n(%)]					
Male	50(79.4)	17(81)	16(76.2)	17(81)	NS
Female	13(20.6)	4(19)	5(23.8)	4(19)	
CA 19-9 [ng(IQR)]	13(64.7)	20(32)	7(62)	5.5(351.7)	NS
CEA [ng(IQR)]	4(6.5)	3.5(26.7)	4(6)	3(17.25)	NS
Hb [g/l(IQR)]	112.5(28.25)	117.5(25)	105(41)	107(27.5)	NS
Chemotherapy [n(%)]					
Yes	19(30.2)	1(4.8)	9(42.9)	9(42.9)	0.004
No	44(69.8)	20(95.2)	12(57.1)	12(57.1)	
Dindo-Claviene					
0	50(79.4)	16(76.2)	18(85.7)	16(76.2)	NS
II	3(4.8)	1(4.8)	1(4.8)	1(4.8)	
IIIa	1(1.6)	0(0)	0(0)	1(4.8)	
IIIb	2(3.2)	0(0)	1(4.8)	1(4.8)	
V	7(11.1)	4(19)	1(4.8)	2(9.5)	
TNM T stage [n(%)]					
1	5(7.9)	0(0)	2(9.5)	3(14.3)	NS
2	1(1.6)	0(0)	0(0)	1(4.8)	
3	36(57.1)	17(81)	8(38.1)	11(52.4)	
4a	8(12.7)	2(9.5)	3(14.3)	3(14.3)	
4b	13(20.6)	2(9.5)	8(38.1)	3(14.3)	
TNM N stage [n(%)]					
0	6(11.1)	0(0)	3(14.3)	3(15)	NS
1	5(9.3)	3(23.1)	2(9.5)	0(0)	
2	15(27.8)	3(23.1)	8(38.1)	4(20)	
3a	9(16.7)	1(7.7)	3(14.3)	5(25)	
3b	19(35.2)	6(46.2)	5(23.8)	8(40)	
UICC stage [n(%)]					
IIIa	2(3.2)	0(0)	1(4.8)	1(4.8)	NS
IIIc	4(6.3)	0(0)	2(9.5)	2(9.5)	
IV	57(90.5)	21(100)	18(85.7)	18(85.7)	
Positive LNs [n(IQR)]	7(17.7)	11(23)	5.5(18.7)	12.5(12.2)	
All LNs [n±SD]	28.2±11.5	18±9	27.6±14.6	26±17	0.028
Grade [n(%)]					
Well	6(12.5)	2(16.7)	2(10)	2(12.5)	NS
Moderate	13(27.1)	4(33.3)	5(25)	4(25)	
Poor	29(60.4)	6(50)	13(65)	10(62.5)	
Type of gastrectomy [n(%)]					
Subtotal	22(34.9)	12(57.1)	6(28.6)	4(19)	NS
Total	34(54)	8(38.1)	14(66.7)	12(57.1)	
Total with distal esophagectomy	4(3.2)	0(0)	0(0)	4(19)	
Distal esophagectomy & proximal gastrectomy	2(1.6)	1(4.8)	1(4.8)	0(0)	
Stump resection	1(1.6)	0(0)	0(0)	1(4.8)	
Location [n(%)]					
Stump	1(1.6)	0(0)	0(0)	1(4.8)	0.045
Entire	6(9.5)	2(9.5)	9(42.9)	3(14.3)	
Proximal	10(15.9)	2(9.5)	9(42.9)	6(28.6)	
Middle	20(31.7)	6(28.6)	2(9.5)	5(23.8)	
Distal	26(41.3)	11(52.4)	1(4.8)	6(28.6)	
ASA score [n(%)]					
I	16(25.4)	6(28.6)	6(28.6)	4(19)	NS
II	32(50.8)	9(42.9)	12(57.1)	11(52.4)	
III	15(23.8)	6(28.6)	3(14.3)	6(28.6)	
Lymphadenectomy [n(%)]					
D1	26(41.3)	17(81)	5(23.8)	4(19)	< 0.0001
D2	37(58.7)	4(19)	16(76.2)	17(81)	
R0 [n(%)]	39(61.9)	0(0)	18(85.7)	21(100)	< 0.0001
Number of liver metastases [n(%)]					
1	23(54.8)	4(19)	19(90.5)	0(0)	< 0.0001
2–3	4(9.5)	2(9.5)	2(9.5)	0(0)	
> 3	15(35.7)	15(71.4)	0(0)	0(0)	
Grade [n(%)]					
Well	6(9.5)	2(16.7)	2(10)	2(12.5)	NS
Moderate	13(27.1)	4(33.3)	5(25)	4(25)	
Poor	29(60.4)	6(50)	13(65)	10(62.5)	
Hospital stay [n(IQR)]	13(8.5)	12(6.5)	13.5(8)	14(12.7)	NS

ASA = American Society for Anaesthesiology; Ca 19-9 = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CG = patients without liver metastases and stage III and IV resectable gastric cancer; Hb = serum hemoglobin levels; IQR = interquartile range; LM0 = patients with gastric cancer and liver metastases in whom liver resection was not performed; LMR = patients with synchronous liver metastases and gastric resection with curative intent; LNs = lymph nodes; NS = not significant; PSM = propensity score-matched; UICC = International Union against Cancer

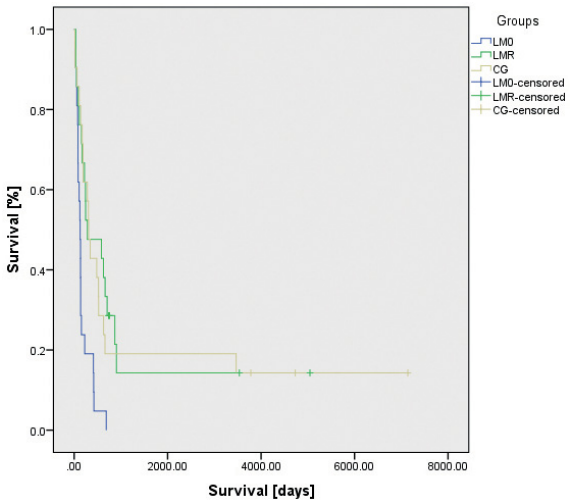

FIGURE 1. Cumulative survivals of patients with liver metastases without resection, with liver resection and in the control group respectively.

TABLE 2. Characteristics of liver resections in the group of patients with synchronous liver metastases and gastric resection with curative intent (LMR)

	n(%)
Segment involvement	
I	0(0)
II	2(8.6)
II/III	3(13)
III	9(39.1)
IV	2(8.6)
V	2(8.6)
VI	0(0)
VII	3(13)
VIII	2(8.6)
Liver resection	
Metastasectomia of 1 metastasis	12(57.1)
Metastasectomia of >1 metastasis	3(14.3)
Segmental resection	3(14.3)
Hepatectomy	1(4.8)
Radio frequency ablation	2(9.5)
Dindo-Claviene morbidity	
0	18(85.7)
II	1(4.8)
IIIa	0(0)
IIIb	1(4.8)
V	1(4.8)
Number of metastases	
1 metastasis	19(90.5)
2–3 metastasis	2(9.5)
> 3 metastasis	0(0)

of the stomach, while the tumour location in CG was evenly distributed in the whole stomach (p = 0.045).

Surgery, morbidity and mortality

There were no significant differences in the perioperative mortality between the three groups. The perioperative morbidity in the LM0, LMR and CG was 23.8%, 14.3%, and 23.8%, respectively. Major morbidity (Dindo-Claviene > IIIb) was observed in 16.7%, 9.6%, and 14.3% in the LM0, LMR and CG group, respectively. The 30-day mortality was 9.5%, 4.8% and 9.5% in the LM0, LMR, and CG group, respectively. Although the differences were insignificant, the patients in the LMR group had the lowest perioperative morbidity and mortality. The results of surgical treatment are presented in Table 1.

The characteristics of liver resections in LMR group are presented in Table 2. Metastasectomy of single metastasis was performed in most cases (57.1%), followed by segmental resection of a single metastasis (14.3%) and metastasectomy of more than 1 metastasis (14.3%). Major resection was performed only in one case (4.8%), and radio frequency ablation was performed in two cases (9.5%). The liver resections for 21 included cases, the involved liver segments and recurrence sites are documented in Table 3. The most frequent recurrence site was the liver followed by peritoneum. Notably 47.6% of cases did not have a documented recurrence after liver resection.

In Table 4 the types of operations in the CG are presented. Additional resection of an involved organ was undertaken in 47.6% of cases. The most commonly infiltrated other organ was the tail of the pancreas (2 cases) and the local peritoneum of the bursa omentalis (8 cases). The most frequent additional resection in CG was the local peritonectomy, followed by left splenopancreatectomy with segmental colon resection and left splenopancreatectomy with left adrenal resection. Left pancreatectomy was associated with most morbidity, while mortality was the highest in patients with no additional resection.

Multivariate analysis

From the included predictors, age, gender, ASA score, Ca 19-9 serum levels, haemoglobin serum levels, additional liver resection, tumour grade, UICC stage, and TNM nodal stage were significantly associated with survival. The hazard ratios, 95% confidence intervals, and the p-values are listed in Table 5.

Survival analysis

None of the patients in the LM0 group survived 5 years. Their survival was significantly shorter compared to patients in the LMR group a cumulative

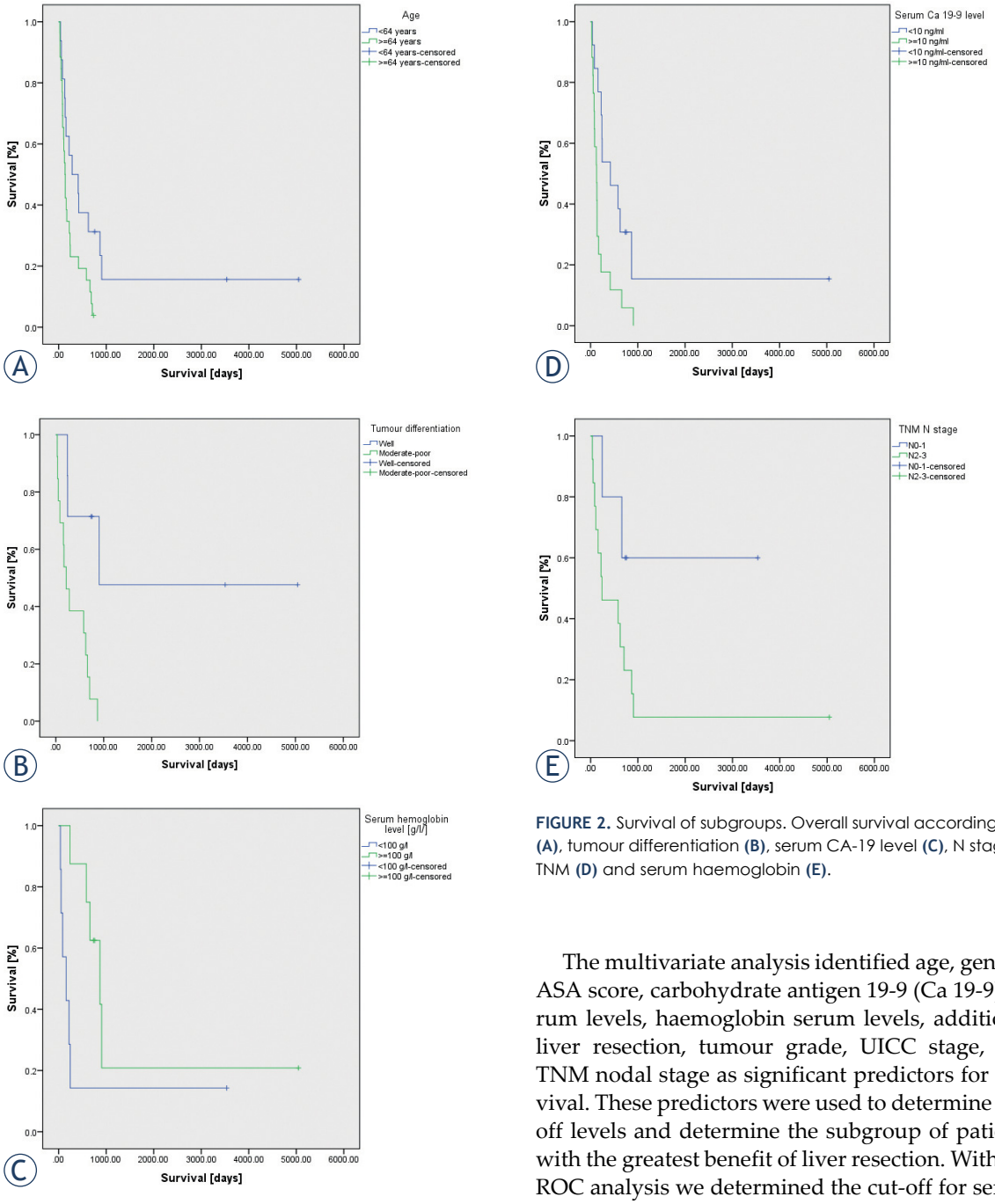

FIGURE 2. Survival of subgroups. Overall survival according age **(A)**, tumour differentiation **(B)**, serum CA-19 level **(C)**, N stage of TNM **(D)** and serum haemoglobin **(E)**.

5-year survival of 14.3% (p = 0.002). The survival of LMR patients was comparable to the survival of CG patients who had a 5-year survival rate of 19%. The median survival was 4.2 months, 9.3 months and 10.2 moths in the LM0, LMR and CG group respectively. The survival plots for the cumulative survival of patients in each group are shown in Figure 1.

The multivariate analysis identified age, gender, ASA score, carbohydrate antigen 19-9 (Ca 19-9) serum levels, haemoglobin serum levels, additional liver resection, tumour grade, UICC stage, and TNM nodal stage as significant predictors for survival. These predictors were used to determine cut-off levels and determine the subgroup of patients with the greatest benefit of liver resection. With the ROC analysis we determined the cut-off for serum levels of Ca19-9, age, haemoglobin serum levels. Patients with Ca19-9 levels above 10 ng/ml had significantly worse survival (5-year survival: 0% *vs.* 15.4%; $p = 0.003$). The survival advantage was lost for R0 resections. Patients with TNM stage N0–1 had an insignificantly better survival compared to patients with TNM stage N2–3. If only R0 patients were included, patients with TNM stage N0–1 had a significantly better survival compared to patients with TNM N stage N2–3 (5-year survival: 60% for N0–1 *vs.* 7.7% for N2–3; $p = 0.007$). Patients with a

TABLE 3. Characteristics of liver metastases and recurrence sites in the group of patients with synchronous liver metastases and gastric resection with curative intent (LMR)

Case No.	Involved segment	Number of metastases	Type of resection	Recurrence site
1	II	1	Segmentectomy	0
2	IV	1	Metastasectomy	0
3	III	1	Segmentectomy	Peritoneal carcinomatosis
4	II/III	1	Segmentectomy	Liver metastases
5	III	1	Metastasectomy	0
6	VII	1	Metastasectomy	0
7	III	1	Metastasectomy	Local recurrence
8	III	1	Segmentectomy	Peritoneal carcinomatosis
9	VIII	1	Metastasectomy	Liver metastases
10	III	1	Segmentectomy	0
11	V	1	Metastasectomy	Local recurrence
12	IV, II	3	Metastasectomy	Liver metastases
13	II/III	1	Metastasectomy	Liver metastases
14	III	1	Metastasectomy	0
15	II/III	1	Left lateral secienectomy	0
16	III	1	Metastasectomy	0
17	III	1	Metastasectomy	Peritoneal carcinomatosis
18	V, VIII	2	Metastasectomy	Liver metastases
19	VII	1	Radio frequency ablation	Liver metastases and peritoneal carcinomatosis
20	VII	1	Radio frequency ablation	0
21	III	1	Segmentectomy	0

TABLE 4. Morbidity and mortality of additional resections in in the control group of patients without liver metastases and stage III and IV resectable gastric cancer (CG)

	N (%)	Morbidity (%)	Mortality (%)
Gastrectomy			
Subtotal	4(19)	0(0)	1(25)
Total	12(57.1)	2(16.6)	1(25)
Total with distal esophagectomy	4(19)	1(25)	0(0)
Stump resection	1(4.8)	0(0)	0(0)
Additional resection			
No additional resection	11(52.4)	1(9.1)	2(18.2)
Local peritonectomy	8(4.8)	1(12.5)	0(0)
Left splenopancreatectomy and segmental colon resection	1(4.8)	0(0)	0(0)
Left splenopancreatectomy and left adrenal resection	1(4.8)	1(100)	0(0)

well differentiated tumour had a significantly better survival compared to patients with moderate and poor tumour differentiation. This difference was more pronounced in patients with R0 resection. Five-year survival in these patients was 47.5% for well-differentiated tumours compared to 0% in patients with moderate or poor tumour differentiation (p = 0.006). Patients younger than 64 years had a 5-year survival of 15.6% compared to 3.8% in patients older than 64 years (p = 0.029). R0 resected patients with serum haemoglobin levels below 100 g/l before the operation had a significantly worse 5-year survival compared to patients with higher haemoglobin levels (5-year survival: 14.3% *vs*. 20.8%; p = 0.09). The multivariate analysis also determined gender and ASA score to be significant predictors for survival; however, we could not determine any cut-off levels for patient stratification. The survival plots of different subgroups are presented in Figure 2.

Discussion

Liver metastases in gastric cancer patients usually occur as part of a systemic failure and rarely present as isolated disease suitable for resection.[1-8,12,15-17] In the present study liver resection has only been performed in 1.36% of patients operated for gastric cancer. As a result of low incidence of resectable liver metastases prospective large-scale randomised controlled trials are not feasible and at present no clear-cut recommendations exist for liver resection of gastric cancer metastases.[1-8,12,15-17] To evaluate potential benefits and prognostic factors for synchronous liver metastases resections in gastric cancer patients we performed a retrospective propensity score-matched study.

The treatment of stage IV gastric cancer patients is still the subject of heated debates. The results of the REGATTA trial suggest that palliative resection in addition to chemotherapy does not improve survival for stage IV gastric cancer patients compared to chemotherapy alone, putting in question the value of surgery in oligometastatic gastric cancer.[21] However, in the REGATTA trail only palliative gastrectomies were performed limiting the value of these results in gastric cancer patients with potentially resectable liver metastases. In the light of emerging evidence proving benefits of liver mestastases resections in oligometastatic gastric cancer patients, we performed a retrospective analysis of stage IV gastric cancer patients with liver metastases. The data from the present study is in accordance with the results of studies that show a significant increase in long-term survival in patients with liver resections in gastric cancer patients.[1-8,12,15-17]

The multivariate analysis confirmed that liver resection is a significant predictor for long-term survival. Median overall survival of 4.2 months in LM0 group was similar to other studies that reported median survival of 0 to 15 months with unresectable liver metastases.[8] In contrast, the median overall survival in LMR group was significantly longer compared to LM0 group. In our study long-term survival of gastric cancer patients was only possible when liver metastases were resected.

The comparison of results from the LM0 and LMR group might support the claim that liver resections have a positive impact on long-term survival[8,12,15-17]; however, the retrospective nature of the study carries some risk of biased selection despite the PSM. At least six patients in LM0 group had potentially resectable metastases. Because we could not determine retrospectively the precise reasons for unresectability of liver metastases in these LM0 patients, local advanced stage, poor general state, anatomical location of the metastasis or some other factor not included in the propensity score calculation might have precluded a safe resection the time of operation. In order to better evaluate the potential benefit of liver resection in gastric cancer patients we compared the results of LMR patients to PSM control group of UICC stage III and IV gastric cancer patients (CG). In both groups, patients were well-balanced according to patients' and tumour characteristics. In addition, no difference was observed in the adjuvant treatment between LMR and CG group. The long-term survival of patients in LMR was comparable to patients in CG. Based on these results, we concluded that liver resection offered a survival benefit comparable to propensity score-matched patients with stage III and IV disease a R0 resection and without liver metastases.

An important aspect of treatment effect evaluation is the safety of the procedure. The perioperative morbidity and mortality in the LMR group was 14.3% and 4.8% that compares favourably to results published in other studies.[1-8,12-17] Notably, perioperative morbidity in LMR group was significantly better compared to CG group. This discrepancy in perioperative morbidity could in part be explained in the additional multivisceral resections in the CG. Pancreatic resections have been identified in previous studies to increase morbidity and mortality.[13,14] In fact, we observed that the pancreas tail resection was associated with 50% morbidity in the CG. This might explain a lower complication rate in the LMR group compared to CG group.

The 5-year survival of LMR patients in our study was 14.3% which was comparable to other studies that reported the 5-year survival of 0% to 42% after liver resection.[1-8,12,15-17] In their seminal multi-centric retrospective analysis of stage IV gastric cancer in Western patients Ministrini *et al.* reported 5-year survival of 11.8%.[22] Although our results compare favourably to results of Ministrini *et al*., some studies reported better long-term survival of up to 32% to 59%.[12, 20] An important reason for better survival after liver resection in these repots might be that patients with metachronous liver resections were included. Metachronous resections have been determined to be a significant prognostic factor.[7] In other studies patients proceeded to liver resection only after a course of chemotherapy, while patients in whom disease progression was determined might have been excluded. In the present report, only synchronous resections have been analysed. It was therefore impossible to exclude patients at risk for progression. In fact, patient selection is the most critical aspect of liver metastases treatment in gastric cancer patients. Unfortunately, no clear recommendations for patients' selection exist yet. In our study, the multivariate analysis identified age, gender, ASA score, Ca 19-9 serum levels, haemoglobin serum levels, additional liver resection, tumour grade, UICC stage, and TNM nodal stage as significant predictors for long-term survival in LMR patients. The most powerful predictor for long-term survival was the TNM N stage of the primary tumour. The 5-year survival of LMR patients with N0-1 stage was 47.5% and even 60% in patients with TNM stage N0-1 and R0 resection. These results are comparable even to results

TABLE 5. Cox proportional hazard model for survival after gastric cancer resection with liver metastases

	HR	95% CI		p
		Lower	Upper	
Age	1.497	1.213	1.846	<0.0001
Gender	55.237	4.626	659.594	0.002
ASA score	0.049	0.009	0.261	<0.0001
Ca 19-9	1	1	1.001	0.02
Hb	0.918	0.864	0.974	0.005
Additional liver resection	0.001	0	0.029	<0.0001
Tumour grade	8.276	1.971	34.753	0.004
UICC stage	0	0	0.003	0.002
TNM N stage	0.386	0.163	0.917	0.031

ASA = American Society for Anaesthesiology; Ca 19-9 = carbohydrate antigen 19-9; CI = confidence interval; Hb = serum hemoglobin levels [g/l]; HR = hazard ratio; UICC = International Union against Cancer

published by Tasubayashi *et al.* who reported a 5-year overall survival of 59%.[12] Our results suggest that patients with a higher nodal stage of the primary tumour were at higher risk for systemic recurrence. They would probably progress after adjuvant treatment and would not be candidates for metachronous resection. Therefore, high nodal stage might be a valuable negative selection criterion when considering synchronous liver resection.

As we further stratified patients, we determined additional subgroups with the greatest survival benefit. Patients with serum levels of Ca 19-9 below 10 ng/ml had a 5-year survival of 15.4%. Similar long-term survival was observed in patients younger than 64 years (15.6%). Patients with preoperative haemoglobin levels of more than 100 g/l had a 5YS of 20.8%. Next to the TNM N stage, tumour grade was found to have the most significant impact on long-term survival. Patients with a well-differentiated tumour had a 5-year survival of 47.5% compared to 0% in moderate to poor differentiated tumour. As these predictors are linked to inherent tumour biology, probably the most important determinants for behaviour of liver metastases are intrinsic tumour properties that have yet to be determined in future studies.

Our study has some limitations. It is a retrospective study with a limited number of included patients. Secondly, although the patients were selected with propensity score-matching, some selection bias could have still been present, since not all selection criteria have been included in the propensity score calculation. And finally, only synchronous metastases have been included in the analysis. Conversely, since isolated liver metastases occur only in small number of resectable gastric cancer, most of the presently published studies have only a small number of cases. Still, these studies have a significant merit as they help build recommendations for the treatment of liver metastases in gastric cancer patients. In the present paper we could show that synchronous liver resection in selected cases is beneficial since patients might expect similar long-term survival as R0 resected stage IV gastric cancer patients without liver metastases. The liver resection was identified as an independent prognostic factor on multivariate analysis. Based on results of our study, we determined selection criteria for liver resection of synchronous gastric cancer metastases.

Conclusions

In conclusion, our results confirm that synchronous liver resection in gastric cancer patients is safe and offers significant survival benefit compared to chemotherapy alone. Moreover, after resection of liver metastases with curative intent, patients might expect similar long-term survival as PSM patients with stage III and IV gastric cancer without liver metastases and R0 resection. In addition, we determined that patients benefiting the most from synchronous liver resection are patients younger than 64 years, with less than three liver metastases, Ca 19-9 serum levels below 10 ng/ml, well-differentiated primary tumours, and TNM N0–1 stage, provided an R0 resection can be obtained. Future prospective randomized studies will have to confirm the value of these selection factors to provide clear-cut guidelines for treatment of gastric cancer patients with liver metastases.

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research article

Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: a preferential benefit for squamous cell carcinoma

Cuimeng Tian[1,2], Guimei Liu[1], Yongxiang Xu[1], Guangrong Xia[1], Tongmei Zhang[3], Jiaqiang Huang[4], Hui Jiang[5], Ji Ming Wang[2], Baolan Li[3]

[1] Department of Radiation Oncology, Beijing Tuberculosis and Thoracic Tumor Research Institute / Beijing Chest Hospital, Capital Medical University, Beijing, China
[2] Laboratory of Cancer ImmunoMetabolism, Center for Cancer Research, National Cancer Institute at Frederick, Frederick, USA
[3] Department of General Medicine, Beijing Tuberculosis and Thoracic Tumor Research Institute / Beijing Chest Hospital, Capital Medical University, Beijing, China
[4] Department of Cellular and Molecular Biology, Beijing Tuberculosis and Thoracic Tumor Research Institute / Beijing Chest Hospital, Capital Medical University, Beijing, China
[5] Division of Technology, Beijing Tuberculosis and Thoracic Tumor Research Institute / Beijing Chest Hospital, Capital Medical University, Beijing, China

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Correspondence to: Dr. Baolan Li, Department of General Medicine, Beijing Tuberculosis and Thoracic Tumor Research Institute / Beijing Chest Hospital, Capital Medical University, No.9, Beiguan Street, Tongzhou District, Beijing, 101149, China. E-mail: libaolan1109@163.com

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Background. The beneficial effect of postoperative radiotherapy (PORT) on completely resected pathological IIIA-N2 (pIIIA-N2) non-small cell lung cancer (NSCLC) has been a subject of interest with controversy. The aim of the study was to distinguish the clinical efficacy of PORT on lung adenocarcinoma (LADC) and lung squamous cell carcinoma (LSCC) among pIIIA-N2 NSCLC.

Patients and methods. Between October 2010 and September 2016, 288 consecutive patients with completely resected pIIIA-N2 NSCLC at Beijing Chest Hospital were retrospectively analyzed, which consisted of 194 cases of LADC and 85 cases of LSCC. There were 42 (21.6%) patients treated with PORT in LADC cases and 19 (22.3%) patients treated with PORT in LSCC cases. The 5-year overall survival (OS), loco-regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS) were calculated using the Kaplan-Meier method. The prognostic factors were determined using Cox's regression model.

Results. Among 194 cases of LADC, the 1-, 3-, and 5-year OS in the PORT group were 95.2%, 61.9% and 40.0%, respectively, while in the non-PORT group were 90.1%, 63.3% and 45.0% ($p = 0.948$). The use of postoperative chemotherapy (POCT) and smoking index ≥ 400 were both prognostic factors of 5-year rates of OS, LRFS and DMFS. On the other hand, among 85 cases of LSCC, the 1-, 3-, and 5-year OS in the PORT group were 94.7%, 63.2% and 63.2%, respectively, whereas in the non-PORT group were 86.4%, 48.5% and 37.1% ($p = 0.026$). In this group, only the use of PORT was a favorable prognostic factor for 5-year OS, LRFS and DMFS.

Conclusions. Due to clinicopathological differences among completely resected pIIIA-N2 NSCLC, PORT may not be suitable to all patients. Our study distinguishes pIIIA-N2 LSCC from LADC by their positive responses to PORT.

Key words: lung squamous cell carcinoma; lung adenocarcinoma; pIIIA-N2; postoperative radiotherapy

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.[1] Non-small cell lung cancer (NSCLC) accounts for 80–85% of all cases of this cancer type. Stage IIIA-N2 NSCLC is a heterogeneous combination of the diseases with poor prognosis even after surgical resection.[2] Therefore, for patients with IIIA-N2 NSCLC, comprehensive treatment is advocated by many institutions.[3] Postoperative radiotherapy (PORT) has been explored to improve treatment outcomes for IIIA-N2 NSCLC patients. A meta-analysis of randomized trials published in 1998 did not reveal a beneficial effect of PORT on N2 NSCLC, except for its safety.[4] A new meta-analysis of eight randomized/controlled trials (RCTs) and eight retrospective studies reported that the addition of PORT (with or without chemotherapy) significantly reduced local recurrence and increased the survival of patients with resected IIIA-N2 NSCLC.[5] To obtain further supportive evidence for the safety and efficacy of PORT, the Lung Adjuvant Radiotherapy Trial (LungART) is conducting a multicenter European prospective phase III trial with resected N2-NSCLC (with a goal of recruiting 700 patients). The trial presented at ESMO 2020 exploring the role of modern mediastinal PORT showed no benefit on disease free survival (DFS).[6]

Evaluation of the risks and benefits of PORT thus remains an issue of intense interest. Some studies suggested that subgroups of different clinicopathological NSCLC may affect the efficacy of PORT. N2 status and other factors including smoking, large primary tumor and male sex played an important role in determining the efficiency of PORT.[7-12] In addition, histological subtypes of NSCLC may also contribute to the sensitivity to PORT. Lung adenocarcinoma (LADC) and squamous cell carcinoma (LSCC) are the most frequent subtypes of NSCLC, accounting for 50% and 30% of the cases, respectively.[13] During the past decades, LADC received additional treatments with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) inhibitors with significantly improved patient prognosis.[14] Unfortunately these inhibitors did not show therapeutic effect on LSCC.[15] Since compared with LADC, LSCC had a higher rate of local recurrence (21% *vs.* 14% for LADC) and lower rate of distant metastasis (7% *vs.* 11% for LADC) in patients with resected NSCLC, rigorous local treatment using PORT may more effectively eradicate micro-residual LSCC to improve the patient OS.[16,17] These considerations prompted us to analyze the effect of PORT on the outcome of a cohort of pIIIA-N2 LADC and LSCC patients who received complete surgical resection.

Patients and methods

Patients

Between October 2010 and September 2016, 288 consecutive patients with pathologically confirmed T1–3N2M0 stage IIIA NSCLC, according to the American Joint Committee on Cancer (AJCC) 7th lung cancer TNM classification, who underwent surgery at the Department of Thoracic Surgery at Beijing Chest Hospital were included in the present retrospective study. The eligibility criteria of the patients included the following: (1) demonstrating an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (2) not having received neo-adjuvant chemotherapy or chemoradiotherapy; (3) information about tumor characteristics, pathology and follow-up data being available. All patients survived at least 4 months after radical resection in Beijing Chest Hospital. The medical records and follow-up data of the patients were retrospectively analyzed, including gender, age, smoking index, histology, pathological T stage, types of surgery, types of N2 (N2a1 N2a2, N2b) were based on The Eighth Edition Lung Cancer Stage Classification, number of positive nodes, positive lymph nodes ratio (PLNR), number of N2 stations, postoperative chemotherapy (POCT), PORT, patterns and times of recurrence, and survival status.[18]

Ethics approval and consent to participate

The ethics committee of Academic Research Project Beijing Tuberculosis and Thoracic Tumor Research Institute/Beijing Chest Hospital, Capital Medical University approved this study and consent was obtained from all participants.

Surgery

Radical resection was performed as follows: (1) either sleeve resection, lobectomy or pneumonectomy; (2) microscopically negative resection margins; (3) mediastinal lymphadenectomy or systematic mediastinal LN sampling.

Postoperative chemotherapy (POCT)

POCT was administered with a cisplatin- or carboplatin-based regimen, used within 4 weeks af-

ter the surgery. Patients excluded from POCT included asthenia condition, refusal of the therapy or based on physicians' decision.

Postoperative radiotherapy (PORT)

PORT, based on radiation oncologists' decision or surgeon's referral, was administered within 6 months after the surgery during or after the POCT cycles. Extensive mediastinal lymph node involvement was the main indication for PORT. Clinical target volume (CTV) included surgical margin, ipsilateral hilum, and high-risk ipsilateral mediastinal drainage lymph area. The planning target volume (PTV) was defined as the CTV plus 0.5–0.8 cm margins.

Therapy with EGFR TKIs or ALK inhibitors

Patients with EGFR or ALK mutations in NSCLC were also treated with EGFR TKIs or ALK inhibitors given when tumors relapsed or metastasized. EGFR TKIs included erlotinib, gefitinib or icotinib. ALK inhibitor used was crizotinib.

Follow-Up

The patients were followed up every 3 months after surgery for the first 2 years and every 6–12 months thereafter. The last follow-up time was December 2019. Regular follow-up included physical examination, hematology tests, chest CT scans, ultrasound of supraclavicular region, ultrasound or CT scanning of the abdomen, and other imaging procedures based on the requirement. Treatment failures were determined by the physicians based on the available information, including clinical assessments, imaging results and/or pathological examination. Follow-up information was also obtained by telephone surveys and reviewing electronic medical records. Disease recurrence at the surgical margin, ipsilateral hilum, and/or mediastinum was considered as local-regional failure (LRF). Tumors appeared at other sites, including the supraclavicular zone, contralateral hilum and distant organs, were considered distant metastasis (DM).

Data analysis

SPSS statistical software (version 23.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Loco-regional recurrence-free survival (LRFS) was defined from the day of surgery to the day of documented LRF or the last follow-up. Distant metastasis-free survival (DMFS) was defined from the day of surgery to the day of documented DM or the last follow-up. Overall survival (OS) was measured from the day of surgery to the date of death from any cause or the last follow-up. A $\chi 2$ test was used to determine the distribution of patient characteristics within the PORT group and the non-PORT group. The 5-year OS, LRFS and DMFS were calculated using the Kaplan-Meier method. To determine prognostic value, study variables were compared with the survival measures using log-rank tests. The prognostic factors were determined using Cox's regression model. A statistically significant difference was set at $p < 0.05$.

Results

Patient characteristics

Detailed patient clinical and pathological characteristics are presented in Tables 1 with 194 cases of LADC and 85 cases of LSCC. Among 194 cases of LADC, the median age was 58 years. The median numbers of lymph nodes resected was 18 (range: 2–57). There were 170 (87.6%) patients treated with POCT and 42 (21.6%) patients treated with PORT. The clinicopathological features of the patients were comparable between PORT and non-PORT groups, with the exception that in the PORT group, there were more patients with T1–2 tumors, treated with lobectomy and POCT. Among 85 cases of LSCC, the median age was 60 years. The median numbers of lymph nodes resected was 21 (range: 5–66). There were 72 (84.7%) patients treated with POCT and 19 (22.3%) treated with PORT. Among 61 PORT cases, the techniques used included three-dimensional conformal radiotherapy (3D-CRT, 21 cases) and intensity modulated radiotherapy (IMRT, 40 cases). The therapies were administered with a linear accelerator using 6–8 MV x-ray at 180–200 cGy per fraction, 5 days per week, to an average total radiation dose of 5918 cGy. PORT was used 4.38 months after surgery as an average and after 2 or 4 cycles of POCT.

Survival

Among 194 cases of LADC, the median survival time was 44.50 months. A total of 112 (57.7%) patients succumbed during follow-up. The 1-, 3-, and 5-year OS rates in the PORT group were 95.2, 61.9 and 40.0%, respectively, whereas the non-PORT group exhibited 1-, 3- and 5-year OS rates of 90.1,

63.3 and 45.0%, respectively (p = 0.948; Figure 1A). On the other hand, among 85 cases of LSCC, the median survival time was 38.00 months. A total of 52 (61.2%) patients succumbed during follow-up. The 1-, 3-, and 5-year OS rates in the PORT group were 94.7, 63.2 and 63.2%, respectively, whereas the non-PORT group exhibited 1-, 3- and 5-year OS rates of 86.4, 48.5 and 37.1%, respectively (p = 0.026; Figure 1B).

Univariate analyses

Univariate analyses were performed to determine the association between clinicopathological factors and the patients' 5-year OS, LRFS and DMFS

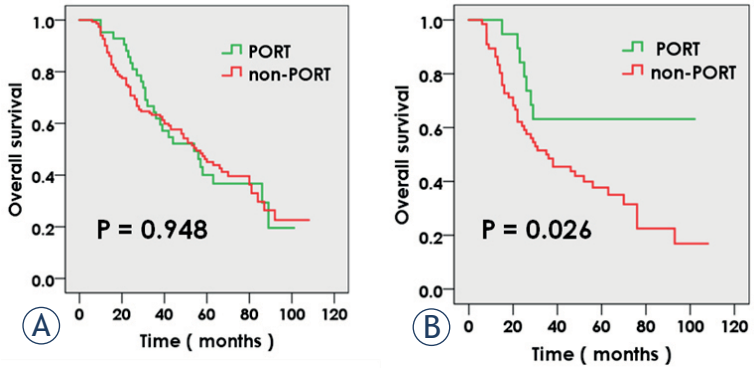

FIGURE 1. The survival of 194 lung adenocarcinoma (LADC) cases with or without postoperative radiotherapy (PORT). **(A)** Overall survival (OS) of PORT and non-PORT patients. **(B)** OS of 85 lung squamous cell carcinoma (LSCC) cases with PORT or non-PORT.

TABLE 1. Patient characteristics

Characteristic	LADC (N = 194)				LSCC (N = 85)			
	Total, n (%)	Non-PORT, n (%)	PORT, n (%)	P	Total, n (%)	Non-PORT, n (%)	PORT, n (%)	P
Gender				0.262				0.593
Female	96(49.5)	72(47.4)	24(57.1)		7(8.2)	6(9.1)	1(5.3)	
Male	98(50.5)	80(52.6)	18(42.9)		78(91.8)	60(90.9)	18(94.7)	
Age (yr)				0.058				0.814
< 65	139(71.6)	104(68.4)	35(83.3)		60(70.6)	47(71.2)	13(68.4)	
≥ 65	55(28.4)	48(31.6)	7(16.7)		25(29.4)	19(28.8)	6(31.6)	
Smoking Index				0.199				0.058
< 400	127(65.5)	96(63.2)	31(73.8)		18(21.2)	11(16.7)	7(36.8)	
≥ 400	67(34.5)	56(36.8)	11(26.2)		67(78.8)	55(83.3)	12(63.2)	
Type of surgery				0.028				0.211
Lobectomy	178(91.8)	136(89.5)	42(100)		57(84.0)	42(63.6)	15(78.9)	
Pneumonectomy	16(8.2)	16(10.5)	0(0.0)		28(16.0)	24(36.4)	4(21.1)	
Pathological T stage				0.044				0.167
T1–2	166(85.6)	126(82.9)	40(95.2)		56(65.9)	46(69.7)	10(52.6)	
T3	28(14.4)	26(17.1)	2(4.8)		29(34.1)	20(30.3)	9(47.4)	
Type of pN2				0.228				0.989
a1	46(23.7)	38(25.0)	8(19.0)		31(36.5)	24(36.4)	7(36.8)	
a2	62(32.0)	44(28.9)	18(42.9)		26(30.6)	20(30.3)	64(31.6)	
b	86(44.3)	70(46.1)	16(38.1)		28(32.9)	22(33.3)	6(31.6)	
N of positive nodes				0.090				0.581
1–3	87(44.8)	73(48.0)	14(33.3)		45(52.9)	36 (54.5)	9(47.4)	
≥ 4	107(55.2)	79(52.0)	28(66.7)		40(47.1)	30(45.5)	10(52.6)	
PLNR				0.060				0.832
< 20%	80(41.2)	68(44.7)	12(28.6)		51(60.0)	40(60.6)	11(57.9)	
≥ 20%	114(58.8)	84(55.3)	30(71.4)		34(40.0)	26(39.4)	8(42.1)	
N of N2 stations				0.422				0.970
Single	46(23.7)	38(25.0)	8(19.0)		31(36.5)	24(36.4)	7(36.8)	
Multiple	148(76.3)	114(75.0)	34(81.0)		54(63.5)	42(63.6)	12(63.2)	
POCT				0.026				0.512
No	24(12.4)	23(15.1)	1(2.4)		13(15.3)	11(16.7)	2(10.5)	
Yes	170(87.6)	129(84.9)	41(97.6)		72(84.7)	55(83.3)	17(89.5)	

LADC = lung adenocarcinoma; LSCC = lung squamous cell carcinoma; PORT = postoperative radiotherapy; PLNR = positive lymph nodes ratio; POCT = postoperative chemotherapy

TABLE 2. Univariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung squamous cell carcinoma (LADC) patients (N = 194)

Characteristics	No.	OS		LRFS		DMFS	
		5-year OS, %	P	5-year LRFS, %	P	5-year DMFS, %	P
Gender			0.071		0.085		0.139
Female	96	48.2		46.9		44.1	
Male	98	39.6		37.1		30.6	
Age(yr)			0.751		0.811		0.494
< 65	139	43.6		41.6		34.5	
≥ 65	55	45.0		42.8		41.3	
Smoking Index			0.001*		0.001*		0.006*
< 400	127	50.4		49.4		44.5	
≥ 400	67	31.0		27.4		22.7	
Types of surgery			0.468		0.158		0.319
Lobectomy	178	44.1		42.3		36.5	
Pneumonectomy	16	41.7		38.5		37.5	
Pathologic T stage			0.032*		0.020*		0.001*
pT1–2	166	46.3		44.0		40.4	
pT3	28	29.5		28.0		15.5	
Types of pN2			0.001*		0.002*		0.000*
a1	46	60.9		58.3		58.8	
a2	62	37.9		38.8		37.8	
b	86	38.7		35.4		22.5	
N of positive nodes			0.000*		0.000*		0.000*
1–3	87	56.6		54.7		53.4	
≥ 4	107	33.3		31.4		20.4	
PLNR			0.000*		0.001*		0.000*
< 20%	80	54.8		52.7		51.8	
≥ 20%	114	35.7		34.0		26.9	
N of N2 stations			0.001*		0.002*		0.001*
Single	46	60.9		58.3		58.8	
Multiple	148	38.3		36.9		29.0	
POCT			0.169		0.280		0.541
No	24	34.4		36.5		37.5	
Yes	170	44.9		43.0		36.6	
PORT			0.948		0.723		0.440
No	152	45.0		43.0		38.8	
Yes	42	40.0		40.0		28.7	

Kaplan-Meier method was used to calculate 5-year OS, LRFS and DMFS. Log-rank tests were used to analyze differences between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy

in LADC and LSCC cases. The results of 194 cases of LADC are presented in Table 2. The 5-year OS in this patient group was significantly increased with a smoking index < 400 ($p = 0.001$), a lower T stage ($p = 0.032$), lower rate (or a single) N2 station metastasis ($p = 0.001$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.000$). In addition, a lower smoking index < 400 ($p = 0.001$), a lower T stage ($p = 0.020$), lower number (or a single) N2 station metastasis ($p = 0.002$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.001$) were as-

TABLE 3. Univariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung adenocarcinoma (LSCC) patients (N = 85)

Characteristics	No	OS		LRFS		DMFS	
		5-year OS, %	P	5-year LRFS, %	P	5-year DMFS, %	P
Gender			0.670		0.784		0.762
Female	7	42.9		42.9		42.9	
Male	78	43.2		39.1		41.3	
Age(yr)			0.362		0.617		0.447
< 65	60	46.4		40.8		43.9	
≥ 65	25	36.0		36.0		36.0	
Smoking Index			0.713		0.659		0.767
< 400	18	55.6		44.4		50.0	
≥ 400	67	39.6		37.8		39.0	
Type of surgery			0.283		0.375		0.498
Lobectomy	57	47.6		42.4		45.5	
Pneumonectomy	28	34.1		33.2		33.9	
Pathologic T stage			0.341		0.289		0.237
pT1–2	56	46.4		44.1		47.1	
pT3	29	37.0		30.3		31.8	
Type of N2			0.625		0.596		0.882
a1	31	50.6		44.4		44.8	
a2	26	41.3		37.8		41.2	
b	28	35.2		34.3		38.1	
N of positive nodes			0.115		0.161		0.431
1–3	45	49.2		45.2		46.1	
≥ 4	40	36.7		34.1		36.1	
PLNR			0.152		0.154		0.265
< 20%	51	48.7		43.8		46.9	
≥ 20%	34	34.4		33.0		33.1	
N2 stations			0.367		0.363		0.654
Single	31	50.6		44.4		44.8	
Multiple	54	38.9		36.9		39.7	
POCT			0.316		0.371		0.525
No	13	30.8		30.8		30.8	
Yes	72	45.3		40.9		43.5	
PORT			0.026*		0.008**		0.018*
No	66	37.7		32.5		35.3	
Yes	19	63.2		63.2		63.2	

Kaplan-Meier method was used to calculate 5-year OS, LRFS and DMFS. Log-rank tests were used to analyze differences between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy

sociated with improved 5-year LRFS. Furthermore, the 5-year DMFS were significantly increased in patients with lower smoking index < 400 ($p = 0.006$), lower T stage ($p = 0.001$), lower (or a single) N2 station metastasis ($p = 0.000$), lower number of positive nodes ($p = 0.000$), and lower percentage of positive nodes ($p = 0.000$). The results of 85 cases of LSCC are presented in Table 3. It was noteworthy that only PORT improved the 5-year OS, LRFS and DMFS, with p values of 0.026, 0.008 and 0.018 respectively.

TABLE 4. Multivariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung squamous cell carcinoma (LADC) patients (N = 194)

Characteristics	OS		LRFS		DMFS	
	HR (95% CI)	P	HR(95% CI)	P	HR (95% CI)	P
Smoking Index		0.000*		0.000*		0.005*
< 400	1		1		1	
≥ 400	2.172(1.471–3.207)		2.098(1.421–3.099)		1.739(1.181–2.560)	
Pathologic T stage		0.074		0.156		0.002*
pT1–2	1		1		1	
pT3	1.560(0.958–2.542)		1.428(0.873–2.337)		2.120(1.308–3.435)	
N of positive nodes		0.255		0.234		0.134
1–3	1		1		1	
≥ 4	1.403(0.783–2.512)		1.441(0.789–2.632)		1.624(0.861–3.062)	
PLNR		0.392		0.435		0.471
< 20%	1		1		1	
≥ 20%	1.313(0.704–2.447)		1.291(0.680–2.452)		1.283(0.651–2.528)	
N of N2 stations		0.015*		0.046*		0.141
Single	1		1		1	
Multiple	2.065(1.148–3.714)		1.818(1.010–3.272)		1.565(0.863–2.839)	
POCT		0.004*		0.031*		0.047*
No	1		1		1	
Yes	0.417(0.230–0.757)		0.524(0.291–0.942)		0.554(0.310–0.992)	
PORT		0.759		0.737		0.444
No	1		1		1	
Yes	1.074(0.680–1.697)		0.924(0.584–1.463)		1.196(0.756–1.891)	

Multivariable Cox proportional hazard models were used to adjust risk factor distributions between patient groups. A statistically significant difference was set as $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy; HR = hazard ratio; CI = confidence interval

Multivariate analyses

Multivariate analyses using Cox's regression model were performed to determine independent prognostic factors for patient survival and disease control. The results of 194 cases of LADC were presented in Table 4. Use of POCT (HR, 0.417; 95% CI, 0.230–0.757; p = 0.004), multiple N2 stations (HR, 2.065; 95% CI, 1.148–3.714; p = 0.015) and smoking index ≥ 400 (HR, 2.172; 95% CI, 1.471–3.207; p = 0.000) were identified as significant independent predictors of OS. The use of POCT (HR, 0.524; 95% CI, 0.291–0.942; p = 0.031), multiple N2 stations (HR, 1.818; 95% CI, 1.010–3.272; p = 0.046) and smoking index ≥ 400 (HR, 2.098; 95% CI, 1.421–3.099; p = 0.000) were identified as significant independent predictors of LRFS. Likewise, use of POCT (HR, 0.554 95% CI, 0.310–0.992; p = 0.047), T3 stage (HR, 2.120; 95% CI, 1.308–3.435; p = 0.002) and smoking index ≥ 400 (HR, 1.739; 95% CI, 1.181–2.560; p = 0.005) were identified as significant independent predictors of DMFS. The results of 85 cases of LSCC were presented in Table 5, which indicates that only patients with the use of PORT showed significantly improved OS (HR, 0.364; 95% CI, 0.159–1.832; p = 0.017), LRFS (HR, 0.308; 95% CI, 0.133–0.712; p = 0.006) and DMFS (HR, 0.349; 95% CI, 0.152–0.802; p = 0.013) (Figure 2).

Toxicities associated with PORT

Twelve patients (19.6%) experienced Common Terminology Criteria for Adverse Events (CTCAE) v4.0 Grade 2 (10 patients) or Grade 3 (2 patients) acute pneumonitis. No patients experienced Grade 4 or higher acute pneumonitis. There were 46 patients (75.4%) experiencing CTCAE v4.0 Grade 1 (35 patients) or higher acute esophagitis (10 with Grade 2 and 1 with Grade 3 toxicity). No patients experienced Grade 4 or higher acute esophagitis.

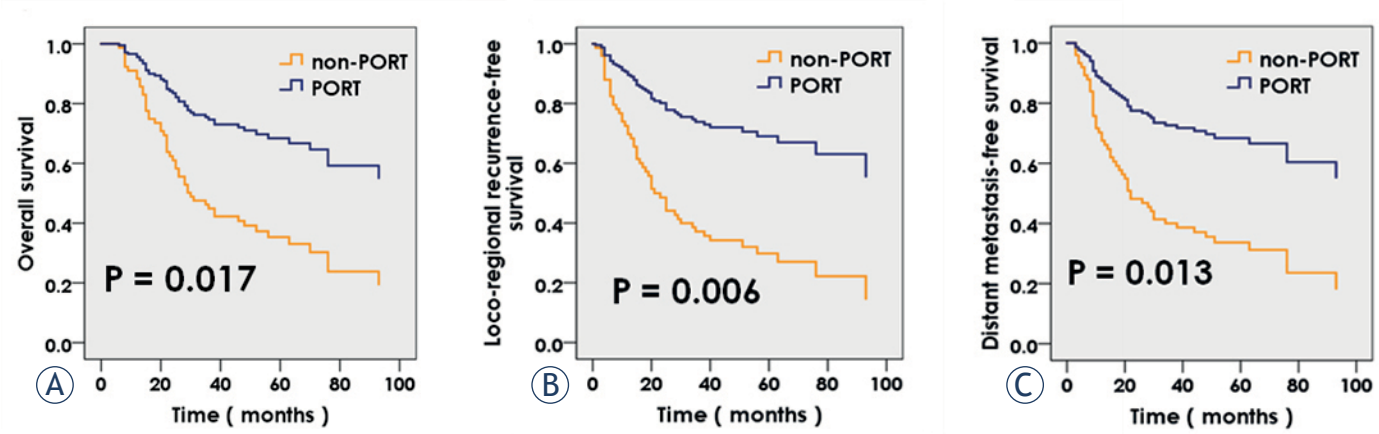

FIGURE 2. The effect of postoperative radiotherapy (PORT) on the survival of 85 lung squamous cell carcinoma (LSCC) patients. **(A)** Overall survival (OS). **(B)** loco-regional recurrence-free survival (LRFS). **(C)** Distant metastasis-free survival (DMFS). PORT alone was a significant positive prognostic factor for OS (p = 0.017) **(A)**; LRFS (p = 0.006 **(B)**; and DMFS (p = 0.013) **(C)**.

TABLE 5. Multivariate analyses of the factors affecting overall survival (OS), loco-regional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS) of lung adenocarcinoma (LSCC) patients (N = 85)

Characteristics	OS		LRFS		DMFS	
	HR (95% CI)	P	HR(95% CI)	P	HR (95% CI)	P
Smoking Index		0.789		0.823		0.563
< 400	1		1		1	
≥ 400	0.905(0.436–1.880)		0.922(0.454–1.874)		0.806(0.389–1.672)	
Pathologic T stage		0.208		0.149		0.151
pT1–2	1		1		1	
pT3	1.436(0.817–2.522)		1.524(0.860–2.701)		1.522(0.858–2.699)	
N of positive nodes		0.257		0.296		0.664
1–3	1		1		1	
≥ 4	1.618(0.704–3.715)		1.556(0.679–3.563)		1.194(0.537–2.657)	
PLNR		0.440		0.454		0.330
< 20%	1		1		1	
≥ 20%	1.322(0.650–2.689)		1.308(0.648–2.643)		1.428(0.697–2.925)	
N of N2 stations		0.922		0.963		0.813
Single	1		1		1	
Multiple	1.043(0.447–2.436)		0.979(0.409–2.343)		0.903(0.385–2.114)	
POCT		0.127		0.224		0.496
No	1		1		1	
Yes	0.523(0.227–1.202)		0.595(0.258–1.374)		0.751(0.328–1.715)	
PORT		0.017*		0.006*		0.013*
No	1		1		1	
Yes	0.364(0.159–1.832)		0.308(0.133–0.712)		0.349(0.152–0.802)	

Multivariable Cox proportional hazard models were used to adjust risk factor distributions between patient groups. A statistically significant difference was set at $p < 0.05$, represented by "*".

PLNR = positive lymph nodes ratio; PORT = postoperative radiotherapy; POCT = postoperative chemotherapy; HR = hazard ratio; CI = confidence interval

All patients completed symptomatic radiotherapy with planned doses. As late radiation toxicity, 2 patients (3.2%) were observed with pulmonary fibrosis.

Discussion

With advancement of the technology, PORT plays an important role in improving the survival of resected pN2-NSCLC patients with no excessive increase in the risk of intercurrent deaths.[19,20] However, the newest result of the first European randomized study evaluating modern PORT after complete resection reported no benefit for DFS.[6] In general, in patients with different clinicopathological features, only selected patients benefit from PORT.[21] Several clinicopathological factors such as number of N2 status, smoking history, tumor size and sex have been reported to be associated with patient survival rates.[7-12] Therefore, the estimate of the benefit of PORT for pIIIA-N2 NSCLC should be individualized. The aim of this study was to assess the potential effect of PORT on histologically different subgroups of completely resected pIIIA-N2 NSCLC. Traditionally, although both LADC and LSCC were categorized as NSCLC, we regard them as different cancer types due to distinct cells of origin, unique molecular characteristics and dissimilar clinical responses to treatments. LSCC typically originates from bronchial epithelium of larger and more proximal airways (basal cells), mostly from central lung and etiologically are more closely associated with smoking and chronic inflammation.[22,23] Patients with LSCC tend to have lower rates of distant dissemination than those of LADC.[24] Therefore, the main therapeutic objective for LSCC patients is to eradicate residual microscopic tumors with tumor-negative resection margin and clearance of mediastinal node areas. In addition, new treatments (i.e., EGFR tyrosine kinase and ALK inhibitors) failed to shown benefits for patients with LSCC, which are also generally chemotherapy-insensitive.[15, 25] However, use of PORT is associated with a significantly lower locoregional recurrence rate in a randomized study of 366 patients with resected pN1-N2 NSCLC.[26] Another randomized study of 230 patients with resected stage II or stage III LSCC showed significantly lower overall recurrence rate by use of PORT in patients bearing N2 disease.[27] PORT was also beneficial for patients with resected pIIIA-N2 LSCC.[28] A comprehensive analysis of our pIIIA-N2 LSCC patient cohort demonstrates that PORT improves 5-year OS, LRFS, and DMFS, supporting the advantage of PORT for pIIIA-N2 LSCC.

LADCs, originating from the bronchiolar or alveolar epithelium (Clara cells or type II pneumocytes), mainly locate in the peripheral smaller airways with glandular histology features with biomarkers consistent with tissues of the distal lung.[22,23] The great risk of distant metastasis shown by LADCs exceeds that of local recurrence at every disease stage, highlighting the systemic threat of the disease.[29] Platinum-based doublets have been the standard postoperative adjuvant therapy for resected stage IB–IIIA NSCLC patients during the past years.[30] In our study of 194 LADC cases, Cox's regression model shows POCT as an independent predictor of OS, LRFS and DMFS. The last decade has seen significant advances in understanding of lung cancer biology and management. EGFR is one of the most important molecular biomarkers in NSCLC, mainly in LADC, in which mutations strongly predict the efficacy and sensitivity to EGFR TKIs.[31] In fact, TKIs have become the first-line treatment choice for patients with advanced NSCLC with EGFR mutations.[32-34] Due to lower toxicity and improved quality of patient life, adjuvant EGFR-TKI therapy is a priority option for completely resected stage II–IIIA (N1–N2) EGFR-mutant NSCLC, resulting in superior disease-free survival.[35] The EGFR-TKI inhibitors may not be curative, but as adjuvant they do provide clinical benefit for most patients with EGFR-mutant tumors.[36] However, in our study, EGFR-TKIs did not demonstrate superior effect on LDAC after surgery, most likely due to targeted therapy is used as a salvage treatment rather than a postoperative adjuvant treatment.

LADC and LSCC are thought to have different cell origin and distinct molecular characteristics. Tobacco smoke is a major risk factor for NSCLC, but LSCCs are more highly associated with tobacco smoke exposure and more often seen in male. In contrast, LADCs occurs more often in women and people who do not have a smoke history.[37] In addition, significant differences were found in microenvironment, dysregulations of miRNAs, epigenetic modifications, cell signal transduction proteins and target genes in various stages of LADC and LSCC.[38] Recent studies have proposed exploring mitochondrial respiratory gene expression profiles in LADC versus LSCC to improve the diagnosis and treatment of patients.[39] One report focusing on the efficacy of PORT in patients with pN2 EGFR wild type LADC and LSCC concludes that female LADC (wild type EGFR) and male LSCC patients

benefited from PORT combined with platinum-based POCT.[40] In our study, pIIIA-N2 LSCC is distinguishable from LADC in their sensitivity to PORT with improved survival.

Our study is based on a relatively smaller data set from patient cohort of a single institution. Further randomized studies of a larger number of patients through multi-institutional collaborations are warranted to more precisely evaluate the therapeutic significance of PORT in NSCLC, especially in LSCC.

Conclusions

It is clear that PORT is not suitable to all patients of completely resected stage IIIA-N2 NSCLC. Rather, PORT displayed its benefit for IIIA-N2 LSCC.

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research article

Radiotherapy-associated angiosarcoma in the breast reconstructed by autologous free-flap and treated with electrochemotherapy

Romi Cencelj-Arnez[1,2], Jerica Novak[1,2], Andreja Klevisar Ivancic[3], Masa Bosnjak[4], Maja Cemazar[4,5], Marko Snoj[1,2]

[1] Department of Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[3] Department of Pathology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[4] Department of Experimental Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[5] University of Primorska, Faculty of Health Sciences, Izola, Slovenia

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Correspondence to: Prof. Marko Snoj, M.D., Ph.D. Institute of Oncology Ljubljana, Department of Surgical Oncology, Zaloška 2, SI-1000 Ljubljana, Slovenia. E-mail: msnoj@onko-i.si

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Background. Radiotherapy-associated angiosarcoma (RAA) of the breast is a rare complication of radiotherapy, which is often difficult to identify and has poor prognosis. It usually presents as violaceous skin, erythema or rapidly growing palpable firm mass that can be confused with other benign skin lesions.

Patients and methods. After reviewing the literature, we found only four cases with RAA after mastectomy and autologous breast reconstruction. The presented case is the first that was treated by electrochemotherapy. The patient presented with secondary angiosarcoma of the breast five years after mastectomy, immediate breast reconstruction with deep inferior epigastric artery perforator free flap and adjuvant radiotherapy.

Results. Electrochemotherapy was feasible, safe and effective in treatment of radiation induced sarcoma. Most of the treated lesions in several consecutive electrochemotherapy sessions responded with complete response, but multiple recurrences occurred in non-treated areas.

Conclusions. Patients with breast cancer after skin-sparing mastectomy and immediate breast reconstruction, who receive radiotherapy, need regular long-term follow up and low threshold for biopsy of any suspicious lesions is mandatory. Electrochemotherapy proved as one of feasible modalities of treatment for RAA.

Key words: radiation-associated angiosarcoma; breast reconstruction; breast cancer; electrochemotherapy; radiotherapy

Introduction

Angiosarcoma of the breast is a rare malignancy, which can occur as primary without a known precursor or as secondary from associated radiotherapy or chronic lymphedema.[1] Although radiotherapy-associated angiosarcoma (RAA) is a rare complication of radiotherapy, it is the most frequent classifiable sarcoma arising in women with breast cancer treated with radiotherapy in the field of irradiated soft tissue.[2] The diagnosis is usually late because initial signs of RAA may be subtle and difficult to identify. Cahn *et al.* suggested the following criteria for the diagnosis of RAA: the sarcoma should arise in the area previously subjected to irradiation, a latent period (in years) must exist between the time of irradiation and development of the sarcoma, and the sarcoma must be confirmed histologically.[3]

Radiotherapy continues to be a mainstay modality in the treatment of breast cancer patients after breast conserving surgery and has a significant role

in preventing local recurrence of breast tumors.[1] After reviewing the literature, we found most of the cases with RAA after breast conserving surgery and only four cases with RAA after mastectomy and autologous breast reconstruction.[4-6] We report a case of RAA after bilateral skin-sparing mastectomy and immediate free flap breast reconstruction to highlight awareness of the disease in an autologous breast reconstruction and the importance of early detection. Furthermore, we want to show that electrochemotherapy, might be applied even in such a rare condition in the palliative intent.[7]

Case report and literature review

A 63-year-old Caucasian female presented with central violaceous or hyperpigmented macule surrounded by an erythematous ring in the lower inner quadrant of her right breast measuring 3 x 5 cm (Figure 1) in June 2016. She had a history of synchronous bilateral hormone positive HER-2 positive breast carcinoma with positive lymph nodes in the right axilla six years ago. After six cycles of the neoadjuvant 5-Fluoro uracil, epirubicin and cyclophosphamide (FEC-100) chemotherapy bilateral skin-sparing mastectomy, axillary lymph node dissection on the right and sentinel node biopsy on the left side followed, and immediate bilateral breast reconstruction with deep inferior epigastric perforator (DIEP) flap was performed in April 2010. Histology showed pathologic complete response of the tumor in the breast, with less than 10% of tumor cells and complete response in the right axilla. Postoperative irradiation of the right mammary region was done with 25 Gy in 2 Gy fractions followed by adjuvant hormonal treatment with letrozole for five years and later extended adjuvant hormonal therapy with tamoxifen.

She had regular follow up and was doing well until the lesion in her right breast was presented in October 2015. First, it was treated as fungal infection with topical ointments and later with corticosteroid ointments. Eight months after the first presentation, fine needle aspiration biopsy was done and suggested a melanocytic lesion, possible melanoma. In June 2016, excision of the lesion was performed and pathological examination revealed RAA, high grade, multinodular, involving dermis and free flap, infiltrating lateral resection margins (Figure 2). Amplification of the MYC oncogene was confirmed using fluorescence in situ hybridization (FISH) method (Figure 3). Patient underwent six cycles of chemotherapy with paclitaxel followed by wide resection of the affected area in January 2017. Pathological examination revealed multifocal residual angiosarcoma in area of 10 cm in diameter, involving skin and subcutaneous tissue with at least 1 cm clear resection margins. Four months after the last operation, in May 2017, she developed second local recurrence with multiple small skin lesion around the scar of the right breast. She received second-line chemotherapy with liposomal doxorubicin with stagnation of the lesions.

In October 2017 resection of the largest skin lesion in combination with electrochemotherapy (ECT) of the smaller 6 skin lesions (indicated in Figure 4), with diameter 0.8–1.2 cm and thickness

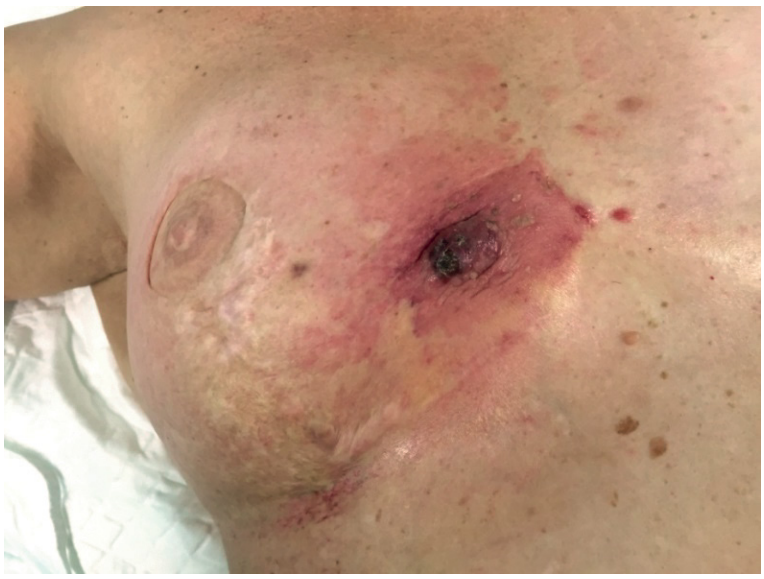

FIGURE 1. Clinical presentation of patient with angiosarcoma of right reconstructed breast.

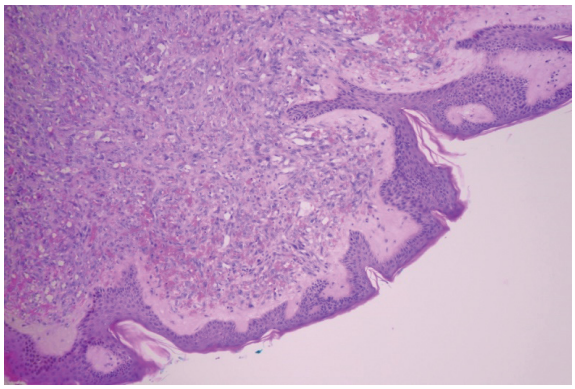

FIGURE 2. Pathologic hematoxylin and eosin (HE) specimen showing radiotherapy-associated angiosarcoma (RAA) involving dermis.

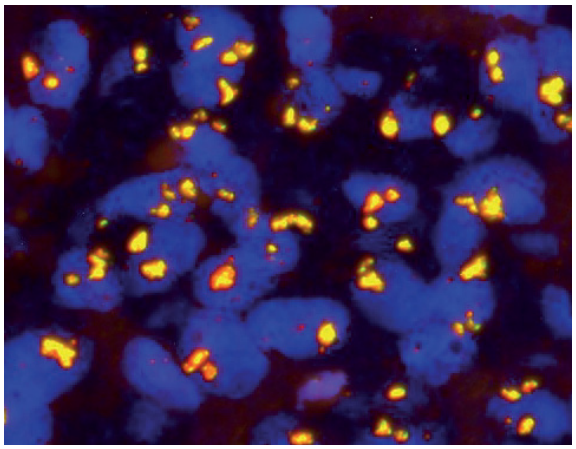

FIGURE 3. Amplification of the MYC oncogene was confirmed using FISH method on tumor specimen.

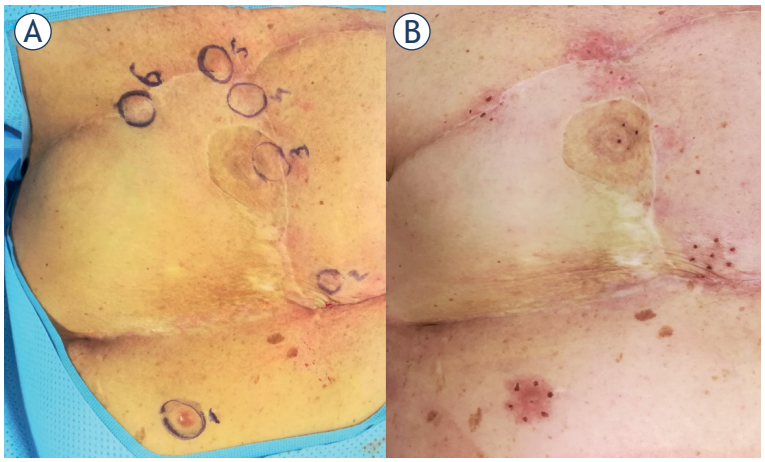

FIGURE 4. Treatment with electrochemotherapy. **(A)** Just before the treatment nodules were marked for evaluation; **(B)** 1 month after the treatment all nodules were in complete response.

0.2–0.4 cm, was performed (Figure 4). ECT was performed 8 minutes after i.v. bleomycin infusion (30,000 IU) lasting 2 minutes using hexagonal electrodes and Cliniporator electric pulse generator (IGEA, s.r.l., Carpi, Italy) according to the SOP.[8,9] Trains of 8 electric pulses (1000 V/cm), each pulse 100 μs long, were delivered to each pair of electrodes consecutively. Altogether 7 electric pulse applications were performed. The patient had complete regression of the area treated 1 month after ECT. In December 2017, two months after the ECT treatment there was a third recurrence outside of the treated area. While other lesions were in complete regression also 2 months after ECT one of the treated lesions recurred. Fine needle biopsy of new and recurred lesion confirmed angiosarcoma metastases. Therefore, additional ECT was performed in January 2018 on 7 lesions, resulting in partial response of 1 lesion, stable disease of 1 lesion and complete response of other 5 lesions, 2 months after the treatment. Treatment was performed in the same way as in the first ECT session. Nevertheless, several new lesions occurred. The lesions were approximately 0.4 cm in diameter and scattered throughout the chest. Although the edema was present at several parts of the chest skin, ECT was performed once again in order to palliate the symptoms in March 2018. Plate electrodes were used to treat 40 small nodules. At next follow up, 1 month after the third ECT session all treated nodules regressed (most of them were in complete response and some of them in partial response). As already observed, new recurrences occurred in an interval less than one month after the last ECT and she received third line of chemotherapy with gemcitabine in May 2018. She received also four lines of target therapy, but despite our best effort she died as a consequence of local tumor progression in May 2019, nearly 36 months after RAA presentation.

While the development of secondary angiosarcoma due to radiation is not uncommon in patients who underwent lumpectomy, the development of RAA in reconstructed breast is extremely rare with only four other cases reported in the literature.[4-6] In all four cases, RAA developed after more than 5 years after radiotherapy. In three cases modified radical mastectomy was done. In all cases the type of reconstruction was autologous - free transverse rectus abdominis muscle (TRAM), free deep inferior epigastric artery perforator (DIEP) flap as in our case and one case of a pedicled flap. In all reported cases, surgery was the most important, and in all but one, the only treatment modality. Table 1 represents the summary of case reports with RAA in the reconstructed breast.

Discussion

Radiotherapy plays an important role for many patients diagnosed with breast cancer to reduce local recurrence after breast-conserving surgery, rarely after mastectomy in specific cases. However, it is associated with increased risk of developing a secondary cancer, including tumors of the skin, such as basal cell carcinoma, squamous cell carcinoma, melanoma and angiosarcoma.[10]

Radiation-associated angiosarcoma of the breast often appears as violaceous skin, erythema, palpa-

TABLE 1. Case reports with radiotherapy-associated angiosarcoma (RAA) after autologous breast reconstruction

First author	Year published	Case #	Years after RT	Type of cancer surgery	Type of breast reconstruction
Hanasono *et al.*[4]	2005	1	6	mastectomy	DIEP flap
Aljarrah *et al.*[5]	2014	2	6	mastectomy	TRAM flap
Yip *et al.*[6]	2019	3	5	mastectomy and axillary lymph node dissection	LD flap
Yip *et al.*[6]	2019	4	10	mastectomy and axillary lymph node dissection	DIEP flap

DIEP = deep inferior epigastric artery perforator; MRM = modified radical mastectomy; RT = radiotherapy; TRAM = transverse rectus abdominis muscle; LD = latissimus dorsi muscle

ble firm mass, skin thickening or skin dimpling, papules and edema that can be confused with other benign skin lesions, such as telangiectasia or changes associated with trauma.[1,11] Atypical post-radiation vascular proliferation (APRVP) is one of vascular radiation-associated lesion that shares similar clinical and histologic features to RAA. The vast majority of APRVP has benign clinical course, although coexistence of APRVP and RAA has been described in some reports and raises the possibility that APRVP represents a precursor of RAA although this theory remains controversial.[12] Immunohistochemical staining and FISH method for MYC are helpful in distinguishing benign and atypical vascular lesions from RAA since amplification of MYC is present in more than 90% of secondary angiosarcomas and is absent in atypical vascular lesions.[1] Subtle clinical signs and rare occurrence of the disease often delay the diagnosis as in our case, so the diagnosis of atypical vascular lesions in violaceous or erythematous skin in irradiated breast should prompt further investigation to rule out RAA. Excision biopsy and pathological examination is necessary for definitive diagnosis .

Angiosarcoma of the breast can develop as primary or secondary malignancy. The distinction between primary breast angiosarcoma and secondary RAA is that the former arises within the mammary parenchyma, whereas the latter is principally a dermal/subcutaneous lesion that may or may not invade the underlying parenchyma and is usually multifocal.[11,13] In our case, the tumor invaded the dermis and also the parenchyma of the free flap. Partial fat necrosis, which usually presents as firm mass, with skin unchanged, is a known complication after breast reconstruction with DIEP flap and can misguide the diagnosis of RAA.[14]

Most of the RAA present as localized and multifocal disease. The median time from the administration of RT for primary breast cancer to the diagnosis of angiosarcoma ranges from four to 11 years, on average 7 years.[15] The presented case and all four reported cases developed RAA five years or more after radiotherapy. Therefore, careful patient evaluation for early disease detection in long-term follow up of patients that received radiotherapy even in cases of autologous breast reconstruction for breast cancer is needed.

Optimal management of angiosarcoma has not yet been defined. The primary treatment remains wide resection of the tumor with negative margins. The retrospective national Finish study observed a greater number of local recurrences in patients when there were less than 1 cm tumor free margins and concluded that management of RAA of the breast currently involves a radical excision of the irradiated breast area.[16] The role of adjuvant and neoadjuvant chemotherapy remains uncertain. Our case and case reported by Aljarrah *et al.*[5] were the only two cases that used adjuvant chemotherapy after radical surgery. In three out of five reported cases surgery was the main and only treatment modality. Lately ECT joined as feasible therapy as there was reported 80% of objective response rate in 20 patients with advanced angiosarcoma that were treated with the use of ECT.[17] In our case, ECT resulted in a complete response in the treated area but new tumors developed outside of the treated area in less than 2 months. Multimodal therapy seems promising in achieving longer survival as in our case, where the patient lived for almost 3 years after the initial diagnosis of RAA. In all other reported cases the follow up was up to one year or it was not defined, therefore we do not know if they had any recurrences after that time.

Conclusions

Women with breast cancer after skin-sparing mastectomy and immediate breast reconstruction rarely receive radiotherapy. Those who receive radiotherapy need regular long-term follow up and low threshold for biopsy of any suspicious lesions is mandatory. ECT proved as one of feasible modalities of treatment.

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research article

Clinical and volumetric predictors of local control after robotic stereotactic radiosurgery for cerebral metastases: active systemic disease may affect local control in the brain

Sławomir Blamek[1], Magdalena Stankiewicz[2], Bogusław Maciejewski[1]

[1] Department of Radiotherapy, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland
[2] Department of Brachytherapy, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland

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Correspondence to: Sławomir Blamek, M.D., Ph.D., Department of Radiotherapy, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, ul. Wybrzeże AK 15, 44-102 Gliwice, Poland. E-mail: slawomir.blamek@io.gliwice.pl

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Background. The aim of the study was to assess the association between physical and biological dose normalized to volume of the metastatic tumor as well as clinical factors with local control in patients with brain metastases who underwent robotic stereotactic radiosurgery.

Patients and methods. A cohort of 69 patients consecutively treated with robotic radiosurgery between 2011 and 2016 was analyzed. The patients were treated with either single fraction radiosurgery or hypofractionated regimens. Biologically effective dose (BED) was calculated assuming alpha/beta value = 10 and both physical dose and BED were normalized to the tumor volume to allow dose-volume effect evaluation. Moreover, clinical and treatment-related variables were evaluated to asses association with local control.

Results. A total of 133 tumors were irradiated and their volumes ranged between 0.001 and 46.99 cm3. Presence of extracranial progression was associated with worse local control whereas higher total dose, BED_{10} > 59 Gy and single metastasis predicted statistically significantly better local outcome. BED_{10}/cm^3 > 36 Gy, and BED_2 > 60 Gy negatively affected local control in univariate analysis. In multivariate analysis performed on all these variables, presence of a single metastasis, BED_{10} > 59 Gy and extracranial progression retained their significance. Excluding a priori the BED_2/cm^3 parameter resulted with a Cox model confirming significance of all remaining variables.

Conclusions. Hypofractionated treatment schemes have similar efficiency to single fraction treatment in terms of local control and the effect depends on BED irrespective of fractionation schedule. Effective control of extracranial sites of the disease is associated with higher probability of local control in the brain which in turn is consistently lower in patients with multiple lesions.

Key words: brain metastases; radiosurgery; radiobiology; local control

Introduction

Although the number of studies focusing on overall survival after radiosurgery for brain metastases is impressive, much less is known about factors affecting local control. Tumor volume/diameter, volume of edema, large (> 15) number of lesions, concurrent chemotherapy and other factors are listed by various authors but without consistency and the findings usually are not reproduced by others.[1-5] Of course, assuming that metastatic tumors contain a constant number of clonogenic cells per volume unit, there is indeed a risk that larger tumors may be treated less effectively. This is because lower doses are used to kill larger number of cancer stem cells per tumor. According to the RTOG 9005 protocol, brain metastases exceeding 3 cm in diameter were treated with a single dose of 15 Gy as opposed to 24

Gy for tumors smaller than 2 cm.[6] This results with almost five times more stem cells treated with less than two thirds of the dose delivered to a smaller tumor. Alternatively, fractionated schemes of still uncertain efficacy can be implemented. Their postulated equivalence to single fraction schedules in terms of biological dose is based on radiobiological calculations but the assumptions taken, need confirmation in clinical studies. The first studies aimed at detailed analysis of the effect of the dose normalized to volume of the lesion and probability of local control were made by Amsbaugh *et al*. but they analyzed single fraction regimens only.[7,8]

The aim of our study was to assess the association between physical and biological dose delivered per volume unit of a metastatic tumor as well as clinical factors with local control in patients with brain metastases after robotic stereotactic radiosurgery.

Patients and methods

All patients treated with the CyberKnife system for cerebral metastases between 2011 and 2016 were retrospectively evaluated to find those with follow-up imaging studies allowing for evaluation of local control. No selection was made in terms of pathology of the tumor, prior treatment or primary tumor status. This resulted with identification of 69 patients for further evaluation.

Patients were immobilized with thermoplastic masks for treatment. CT and MR images were made and the target volume and critical structures were defined on registered images. Usually, no additional margin was added to the GTV. Patients were qualified to a single fraction or hypofractionated treatment after individual assessment of the target volume and proximity of organs at risk. Single doses were prescribed following the RTOG 9005 study. If V_{12} exceeded 10 cm^3 or dose constraints for critical structures were violated, fractionated treatment was prescribed. The dose was specified to isodose encompassing the target, usually between 78 and 90%. All patients were treated with the CyberKnife VSI system.

Biologically effective dose (BED) was calculated assuming the alpha/beta value of 10. The total physical dose (TD) and BED were normalized to the tumor volume to allow better evaluation of the dose effect. Prescription dose was taken as reference for calculation. Threshold values of BED and BED/cm^3 were determined after a stepwise analysis and further included into statistical analysis as categorical variables. Age, gender, pathology, primary tumor status, WBRT use and other variables potentially associated with local control and survival were also analyzed. MR imaging after treatment was performed usually every 3-4 months during the first year and every 6-12 months thereafter. Local control (LC) was defined as lack of progression (complete or partial response or stable disease) of the irradiated lesion. Any increase in lesion size without evidence of radiation-induced necrosis was qualified as local progression. Local progression-free survival (LPFS) was defined as time between treatment and the first imaging showing progression of the irradiated lesion. Local progression (LP) was defined as growth of the irradiated lesion irrespective of the status of other lesions. Distant progression-free survival defined as time to development of new brain metastases (outside the irradiated lesions) was not evaluated.

TABLE 1. Basic characteristics of the study population

	Median (range)
Age	58 (32–84)
KPS	80 (70–100)
Number of lesions (1-9)	1 (1–9)
	Number of patients
1	40
2	12
3	9
4	4
5	1
6	2
9	1
Gender (M/F)	22/47
WBRT before SRS	
Yes	34
No	35
Location of the primary tumour	
Lung	23
Breast	20
Kidney	5
Skin (melanoma)	5
Colon	3
Unknown primary	3
Uterine corpus	2
Other*	8
Disease status	
Stable/NED	42
Progressive	27
Primary tumor controlled	
Yes	62
No	7
Extracranial metastases	
Present	39
No	30

* = One case of each: intestinal sarcoma, thyroid cancer, uterine cervix carcinoma, esophageal, gastric, oral cavity, ovarian, and bladder cancer; F = female; KPS = Karnofsky performance status; M = male; NED = no evidence of disease; SRS = stereotactic radiosurgery; WBRT = whole brain radiotherapy

TABLE 2. Dosimetric and volumetric characteristics of the group

Variable	Median (range)	p
Total dose in SRS	18 Gy (5–24)	**p = 0.0036***
Total dose in HSRT	20 Gy (12–30)	
Dose per fraction in HSRT	7.25 Gy (6–13)	
BED_{10} in SRS	50.4 (7.5–81.6)	**p = 0.0237***
BED_{10} in HSRT	35.7 (19.2–60)	
Lesion volume	1.74 cm^3 (0.001–46.99)	
Single metastasis	4.68 cm^3 (0.05–39.2)	**p = 0.0002***
Multiple metastases	0.96 cm3 (0.001–46.99)	
Total tumor volume	4.9 cm^3 (0.05–63.95)	
Single metastasis volume	4.68 cm^3 (0.05–39.2)	**p = 0.0371***
Multiple metastases volume	4.90 cm^3 (0.48–63.95)	

*= comparison between groups, Mann-Whitney U test; BED_{10} = biologically effective dose for alpha/beta =10; HSRT = hypofractionated stereotactic radiotherapy; SRS – stereotactic radiosurgery

TABLE 3. Association of selected variables with local control

Variable	p	
	univariate	Multivariate
Single vs. multiple lesions	**0.00001**	**0.0161**
Gender	0.2508	
Total dose*	**0.0011**	0.0886
BED_{10}*	0.7026	
BED_{10} > 59 Gy	**0.0026**	**0.0105**
Fractionation (SRS vs. HSRT)	0.1265	
Tumor volume¶	0.1777	
Total tumor volume¶	0.8950	
Chemotherapy before SRS/HSRT	0.3785	
Chemotherapy after SRS/HSRT	0.2174	
Chemotherapy before and after SRS/HSRT	0.2606	
Time between diagnosis of primary and metastases*	0.6551	
BED_{10} per 1 ml tumor volume > median (24.3 Gy)	0.3709	
BED_{10} per 1 ml tumor volume > 36 Gy	**0.0281**	0.3032
Total dose/ml tumor volume > median (11 Gy)	0.3882	
Extracranial metastases	0.3130	
Control of primary tumor	0.8681	
Extracranial progression**	**0.0078**	**0.0011**
RPA class	0.8627	
WBRT use	0.3918	
BED_2/cm^3 > 60	**0.0392**	0.8638

* = above vs. below or equal median; ** = progression of primary tumor or any of extracranial metastases; SRS = stereotactic radiosurgery; HSRT = hypofractionated stereotactic radiotherapy; BED_{10}, BED_2 = biologically effective dose for alpha/beta =10 and 2, respectively; WBRT = whole brain radiotherapy; RPA = recursive partitioning analysis

Kaplan-Meier method and log-rank test were used for calculations and intergroup comparisons. Kaplan-Meier estimations were calculated per lesion (progression of the index lesion was an event). If a new lesion occurred, the patient was censored for the purpose of the analysis (only the irradiated lesions were the subject of analysis and it was assumed that dose delivered to an existing lesion will not affect the probability of progression elsewhere in the brain). Patients dying without evidence of progression of the irradiated lesion were censored at the time of death. Cox regression was used for multivariate analysis which was performed on the set of variables significant in the univariate analysis. Mann-Whitney U test was used for intergroup comparisons. The p value < 0.05 was considered significant.

The study follows the principles of the Declaration of Helsinki.

Results

A total of 133 tumors in 69 patients were irradiated and their volumes ranged between 0.001 and 46.99 cm^3 (median 1.86). Basic patient characteristics is shown in Table 1.

Median total intracranial tumor volume was 4.1 cm^3. The doses used resulted with BED_{10} values of 11.9 – 81.6 Gy (median 46.2 Gy). Physical doses and BED per 1 cm^3 of tumor volume ranged between 0.3 - 1322 Gy (median 11), and 4.6-119733.5 Gy (median 24.3), respectively. Detailed dosimetric characteristics is shown in Table 2.

Median LPFS was 10.7 months. Actuarial 1-year local progression-free survival was 46%. No association between the volume of the tumor and local control could be found. Total dose, BED_{10} above 59 Gy (Figure 1), presence of a single metastasis (Figure 2), and extracranial progression (Figure 3) were significantly associated with LC variables. Presence of extracranial progression was associated with worse local control whereas higher TD, BED_{10} > 59 Gy and single metastasis predicted better local outcome. Moreover, negative association with BED_{10}/cm^3 (Figure 4), and BED_2/cm^3 and LC was identified (Table 3).

In multivariate analysis only presence of a single metastasis, BED_{10} > 59 Gy and extracranial progression retained their significance. Excluding a priori the BED_2/cm^3 parameter, which can be considered redundant in construction of the Cox model resulted with confirmation of significance of all of the remaining.

The results of analysis prompted to check also the difference in local control between patients with 1-3 and more metastases which was also highly significant (p = 0.0000), with median LPFS of 7.1 and 17.1 months, respectively. All patients with

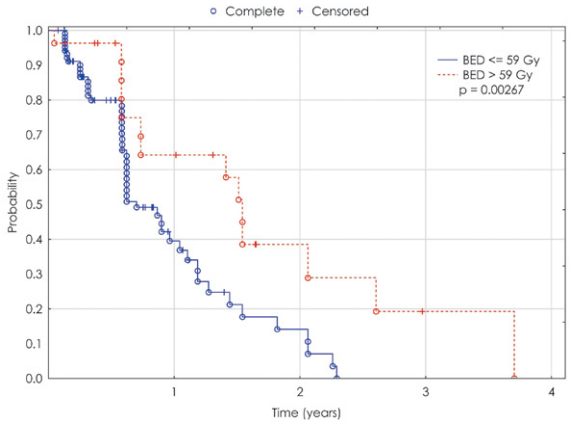

FIGURE 1. Local progression-free survival according to biologically effective dose $(BED)_{10}$. Doses above 59 Gy_{10} (red, dashed line) were associated with significantly longer local progression-free survival (LPFS) (median 7.5 *vs.* 18.4 months).

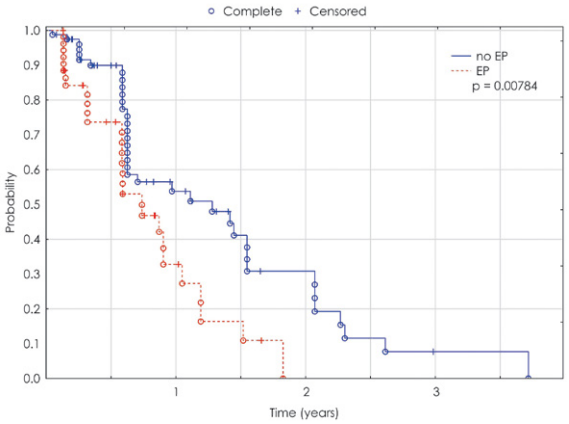

FIGURE 3. Local progression-free survival according to systemic disease status. Extracranial progression (red, dashed line) was an adverse prognostic factor.

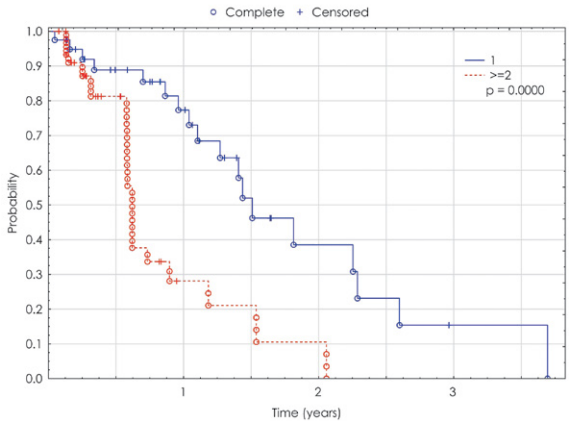

FIGURE 2. Local progression-free survival according to number of metastases. Presence of a single metastasis (blue, solid line) was a favorable prognostic factor.

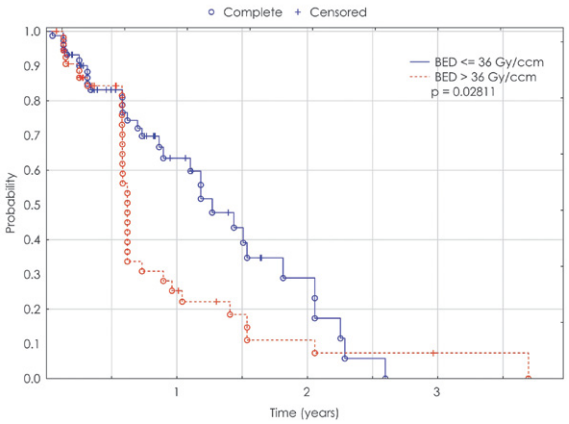

FIGURE 4. Local progression-free survival according to biologically effective dose $(BED)_{10}$ normalized to tumor volume. Exceeding the threshold value of 36 Gy_{10}/cm^3 (red, dashed line) was associated with reduced chances of maintaining local control.

more than 3 metastases failed locally before one year whereas actuarial 1-year LPFS in the group with 1-3 metastases was 68%.

Discussion

To the best knowledge of the authors this is the first study in which dose normalized to tumor volume is analyzed as a prognostic factor for local control for both single-fraction and hypofractionated regimens. Amsbaugh *et al*. used the dose per lesion diameter and dose per volume parameters to construct dose-volume response relationships.[7,8] They found strong correlation between doses and volumes of the tumor which was quite obvious because all patients in their series were treated with single fraction, so the larger the volume, the smaller total dose was used. This resulted with worse results in patients with larger metastases who were treated with lower doses. Similar patients in ours were treated with fractionated regimens which theoretically should result with similar effectiveness like after a large, single fraction. And indeed, no clear association between tumor volume and outcome could be identified here as opposed to increasing rates of local control corresponding to maximum dose per mm of tumor diameter (80%, 85%, and 90% for 1.67 Gy/mm, 2.86 Gy/mm, and 4.4 Gy/mm, respectively) reported in the Amsbaugh's paper.[7] They identified also a relationship between mean dose per volume and local control. Finally, they observed that patients with fewer number of metastases had worse local control (OR: 0.815,

95% CI: 0.72-0.93).[8] Similar observation was made by Yamamoto *et al*. in their study on stereotactic radiosurgery for multiple brain metastases.[9] They observed significant difference in local recurrence ratio and need for repeat treatment between group with 2-9 metastases (more recurrences) and group with 10 and more lesions. At the same time they admitted that the reason for that finding remains obscure. Contrary to their findings, in our series patients with larger number of metastases had worse local control than patients treated for single lesion. This is not an obvious finding whatsoever, especially knowing that the median volume of the tumor was significantly larger in patients with single lesion (median 4.68 cm^3) than in patients with multiple metastases (median 0.96 cm^3). Nevertheless, the effect was stunning which was confirmed by secondary analysis showing that all patients with more than 3 metastases fail locally before one year.

BED above 59 Gy_{10} was associated with improved chances of local control. This parameter retained significance in multivariate analysis indicating that appropriate biologically effective dose increases the probability of local control irrespective of the fractionation method. What is more intriguing, biological doses normalized to tumor volume above 36 Gy_{10}/cm^3 (the threshold value calculated for the nervous tissue - BED_2 was 60 Gy_2/cm^3 and was also significant) resulted with significantly worse local control. This phenomenon did not retain significance in multivariate analysis including all variables significant in the univariate analysis. However, in an additionally constructed model without incorporating BED_2/cm^3 it did. Amsbaugh *et al*. did not identify a threshold dose per cm^3 of tumor volume associated with plateau of local effect or local control decrease. The exact meaning of this finding is uncertain and it may be just a statistical artifact. One could also speculate that it may indicate existence of some kind of threshold dose and after reaching the optimal dose level its further escalation might facilitate concurrent negative processes. In situ recurrence of the radiosurgically ablated tumor due to damage of the surrounding tissues resulting with easier penetration of the circulating tumor cells may be one of possible explanations. Local progression was significantly associated also with extracranial progression which may further support this theory of re-seeding of the site of previously ablated tumor by circulating cells originating from extracranial foci. The concept of radiation-induced metastases, and more generally – treatment-induced metastases (TIM), although described in the 50—ties of the XX-th century, was mostly forgotten but regained attention in recent years.[10–12] In this specific case it would be rather treatment-induced/facilitated local recurrence associated with exceeding a safe dose for local microenvironment. Of course we cannot provide a proof of sterilization of the irradiated tumor or distinct characteristics of the progressing lesion but we believe our observation is worth further studies. Radiation resistance associated with general resistance to the treatment also can be an explanation and presumably should be given first, as a more probable one. In this case, in spite of delivering high doses to low-volume lesions, we would face local failure without prior elimination of the lesion. Currently, it can be only concluded that patients with systemic progression are more likely to progress also in the brain.

Better outcome after larger single dose in terms of probability of local control was confirmed for example by Mohammadi *et al*. They found that tumors smaller than 2 cm of diameter are better controlled with 24 Gy than lower doses.[13] This finding supports the assumption that there is a dose-response relationship but, on the other hand, it shows the drawbacks of using a single fraction in case of tumors which cannot be treated with sufficiently large doses. In our series, the dose-response relationship was also identified but was best seen when the dose exceeded 59 Gy_{10}, irrespective of the fractionation method and tumor volume. Interestingly, some authors did not find any correlation between local control and dosimetric or clinical factors.[5] The only factor significantly associated with local control in the study by Loo *et al*. for example, was the total volume of edema, not volume of the tumors or dose delivered.[2]

Our study has drawbacks typical for retrospective evaluations. We cannot exclude patient selection bias and we did not have follow-up imaging available for every patient treated in our center which limited the study sample. We realize also that metastases in a single patients share a lot of common properties important for the prognosis and their independent analysis may be somewhat misleading. On the other hand, it should facilitate demonstration of the dose and volume effect because lesions of various sizes in one patient were often irradiated with different doses.

Our results suggest that local control in the brain can depend on several factors including those not directly related to the local treatment and may be associated also with systemic progression. In turn, this may influence overall survival in much more complex way than we assume. The results suggest

also that escalating the dose above certain limits may not be beneficial. The threshold dose for this effect calculated for the nervous tissue is similar to the dose of 60 Gy used in conventional radiotherapy for primary brain tumors. Further escalation did not prove beneficial but was associated with increased risk of adverse effects.[14]

Conclusions

Hypofractionated treatment schemes have similar efficiency to single fraction treatment in terms of local control and the effect depends on BED, irrespective of fractionation schedule. Effective control of extracranial sites of the disease is associated with probability of local control in the brain which is consistently lower in patients with multiple lesions.

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research article

Prospective evaluation of probabilistic dose-escalated IMRT in prostate cancer

Daniel Wegener[1], Bernhard Berger[2], Zhoulika Outtagarts[1], Daniel Zips[1,3], Frank Paulsen[1], Martin Bleif[4], Daniela Thorwarth[5], Markus Alber[6], Oliver Dohm[5], Arndt-Christian Müller[1]

[1] Department of Radiation Oncology, University Hospital Tübingen, Germany
[2] Clinic for Radiation Oncology, St. Elisabethen-Clinic, Ravensburg, Germany
[3] German Cancer Consortium (DKTK), Partner Site Tübingen; and German Cancer Research Center (DKFZ), Heidelberg, Germany
[4] Clinic for Radiology and Radiation Oncology, Alb Fils Clinic Göppingen, Germany
[5] Section for Biomedical Physics, Department of Radiation Oncology, University Hospital Tübingen, Germany
[6] Clinic for Radiation Oncology, University Hospital Heidelberg, Germany

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Correspondence to: Daniel Wegener, Department of Radiation Oncology, University Hospital Tübingen, Eberhard Karls University Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen. E-Mail: daniel.wegener@med.uni-tuebingen.de

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Background. Cure- and toxicity rates after intensity-modulated radiotherapy (IMRT) of prostate cancer are dose- and volume dependent. We prospectively studied the potential for organ at risk (OAR) sparing and compensation of tumor movement with the coverage probability (CovP) concept.

Patients and methods. Twenty-eight prostate cancer patients (median age 70) with localized disease (cT1c–2c, N0, M0) and intermediate risk features (prostate-specific antigen [PSA] < 20, Gleason score ≤ 7b) were treated in a prospective study with the CovP concept. Planning-CTs were performed on three subsequent days to capture form changes and movement of prostate and OARs. The clinical target volume (CTV) prostate and the OARs (bladder and rectum) were contoured in each CT. The union of CTV1–3 was encompassed by an isotropic margin of 7 mm to define the internal target volume (ITV). Dose prescription/escalation depended on coverage of all CTVs within the ITV. IMRT was given in 39 fractions to 78 Gy using the Monte-Carlo algorithm. Short-term androgen deprivation was recommended and given in 78.6% of patients.

Results. Long-term toxicity was evaluated in 26/28 patients after a median follow-up of 7.1 years. At last follow-up, late bladder toxicity (Radiation Therapy Oncology Group, RTOG) G1 was observed in 14.3% of patients and late rectal toxicities (RTOG) of G1 (7.1%) and of G2 (3.6%) were observed. No higher graded toxicity occurred. After 7.1 years, biochemical control (biochemically no evidence of disease, bNED) was 95.5%, prostate cancer-specific survival and the distant metastasis-free survival after 7.1 years were 100% each.

Conclusions. CovP-based IMRT was feasible in a clinical study. Dose escalation with the CovP concept was associated by a low rate of toxicity and a high efficacy regarding local and distant control.

Key words: probabilistic planned IMRT; coverage probability concept; prostate cancer; IMRT; dose escalation

Background

Cure- and toxicity rates after intensity modulated radiotherapy (IMRT) of prostate cancer are dose-dependent.[1] Dose-escalated radiotherapy (RT) up to 80 Gy is a standard RT-technique[2] and performed with (daily) image-guided RT (IGRT) combined with rapid treatment administration using volumetric modulated arc therapy (VMAT) or comparable techniques.[2-4] Current improvements in regard to outcome and toxicity focus either on dose escalation or margin adaption. Dose escala-

tion can be performed by using hypofractionated schedules of the whole prostate or of the dominant lesion alone[5], Margin adaption *i.e.* reduction to reduce toxicity +/- dose-escalation is performed by target tracking or (online) adaptive strategies. However, these techniques require not only modern RT instruments, which are not available yet for the majority of radiooncology departments, but also more time consumption per patient.[6]

Also, planning target volume (PTV) margins still need to account for intra- and interfraction prostate motion to prevent target miss, while respecting the surrounding organs at risk (OAR), especially bladder and rectum. Therefore, alternative concepts which are applicable in width and which combine both dose escalation and toxicity reduction are of interest.

A promising concept to achieve a favorable PTV-coverage while individually sparing OARs represents Coverage probability based IMRT which does not need daily imaging due to its pre-adaptive planning approach.[7-9] We studied the potential for Organ at Risk (OAR) sparing and compensation of tumor movement of the Coverage probability (CovP) concept within a prospective study and report 7-year outcome and toxicity rates.

Patients and methods

The coverage probability concept was investigated within a prospective study to evaluate in intermediate-risk prostate cancer patients' feasibility, toxicity and outcome parameter. The study was approved by the research board of the University Clinic of Tuebingen on 06/27/2007 (project-number: 257/2007B01).

Patient enrollment

Inclusion criteria were histopathologically confirmed adenocarcinoma of the prostate, intermediate-risk in D`Amico classification, age ≤ 85 years at enrollment, Karnofsky-performance-status ≥ 70%, localized disease (bone scan, abdominal/pelvic CT) and informed consent. Exclusion criteria were prior prostatectomy, prior transurethral resection (TURP) or previous irradiation of pelvis, a second malignancy or another severe, clinically prominent illness (*e.g.* decompensated heart insufficiency, chronic inflammatory bowel disease, blood coagulation restrictions etc.).

Coverage probability concept

A planning CT (pCT; SOMATOM Sensation 64, Siemens Healthcare, Erlangen) was performed daily over three days with a rectum- and bladder protocol in use. The pCT`s were registered with Oncentra Masterplan® (Theranostic GmbH, Solingen, Germany), then target volume and organ at risks (OAR's) were contoured in each pCT. The clinical target volume's (CTV) of each pCT (prostate + 1 cm seminal vesicle) were merged to create a CTVunion,

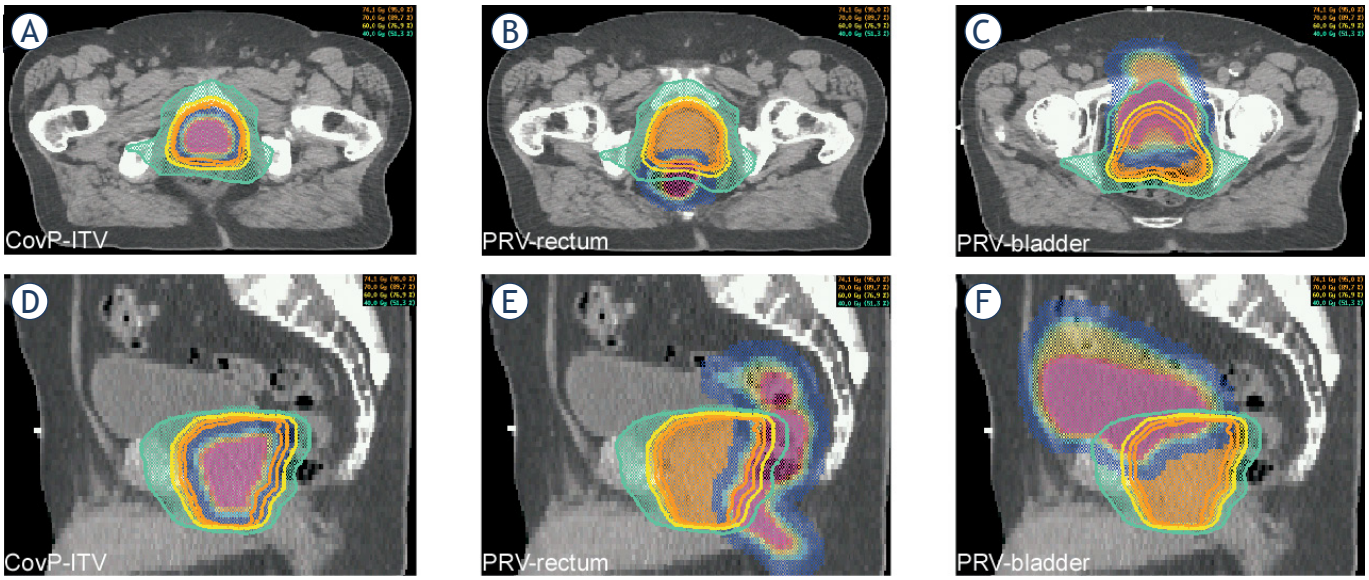

FIGURE 1. Coverage probability (CovP) concept: an example case is shown to indicate CovP-internal target volume (ITV) and planning organ at risk volumes (PRVs).

TABLE 1. Patient characteristics of the study cohort

Parameter	Mean (min.-max.)	Median	n (%)
Age at treatment (years)	70 (56–83)	70	
Duration of radiotherapy (weeks)	7.9 (7.4–8.7)	7.9	
Gleason-Score (n, %)			
6			4 (14.3 %)
7a (3+4)			15 (53.6 %)
7b (4+3)			9 (32.1 %)
cTNM (n, %)			
cT1c			8 (28.6 %)
cT2a			8 (28.6 %)
cT2b			3 (10.7 %)
cT2c			9 (32.1 %)
Neoadjuvant ADT (n, %)			22 (78.6 %)
Duration of ADT (months, range)	8.9 (3.0–27.0)	6.0	
Initial PSA peak in ng/ml (range)	9.1 (1.9–19.8)	8.3	
PSA-peak by subgroup			
0 < x ≤ 5			3 (10.7 %)
5 < x ≤ 10			15 (53.6 %)
10 < x ≤ 15			8 (28.6 %)
15 < x ≤ 20			2 (7.1 %)

ADT = androgen deprivation therapy; PSA = prostate-specific antigen

which was expanded by 7 mm to define an internal target volume (CovP-internal target volume [ITV]). The same margin of 7 mm was added to the merged OARs (rectum and bladder) to create planning OAR volumes (PRV). The coverage-probability approach uses spatially variable weight factors for "cost functions" for both ITV and OAR's. These weight factors are based on the probabilities of systematic organ shifts, estimated by the three planning CTs. For RT planning, "class solutions" were employed including OAR constraints, aimed target doses, optimal gantry angles as described elsewhere.[7-9] (Figure 1).

Treatment

RT was performed as step-and-shoot IMRT with 78 Gy in 39 fractions. Planning software were Hyperion® versions 2.2.5, 2.2.6 and 2.3 (University Tuebingen, Germany; based on Monte Carlo algorithm). All patients were treated in supine position on a 15 MV linear accelerator (Elekta Synergy S, Elekta Oncology Systems®, Crawley, UK) equipped with a 4 mm multileaf collimator. Cone-beam CT (CBCT) was initially performed daily for three days and then the average positioning error was calculated and corrected for the next fraction. Thereafter, CBCT was routinely performed twice weekly to account for random positioning errors. In case of a positioning error of >3 mm, CBCT was repeated at the next RT treatment. Additional short term androgen deprivation therapy (ADT) for six months was recommended according to national guidelines. Further treatment specifications are given elsewhere.[9,10]

Patient follow-up and evaluation

For each patient, baseline parameters for genitourinary (GU) and gastrointestinal (GI) functions were assessed and acute- and late toxicities were scored by a physician using common terminology criteria for adverse events (CTCAE)[10] and/or Radiation Therapy Oncology Group (RTOG) Classification.[11] Initially, CTCAE version 2.0 was used, which was transferred in 2009 into version 4.0 for comparability.[12] A physical examination, combined with scoring of late toxicity and measurement of features prostate-specific antigen (PSA)-level, was performed three months after RT and then once a year.

Primary outcome parameter was relapse-free survival (biological no evidence of disease, bNED). Biochemical relapse was defined by the Phoenix-criteria.[13] Secondary outcome parameters were overall survival (OS), prostate-cancer specific survival (PCSS) and distant metastasis-free survival (DMFS). The outcome parameters were calculated from start of radiotherapy.

Statistical analysis

Descriptive statistics were performed with Microsoft Excel 2010 (Version 14.0.7145.5000). Further calculations, graphs and Kaplan-Meier estimations were performed with SPSS (Statistical Package for Social Sciences 'IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, N.Y., USA)).

Results

Patient characteristics and treatment

Twentyeight patients were treated between 09/2008 and 10/2010 in this prospective study. Patient characteristics are given in Table 1. Dose escalation to 78 Gy was performed in all patients, the coverage probability concept was realized in 27/28 patients. In one patient, the study therapy was not accomplished due to unknown reasons (but a "standard" step-and shot IMRT to 78 Gy was performed based on one pCT). Neoadjuvant ADT was administered to 78.6% of patients with a mean duration of 8.9 months.

Survival endpoints

Median follow-up (FU) time was 7.4 years (range 0.7–9.3 years; mean 7.1 years). Median FU for PSA-control was 7.0 years (range 3.3–9.1 years; mean 6.8 years). PSA-nadir was reached on average after 2.7

years (min.: 0.2 years; max.: 8.3 years; median: 1.3 years). Biochemical control is shown in Figure 2. Two patients developed a biochemical recurrence. PCSS and DMFS after 7 years were 100% each. One patient died after a FU of 4.5 years due to a metastatic GIST which was detected 51 months after RT and located outside of the treated RT-field. Another patient was lost to FU.

Acute toxicity

Acute toxicity was defined as toxicity occurring from start of RT until the first FU-investigation ≤ 90 days after end of RT. Weekly RTOG scoring results as well as maximum toxicity scores for GI- and GU-toxicity are given in Supplement Figure 3. 46.4% of patients developed acute GU toxicity of maximum grade 1 and 42.9% developed acute GU toxicity of maximum grade 2. No higher graded toxicity occurred. Acute GI toxicity of maximum grade 1 and 2 was found in 46.4% and 35.7% of patients, respectively. No higher graded GI-toxicity occurred. Maximal GI- and GU-toxicity was seen in week 7 and 8 of radiotherapy. Additionally, CTCAE urinary incontinence was assessed: most patients (n = 22; 78.6%) did not develop incontinence. At first FU, two patients (7.1%) reported grade 1 toxicity (no pads necessary) and no higher toxicity was reported. Skin erythema of RTOG grade 1 or 2 was present towards the end of radiotherapy in 78.6% (n = 22) of patients and no higher graded skin toxicity occurred. At first FU, only one patient still suffered from RTOG grade 1 skin toxicity.

Late toxicity

Long-term toxicity was evaluated in 26/28 patients after a median FU of 7.4 years (range 0.7–9.3 years; mean 7.1 years). Toxicity was scored as cumulative maximum over study period and as toxicity at last follow-up (LFU).

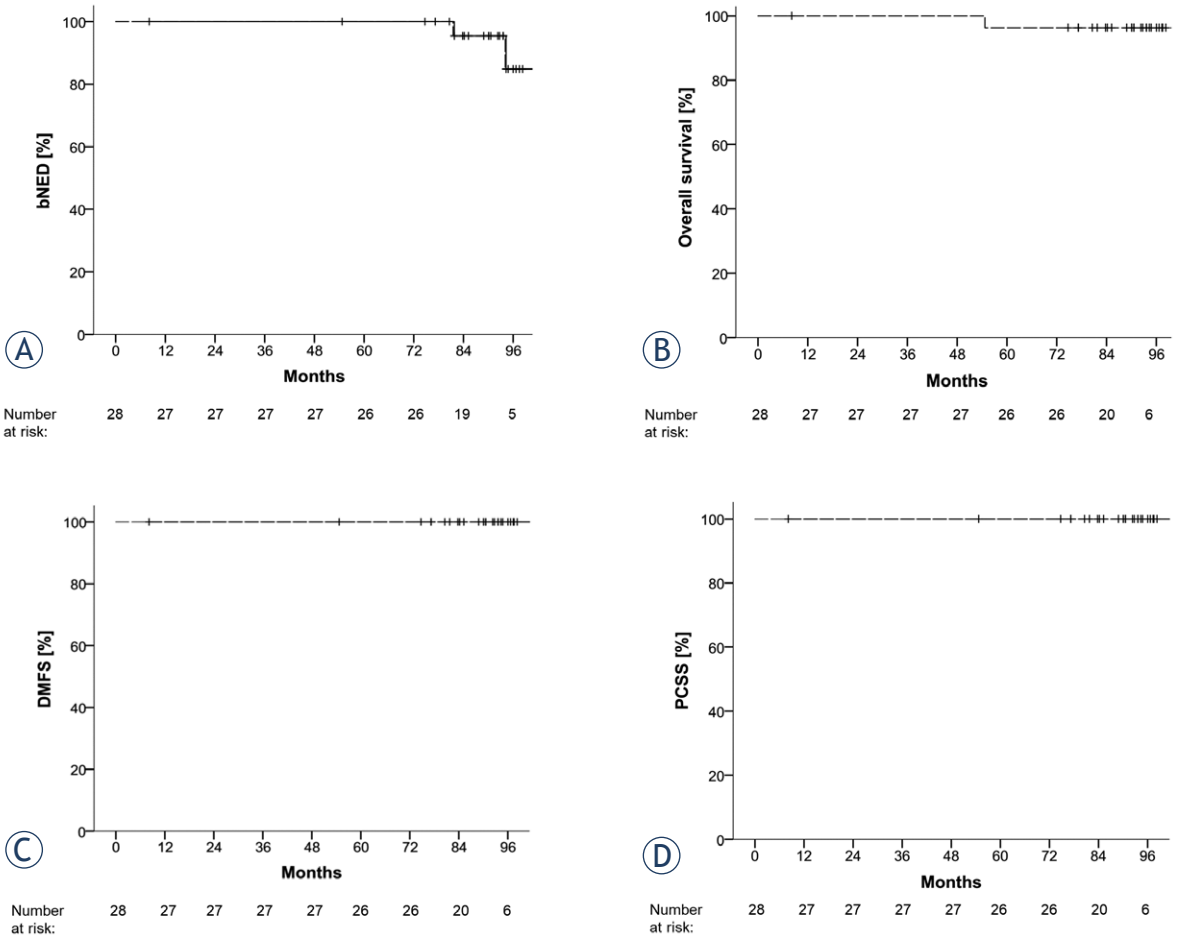

FIGURE 2. Survival outcomes: Kaplan-Meier curves of biochemically no evidence of disease (bNED), overall survival (OS), distant metastasis-free survival (DMFS) and prostate-cancer specific survival (PCSS).

Late GU-toxicity

Most late GU-toxicity occurred 3–5 years post RT and seemed to decrease in prevalence towards LFU. Mild late bladder toxicity (RTOG G1) at LFU was observed in 14.3% of patients and no higher toxicity occurred (Figure 3). At LFU, 14.3% and 10.7% of patients reported urinary frequency of CTC grades 1 and 2, respectively and no higher toxicity occurred. A urinary retention of CTC grade 1 and 2 was seen in 21.4% and 7.1% of patients at LFU (Figure 3). Urinary urgency of CTC grade 1 and 2 at LFU was present in 10.7% and 3.6% of patients showing no increase in prevalence over time. Urinary incontinence of CTC grade 1 (no pads needed) was reported by 21.4% of patients at LFU. Incontinence peaked 4–5 years after RT and then showed a decrease over time (supplement data).

GI Toxicity

Late rectal toxicities (RTOG) at LFU of grade 1 (7.1% of patients) and of grade 2 (3.6%) were observed (Figure 4). A peak in late GI-toxicity (RTOG) of grade 1 was seen 4 years post RT and then seemed to decrease again in prevalence. Gastrointestinal grade 3 toxicity, presenting with rectal bleeding, was observed in two patients (RTOG GI late, CTC rectal hemorrhage and CTC proctitis due to overlapping toxicity scoring). Both patients had pre-existing hemorrhoids and hemorrhoidal operations in their medical history. This occurred 9 months and 19 months post RT, respectively. After treatment with Argon-Plasma-Coagulation, no further grade 3 toxicity occurred in these two patients or others. Mild rectal hemorrhaging (CTC grade 1) was present in 14.3% of patients at LFU. Proctitis

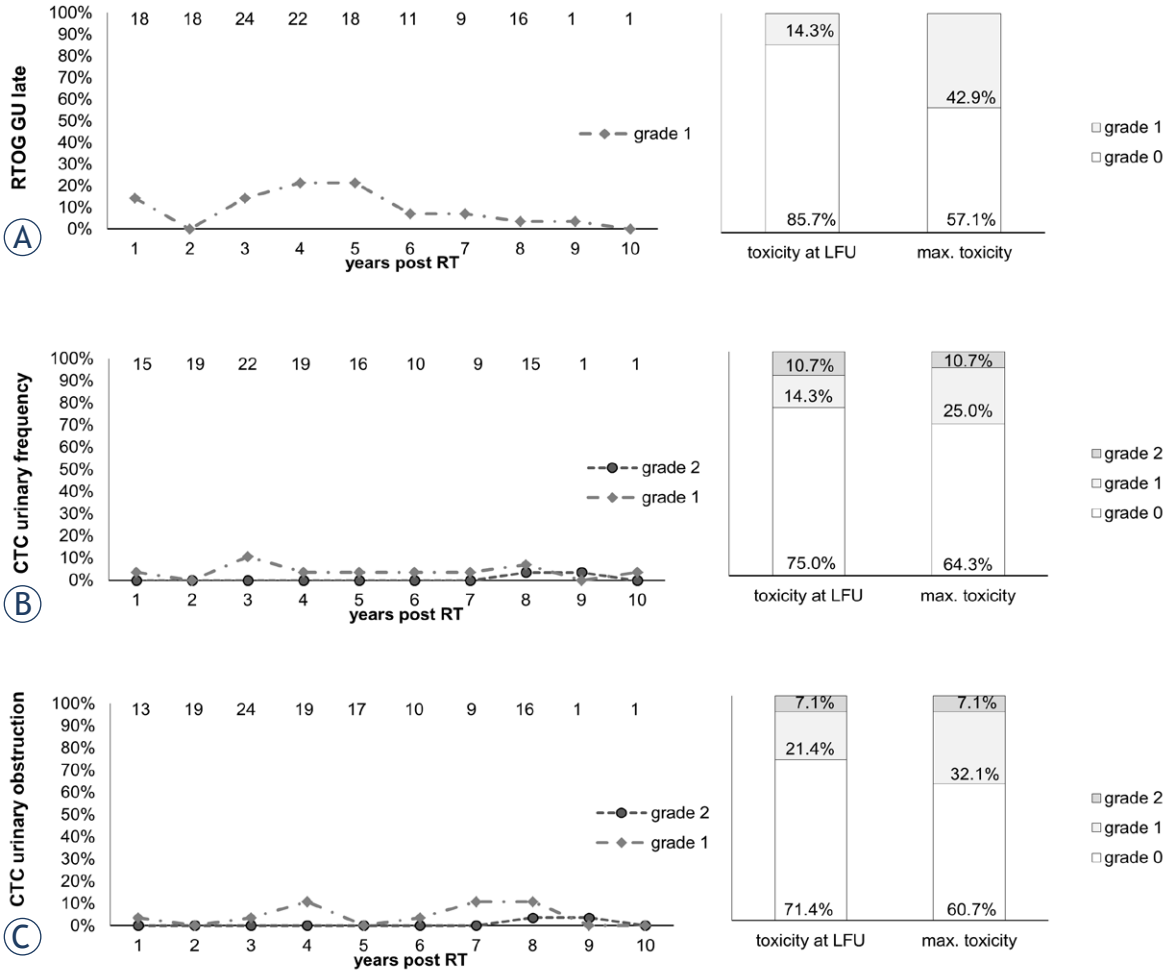

FIGURE 3. Late genitourinary (GU) toxicity items *Radiation Therapy Oncology Group (RTOG) bladder late, common terminology criteria (CTC) urinary frequency* and *CTC urinary obstruction* scored over the follow up (FU) period (left).

Y-axis: percentage of patients reporting the toxicity item. Top X-axis: number n of patients with data available. Lower X-axis: years after radiotherapy. Right column: maximum late toxicity summed up by grade

of CTC grade 1 (2) was present in 10.7% (7.1%) of patients at LFU (Figure 4). Diarrhea of CTC grade 1 and 2 were present in 10.7% and 3.6% of patients, respectively. While diarrhea symptoms subsided 2 years post RT, it was reported again in one patient 8 years after radiotherapy (supplement data). Fecal incontinence of grade 1 and 2 occurred each in one patient (3.6%), undulating over the FU period with no increase of severity of the symptom (supplement data).

Dose-volume-histogram parameter

Mean V70 PRV-bladder was 11.08% with this approach (accepted threshold: V70 bladder <35%). Mean V70 PRV-rectum was 13.03% (accepted threshold: V70 rectum <15%). These constraints were based on the QUANTEC data and adjusted according to house standard. Due to these constraints, the mean CovP-ITV dose was 75.40 Gy (V78 = 26.77%).

Discussion

In this prospective study, we report the feasibility and safety of a probabilistic planning concept for radiotherapy of intermediate risk prostate cancer patients based on the coverage probability. Dose-escalation to 78 Gy was aimed with this technique showing very high long-term biochemical control rates and excellent survival rates. The toxicity profile was moderate with 85% of patients presenting without any GU/GI-toxicity at last follow-up in-

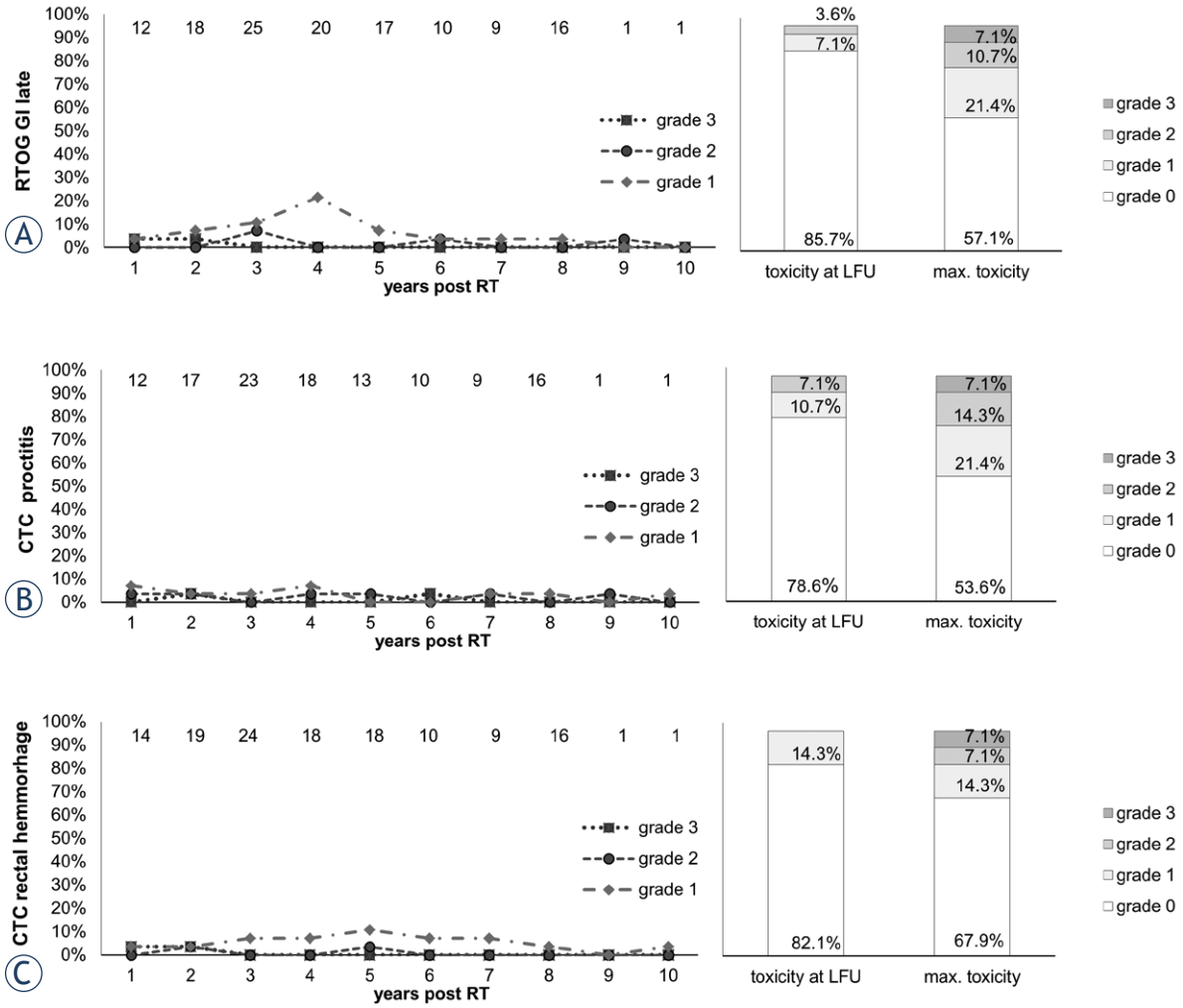

FIGURE 4. Late gastrointestinal (GI) toxicity items *Radiation Therapy Oncology Group (RTOG) rectum late*, *common terminology criteria (CTC) proctitis* and *CTC rectal hemorrhage* scored over the follow up (FU) period (left).

Y-axis: percentage of patients reporting the toxicity item. Top X-axis: Number n of patients with data available. Lower X-axis: years after radiotherapy. Right column: maximum late toxicity summed up by grade.

dicating that CovP is a robust plan optimization achieving both low toxicity and favorable outcome.

In the planning phase of this study in 2007, dose escalation to 78 Gy was a novel concept in need of evaluation of safety and superiority to the former "standard" therapies of 3D-RT or IMRT of the prostate up to 70 Gy. Meanwhile, several studies could show a benefit to PCSS of dose escalation[14-17] and a total dose of 74 to 80 Gy is the current standard of care and recommended in national guidelines.[2,3] Our study concept on probabilistic treatment planning is substantiated by excellent bNED-rates of 95.5% after 7.1 years (DMFS: 100%, OS: 96.4%). Two patients developed a biochemical recurrence. In one of these two patients, PSMA-PET-CT showed a local recurrence in the prostate. This patient had not received ADT due to cardiac diseases. In the other patient, a biochemical recurrence occurred at LFU and no further information on staging was available at the time of analysis of this study. Large studies of similar patient cohorts reached bNED-rates of 55–90% and DMFS of 88-100% (in the dose-escalated study arms treated with normofractionated RT with 74-86.4 Gy total dose) after 5 years of FU.[14-16,18-20] Compared to the 7.1 years FU of this study, only the M.D. Anderson trial could provide a longer FU period of 8.7 years in the mean.[16] Our results are especially interesting in regard to the achieved mean ITV-dose of 75.40 Gy (V78 = 26.7%) because this dose is in the lower dose range of the mentioned studies. Therefore, it could be hypothesized that robust treatment planning implementing probabilities of target volumes and OARs might be more relevant than dose-escalation to at least 78 Gy. And the standard one-CTV/PTV approach might be more at risk for target miss compared to a robust ITV concept, as was examined in another publication by our deparmenten.[9] However, there are restrictions in comparability due to differences in the included tumor stages, ADT (no information about ADT in the study of Goldner *et al*.; no ADT in the M.D. Anderson trial.[16,20] Taken together, the study treatment compares well to current standard treatments in PCSS and bNED.

The toxicity of this treatment approach is a central quality parameter, especially considering the potentially larger target volume (CovP-ITV) compared to a one-pCT approach. Acute GU- and GI-toxicity was acceptable with only grade 1 and grade 2 (RTOG, CTC scores) and no grade 3+ toxicity. While certain items showed a peak after 3 weeks of RT (RTOG bladder acute) or 5 weeks (CTC urinary Incontinence, RTOG GI acute), most items showed an increase of toxicity prevalence towards the end of RT and the early peaks most likely origin in coincidental accumulation due to the limited patient size of the study. Towards the first FU-examination 3 months post RT, mostly grade 1 toxicity persisted. It is noteworthy that using the CTC-classification probably overestimates the item urinary incontinence in comparison to other studies since for example in the PROTECT-study, incontinence of grade 1 was defined as need of ≥1 pad per day which equals CTC incontinence of grade 2.[21] In contrast, CTC incontinence of grade 1 – as measured in this study - is defined as occasional incontinence (pressure, coughing) not requiring pads.

Interestingly, late GU-toxicity of grade 1 or 2 (RTOG bladder late, CTC incontinence, CTC urgency) occurred only temporarily in this study population and decreased in prevalence after 5 years after RT. To date, consensus understanding of radiation biology is the continuous increase of late effects over time.[22] No further data describing decreasing late toxicity after pelvic radiation is known to the authors.[23,24] Due to the small sample size, random distribution of data and/or psychological factors such as patient habituation or recall bias cannot be ruled out.

Late GI-toxicity also showed no sign of increment over time and was generally rare: At LFU RTOG grade 2 toxicity was only present in one patient. Regarding rectal hemorrhaging, we suppose that the predisposition of hemorrhoids in those patients who developed this toxicity can be regarded as the (established) major risk factor.[25] Taken together, the low toxicity rates in this cohort compare well to larger studies and demonstrate a favorable therapeutic window of the CovP-concept.[14-16,18,20,23,26,27] The coverage concept has been described before in detail.[7,8,9] The advantages include a safe margin with high PTV coverage, based on the individual OAR- and prostate motion of each patient, and measured by three planning-CTs. The idea behind the concept is a foreseen adaption of intra- and interfractional motion and deformation and therefore reduced verification intervals are needed. The efficacy of this method could be demonstrated in this study. Additionally, toxicity rates were not increased compared to standard techniques. The CovP-concept with 7 mm margin does not require daily image guidance due to its robustness as shown elsewhere.[9] This might save radiation dose and on-table time for the department. Especially in patients who cannot undergo fiducial implementation or other invasive procedures such as rectum spacers[4,28] or patients with larger positional varia-

tion of the prostate, this technique presents a useful and safe alternative.[7]

This study has several limitations: Further evaluation of outcome data in a larger study population is necessary. Additionally, there was no control group to compare toxicity and outcome to. In one patient, the study therapy was not accomplished due to unknown reasons. Three planning-CTs are necessary for this method, causing extra burden on staff and patient, including additional radiation dose for the latter. However, we believe that the benefits, especially the reduced need for image verification or implantation of fiducials *etc.*, outweigh the disadvantages and might even save radiation dose to the patient. Lastly, the performed step-and-shoot IMRT technique is mainly replaced by VMAT-techniques which leave slightly more options for OAR dose reduction and target dose escalation.[9] However, the excellent late toxicity data and bNED rates support the relevance of this approach leading to an implementation in current study protocols.[29]

Conclusions

Coverage probability-based IMRT was feasible in a clinical study. Dose escalation with the CovP-concept was associated with a low rate of toxicity and a high efficacy regarding local and distant control, comparing well to studies with similar patient cohorts. Benefits include reduced target miss due to inclusion of potential inter- and intrafraction motion and reduced radiation dose due to less need for verification images. Utilization in other tumor entities and/or with contemporary RT techniques is being currently tested (NCT03617133).

Availability of data and material and authors contributions

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

BB, MA. OD, FP and MB were responsible for the creation of the study protocol, ethical approval, patient enrollment and study therapy. DW, ZO and ACM were responsible for data acquisition, statistical analysis and writing of the manuscript. DT, DZ, FP and MA were responsible for manuscript revision and proof reading.

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research article

Effect of the oral intake of astaxanthin on semen parameters in patients with oligo-astheno-teratozoospermia: a randomized double-blind placebo-controlled trial

Senka Imamovic Kumalic[1,2], Irma Virant Klun[1,2], Eda Vrtacnik Bokal[1,2], Bojana Pinter[1,2]

[1] Division of Obstetrics and Gynecology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[2] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

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Correspondence to: Assoc. Prof. Bojana Pinter, M.D., Ph.D., M.S. (Econ), Specialist in Obstetrics and Gynecology, University Medical Centre Ljubljana, Division of Obstetrics and Gynecology; Faculty of Medicine University of Ljubljana, Šlajmerjeva 3, 1000 Ljubljana, Slovenia.
E-mail: bojana.pinter@guest.arnes.si

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Background. Higher concentrations of seminal reactive oxygen species may be related to male infertility. Astaxanthin with high antioxidant activity can have an impact on the prevention and treatment of various health conditions, including cancer. However, efficacy studies on astaxanthin in patients with oligospermia with/without astheno- or teratozoospermia (O±A±T) have not yet been reported. Our aim was to evaluate the effect of the oral intake of astaxanthin on semen parameters.

Patients and methods. In a randomized double-blind trial, 80 men with O±A±T were allocated to intervention with 16 mg astaxanthin orally daily or placebo. At baseline and after three months basic semen parameters, sperm deoxyribonucleic acid (DNA) fragmentation and mitochondrial membrane potential (MMP) of spermatozoa and serum follicle-stimulating hormone (FSH) value were measured.

Results. Analysis of the results of 72 patients completing the study (37 in the study group, 35 in the placebo group) did not show any statistically significant change, in the astaxanthin group no improvements in the total number of spermatozoa, concentration of spermatozoa, total motility of spermatozoa, morphology of spermatozoa, DNA fragmentation and mitochondrial membrane potential of spermatozoa or serum FSH were determined. In the placebo group, statistically significant changes in the total number and concentration of spermatozoa were determined.

Conclusions. The oral intake of astaxanthin did not affect any semen parameters in patients with O±A±T.

Key words: antioxidant; male infertility; oligo-astheno-teratozoospermia; semen quality; DNA fragmentation; cancer

Introduction

Currently, almost every seventh couple is infertile. The male factor as the single or additional reason for infertility is presented in nearly 50% of infertile couples.[1] World Health Organization (WHO) defines oligo-astheno-teratozoospermia (OAT) as the concentration and the proportions of motile and morphologically normal spermatozoa below the reference values.[2]

One of the many pathophysiological factors of male infertility are higher concentrations of seminal reactive oxygen species (ROS).[3] The uncontrolled production of these molecules may be harmful to cells and different biomolecules such as carbohydrates, amino acids, proteins, lipids, and deoxyribonucleic acid (DNA), which can be damaged. ROS can have a negative influence on sperm function and quality[4-7] due to the reduced motility of spermatozoa[8], DNA damage[9-11] and the

impaired integrity of the cellular membrane.[7,12,13] It was revealed that infertile men with low semen concentration, poor semen motility, and a high proportion of morphologically abnormal spermatozoa were associated with an increased risk of testicular cancer.[14,15] Several antioxidants are present within the ejaculate as protection against excessive ROS-induced lipid peroxidation.[16] It has been confirmed that antioxidant capacity in semen is decreased in infertile men and men with testicular cancer with a high ROS proportion, compared to men with a normal proportion of ROS.[17–19]

Sperm function tests have arisen as a supplement to standard semen analysis.[20] The DNA integrity of spermatozoa has a critical impact in determining sperm competence[21,22] which is related to ROS levels[9,10] and can be measured by sperm DNA fragmentation (SDF) assays.[21,22] A recent meta-analysis of 28 studies demonstrated that SDF is more accurate in determining the function of spermatozoa compared to conventional semen parameters.[23] A study of apoptotic DNA fragmentation in human spermatozoa found a significant increase in apoptotic SDF in the semen of testicular cancer patients post-orchiectomy and in OAT patients compared to a control group of healthy men.[24] In addition to DNA integrity, mitochondria have an important impact on cell function[25], and the sperm mitochondrial membrane potential (MMP) contributes some benefit to male fertility potential and sperm quality.[26] Combined SDF and MMP may act as better predictors of natural conception than standard semen parameters.[27]

Regarding the role of seminal antioxidant capacity in male infertility, several trials on the impact of antioxidants on semen characteristics have been performed. The review of randomized and placebo-controlled trials affirmed the favorable impact of some types of antioxidants on different semen characteristics.[28] Several studies have shown favorable effects, especially on the motility of spermatozoa.[29-34] In some trials, antioxidant combinations (coenzyme Q10, vitamin C, vitamin E, selenium, zinc, L-carnitine, etc.) were assessed.[35–40] The most recent Cohrane review shows that for couples attending fertility clinics, pregnancy rates and live births may be improved with antioxidant supplementation in subfertile males.[41]

As one of many antioxidants, ketocarotenoid astaxanthin has the potential to prevent and treat various diseases, including diabetes, liver and renal diseases, cancer, chronic inflammatory diseases, cardiovascular diseases, eye and skin diseases, metabolic syndrome, gastrointestinal diseases, and neurodegenerative diseases.[42] Astaxanthin accumulates in the microalga *Haematococcus pluvialis,* and compared to vitamin E, this compound has up to 100 times higher antioxidant activity.[43] Astaxanthin is a food supplement and widely available over-the-counter. Until now, there were two "in vitro" studies that first showed the positive effect of astaxanthin on sperm capacitation in 24 healthy, fertile men[44]; subsequently, the positive effect on sperm capacitation in 27 men from couples who did not succeed to conceive after at least twelve months of regular unprotected intercourse was confirmed.[45] On the other hand, there has been only one clinical trial investigating the influence of astaxanthin on male fertility published until now. The trial included a low number of patients with a history of male infertility – 11 patients in the study group and 19 patients in the placebo group; however, these patients were enrolled without regard for semen characteristics.[46] Favorable changes in inhibin B concentration, sperm linear velocity and ROS levels, and pregnancy rate were determined. However, the efficacy of astaxanthin oral intake on semen parameters in OAT patients treated for infertility has not yet been reported.

The aim of this prospective randomized double-blind placebo-controlled clinical trial was to assess the effect of three-month intake of astaxanthin in infertile men with oligospermia with/without astheno- or teratozoospermia (O±A±T) on basic semen parameters, DNA fragmentation and mitochondrial membrane potential of spermatozoa, and serum level of follicle-stimulating hormone (FSH).

Patients and methods

The prospective randomized double-blind placebo-controlled trial was performed from November 2014 to January 2019 at the outpatient infertility clinic, Department of Human Reproduction, Division of Obstetrics and Gynecology of the University Medical Centre Ljubljana, Slovenia. The study was approved by the Slovenian National Medical Ethics Committee (consent number 145/02/14) and was registered at ClinicalTrials.gov, NCT02310087. All participants were enrolled after they provided written informed consent to participate in the trial.

Participants

A total of 80 infertile men with O±A±T were enrolled after they signed a written informed consent

to participate in this trial. They were considered O±A±T after at least two previous semen analysis (seminogram) and andrological examination in the frame of their infertility treatment after their partner being unable to conceive for at least 12 months of unprotected sexual intercourse or after a failed assisted conception procedure. Semen quality was defined as O±A±T according to the WHO 2010 guidelines: oligospermia (O) − sperm concentration < 15 million/ml; asthenozoospermia (A) − progressive motility of spermatozoa < 32%; teratozoospermia (T) − < 4% spermatozoa with normal morphology.[20] The exclusion criteria were smoking more than 20 cigarettes per day, genetic causes of infertility, endocrinopathies, genital tract infections, undescended testis, systemic diseases, history of testicular cancer and treatment with other drugs and food supplements, such as antioxidants, during the last three months before enrolling in this study.

Intervention and methods

Eighty eligible infertile men with O±A±T were allocated at random to daily intake of 16 mg of astaxanthin capsules (Astasan) or placebo capsules, both produced by the same manufacturer (Sensilab). Astaxanthin capsules contained astaxanthin, vitamin E as a stabilizer, safflower oil, gelatin, water and glycerine. Placebo capsules were identical both in appearance and taste, containing gelatine, water and glycerine only. A computerized randomization table was used for the purpose of randomization. A random allocation sequence was generated and participants were enrolled and assigned to interventions by a third party, thus ensuring that both the enrolled participants and researchers were blinded. At baseline and after three months of treatment, all participants answered a questionnaire about their age, height, weight, smoking status and the history of current occupational exposure to high temperatures, ultraviolet or radiology radiation, chemicals, or a predominant sedentary job in order to exclude the potential effect of these factors on semen quality. The semen samples were obtained by masturbation after 2–5 days of sexual abstinence. Semen quality was assessed according to the WHO guidelines.[20] The total number, concentration, motility and morphology were determined by international standard laboratory microscopic analyses.[47]

Sperm DNA fragmentation in our study was evaluated using a TUNEL assay – measuring DNA fragmentation in spermatozoa using terminal deoxyribonucleotidyl transferase (TdT)-mediated dUTP nick-end labelling.[48] The calculated threshold value for the TUNEL assay to distinguish between normal and abnormal semen samples in men was 20%.[49] MMP was measured by means of 3,3'-dihexyloxacarbocyanine iodide (DiOC6(3)) staining as an indicator of mitochondrial membrane integrity and the mitochondrial potential capacity to generate ATP by oxidative phosphorylation.[50] Propidium iodide (PI) was used as a supravital fluorescent dye and stained spermatozoa were analyzed by flow cytometry. MMP was considered to be normal in our laboratory setting when the proportion of spermatozoa with normal MMP (attributed to cells with high fluorescence signals) was higher than 60%.[27] The serum level of FSH was measured by a solid-phase, two-site chemiluminescent immunometric assay. The normal FSH values for males in our laboratory setting were 0.7–11.1 IU/L.

Sample size calculation

To estimate the sample size for the study, we anticipated an increase in sperm concentration in the astaxanthin group, as reported in the only clinical study until now.[46] With the assumption of a 34% increase as reported, with alpha 0.05 and power 80%, 32 cases were needed in each group. To account for drop-outs, we aimed to recruit 40 cases in each group.

Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Science (SPSS), version 25, IBM Corp, Armonk, NY, USA. An independent Student's t-test was used to analyze normally distributed data, and the Mann-Whitney test was used to analyze data that were not distributed normally. A paired t-test or the Wilcoxon test were applied to analyze the differences in the semen variables within groups. The chi-square test was applied to compare the exposure to occupational factors between groups. The results of continuous variables were expressed as the mean ± SD. P-values < 0.05 were considered significant.

Results

A group of 256 men was assessed for eligibility; half (126 men, 49.2%) declined to participate, and 50 did not meet the inclusion criteria; 80 men were eligible and willing to participate and these indi-

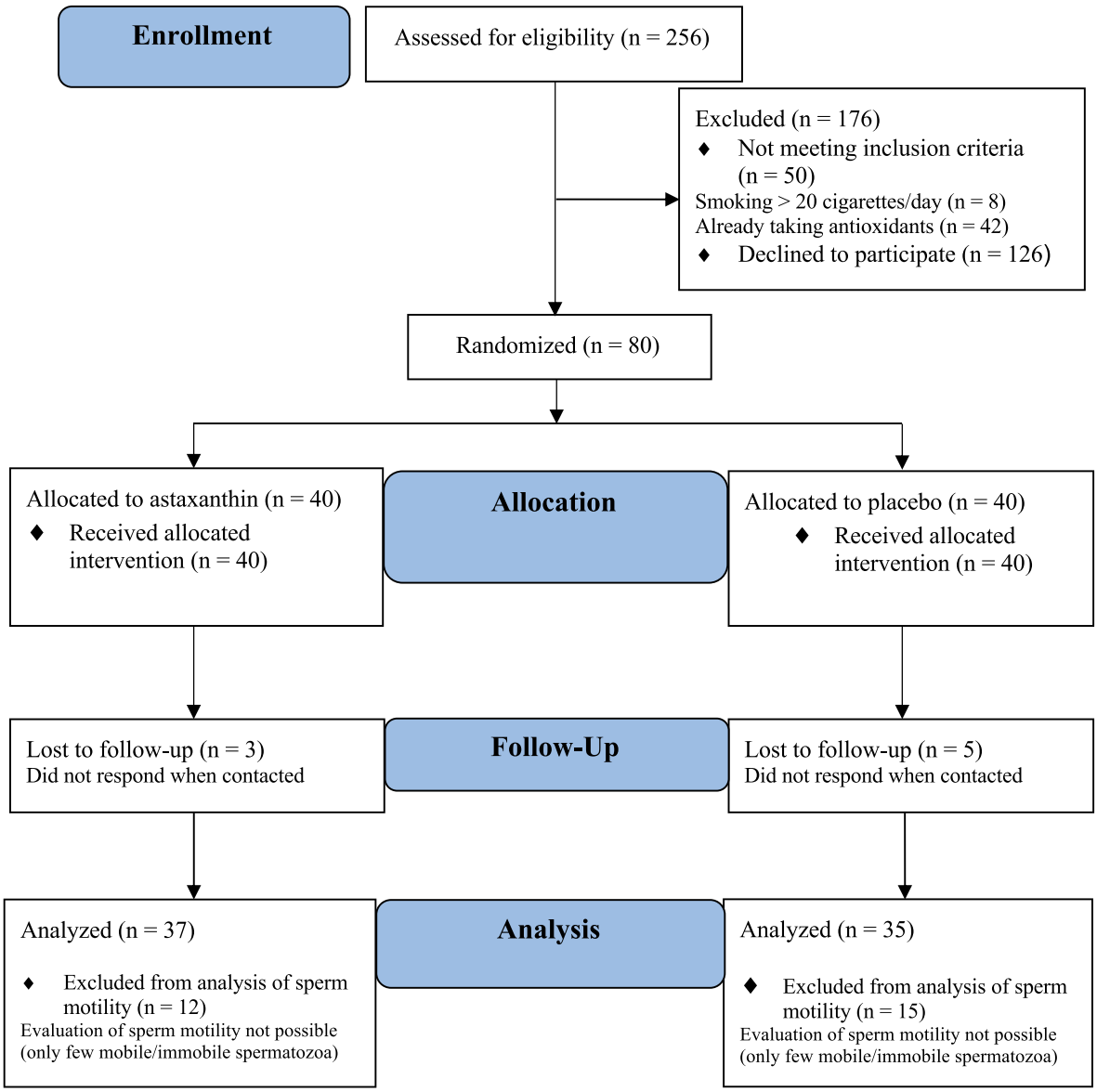

FIGURE 1. CONSORT flow chart of study presenting the inclusion criteria, randomization and follow-up of participants.

viduals were randomized. Eight patients in both groups (10%) dropped out for personal reasons during the treatment, and thus, 72 patients completed the trial. No adverse effects during the treatment were reported. Finally, we analyzed the effect of treatment in 37 patients in the astaxanthin and 35 patients in the placebo group (Figure 1).

Five patients were not included in the statistical analyses on changes in sperm total number and concentration and 27 patients were not included in the statistical analyses on the motility of spermatozoa as in these patients only a few mobile or immobile spermatozoa in the semen sample were present. At baseline, all patients in the astaxanthin group were in accordance with WHO criteria for OAT. In the placebo group, all patients were in accordance with the WHO criteria for oligo-teratozoospermia and two-thirds for asthenozoospermia.

The epidemiological and semen characteristics of the included patients are summarized in Table 1. There were no statistically significant differences between all parameters of both groups of patients upon enrollment. In addition, exposure of patients to chemicals, ultraviolet rays, X-ray radiation, high temperature, and a sedentary job according to their history (questionnaire) have not been related to the semen parameters in the studied population of men.

The pre- and post-treatment semen parameters and hormonal levels of both groups of patients are displayed in Table 2. The three-month treatment of patients with astaxanthin did not affect the semen parameters or serum FSH levels in any way. Interestingly, the significant change after the three-month period was the increased total number (16.0 ± 21.1 *vs*. 38.4 ± 69.2 million/ejaculate, p = 0.002) and concentration (5.7 ± 5.9 *vs*. 10.2 ± 15.7 million/ml, p = 0.024) of spermatozoa in the placebo group, but not in the astaxanthin group (24.6 ± 28.6 *vs*. 31.7 ± 33.4 million/ejaculate, p = 0.186, and 7.0 ± 5.6 *vs*. 9.2 ± 7.9 million/ml, p = 0.100).

To address the increase in the concentration of spermatozoa in the placebo group, we separately analyzed the seasonal inclusion of patients into the trial to review the potential seasonal changes of semen quality. Nineteen patients in the astaxanthin group and 18 patients in the placebo group were enrolled in the study during the winter/spring period, and 18 patients in the astaxanthin group and 17 patients in the placebo group were enrolled during the summer/fall seasons. There was no significant difference in the seasonal inclusion of patients in the trial (p = 0.995).

TABLE 1. Comparison of baseline characteristics of patients in astaxanthin and placebo groups

Characteristic	Astaxanthin (n = 37)	Placebo (n = 35)	p-value
Age (years)	35.0 ± 5.2	36.4 ± 5.5	0.276
BMI (kg/m^2)	25.9 ± 3.8	27.1 ± 4.6	0.162
Smoking (no. of cigarettes smoked / day)	4.8 ± 6.8	3.6 ± 6.8	0.264
Sperm concentration (million /ml)*	6.9 ± 5.7	5.4 ± 5.8	0.297
Total sperm number (million/ejaculate)*	23.9 ± 28.4	15.6 ± 21.0	0.164
Total sperm motility (%)**	29.9 ± 14.8	38.2 ± 14.8	0.063
Progressive sperm motility (%)**	25.1 ± 14.5	33.3 ± 14.6	0.063
Sperm morphology (%)	1.8 ± 2.1	1.9 ± 2.0	0.663
Sperm head defect (%)	95.1 ± 16.2	97.5 ± 3.3	0.936
Sperm neck + midpiece defect (%)	2.9 ± 16.4	0.2 ± 0.8	0.981
Sperm tail defect (%)	0.2 ± 0.6	0.5 ± 1.0	0.424
Leukocytes with peroxidase (million/ml)	0.3 ± 0.3	0.5 ± 0.8	0.976
Mitochondrial membrane potential (%)***	27.5 ± 18.5	26.9 ± 15.3	0.888
DNA fragmentation (%)	50.5 ± 23.9	45.8 ± 21.8	0.424
FSH (IU/l)	9.7 ± 7.8	9.2 ± 5.8	0.919
Chemicals at work (% exposed)	5.4	14.3	0.204
Ultraviolet rays at work (% exposed)	2.7	0	0.327
X-ray at work (% exposed)	0	11.4	0.051
High temperature at work (% exposed)	13.5	14.3	0.925
Sedentary job (% exposed)	45.9	40.0	0.611

Results are presented as average (± SD) or percentage (%). Differences at baseline assessed with independent Student t-test, Mann-Whitney U-test or Chi-square test, as appropriate.

* = the analysis for total sperm number and sperm concentration was made for 34/37 patients from the astaxanthin group and 35/35 patients from the placebo group, since the excluded patients only had a few mobile or immobile spermatozoa in the semen sample;

** = the analysis for total and progressive sperm motility was made for 25/37 patients from the astaxanthin group and 20/35 patients from placebo group, since the excluded patients only had a few mobile or immobile spermatozoa in the semen sample;

***= the proportion of spermatozoa with normal MMP;

BMI = body mass index; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone

Discussion

The present study is the first study of astaxanthin efficacy on semen parameters in oligo-astheno-teratozoospermic patients who were treated for infertility. Our results did not show any significant improvements in the basic semen parameters or at the cellular level (SDF, MMP) or serum FSH values after oral intake of astaxanthin. In previously published studies on the effects of antioxidants in semen quality[28,32,38,39], the semen quality was defined according to the WHO 1999 guidelines. On the other hand, our patients were included based on their semen quality in line with the WHO 2010 guidelines, which have lower threshold values. Therefore, our patients were enrolled in the study with considerably poorer semen quality compared to patients in previous studies, which followed older WHO guidelines. Considering cancer patients, both chemotherapy and radiation have measurable effects on the sperm number, motility, morphology, and DNA integrity.[51] Although treatment usually represents the greatest threat to the fertility of male survivors, the underlying malignancy may additionally affect semen production and quality. In cases of testicular cancer, the rates of oligospermia and azoospermia at presentation are 50% and 10%, respectively.[52–55] Similarly, Hodgkin Lymphoma is associated with oligospermia and azoospermia before the treatment, and depending on the treatment regimen, also after.[56–58] According to poor starting values of basic sperm parameters in our patients, in addition to their low MMP and very high DNA fragmentation, it can be concluded that our patients, in general, had poorer semen quality as subjects in the previous studies due to the lower threshold of the new WHO guidelines.

TABLE 2. Comparison of basic semen parameters, sperm MMP, DNA fragmentation, serum FSH values in astaxanthin and placebo groups after three-month treatment period

Parameter	Astaxanthin (n = 37)			Placebo (n = 35)		
	Baseline	After 3 months	p-value	Baseline	After 3 months	p-value
Sperm concentration (million /ml)*	7.0 ± 5.6	9.2 ± 7.9	0.100	5.7 ± 5.9	10.2 ± 15.7	0.024
Total sperm number (million/ejaculate)*	24.6 ± 28.6	31.7 ± 33.4	0.186	16.0 ± 21.1	38.4 ± 69.2	0.002
Total sperm motility (%)**	32.3 ± 14.0	37.9 ± 14.7	0.172	38.0 ± 15.0	43.1 ± 12.8	0.164
Progressive sperm motility (%)**	27.3 ± 14.0	33.0 ± 14.7	0.171	33.1 ± 14.7	38.1 ± 12.8	0.176
Sperm morphology (%)	1.8 ± 2.1	1.6 ± 1.4	0.471	1.9 ± 2.0	2.0 ± 1.7	0.913
Sperm head defect (%)	95.1 ± 16.2	97.8 ± 2.2	0.785	97.5 ± 3.3	97.2 ± 2.7	0.836
Sperm neck + midpiece defect (%)	2.9 ± 16.4	0.2 ± 0.7	0.916	0.2 ± 0.8	0.3 ± 0.8	0.472
Sperm tail defect (%)	0.2 ± 0.6	0.4 ± 0.9	0.253	0.5 ± 1.0	0.5 ± 0.9	0.872
Leukocytes with peroxidase (million/ml)	0.3 ± 0.3	0.5 ± 0.7	0.155	0.5 ± 0.8	0.6 ± 0.9	0.365
Mitochondrial membrane potential (%)***	27.5 ± 18.5	26.3 ± 18.5	0.375	26.9 ± 15.3	27.1 ± 15.9	0.925
DNA fragmentation (%)	50.5 ± 23.9	51.2 ± 17.9	0.958	45.8 ± 21.8	49.8 ± 16.9	0.116
FSH IU/l)	9.7 ± 7.8	10.0 ± 8.3	0.200	9.2 ± 5.8	9.7 ± 6.5	0.345

Results presented as average (±SD) or percentage (%). Differences within groups between baseline and after 3 months assessed with paired t-test and Wilcoxon test, as appropriate.

* = the analysis for total sperm number and sperm concentration was made for 33/37 patients from the astaxanthin group and 34/35 patients from the placebo group, since the excluded patients only had a few mobile or immobile spermatozoa in the semen sample;

** = the analysis for total and progressive sperm motility was made for 22/37 patients from the astaxanthin group and 16/35 patients from the placebo group, since the excluded patients only had a few mobile or immobile spermatozoa in the semen sample;

***: the proportion of spermatozoa with normal sperm mitochondrial membrane potential (MMP);

DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone

Under these conditions, our study revealed that antioxidant astaxanthin could not improve semen quality in cases of very poor semen quality, which could also be of great importance for cancer patients.

Our results are in contrast to a previous study by Comhaire, which determined favorable changes in the inhibin B concentration, sperm linear velocity and ROS levels, and pregnancy rate after astaxanthin treatment in the same dosage of astaxanthin as in our study. However, the study enrolled a low number of infertile males (11 in the study group and 19 in the placebo group) and was not based on semen analysis but rather on a more than twelve months' infertility history of female partners having no verifiable cause of infertility.[46] Interestingly, another recent study, similar to our study, showed that different antioxidants did not affect the semen quality in a larger group of infertile patients.[59] Similar results of no effect of antioxidants were found in some other studies.[38,60–63] These data show that antioxidants are interesting, but the clinical data should be comprehended with prudence.

The improved total number and concentrations of spermatozoa after three months of treatment with a placebo could reflect the beneficial psychological effect of placebo on patients. In the literature, the strength of expectations is connected to the degree of the placebo effect.[64,65] The appearance of a medication, past experience, verbal information, and relationship between a patient and physician may influence the patient's expectations.[66] However, previously published reviews on the effects of oral antioxidants on semen quality did not show any positive effect of the placebo in the placebo-controlled studies.[28,67]

On average, the FSH value in the studied population was relatively high thus indicating the imbalance of the pituitary-gonadal endocrine axis and hypogonadism with a serious damage of spermatogenesis. In infertile men, a higher concentration of FSH is considered to be a reliable indicator of germinal epithelial damage, and was shown to be associated with azoospermia and severe oligozoospermia.[68] This indicates that the studied population of men in our study was facing severe male infertility (severe OAT).

The advantage of our prospective, double-blind study includes the good randomization of patients for astaxanthin or placebo treatment. At baseline, both groups were comparable by their characteristics. We included patients based on their previous seminograms, and they were all clinically examined by an experienced andrologist. Additionally, strict exclusion criteria were used. Besides, this is the first clinical study of the efficacy of astaxanthin oral intake on semen parameters in severe oligo-astheno-teratozoospermic patients treated for infertility. The number of patients included is higher compared to similar placebo-controlled studies of other antioxidants.[32,39,69,70] Astaxanthin group was homogenous because all patients accorded with WHO 2010 criteria for O+A+T. In the placebo group, two-thirds of patients also met the criteria for O+A+T; the average progressive motility of spermatozoa was just above the reference value (33.1 ± 14.7%), but the average total motility of spermatozoa was below the reference value. Therefore, the placebo group was also considered to be homogenous. Nevertheless, our study had some limitations, since one-third of patients had only a few mobile or immobile spermatozoa during the semen analysis; therefore, the measurements and statistical analysis for the total number, concentration and motility of spermatozoa in these patients were not possible. In addition, a relatively high proportion of patients declined to participate in this study.

As our study was performed with humans who gave consent to participate, it is our ethical obligation to also report the results with no evidence of an effect.[71,72] Also, our study delivers an important fact that the clinical study on the astaxanthin effect in oligo-astheno-teratozoospermia was carried out. Unreported or unpublished negative findings introduce a bias in meta-analysis.[73] Last but not least, the results could be an important part of future scientifically fair and flawless meta-analyses and reviews of the effects of antioxidants in infertile men.

Conclusions

In conclusion, the oral intake of 16 mg astaxanthin daily for three months did not significantly improve the semen parameters in patients with oligo-astheno-teratozoospermia compared to placebo. Our findings are important for the treatment and counselling on possible improvements in semen quality and fertilizing potential in infertile, and also post-testicular cancer patients. As a wide range of different antioxidant supplements is available, including astaxanthin, these findings are also significant concerning the efficacy of supplements in the treatment of male infertility.

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research article

Semi-supervised planning method for breast electronic tissue compensation treatments based on breast radius and separation

Alexander R. Podgorsak[1,2], Lalith K. Kumaraswamy[1,2]

[1] State University of New York at Buffalo, Department of Medical Physics, Buffalo, New York, United States
[2] Roswell Park Comprehensive Cancer Center, Department of Radiation Medicine, Buffalo, New York, United States

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Correspondence to: Alexander R. Podgoršak, Ph.D., 8052 Clinical Translational Research Center, 875 Ellicott Street, Buffalo, New York 14203. E-mail: arpodgor@buffalo.edu

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Background. The aim of the study was to develop and assess a technique for the optimization of breast electronic tissue compensation (ECOMP) treatment plans based on the breast radius and separation.

Materials and methods. Ten ECOMP plans for 10 breast cancer patients delivered at our institute were collected for this work. Pre-treatment CT-simulation images were anonymized and input to a framework for estimation of the breast radius and separation for each axial slice. Optimal treatment fluence was estimated based on the breast radius and separation, and a total beam fluence map for both medial and lateral fields was generated. These maps were then imported into the Eclipse Treatment Planning System and used to calculate a dose distribution. The distribution was compared to the original treatment hand-optimized by a medical dosimetrist. An additional comparison was performed by generating plans assuming a single tissue penetration depth determined by averaging the breast radius and separation over the entire treatment volume. Comparisons between treatment plans used the dose homogeneity index (HI; lower number is better).

Results. HI was non-inferior between our algorithm (HI = 12.6) and the dosimetrist plans (HI = 9.9) (p-value > 0.05), and was superior than plans obtained using a single penetration depth (HI = 17.0) (p-value < 0.05) averaged over the 10 collected plans. Our semi-supervised algorithm takes approximately 20 seconds for treatment plan generation and runs with minimal user input, which compares favorably with the dosimetrist plans that can take up to 30 minutes of attention for full optimization.

Conclusions. This work indicates the potential clinical utility of a technique for the optimization of ECOMP breast treatments.

Key words: electronic compensation; dose homogeneity index; plan optimization

Introduction

It is estimated that approximately 276,480 new cases of invasive breast cancer will be diagnosed in women in the United States by the end of 2020.[1] One of the techniques used for breast radiation therapy employs two electronically compensated tangent x-ray fields. Such a technique has been found to minimize irradiation of the surrounding lung and cardiac tissue, while improving the homogeneity of the delivered dose within the breast.[2-4] This is important as it is reported that women treated for breast cancer have higher incidence of coronary artery disease and myocardial infarction.[5-7] Additionally, dose inhomogeneity reduction has been shown to reduce adverse effects such as acute radiation toxicity, particularly in women with large breast size.[8,9]

Electronic compensation (ECOMP) is a forward-planned intensity modulated radiation therapy technique which can account for variation in the breast size and shape in both the anterior-posterior

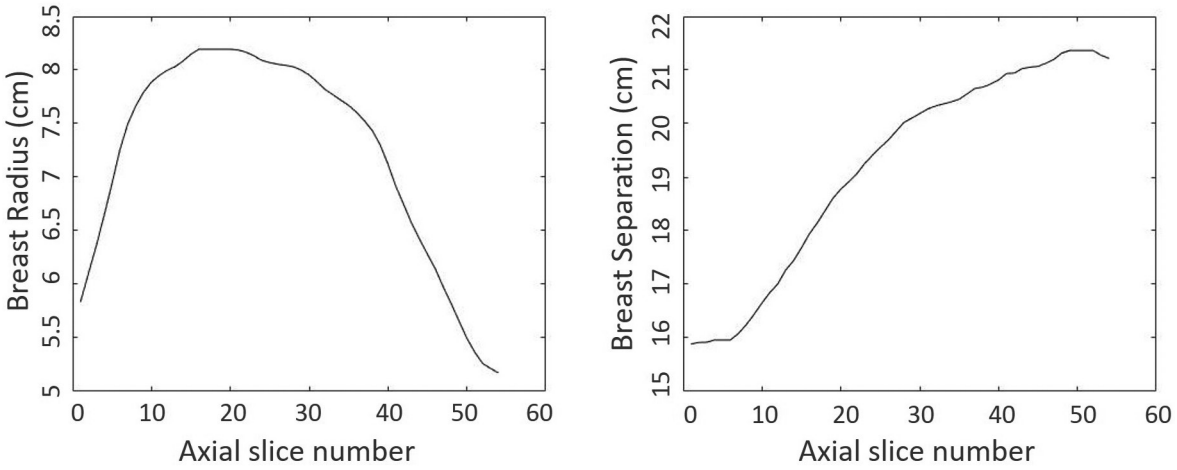

FIGURE 1. Left shows how the breast radius varies in the cranio-caudal direction, right shows how the breast separation varies in the cranio-caudal direction for the same collected patient breast.

and cranio-caudal direction.[10-14] It achieves its improvement in dose homogeneity through dynamic multi-leaf collimator motion. Within the Eclipse (Varian Medical Systems, Palo Alto, United States) treatment planning software (TPS), the irregular compensation surface is defined by a transmission penetration depth (TPD). The TPD is the point along every ray in the field that tissue compensation occurs. If the TPD is reduced, the compensation surface is moved closer to the surface of the breast. Clinically, the TPD is currently selected based on prior knowledge of the treatment planner. Dose profiles are computed within the TPS, and the homogeneity is improved via manual editing of the x-ray fluence maps. This can be a time-consuming process, with large variability between users depending on the skill or experience of the planner.

Published work exists which attempted to correlate the size and shape of the breast to the TPD which yielded the most homogenous dose distribution. Friend *et al.* reported the use of a constant TPD rule depending on breast separation, TPD of 40% if separation is greater than 24 cm, TPD of 50% otherwise.[15] Emmens and James reported the use of smaller TPD with larger breast separation producing a more homogenous dose distribution, yet the full breast volume should be used to attain the most homogenous distribution.[11] These works used a single TPD for all axial breast slices, ignoring the variation in breast size and shape in the cranio-caudal direction. Alghufaili *et al.* correlated the full contour of the breast to the optimal TPD in-terms of achieving a homogenous dose distribution.[16] Three TPDs were output for three regions of the breast (superior, middle, inferior) using the average breast separation and radius in those regions. Our work looks to extend this idea, but use the breast size and shape in *each* axial slice to determine the optimal TPD slice-by-slice.

Materials and methods

Figure 1 shows how the breast radius and separation may change in the cranio-caudal direction for an example patient. Figure 2 shows the hand-calculated optimal TPD over each axial slice in the cranio-caudal direction using the model proposed

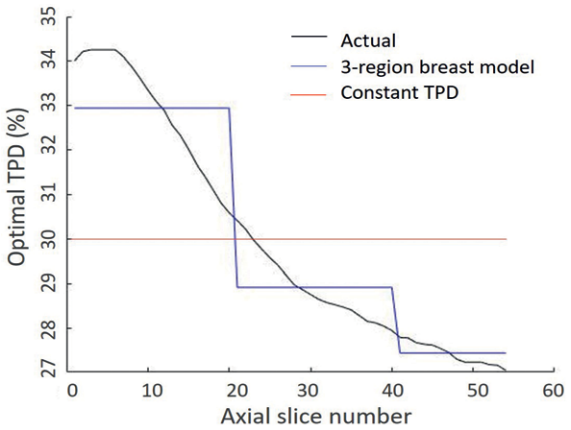

FIGURE 2. Variation in the optimal transmission penetration depth (TPD) over all slices in the cranio-caudal direction compared with the TPD considering a constant TPD or a TPD using the three-region breast approach.

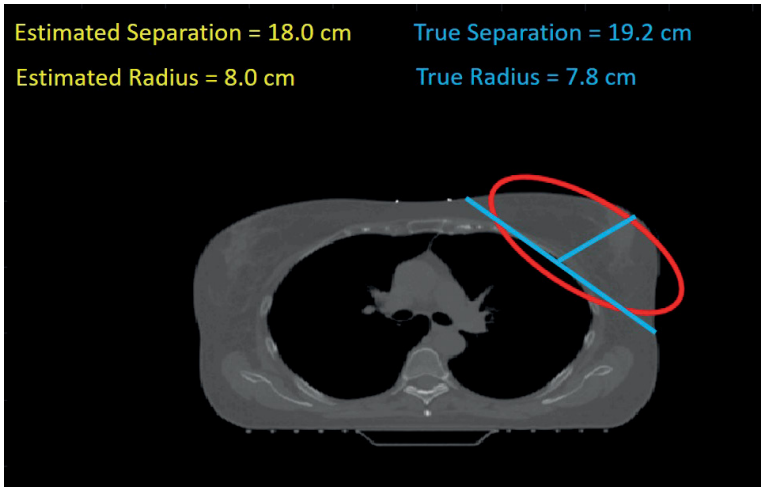

FIGURE 3. CT-simulation axial slice with fitted ellipse (red) and breast radius and separation estimation (yellow) and hand-measurement (blue) of left breast overlaid. Included is the location of the hand measurement for radius and separation in blue.

by Alghufaili, compared with averaging the optimal TPD considering one (constant TPD) and three breast regions. Attempting to select a single or few optimal TPDs over the entire cranio-caudal direction is difficult. With this variation in breast shape and size, and the optimal TPD in the cranio-caudal direction, it seems likely that improvements in ECOMP treatment planning may be realized with a higher-resolution correlation of breast shape and size to the optimal x-ray beam fluence. We look to do this optimal TPD selection with a weakly supervised framework that will estimate the breast separation and radius from input CT-simulation data.

To this end, 10 ECOMP breast plans for 10 breast cancer patients delivered at our institute with a Varian Trilogy LINAC and millennium model 120 multi-leaf collimators were retrospectively collected. CT-simulation data were anonymized for each patient and used to develop our semi-supervised framework for measurement of breast size and separation. Two left-sided and 1 right-sided treatment were used for hand-measurement of the breast separation and radius at each axial location within the treatment volume determined by the placement of superior and inferior markers prior to simulation. It should be noted that a breath hold technique was employed in the left-sided breast cases, both during imaging and treatment. We defined breast separation as the distance along the posterior edge of the breast, and breast radius as the distance from the chest wall to the anterior apex of the breast. Hand measurements were used to assess the accuracy of the semi-supervised breast separation and radius measurement framework.

The first step of the framework is the identification of medial and ipsilateral platinum markers placed prior to CT-simulation. Two square regions are required as input for marker identification. That is the only user supervision the algorithm requires. If the medial marker is found to be to the right of the ipsilateral marker (by x-position), it is a left-sided treatment, otherwise it is a right-sided treatment. A vector is created connecting the medial and ipsilateral markers, extrapolated out to the image boundary, and all image structure beneath the vector is removed from the image data leaving only the targeted breast. An ellipse is fitted to the remaining breast structure using the elliptical Hough transform.[17] The major axis of the fitted ellipse is the estimated breast separation; half of the minor axis is the estimated breast radius. Figure 3 shows an example axial CT-simulation slice with the fitted ellipse and the estimated (yellow) and hand-measured (blue) separation and radius measurement in cm overlaid. For each axial slice in the three breast volumes, the hand-measured separation and radius were compared with the automatically estimated separation and radius using the average percent difference between them.

Previous work has correlated the breast separation and radius to the TPD which will yield the most homogenous dose distribution.[11,15,16] The TPS is still required to compute the fluence profile to deliver the prescribed TPD. We looked to correlate the breast size and shape to that optimal fluence profile, such that the x-ray fluence map needed to achieve the most homogenous dose could be attained without the use of the TPS. To do this, uniform semi-elliptical phantoms simulating axial slices of the breast with varying separation and radius ranging from a separation of 12 cm to 24 cm and a radius of 5 cm to 12 cm were generated. These phantoms were input to Eclipse TPS, and the TPD was set in accordance with the model proposed by Alghufaili *et al*.[16] The TPS was used to measure the x-ray fluence needed to deliver the homogenous dose profile, and correlate it with the breast size and shape. A mathematical model computing the optimal fluence as a function of breast separation and radius was acquired using a least-squares minimization bilateral fitting to the individual fluence measurements. This model can then be used to compute a mapping of the x-ray fluence at the surface of the breast needed to deliver the most homogenous dose, across all axial slices in the treatment volume. It is important to note that this model is dependent on beam energy. As each ray passes through the breast volume, we

assumed exponential drop-off of the fluence governed by the Beer-Lambert-Bouguer Law.[18-20] In this way, we created 2D x-ray fluence maps needed to deliver the most homogenous dose profile, considering each axial slice in the treatment volume, using a semi-supervised processing framework.

The 10 retrospectively collected ECOMP breast plans were re-planned within Eclipse using x-ray fluence maps generated with our proposed semi-supervised framework. The resultant dose distributions were compared with those from the original plans created and optimized by an experienced dosimetrist. Two additional comparisons were carried out with plans generated in Eclipse, the first by assuming a single TPD determined over the entire treatment volume (current model in Eclipse TPS), and no manual editing of the fluence maps to correct any dose inhomogeneities. The second is using Alghufaili's three-region breast model, where three TPD's are used, the optimal TPD for the superior, medial, and inferior portions of the treatment volume. Quantitative comparison between the four plans across the ten patients used the dose homogeneity index (HI, lower is better)[21], mathematically described in Equation 1 as

$$[\text{eq. 1}] \quad HI = \frac{D_2 - D_{98}}{D_p} \times 100\%$$

where D_2 and D_{98} represent doses to 2% and 98% of the PTV respectively, and D_p represents the prescription dose, along with Pearson correlation coefficients[22], and single-tailed heteroscedastic *t*-tests to assess the significance of any differences between plans (p-value < 0.05). Our goal was to achieve a more homogenous dose profile using our semi-supervised algorithm compared with the use of a single TPD over all axial slices in the treatment volume or the 3-region breast model of Alghufaili, and to achieve a statistically non-inferior dose homogeneity compared with the dosimetrist treatment plans. Our institute places constraints on ECOMP plans which mandate global maximum dose less than 108% the prescription and treatment volume dose greater than 95% the prescription. We compared how each of the four techniques created plans which met these dose constraints or otherwise.

The weakly-supervised breast radius and separation estimation process, fitting of the x-ray beam fluence to the mathematical models, and statistical analyses were all done in MATLAB.

Results

Treatment plans were generated in around 20 seconds by our proposed algorithm. This number includes the time it takes for breast radius and separation estimation, and compares well with the medical dosimetrist plans which can take up to 30 minutes due to the iterative and manual process of editing the fluence maps to bring the generated plans within institutional dose constraints. It is also important to note that our proposed algorithm requires much less user input than the fully-supervised forward-planned iterative method, indicating an improvement in the clinical workflow.

TABLE 1. Agreement between breast radius and separation hand-measurements and automatic algorithm measurement in centimeter (cm) difference and percent difference

Radius		
Number	**% Difference**	**Difference (cm)**
1	9.6 [9.3–9.9]	0.70 [0.68–0.72]
2	6.2 [5.7–6.7]	0.40 [0.39–0.41]
3	22.0 [21.5–22.5]	1.00 [0.98–1.02]
Average	12.6 [10.4–14.8]	0.69 [0.59–0.79]
Separation		
Number	**% Difference**	**Difference (cm)**
1	6.1 [5.0–7.2]	1.13 [1.11–1.15]
2	4.2 [4.1–4.3]	0.71 [0.68–0.74]
3	5.3 [5.1–5.5]	0.91 [0.71–1.11]
Average	5.2 [5.1–5.3]	0.92 [0.79–1.05]

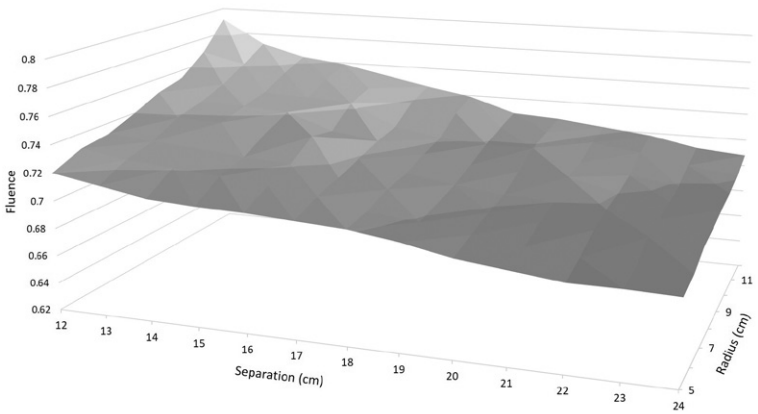

FIGURE 4. Correlation between breast separation and radius with the x-ray fluence needed to deliver homogenous dose distribution to the breast treatment volume using a 6 MV beam.

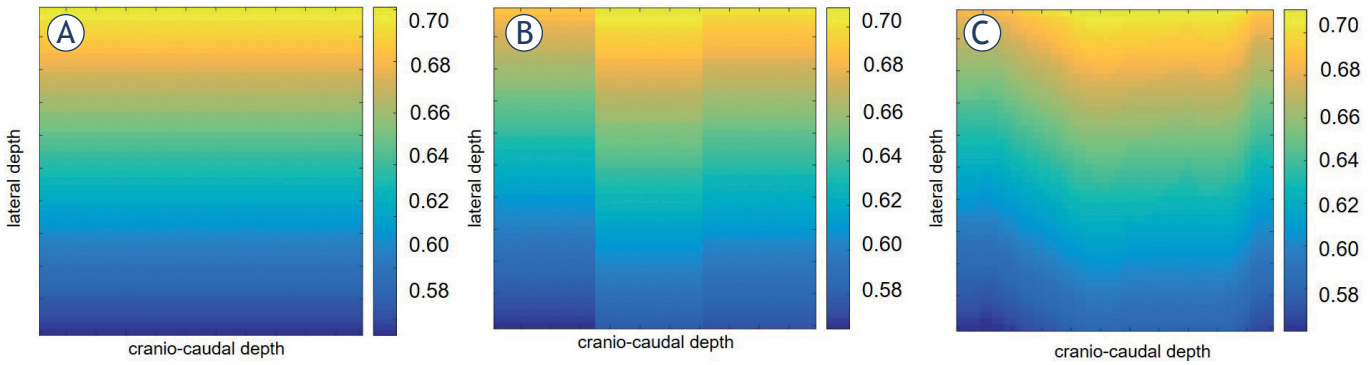

FIGURE 5. Optimal fluence maps from **(A)** assuming a single penetration depth, from **(B)** assuming a three-region breast model, and **(C)** our proposed model. Colorbar shows beam fluence.

Average percent difference and average distance in cm between the automatic-algorithm-measured and hand-measured breast radius and separation over the three test volumes can be found in Table 1. Average percent difference between the breast radius measurements over the three test volumes was 12.6% (95% confidence interval 10.4% – 14.8%), corresponding to an actual measurement error of 0.69 cm (0.59 cm – 0.79 cm). Average percent difference between the breast separation measurements over the three test volumes was 5.2% (95% confidence interval 5.1% – 5.3%), corresponding to an actual measurement error of 0.92 cm (0.79 cm – 1.05 cm). It should be noted that the reconstructed voxel size was 1.269 mm, hence these errors are below 8 pixels at a measurement error value of 1 cm.

Figure 4 displays the correlation between the breast separation and radius with the optimal transmission fluence at the breast surface needed to deliver the most homogenous dose distribution to the breast volume using a 6 MV x-ray beam. This plot indicates an increase in the x-ray fluence needed as the breast separation decreases and the radius increases. Following the fitting of a plane to the model, the relationship in Equation 2 was acquired, where *f* is the optimal fluence for the axial slice with a radius and separation measurement from the semi-supervised framework.

[eq. 2] $f\,(radius, separation, 6\ MV) = 0.753 + 0.006 * radius - 0.005 * separation$

These results are in agreement with the work of Emmens[11] and Alghufaili[16], which reported correlation between a decreasing separation and an increase in radius with the TPD. The TPD is related with x-ray fluence, in that more fluence is needed to attain a deeper penetration depth. The mathematical relationship between breast size and shape and the optimal fluence for a 23 MV beam can be found in Equation 3. To simplify the number of parameters in the Equation and improve the generalizability of the model, we assumed a bilinear fit for each of the three models.

[eq. 3] $f\,(radius, separation, 23\ MV) = 0.888 + 0.006 * radius - 0.007 * separation$

Figure 5 shows optimal fluence maps generated using a single TPD throughout the treatment volume, using three TPDs assuming a three-region

TABLE 2. Summary of dose homogeneity indices (HI) for all ten collected treatment courses. Compared are the treatments generated with our proposed algorithm, plans created using the 3-region breast model proposed by Alghufaili, those plans optimized by a medical dosimetrist, and plans generated by assuming a single transmission penetration depth (TPD) within the treatment planning software

Number	Proposed Work HI	3-region breast model	Dosimetrist Optimized HI	Single TPD HI
1	26.7	22.4	16.5	23.0
2	17.8	19.2	14.1	19.1
3	10.6	15.2	11.2	17.2
4	11.8	14.6	9.51	13.3
5	8.49	7.87	3.32	8.04
6	8.79	14.1	6.64	12.6
7	4.59	7.44	3.82	8.19
8	7.57	21.5	8.84	23.5
9	11.3	17.9	8.29	18.7
10	10.6	16.0	10.5	17.8
Average	**12.6**	**15.6**	**9.87**	**17.0**

TABLE 3. Summary of global dose maximum and clinical target volume (CTV) minimum values for all ten collected treatment courses. Compared are the treatments generated with our proposed algorithm, plans created using the 3-region breast model proposed by Alghufaili, those plans optimized by a medical dosimetrist, and plans generated by assuming a single transmission penetration depth (TPD) within the treatment planning software

	Global dose max (%)				CTV dose min (%)			
Number	Proposed work	3-region breast model	Dosimetrist optimized	Single TPD	Proposed work	3-region breast model	Dosimetrist optimized	Single TPD
1	107.7	108.5	109.1	113.3	96.9	97.3	104.1	96.0
2	109.7	111.3	106.5	111.8	74.4	75.0	76.9	74.2
3	107.4	108.1	107.5	112.7	95.5	88.7	95.3	89.1
4	107.5	110.4	105.9	109.8	95.5	95.2	95.0	96.8
5	107.7	109.7	104.0	105.0	95.1	95.9	98.1	87.8
6	107.5	108.7	105.5	111.4	97.9	96.0	99.3	97.4
7	108.0	114.2	105.9	116.3	95.4	95.4	95.7	95.4
8	107.6	112.6	106.6	114.6	95.3	92.8	97.8	94.1
9	107.5	115.5	106.0	118.1	95.6	95.6	95.1	95.0
10	107.5	108.6	107.8	114.4	86.1	81.6	87.8	87.2
Average	**107.8**	**111.2**	**106.5**	**112.7**	**92.7**	**91.4**	**94.5**	**91.3**

TABLE 4. Summary of mean dose to the heart and ipsilateral lung V20 Gy for all ten collected courses. Compared are the treatments generated with our proposed algorithm, plans created using the 3-region breast model proposed by Alghufaili, those plans optimized by a medical dosimetrist, and plans generated by assuming a single transmission penetration depth (TPD) within the treatment planning software

	Mean dose to the heart (cGy)				Ipsilateral lung $V_{20\,Gy}$ (%)			
Number	Proposed Work	3-region breast model	Dosimetrist Optimized	Single TPD	Proposed Work	3-region breast model	Dosimetrist Optimized	Single TPD
1	11.0	15.0	13.7	13.4	0.42	2.30	2.41	2.05
2	298	296	294	327	18.2	18.3	16.7	20.3
3	177	165	109	160	5.12	4.91	3.56	4.65
4	271	267	149	250	9.09	9.03	8.07	7.93
5	40.8	44.9	39.7	42.0	16.6	16.8	15.8	16.2
6	113	112	108	111	8.95	8.84	8.33	8.59
7	47.0	52.4	47.7	51.7	9.56	11.2	9.9	10.9
8	26.9	28.9	26.5	28.7	11.4	11.2	11.4	10.9
9	95.9	128	89.5	125	9.18	10.8	7.8	10.6
10	406	402	159	397	18.7	18.5	12.4	18.2
Average	**149**	**151**	**104**	**151**	**10.7**	**11.2**	**9.65**	**11.0**

breast model, and using a different TPD for each slice throughout the treatment volume. It should be noted that the resolution of these maps is consistent with that of the imaging (1.269 mm).

Table 2 summarizes the HI for each of the collected ECOMP plans comparing the original medical dosimetrist plans, plans from our proposed algorithm, plans generated using the 3-region breast model proposed by Alghufaili, and plans from the use of a single TPD over the entire treatment volume. Over the collected plans, there is no statistical difference between the medical dosimetrist plans and our algorithm's plans in terms of the dose homogeneity index. Table 3 summarizes the global

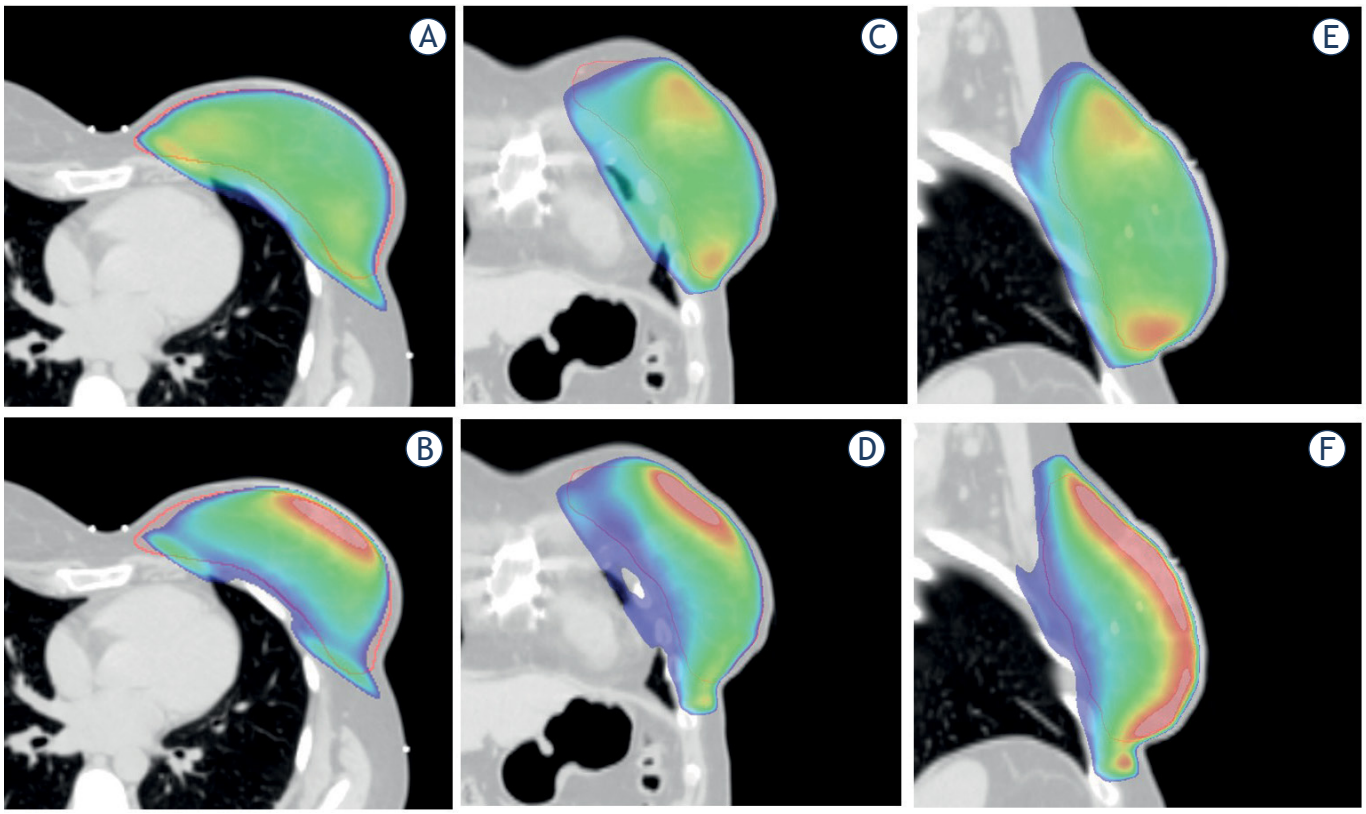

FIGURE 6. (A, C, E) axial, coronal, and sagittal views of the breast treatment volume showing the isodose color washes from the treatment plan generated with the proposed algorithm. **(B, D, F)** axial, coronal, and sagittal views of the breast treatment volume showing the isodose color washes from the treatment plan generated by assuming a constant transmission penetration depth of 30%.

dose maximum and treatment volume dose minimum for each of the 10 collected plans. Compared with the use of a single TPD, our algorithm is able to generate fluence maps which yield global maximum doses and treatment volume dose minimums that are within our institution's constraints that is in better agreement with the medical dosimetrist plans. Table 4 summarizes the mean dose to the heart and summarizes the volume percent above 20 Gy for the ipsilateral lung ($V_{20\ Gy}$) over the 10 collected plans. There is no statistical difference between the medical dosimetrist plans and our algorithm plans in terms of the heart mean dose or the ipsilateral lung $V_{20\ Gy}$.

Figure 6 demonstrates isodose color washes in the axial, sagittal, and coronal planes, one set generated from fluence maps generated with our proposed algorithm, the other from the current model utilized in the Eclipse TPS that assumes a constant TPD over the entire treatment volume. Our proposed algorithm creates a plan that has more homogenous coverage of the breast and a reduced anterior hotspot. This specific case had a HI of 10.6 from the plan generated using our proposed algorithm and 17.2 from the plan assuming a constant TPD of 30% throughout the breast volume. Using the 3-region breast model to generate the treatment plan yielded an HI of 15.2.

Discussion

This study proposed a semi-supervised scheme for the determination of the optimal x-ray fluence map needed to deliver the most homogenous dose distribution to the breast volume in ECOMP treatment plans. Our algorithm takes as input the CT-simulation data from pre-treatment imaging and

uses the breast radius and separation measurement over the entire treatment volume to output tangential maps of the x-ray fluence that describes how to deliver the most homogenous dose profiles such that acute late effects due to radiation toxicity caused by radiation dose in-homogeneities can be reduced. This fluence determination takes into consideration the variation in breast separation and radius in the cranio-caudal direction, and extends on previous work by using each axial slice in the volume to optimize the homogeneity instead of just a single or a couple slices. Figures 1, 2, and 5 emphasize the importance in considering this variation in the size and shape of the breast in the cranio-caudal direction. The three fluence maps in Figure 5 show how the optimal fluence maps change when the breast is broken up into finer resolution sections, from a single uniform shape in Figure 5A, three uniform shapes in Figure 5B, to estimating the exact shape at each axial slice in Figure 5C. Our results indicate that the proposed algorithm can create plans that are statistically non-inferior in terms of the dose homogeneity to those plans manually edited by a dosimetrist. Additionally, our algorithm is able to produce plans that are within our institution's dose constraints for the global dose maximum and target dose minimum.

A comparison of the isodose color washes in Figure 6 show a better coverage of the green color wash over more of the treatment volume when the proposed algorithm is used instead of a constant TPD of 30%. In the axial slice (Figure 6 A and 6B), the green wash extends closer to the posterior edge of the breast volume against the lung volume. The sagittal view (Figure 6E and 6F) shows an advantage to our proposed algorithm in the coverage of the green wash towards the inferior portion of the breast volume. In all three anatomical planes, the green wash is more homogenous throughout the treatment volume, as confirmed with the homogeneity index for this specific case (10.6 for the proposed algorithm, 17.2 for the constant TPD). There is also a reduction in the anterior hot spot that is prevalent in all three of the views from the single TPD treatments.

The mathematical models fitted for the 6 MV and 23 MV beams (Equations 2 & 3, respectively), are both dominated by the 0^{th} degree additive constant. The breast radius and separation play a role (additive for the radius, subtractive for the separation), but it is small.

With breasts of small radius and separation, our semi-supervised size measurement algorithm tends to overestimate the radius and separation of the breast, thereby generating plans that have regions where the dose potentially would exceed the maximum dose constraint. It would be these cases where manual optimization by the medical dosimetrist would still be necessary to reduce the hotspots potentially present in the dose profile. Patients 1 and 5 in Table 2 are examples of this. They both had overestimations in the breast radius and separation, causing the homogeneity to be worse compared with the medical dosimetrist plans due to the presence of several local dose hotspots that didn't go above the 108% global maximum dose constraint, but still reduced homogeneity.

This work can be thought of as a more homogenous starting point for the iterative optimization process of the medical dosimetrist. Currently, a single TPD is empirically selected within Eclipse and the resultant fluence maps are manually edited to improve the homogeneity of the computed dose profiles to bring the plan within institutional dose constraints. Our work has shown that an algorithm that measures the breast separation and radius over the entire breast volume and relates them to the optimal x-ray fluence maps can lead to more homogenous plans than the use of a single TPD. It seems possible that these improvements were realized with the higher-resolution correlation of breast size and shape to the x-ray beam fluence. This work may lead to a quicker, less manually intensive process for the dosimetrist to bring the ECOMP plans within dose constraints. In every collected case, some combination of the global dose maximum being too high or treatment volume minimum dose being too low led to the necessity of optimization of the single TPD plans by the dosimetrist. In the cases that met dose constraints with dosimetrist editing, our algorithm was able to create plans that met dose constraints with no manual editing required. There still may be manual editing required to achieve equivalent dose homogeneity with the dosimetrist-edited plans, however compared with the use of a single TPD or a three-region breast model, the plans from our algorithm attain a higher level of homogeneity and are more deliverable when considering institutional dose constraints.

Our work extends on the literature in this problem space in several important ways. Firstly, our work accounts for the variation in breast radius and separation in the cranio-caudal direction, axial slice by axial slice, by estimating the breast radius and separation at each slice and correlating it with the optimal (in terms of beam homogeneity) beam penetration using the TPD value. Secondly,

we took this TPD value and determined a mathematical model, which governed what beam fluences would be needed to deliver parallel-opposed beams of the prescribed TPD. In this manner, the TPS would not be needed to obtain the optimized x-ray fluence map.

A limitation of this current work is our model assumes exponential drop-off of the beam governed by the Beer-Lambert-Bouguer Law. This assumes a homogenous material that the x-rays are traveling through, and will not be the case in the breast volume. This may cause the assumed fluences to not be exactly what would be achieved with the delivery of a particular TPD deemed optimal for the breast separation and radius slice-by-slice. An additional limitation is in cases where there is skin folding at the breast surface, as may occur in the case of a large, pendulous breast. A challenging situation is created in that the breast radius and separation would not be impacted, yet the optimal TPD and x-ray fluence would be changed. Such a condition was not included in the development of our model, so it may lead to the creation of suboptimal plans. One final limitation is at this point, our algorithm still requires an operator for medial and ipsilateral marker identification. The supervision amount is low compared to the current clinical workflow, however a fully automated framework would improve the clinical applicability of this algorithm.

Conclusions

This work indicates the advantages to the consideration of the full volumetric shape of the breast to determine the optimal TPD needed to deliver a homogenous dose distribution to the breast treatment volume. This volumetric shape is defined by the measurement of the breast separation along the posterior edge and radius from the isocenter at the posterior border to the apex anteriorly, considering all axial slices in the cranio-caudal direction. This work also detailed a method for the semi-supervised determination of this volumetric shape, resulting in the output of the x-ray fluence needed for the delivery of the optimal dose distribution. We envision this process used to attain a more homogenous, consistent starting point for the medical dosimetrist as they optimize the ECOMP treatment plans, compared with assuming a constant shape of the breast in the cranio-caudal direction.

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research article

Efficacy of breast shielding during head computed tomography examination

Nika Zalokar, Nejc Mekis

University of Ljubljana, Faculty of Health Sciences, Medical Imaging and Radiotherapy Department, Ljubljana, Slovenia

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Correspondence to: Nejc Mekiš, Ph.D., Zdravstvena pot 5, SI-1000 Ljubljana, Slovenia. E-mail: nejc.mekis@zf.uni-lj.si

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Background. Female breasts are exposed to scattered radiation regardless of not being included in the primary field during head CT. This study aimed to investigate whether the use of lead shielding is beneficial in dose reduction to the breasts during head CT.

Patients and methods. The study was performed in two different hospitals on two different CT units and included 120 patients. Half of the measurements (n = 60) was conducted without the use of lead shielding and the other half (n = 60) with the use of lead shielding of 0.5 mm equivalent thickness.

Results. Significant skin dose reduction to the breasts during head CT in both hospitals with the use of lead shielding was discovered; 81% (338.2 ± 43.7 μGy to 64.3 ± 18.8 μGy) in Hospital A and 74% (from 253.1 ± 35.1 μGy to 65.3 ± 16.9 μGy) in Hospital B.

Conclusions. Considering the assumed carcinogenic effect of low doses of radiation, high frequency of the head CT scans and the significant reduction of radiation doses to the highly radiosensitive breasts, the use of lead shielding is highly recommendable.

Key words: scatter radiation; head CT; lead shielding; breasts; dose reduction

Introduction

Computed tomography (CT) is a valuable diagnostic tool for many conditions.[1] According to the International Atomic Energy Agency (IAEA) an individual receives 2.4 mSv of the total annual dose of natural radiation[2] and the typical effective radiation dose received during a standard CT scan ranges from 1 to 14 mSv.[3] Head CT is one of the most frequently performed examinations[4,5] and accounts for 50% of all CT scans and 25% of the collective radiation dose from CT.[5] High effective doses received during CT examinations raise concerns[1,6], so an effort to minimize it is crucial.[1] Due to concerns over radiation exposure, the very valuable principle ''as low as reasonably achievable'' (ALARA) was established to stress the importance of minimizing radiation exposure.[7] Many CT shielding techniques have been developed as a result, among them radiation protection shields, which are one of the simplest mechanisms by which radiation dose can be reduced.[3]

The use of lead shielding is a long-accepted method to minimize the dose from scatter radiation in radiographic procedures.[1,8] In head CT, the head as the main target under investigation is included in the primary beam, while radiosensitive organs such as the breasts are located outside the primary beam. Radiosensitive structures that lie in the primary beam cannot be easily protected, while the organs outside the primary beam, which are mainly exposed to scattered radiation, can be easily protected against it. Scattered radiation distributes caudally through patient's neck thereby inevitably exposing the breasts. However, scattered radiation produced in gantry and patient's head reaching the breasts from outside can be effectively diminished by the lead shielding.[8] Radiation dose

to the breasts is significant enough to be a matter of concern[9] regardless of all the current dose reduction techniques.[5]

Female breast tissue is highly sensitive to radiation's carcinogenic effects. Its tissue weighting factor has risen from 0.05 to 0.12.[7] The exposure of breasts to ionising radiation is a strong risk factor for breast cancer. The study by Preston *et al*.[10] showed that the increased risk is directly proportional to the radiation dose received and inversely related to age at irradiation. The use of radiation shields, if applied properly, is one of the simplest implementations by which radiation dose can be diminished without the negative impact on diagnostic image quality.[3]

The benefit of shielding to radiosensitive organs in many diagnostic procedures has been acknowledged in many studies.[1,5,8,11-13] Brnić *et al*.[8] recommend lead shielding of the breasts during head CT since a recognizable reduction (57%) of the exposure was found. The study by Williams and Adams[5] also discovered a significant dose reduction (58–47%) with a lead bib protecting the thyroid. Beaconsfield *et al*.[11] also claim a significant dose reduction (76%) during head CT due to lead shielding of breasts. However, Brnić *et al*.[8] measured the exposure with thermoluminescent dosimeters (TLD) during shielding of only one breast while the other remained unshielded, the study by Williams and Adams[5] performed measurements while investigating the benefit of thyroid shielding on an anthropomorphic phantom and Beaconsfield *et al*.[11] have performed only 20 measurements with the use of breast shielding during axial head CT examination.

For the above-mentioned reasons and given the high frequency of head CT scans and high sensitivity of breasts to ionising radiation, the purpose of this study was to determine the effectiveness of breast shielding during the routine helical head CT scan in real clinical practice with an electronic dosimeter and a lead apron of 0.5 mm lead equivalent, which is the most commonly used protective shield in Slovenia. Lead shielding is not routinely used in the breast area during head CT examination so the results could clarify the dilemma whether the shielding is beneficial in protecting the breasts. Possible changes in clinical practice might be expected in the future.

Patients and methods

The study was performed in two major hospitals in Slovenia. The sample size was calculated based on the study performed by Brnić *et al*.[8], with the G*Power 3.1 (Allgemeine Psychologie und Arbeitspsychologie, University Dusseldorf) programme. 120 female patients referred to a spiral head CT scan participated in our study (age range 23–92 years with average age of 67.9 ± 16.7 years). 60 measurements were conducted in Hospital A on Siemens Somatom Definition (Siemens Medical Systems, Germany) CT unit and 60 measurements in Hospital B with Toshiba Aquilion 64 slice (Toshiba Medical Systems, Otawara, Japan) CT unit. All results of the quality assurance tests for both CT units, performed prior to the study by the medical physicist, were under the remedial level. Half of the measurements in each hospital (n = 30) were performed with the use of lead shielding and half of the measurements (n = 30) without the lead shielding. Randomized sampling was used in this study.

The Unfors EDD 30 (Unfors, Sweden) unit was used to measure the skin dose at the surface of the breast in real time during CT of the head. According to the manufacturer, the dosimeter offers a dose range from 1 nGy to 9999 Gy with the start trigger level at 0.05 mSv/h. The manufacturer also claims that the EDD 30's inaccuracy is ± 6% at calibration point with 80 kVp, 2 mm of Cu and 4 mm of Al. The dosimeter was tested and showed the best and consistent response of the dosimeter when it was in alignment to the horizontal plane and the cable of the dosimeter was positioned away from the source of scattered radiation (not contained in the scanning area). The dose was read on the display.

Acquisition parameters are shown in Table 1. Same protocols as used in clinical practice in each hospital were used during the study.

The sensor of the dosimeter was attached to the centre of the breast in the alternating order, in a way that the dosimeter was always in alignment with the examination table to ensure minimal effect of the angulation dependence of the dosimeter. The breast area was wrapped with lead apron (Mavig, Germany) of 0.5 mm equivalent lead

TABLE 1. Acquisition parameters

Hospital	A	B
Pitch	0.55	0.656
Rotation time (s)	1	0.6
kV	120	120
mA	480	200

thickness as tightly as possible around the patient (shoulders were not draped). The example of the shielding position is presented on Figure 1 using an anthropomorphic phantom.

Our study was approved by the hospital's Ethics Committee and by the National Medical Ethics Committee prior to the initiation. A written informed consent was obtained from all patients. All the measurements were processed with the IBM SPSS STATISTICS version 25 (IBM, USA). The Shapiro-Wilk test was used to check the normal distribution of the sample. A student T-test was performed to determine the statistical significance of the difference of the skin dose between the shielded and unshielded breasts in each hospital. A significance of $p < 0.05$ was used for all the tests.

Results

In Hospital A the mean skin dose to the breast was 338.2 ± 43.7 μGy without the lead shielding and 64.3 ± 18.8 μGy when the lead shielding was used. The difference between the doses was statistically significant ($p < 0.001$) with the dose reduction of approximately 81%. In Hospital B, the mean skin dose to the unprotected breasts was 253.1 ± 35.1 μGy compared to 65.3 ± 16.9 μGy to the breasts protected with the lead shielding. The dose reduction of 74% was statistically different ($p < 0.001$). Table 2 and Figure 2 summarize the results.

Discussion

This study provides evidence, that lead shielding significantly reduced the amount of scatter radiation to the breasts in both Hospitals.

Radiosensitive structures that lie in the primary field cannot be easily protected, meanwhile the structures outside the CT scanning plane, such as the breasts during the head CT examination, can be easily protected against the scatter radiation. During the head CT examination the use of lead shielding can significantly reduce the exposure from scattered radiation generated in patient's head and in gantry.[8,14]

FIGURE 1. Presentation of the shielding position used in the study.

Our results showed that the breast exposure in Hospital A and B was reduced by 81% and 74%, respectively, with the use of 0.5 mm lead shielding. Nevertheless, a noticeably higher mean skin dose to breasts without the shielding in Hospital A, compared to Hospital B has been detected. This

TABLE 2. Mean measured skin dose to the breasts in both investigated hospitals

	Hospital A		Hospital B	
	unshielded	shielded	unshielded	shielded
Mean skin dose to breast (μGy)	338.2 ± 43.7	64.3 ± 18.8	253.1 ± 35.1	65.3 ± 16.9
Dose reduction	81%		74%	

difference might be the result of the higher mA setting, longer scan lengths (were not noted) and the angular dependence of the dosimeter. Further investigation could be made.

The study from Beaconsfield *et al.*[11] reported an average 76% dose reduction using a 0.5 mm lead equivalent thickness, which is similar to our study. They used the axial imaging technique of the head CT examination and not the spiral, as did we in our study. The axial imaging technique was also used in the study by Brnić *et al.*[8], which reported lower reduction in dose; 57%. However, their study used a 0.35 mm lead shield, and only one breast was shielded during the measurements, so a lower dose reduction is expected. However, Williams and Adams[5] did use the same CT imaging technique – the spiral scanning. They have investigated the impact of thyroid shielding on dose to the patient during head CT. They have measured a 58% dose reduction on the thyroid during the spiral head CT examination. The thyroid, however, cannot be protected from the X-rays scattered from within the patient.[11] All mentioned studies used thermo-luminescent dosimeters to measure the radiation dose. In contrary, our study used an electronic dosimeter so the skin dose on the breasts was read out on the display as soon as the scanning was finished.

The International Commission on Radiological Protection (ICRP) has published new tissue weighting factors for the breast and other organs in 2007. The breast tissue weighting factor was increased from 0.05 to 0.12.[7] One of the strongest risk factors for breast cancer is the radiation exposure at a young age.[10,15] According to the ALARA principle all effort should be made to reduce irradiation of the breasts using shielding. In addition to breast shielding some other radiosensitive tissues will also be protected against the external scatter radiation, particularly bone marrow (42% of bone marrow is found in the thorax).[8,11] Based on the ICRP103[7], bone marrow is a radiosensitive organ with the same tissue weighting factor as the breasts – 0.12, however, the effect of shielding on the bone marrow was not investigated in our study.

The study was conducted on female patients and not on an anthropomorphic phantom as the study by Williams and Adams[5], so the measurements were performed on real body tissue in real clinical circumstances. In addition, patient positioning and diverse body geometry of the patients influenced the shielding possibilities. Shielding in the present study was wrapped around the chest of the patient so both breasts were shielded simultaneously and not one breast only like in the study by Brnić *et al.*[8]

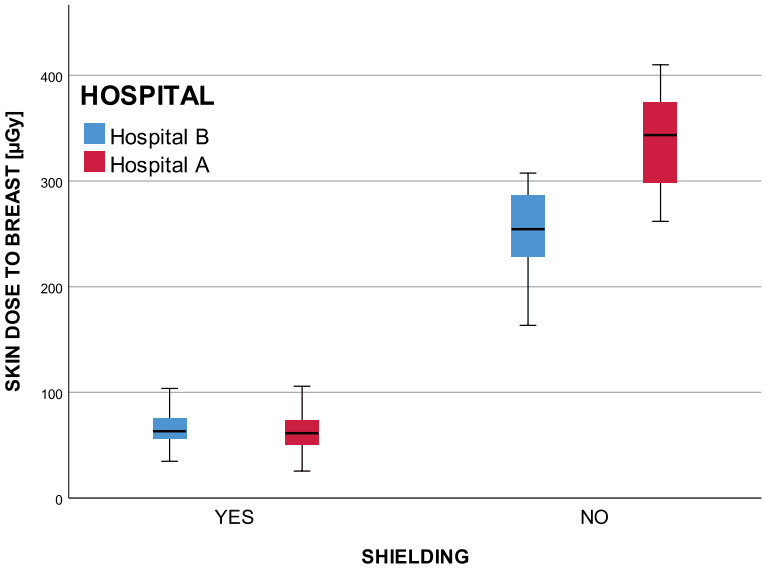

FIGURE 2. Mean skin dose to breast in both hospitals with and without the shielding.

Wrapped-around shielding is also the routine way of shielding in CT diagnostics' clinical practice, and not covering only one radiosensitive organ. Since shielded and unshielded measurements on the same patient could not be performed, a large sample was necessary for statistical accuracy. In total, 60 measurements of radiation dose to the breasts under the shielding were performed compared to the 20 measurements performed in the study by Beaconsfield *et al.*[11] In the present study the measurements were performed in two different institutions on two different CT units with different exposure parameters. All the above contributes to the additional value of the present work.

Our study has proven that the use of lead shielding significantly reduced the skin dose to the breasts. Nevertheless, special attention still needs to be payed to the positioning of the apron. The lead shielding must be positioned so it does not enter the primary field. If the shielding enters the primary field of imaging, it would produce significant image artefacts or, if the automatic exposure control is used, the system would drastically increase the tube output in order to compensate the absorption in lead. Caution must also be taken to wrap the shielding around the patient as tightly as possible, so there is no air gap between the chest and the shielding.

This study was performed with a lead shield, which is the most commonly used form of shielding in Slovenia. New shielding materials are emerging, among them the Antimony-Bismuth shields, which

are positioned in the primary field and only partially block the beam. Further investigation could be performed. Nevertheless, the breasts are located outside the primary field so the lead shielding can be applied to reduce the scattered radiation to the breasts.

This study showed that the lead shielding significantly reduced the amount of scatter radiation irradiating the breasts. The dose was reduced by a minimum of 74% and a maximum of 81%. Head CT is one of the most frequently performed CT examinations and the breasts are one of the most radiosensitive organs so patients undergoing a head CT scan will benefit significantly when lead shielding is used. Our work could be continued by investigating the efficiency of the newly emerging shielding materials, its efficiency in correlation to material thickness and the frequency of using the shielding in different departments.

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Umetna inteligenca v mišičnoskeletni onkološki radiologiji

Vogrin M, Trojner T, Kelc R

Izhodišča. Primarni kostni tumorji so razmeroma redki, zato njihova obravnava pogosto terja izkušenega mišičnoskeletnega radiologa. Želimo čim natančneje prepoznavati novotvorbe ter zmanjševati verjetnost človeškega dejavnika in napak, zato v zadnjih letih pospešeno razvijamo in implementiramo sisteme umetne inteligence v klinično prakso. Predstavljamo najbolj obetavne sisteme za diagnostiko primarnih in sekundarnih kostnih tumorjev ter novotvorbe dojke, pljuč in črevesja.

Zaključki. Navkljub pomanjkanju dolgoročnih raziskav, ki bi potrdile učinkovitost in superiornost računalniških ekspertnih sistemov, imajo le-ti velik potencial pri diagnostiki kostnih tumorjev in tumorjev mehkih tkiv.

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Telesna aktivnost in tveganje za pojavnost raka. Sodobna znanja in možni biološki mehanizmi

Jurdana M

Izhodišča. Številne raziskave potrjujejo, da telesna aktivnost zmanjša tveganje za razvoj raka. Biološki mehanizmi, ki povezujejo zaščitni vpliv telesne aktivnosti na pojavnost raka vključujejo znižanje: sistemskega vnetja, hiperinzulinemije, inzulinu podobnega rastnega dejavnika (IGF-I), spolnih hormonov, vnetnega leptina in drugih mediatorjev vnetja, povezanih z debelostjo. Poleg omenjenega, telesna aktivnost zvišuje vrednosti protivnetnega adiponektina, izboljša imunski odziv ter sestavo in raznolikost bakterijskih vrst, ki so del črevesne bakterijske združbe. Zmerna telesna aktivnost dokazano preprečuje tveganje za razvoj raka, večje učinke pa povezujejo s telesno aktivnostjo višje intenzivnosti. Za preprečevanje nekaterih vrst raka bodo potrebne nadaljnje raziskave o vrsti, intenzivnosti in trajanju telesne aktivnosti ter oblikovanje natančnih priporočil za posamezne vrste raka.

Zaključki. Obstajajo prepričljivi dokazi, da zmerna do intenzivna telesna aktivnost ščiti pred rakom debelega črevesa in rakom dojk. Prav tako so opazni pozitivni učinki telesne aktivnosti v preventivi pred drugimi raki.

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Klinični pomen preiskave ^{18}F-FDG PET/CT za pooperativno spremljanje bolnikov z medularnim rakom ščitnice

Šaponjski J, Macut D, Šobić Šaranović D, Radović B, Artiko V

Izhodišča. Cilj raziskave je bil oceniti pomen 18-fluor deoksiglokoze (^{18}F-FDG) pozitronske emisijske tomografije z računalniško tomografijo (PET/CT) za odkrivanje aktivne bolezni pri bolnikih s sumom na ponovitev medularnega raka ščitnice.

Bolniki in metode. V obdobju od 2010 do 2019 smo preiskavo ^{18}F-FDG PET/CT naredili pri 67 bolnikih, nato pa jih spremljali od 6 do 116 mesecev po operaciji (srednja vrednost 16,5 meseca, $\bar{x}$ ± standardna deviacija [SD] = 29 ± 28,9 meseca). 25 od 67 bolnikom smo opravili scintigrafijo z 99m-tehnecij dimerkaptosucinsko kislino (99mTc-DMSA), 11 scintigrafijo somatostatinskega receptorja z 99mTc-HYNIC TOC, medtem ko smo pri 11 bolnikih opravili scintigrafijo z ^{123}I-meta-jod-benzil-gvanidinom (^{123}I-MIBG).

Rezultati. Od 67 bolnikov je imelo 35 (52,2 %) resnično pozitivnih ^{18}F-FDG PET/CT ugotovitev. Povprečna maksimalna standardizirana vrednost prevzema (SUVmax) za vse resnično pozitivne lezije je bila 5,01 + 3,6. Ugotovitve pri 25 (37,3 %) bolnikov so bile resnično negativne. Štirje bolniki (6 %) so imeli lažno pozitivne ugotovitve, trije (4,5 %) pa lažno negativne. Tako je bila občutljivost preiskave ^{18}F-FDG PET/CT 92,11 %, specifičnost 86,21 %, pozitivna napovedna vrednost 89,74 %, negativna napovedna vrednost 89,29 % in natančnost 89,55 %. Pri 27 bolnikih (40,0 %) je ugotovitev ^{18}F-FDG PET/CT vplivala na nadaljnje vodenje bolnika.

Zaključki. ^{18}F-FDG PET/CT ima visoko natančnost pri odkrivanju metastaz/recidivov medularnega raka ščitnice pri bolnikih po tiroidektomiji, pa tudi pri oceni učinkovitosti in izbiri ustreznega zdravljenja.

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Radiološka ocena novonastalega glioma visoke stopnje malignosti. Proučevanje hitrosti diametričnega širjenja in pospešitvenega časa

Altieri R, Certo F, La Rocca G, Melcarne A, Garbossa D, Bianchi A, Crimi S, Pluchino A, Peschillo S, Barbagallo GMV

Izhodišča. Spoznavanje etiopatogeneze, fiziologije in patologije gliomov ostaja pomemben izziv sodobne nevroonkologije. Številne raziskave so pokazale jasno povezavo med radiološkimi značilnostmi in biološkimi lastnostmi gliomov. Znano je, da je hitrost diametrične ekspanzije povezana z agresivnostjo nizko malignih gliomov. Pri visoko malignih gliomih enako močnih dokazov nimamo, saj je število predoperativnih MRI preiskav manjše.

Bolniki in metode. Predstavljamo skupino štirih bolnikov (dva moška in dve ženski) z visoko malignim gliomom, ki smo jih sledili od 2014 do januarja 2019. Dva sta imela histološko potrjen glioblastom, eden anaplastični astrocitom, en bolnik pa je imel nevroradiološko diagnozo glioblastoma. Hitrost diametrične ekspanzije in pospešitveni čas smo izračunali za prostornino tumorja in za nodul. Pri izračunu za prostornino tumorja smo uporabili slikanje z magnetno resonančno metodo z izločanjem signalov tekočin (*angl. fluid attenuated inversion recovery*, FLAIR) pri izračunu za nodul pa postkontrastni ojačani signal. Povprečen razmik med zaporednimi MRI je bil 413 dni.

Rezultati. Povprečna hitrost diametrične ekspanzije za povečanje prostornine tumorja na FLAIR je bila 39,91 mm/leto. Povprečno odstotno razmerje med najvišjimi vrednostmi in povprečno vrednostjo pospešitve je bilo 282,7 %. Srednji čas od prve MRI do pojava postkontrastnega ojačanega signala je bil 432 dni. Povprečna hitrost diametrične ekspanzije za postkontrastni ojačani signal je bila 45,02 mm/leto, povprečno odstotno razmerje med najvišjimi vrednostmi in povprečno vrednostjo pospešitve pa 257,52 %.

Zaključki. Po našem vedenju je to prvo poročilo o hitrosti diametrične ekspanzije in pospeševanju rasti pri visoko malignih gliomih, ki potrjuje njihovo agresivno naravo. V primerih, ko moramo ponoviti predoperativno MRI, je potrebno čas med zaporednimi slikanji skrajšati na največ 15–20 dni in operacijo izvesti čim prej.

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Volumen tumorja, izmerjen predoperativno z magnetnoresonančnim slikanjem, je povezan s preživetjem pri bolnicah z rakom endometrija

Coronado PJ, de Santiago-López J, de Santiago-García J, Méndez R, Fasero M, Herraiz MA

Izhodišča. Namen raziskave je bil ugotoviti, ali je tumorski volumen pri raku endometrija, izmerjen z magnetnoresonančnim slikanjem, povezan s preživetjem bolnic in metastaziranjem v bezgavke.

Bolnice in metode. Ocenili smo predoperativni MRI in podatke 341 bolnic z rakom endometrija, ki smo jih zdravili od leta 2008 do 2018. Z MRI smo izračunali tumorski volumen in uporabili elipsoidno formulo, ki je upoštevala tri pravokotne premere tumorja. Dodatno smo analizirali invazijo tumorja v miometrij.

Rezultati. Z MRI izmerjen večji tumorski volumen je bil povezan s starostjo ≥ 65 let, ne-endometrioidnimi tumorji, gradusom 3, globoko miometrijsko invazijo, metastaziranjem v bezgavke in napredovalim stadijem FIGO. 37 (8,8 %) bolnic je imelo metastaze v bezgavkah. Ne-endometrioidni tumorji, globoka miometrijska invazija, gradus 3 in tumorski volumen ≥ 10 cm^3 so bili dejavniki povezani z metastaziranjem v bezgavke. Z analizo krivulje ROC smo postavili mejo tumorskega volumna 10 cm^3 (površina pod krivuljo = 0,70; 95 % interval zaupanja [CI]: 0,61–0,73). To je meja, ki je pomembna za preživetje bolnic. Pet-letno preživetje brez bolezni (DFS) in celokupno preživetje (OS) bolnic je bilo pri magnetnoresonančnem tumorskem volumnu ≥ 10 cm^3 bistveno nižje v primerjavi s tistim pod to mejo (69,3 % proti 84,5 % in 75,4 % proti 96,1 %). Magnetnoresonančni tumorski volumen se je v multivariatni analizi izkazal kot neodvisni dejavnik za DFS (razmerje obetov [HR]: 2,20, 95 % CI: 1,09–4,45, p = 0,029) in OS (HR: 3,88, 95 % CI: 1,34–11,24, p = 0,012).

Zaključki. Z MRI izmerjen tumorski volumen je bil povezan z metastaziranjem v bezgavke. Vrednost magnetnoresonančnega tumorskega volumna ≥ 10 cm^3 je bila neodvisni napovedni dejavnik za DFS in OS. Informacija o z MRI izmerjenem tumorskem volumnu lahko pomaga pri načrtovanju kirurškega in dodatnega zdravljenja žensk z rakom endometrija.

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Časovni trend preživetja bolnikov z rakom v Sloveniji

Zadnik V, Žagar T, Lokar K, Tomšič S, Duratović Konjević A, Zakotnik B

Izhodišča. Namen raziskave je opisati preživetje slovenskih bolnikov z rakom, diagnosticiranih v zadnjih dvajsetih letih. Prikazujemo izboljšanje preživetij pri različnih vrstah raka, populacijskih skupinah in napovednih dejavnikih.

Metode. Osnovni vir podatkov je Register raka Republike Slovenije. V analizo preživetja smo vključili bolnike, ki jim je bila diagnoza rak postavljena med leti 1997 in 2016. Dvajsetletno obdobje smo razdelili na štiri zaporedna petletna obdobja. Poleg tega je bila analiza narejena še ločeno glede na vrsto raka, spol, starost in stadij bolezni ob diagnozi. Preživetje smo ocenili s čistim preživetjem, izračunanim po metodi Pohar-Perme, za vključevanje podatkov pa smo uporabili popolno metodo.

Rezultati. Preživetje slovenskih bolnikov z rakom se s časom povečuje. V opazovanih dvajsetih letih se je petletno čisto preživetje povečalo za 11 odstotnih točk. Znatno bolj se je izboljšalo preživetje pri moških. Starost in stadij ob diagnozi sta še vedno ključna za preživetje bolnikov z rakom. Petletno čisto preživetje je najnižje pri osebah starejših od 75 let ob diagnozi, vendar se je v zadnjih dvajsetih letih tudi pri najstarejših izboljšalo za sedem odstotnih točk. Petletno čisto preživetje bolnikov diagnosticiranih z omejeno boleznijo se je v dvajsetih letih povečalo za deset odstotnih točk. Preživetje bolnikov z razsejano boleznijo ob diagnozi se ni izboljševalo. Pri obeh spolih se je preživetje bolnikov z melanomom, rakom debelega črevesa in danke ter s pljučnim rakom v zadnjih dvajsetih letih značilno izboljšalo. Napredek je bil dosežen tudi pri dveh, pri vsakem na spol vezanih, najpogostejših rakih: raku dojke pri ženskah in raku prostate pri moških. Kljub vsemu pa je pomemben napredek pri raku prostate verjetno predvsem posledica pristranosti časa prednosti, saj je Slovenija v obdobju raziskave precej nekritično uporabljala testiranje PSA, kar je verjetno umetno podaljšalo preživetje.

Zaključki. Izboljšanje preživetja slovenskih bolnikov z rakom, ki ga opazujemo v zadnjih letih, predstavlja osnovo in spodbudo za nadaljnje izboljšave. Učinkovitost obvladovanja epidemije raka je smiselno tudi v prihodnje spremljati z uporabo kakovostnih podatkov in znanstveno utemeljenih metodoloških pristopov. V tem procesu imajo ključno vlogo dobro organizirani populacijski registri raka.

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Zdravljenje regionalnih zasevkov kožnega melanoma. 15 let izkušenj terciarnega centra

Perić B, Miličević S, Perhavec A, Hočevar M, Žgajnar J

Izhodišča. Na podlagi rezultatov dveh randomiziranih prospektivnih raziskav ter razvoja dopolnilnega zdravljenja se je temeljito spremenila obravnava bolnikov s kožnim melanomom po biopsiji varovalne bezgavke (*angl. sentinel lymph node*). Namen raziskave je bil primerjati retrospektivne rezultate zdravljenja slovenskih bolnikov s kožnim melanomom III. stadija s sedanjimi mednarodnimi priporočili.

Bolniki in metode. Vse bolnike s kožnim melanomom stadija ≥ TIb zdravljene na Onkološkem inštitutu Ljubljana smo od leta 2000 dalje prospektivno vključevali v podatkovno bazo. Opravili smo retrospektivno analizo podatkov bolnikov zdravljenih do leta 2015. Med njimi jih je bilo 2426 takih po opravljeni biopsiji varovalne bezgavke ter 789 bolnikov po limfadenektomiji bezgavčne lože. Izrisali smo Kaplan-Meierjeve krivulje preživetja in rezultate primerjali z log-rank testom.

Rezultati. Izmed 2426 bolnikov je bil zasevek v varovalni bezgavki odkrit pri 519 (519/2426, 21.4 %) bolnikih, 455 bolnikov jih je zdravljenje nadaljevalo z limfadenektomijo. Celokupna 5-letna preživetja glede na zasevke v regionalnih bezgavkah so bila: po dokončanju limfadenektomije 58 %, z metahronimi zasevki v bezgavkah in limfadenektomijo 47 % (p = 0,003) ter z regionalno boleznijo neznanega izvora 45 % in ob sinhronih regionalnih zasevkih 21 %. Celokupno preživetje bolnikov z zasevki varovalne bezgavke < 0.3 mm je bilo primerljivo s tistimi brez zasevka (86 % vs. 85 %, p = 0,926). Bolniki s zasevkom > 1 mm so imeli preživetje primerljivo s tistimi, ki so imeli metahrone zasevke v bezgavkah (49 % vs. 47 %, p = 0.280).

Zaključki. Preživetja bolnikov s III. stadijem kožnega melanoma se znatno razlikujejo. Dokončanje limfadenektomije po odkritju zasevka v varovalni bezgavki ostaja učinkovito zdravljenje v skrbno izbranih primerih.

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Sinhrona odstranitev jetrnih metastaz pri bolnikih z rakom želodca. Primerjava uravnoteženih skupin bolnikov

Jagrič T, Horvat M

Izhodišča. Cilj raziskave je bil ugotoviti pomen sinhronih odstranitev jetrnih metastaz pri bolnikih z oligometastatskim rakom želodca in določiti napovedne dejavnike za napoved poteka bolezni.

Bolniki in metode. Primerjali smo rezultate sinhrone odstranitve jetrnih metastaz in želodca pri 21 bolnikih z rakom želodca (LMR) z rezultati 21 uravnoteženih bolnikov z rakom želodca in metastazami v jetrih, kjer smo odstranili le želodec (LM0). Kot kontrolno skupino smo vključili uravnotežene bolnike z rakom želodca in stadijem III in IV brez jetrnih metastaz (CG).

Rezultati. Celokupno 5-letna preživetja bolnikov skupin LMR, LM0 in CG so bila 14.3 %, 0 % in 19 % (p = 0.002). Celokupno 5-letno preživetje bolnikov z operacijo jetrnih zasevkov in dobro diferenciranim rakom želodca je bilo 47,5 %, pri bolnikih z zmerno in slabo diferenciranim rakom pa 0 % (p = 0.006). Pri bolnikih z R0 operacijo jetrnih zasevkov in s stadiji primarnega tumorja TNM N0–1 je bilo celokupno 5-letno preživetje bistveno boljše kot pri bolnikih s stadiji primarnega tumorja TNM N2–3 (5-letno preživetje: 60 % pri N0–1 in 7,7 % pri N2–3; p = 0.007).

Zaključki. Rezultati raziskave podpirajo sinhrone odstranitve jetrnih zasevkov pri bolnikih z rakom želodca in podajajo kriterije za izbor primernih kandidatov za takšno zdravljenje.

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Pooperativno obsevanje za bolnike s popolno reseciranim nedrobnoceličnim pljučnim rakom patološkega stadija IIIA-N2. Večja korist za ploščatocelični rak

Tian C, Liu G, Xu Y, Xia G, Zhang T, Huang J, Jiang H, Wang J, Li B

Izhodišča. Ugoden učinek pooperativnega obsevanja pri popolni patološki resekciji nedrobnoceličnega pljučnega raka in s stadijem IIIA-N2 (pIIIA-N2) je še vedno diskutabilen. Namen raziskave je bil oceniti klinično učinkovitost pooperativnega obsevanja pri nedrobnoceličnem pljučnem raku pIIIA-N2 ločeno za žlezni rak in ploščatocelični rak.

Bolniki in metode. Analizirali smo 288 zaporednih bolnikov, ki smo jih zdravili med oktobrom 2010 in septembrom 2016 v Pekinški bolnišnici. Vsem bolnikom smo radikalno operirali nedrobnocelični rak pljuč stadija pIIIA-N2. 194 bolnikov je imelo žlezni rak in 85 ploščatoceličnega. Med bolniki z žleznim rakom je bilo 42 (21,6%) zdravljenih s pooperativnim obsevanjem, med bolniki s ploščatoceličnim pa 19 (22,3%). Petletno celokupno preživetje, preživetje brez loko-regionalne ponovitve bolezni in preživetje brez oddaljenih metastaz smo izračunali z metodo Kaplan-Meier. Napovedne dejavnike smo določili z uporabo Coxovega regresijskega modela.

Rezultati. Med 194 bolniki z žleznim rakom je bilo 1-, 3- in 5-letno celokupno preživetje v skupini pooperativno obsevanih 95,2 %, 61,9 % in 40,0 %; v skupini brez pooperativnega obsevanja pa 90,1 %, 63,3 % in 45,0 % (p = 0,948). Pooperativna kemoterapija, pozitivne bezgavke v več regijah in indeks kajenja ≥ 400 so bili napovedni dejavniki petletnih preživetij tako za celokupno preživetje, kot tudi za preživetje brez loko-regionalne ponovitve bolezni in preživetje brez oddaljenih metastaz. Po drugi strani je bilo med 85 bolniki s ploščatoceličnim rakom 1-, 3- in 5- letno celokupno preživetje v skupini pooperativno obsevanih 94,7 %, 63,2 % in 63,2 %, medtem ko je bilo v skupini brez pooperativnega obsevanja 86,4 %, 48,5 % in 37,1 % (p = 0,026). V tej skupini je bila le uporaba pooperativnega obsevanja ugoden napovedni dejavnik za 5-letno celokupno preživetje, preživetje brez loko-regionalne ponovitve bolezni in preživetje brez oddaljenih metastaz.

Zaključki. Zaradi klinično-patoloških razlik med radikalno operiranimi bolniki z nedrobnoceličnim rakom pljuč stadija pIIIA-N2 verjetno pooperativno obsevanje ni primerno za vse bolnike. Pričujoča raziskava je pokazala, da bi lahko imeli bolniki s ploščatoceličnim rakom stadija pIIIA-N2 večjo korist od pooperativnega obsevanja kot bolniki z žleznim rakom.

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Z obsevanjem povezan angiosarkom v področju dojke, rekonstruirane s telesu lastnim tkivom in zdravljen z elektrokemoterapijo

Cencelj-Arnež R, Novak J, Klevišar Ivančič A, Bošnjak M, Čemažar M, Snoj M

Izhodišča. Z radioterapijo povezan angiosarkom dojke je redek kasni zaplet obsevanja, ki ga je pogosto težko prepoznati. Napoved bolezni je slaba. Največkrat se kaže kot vijolično obarvana koža, eritem ali hitro rastoča tipna rezistenca, ki jo lahko zamenjamo z drugimi benignimi kožnimi lezijami.

Bolniki in metode. Po pregledu literature smo po mastektomiji in rekonstrukciji dojk s telesu lastnim tkivom našli opisane le 4 takšne primere z radioterapijo povezanega angiosarkoma. Predstavljeni primer je prvi, ki prikazuje zdravljenje z elektrokemoterapijo. Predstavljamo bolnico s sekundarnim angiosarkomom dojke, pet let po mastektomiji z rekonstrukcijo dojke in dopolnilno radioterapijo.

Rezultati. Elektrokemoterapija je bila izvedljiv, varen in učinkovit način zdravljenja angiosarkoma povezanega z obsevanjem. Večina zdravljenih lezij je v več zaporednih zdravljenjih z elektrokemoterapijo popolnoma odgovorila na zdravljenje, vendar so se na nezdravljenem področju večkrat pojavile nove lezije.

Zaključki. Bolnice z rakom dojk po mastektomiji z ohranitvijo kože in takojšnjo rekonstrukcijo dojk, ki so bile obsevane, potrebujejo redno dolgotrajno spremljanje in takojšnjo biopsijo kakršnekoli sumljive lezije. Elektrokemoterapija se je izkazala kot eden izmed možnih načinov zdravljenja z radioterapijo povezanega angiosarkoma.

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Klinični in volumetrični napovedniki za lokalno kontrolo bolezni po robotski stereotaktični radioterapiji možganskih matastaz. Aktivna sistemska bolezen lahko vpliva na lokalno kontrolo bolezni v možganih

Blamek S, Stankiewicz M, Maciejewski B

Izhodišča. Namen raziskave je bil ugotoviti povezavo med fizikalno in biološko dozo normalizirano na volumen metastatskega tumorja ter kliničnimi faktorji, ki vplivajo na lokalno kontrolo tumorja pri bolnikih z možganskimi metastazami, ki smo jih zdravili z robotsko stereotaktično radioterapijo.

Bolniki in metaode. Analizirali smo skupino 69 bolnikov, ki smo jih zdravili z robotsko radiokirurgijo v času med 2011 in 2026. Obsevanje je bilo enodozno ali hipofrakcionirano. Biološko učinkovito dozo (*angl. biologically effective dose;* BED) smo izračunali na osnovi predpostavke za razmerje alfa/beta = 10. Fizikalno dozo in BED smo normalizirali na velikost tumorja in tako omogočili analizo učinka doza-volumen. Dodatno smo analizirali klinične parametre povezane z zdravljenjem, da bi jih povezali z učinkom lokalne kontrole tumorjev.

Reultati. Obsevali smo 133 tumorjev velikosti 0,001 do 46.99 cm^3. Napredovanje bolezni izven glave je bilo povezano s slabšo lokalno kontrolo bolezni, med tem ko so bili višja skupna doza, BED_{10} > 59 Gy in posamezne mezastaze statistično značilno povezani z daljšo lokalno kontrolo. BED10/cm^3 > 36 Gy in BED2 > 60 Gy sta negatvno vplivali na lokalno kontrolo bolezni. V multivariatni analizi vseh spremenljivk so prisotnost ene metastaze, BED_{10} > 59 Gy in napredovanje bolezni izven glave ohranili statistično značilno razliko. Če smo izključili napovednik BED_2/cm^3, pa so v Cox-ovem modelu tudi vse preostale spremenljivke ohranile statistično zančilno povezavo z lokalno kontrolo bolezni.

Zaključki. Hipofrakcionacija je imela podoben učinek, kot enodozno obasevanje pri lokalni kontroli mezastaz, je pa bil učinek obeh režimov obsevanj odvisen od BED. Učinkovita kontrola bolezni izven glave je povezana z večjo verjetnostjo lokalne kontrole bolezni, vendar je učinek veliko slabši pri multiplih lezijah.

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Prospektivna ocena verjetne dozno eskalirajoče intenzitetno modulirane radioterapije (IMRT) pri raku prostate

Wegener D, Berger B, Outaggarts Z, Zips D, Paulsen F, Bleif M, Thorwarth D, Alber M, Dohm O, Müller AC

Izhodišča. Stopnja ozdravitve in toksičnosti po intenzitetno modulirani radioterapiji (IMRT) raka prostate je odvisna od sevalne doze in obsevalnega volumna. Prospektivno smo ugotavljali možnost koncepta verjetnosti pokritja (*ang. Coverage Probability, CovP*) za zaščito kritičnih organov in kompenzacijo premikov tumorja.

Bolniki in metode. 28 bolnikov (srednja starost 70 let) z lokaliziranim rakom prostate (cT1c–2c, N0, M0) in srednje stopnje tveganja (PSA < 20, seštevek po Gleasonu ≤ 7b) smo zdravili v prospektivni raziskavi s konceptom *CovP*. Planirne slike CT-ja smo naredili v treh zaporednih dneh, da bi registrirati spremembe oblike ter premike prostate in kritičnih organov. Na vsakem CT-ju smo obkrožili klinični tarčni volumen (CTV, prostata) ter kritične organe (mehur in danko). Vsoti CTV1–3 smo dodali izotropni rob 7 mm, ki je opredelil notranji tarčni volumen (ITV). Predpisana/eskalirana doza je bila odvisna od pokritja vseh CTV-jev znotraj ITV-ja. Bolniki so prejeli IMRT v 39 frakcijah do 78 Gy, pri čemer smo uporabili algoritem Monte-Carlo. Priporočili smo kratkotrajno androgenska odtegnitev, ki smo jo izvedli pri 78,6 % bolnikov.

Rezultati. Kasno toksičnost smo ocenili pri 26/28 bolnikih po srednjem času sledenja 7,1 let. Ob zadnjem pregledu so bili kasni neželeni učinki na mehurju (po klasifikaciji *angl. Radiation Therapy Oncology Group,* RTOG) G1 ugotovljeni pri 14,3 % bolnikov ter kasna črevesna toksičnost (RTOG) G1 pri 7,1 % in G2 pri 3.6% bolnikov. Toksičnost višjih stopenj se ni razvila. Po 7,1 letih je bila biokemična kontrola bolezni (biokemično brez znakov bolezni) 95,5 %, za raka prostate specifično preživetje in preživetje brez oddaljenih zasevkov pa sta bila 100%.

Zaključki. IMRT, ki temelji na konceptu *CovP*, je izvedljiva v klinični raziskavi. Eskalacijo doze so spremljali nizka toksičnost, ter učinkovita kontrola lokalne in oddaljene bolezni.

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Vpliv peroralnega jemanja astaksantina na kakovost semena pri bolnikih z oligoastenoteratozoospermijo. Randomizirana dvojno slepa, s placebom kontrolirana raziskava

Imamović Kumalić S, Virant Klun I, Vrtačnik Bokal E, Pinter B

Izhodišča. Višje koncentracije reaktivnih kisikovih spojih so lahko vzrok za moško neplodnost. Astaksantin z močnim antioksidativnim delovanjem ima potencialno zdravju koristne učinke za preprečevanje in zdravljenje različnih bolezni, tudi raka. Vpliv astaksantina na kakovost semenčic pri neplodnih moških s slabo kakovostjo semena, vključno z oligo- z/brez asteno- z/brez teratozoospermijo (O±A±T) doslej še ni bila raziskovan. Namen raziskave je bil preučiti vpliv peroralnega jemanja astaksantina na kakovost semena.

Bolniki in metode. V klinično prospektivno randomizirano dvojno slepo raziskavo smo vključili 80 moških, pri katerih je bila diagnosticirana O±A±T in so jemali bodisi 16 mg astaksantina ali placebo. Ob vstopu v raziskavo in po treh mesecih jemanja zdravila ali placeba smo pri vseh bolnikih določili parametre spermiograma, mitohondrijski membranski potencial semenčic, fragmentacijo deoksiribonukleinske kisline (DNK) semenčic in nivo folikle stimulirajočega hormona (FSH) v serumu.

Rezultati. Analiza rezultatov 72 preiskovancev, ki so zaključili raziskavo (37 v študijski skupini in 35 v kontrolni skupini) ni pokazala statistično pomembnih razlik. V študijski skupini nismo ugotovili sprememb v koncentraciji semenčic, skupnem številu semenčic, skupni gibljivosti semenčic, morfologiji semenčic, mitohondrijskem membranskem potencialu semenčic, fragmentaciji DNK ali v serumskih nivojih FSH. V kontrolni skupini smo našli statistično pomembne spremembe v koncentraciji semenčic in v skupnem številu semenčic.

Zaključki. Peroralno jemanje astaksantina ni vplivalo na nobenega od parametrov kakovosti semena pri pacientih z O±A±T.

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Delno nadzorovana načrtovalna metoda za obsevanje dojk ob upoštevanju njihovega polmera in medsebojne razdalje ter elektronske kompenzacije tkiva

Podgoršak AR, Kumaraswamy LK

Izhodišča. Namen raziskave je bil razviti in oceniti tehniko za optimiziranje obsevalnih načrtov za obsevanje dojk, ki temelji na polmeru dojk in na njuni medsebojni razdalji, upoštevaje elektronsko kompenzacijo tkiva.

Bolnice in metode. Za raziskavo smo uporabili deset obsevalnih načrtov za obsevanje dojk, izdelanih na našem inštitutu, pri čemer smo upoštevali elektronsko kompenzacijo tkiva. Za oceno polmera dojk in določitev medsebojno razdalje med dojkama smo uporabili aksialne reze simulacijskih računalniškotomografskih slik. Vse uporabljene podatke smo predhodno anonimizirali. Optimalni obsevalni načrt smo določili na podlagi medsebojne razdalje med dojkama in polmera dojke ter fluenčne mape za vsa obsevalna polja. Fluenčne mape smo uvozili v načrtovalni sistem Eclipse in jih uporabili za izračun dozne porazdelitve. Izračunano dozno porazdelitev smo primerjali z dozno porazdelitvijo pri obsevalnem načrtu, ki ga je izdelal dozimetrist z ročno optimizacijo. Za primerjavo obsevalnih načrtov smo uporabili indeks dozne homogenosti HI, pri čemer smo upoštevali, da je nižja vrednost HI boljša.

Rezultati. Primerjava povprečnih vrednosti HI desetih obsevalnih načrtov ni pokazala pomembnih razlik (p-vrednost > 0,05) med našim algoritmom (HI = 12,6) in obsevalnimi načrti, ki jih je izdelal dozimetrist (HI = 9,9). Ob uporabi delno nadzorovanega algoritma smo za izdelavo obsevalnega načrta potrebovali približno 20 sekund, medtem ko je dozimetrist potreboval 30 minut za izdelavo optimiziranega obsevalnega načrta.

Zaključki. Raziskava nakazuje potencialno klinično uporabnost opisane tehnike optimizacije obsevalnih načrtov z upoštevanjem elektronske kompenzacije tkiva.

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Vpliv uporabe svinčene zaščite na sevalno dozo, ki jo prejmejo dojke med slikanjem glave z računalniško tomografijo

Zalokar N, Mekiš N

Izhodišča. Med računalniško tomografijo (CT) glave dojke niso v primarnem polju slikanja, vendar so izpostavljene dozi sipanega sevanja. Namen raziskave je bil ugotoviti, ali uporaba svinčene zaščite pomembno vpliva na prejeto dozo na dojke med slikanjem glave s CT-jem v dveh slovenskih bolnišnicah.

Pacientke in metode. V raziskavo smo vključili 120 pacientk, polovico (n = 60) iz bolnišnice A in polovico iz bolnišnice B. Uporabili smo dva različna CT aparata s spiralno tehniko slikanja. Polovico meritev smo izvedli brez uporabe svinčene zaščite, polovico meritev pa s svinčeno zaščito 0,5 mm ekvivalentne debeline svinca, ki smo jo ovili okoli trupa pacientke. Za merjenje doze smo uporabili elektronski dozimeter EDD 30.

Rezultati. Kožna doza na dojke se je ob uporabi svinčene zaščite statistično značilno pomembno znižala v obeh bolnišnicah. V bolnišnici A za 81 % (iz 338,2 ± 43,7 μGy na 64,3 ± 18,8 μGy), v bolnišnici B pa za 74 % (iz 253,1 ± 35,1 μGy na 65,3 ± 16,9 μGy).

Zaključki. Glede na visoko povprečno statistično značilno znižanje sevalne doze na dojke (78 %), škodljive učinke ionizirajočega sevanja, vedno bolj pogostih doznoobremenjujočih slikanj glave s CT-jem in visoko občutljivost dojk na učinke ionizirajočega sevanja priporočamo uporabo svinčene zaščite med slikanjem glave s CT-jem.

Fundacija "Docent dr. J. Cholewa"
je neprofitno, neinstitucionalno in nestrankarsko
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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the first quarter of 2021

Doc. Dr. Josip Cholewa Foundation for cancer research and education continues with its planned activities in the first quarter of 2021 and is commencing to prepare for the activities the whole year. Its primary focus remains the provision of grants and scholarships and other forms of financial assistance for basic, clinical and public health research in the field of oncology. An analysis of the ongoing activities in the last year was made in order to make an assessment of the impact of Foundation's activities, thus providing a basis for developing new strategies and approaches in its scope of fight against cancer.

The Foundation continues to provide support for »Radiology and Oncology«, a quarterly scientific magazine with a respectable impact factor that publishes research and review articles about all aspects of cancer. The magazine is edited and published in Ljubljana, Slovenia. »Radiology and Oncology« is an open access journal available to everyone free of charge. Its long tradition represents a guarantee for the continuity of international exchange of ideas and research results in the field of oncology for all in Slovenia that are interested and involved in helping people affected by many different aspects of cancer.

The Foundation makes great efforts to provide financial and other kinds of support for the organisation of various forms of meetings to extend and broaden the knowledge about prevention of cancer, early detection of various types of cancer, its treatment and rehabilitation of cancer patients. The advances in knowledge of all aspects of dealing with cancer should be in Foundation's opinion available to all the professionals that treat cancer patients, to the patients themselves and their closest relatives and friends, and finally also to the general public.

The problems associated with cancer affect more and more people and their relatives in Slovenia and elsewhere. The Foundation will therefore continue with its activities in the years to come. Treatment of cancer is ever more successful with many patients surviving decades after the start of their treatment and many new problems and challenges have thus come into place. Longer survival of an increasing number of patients with previously incurable cancer conditions adds many new dimensions to their life and to the life of their families. It also confronts cancer specialists, all the other experts and lay public dealing with cancer with new challenges and new goals to achieve.

Andrej Plesničar, M.D., M.Sc.

Viljem Kovač M.D., Ph.D.

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila.

Imfinzi 50 mg/ml koncentrat za raztopino za infundiranje

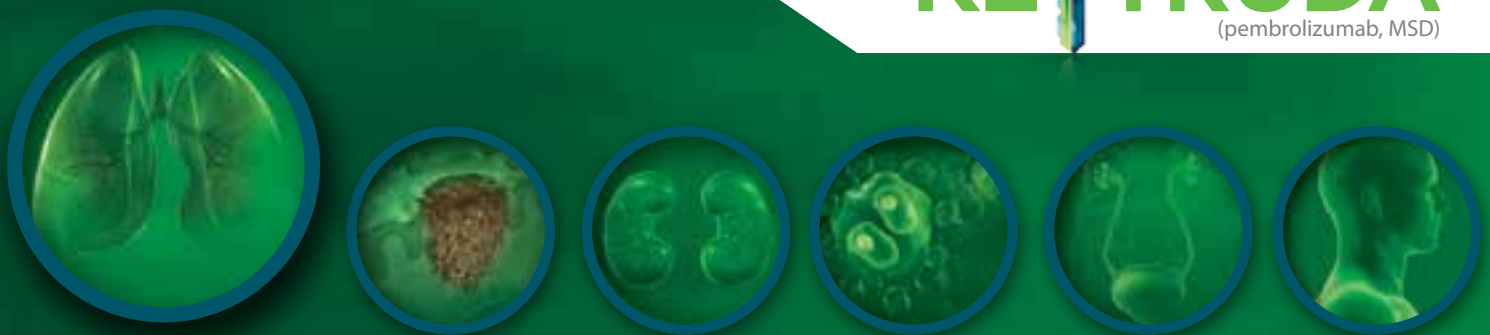
SESTAVA: 1 ml koncentrata za raztopino za infundiranje vsebuje 50 mg durvalumaba. Ena viala z 2,4 ml koncentrata vsebuje 120 mg durvalumaba. Ena viala z 10 ml koncentrata vsebuje 500 mg durvalumaba. **INDIKACIJE:** Zdravilo Imfinzi je kot samostojno zdravljenje indicirano za zdravljenje lokalno napredovalega, neoperabilnega nedrobnoceličnega raka pljuč (NSCLC – "non small cell lung cancer") pri odraslih, ki imajo tumorje z ≥ 1 % izraženostjo PD-L1 na tumorskih celic in pri katerih bolezen ni napredovala po kemoradioterapiji na osnovi platine. 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"). **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 je 10 mg/kg na 2 tedna ali 1500 mg na 4 tedne do napredovanja bolezni, nesprejemljivih toksičnih učinkov ali največ 12 mesecev . Bolniki s telesno maso 30 kg ali manj morajo prejemati odmerke na podlagi telesne mase, in sicer 10 mg/kg na 2 tedna ali 20 mg/kg na 4 tedne kot samostojno zdravljenje, dokler se telesna masa ne poveča na več kot 30 kg. V kombinaciji s kemoterapijo 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. Zdravilo Imfinzi se uporablja v intravenski infuziji, ki traja 1 uro. Povečevanje ali zmanjševanje odmerka ni priporočljivo. Glede na individualno varnost in prenašanje je lahko potrebna odložitev odmerka ali prenehanje uporabe zdravila. V primeru domnevnih imunsko pogojenih neželenih učinkov je treba opraviti ustrezno ovrednotenje za potrditev etiologije oziroma izključitev druge etiologije. 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 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. Če se imunsko pogojeni neželeni učinki 3. ali 4. stopnje (močno izraženi ali življenjsko nevarni) ponavljajo, je treba zdravilo Imfinzi dokončno ukiniti. Pri ne imunsko pogojenih neželenih učinkih velja v primeru 2. ali 3. stopnje izraženosti razmisliti o odložitvi uporabe zdravila Imfinzi do izboljšanja neželenih učinkov na ≤ 1. stopnjo ali na izhodiščno raven. Z uporabo zdravila Imfinzi je treba prenehati v primeru neželenih učinkov 4. stopnje (razen v primeru laboratorijskih nepravilnosti 4. stopnje, pri katerih naj odločitev o prekinitvi uporabe zdravila temelji na spremljajočih kliničnih znakih oziroma simptomih in na klinični presoji zdravnika). Zdravilo Imfinzi je namenjeno za intravensko uporabo. Dati ga je treba kot raztopino za intravensko infundiranje v obdobju 1 ure. **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, sta se pojavila imunsko pogojeni pnevmonitis ali intersticijska bolezen pljuč, opredeljeno kot potreba po uporabi sistemskih kortikosteroidov in brez jasne druge etiologije.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 preizkušanja, 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, se je pojavil imunsko pogojeni hepatitis, opredeljen kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojeni kolitis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, sta se pojavila imunsko pogojeni kolitis ali driska, opredeljeno kot potreba po sistemskih kortikosteroidih in brez jasne druge etiologije. Imunsko pogojene endokrinopatije: Imunsko pogojeni hipotiroidizem, hipertiroidizem in tiroiditis: Pri bolnikih, ki so prejemali zdravilo Imfinzi, so se pojavili imunsko pogojeni hipotiroidizem,hipertiroidizem in s 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 pogojeni hipotiroidizem,hipertiroidizem in tiroiditis je treba obravnavati, in ukrepati, kot je priporočeno v povzetku glavnih značilnosti zdravila. Imunsko pogojena adrenalna insuficienca: Pri bolnikih, ki so prejemali zdravilo Imfinzi, 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, se je pojavila imunsko pogojena sladkorna bolezen tipa 1. Bolnike je treba spremljati glede kliničnih znakov in simptomov sladkorne bolezni tipa 1. Imunsko pogojeni hipofizitis/hipopituitarizem: Pri bolnikih, ki so prejemali zdravilo Imfinzi, 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, 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, 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. Drugi imunsko pogojeni neželeni učinki: Glede na mehanizem delovanja zdravila Imfinzi 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: miastenija gravis, miokarditis, miozitis, polimiozitis, meningitis, encefalitis,Guillain Barréjev sindrom in imunska trombocitopenija. V programu kliničnih študij so pri bolnikih poročali o primerih pankreatitisa. Bolnike je treba spremljati glede znakov in simptomov in ukrepati, kot je priporočeno za druge imunsko pogojene neželene učinke. Z infundiranjem povezane reakcije: Bolnike je treba spremljati glede znakov in simptomov z infundiranjem povezanih reakcij. Pri bolnikih, ki so prejemali zdravilo Imfinzi, so bile opisane hude z infundiranjem povezane reakcije. Bolniki, ki niso bili vključeni v klinična preizkušanja: V klinična preskušanja 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. **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 nosečnicah 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 %). Ugotovitve o varnosti zdravila Imfinzi v kombinaciji s kemoterapijo temeljijo na podatkih 265 bolnikov z SCLC. Zdravilo Imfinzi so uporabljali v odmerku 1500 mg na 3 tedne v kombinaciji s kemoterapijo in nato pri samostojnem zdravljenju na 4 tedne. Najpogostejši neželeni učinki (> 20 %) so bili nevtropenija (48,7 %), anemija (38,5 %), navzea (33,6 %), utrujenost (32,1 %), alopecija (31,3 %), trombocitopenija (21,1 %) in levkopenija (20,0 %). Zdravilo Imfinzi pri samostojnem zdravljenju: Zelo pogosti neželeni učinki: okužbe zgornjih dihal,, hipotiroidizem, kašelj/produktiven kašelj, driska, bolečine v trebuhu, izpuščaj, srbenje, zvišana telesna temperatura. Pogosti neželeni učinki: pljučnica, zobne okužbe in okužbe ustnih mehkih tkiv, oralna kandidoza, gripa, hipertiroidizem, pnevmonitis, disfonija, zvišanje vrednosti aspartat aminotransferaze ali zvišanje vrednosti alanin aminotransferaze, nočno znojenje, dermatitis, mialgija, zvišanje vrednosti kreatinina v krvi, disurija, periferni edemi, z infundiranjem povezane reakcije. Občasni neželeni učinki: tiroiditis, adrenalna insuficienca, intersticijska bolezen pljuč, kolitis, hepatitis, dermatitis, miozitis, nefritis. Redki neželeni učinki: sladkorna bolezen tipa 1, hipofizitis / hipopituitarizem, diabetes insipidus, miastenija gravis, meningitis, miokarditis, pemfigois, polimiozitis, imunska trombocitopenija. Zdravilo Imfinzi v kombinaciji s kemoterapijo: Zelo pogosti neželeni učinki: nevtropenija, anemija, trombocitopenija, levkopenija, zmanjšan apetit, kašelj/produktiven kašelj, navzea, zaprtost, bruhanje, izpadanje las, utrujenost. Pogosti neželeni učinki: okužbe zgornjih dihal, pljučnica, zobne okužbe in okužbe ustnih mehkih tkiv, febrilna nevtropenija, pancitopenija, hipotiroidizem, hipertiroidizem, tiroiditis, adrenalna insuficienca, pnevmonitis, driska, bolečine v trebuhu, stomatitis, zvišanje vrednosti aspartat aminotransferaze ali zvišanje vrednosti alanin aminotransferaze, hepatitis, izpuščaj, srbenje, dermatitis, mialgija, zvišanje vrednosti kreatinina v krvi, disurija, zvišana telesna temperatura. Občasni neželeni učinki: gripa, sladkorna bolezen tipa 1 disfonija, intersticijska bolezen pljuč. **VRSTA IN VSEBINA OVOJNINE:** 2,4 ml koncentrata v stekleni viali iz stekla tipa 1 z elastomernim zamaškom in sivo snemno aluminijsko zaporo; viala vsebuje 120 mg durvalumaba. Pakiranje vsebuje 1 vialo. 10 ml koncentrata v stekleni viali iz stekla tipa 1 z elastomernim zamaškom in belo snemno aluminijsko zaporo; viala vsebuje 500 mg durvalumaba. Pakiranje vsebuje 1 vialo. **NAČIN IZDAJANJA ZDRAVILA:** samo na recept. **DATUM REVIZIJA BESEDILA:** januar 2021 (SI-1273). **IMETNIK DOVOLJENJA ZA PROMET:** AstraZeneca AB, S-151 85, Sodertalje, Švedska

Pred predpisovanjem, prosimo, preberite celoten povzetek glavnih značilnosti zdravila. Datum priprave informacije: januar 2021.
Dodatne informacije so na voljo pri družbi AstraZeneca UK Limited, Podružnica v Sloveniji, Verovškova 55, Ljubljana.

AstraZeneca

SI-1282

KEYTRUDA®
(pembrolizumab, MSD)



Nedrobnocelični pljučni rak[1] | Melanom[1] | Rak ledvičnih celic[1] | Hodgkinov limfom[1] | Urotelijski karcinom[1] | Ploščatocelični karcinom glave in vratu[1]

References: 1. Keytruda EU SmPC

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila!

Ime zdravila: KEYTRUDA 25 mg/ml koncentrat za raztopino za infundiranje vsebuje pembrolizumab.

Terapevtske indikacije: Zdravilo KEYTRUDA je kot samostojno zdravljenje indicirano za zdravljenje: napredovalega (neoperabilnega ali metastatskega) melanoma pri odraslih; za adjuvantno zdravljenje odraslih z melanomom v stadiju III, ki se je razširil na bezgavke, 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 bolnikov s ponovljenim ali neodzivnim klasičnim Hodgkinovim limfomom (cHL), pri katerih avtologna presaditev matičnih celic (ASCT) in zdravljenje z brentuksimabom vedotinom (BV) nista bila uspešna, in odraslih bolnikov, ki za presaditev niso primerni, zdravljenje z BV pa pri njih ni bilo uspešno; 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. 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 je indicirano za prvo linijo zdravljenja napredovalega raka ledvičnih celic (RCC) pri odraslih. **Odmerjanje in način uporabe**: Testiranje PD-L1 pri bolnikih z NSCLC, urotelijskim rakom ali HNSCC: Za samostojno zdravljenje z zdravilom KEYTRUDA je priporočljivo opraviti testiranje izraženosti PD-L1 tumorja z validirano preiskavo, da izberemo bolnike z NSCLC ali predhodno nezdravljenim urotelijskim rakom. Bolnike s HNSCC je treba za samostojno zdravljenje z zdravilom KEYTRUDA ali v kombinaciji s kemoterapijo s platino in 5-fluorouracilom (5-FU) izbrati na podlagi izraženosti PD-L1, potrjene z validirano preiskavo. Odmerjanje: Priporočeni odmerek zdravila KEYTRUDA za samostojno zdravljenje je bodisi 200 mg na 3 tedne ali 400 mg na 6 tednov, apliciran z intravensko infuzijo v 30 minutah. Priporočeni odmerek za kombinirano zdravljenje je 200 mg na 3 tedne, apliciran z intravensko infuzijo v 30 minutah. Za uporabo v kombinaciji glejte povzetke glavnih značilnosti 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. Pri adjuvantnem zdravljenju melanoma je treba zdravilo uporabljati do ponovitve bolezni, pojava nesprejemljivih toksičnih učinkov oziroma mora zdravljenje trajati do enega leta. 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. Pri bolnikih starih ≥ 65 let, bolnikih z blago do zmerno okvaro ledvic, bolnikih z blago 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 5.884 bolnikih z napredovalim melanomom, kirurško odstranjenim melanomom v stadiju III (adjuvantno zdravljenje), NSCLC, cHL, urotelijskim rakom ali HNSCC s štirimi odmerki (2 mg/kg na 3 tedne, 200 mg na 3 tedne in 10 mg/kg na 2 ali 3 tedne). V tej populaciji bolnikov je mediani čas opazovanja znašal 7,3 mesece (v razponu od 1 dneva do 31 mesecev), najpogostejši neželeni učinki zdravljenja s pembrolizumabom so bili utrujenost (32 %), navzea (20 %) in diareja (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. Varnost pembrolizumaba pri kombiniranem zdravljenju s kemoterapijo so ocenili pri 1.067 bolnikih NSCLC ali HNSCC, ki so v kliničnih študijah prejemali pembrolizumab v odmerkih 200 mg, 2 mg/kg ali 10 mg/kg na vsake 3 tedne. V tej populaciji bolnikov so bili najpogostejši neželeni učinki naslednji: anemija (50 %), navzea (50 %), utrujenost (37 %), zaprtost (35%), diareja (30 %), nevtropenija (30 %), zmanjšanje apetita (28 %) in bruhanje (25 %). Pri kombiniranem zdravljenju s pembrolizumabom je pri bolnikih z NSCLC pojavnost neželenih učinkov 3. do 5. stopnje znašala 67 %, pri zdravljenju samo s kemoterapijo pa 66 %, pri kombiniranem zdravljenju s pembrolizumabom pri bolnikih s HNSCC 85 % in pri zdravljenju s kemoterapijo v kombinaciji s cetuksimabom 84 %. Varnost pembrolizumaba v kombinaciji z aksitinibom so ocenili v klinični študiji pri 429 bolnikih z napredovalim rakom ledvičnih celic, ki so prejemali 200 mg pembrolizumaba na 3 tedne in 5 mg aksitiniba dvakrat na dan. V tej populaciji bolnikov so bili najpogostejši neželeni učinki diareja (54 %), hipertenzija (45 %), utrujenost (38 %), hipotiroidizem (35 %), zmanjšan apetit (30 %), sindrom palmarno-plantarne eritrodisestezije (28 %), navzea (28 %), zvišanje vrednosti ALT (27 %), zvišanje vrednosti AST (26 %), disfonija (25 %), kašelj (21 %) in zaprtost (21 %). Pojavnost neželenih učinkov 3. do 5. stopnje je bila med kombiniranim zdravljenjem s pembrolizumabom 76 % in pri zdravljenju s sunitinibom samim 71 %. Za celoten seznam neželenih učinkov, prosimo, glejte celoten Povzetek glavnih značilnosti zdravila

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, Nizozemska.

MSD

Merck Sharp & Dohme inovativna zdravila d.o.o.,
Šmartinska cesta 140, 1000 Ljubljana, tel: +386 1/ 520 42 01, fax: +386 1/ 520 43 50
Pripravljeno v Sloveniji, September 2020; SI-KEY-00145 EXP: 09/2022

Samo za strokovno javnost.

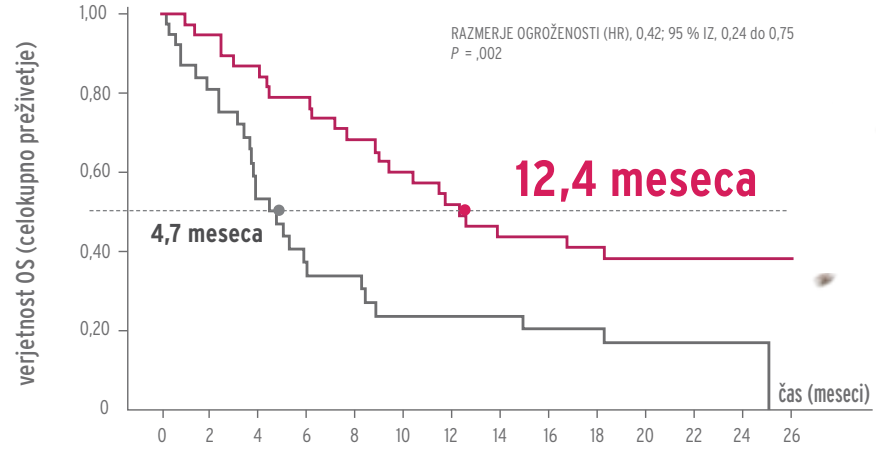
H - Predpisovanje in izdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Pred predpisovanjem, prosimo, preberite celoten Povzetek glavnih značilnosti zdravila Keytruda, ki je na voljo pri naših strokovnih sodelavcih ali na lokalnem sedežu družbe.

Razvrščeno na listo bolnišničnih zdravil

Zdravilo POLIVY v kombinaciji z bendamustinom in rituksimabom

za več kot 2x podaljša celokupno preživetje.[1,2]

R/R DVCLB



Zdravilo POLIVY (polatuzumab vedotin) je v kombinaciji z bendamustinom in rituksimabom (BR) indicirano za zdravljenje odraslih bolnikov z difuznim velikoceličnim limfomom B (DVCLB), ki se na prejšnje zdravljenje niso odzvali ali pa se je bolezen pri njih ponovila in niso primerni za presaditev krvotvornih matičnih celic.[1]

*30 mg viale ni na voljo na slovenskem trgu.

Referenci: 1. Povzetek glavnih značilnosti zdravila POLIVY. Dostopano (30.07.2020) na https://www.ema.europa.eu/en/documents/product-information/POLIVY-epar-product-information_sl.pdf. **2.** Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-165.

R/R – ponovitev bolezni ali neodzivnost na zdravljenje • DVCLB – difuzni velikocelični limfom B • BR – bendamustin, rituksimab • IZ – interval zaupanja • P – p vrednost

POLIVY®▼
polatuzumab vedotin

SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA POLIVY

▼ Za to zdravilo se izvaja dodatno spremljanje varnosti. Tako bodo hitreje na voljo nove informacije o njegovi varnosti. Zdravstvene delavce naprošamo, da poročajo o katerem koli domnevnem neželenem učinku zdravila. Kako poročati o neželenih učinkih, si poglejte skrajšani povzetek glavnih značilnosti zdravila POLIVY pod "Poročanje o domnevnih neželenih učinkih".

Ime zdravila: Polivy 30 mg prašek za koncentrat za raztopino za infundiranje in Polivy 140 mg prašek za koncentrat za raztopino za infundiranje. **Kakovostna in količinska sestava:** Polivy 30 mg: Ena viala s praškom za koncentrat za raztopino z vsebuje 30 mg polatuzumaba vedotina. Po rekonstituciji en mililiter vsebuje 20 mg polatuzumaba vedotina. Polivy 140 mg: Ena viala s praškom za koncentrat za raztopino za infundiranje vsebuje 140 mg polatuzumaba vedotina. Po rekonstituciji en mililiter vsebuje 20 mg polatuzumaba vedotina. Polatuzumab vedotin je konjugat protitelesa in zdravila, sestavljen iz antimitotičnega sredstva monometil-avristatina E (MMAE), kovalentno konjugiranega na monoklonsko protitelo, ki je usmerjeno proti CD79b. **Terapevtske indikacije:** Zdravilo Polivy je v kombinaciji z bendamustinom in rituksimabom indicirano za zdravljenje odraslih bolnikov z difuznim velikoceličnim limfomom B (DVCLB), ki se na prejšnje zdravljenje niso odzvali ali pa se je bolezen pri njih ponovila in niso primerni za presaditev krvotvornih matičnih celic. **Odmerjanje in način uporabe:** Odmerjanje: Priporočeni odmerek zdravila Polivy je 1,8 mg/kg v intravenski infuziji na 21 dni v kombinaciji z bendamustinom in rituksimabom v trajanju 6 ciklov. Način uporabe: Zdravilo Polivy je namenjeno intravenski uporabi. Začetni odmerek zdravila Polivy je treba dati v 90-minutni intravenski infuziji. Bolnike je treba med infundiranjem in vsaj še 90 minut po končani infuziji začetnega odmerka nadzorovati glede reakcij, povezanih z infundiranjem in preobčutljivostnih reakcij. Če je bolnik prejšnje infundiranje dobro prenesel, je mogoče nadaljnje odmerke zdravila Polivy dati v 30-minutni infuziji, bolnika pa je treba nadzirati med infundiranjem in vsaj še 30 minut po končani infuziji. Zdravilo Polivy je treba rekonstituirati in razredčiti z upoštevanjem aseptičnega postopka in pod nadzorom zdravstvenega delavca. Treba ga je aplicirati v intravenski infuziji po namenski infuzijski liniji, opremljeni s sterilnim nepirogenim filtrom, ki malo veže beljakovine in s katetrom. Zdravila Polivy se ne sme aplicirati kot hiter intravenski odmerek ali bolus. *Previdnostni ukrepi, potrebni pred ravnanjem z zdravilom ali dajanjem zdravila:* Zdravilo Polivy vsebuje citotoksično komponento, ki je kovalentno vezana na monoklonsko protitelo. Upoštevajte ustrezen postopek za ravnanje in odstranjevanje. **Kontraindikacije:** Preobčutljivost na učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** Sledljivost: Z namenom izboljšanja sledljivosti bioloških zdravil je treba jasno zabeležiti ime in številko serije uporabljenega zdravila. Mielosupresija: Pri bolnikih, zdravljenih z zdravilom Polivy, so poročali o resni in hudi nevtropeniji in febrilni nevtropeniji že v prvem ciklu zdravljenja. Treba je razmisliti o profilaktični uporabi granulocitnega rastnega dejavnika (G-CSF), saj je bila med kliničnim razvojem zdravila potrebna njegova uporaba. Med uporabo zdravila Polivy se lahko pojavi tudi trombocitopenija ali anemija 3. ali 4. stopnje. Pred vsakim odmerkom zdravila Polivy je treba kontrolirati celotno krvno sliko. Pri bolnikih z nevtropenijo in/ali trombocitopenijo 3. ali 4. stopnje je treba pretehtati opravljanje pogostejših laboratorijskih kontrol in/ali odložitev ali ukinitev uporabe zdravila Polivy. Periferna nevropatija: Pri bolnikih, zdravljenih z zdravilom Polivy, so poročali o periferni nevropatiji že v prvem ciklu zdravljenja; tveganje se povečuje z zaporednimi odmerki. Bolnikom z že obstoječo periferno nevropatijo se nevropatija lahko poslabša. Bolnike je treba nadzorovati glede simptomov periferne nevropatije. Bolnikom, pri katerih se pojavi novonastala periferna nevropatija ali se poslabša obstoječa periferna nevropatija, bo morda treba odmerek zdravila Polivy odložiti, zmanjšati ali uporabo zdravila Polivy ukiniti. Okužbe: Pri bolnikih, zdravljenih z zdravilom Polivy, so poročali o resnih, življenje ogrožajočih ali smrtnih okužbah, vključno z oportunističnimi okužbami. Poročali so tudi o ponovni aktivaciji latentnih okužb. Bolnike je treba med zdravljenjem skrbno nadzorovati glede znakov bakterijskih, glivnih ali virusnih okužb; če se pojavijo znaki in simptomi okužbe, mora bolnik poiskati zdravniško pomoč. Razmisliti je treba o profilaksi z zdravili proti okužbam v celotnem obdobju zdravljenja z zdravilom Polivy. Zdravila Polivy se ob prisotnosti aktivne hude okužbe ne sme aplicirati. Pri bolnikih, pri katerih se pojavijo resne okužbe, je treba ukiniti zdravilo Polivy in sočasno kemoterapijo. Imunizacija: Sočasno z zdravljenjem se bolnikom ne sme dajati živih in živih oslabljenih cepiv. Progresivna multifokalna levkoencefalopatija (PML): Med zdravljenjem z zdravilom Polivy so poročali o pojavu PML. Bolnike je treba skrbno nadzorovati glede novonastalih nevroloških, kognitivnih ali vedenjskih sprememb, ki nakazujejo na PML, oziroma glede poslabšanja takšnih sprememb. V primeru suma na PML je treba uporabo zdravila Polivy in morebitne sočasne kemoterapije odložiti, v primeru potrjene diagnoze pa ukiniti. Sindrom razpada tumorja: Bolniki z velikim tumorskim bremenom in hitro proliferirajočim tumorjem imajo lahko večje tveganje za sindrom razpada tumorja. Pred zdravljenjem z zdravilom Polivy je treba uporabiti ustrezne profilaktične ukrepe v skladu z lokalnimi smernicami. Bolnike je treba med zdravljenjem z zdravilom Polivy skrbno spremljati glede pojava sindroma razpada tumorja. Reakcije, povezane z infundiranjem: Zdravilo Polivy lahko povzroči reakcije, povezane z infundiranjem, vključno s hudimi primeri. Zapoznele reakcije, povezane z infundiranjem, so se pojavile tudi 24 ur po prejetju zdravila Polivy. Pred zdravilom Polivy je treba aplicirati antihistaminik in antipiretik in skrbno spremljati bolnike ves čas infundiranja. Če se pojavi reakcija, povezana z infundiranjem, infundiranje prekinite in ustrezno ravnajte oziroma zdravite. Embrio-fetalna toksičnost: Glede ne mehanizem delovanja in rezultate predkliničnih študij lahko pri nosečnici uporabljeno zdravilo Polivy škoduje plodu. Nosečnicam je treba svetovati glede tveganja za plod. Ženskam v rodni dobi je treba svetovati, naj uporabljajo učinkovito kontracepcijo med zdravljenjem z zdravilom Polivy in še vsaj 9 mesecev po zadnjem odmerku. Moškim, ki imajo partnerke v rodni dobi, je treba svetovati, naj uporabljajo učinkovito kontracepcijo med zdravljenjem z zdravilom Polivy in še vsaj 6 mesecev po zadnjem odmerku. Plodnost: Za moške, ki se bodo zdravili z zdravilom Polivy, je priporočljivo pred zdravljenjem shraniti seme. Starejši bolniki: Bolniki, stari 65 let ali več, so imeli podobno incidenco resnih neželenih učinkov kot bolniki, mlajši od 65 let. Klinične študije z zdravilom Polivy niso vključevale zadostnega števila bolnikov, starih 65 let ali več, da bi lahko določili, ali se odzovejo drugače od mlajših bolnikov. Hepatotoksičnost: Pri bolnikih, zdravljenih z zdravilom Polivy, so se pojavili resni primeri hepatotoksičnosti. Predhodna bolezen jeter, izhodiščno zvišani jetrni encimi in uporaba sočasnih zdravil lahko tveganje povečajo. Kontrolirati je treba raven jetrnih encimov in bilirubina. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Namenskih kliničnih študij medsebojnega delovanja zdravil s polatuzumabom vedotinom pri človeku niso izvedli. Pri sočasnem zdravljenju z zaviralcem CYP3A4 je potrebna previdnost. Bolnike, ki sočasno prejemajo močne zaviralce CYP3A4, je treba skrbneje nadzorovati glede znakov toksičnosti. Močni induktorji CYP3A4 lahko zmanjšajo izpostavljenost nekonjugiranemu MMAE. Sočasna uporaba polatuzumaba vedotina ne vpliva na farmakokinetiko rituksimaba in bendamustina. **Neželeni učinki:** Najpogosteje zabeleženi neželeni učinki pri bolnikih, zdravljenih z zdravilom Polivy v kombinaciji z BR, so bili anemija, trombocitopenija, nevtropenija, driska, navzea in periferna nevropatija. O resnih neželenih učinkih so poročali pri 42,4 % bolnikov, zdravljenih z zdravilom Polivy in BR. Najbolj pogosti neželeni resni učinki, o katerih so poročali pri > 5 % bolnikov, so bili febrilna nevtropenija, sepsa, z infundiranjem povezane reakcije, pljučnica in zvišana telesna temperatura. Poročanje o domnevnih neželenih učinkih: Poročanje o domnevnih neželenih učinkih zdravila po izdaji dovoljenja za promet je pomembno. Omogoča namreč stalno spremljanje razmerja med koristmi in tveganji zdravila. Od zdravstvenih delavcev se zahteva, da poročajo o katerem koli domnevnem neželenem učinku zdravila na: Javna agencija Republike Slovenije za zdravila in medicinske pripomočke, Sektor za farmakovigilanco, Nacionalni center za farmakovigilanco, Slovenčeva ulica 22, SI-1000 Ljubljana, Tel: +386 (0)8 2000 500, Faks: +386 (0)8 2000 510, e-pošta: h-farmakovigilanca@jazmp.si, spletna stran: www.jazmp.si. Za zagotavljanje sledljivosti zdravila je pomembno, da pri izpolnjevanju obrazca o domnevnih neželenih učinkihzdravila navedete številko serije biološkega zdravila. **Režim izdaje zdravila:** H. **Imetnik dovoljenja za promet:** Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Nemčija. **Verzija: 3.0/20**
Informacija pripravljena: januar 2021

M-SI-00000205

DODATNE INFORMACIJE SO NA VOLJO PRI: Roche farmacevtska družba d.o.o., Stegne 13G, 1000 Ljubljana

Samo za strokovno javnost

ONIVYDE: IZDELAN POSEBEJ ZA BOJ PROTI RAKU TREBUŠNE SLINAVKE

ONIVYDE pegylated liposomal je odobren za zdravljenje metastatskega adenokarcinoma trebušne slinavke v kombinaciji s 5-fluorouracilom (5-FU) in levkovorinom (LV) pri odraslih bolnikih, pri katerih je bolezen po zdravljenju na osnovi gemcitabina napredovala.[1]

ONIVYDE JE PEGILIRANI LIPOSOM Z IRINOTEKANOM, IZDELAN POSEBEJ ZA UČINKOVITO ZDRAVLJENJE TE AGRESIVNE BOLEZNI[2–5]

KLINIČNI PODATKI ŠTUDIJE 3. FAZE POTRJUJEJO EDINSTVENO KLINIČNO VREDNOST ZDRAVILA ONIVYDE V KOMBINACIJI S 5-FU/LV:

- skladni podatki o učinkovitosti pri vseh opazovanih dogodkih: pomembno podaljšanje preživetja in povečana stopnja odziva[6–8]
- ohranjena kakovost življenja[6,9]
- dobro poznan varnostni profil[1,6,7]

POMEMBNA UČINKOVITOST ONIVYDE + 5-FU/LV JE POTRJENA V KLINIČNI PRAKSI[10–12]

ONIVYDE + 5-FU/LV PRIPOROČAJO VSE GLAVNE MEDNARODNE SMERNICE[13–16]

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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA ONIVYDE pegylated liposomal 4,3 mg/ml SESTAVA*: ONIVYDE pegylated liposomal 4,3 mg/ml koncentrat za disperzijo za infundiranje: ena viala z 10 ml koncentrata vsebuje 43 mg brezvodnega irinotekana (v obliki irinotekanijeve soli saharoznega oktasulfata v pegilirani liposomski formulaciji). **TERAPEVTSKE INDIKACIJE*:** Zdravljenje metastatskega adenokarcinoma trebušne slinavke v kombinaciji s 5-fluorouracilom (5-FU) in levkovorinom (LV) pri odraslih bolnikih, pri katerih je bolezen po zdravljenju na osnovi gemcitabina napredovala. **ODMERJANJE IN NAČIN UPORABE*:** ONIVYDE pegylated liposomal (irinotekan) smejo bolnikom predpisati in dajati samo zdravstveni delavci, ki imajo izkušnje pri uporabi zdravil za zdravljenje raka. Priporočeni odmerek in režim odmerjanja zdravila ONIVYDE pegylated liposomal je 70 mg/m^2 intravensko 90 minut, čemur sledi LV 400 mg/m^2 intravensko 30 minut in nato 5FU 2400 mg/m^2 intravensko 46 ur, vsaka 2 tedna. Zdravilo ONIVYDE pegylated liposomal se ne daje kot samostojno zdravilo. Pri bolnikih z znano homozigotnostjo za alel UGT1A1*28 je treba razmisliti o manjšem začetnem odmerku zdravila ONIVYDE pegylated liposomal 50 mg/m^2. Če zdravilo bolniki dobro prenašajo, lahko v naslednjih ciklih razmislimo o odmerku zdravila ONIVYDE pegylated liposomal 70 mg/m^2. Prilagajanje odmerkov se priporoča za obvladovanje toksičnosti 3. ali 4. stopnje, povezane z zdravilom ONIVYDE pegylated liposomal. **KONTRAINDIKACIJE*:** Anamneza hude preobčutljivosti na irinotekan ali katero koli pomožno snov. Dojenje. **OPOZORILA*:** Zdravilo ONIVYDE pegylated liposomal (irinotekan) ni enakovredno drugim neliposomskim formulacijam irinotekana, zato jih ne smemo zamenjevati. *Mielosupresija/nevtropenija:* Med zdravljenjem se priporoča nadziranje celotne krvne slike. Bolniki se morajo zavedati tveganja za nevtropenijo in pomena povišane telesne temperature. Febrilno nevtropenijo je treba nujno zdraviti v bolnišnici s širokospektralnimi intravenskimi antibiotiki. Pri bolnikih, ki doživijo hude hematološke neželene učinke, se priporoča zmanjšanje odmerka ali prekinitev zdravljenja. Bolnikov s hudo odpovedjo kostnega mozga ne smemo zdraviti z zdravilom ONIVYDE pegylated liposomal. *Imunosupresivni učinki in cepiva*: Dajanje živih ali atenuiranih cepiv bolnikom z oslabljenim imunskim sistemom lahko povzroči resne ali smrtne okužbe. Bolniki azijskega porekla imajo večje tveganje za hudo in febrilno nevtropenijo. Posamezniki s homozigotnostjo 7/7 za alel UGT1A1*28 imajo povečano tveganje za nevtropenijo. *Interakcije z močnimi induktorji encima CYP3A4, močnimi zaviralci encima CYP3A4 in močnimi zaviralci encima UGT1A1*: Zdravila ONIVYDE pegylated liposomal ne smemo dajati skupaj z močnimi induktorji encima CYP3A4 (kot so antikonvulzivi, rifampicin, rifabutin in šentjanževka), močnimi zaviralci encima CYP3A4 (npr. grenivkinim sokom, klaritromicinom, indinavirjem, itrakonazolom, lopinavirjem, nefazodonom, nelfinavirjem, ritonavirjem, sakvinavirjem, telaprevirjem, vorikonazolom) ali z močnimi zaviralci encima UGT1A1, razen če ni drugih terapevtskih možnosti. Zdravljenje z močnimi zaviralci encima CYP3A4 moramo prekiniti vsaj 1 teden pred začetkom zdravljenja z zdravilom ONIVYDE pegylated liposomal. *Driska*: Pri bolnikih, ki doživijo zgodnji pojav driske (v ≤ 24 urah po začetku zdravljenja z zdravilom ONIVYDE pegylated liposomal), je treba razmisliti o terapevtskem in profilaktičnem zdravljenju z atropinom, razen če je kontraindicirano. Bolnike je treba opozoriti na tveganje za zapoznelo drisko (> 24 ur), ki je izčrpavajoča in v redkih primerih tudi življenjsko nevarna. Če driska traja tudi, ko bolnik prejema loperamid več kot 24 ur, je treba razmisliti o dodatni peroralni antibiotični podpori. Zdravljenje z zdravilom ONIVYDE pegylated liposomal je treba odložiti, dokler se driska ne umiri do ≤ 1. stopnje (2–3 odvajanja/dan več kot pred zdravljenjem). Zdravila ONIVYDE pegylated liposomal ne smemo dajati bolnikom z zaporo črevesja ali kronično vnetno črevesno boleznijo, dokler se ta ne pozdravi. *Holinergične reakcije*: Zgodnjo drisko lahko spremljajo rinitis, povečano slinjenje, zardevanje, diaforeza, bradikardija, mioza in hiperperistaltika. Uporabiti je treba atropin. *Akutne infuzijske in povezane reakcije:* V primeru hudih preobčutljivostnih reakcij je treba zdravljenje z zdravilom ONIVYDE pegylated liposomal prekiniti. *Predhodna Whipplova operacija*: Večje tveganje za resne okužbe. Bolnike je treba spremljati glede znakov okužbe. *Žilne bolezni:* Zdravilo ONIVYDE pegylated liposomal je bilo povezano s trombemboličnimi dogodki, kot so pljučna embolija, venska tromboza in arterijska trombembolija. Treba je pridobiti podrobno zdravstveno anamnezo, da bi prepoznali bolnike z več dejavniki tveganja poleg osnovne neoplazme. Bolnike je treba obvestiti o znakih in simptomih trombembolije in jim svetovati, da se v primeru katerega od teh znakov ali simptomov takoj obrnejo na svojega zdravnika ali medicinsko sestro. *Pljučna toksičnost:* Pri bolnikih, ki so prejemali neliposomski irinotekan, so se pojavili dogodki, podobni intersticijski pljučni bolezni (IPB), ki so vodili do smrtnih primerov. Pri bolnikih z dejavniki tveganja (obstoječo pljučno boleznijo, uporabo pnevmotoksičnih zdravil, kolonije stimulirajočimi dejavniki ali predhodnim zdravljenjem z obsevanjem) je treba pred zdravljenjem z zdravilom ONIVYDE pegylated liposomal in po njem skrbno nadzirati respiratorne simptome. Dokler ni opravljena diagnostična ocena, je treba ob pojavu nove ali napredovale dispneje, kašlja in povišane telesne temperature zdravljenje z zdravilom ONIVYDE pegylated liposomal začasno prekiniti. Pri bolnikih s potrjeno diagnozo IPB moramo zdravljenje z zdravilom ONIVYDE pegylated liposomal dokončno prekiniti. *Jetrna okvara:* Bolniki s hiperbilirubinemijo so imeli povišane koncentracije skupnega SN-38, zato je tveganje za nevtropenijo povečano. Pri bolnikih z vrednostjo skupnega bilirubina 1,0–2,0 mg/dl je treba redno nadzirati celotno krvno sliko. Previdnost je potrebna pri bolnikih z jetrno okvaro (bilirubin > 2-kratna zgornja meja normalnih vrednosti [ULN]; aminotransferaze > 5-kratna ULN). *Ledvična okvara:* Uporaba zdravila pri bolnikih s pomembno ledvično okvaro ni bila ocenjena. *Bolniki s premajhno telesno maso (indeks telesne mase < 18,5 kg/m^2):* Potrebna je previdnost. *Pomožne snovi:* En mililiter zdravila ONIVYDE pegylated liposomal vsebuje 0,144 mmol (3,31 mg) natrija. **INTERAKCIJE*:** *Previdnostni ukrepi*: Sočasno dajanje z induktorji encima CYP3A4 lahko zmanjša sistemsko izpostavljenost zdravilu ONIVYDE pegylated liposomal. Sočasno dajanje z zaviralci encima CYP3A4 ali encima UGT1A1 (npr. atazanavirja, gemfibrozila, indinavirja, regorafeniba) lahko poveča sistemsko izpostavljenost zdravilu ONIVYDE pegylated liposomal. **PLODNOST* NOSEČNOST*:** Uporaba ni priporočljiva. **DOJENJE*:** Zdravilo je kontraindicirano. **KONTRACEPCIJA*:** Ženske v rodni dobi morajo med zdravljenjem in še 1 mesec po zdravljenju uporabljati učinkovito kontracepcijo. Moški morajo med zdravljenjem in 4 mesece po zdravljenju uporabljati kondome. **VPLIV NA SPOSOBNOST VOŽNJE IN UPRAVLJANJA STROJEV*:** Bolniki morajo biti med zdravljenjem pri vožnji in upravljanju strojev previdni. **NEŽELENI UČINKI*:** *Zelo pogosti:* nevtropenija, levkopenija, anemija, trombocitopenija, hipokaliemija, hipomagneziemija, dehidracija, zmanjšan apetit, omotica, driska, bruhanje, navzea, bolečine v trebuhu, stomatitis, alopecija, pireksija, periferni edem, vnetje sluznic, utrujenost, astenija, zmanjšana telesna masa. *Pogosti:* septični šok, sepsa, pljučnica, febrilna nevtropenija, gastroenteritis, oralna kandidoza, limfopenija, hipoglikemija, hiponatriemija, hipofosfatemija, nespečnost, holinergični sindrom, dizgevzija, hipotenzija, pljučna embolija, embolija, globoka venska tromboza, dispneja, disfonija, kolitis, hemoroidi, hipoalbuminemija, akutna ledvična odpoved, z infuzijo povezana reakcija, edem, zvišana raven bilirubina, zvišana raven alanin-aminotransferaze, zvišana raven aspartat-aminotransferaze, zvišano mednarodno umerjeno razmerje. *Občasni:* biliarna sepsa, preobčutljivost, tromboza, hipoksija, ezofagitis, proktitis, makulopapulozni izpuščaj, obarvanje nohtov. **PREVELIKO ODMERJANJE*:** Za preveliko odmerjanje zdravila ni znanega antidota. Treba je uvesti maksimalno podporno nego, s katero preprečimo dehidracijo zaradi driske in zdravimo zaplete zaradi okužb. **FARMAKODINAMIČNE LASTNOSTI*:** Učinkovina zdravila ONIVYDE pegylated liposomal je irinotekan (zaviralec topoizomeraze I), inkapsuliran v vezikel z lipidnim dvoslojem oziroma liposom. Irinotekan je derivat kamptotecina. Kamptotecini delujejo kot specifični zaviralci encima DNA-topoizomeraza I. Irinotekan in njegov aktivni presnovek SN-38 se reverzibilno vežeta na kompleks topoizomeraze I in DNA ter sprožita poškodbe v enoverižni DNA, kar zaustavi replikacijske vilice pri podvajanju DNA in povzroča citotoksičnost. Irinotekan se presnavlja s karboksilesterazo do SN-38. SN-38 je približno 1.000-krat močnejši zaviralec topoizomeraze I, očiščene iz tumorskih celičnih linij človeka in glodavcev, kot irinotekan. **PAKIRANJE*:** Pakiranje vsebuje eno vialo z 10 ml koncentrata. **NAČIN PREDPISOVANJA IN IZDAJE ZDRAVILA:** Rp/Spec. **DATUM ZADNJE REVIZIJE BESEDILA: avgust 2020. Imetnik dovoljenja za promet:** Les Laboratoires Servier, 50, rue Carnot, 92284 Suresnes cedex, Francija. **Številka dovoljenja za promet z zdravilom:** EU/1/16/1130/001. ***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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Za zdravljenje lokalno napredovalega ali metastatskega HR+/HER2- raka dojk:

- v kombinaciji z zaviralcem aromataze,
- v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje.

Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina (*LHRH – Luteinizing Hormone-Releasing Hormone*).

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Sestava in oblika zdravila: (1) Ena trda kapsula vsebuje 75 mg, 100 mg ali 125 mg palbocikliba in 56 mg, 74 mg ali 93 mg laktoze (v obliki monohidrata). (2) Ena filmsko obložena tableta vsebuje 75 mg, 100 mg ali 125 mg palbociklib. **Indikacije:** Zdravljenje lokalno napredovalega ali metastatskega na hormonske receptorje (HR – *Hormone Receptors*) pozitivnega in na receptorje humanega epidermalnega rastnega faktorja 2 (HER2 – *Human Epidermal growth factor Receptor 2*) negativnega raka dojk: v kombinaciji z zaviralcem aromataze ali v kombinaciji s fulvestrantom pri ženskah, ki so prejele predhodno endokrino zdravljenje. Pri ženskah v pred- in perimenopavzi je treba endokrino zdravljenje kombinirati z agonistom gonadoliberina. **Odmerjanje in način uporabe:** Zdravljenje mora uvesti in nadzorovati zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. Priporočeni odmerek je 125 mg enkrat na dan 21 zaporednih dni, sledi 7 dni brez zdravljenja (shema 3/1), celotni cikel traja 28 dni. Zdravljenje je treba nadaljevati, dokler ima bolnik od zdravljenja klinično korist ali dokler se ne pojavi nesprejemljiva toksičnost. Pri sočasnem dajanju s palbociklibom je treba zaviralec aromataze dajati v skladu s shemo odmerjanja, ki je navedena v Povzetku glavnih značilnosti zdravila (PGZZ). Pri sočasnem dajanju s palbociklibom je priporočeni odmerek fulvestranta 500 mg intramuskularno 1., 15. in 29. dan ter nato enkrat na mesec, glejte PGZZ za fulvestrant. Prilagajanja odmerkov: Za prilagajanja odmerkov zaradi hematološke toksičnosti glejte preglednico 2, zaradi nehematološke toksičnosti pa preglednico 3 v PGZZ-ju. Pri bolnikih s hudo intersticijsko boleznijo pljuč (ILD)/pnevmonitisom je treba zdravljenje trajno prekiniti. Posebne skupine bolnikov: *Starejši:* Prilagajanje odmerka ni potrebno. *Okvara jeter ali ledvic*: Pri bolnikih z blago ali zmerno okvaro jeter ali blago, zmerno ali hudo okvaro ledvic prilagajanje odmerka ni potrebno. Pri bolnikih s hudo okvaro jeter je priporočeni odmerek 75 mg enkrat na dan po shemi 3/1. *Pediatrična populacija*: Varnost in učinkovitost pri otrocih in mladostnikih, starih < 18 let, nista bili dokazani. Način uporabe: Peroralna uporaba. (1) Jemanje s hrano, priporočljivo z obrokom. (2) Tablete se lahko jemlje s hrano ali brez nje. (1, 2) Ne smemo jemati z grenivko ali grenivkinim sokom. Kapsule oz. tablete zdravila je treba pogoltniti cele. **Kontraindikacije:** Preobčutljivost na učinkovino ali katerokoli pomožno snov. Uporaba pripravkov s šentjanževko. **Posebna opozorila in previdnostni ukrepi:** Ženske v pred- in perimenopavzi: Kadar zdravilo uporabljamo v kombinaciji z zaviralcem aromataze je obvezna ovarijska ablacija ali supresija z agonistom gonadoliberina. Hematološke bolezni: Pri nevtropeniji stopnje 3 ali 4 je priporočljiva prekinitev odmerjanja, zmanjšanje odmerka ali odložitev začetka ciklov zdravljenja, bolnike pa je treba ustrezno spremljati. ILD/pnevmonitis: Pri bolnikih se lahko pojavita huda, življenjsko ogrožajoča ali smrtna ILD in/ali pnevmonitis, kadar zdravilo jemljejo v kombinaciji z endokrinim zdravljenjem. Bolnike je treba spremljati glede pljučnih simptomov, ki kažejo na ILD/pnevmonitis (npr. hipoksija, kašelj, dispneja), in pri pojavu novih ali poslabšanju respiratornih simptomov oz. sumu na ILD/pnevmonitis zdravljenje prekiniti. Okužbe: Zdravilo lahko poveča nagnjenost k okužbam, zato je bolnike treba spremljati glede znakov in simptomov okužbe ter jih ustrezno zdraviti. Okvara jeter ali ledvic: Pri bolnikih z zmerno ali hudo okvaro jeter ali ledvic je treba zdravilo uporabljati previdno in skrbno spremljati znake toksičnosti. (1) 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:** Učinki drugih zdravil na farmakokinetiko palbociklibа: *Zaviralci CYP3A:* Sočasni uporabi močnih zaviralcev CYP3A, med drugim klaritromicina, indinavirja, itrakonazola, ketokonazola, lopinavirja/ritonavirja, nefazodona, nelfinavirja, posakonazola, sakvinavirja, telaprevirja, telitromicina, vorikonazola in grenivke ali grenivkinega soka, se je treba izogibati. *Induktorji CYP3A:* Sočasni uporabi močnih induktorjev CYP3A, med drugim karbamazepina, enzalutamida, fenitoina, rifampicina in šentjanževke, se je treba izogibati. Učinek zdravil za zmanjševanje kisline: (1) Če palbociklib zaužijemo s hrano, klinično pomembnega učinka na izpostavljenost palbociklibu ni pričakovati. (2) Klinično pomembnega učinka na izpostavljenost palbociklibu ni pričakovati. Učinki palbociklibа na farmakokinetiko drugih zdravil: Pri sočasni uporabi bo morda treba zmanjšati odmerek občutljivih substratov CYP3A z ozkim terapevtskim indeksom (npr. alfentanil, ciklosporin, dihidroergotamin, ergotamin, everolimus, fentanil, pimozid, kinidin, sirolimus in takrolimus), saj IBRANCE lahko poveča izpostavljenost tem zdravilom. Študije *in vitro* s prenašalci: Palbociklib lahko zavira prenos, posredovan s P-gp v prebavilih in beljakovino odpornosti pri raku dojk (BCRP). Uporaba palbociklibа z zdravili, ki so substrati P-gp (npr. digoksin, dabigatran, kolhicin) ali BCRP (npr. pravastatin, rosuvastatin, sulfasalazin) lahko poveča njihov terapevtski učinek in neželene učinke. Palbociklib lahko zavira privzemni prenašalec organskih kationov OCT1. **Plodnost, nosečnost in dojenje:** Med zdravljenjem in vsaj 3 tedne (ženske) oziroma 14 tednov (moški) po koncu zdravljenja je treba uporabljati ustrezne kontracepcijske metode. Zdravila ne uporabljajte pri nosečnicah in ženskah v rodni dobi, ki ne uporabljajo kontracepcije. Bolnice, ki prejemajo palbociklib, ne smejo dojiti. Zdravljenje s palbociklibom lahko ogrozi plodnost pri moških. Pred začetkom zdravljenja naj moški zato razmislijo o hrambi sperme. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Ima blag vpliv na sposobnost vožnje in upravljanja strojev. Potrebna je previdnost. **Neželeni učinki:** Zelo pogosti: okužbe, nevtropenija, levkopenija, anemija, trombocitopenija, pomanjkanje teka, stomatitis, navzea, diareja, bruhanje, izpuščaj, alopecija, suha koža, utrujenost, astenija, pireksija, povečane vrednosti ALT/AST. **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:** 09.11.2020

Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

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HR+/HER2- = pozitiven na hormonske receptorje in negativen na receptorje humanega epidermalnega rastnega faktorja 2.
Literatura: Povzetek glavnih značilnosti zdravila Ibrance, 9.11.2020.

Pfizer

Pfizer Luxembourg SARL, GRAND DUCHY OF LUXEMBOURG,
51, Avenue J. F. Kennedy, L-1855
Pfizer, podružnica Ljubljana, Letališka cesta 29a, Ljubljana

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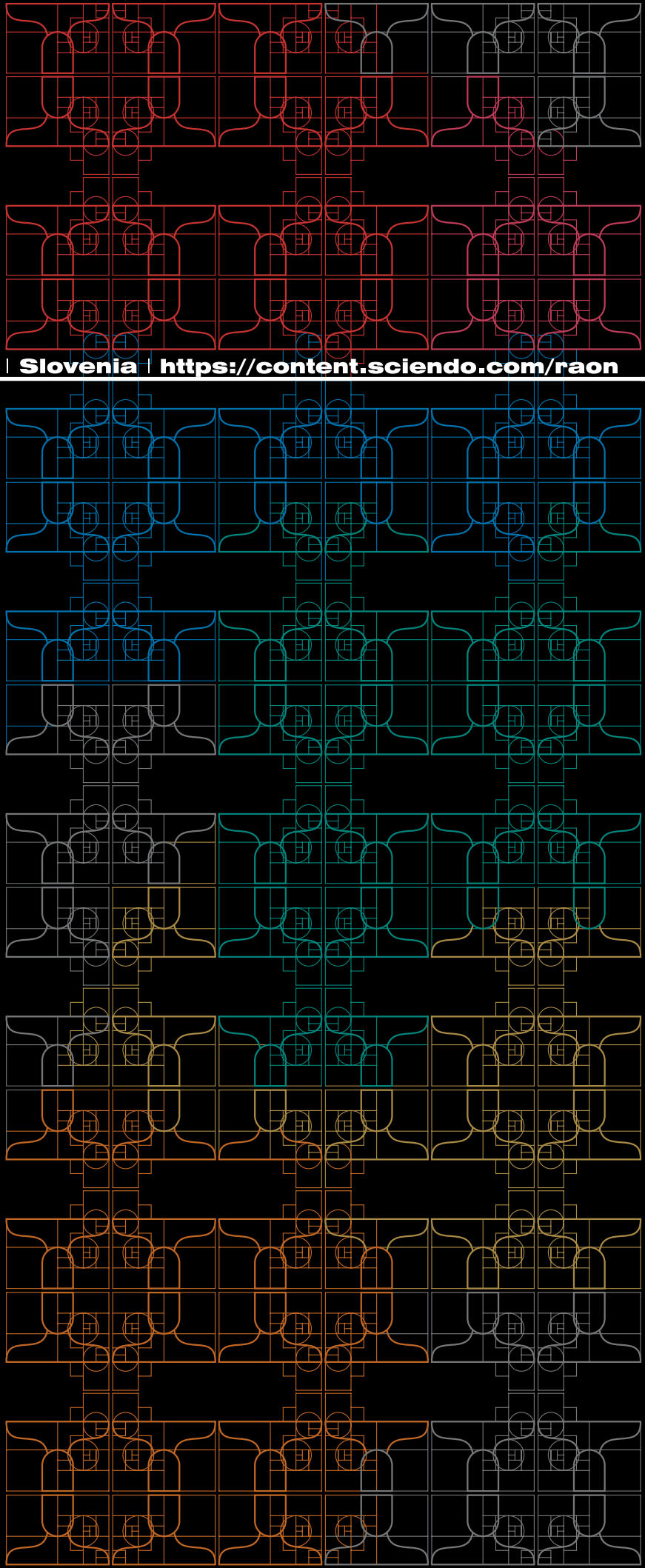

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