RADIOLOGY AND ONCOLOGY

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Halaven®
eribulin

NOVA SMER DO PODALJŠANJA **CELOKUPNEGA PREŽIVETJA**

Eisai

Prva in edina samostojna kemoterapija,
ki v primerjavi z ostalimi možnostmi zdravljenja
z enim zdravilom, pri bolnicah s predhodno že
večkratno zdravljenim metastatskim rakom dojke,
dokazano značilno podaljša celokupno preživetje.[1,2]

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- Monoterapija z zdravilom HALAVEN je indicirana za zdravljenje bolnic z lokalno napredovalim ali metastatskim rakom dojke, ki je napredoval po vsaj dveh režimih kemoterapije za napredovalo bolezen. Predhodna zdravljenja morajo vključevati antraciklin in taksan, razen če to zdravljenje za bolnice ni bilo primerno.[1]
- Priporočeni odmerek 1,23 mg/m^2, intravensko, v obliki 2- do 5-minutne infuzije, 1. in 8. dan vsakega 21-dnevnega cikla.
- Ena 2 ml viala vsebuje 0,88 mg eribulina.
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SKRAJŠAN POVZETEK GLAVNIH ZNAČILNOSTI ZDRAVILA

HALAVEN 0,44 mg/ml raztopina za injiciranje (eribulin)
TERAPEVTSKE INDIKACIJE: Zdravljenje lokalno napredovalega ali metastatskega raka dojke, ki je napredoval po vsaj dveh režimih kemoterapije za napredovalo bolezen vključno z antraciklinom in taksanom, razen če to ni bilo primerno. **ODMERJANJE IN NAČIN UPORABE:** Halaven se daje v enotah, specializiranih za dajanje citotoksične kemoterapije, in le pod nadzorom usposobljenega zdravnika z izkušnjami v uporabi citotoksičnih zdravil. **ODMERJANJE:** Priporočeni odmerek eribulina v obliki raztopine je 1,23 mg/m^2 i. v. obliki 2- do 5- minutne infuzije 1. in 8. dan vsakega 21-dnevnega cikla. Bolnikom je lahko slabo ali bruhajo. Treba je razmisliti o antiemetični profilaksi, vključno s kortikosteroidi. **Preložitev odmerka med zdravljenjem:** Dajanje Halavena je treba preložiti, če se pojavi kaj od naslednjega: absolutno število nevtrofilcev (ANC) < 1 x 10^9/l, trombociti < 75 x 10^9/l ali nehematološki neželeni učinki 3. ali 4. stopnje. **Zmanjšanje odmerka med zdravljenjem:** Za priporočila za zmanjšanje odmerka ob pojavu hematoloških ali nehematoloških neželenih učinkov glejte celoten povzetek glavnih značilnosti zdravila. **Okvara jeter zaradi zasevkov:** Priporočeni odmerek pri blagi okvari jeter (stopnje A po Child-Pughu) je 0,97 mg/m^2 v obliki 2- do 5- minutne i. v. infuzije 1. in 8. dan 21-dnevnega cikla. Priporočeni odmerek pri zmerni okvari jeter (stopnje B po Child-Pughu) je 0,62 mg/m^2 v obliki 2- do 5- minutne i. v. infuzije 1. in 8. dan 21-dnevnega cikla. 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Dojenje. **POSEBNA OPOZORILA IN PREVIDNOSTNI UKREPI:** Mielosupresija je odvisna od odmerka in se kaže kot nevtropenija. Pred vsakim odmerkom eribulina je treba opraviti pregled celotne krvne slike. Zdravljenje z eribulinom se lahko uvede le pri bolnikih z vrednostmi ANC ≥ 1,5 x 10^9/l in s trombociti > 100 x 10^9/l. Bolnike, pri katerih se pojavijo febrilna nevtropenija, huda nevtropenija ali trombocitopenija, je treba zdraviti v skladu s priporočili v celotnem povzetku glavnih značilnosti zdravila. Hudo nevtropenijo se lahko zdravi z uporabo G-CSF ali enakovrednim zdravilom v skladu s smernicami. Bolnike je treba skrbno nadzirati za znake periferne motorične in senzorične nevropatije. Pri razvoju hude periferne nevrotoksičnosti je treba odmerek prestaviti ali zmanjšati. Če začnemo zdravljenje pri bolnikih s kongestivnim srčnim popuščanjem, z bradiaritmijami, z zdravili, za katera je znano, da podaljšujejo interval QT, vključno z antiaritmiki razreda Ia in III, in z elektrolitskimi motnjami, je priporočljivo spremljanje EKG. Pred začetkom zdravljenja s Halavenom je treba popraviti hipokaliemijo in hipomagneziemijo in te elektrolite je treba občasno kontrolirati med zdravljenjem. Halavena ne smemo dajati bolnikom s prirojenim sindromom dolgega intervala QT. To zdravilo vsebuje majhne količine etanola (alkohola), manj kot 100 mg na odmerek. Eribulin je pri podganah embriotoksičen, fetotoksičen in teratogen. Halavena se ne sme uporabljati med nosečnostjo, razen kadar je to nujno potrebno. Ženske v rodni dobi naj ne zanosijo v času, ko same ali njihov moški partner dobivajo Halaven, in naj med zdravljenjem in še do 3 mesece po njem uporabljajo učinkovito kontracepcijo. Moški naj se pred zdravljenjem posvetujejo o shranjevanju sperme zaradi možnosti nepopravljive neplodnosti. **INTERAKCIJE:** Eribulin se izloča do 70 % prek žolča. Sočasna uporaba učinkovin, ki zavirajo jetrne transportne beljakovine, kot so beljakovine za prenos organskih anionov, P-glikoprotein, beljakovine, odporne na številna zdravila, z eribulinom se ne priporoča (npr. ciklosporin, ritonavir, sakvinavir, lopinavir in nekateri drugi zaviralci proteaze, efavirenz, emtricitabin, verapamil, klaritromicin, kinin, kinidin, dizopiramid itd). Sočasno zdravljenje z indukcijskimi učinkovinami, kot so rifampicin, karbamazepin, fenitoin, šentjanževka lahko povzroči znižanje koncentracij eribulina v plazmi, zato je ob sočasni uporabi induktorjev potrebna previdnost. Eribulin lahko zavira encim CYP3A4. Pri sočasni uporabi z učinkovinami, ki jih v glavnem presnavlja encim CYP3A4, se priporoča skrbno spremljanje zaradi povečanih koncentracij sočasno uporabljene učinkovine v plazmi. Če ima učinkovina ozek terapevtski razpon, je ne uporabljajte sočasno. **NEŽELENI UČINKI:** *Zelo pogosti (≥1/10):* nevtropenija (54,5 %), (3./4. stopnje: 48,3 %), levkopenija (22,1 %), (3./4. stopnje: 14 %), anemija (20,3 %), (3./4. stopnje: 1,4 %), zmanjšan apetit, periferna nevropatija (32,0 %), (3./4. stopnje: 6,9 %), glavobol, slabost (35,1 %), (3./4. stopnje: 1,1 %), zaprtost, driska, bruhanje, alopecija, artralgija in mialgija, utrujenost/astenija (52,8 %), (3./4. stopnje: 8,4 %), pireksija. *Pogosti (≥1/100 do <1/10):* okužba sečil, ustna kandidiaza, okužba zgornjih dihal, nazofaringitis, rinitis, febrilna nevtropenija (4,7 %), (3./4. stopnje: 4,6 %), trombocitopenija, limfopenija, hipokaliemija, hipomagneziemija, dehidracija, hiperglikemija, hipofosfatemija, nespečnost, depresija, disgevzija, omotičnost, hipoestezija, letargija, nevrotoksičnost, obilnejše solzenje, konjunktivitis, vrtoglavica, tahikardija, vročinski valovi, dispnea, kašelj, orofaringealna bolečina, epistaksa, rinoreja, bolečina v trebuhu, stomatitis, suha usta, dispepsija, gastroezofagealna refluksna bolezen, razjede v ustih, napihnjenost želodca, zvišanje alanin aminotransferaze (3,0 %), (3./4. stopnje: 1,1 %) in aspartat aminotransferaze, izpuščaj, pruritus, bolezni nohtov, nočno potenje, palmarno-plantarna eritrodisestezija, suha koža, eritem, hiperhidroza, bolečina v okončinah, mišični spazmi, mišično-skeletna bolečina in mišično-skeletna bolečina v prsih, mišična oslabelost, bolečina v kosteh, bolečina v hrbtu, vnetje sluznice (9,8 %), (3./4. stopnje: 1,3 %), periferni edem, bolečina, mrzlica, gripi podobna bolezen, bolečina v prsih, zmanjšanje telesne mase. *Občasni (≥1/1.000 do <1/100):* pljučnica, nevtropenična sepsa, ustni herpes, herpes zoster, tinitus, globoka venska tromboza, pljučna embolija, intersticijska pljučna bolezen, hiperbilirubinemija, angioedem, disurija, hematurija, proteinurija, odpoved ledvic. *Redki (≥1/10.000 do <1/1.000):* pankreatitis. 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Viri: (1) Povzetek glavnih značilnosti zdravila Halaven, november 2012; (2) Cortes J *et al. Lancet* 2011; 377: 914–23

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Radiology and Oncology is steadily growing

Dear friends, authors, readers, members of Editorial Board. Radiology and Oncology has continued its struggle with the renowned publishers and remained within the well-recognized journals. After the drop of impact factor (IF) in 2012, in 2013 our journal has obtained an IF of 1.6. This enlists our journal in the 4th quarter of the journals in the field of Oncology, very close to the 3rd quarter. In the future it is our goal to remain in this category of journals, and strive for the continuous growth.

Therefore, we will restrain to the limited growth of the published papers, up to 5-10% of increase of the published papers per year, maintain the high quality of the published papers, by rigorous review process, and strive for the internationality. The rejection rate of the papers is now approximately 75%. The published papers in the last three years in Radiology and Oncology are from 33 different European, and other countries.

The aim of the journal is to gradually become solely open access journal. However, until we reach that level, we will publish both the printed and electronic version of the journal. Due to the increasing cost of publishing the journal, we are forced to switch to "authors pay model". This means that now we charge 500 EUR (+VAT when applicable) for the publication of the accepted article. All articles are published in print and open access. The articles are also included in Web of Science and PubMed as well as in PubMed Central. Exceptionally, upon lack of funds, the authors can negotiate with the editors for reduced fee or weaver of it. All these steps have been necessary to ensure regular and swift publication of the papers, also in the open access form.

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The Editors of Radiology and Oncology will continue in their best effort to the continuous growth of Radiology and Oncology. We believe that the broad coverage of the topics in the field of diagnostic imaging and oncology will continue to attract many authors and also readers to our journal. The visibility of Radiology and Oncology in many databases is, however, also the guarantee to the authors for the international recognition of their papers.

We would like to thank the authors, Editors, Editorial board and specially the reviewers for their efforts, and ask them to continue supporting our journal.

Best regards,

Prof. Gregor Serša, Ph.D.
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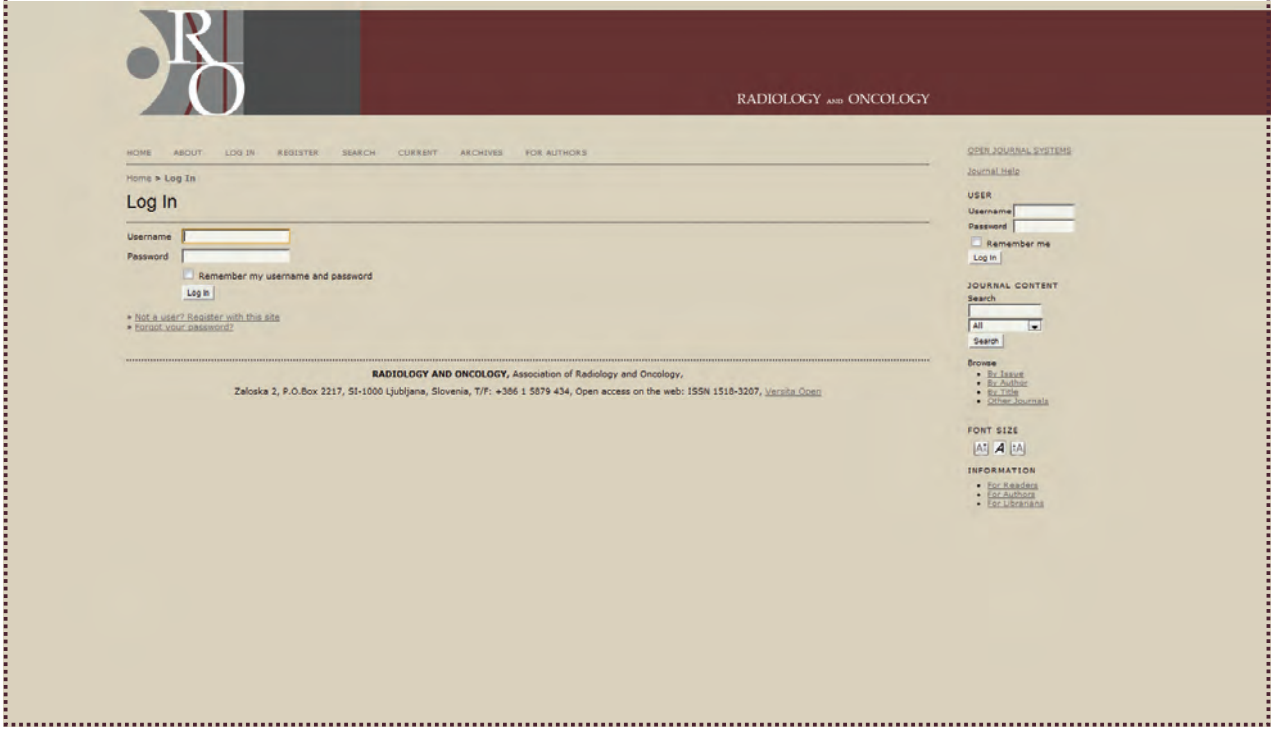

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review

Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature

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Background. Head and neck squamous cell carcinoma (HNSCC) is a disease of middle-aged to elderly adults. However, an increased incidence of HNSCC in young people under 45 years of age has been reported recently. In the present review, we focused on the epidemiology and aetiology of HNSCC in adults under 45 years of age.

Methods. We reviewed literature related to HNSCC in adult patients less than 45 years of age and discussed current treatment options and prognosis.

Results. HNSCC in young adults is associated with a higher incidence rate in nonsmokers, lower female-to-male ratio, a higher percentage of oral cavity and oropharynx tumours, and fewer second primary tumours. However, aside from traditional risk factors of tobacco and alcohol exposure, the causes of these cancers in young adults remain unclear. Agents that might contribute to risk include infection with high-risk human papillomavirus subtypes as well as genetic factors or immunodeficiency status. The expected increase in incidence and mortality of the young with HNSCC may become a major public health concern if current trends persist, particularly lifestyle habits that may contribute to this disease.

Conclusions. Given the younger age and potential long-term adverse sequelae of traditional HNSCC treatments, young adults should be treated on a case-by-case basis and post-therapy quality of life must be considered in any treatment-decision making process.

Key words: head and neck cancer; squamous cell carcinoma; young adults; quality of life

Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is primarily a disease of older adults, occurring most frequently in patients older than age 45. Epidemiological studies over last 20 years have shown a steady rise in the incidence of these cancers in younger adults (age 18–45 years), especially in cancers of the oropharynx and oral cavity.[1,2] The predilection for these particular subsites *vs.* other sites such as the larynx or the hypopharynx remains unclear. Likewise, the aetiology for early onset of these neoplasms is not well understood.

Many conflicting reports have been published on the aetiology, natural history, and prognosis of HNSCC in young adults since this disease was recognized as a distinct clinical entity in youngers in the year 1974.[3] In contrast to the "typical" patient with HNSCC, younger patients often do not present the traditional risk factors of alcohol and/or tobacco exposure.[4] This leads us to suspect that other potential agents, such as inherent genetic fac-

tors, viral infections, and behavioural risk factors may be involved.

Numerous early reports of squamous cell carcinoma (SCC) concluded that the disease was more aggressive and the prognosis poorer in young adults *vs*. older adults.[5–7] However, findings from more recent studies, such as those by Gilroy *et al*., Goldenberg *et al*. or Hafkamp *et al*. have not found any significant differences in outcomes between different age groups.[8–10] Recently, superior survival of younger patients with oropharyngeal SCC was found to be related to a high-risk human papillomavirus (HPV) infection.[11]

Nevertheless, due to differences in patient's age (younger or older than age 45), aetiology and tumorigenetic process or prognosis, we must at least consider the possibility that different groups may require different treatment approaches. This is especially true given the fact that the conventional treatment (*i.e*., surgical resection and adjuvant radio[chemo]therapy) can be functionally debilitating in young adults and may cause long-term adverse *sequelae*.

In the present study, we review the available literature on this topic and discuss key considerations in the treatment of HNSCC in patients under age 45.

Epidemiology

HNSCC is an anatomically heterogeneous group of neoplasms arising from the mucosal surface of the oral cavity, oropharynx, hypopharynx, larynx, sinuses and other sites within the upper aerodigestive tract. The global incidence and mortality rates for HNSCC are 540 000 and 271 000 annually, respectively.[12] In most countries, incidence and mortality rates have either remained stable or increased during the past four decades. Many studies have reported that, since the 1960s, the international incidence of HNSCC (particularly of the oral tongue and oropharynx), has increased in young adults.[13] Surprisingly, this increase has occurred concurrently with a decreasing prevalence of cigarette smoking in the general population; importantly, this observation would not be expected if the only primary risk factors for all HNSCC were alcohol and tobacco abuse.[4]

Despite the fact that, the SCC in the oral cavity (OC) and oropharynx (OP) is traditionally regarded as a disease of the elderly, the incidence of OCSCC and OPSCC in patients under age 45 increases and accounts for approximately 1–6%.[14,15] In countries where betel quid is frequently chewed, such as in Taiwan, young patients account for 16% and 28% of all oral tongue cancer patients.[16] In fact, evidence by Gupta suggests that oral cancer may now be considered a "new epidemic", as incidence rates are reaching high proportions possibly due to the availability of manufactured areca nut products.[17] This rising incidence is most strongly seen in developing countries in South and Southeast Asia, where oral carcinoma is often the first or second most common site for malignant cancer.[18] In Western countries, over the past 30 years, the incidence of OCSCC has been decreasing, while the frequency of OPSCC has been noted to increase.[1]

The majority of research on the changing epidemiology has focused on the HPV and its association with HNSCC, particularly in primary tumours of the oropharynx. An analysis of Swedish Cancer registry data (1958–1996) showed that husbands of women with cervical carcinoma had a significantly increased risk of developing either base of tongue or tonsil cancer.[19] In the United States (U.S.), rates of HPV-related oropharyngeal SCC increased in the period from 1973–2004, especially for tonsillar cancer.[1,20] In Australia, the incidence of HPV-related sites in the oropharynx increased by 1% per year between 1982 and 2005 in men and women.[21]

Interestingly, although the rate of OCSCC is observed to be decreasing in young individuals, the incidence of oral tongue squamous cell carcinoma (OTSCC) has been rising especially in young white women, age 18–44 years[22], what is more surprising given the fact that OCSCC, unlike OPSCC, are not typically associated with the HPV infection (approximately 50% of patients with OPSCC and less than 20% of patients with OCSCC are positive for HPV16 DNA).[23] Consequently, young white women form a unique subgroup of patients with no traditional risk factors of tobacco and alcohol abuse and who can not be associated with HPV infection.[22] Presumably, other environmental exposure, genetic abnormalities, and other oncogenic viral infections must play an essential role in the oncogenesis process.

Both oral cavity and oropharyngeal cancers are more common in patients of African descent, as Slotman *et al.* reported in a study carried out in the U.S. Of patients under age 45, African-Americans accounted for 13% of oral cavity cancers *vs*. only 3% for white patients. For oropharyngeal cancers, the results were similar, with young African-Americans accounting for 15.3% of diagnoses *vs*. only 2% of young white patients. Slotman *et al.* also noted a lower 5-year survival rate for African-

Americans in all age groups.[24] The poor survival, particularly in black Americans has been attributed to differences in socioeconomic status and more advanced stage of disease at presentation.[3]

Other locations of head and neck tumours like *e.g*. nasopharynx, larynx, and hypopharynx constitute a rather rare and distinct group of neoplasms in patients less than 45 years of age. For example, according to the literature in the U.S. and Europe, the annual incidence of nasopharyngeal cancer in people younger than 30 years is estimated to range from 1 to 2 per million, and African-Americans are at higher risk.[25,26] However, it is still more common in older adults than in younger ones. Moreover, the above-mentioned heterogeneous group of malignancies is characterized by quite different biology and aetiology factors than oropharyngeal and oral cavity cancers. That is why they are not further analyzed.

Aetiology

Tobacco and alcohol

Tobacco and alcohol have long been implicated as the traditional risk factors for HNSCC in adults, regardless of age. Individuals who smoke more than 20 cigarettes a day and consume more than 100 g of alcohol a day are believed to be at increased risk for oral epithelial dysplasia.[27] In addition, alcohol has been found to be an independent risk factor for OCSCC among non-smokers and tobacco smoke in non-drinkers.[28] Moreover, both factors together seem to enhance the carcinogenic effect.

Interestingly, many patients under age 45 declare never having smoked or consumed alcohol excessively, as Kuriakose *et al.* reported. Moreover, it has been suggested that exposure to such carcinogens might be of too short a duration for malignant transformation to occur in younger patients.[29] Nevertheless, Llewellyn *et al*. and Lipkin *et al*. have both found that many young patients are heavy smokers and drinkers prior to their 40th birthday.[30,31] According to the findings reported by these researchers, tobacco consumption for more than 21 years results in an elevated risk of oral cancer. Llewellyn, in fact, noted that tobacco use often begins during adolescence (in many cases before age 16), thus making it quite probable that many patients have accumulated more than 21 years of addiction, with the increased risk of cancer that this implies, before age 40.

The rising mortality and increasing incidence of cancer of the tongue amongst young patients in the U.S. has been attributed to the use of smokeless tobacco products.[32] However, this possible etiological risk factors has not been confirmed by subsequent studies. For instance, one study reported that smokeless tobacco was not implicated in the increase in incidence of oral cavity SCC in the United Kingdom during last 30 years.[32] In another study, Thomas and Wilson evaluated betel-quid chewing as a risk factor for oral cancer, and studies in India have examined the role of betel-quid with and without tobacco in oral cancer cases, concluding that adding tobacco to the betel-quid significantly increases the risk of developing malignancies.[33]

Marijuana and HNSCC

The first epidemiological study showing that marijuana smoking elevates the risk of head and neck cancers was published in 1999.[34] Since that time, several case studies have been published that suggest an association between marijuana smoking and head and neck cancers, respiratory cancers and oral premalignant lesions. However, the carcinogenicity of tetrahydrocannabinol (THC) – the major psychoactive ingredient in marijuana – is still not clear. The tar component of marijuana contains similar carcinogens to tobacco, but each marijuana cigarette may be more harmful than a tobacco cigarette due to the characteristics of marijuana smoking: greater inhalation of tar, longer retention of marijuana smoke, and greater volume of marijuana smoke inhaled.[35]

In studies focusing directly on the tumour development and growth, cannabinoids have been shown to have both tumorigenic and antitumor properties.[36,37] Reports of young adults with oral cavity SCC and other respiratory tract cancers raised the question of whether marijuana use really contributes to these malignancies. For instance, Rosenblatt *et al.*, in a large, population-based study, found no association between marijuana use and oral cavity SCC risk.[38] In contrast, Liang *et al*. found that moderate marijuana use was significantly associated with reduced risk of HNSCC, a finding that did not differ across tumour sites or by HPV-16 antibody status. Moreover, they observed that marijuana use modified the interaction between alcohol and tobacco, resulting in a decreased HNSCC risk among moderate smokers and drinkers, and that it also an attenuated risk among the heaviest smokers and drinkers.[39] However, this inverse association still needs to be confirmed by further studies.

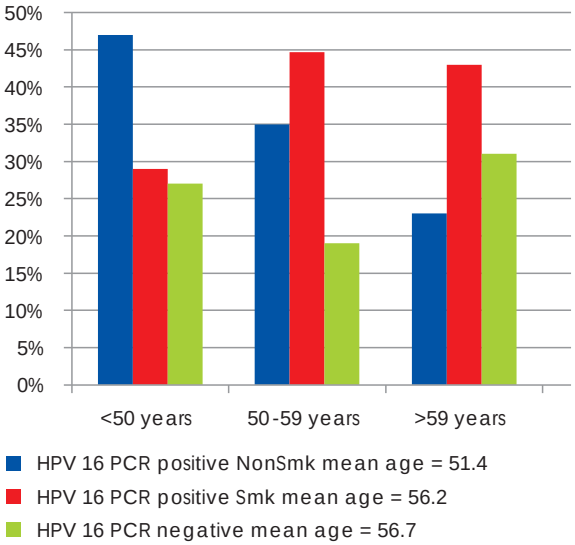

FIGURE 1. Oropharyngeal Cancer Patients (segregated by age, presence of HPV-16 infection and smoking).[41]

Human papillomavirus

Cervical cancer is the most widely accepted human papilloma virus (HPV)-associated malignancy. Recently, epidemiological and molecular data have suggested HPV, especially type 16, to be an independent risk factor in the development of HNSCC.[40] The anatomical structures of oropharynx, most of all base of tongue and tonsils, seem to be favoured. Approximately 50% of patients with OPSCC are positive for HPV-16 DNA. On the contrary to this finding, oral SCCs are not typically associated with HPV presence, what could be due to the fact that the epithelial tissue of oral cavity differs from that in oropharynx structures, and only 20% of individuals with OCSCC are HPV-16 DNA positive.[23]

A strong association between HPV-16 positivity and oropharyngeal primary cancers was reported by Gillison *et al.* in a case control analysis.[41] In addition, a higher proportion of these HPV-16 positive cases were young patients (Figure 1). A high number of lifetime vaginal and oral sexual partners, young age of onset of sexual activity, history of anogenital warts in men may be a potential source of viral colonization of the oral mucosa. However, patients with oropharyngeal SCC and higher numbers of sexual partners constitute only a small part of head and neck squamous cell carcinoma patients. Therefore, a low number of sexual partners does not exclude the diagnosis; husbands of women with *in-situ* and invasive cervical cancer, patients with a history of HPV-associated anogenital cancers, immunocompromised individuals (posttransplant patients and HIV infected ones) are also at high risk of developing HPV-associated HNSCC.[42]

Clinically, high risk HPV-related HNSCC tends to present with lymph node positive disease. Histologically, these neoplasms are usually high-grade and exhibit a basaloid morphology.[43] On a molecular level, the HPV oncoproteins E6 and E7 bind with a high affinity to the p53 and retinoblastoma (Rb) tumour suppressor proteins, inducing their degradation (Figure 2). pRb is a negative regulator of p16 protein at the transcriptional level, with low pRb levels leading to subsequent p16 upregulation. Therefore, HPV-associated cancers are characterized with high p16 levels, low pRb and cyclin D1 protein levels, and wild-type p53 and pRb genes.[44,45] On the contrary, typical for tobacco/ alcohol-associated head and neck cancers are downregulation of p16 protein, p53 gene mutation and overexpression of pRb and cyclin D1.[44] Consequently, p16 overexpression proved to be a marker for oropharyngeal primary site and HPV-association.[46]

The incidence and clinical implications of biologically relevant HPV-16 infection through p16 protein expression in a cohort of OPSCC patients were studied at Yale University.[47] The research resulted in delineation of three tumour classes with distinct molecular and clinical features on the basis of the presence of HPV-16 DNA and p16 expression status: HPV-16 negative/p16 nonexpressing (class I), HPV-16 positive/ p16 nonexpressing (class II), and HPV-16 positive/ p16 expressing (class III) oropharyngeal tumours. The multivariate survival analysis clearly showed that only HPV-16 posistive/p16 expressing tumours were associated with the favourable prognosis.

To summarize, HPV-related HNSCC patients constitute a unique population of patients who are typically younger, less likely to smoke and drink. These neoplasms usually exhibit a distinct biologic behaviour including improved response to (chemo)-radiation and survival when comparing to HPV-negative HNSCC. Moreover, because these patients do not smoke, there is often a delay in seeking medical care for their cancer related symptoms. More research is needed into the role of HPV in HNSCC, especially its connection to a treatment response.

Human immunodeficiency virus (HIV) infection

Traditionally, the most common type of head and neck cancer in patients with HIV infection is Kaposi's sarcoma and non-Hodgkin's lymphoma.

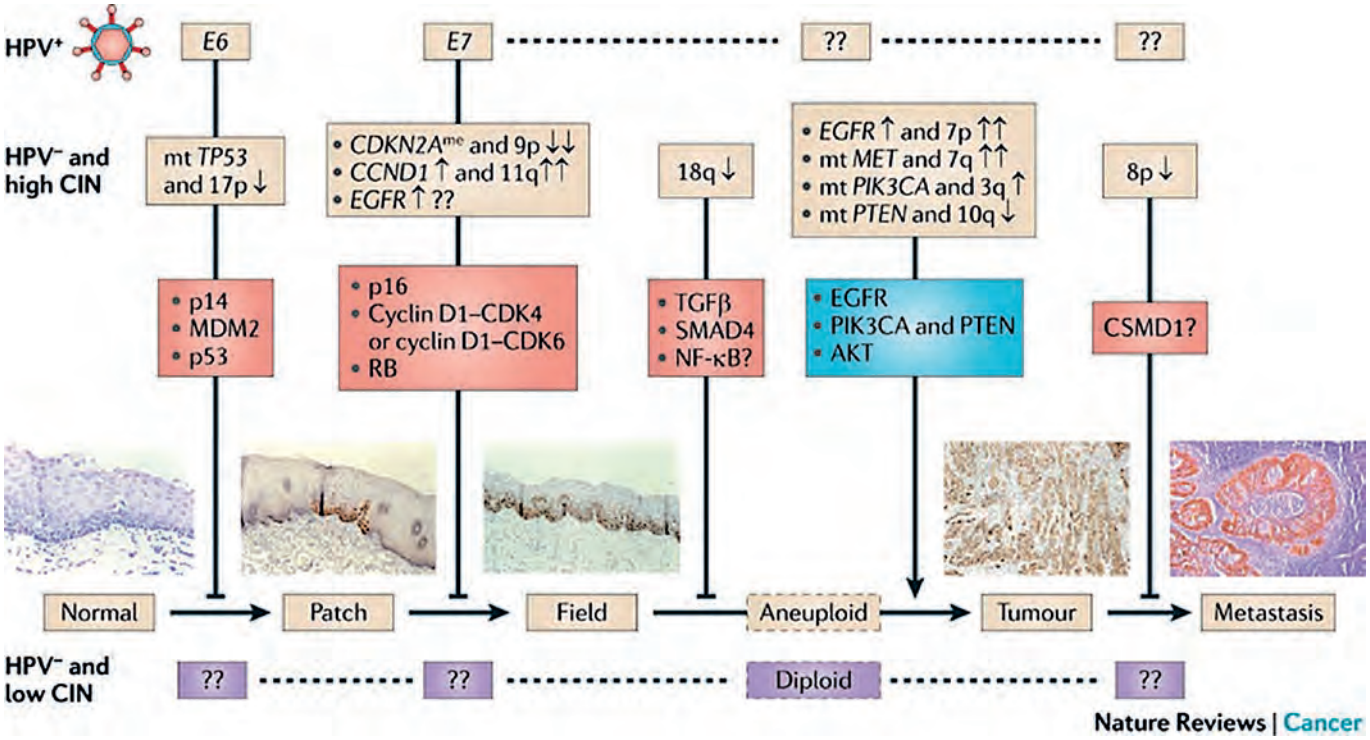

FIGURE 2. Proposal of an integrated model of molecular carcinogenesis for head and neck squamous cell carcinoma according to Leemans *et al.*[48]

However, HNSCC occur frequently in this HIV-positive population. Recent publications have speculated whether the increased risk of HNSCC and lung cancer in HIV-infected populations is coincidental or related to the primary disease. Possible risk factors for carcinogenesis among these patients, apart from tobacco and alcohol exposure, include immunosuppression, opportunistic infections, and high-risk HPV subtypes.[49,50]

The relation between HIV infection and HPV-related HNSCC is complex. In a large population of HIV-seropositive and HIV-seronegative adults, Kreimer *et al.* found the prevalence of high-risk oral HPV infection greater in HIV-seropositive individuals (13.7% compared with 4.5%).[51] Case-control studies of patients in the era prior to highly-active antiretroviral therapy (HAART) have suggested a younger age of diagnosis and a more aggressive clinical course in HNSCC patients with HIV infection. However, since the introduction of HAART, HIV-positive individuals with advanced aerodigestive tract cancer may now have a similar outcome as patients without HIV.[52]

Genetic factors

It seems likely that there is a genetic predisposition for the cancer development at a young age, particularly in those patients with no recognized risk factors. It has been shown that patients younger than 30 years exhibit a significantly increased chromosome fragility following mutagen exposure when compared to older patients; it is thought that this fragility may lead to genetic abnormalities (associated with alterations in DNA repair genes).[53] In addition, a higher frequency of microsatellite instability has been found in younger patients. Conversely, no significant differences between patients <35 years *vs.* patients > 75 years have been found in the expression of p53, p21, Rb and MDM2 proteins.[54,55]

When stratified by age, the younger cohort does not have the genetic alterations that are seen so consistently in older head and neck SCC patients. In fact, the mean number of aberrations in young non-smokers is less than 50% of that observed in older smokers.[32] Moreover, Koch *et al*. found fewer genetic abnormalities in HNSCC of young non-smokers than in young smoking patients, results that imply that the genetic alterations in this group of patients are still unknown.[56] Toner *et al*. performed molecular studies of young nonsmoking patients with HNSCC, finding that cancers in this group of patients is markedly different, not necessarily in any recognizable phenotypic way, but undoubtedly at the genetic level.[32]

Finally, family predisposition must be considered. Copper *et al*. and Foulkes *et al*. both found

TABLE 1. Suspicion of familial predisposition.[57]

When familial predisposition is suspected?
First degree relative with same or related cancer with other features in common
Two or more first degree relatives with same cancer, rare cancer
Two or more relatives in 2 or more generations with tumors of the same site

TABLE 2. Features of familial cancer syndromes.[57]

Familial cancer syndromes
Increased frequency
Shorter latency
Supporting events
Increased aggressiveness and treatment resistance Multiple primaries
Involved genes often mutated in sporadic cancers from the same site

a significant relative risk of squamous cell carcinoma if first degree family members suffered from HNSCC, particularly so if the onset occurred before age 50, in which case risk increased more than two-fold in the case of siblings (Table 1, Table 2).[57]

Other risk factors

Apart from the previously discussed risk factors for HNSCC, there are several other factors that may play an important role in cancerogenesis in the young, including chronic immunodeficiency states (Bloom syndrome, Wiskott-Aldrich syndrome)[58], immunosuppression regimes following organ transplantation[59], and anaemia occurring in Patterson Kelly/Plummer Vinson syndrome.[32] Additionally, Fanconi anaemia, an autosomal recessive syndrome caused by defects in DNA repair, is associated with a high risk of developing malignancy at a young age (the incidence of HNSCC in this population is estimated to be 14% by age 40).[60] Diets high in fruits and vegetables and fish oils are generally inversely correlated with a risk of oral cancer. Based on the studies by Llewellyn *et al*., this is also true for young adults.[13]

A distinct group of young patients with HNSCC consists of childhood cancer survivors. It is known that cancer patients have some risk of second synchronous or metachronous primary tumour. In 20-year survivors above-mentioned chance is estimated at the level of 3–12%. Chemotherapy drugs and radiation therapy are known for their long term carcinogenic effects; therefore, induced malignancies are one of the most serious side effects of the treatment of childhood cancer survivors.[61,62]

Treatment and prognosis

HNSCC treatment recommendations and prognosis are currently based on TNM staging, status of the surgical margin, presence of lymph node extracapsular tumour spread and, in some instances, also on tumour differentiation, thickness, and presence of perineural and perivascular invasion. In the literature, many studies have commented on differences in stage between younger and older patients at the time of diagnosis.

Soudry *et al*. reviewed the 1992–2007 tertiary referral centre database and found young adults with oral tongue cancer to have a significantly worse clinical/radiological N stage at diagnosis and more evidence of perineural invasion on histopathological examination. However, those authors did not find any significant differences between younger and older patients in terms of histological grade, tumour depth, or presence of lymph node extracapsular extension.[61] Similarly, Veness *et al*. and Verschuur *et al*. found a higher incidence of nodal metastases in younger patients.[63,64]

Sturgis *et al*. indicated higher percentage of advanced HNSCC in young adults. According to their review, 73% of HNSCC were stage III or IV at presentation.[65] In contrast, a research performed by Funk *et al*. reported that younger patients typically had an earlier stage of disease on presentation and, consequently, a higher proportion of stage I cancer was noted in younger age groups.[66] Compared to HPV-negative patients, those with HPV-positive oropharyngel tumours have more frequently early-stage primary tumours and more advanced neck disease at the time of diagnosis.[11]

Oral cavity squamous cell cancers

Traditionally, patients with HNSCC are treated with surgical resection and when indicated postoperative adjuvant radiotherapy. But such procedure may have a devastating effect on major functions like breathing, swallowing, speech and in consequence negative impact on the quality of the remaining life.[67] As more and more people are

surviving HNSCC also terms of appearance, function and shoulder mobility seem to be much more important.

Individuals, who develop HNSCC when young (40 years of age or less) and survive, create a different patient subgroup from the elderly people who develop cancer in their fifties through seventies. Young patients are usually healthy, active and have a long life expectancy.[68]

The local-regional control of oral cavity SCC has been increased mostly because of more aggressive surgical resection facilitated by modern reconstructive methods and advances in radiotherapy.[69–71] Simultaneous postoperative chemoradiotherapy is believed to improve a local-regional control in patients possessing high risk features such as positive surgical margins and extracapsular tumour extension. However, distant recurrences still remain a problem in patients treated for oral cavity cancer. Also survival rates have improved only frugally over the past 3 decades.[72]

Considering the above data, new therapeutic options have been explored. Kies *et al.* performed a trial of induction chemotherapy followed by surgery for OTSCC in young adults (23 patients with OTSCC, T2–3, N0–2, M0).[73] They believed that induction chemotherapy may have the potential to reduce the intensity and morbidity of subsequent local-regional treatment procedures (surgery and radiotherapy) and consequently increase quality of life. On the basis of pathologic review of the surgical specimen, 9 patients (39%) had a complete or major response at the tongue, 8 (35%) had no response or had progression of the primary tumour. In the neck, 9 patients (39%) had a complete response or remained node negative, and 6 (26%) had an increase in nodal stage. Distant recurrence rate of 30% observed in this trial raised assumption that induction chemotherapy selects the most aggressive subpopulations to survive, which resulted in distant recurrence.

Licitra *et al*. has also suggested that neoadjuvant chemotherapy may have a role in function preservation as well as in avoiding radiotherapy in younger patients with HNSCC, especially those with oral cancer.[74] Similar findings have been reported by Sturgis *et al*., who have suggested that postoperative radiotherapy may not be necessary in some patients who undergo neoadjuvant chemotherapy.[65] On the contrary to these observations, data presented at the American Society of Clinical Oncology (ASCO) 2012 annual meeting suggested no survival advantage of induction chemotherapy prior to chemoradiotherapy over chemoradiotherapy alone, which makes the role of neoadjuvant chemotherapy highly questionable.[75,76]

In many fields, the search for biological markers of disease is intense nowadays, and HNSCC is no exception. Molecular profiling of tumours has been driven by changes in epidemiologic patterns and the development of effective biologic agents directed against specific molecular targets. As Thomas *et al*. noticed EGFR overexpression in oral cavity tumours of young adults predisposes to a poor prognosis with a consequent adverse survival. Mixed results for OTSCC treatment with anti-EGFR antibodies have been presented in the literature. Nonetheless, EGFR overexpression may be a prognostic indicator in identifying patients who warrant a more radical approach to the treatment.[77]

Oropharyngeal squamous cell cancers

At present, it remains speculative whether patients with HPV-positive HNSCC should be treated differently from those with HPV-negative tumors.[41] Molecular profiling of HPV-positive tumours that are typically found in the oropharynx, has shown that these tumours seem to be commonly associated with p16 overexpression, whereas tumours not associated with HPV are seldom p16 positive. P16 positivity has been shown to be connected with improved outcomes, regardless of HPV infection status. Therefore, p16 positivity has been proposed to be a more reliable and reproducible prognostic marker in HNSCC.[78] Furthermore, prognostic power of extracapsular tumour spread seems to be diminished in surgically treated p16-positive oropharyngeal SCC.[79]

However, the increasing recognition that HPV-related HNSCC are notably sensitive to radiation therapy has prompted investigators to question whether patients with HPV-associated HNSCC might be overtreated and unnecessarily subjected to the toxicity of intensive treatment strategies using chemoradiotherapy.[80] HPV-positive HNSCC patients are consistently proved to have an improved prognosis when comparing to those with HPV-negative tumours. Moreover, it has been demonstrated by Chen *et al*. that clinical outcome among patients treated by radiotherapy alone for HPV-positive HNSCC appear to compare favourably to those treated by more intensive chemoradiotherapy approaches.[80] Recently Ang *et al*. and O'Sulivan *et al*. identified group of patients, characterized by T1–3 and N0–2b HPV-positive oropharyngeal SCCs (in case of N2b disease, patients should be nonsmokers/minimal smokers) that would not necessarily

need intensive chemoradiation and are candidates for treatment de-escalation clinical trials.[81,82]

The mechanism of HPV-mediated radio-response is unclear. The most direct explanation is that by the interference with the normal function of p53 and pRb, the viral products E6 and E7 render the host tumour cell more susceptible to radiation-induced apoptosis.[80] This hypothesis was demonstrated by Pang *et al*. who showed that transfection of the E6 transcript in HPV-negative SCC cell lines resulted in sensitization to radiation-induced cell death.[83]

Although there are mainly clinical researches convicting much better prognosis for patients with HPV-positive HNSCC, it is still uncertain whether it is the improved radiosensitivity that drives the superior survival of these individuals. Namely, HPV-positive patients treated by surgery have also been shown to have better prognosis than HPV-negative ones.[84]

Two commercial HPV vaccines are available nowadays for the prevention of cervical cancer and genital warts: the quadrivalent vaccine Gardasil (Merck & Co. Inc., Collegeville, Pennsylvania, USA) targets HPV subtypes 6, 11, 16 and 18, and the bivalent vaccine Cervarix (GlaxoSmithKline, Research Triangle Park, North Carolina, USA) targets the subtypes 16 and 18. Both, they are able to elicit a robust immune response and in consequence significantly decrease the incidence of persistent HPV-16 and HPV-18 infections and associated moderate-to-high grade cervical neoplasia CIN2/3.[85] Whether there is impact of these vaccines on the incidence of persistent oral HPV infection still must be identified.

Treatment outcomes – the effect of patient's age

Even though Byers first suggested as far back as 1975 that HNSCC in young adults should be considered a distinct subgroup, the question as to whether age has a significant impact or not on treatment outcomes still remains unanswered.[86] However, several studies – *e.g*. von Doersten *et al*.[22] and Funk *et al*.[66] – have shown that patients under age 45 have a higher 5-year survival rate. Gilroy *et al*. found a significant difference in the overall survival in favour of younger patients, as did Verschuur.[8,64] In fact, both of those studies reported similar findings in terms of cause-specific survival, locoregional control rates, and distant metastatic rates. Liao *et al*. evaluated 296 patients and found no differences in therapeutic outcome between young and older patients who had similar tumour characteristics, therapeutic modalities, and pathological risk factors. However, although they found no significant differences in local control rate or neck control rate, they did observe a higher rate of distant failure in young adults.[87] Soudry *et al*. concluded that, in general, patients younger than 45 years have the same outcome as older patients.[61] However, within the younger group two distinct patterns of disease were observed: an extremely aggressive course with a high mortality rate within 2 years and a more indolent course with a lower mortality rate. Veness *et al*. found a higher rate of locoregional recurrence in younger *vs*. older patients.[63] In contrast, Van Doersten *et al*., in a multivariate analysis of 155 patients, found that age had no effect on recurrence rates.[22] Verschuur concluded that younger patients had a significantly lower incidence of second primary cancers compared with an older cohort.[64] In contrast, Friedlander *et al*. reported the incidence of a second primary tumour to be similar between younger and older patients, and with no difference between groups in tobacco and alcohol use.[88]

Conclusions

Many controversies still surround HNSCC in young adults. An important and still unanswered question is whether HNSCC in the young is a distinct clinical entity. Moreover, doubts about differences in etiologic risk factors between younger and older patients are still considerable, as are questions about the possible influence of younger age on prognosis. Moreover, the relatively low incidence of HNSCC in young adults hampers progress as it is difficult to perform studies and reach meaningful conclusions due to the limited numbers of patients.

Nevertheless, one thing is clear. Although young people have a lower incidence rate for HNSCC, physicians need to be aware that the incidence is growing and these types of cancers must be suspected in any patient with worrying signs and symptoms, regardless of age.

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review

Pancreatic involvement in small cell lung cancer

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Background. Few data are available concerning incidence, clinical picture, and prognosis for pancreatic metastases of small cell lung carcinoma. In this paper we review the related literature available in English language.

Conclusions. Although pancreatic metastases are generally asymptomatic, they can rarely produce clinical symptoms or functional abnormalities. The widespread use of multi-detector computerised tomography (CT) in contemporary medical practice has led to an increased detection of pancreatic metastases in oncology patients. Tissue diagnosis is imperative because radiological techniques alone are incapable of differentiating them from primary pancreatic tumours. Pancreatic metastases occur in the relative end stage of small cell lung cancer. The main complications of these lesions, although rare, are acute pancreatitis and obstructive jaundice. Early chemotherapy can provide a survival benefit even in patients with mild acute pancreatitis or extrahepatic biliary obstruction.

Key words: lung neoplasms; carcinoma; small cell; neoplasm metastasis; pancreas

Introduction

With the improvement of imaging techniques, pancreas metastases are much more frequent than commonly appreciated. There were limited data about pancreas metastases of small cell lung cancer. Few guidelines are available on the appropriate management of such cases. The aim of this study is to review the pancreatic involvement due to small cell carcinoma of the lung.

Methods

A computerised research of literature (English language only) was performed to identify the relevant articles dealing with the subject. Using the medical subject headings and terms "pancreas metastasis or pancreatic metastases", "small cell", and "lung" we reviewed *PubMed* and *Web of science* databases between 1970 and 2012. The selection criteria included patients with published demographic and clinical data regarding the treatment for cancer metastasized to pancreas. Exclusion criteria for this research included publications of patients' data in non-English language, patients without previous translation and lack of relevance of the analysis of pancreatic metastasis. Each paper was inspected and the reference lists of the selected articles were also screened systematically for additional studies of interest. More than 20 cases of primary small cell carcinoma of the pancreas were excluded.[1-6] Additionally, some cases with small cell cancer in the studies were analysed just to some extent because they did not describe the detailed clinical findings [7-18] Information regarding patient presentation, site of primary neoplasia, characteristics of metastasis in the pancreas, treatment, and patient demographics were summarised using descriptive statistics. All tests were performed using SPSS 15.0 for Windows.

Frequency of pancreatic metastasis

The precise prevalence of pancreatic metastasis is not clear. The reported frequency of pancreatic metastases was 1.6% in 4955 adult autopsy cases.[9] This rate was 5.9% in 1740 autopsies of another study.[11] Pancreas metastasis has been observed in 25 (2.1%) patients of 1172 pancreatic endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA).[19] This rate was, respectively 10.7%, 2.4%, and 0.7% in different studies.[18,20,21] Because the radiological examination is generally conducted in an early stage, the occurrence of pancreatic metastases in cancer patients undergoing computerised tomography (CT) should be significantly lower than in patients who have died of cancer.[22] On the other hand, the metastases have been only detected at the microscopic level in 25% of the patients in autopsy series.[9]

The primary site of metastatic pancreatic tumour differs according to the study. The most common site can be lung carcinoma, renal cell carcinoma, colon carcinoma, or stomach carcinoma.[9-13,15,16,18,19,21-27] Mesa *et al.* reviewed all secondary tumours of pancreas in literature by Medline between 1966 and 2003.[18] Lungs (18.7%), gastrointestinal tract (17.7%), kidneys (16.3%), breasts (10.6%), and lymphomas (7.9%) were the most frequent secondary neoplasms in 699 cases. The reported incidence by site of origin reflects the overall incidence of cancers in the general population. However, there are a disproportionately high number of reports of metastases from renal cell carcinoma. Another review in 2004 showed that the predominant primary tumour was renal cell carcinoma in 150 cases (45%), followed by lung carcinoma in 49 cases (14.7%), breast carcinoma in 25 cases (7.5%), and colon cancer in 22 cases (6.6%).[28] Sweeney *et al.* searched PubMed using the terms "pancreatic metastasis" and "cancer metastatic to the pancreas" after 2004.[29] They found that the most common primary tumour site was kidney (70.5%), followed by breast (6.8%), lung (5.9%), and colorectal (5.5%) for 220 patients. It has been suggested that pancreatic metastases may arise from local lymphatic or venous dissemination because the pancreas and kidneys are located close to one another within the retroperitoneal compartment.[25]

Smith reviewed the incidence of metastasis to the hepatic-pancreatic-biliary axis in primary carcinoma of the lung.[30] A total of 679 (10%) patients were found in 6807 autopsies between 1929 and 1975. On searching medical records of 850 patients with lung cancer, 26 (3.1%) cases were identified with pancreatic metastasis.[31] Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is a powerful tool for oncology imaging. Pancreatic metastases were found in 1.9% of 573 cases with lung cancer by FDG-PET/CT study.[7] However, only one of the pancreatic lesions had histological confirmation in this study. Because primary pancreatic cancer and pancreatitis also show FDG accumulation, the actual rate of metastasis to pancreas in lung cancer may be lower than 1.9 percent. A pathological confirmation is sometimes considered unjustifiable both from the patient's and an economic standpoint. This problem also alters the true incidence of metastatic disease of the pancreas.

The most common histological type of lung cancer that is related to pancreatic metastasis was reported as small cell lung cancer, followed by large cell carcinoma, squamous cell carcinoma, and adenocarcinoma.[12,30,32-35] For metastasis-induced acute pancreatitis patients with lung cancer, the rate of small cell carcinoma to non-small cell carcinoma was 15/18 in one study and 5/15 in another study.[8,36]

Clinical picture

The symptoms produced by metastasis to the pancreas are variable. Most patients (50-83%) are free of organ-specific complaints (abdominal pain, jaundice, abdominal discomfort, weight loss) when the metastasis are detected incidentally on CT during periodic clinical surveillance or follow-up. [25,37,38] Metastases can directly invade pancreatic ductal epithelium and thus may clinically mimic primary pancreatic adenocarcinoma.[37] Organ-related clinical symptoms were observed in only 6 of our 18 patients.[10] In a review of 220 patients, the most common presenting symptoms were jaundice (25.2%), and abdominal pain (11.4%). In their survey, 27.6% of the patients were asymptomatic.[29] Male/female ratio was 48/22 in our survey. Mean age was 59±10 (range 37–83). The most common location was the left lung (59%).

Time of metastasis

Pancreatic metastasis generally constitutes a late manifestation of widespread disseminated metastasis in cancer patients.[39] In Mayo Clinic series, only 27 of 1357 patients (2%) with solitary pancreatic masses had secondary pancreatic tumour.[26] For small cell lung cancer, all ten patients in autopsy series and all eight patients in clinical series are

TABLE 1. The characteristics of the patients with pancreatic metastasis-induced obstructive jaundice in small cell lung cancer

References	Gender	Age	Side of primary tumour	Location of secondary tumour	Pattern of metastasis	Other metastases	Treatment	Response to chemotherapy	Survival
Smith HJ.[30]	NA	NA	NA	NA	NA	Present	Supportive	NA	4 weeks
Smith HJ.[30]	NA	NA	NA	NA	NA	Present	cholecystojejunostomy	NA	10 weeks
Smith HJ.[30]	NA	Na	NA	Na	NA	Present	Supportive	NA	<2 weeks
Jeong IB *et al.*[34]	Female	65	Left	Head	multiple	Absent	Percutaneous transhepatic biliary drainage following chemotherapy	Complete remission	>11 months
Howe HR *et al.*[35]	Female	40	Right	Head	solitary	Present	Choledochojejunostomy, irradiation, chemotherapy	Minimal response	1 month
Howe HR *et al.*[35]	Male	53	Right	Head	solitary	Present	Gastrojejunostomy + cholecystojejunostomy	NA	<2 weeks
Obara M *et al.*[40]	Male	69	Left	Head	multiple	Present	Percutaneous transhepatic biliary drainage followed chemotherapy	Partial remission	10 months
Kotan C *et al.*[41]	Male	46	Right	Head	solitary	Present	Pancreaticoduodenectomy followed chemotherapy	NA	11 months
Sakar A *et al.*[42]	Male	64	Right	Head	solitary	Absent	Gastrojejunostomy + cholecystojejunostomy	NA	<2 weeks
Singh D *et al.*[43]	Female	50	Right	NA	multiple	Absent	Endoscopic retrograde cholangiopancreatography	NA	NA
Ochi N *et al.*[44]	Male	64	Left	Head	solitary	Absent	Endoscopic retrograde biliary drainage, chemotherapy	Partial remission	25 months
Ochi N *et al.*[44]	Male	74	Left	Head	solitary	Present	Endoscopic retrograde biliary drainage, chemotherapy	Partial remission	4 months
Dunkerley RC and Dunn GD[45]	Male	72	Left	Head	solitary	Present	Endoscopic retrograde biliary drainage, radiotherapy	NA	6 months

NA = not available

presented as disseminated disease.[9,38] In addition to these 18 patients, another 49 patients (Table 1, 2, and 3) also had other metastases, but 10 had solitary pancreatic metastasis. Consequently, the rate of solitary pancreatic metastasis to disseminated metastases was 10/67. The overall survival of these patients may be lower because of the extensive disease. The presence of pancreatic metastases indicates the visceral widespread and is of ominous prognostic importance. Median survival for 4 patients who had not other metastasis was 8.25 months but 1.7 months for 29 patients with extensive disease in our survey.

Jaundice due to small cell lung cancer

Lung cancer can cause biliary tract obstruction by metastasising to lymph nodes in the porta hepatis, pancreas or hepatic parenchyma.[40] Johnson *et al*. reported that 12 (9.6%) among 125 patients presented with hyperbilirubinaemia with small cell lung cancer at diagnosis.[14] Five of these patients had pancreatic metastasis resulting in extrahepatic biliary obstruction, and seven had diffuse hepatic metastasis without extrahepatic biliary obstruction. When compared to extrahepatic obstruction, the resolution of jaundice is more difficult in patients with diffuse hepatic metastasis. Of 19 patients reported by Smith, eight (66%) patients with small cell lung cancer had evidence of extrahepatic bile duct obstruction.[30] Tumours located in the head of the gland usually cause obstructive jaundice (Table 1), whereas tumours in the body and tail of the pancreas may lead to dilatation of Wirsung's duct.[62] Palliative treatment by surgical biliary bypass and postoperative chemotherapy are indicated in such patients even though the patients had diffuse hepatic metastases.[40] This approach may produce extended survival exceeding 4 months. Table 1 shows that patients treated only with surgery survive several weeks. Median survival for 6 patients treated with chemotherapy was 10.5 months but 2 weeks for 5patients treated with conservative treatment in our survey.

Acute pancreatitis due to small cell lung cancer

Associated pathological findings in cases with secondary pancreatic tumours were reported as fat necrosis (19%), chronic pancreatitis (11%), acute pancreatitis (8%), and acute terminal pancreatitis (6%).[11] Although gastric cancer has been noted the most common nonpancreatic tumour associated with pancreatitis, small cell lung carcinoma has been reported to be the most common (6 of 10 patients) lung tumour causing metastasis-induced acute pancreatitis.[46,47] Some lung cancer patients with metastasis-induced acute pancreatitis, especially patients with small cell lung cancer, have no

obvious symptoms, and were easily underdiagnosed.[36]

In 1973, Levine and Danovitch first described a patient with small cell lung cancer in whom acute pancreatitis developed during the progression of the malignancy.[48] In a series of 40 consecutive cases of small cell cancer of the lung during the period from August 1974 to August 1977, three cases of metastasis-induced acute pancreatitis were discovered. This represented an occurrence rate of 7.5 per cent.[49] Although the frequency of the clinical picture was 3.3% in another series, the rate of metastasis-induced acute pancreatitis was reported as 0.12% in the largest study consisting of 802 patients.[47,50]

There are several mechanisms by which a metastatic tumour might induce acute pancreatitis. The first is the obstruction of the pancreatic duct by metastases or peripancreatic compression secondary to regional lymph nodes. This can lead to the activation of the pancreatic proteases, resulting in subsequent autolysis. The second is the vascular compromise by neoplastic destruction.[10,49] In a series, almost 40% of patients with metastatic lesions had obstruction of the main pancreatic duct.[22] More than half of these patients had neoplasms in the pancreatic head with associated biliary ductal obstruction.

In some patients, the possible causes of acute pancreatitis such as alcohol consumption, gallstone disease, or the use of antineoplastic agents such as ifosfamide, vinorelbine, and cisplatin can be found.[8,33,46-53] On the other hand, pathological investigation showed no evidence of metastatic tumour in some patients.[52] This finding suggested that acute pancreatitis could be a paraneoplastic syndrome. Pancreatic metastasis could be confirmed by pancreatic biopsy, but it is often difficult to obtain a tissue diagnosis in these seriously ill patients due to high morbidity and false negative rate of biopsy.[46] In our survey, thirteen patients (7 of them had post-mortem diagnosis) had tissue confirmation of pancreatic metastasis, but 13 patients had not had a pathological sampling of pancreatic tumour (Table 2). Interestingly, we found left lung predominance (11/7) in patients with acute pancreatitis. It is necessary to investigate the lymphatic communication between the left lung and pancreas.

Treatment for tumour-induced acute pancreatitis is initially supportive. In patients with mild pancreatitis, chemotherapy may favourably influence the recovery from pancreatitis. However, chemotherapy is poorly tolerated by patients with severe pancreatitis and it is therefore inadvisable in patients with high (>3) Ranson scores.[50] Of the two cases reported, one patient receiving supportive treatment died in one month, and the other patient survived only seven weeks in spite of palliative abdominal radiotherapy.[48] There was only one study that investigated the prognostic factors for metastasis-induced acute pancreatitis patients with lung cancer.[36] Chemotherapy and performance status have been found to be significant factors for survival. In our survey median survival for 6 patients treated with chemotherapy was 6 months, but two weeks for 5 patients treated with conservative treatment.

Radiographic features

Lesions are primarily diagnosed on radiographic techniques. Imaging techniques are able to delineate the mass and evaluate its size and lymph node status, as well as the extent of vascular invasion. Pancreatic metastasis must be distinguished from local invasion of malignant gastrointestinal tumours. Although abdominal ultrasound is the first-line imaging, CT is the most frequently used method for studying pancreatic cancer.[67] Ultrasonography also helps to distinguish the aetiology of the common causes of pancreatitis and it is important to exclude cholelithiasis if chemotherapy is to be considered.[54]

The sensitivity of abdominal ultrasound in the detection of all tumours in the pancreas was found as 89% in a prospective study.[68] The sonographic appearance of metastasis appeared as homogenous, well-demarcated solid lesion with a more hypoechoic internal structure than the pancreatic parenchyma. The pancreatic duct is usually not dilated. Although metastases can be hypovascular or hypervascular depending on the primary malignancy, a pancreatic mass rich in blood flow, as indicated by colour Doppler ultrasound, is more likely to be a metastasis than a primary pancreatic carcinoma.[39,69,70] The metastatic lesion from a renal cell carcinoma is usually highly vascular, and contrast-enhanced ultrasound or angiography is very useful for diagnosis.[12] Endoscopic ultrasound can show invisible metastases in abdominal ultrasound.[55] Interestingly, abdominal ultrasound can show invisible metastases in CT.[56] Endoscopic ultrasound features of primary pancreatic cancer and metastatic lesion were similar with respect to tumour size, echogenicity, or consistency. Although endoscopic ultrasound is probably superior for de-

TABLE 2. The characteristics of the patients with metastasis-induced acute pancreatitis in small cell lung cancer

References	Gender	Age	Side of primary tumor	Location of secondary tumor	Pattern of metastasis	Tissue diagnosis	Other metastases	Treatment	Response to chemotherapy	Survival
Woo JS *et al.*[33]	Female	45	Left	Head	multiple	No	Yes	Endoscopic stenting	NA	NA
Liu SF *et al.*[36]	Male	44	NA	NA	NA	Yes	Yes	Chemotherapy	NA	7.6 months
Liu SF *et al.*[36]	Female	44	NA	NA	NA	Yes	Yes	Chemotherapy	NA	3.2 months
Liu SF *et al.*[36]	Male	51	NA	NA	NA	Yes	Yes	Chemotherapy	NA	9 months
Liu SF *et al.*[36]	Male	75	NA	NA	NA	Yes	Yes	Chemotherapy	NA	1 month
Liu SF *et al.*[36]	Female	68	NA	NA	NA	Yes	Yes	Conservative	NA	2.7 months
Kim KH *et al.*[46]	Male	63	Right	NA	multiple	No	Yes	Conservative	NA	NA
Chowhan NM *et al.*[47]	Male	55	Left	Tail	NA	No	Yes	Conservative	NA	2 weeks
Chowhan NM *et al.*[47]	Male	48	Right	Head	Solitary	No	Yes	Conservative	NA	2 weeks
Levine M *et al.*[48]	Male	45	Right	All	NA	Autopsy	Yes	Conservative	NA	1 month
Yeung KY *et al.*[49]	Male	53	Left	Head and body	Diffuse enlargement	Autopsy	Yes	Chemotherapy	Partial remission	5.5 months
Yeung KY *et al.*[49]	Male	53	Right	NA	NA	Autopsy	Yes	Chemotherapy	Partial remission	5.5 months
Yeung KY *et al.*[49]	Female	37	Right	NA	Diffuse enlargement	No	No	Chemotherapy	Complete remission	3.5 months
Stewart KC *et al.*[50]	Female	44	Left	Head	Solitary	No	Yes	Chemotherapy	Partial remission	>6 months
Papagiannis A *et al.*[51]	Male	52	Left	NA	Diffuse enlargement	No	?	Conservative	NA	3 weeks
Allan SG *et al.*[52]	Female	73	Left	NA	Diffuse enlargement	No	Yes	Conservative	NA	5 days
Allan SG *et al.*[52]	Male	67	NA	NA	Diffuse enlargement	No malignity	Yes	Conservative	NA	10 days
Huang YW *et al.*[53]	Female	68	Left	NA	Diffuse enlargement	No	Yes	Conservative	NA	9 days
Hall M *et al.*[54]	Male	67	Left	Head	NA	Autopsy	Yes	Conservative	NA	2 weeks
Wurm Johansson G *et al.*[55]	Female	52	NA	Head and body	multiple	EUS-FNA	NA	Biliary stent + chemotherapy	NA	NA
Tanaka H *et al.*[56]	Female	51	Left	Body and tail	multiple	No	Yes	Chemotherapy	Complete remission	8 months
Noseda A *et al.*[57]	Male	58	Left	Head	Solitary	No	Yes	Conservative	NA	7 weeks
Schmitt JK[58]	Male	58	Left	NA	NA	Autopsy	Yes	Chemotherapy	NA	6.5 weeks
Evans AT[59]	Female	45	Right	NA	Diffuse enlargement	Autopsy	Yes	Conservative	NA	8 days
Chao WC *et al.*[60]	Female	65	Left	NA	multiple	No	Yes	Conservative	NA	20 days
Maclennan AC *et al.*[61]	Female	56	Right	All	multiple	Autopsy	?	Conservative	NA	5 weeks

NA = not available; EUS-FNA = ultrasound-guided fine-needle aspiration

tection of small tumours, helical CT appears equal to or perhaps even better than endoscopic ultrasound for staging pancreatic neoplasms.[20]

For 12 patients with pancreas metastasis, abdominal ultrasonography had reported hypoechoic lesion in 6 patients, a hypertrophic aspect involving the head of the pancreas with dilatation of the main pancreatic duct in one patient, and an aspect suggestive of acute pancreatitis in one patient.[15] In their study, abdominal CT was performed in 19 patients and revealed tumours in 13 patients, increased pancreatic volume in 5 patients, and an aspect compatible with pancreatitis in one patient. CT technology has improved greatly over the last decade. For primary pancreatic cancer, an accuracy of 99% has been reported for prediction of vascular invasion by tumour with multi-detector helical CT (MDCT).[71] Although the sensitivity of modern MDCT scanners in demonstrating pancreatic metastasis is still not known, MDCT with 2D multiplanar reconstructions (MPR) and three-dimensional rendering allows detection of lesions that are not visible on routine CT images.[53] In a study of 11 cases, nearly 30% of pancreatic metastases were missed on routine transaxial images and detected only on thin slice or MPR images.[7] There was only one study that investigated the diagnostic performance of MDCT in pancreatic metastases.[67] All metastatic lesions in 17 patients, ranged between 8 and 40 mm, were demonstrated by MDCT.

Precontrast CT images of the pancreas show either isodense or hypodense lesions when compared to the normal parenchyma, with rare regions of calcification.[69] Solitary metastases typically demonstrate areas of low attenuation (probably indicative for necrotic foci) on contrast enhanced CT, while the diffuse form of metastasis remains isodense following intravenous contrast medium.[10,41] A peripheral rim of enhancement after intravenous contrast medium is usually demonstrated. Rim enhancement is especially common in lesions larger than 1.5 cm in size, whereas smaller tumours display a more uniform vascular pattern.[41] Although some authors did not observe a correlation between tumour size and pattern of enhancement, they also found a peripheral enhancement in 73% of the patients.[24] The peripheral enhancement of tumour tissue observed in many cases reflects a degree of vascular perfusion that is not typical of primary pancreatic adenocarcinoma, whereas ductal adenocarcinoma of the pancreas typically appears as a uniformly nonenhancing mass at contrast-enhanced.[22,24]

CT can occasionally fail to show subtle differences in attenuation between normal pancreatic tissue and non-necrotic or non-cystic neoplastic tissue.[23] Of 34 patients with autopsy-proven secondary tumour, pancreatic abnormalities were documented on non-helical abdominal CT only in 18 (53.8%) cases. Initial CT of the pancreas can be normal in appearance in patients with metastasis.[10] Lymphatic metastasis of the pancreas can occur without any tumour formation, what is often seen in stomach carcinoma.[11]

On magnetic resonance imaging, pancreatic metastases typically appear hypointense and well circumscribed compared with normal gland tissue on unenhanced T1-weighted images, both with and without fat saturation. Following intravenous gadopentetate dimeglumine administration, a rim of enhancement is usually visible in larger lesions and homogenous enhancement is typically demonstrated in smaller tumours. On T2-weighted images, the lesions are slightly heterogeneous and moderately hyperintense. Hypointense nodules are sometimes visible on T2-weighted images, especially in the diffusely enlarged type.[38,41]

A definitive diagnosis requires a pathologic examination of a biopsy or surgical specimen. Endoscopic ultrasound-guided fine-needle aspiration has become the preferred method for cytologic-tissue acquisition of pancreatic masses, especially following equivocal CT imaging.[69] Nevertheless, the histological distinction between primary pancreatic cancer and metastatic tumour is sometimes difficult to establish.[15]

Radiological pattern of metastasis

The majority of overall metastatic lesions were found in the head of the pancreas.[16,20,29,32] For lung cancer, some authors reported that the majority of metastatic lesions were observed in the body or the head of the pancreas.[33,38] However, our review showed that the most common macroscopic location is the head (76%) of the gland for small cell lung cancer (Table 1, Table 2, and Table 3). The body was the second most common site (15%) for solitary involvements.

Three patterns of metastatic involvement of the pancreas have been described. The first and most common, reported in 50-80% of cases, is that of a single localised mass.[19] A second pattern of diffuse pancreatic enlargement has been reported in 15-44% of cases. Diffuse enlargement is characterised by a diffuse infiltration of malignant cells along the interlobular septa, which causes the destruction of large parts of the pancreatic lobules.[23] The gland has homogenous density in CT appearance. The third pattern is multiple pancreatic nodules (10-44%), represented by many small nodules which can coalesce occasionally into larger masses.[12,22,23,37] The attenuation of the neoplastic nodules may be variable.[49]

Solitary nodule was the usual pattern of pancreatic metastasis, both for overall tumours and for lung cancer.[16,22-25,31] Although the most common cause of diffuse infiltrative type of metastasis reported is small cell carcinoma of the lung [10], in our survey of 50 patients with small cell lung cancer, we observed a solitary nodule in 29 patients (57%), multiple nodules in 14 patients (27%), and diffuse enlargement in 8 (16%) the patients. Radiological pattern can be related to the invasiveness of metastatic carcinoma.[10] Interestingly, we found that diffuse enlargement is the most common pattern (50%) in patients with acute pancreatitis (Table 2). On the other hand, the most common type of metastasis was diffuse involvement in histological examination.[10]

Conclusions

The frequency of pancreatic metastasis varies between 1.6% and 10.6% in autopsy studies.

TABLE 3. Pattern of metastasis in small cell lung cancer

References	Gender	Age	Location	Type	Other metastases
Sato M *et al.*[7]	male	78	body	solitary	Yes
Sato M *et al.*[7]	male	58	NA	NA	Yes
Sato M *et al.*[7]	male	75	NA	NA	Yes
Muranaka T *et al.*[10]	male	60	NA	Diffuse enlargement	NA
Volmar KE *et al.*[16]	male	58	NA	NA	No
Volmar KE *et al.*[16]	male	65	NA	NA	No
Mesa H *et al.*[18]	NA	NA	body	NA	NA
Gilbert CM *et al.*[19]	male	65	head	multiple	NA
Gilbert CM *et al.*[19]	male	58	head	solitary	NA
Gilbert CM *et al.*[19]	female	58	body	solitary	NA
Layfield LJ *et al.*[21]	female	57	head	NA	NA
Tsitouridis I *et al.*[24]	male	69	Head, body, tail	multiple	Yes
Tsitouridis I *et al.*[24]	male	59	Head and tail	multiple	yes
DeWitt J *et al.*[32]	female	49	head	solitary	Yes
DeWitt J *et al.*[32]	female	75	head	solitary	Yes
DeWitt J *et al.*[32]	male	49	head	solitary	NA
DeWitt J *et al.*[32]	male	65	head	solitary	NA
Scatarige JC *et al.*[37]	male	48	head	solitary	Yes
Scatarige JC *et al.*[37]	female	68	Head and body	multiple	NA
Xi-wen S *et al.*[38]	male	74	body	solitary	Yes
Xi-wen S *et al.*[38]	male	50	NA	solitary	Yes
Xi-wen S *et al.*[38]	male	68	NA	solitary	Yes
Xi-wen S *et al.*[38]	male	52	NA	solitary	Yes
Xi-wen S *et al.*[38]	female	39	NA	solitary	Yes
Xi-wen S *et al.*[38]	male	53	NA	solitary	Yes
Xi-wen S *et al.*[38]	male	53	NA	multiple	Yes
Xi-wen S *et al.*[38]	male	76	NA	solitary	yes
Katsuura Y *et al.*[39]	male	83	body	solitary	Yes
Merkle EM *et al.*[62]	male	55	tail	solitary	NA
Das DK *et al.*[63]	male	66	tail	solitary	NA
Walshe T *et al.*[64]	female	60	neck	solitary	No
Boo SJ *et al.*[65]	male	44	head	NA	No
Boo SJ *et al.*[65]	male	75	head	NA	No
Boo SJ *et al.*[65]	male	61	head	NA	Yes
Ottaiano A *et al.*[66]	male	65	Head, body, tail	NA	No

NA = not available

Secondary tumours constitute 3-17% of all pancreatic tumours in clinical studies, but 43-65% in autopsy studies. The most common pattern for small cell lung cancer is a single localised mass in the head of the gland. The primary tumour is generally found in the left lung. Less than 15% of the patients had solitary pancreatic metastasis but other extensive disease. In spite of the advent of other imaging modalities, CT is still the gold standard for the evaluation of pancreatic pathology. In the patients

with jaundice, systemic chemotherapy might resolve the obstruction with symptomatic relief for the patient. Metastasis-induced acute pancreatitis can be a lethal event, and the diagnosis should be considered in any patient with known small cell carcinoma in whom an acute abdomen develops. Because of the aggressive nature of the tumour, all patients who had an appropriate performance status should receive systemic chemotherapy. The prognosis is better in patients with solitary pancreatic metastasis.

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research article

Consequence of the introduction of routine FCH PET/CT imaging for patients with prostate cancer: a dual centre survey

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Background. Fluorocholine(18F) (FCH) was introduced at the beginning of April 2010 in France, Slovenia and three other EU member states for the localisation of bone metastases of prostate cancer with PET. The aim of the study was to compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical FCH, observed in France and in Slovenia, and to quantify the consequence of the results of new imaging modality on the detection rate of abnormal metastases and recurrences of prostate cancer.

Patients and methods. In two centres (France/Slovenia), a survey of the number of nuclear medicine examinations in patients with prostate cancer was performed, covering 5 quarters of the year since the introduction of FCH. For each examination, the clinical and biological circumstances were recorded, as well as the detection of bone or soft tissue foci.

Results. Six hundred and eighty-eight nuclear medicine examinations were performed impatients with prostate cancer. Nuclear medicine examinations were performed for therapy monitoring and follow-up in 23% of cases. The number of FCH PET/CT grew rapidly between the 1st and 5th period of the observation (+220%), while the number of bone scintigraphies (BS) and fluoride(18F) PET/CTs decreased (-42% and -23% respectively). Fluorodeoxyglucose(18F) (FDG) PET/CT remained limited to few cases of castrate-resistant or metastatic prostate cancer in Paris. The proportion of negative results was significantly lower with FCH PET/CT (14%) than with BS (49%) or fluoride(18F) PET/CT (54%). For bone metastases, the detection rate was similar, but FCH PET/CT was performed on average at lower prostate-specific antigen (PSA) levels and was less frequently doubtful (4% *vs*. 28% for BS). FCH PET/CT also showed foci in prostatic bed (53% of cases) or in soft tissue (35% of cases).

Conclusions. A rapid development of FCH PET/CT was observed in both centres and led to a higher detection rate of prostate cancer lesions.

Key words: prostate cancer; PET/CT; fluorocholine (FCH); fluoride(18F); bone scintigraphy; indication of imaging

Introduction

Among nuclear medicine diagnostic procedures, four are currently routinely used in patients with prostate cancer: bone scintigraphy (BS); fluoride(18F) PET/CT; fluorodeoxyglucose(18F) (FDG) PET/CT; fluorocholine(18F) (FCH) PET/CT. There is a clear difference between BS and

TABLE 1. The two centres participating in the survey

Centre	Type	BS may be completed with	FNa PET/CT	FDG PET/CT	FCH PET/CT
France, Paris	Public university hospital	SPECT	since April 2008	since July 2004	since September 2004
Slovenia, Ljubljana	Public university hospital	SPECT/CT	Not available	since December 2009	since April 2010

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F); SPECT = single photon emission computed tomography

fluoride(18F) PET/CT which are suited only for the detection of bone metastasis, and FCH and FDG PET/CT which can also detect primary tumour and soft tissue lesions.

In France bisphosphonates (99mTc) were registered in 1992, FDG in 1998, fluoride(18F) in 2008 and FCH (IasoCholine, IASON, Graz, Austria) become available in 2010. We published a survey that showed the shift in the prescription of nuclear medicine imaging favouring FCH PET/CT at Hospital Tenon in Paris, after its registration.[1] All those radiopharmaceuticals have marketing authorisation and are available for the routine use also in five other EU member states: Austria, France, Germany, Poland and Slovenia.

The aim of the present article is to compare the evolution of diagnostic imaging in patients with prostate cancer using a new radiopharmaceutical FCH observed in France (Paris, Hospital Tenon), with evolution of corresponding imaging in an Central European country (Slovenia, University Medical Centre Ljubljana), and to quantify the consequence of the results of new imaging modality on the detection rate of metastases and recurrence of prostate cancer.

Patients and methods

Centres and data collection

Covering a period from 2nd April 2010 to 1st July 2011 (both included), *i.e.* 5 quarters, in two nuclear medicine centres (Table 1), the data base includes: the age of the patient; the type of nuclear medicine examination; the indication: initial staging, follow-up during or just after treatment, restaging (of a known recurrence), or occult biological recurrence; the total number of previous nuclear medicine

TABLE 2. Evolution of the number of examinations per quarter in Paris

	1st quarter	2nd quarter	3rd quarter	4th quarter	5th quarter	Total 1st-5th quarters
BS	20 (28%)	20 (22%)	24 (26%)	25 (28%)	14 (16%)	103
FNa PET/CT	35 (49%)	31 (34%)	39 (42%)	17 (19%)	24 (29%)	146
FDG PET/CT	8 (11%)	6 (7%)	6 (6%)	7 (8%)	7 (8%)	34
FCH PET/CT	8 (11%)	33 (37%)	24 (26%)	41 (46%)	39 (46%)	145
Total (100%)	71	90	93	90	84	428

BS = bone scintigraphy; FNa = fluoride(18F); FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F)

TABLE 3. Evolution of the number of examinations per quarter in Ljubljana

	1st quarter	2nd quarter	3rd quarter	4th quarter	5th quarter	Total 1st-5th quarters
BS	6 (21%)	8 (19%)	6 (9%)	8 (13%)	1 (2%)	29
FDG PET/CT	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1
FCH PET/CT	23 (79%)	35 (81%)	58 (89%)	54 (87%)	60 (98%)	230
Total (100%)	29	43	65	62	61	260

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F)

examinations; a quotation of the result of each examination performed by two independent nuclear medicine specialists experienced in the 4 types of examinations (S.B. and M.V.) from the images and the report: negative, doubt for bone metastasis, highly evocative of bone metastasis, focus (foci) in the prostatic bed, doubtful soft tissue focus or foci, highly evocative of soft tissue metastasis. For one abnormal examination, several categories could thus be quoted.

In some cases, there were also available: the serum prostate-specific antigen (PSA) levels (ng/mL) at the time of the nuclear medicine examination (502 cases); the initial Gleason score (361 cases); and both: PSA level and Gleason score (299 cases). The investigators followed recommendations of the Helsinki Declaration. The study protocol was approved by the ethic committees of both participating centres.

Data processing and statistics

The number of examinations performed in patients with prostate cancer disease was determined for each of the 4 nuclear medicine examinations, for each quarter and for each centre. The comparison of the 1st and 5th quarter is of particular interest; since they correspond to the same months (April to June) of 2 consecutive years (2010 and 2011) avoiding the consequences of an influence of the season (feasts, vacations…) on the number of prescribed nuclear medicine examinations. Those proportions were compared using chi-square test.

Differences in age, serum PSA levels, and Gleason score between the patients, according to the prescribed nuclear medicine examination, were tested by Kruskal-Wallis test. In case only two alternatives exist, the Mann-Whitney test was used. In patients who benefited from several nuclear medicine examinations during the survey period, the number, the type and the sequence of the prescribed examinations were reported and analysed.

Results

Evolution of the prescription of nuclear medicine examinations

Overall, 688 nuclear medicine examinations were performed in 577 patients with prostate cancer during the survey period. In Paris, the most frequently prescribed examination was fluoride(18F) PET/CT (147 cases), very close to FCH PET/CT (145 cases), then BS (103 cases) and finally FDG PET/CT (34 cases) mostly prescribed in case of advanced cancer, with frequent repetition in the same patient during the survey period. During the same period of time, a total of 951 BS and 3896 whole-body PET/CT were performed in this centre: prostate cancer was the indication of 103 out of 951 BS (10.8%) and in 326 out of 3896 PET/CT (8.4%). The ratio of BS in patients with prostate cancer disease decreased from 15% in the 1st quarter to 6% in the 5th quarter. Conversely, PET/CT examinations in patients with prostate cancer increased from 6% in the 1st quarter to 9% in the 5th quarter (Table 2).

In Ljubljana, fluoride(18F) PET/CT was not available and the most frequently prescribed examination in patients with prostate cancer was FCH PET/CT (230 cases), BS (29 cases) and FDG PET/CT (1 case). During the same period of time, a total of 1757 BS and 2069 PET/CT were performed in this centre: prostate cancer was the indication in 29 out of 1757 BS (1.7%) and in 213 out of 2069 PET/CT (10.3%) (Table 3).

Tables 2 and 3 illustrate the evolution of the prescribed nuclear medicine examination during the 5 successive quarters in each centre. The chi-square test is very significant ($p << 0.001$): there was an increase in the proportion of FCH PET/CT with time, and a decrease in the proportion of BS in both centres and also of fluoride(18F) PET/CT in Paris.

Multiple nuclear medicine examinations in the same patient during the survey period

Sixty-seven patients had multiple nuclear medicine examinations, ranging between 2 and 11 examinations per patient (in Ljubljana, a maximum of 2 examinations were performed for one single patient during the 5 quarters).

The main prescription patterns were:

a) 2 or 3 examinations of the same type in the mentioned interval: BS in 2 patients, fluoride(18F) PET/CT in 3 patients, FDG PET/CT in 1 patient, FCH PET/CT in 8 patients.
b) 2 examinations of different type within less than one month: fluoride(18F) PET/CT and FCH PET/CT in 3 patients, fluoride(18F) PET/CT and FDG PET/CT in 1 patient and, most frequently in Ljubljana, BS and then FCH PET/CT in 19 patients, the reverse in only 1 patient.
c) a shift to another type of examination prescribed on the next visit, after several months: fluoride(18F) PET/CT to FCH PET/CT in 4 pa-

TABLE 4. Indication of the nuclear medicine examination

Indication	Initial	Follow-up	Restaging	Occult recurrence	All indications
BS	60	26	22	24	132
FNa PET/CT	77	27	18	24	146
FDG PET/CT	2	17	14	2	35
FCH PET/CT	97	85	54	139	375
All examinations	236	155	108	189	688

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F); SPECT = single photon emission computed tomography

TABLE 5. Examination-based interpretation. For both "bone" and "soft tissue" "doubt" was only quoted if no focus evocative of malignancy was observed. % correspond to the frequency of this interpretation for each modality; since fluorodeoxyglucose(18F) (FDG) PET/CT and fluorocholine(18F) (FCH) PET/CT can detect foci in the prostatic bed, the soft tissue and the skeleton, the total is greater than 100%

Interpretation	Number of examinations	Negative	Doubt bone	Bone metastasis	Prostate focus	Doubt soft tissue	Malignant soft tissue
BS	132	65 (49%)	37 (28%)	30 (23%)	0	0	0
FNa PET/CT	146	79 (54%)	32 (22%)	35 (24%)	0	0	1 (1%)
FDG PET/CT	35	2 (3%)	1 (3%)	29 (83%)	1 (3%)	3 (9%)	8 (23%)
FCH PET/CT	375	52 (14%)	15 (4%)	86 (23%)	198 (53%)	21 (6%)	132 (35%)

BS = bone scintigraphy; FCH = fluorocholine(18F); FDG = fluorodeoxyglucose(18F); FNa = fluoride(18F)

tients, fluoride(18F) PET/CT to FDG PET/CT in 1 patient, FCH PET/CT to FDG PET/CT in 2 patients, BS to FCH PET/CT in 13 patients, BS to fluoride(18F) PET/CT in 1 patient.

d) at least 3 different types of examination repeated within the survey period in 8 patients.

Clinical context

Mean age of patients included in the study was 68.4 years (range 45-97 years). As expected, there was a significant difference in age according to the indication of the nuclear medicine examination. The patients being referred for initial staging being younger (mean age 67.2 years) and the patients referred for occult recurrence older (mean age 69.8 years) (p=0.01).

The choice of the nuclear medicine examination was in relation with the indication (p <<0.001) (Table 4). BS and fluoride(18F) PET/CT were performed more frequently for the initial staging, while FCH PET/CT was performed in almost half of the cases for an occult recurrence. As already mentioned, FDG PET/CT was mostly used for therapy follow-up or restaging of advanced castration-resistant forms.

In accordance, the number of previous nuclear medicine examinations performed in the patient and recorded by the centre was significantly greater when FDG PET/CT was requested. The mean number of previous examinations was 0.4 when BS was prescribed, 0.8 when fluoride(18F) PET/CT was prescribed, 0.7 when FCH PET/CT was prescribed *vs*. 4.8 for FDG PET/CT.

Biological context

A significant relation was observed between the PSA serum levels and the type of the prescribed nuclear medicine examination (p<<0.001). The mean PSA level was 26 ng/ml when FCH PET/CT was prescribed, 24 ng/ml in case of FDG PET/CT, 74 ng/ml in case of fluoride(18F) PET/CT and 175 ng/ml when the patient was referred for BS. The difference in PSA levels according to the indication did not reach the level of significance. The initial Gleason score of the patients referred for FDG PET/CT (mean 8.4) was significantly greater than

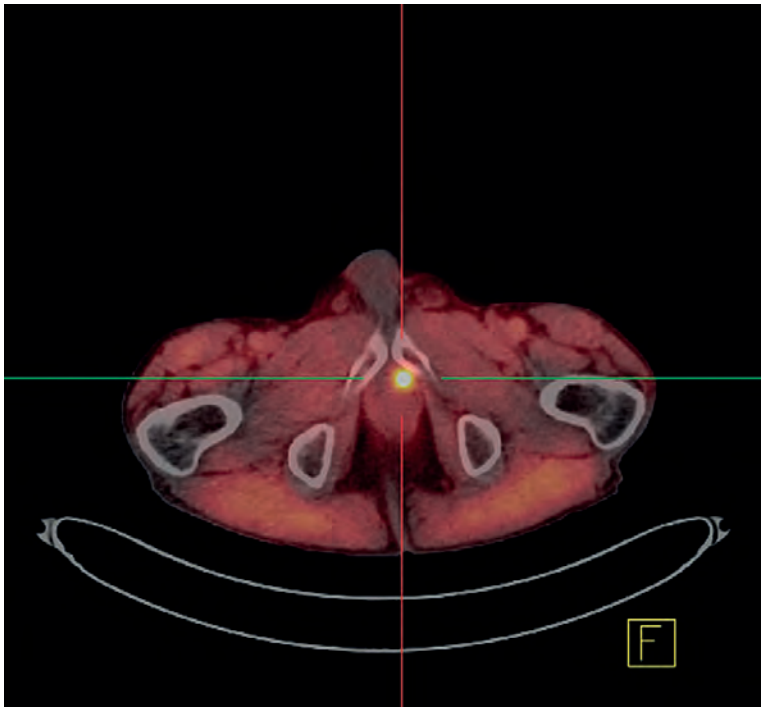

FIGURE 1. FCH PET/CT: Local recurrence of prostate cancer after radical prostatectomy (Gleason score 8, [PSA] 0.2 ng/ml).

that of patients referred for all other examinations (mean 7.4 for BS, 7.6 for fluoride(18F) PET/CT and 7.3 for FCH PET/CT); it was also higher in patients referred for the treatment follow-up (mean 7.8) or restaging (mean 7.8) than in case of initial staging (mean 7.4) or occult recurrence (mean 7.2).

Nuclear medicine examination report: normal, positive, doubtful

Table 5 illustrates the result of the report summarized on an examination-based manner, according to the findings and the type of nuclear medicine examination. BS or fluoride(18F) PET/CT was interpreted as normal in around one half of cases, without difference in the distribution of the "positive" and "doubtful" conclusions (on a per-examination level) between those two modalities. In one patient, a large lymph node took-up fluoride(18F).

FDG PET/CT results favoured bone metastases in 85% of patients and less frequently reported soft tissue foci evocative of malignancy. This does not mean that FDG is better than fluoride(18F) or FCH to detect bone metastases but, in accordance with previous results, that FDG PET/CT was prescribed in patients with advanced forms of the disease, mostly castration-resistant and metastatic to the skeleton, for restaging or chemotherapy monitoring.

FCH PET/CT was abnormal in 86% of patients and doubtful in a small minority of the examinations. It showed the primary tumour or a local recurrence in the prostatic bed in about half of the patients (Figure 1), foci suspicious for soft tissue malignancy in about one third, and also foci evocative of bone metastases, in a proportion of patients (23%) similar to that of BS or fluoride(18F) PET/CT ($p>0.9$), but with significantly less doubtful cases ($p< 0.001$) (Figure 2).

Reporting can also be analysed according to the indication of nuclear medicine imaging. As already mentioned, FDG PET/CT was most frequently prescribed for restaging and follow-up of response to treatment, in patients whose advanced prostate cancer was already known to be metastatic. In this context, the metastatic spread, in particular to the skeleton, was visible on FDG PET/CT in 97% of cases.

In the search for bone metastases, no difference in the frequency of detection was found according to the indication with BS while fluoride(18F) PET/CT and FCH PET/CT showed more frequently suspicious bone foci when performed for restaging or treatment follow-up, probably in relation with already known metastatic dissemination in those patients. The frequency of detection of suspicious bone foci in patients with a Gleason score less than or equal to 7, was 5% for BS, 8% for fluoride(18F) and 12% for FCH, in patients with a Gleason score greater than or equal to 8, the corresponding values were 35%, 23%, and 32% (the difference was significant for BS and FCH PET/CT).

Searching for malignant deposits in soft tissue, FCH PET/CT was more frequently positive in patients referred for restaging or occult recurrence than at initial staging ($p<0.01$). The detection rate of suspicious soft tissue foci was 27% in patients with a Gleason score less than or equal to 7, *vs*. 31% in patients with a Gleason score greater than or equal to 8 ($p > 0.6$).

In our centres, some examinations were performed at initial staging in patients who did not fulfil accepted criteria to refer patients at initial staging to nuclear medicine imaging, *i.e*. PSA levels less than or equal to 10 ng/ml and Gleason score less than 8. They corresponded to 36 of the 132 examinations (27%) performed for initial staging in patients whose PSA serum levels and Gleason score were mentioned on the prescription.

In case of biochemical recurrence following prostatectomy, the NCCN Guidelines mention a

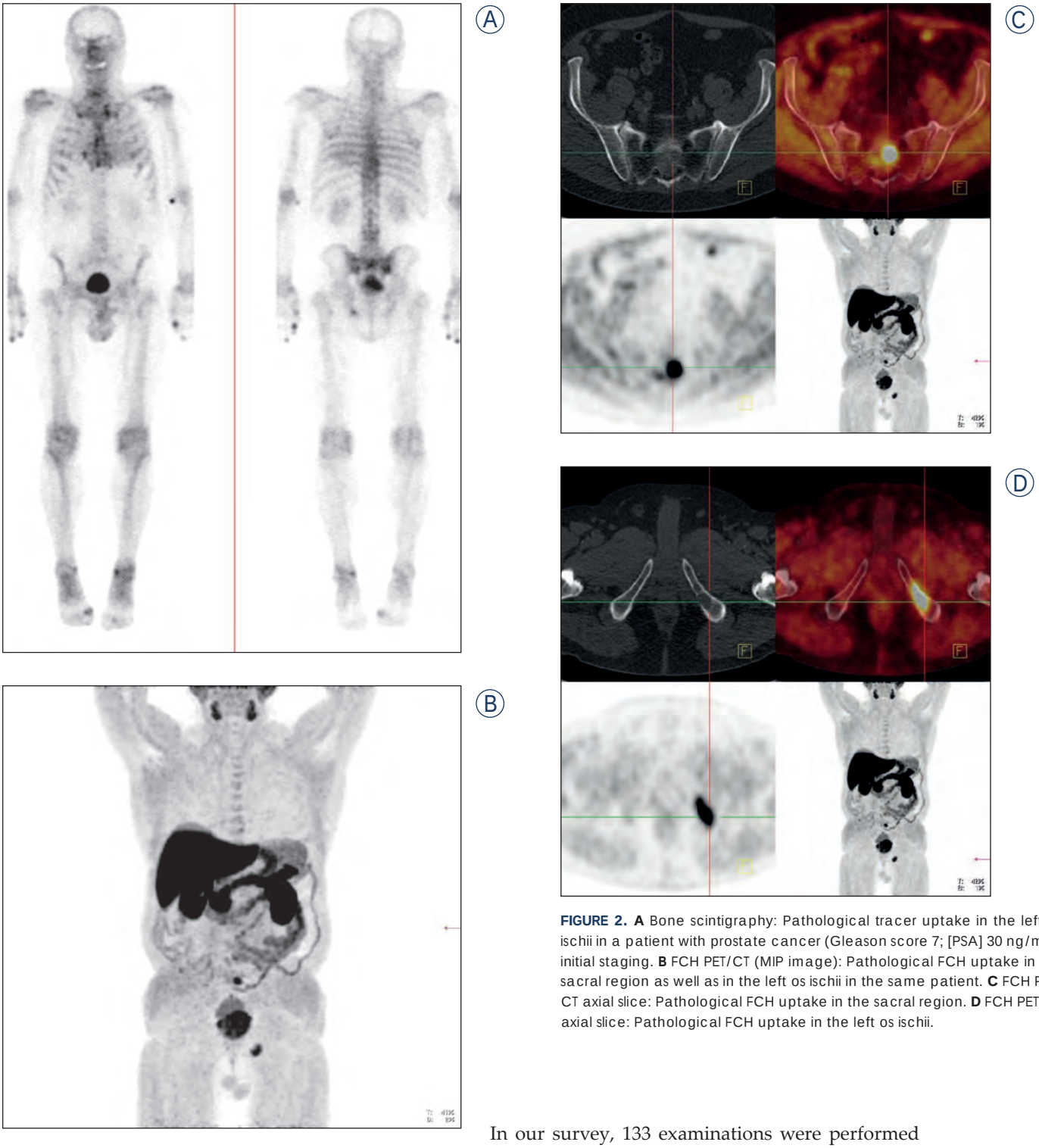

FIGURE 2. A Bone scintigraphy: Pathological tracer uptake in the left os ischii in a patient with prostate cancer (Gleason score 7; [PSA] 30 ng/ml) – initial staging. **B** FCH PET/CT (MIP image): Pathological FCH uptake in the sacral region as well as in the left os ischii in the same patient. **C** FCH PET/CT axial slice: Pathological FCH uptake in the sacral region. **D** FCH PET/CT axial slice: Pathological FCH uptake in the left os ischii.

potential indication for BS without precise target PSA value. NCCN Guidelines also recommends BS in case of post-irradiation recurrence in patients who are considered candidates for local therapy, with PSA less than 10 ng/ml among other criteria.[2]

In our survey, 133 examinations were performed for restaging or detection of occult recurrence in patients with PSA levels less than 10 ng/ml. Foci suspicious to correspond to malignant tissue out of the prostatic bed were reported in 1 out of 10 BS, 2 out of 15 fluoride(18F) PET/CT, 1 out of 1 FDG PET/CT and 50 out of 117 FCH PET/CT. This very significant superiority of FCH PET/CT over bone nu-

clear medicine imaging ($p<0.01$) is due to its ability to detect soft tissue lesions as well as bone lesions. In those patients, FCH PET/CT also showed foci in the prostatic bed suspicious for local recurrence in 41 cases (35%). In this context of recurrent disease, FCH PET/CT was prescribed in 23 patients with PSA levels < 2 ng/ml and initial Gleason score less than or equal to 7: its detection rate (including local recurrence) was still 35%.

Discussion

As its first result, this dual centre study confirms, in two independent nuclear medicine centres, the rapid rise in the demand for FCH PET/CT, as soon as FCH was registered.[1] At the same time, there was a marked decline in the prescription of BS in patients with prostate cancer. This shift was associated with a rise of the total number of prostate cancer patients referred for nuclear medicine examinations. The transfer of prescription to FCH PET/CT was more progressive in Paris than in Ljubljana. Bone PET/CT with fluoride(18F) has been available in Paris for one year and a half when FCH was registered, yielding images with PET quality and a superior resolution as compared to BS or bone single photon emission computed tomography (SPECT). Even for the most informed prescribers, the introduction of FCH meant two successive shifts in a limited period of time. Another reason can be the relation with the environment. The Paris area has 11.7 millions inhabitants and 42 nuclear medicine centres, 20 of which are equipped with PET/CT, which means a rather large resource for the prescriber, while Slovenia has 2 million inhabitants, 7 nuclear medicine centres and 2 PET/CT centres (FCH is being performed in one), which probably enables a more rapid diffusion of new PET imaging modalities.

The other aim of this survey was to record the detection of abnormal foci by the available nuclear medicine examinations, but not to compare their performance according to a standard of truth. Actually most patients only had one examination, and head to head comparison of results, according to the imaging modality, is not possible. Nevertheless, it is of importance to check how this concordant and rapid evolution in Paris and Ljubljana is based on evidence and matches results obtained in other centres.

The initial shift from BS to bone PET/CT with fluoride(18F), which has been observed in Paris[1], is in agreement with the results of the comparative study of Even-Sapir *et al*., in 44 patients with a high-risk prostate cancer.[3] Fluoride(18F) PET/CT was statistically more sensitive and more specific than planar BS or bone SPECT ($p < 0.05$). In our survey, the majority of fluoride(18F) PET/CT has been performed to search for bone metastases at initial staging, to profit from the better sensitivity. The advantage of fluoride(18F) PET/CT over BS and bone SPECT was not so obvious when examining reporting of examinations (Table 5) because fluoride(18F) PET/CT mostly results in the detection of a greater number of bone lesions as compared to BS, while the analysis of our results was based on a per-patient level rather than a per-lesion level. The further shift from fluoride(18F) to FCH as the PET/CT tracer to detect bone metastases is evaluated by the comparative studies from the team in Linz in co-operation with our team in Paris.[4] In this study, there was no significant difference in sensitivity between the two PET tracers, but FCH was significantly more specific on a lesion-based analysis. In the present survey, the use of FCH instead of BS, bone SPECT or fluoride(18F) PET/CT resulted in a similar proportion of examinations interpreted as positive for bone metastases, and in a decrease in the frequency of doubtful reports: in contrast with bisphosponate (99mTc) or fluoride(18F), FCH is not taken-up by non-inflammatory degenerative changes in the skeleton and its interpretation is more straightforward.[5]

Concerning the detection of lesions in the prostatic bed, locoregional lymph nodes and distant soft tissue, FCH is in competition with FDG. FDG has a low diagnostic performance in the general population of prostate cancer patients, but may be of interest in case of aggressive or castration-resistant prostate cancer. The analysis of the US national oncologic PET registry for the first 2 years of data by Hillner *et al*. revealed that, from 40,863 PET scans, prostate cancer was the most frequent indication corresponding to 5,309 FDG examinations, with change in management in 35% of cases.[6] However, also FCH is taken-up by androgen-independent prostate cancer, as showed as early as 2002 by Price *et al*. in 9 patients[7] and confirmed recently by Mc Carthy *et al*., in 26 patients.[8] In the present survey, FDG PET/CT was performed, in Paris only, in a very limited number of patients with a high Gleason score, to restage a known recurrence and to monitor therapy of metastatic forms, when restaging FCH PET/CT was positive. The prescription of FDG PET/CT in prostate cancer was not increasing with time, in contrast with that of FCH PET/CT.

The utility of FCH PET/CT to detect recurrent prostate cancer has been demonstrated by several teams since 2005[9], a special attention being paid to the rate of positive examinations according to PSA levels[10-14] or PSA doubling time or velocity[15,16], or initial Gleason score.[11] In our survey, 51% of the FCH PET/CT was performed for restaging a known recurrence or localising an occult biological recurrence. The reported relation between the frequency of positivity and PSA levels and the initial Gleason score has been observed in our series. However, FCH PET/CT detected suspicious foci in 35% of patients with PSA levels < 2 ng/mL and initial Gleason score less than or equal to 7. According to Pelosi *et al*., its detection rate was still 20% when PSA levels were < 1 ng/ml.[13] Even though FCH is for the moment only registered for the detection of bone metastases, it is also able to detect local recurrences (Figure 1) and locoregional lymph node metastases.

The utility of FCH PET/CT in the initial staging of prostate cancer has been addressed by Beheshti *et al*.[17] In this context, FCH PET/CT has limited value in the detection of malignant lymph nodes especially when smaller than 5 mm, but it led to changes in the therapeutic management of 20% of prostate cancer patients at a high risk for extracapsular disease, suggesting that it will be helpful in triaging care of this type of patient cohort. Patient-based sensitivity was 73% and specificity 88% in 210 intermediate or high-risk patients showing FCH PET/CT to be effective to detect N+ patients.[18] In our survey, 26% of the FCH PET/CT were performed at initial staging and not only visualised the primary cancer but also detected suspicious foci in soft tissue or in the skeleton in 31% of patients (Table 5). A recent study confirmed that, at staging, when PSA levels (> 20 ng/l) and/or Gleason score (8-10) are high, both FCH and fluoride(18F) PET/CT were effective and impacted on the treatment plan for 20% of the patients.[19] Should the classical criteria recommended for performing BS, *i.e*. PSA levels greater than or equal to 10 ng/ml or Gleason score of at least 8, also apply to PET/CT?[20] In our series, its yield was actually rather low when those criteria were not met: 2 cases of extraprostatic foci in 14 examinations. In the survey of Lavery *et al*. "overuse" of BS in patients who did not fulfil somewhat less though criteria (a Gleason score of 7 was accepted for indication) occurred in 241 of 667 preoperative imaging examinations (36%); BS were read as positive in 21 cases (9%) which all corresponded to false-positive results.[21] When the criteria used by Lavery *et al*.[21] were applied to examinations performed in our series at initial staging, only 20% of BS, 15% of fluoride(18F) PET/CT and 7% FCH PET/CT should not have been performed, but their yield was even lower than with "classical" criteria: positivity was reported in none of the BS, 1 fluoride(18F) PET/CT and 1 FCH PET/CT. Thus, in staging prostate cancer, the overuse of nuclear medicine imaging was less frequent in Paris and Ljubljana than the overuse of BS in New York, but our survey confirms that its yield is low when the criteria are not fulfilled, even by using FCH PET/CT which is more expensive than BS.

Another interesting result of the present survey was the rather frequent indication of nuclear medicine examinations in the follow-up of therapy: 23% of the examinations. In this indication, FCH PET/CT has an important advantage over BS and fluoride(18F) PET/CT which are limited to the monitoring of bone lesions. Even for monitoring the metabolic response of bone metastases to therapy, FCH has the advantage to show the viable prostate cancer tissue while BS and fluoride(18F) PET/CT show the reaction of the normal cortical bone to the insult by the metastatic tissue. This difference in the mechanism of functional imaging explains the "bone flare phenomenon" observed on BS at the beginning of an active hormone therapy, which has even been proposed as a criterion to improve both sensitivity and specificity of BS in prostate cancer.[22] In the evaluation of new therapeutic agents such as abiraterone, the effect of BS flare on the patient management and interpretation of results is clearly "confounding".[23] Nevertheless, NCCN recommends that patients treated with abiraterone or cabazitaxel with prednisone, must be monitored closely, in particular with BS, for evidence of progression.[2] We foresee from the present survey that the application of FCH PET/CT to treatment monitoring will develop when this examination will become more widely available.

Conclusions

In two PET centres of public hospitals of two EU member states, with a rather different context, the introduction of FCH PET/CT led to a rapid increase in its use, with a concomitant decrease in the number of nuclear medicine examinations devoted to the detection of bone metastases, but with an increase in the overall part of prostate cancer in nuclear medicine diagnostic practice: +24% in Paris and +100% in Ljubljana within one year. This shift for FCH PET/CT resulted in a greater proportion

of positive examinations. Given the trend that was observed in our survey, it seems likely that FCH PET/CT will become the first line nuclear medicine examination in patients with prostate cancer disease. As prostate cancer is a frequent malignancy and the number of PET/CT machines is not sufficient in France and in Slovenia, more evidence-based criteria for its indication will be needed. It appears important that the referring physician mentions the initial Gleason score, the current PSA serum level, the recent evaluation of PSA level and all the therapeutic modalities. In our survey, the PSA levels and the Gleason score were available in only 43% of the prescriptions. According to our results, the criteria for referring patients at initial staging to BS appear to be suited for fluoride(18F) or FCH PET/CT. In contrast, the criteria for referring patients to BS in case of recurrent prostate cancer cannot apply to FCH PET/CT, which is more sensitive and specific and is also able to detect local recurrence and soft tissue invasion. The kinetics of variation of PSA levels may offer the best criteria in this context. FCH still lacks registration in the detection of prostate cancer in soft tissue as well as for therapy monitoring. It is unclear whether FDG will still have a role to play in the restaging and therapy monitoring of advanced forms of prostate cancer if FCH would be registered in those settings.

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research article

The role of ultrasound and ultrasound-guided fine needle aspiration biopsy of lymph nodes in patients with skin tumours

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Background. The primary aim of this study was to evaluate the diagnostic accuracy of ultrasound (US) in the study of superficial lymph nodes during the follow-up of patients surgically treated for skin tumours. The secondary objective was to compare positive cytological results with histological reports.

Patients and methods. From 2004 to 2011, 480 patients (male/female: 285/195; median age 57 years; prevalent skin tumour: melanoma) underwent US-guided fine-needle aspiration biopsy (FNAB) of suspicious recurrent lymph nodes. An expert radiologist first performed US testing of the lymph nodes, expressing either a negative or positive outcome of the test. Subsequently, US-guided FNAB was performed. FNAB positive patients were subjected to lymphadenectomy; the patients who tested negative underwent the follow-up.

Results. The size of lymph nodes was ≤ 2 cm in 90% of cases. Out of the 336 (70%) US "positive" patients, 231 (68.8%) were FNAB positives. Out of the 144 (30%) US "negatives", 132 (91.7%) were FNAB negatives. The sensitivity and specificity of the US were 95% and 55.7%, respectively; the negative predictive value was 91.7% and the positive predictive value was 68.8%. Definitive histological results confirmed FNAB positivity in 97.5% of lymphadenectomies.

Conclusions. US is a sensitive method in the evaluation of superficial lymph nodes during the follow-up of patients with skin tumours. High positive predictive value of cytology was confirmed.

Key words: skin tumours; ultrasound; fine needle aspiration biopsy, follow-up

Introduction

Ultrasound (US) still represents the main method for evaluating superficial lymph nodes in skin cancers, especially in cutaneous melanoma.[1,2]

Specifically, US is the preferred technique in determining superficial lymph node metastases, during the follow-up of patients with melanoma.[3] In fact, US has proved to be superior to clinical examination in identifying lymph node metastases.[4,5] Moreover, a recent meta-analysis has demonstrated that US examination is superior to other imaging techniques as computerized tomography (CT) and positron emission tomography (PET) in identifying secondary localizations in superficial lymph nodes.[6]

Although there is no general consensus on the utility and management of the follow-up of patients with cutaneous melanoma, the issue has been widely debated in literature.[3,7-9] As there are no large-scale prospective studies[10], some authors have even questioned the clinical efficacy

of follow-up; as a matter of fact no evidence of prognostic advantage in terms of life expectancy nor improvement in the quality of life was reported.[8,9] Nevertheless, many authors agree to plan frequent and long-term clinical checks, possibly associated with the use of US and other imaging techniques.[3,11-13] While there are many studies on the use of US in lymph node pre-surgery stage of melanoma and in the identification of the sentinel lymph node[6,14,15], there are relatively few studies on the diagnostic role of US as compared to fine-needle aspiration biopsy (FNAB) and the value of US-guided FNAB in the assessment of lymph node metastases from skin cancers during the follow-up.[16,17]

The aim of this study was to evaluate the diagnostic accuracy of US in the assessment of superficial lymph nodes, as compared to FNAB during the follow-up of patients previously surgically treated for skin tumours. The secondary aim was to evaluate the correlation between FNAB and the respective histology report in the subgroup of patients with a positive cytopathology result who subsequently underwent lymphadenectomy.

Patients and methods

Study population

All the patients in the follow-up at our institute (IRCCS San Gallicano Dermatological Institute, Rome, Italy), surgically treated for skin cancers and referred to the Radiology Service for US-guided FNAB of superficial lymph nodes, were considered eligible for the study. From January 2004 to January 2011, 480 patients underwent US-guided FNAB of superficial lymph nodes due to clinical evidence of enlarged lymph nodes or with US pattern suspected for metastasis. The population was characterized by a prevalence of males (1.46 male/female ratio) and by a median age of 57 years (range of 22–84 years). The prevalent skin tumour was melanoma (85%) of pathological stage I/II (Breslow thickness ≤ 1 mm, $N = 327$; 1.01–2.00 mm, $N = 65$; 2.01–4 mm, $N = 16$). A sentinel lymph node biopsy was performed in 19.8% of patients with melanoma ($N = 81$); the histological examination was negative in 56 patients and positive in the remaining 25.

The median time interval between the excision of the skin cancer and emergence of suspicious lymph node was 13 months (range of 12–16 months) (Table 1). Relevant medical history and clinical data of the patients were collected in a data sheet upon enrolment in the study (age, sex, ethnic group, weight, date of cutaneous neoplasm excision, and histology type). All instrumental examinations were performed by the same operator (FMS), a radiologist with 30 years of experience (about 2500 US examinations yearly performed in patients affected by dermatologic diseases). The operator performed a preliminary US evaluation of the lymph node concerned, with a yes/no assessment – negative or positive to the test – according to the detailed criteria in the following Ultrasound Image Analysis section; all data were reported on a specific data sheet. The FNAB examination was subsequently performed and the cytological specimens sent to the pathologist for cytological examination. In the case of inadequate material, the FNAB was repeated (7-10 days after the first examination). In the cases testing negative for neoplastic cells checks were performed to ensure that the cytological specimen contained a sufficient quantity of lymphocytes; sampling was repeated in the event of an insufficient quantity of cellular elements. All patients with a positive cytology report underwent surgical excision of the lymph node concerned and the related histology reports were acquired and used as standard for the comparison. All patients that tested negative to the cytological examination underwent clinical and instrumental monitoring in accordance with the Institute's follow-up protocol.

Ultrasound image analysis

US examinations were performed with a MyLab 70 XVC US system (Esaote s.p.a., Genoa, Italy) utilizing a LA 435 linear sensor, with frequency of between 6 and 18 MHz, or LA 523 (4-13 MHz). The examined lymph node was classified "negative" or "positive" on the basis of the radiologist's opinion considering the US features.[18] Specifically, lymph nodes that possessed at least one of the following characteristics were classified as "positive": 1) round morphology (relation between the axial and longitudinal diameters < 2 in normal lymph nodes); 2) absence, attenuation or dislocation of the chillum; 3) eccentric cortical thickening or alteration of the contour of the lymph node; 4) lack of homogeneity in the cortical structure; 5) extracapsular extension; 6) one or more of the following vascular patterns: a) decrease in global vascularisation; b) cortical vascular structures of irregular calibre with a sharp interruption, tangential to the chillum rather than radial; c) absence of vascularisation in the chillum; d) the presence of peripheral vascular structures which penetrate into the cortical; e) highly or moderately resistant arterial signs

or signs of a grossly altered morphology.[14,18,19] In the absence of the above mentioned characteristics, the examination was classified as "negative".

FNAB, cytological and histological examination

The FNAB procedure was US-guided, with suitable settings for needle-tip identification. The freehand sampling technique was used, without any type of mechanical guidance. On average, the procedure took five-ten minutes subsequent to completion of the informed consent process, examination of previous imaging documentation and positioning of the patient on the bed. Position of the needle inside the target lesion was documented with imaging. Chiba-type needles were used, of a length between 17 and 60 mm, of variable calibre between 19 and 25 G, based on the operator's choice, with overall prevalence of 23 G. Sampling was nearly always capillary (98%), hardly ever applying a significant depression, either mechanical or with a syringe. Two samplings from two different areas of the same lymph node were usually carried out; three samplings were done in 50 cases and only one sampling in 22 cases, as the material obtained was sufficient for diagnostic purposes. The material obtained from the FNAB was treated according to two different methods: a) smeared on clean glass slide and fixed with an alcohol-based spray (until 2009); b) directly treated in liquid solution (PreservCyt®) (from 2009 onwards). The samples were sent to the Pathologic Anatomy Laboratory of I.F.O., where they were prepared according to the ThinPrep Pap Test (Thin-Prep®).[20] All the cytology slides were stained using the Papanicolaou technique.

FNABs were considered adequate in presence of at least six groups of cells, each including 10-15 cells obtained from two aspirations of one lymph-node.

In the case of uncertain cytomorphology, immunocytochemical staining was carried out in order to reach a conclusive diagnosis. Specifically, paraffin-imbedded sections on glass slides were stained for HMB-45, MART-1, S100b protein markers in the case of suspected melanoma. In the case of suspected carcinoma metastasis, cytokeratin staining was performed.

The samples indicating massive necrosis, but in the absence of readable cells (2% of the cohort), were considered suspicious and were sent for surgical resection. The cases cytologically assessed as suspicious for cancer were considered positive for statistical purposes. The material obtained through surgical biopsy was fixed in formalin and included in paraffin; the 3-μm sections were stained with standard haematoxylin and eosin. In many cases, the histological diagnosis was backed up by immunohistochemical staining in order to clarify uncertain histomorphology.

TABLE 1. Patient characteristics (N = 480), tumour histotype and time interval between procedures

Age (years) – median (range)	57 (22–84)
Gender – no. (%)	
Male	285 (59.4)
Female	195 (40.6)
Weight (kg) – median (range)	72 (52–98)
Race or ethnic group – no. (%)	
White	453 (94.4)
Black	2 (0.4)
Other	25 (5.2)
Histotype– no. (%)	
Melanoma	408 (85)
Squamous Cell Carcinoma(SCC)	57 (11.8)
Other	15 (3.2)
Time interval between first surgical procedure and US (months)	
Median (range)	13 (10–15)

TABLE 2. Lymph-node characteristics (N = 480)

Lymph- node sites	
Axilla	192 (40%)
Inguinal Area	192 (40%)
Others	
(neck, popliteal and clavicular fossa)	96 (20%)
Lymph- node Size	
> 2 cm	48 (10 %)
1.5–2 cm	303 (63.1%)
< 1.5 cm	129 (26.9%)

Statistical analysis

Continuous data were described with the mean or median value and the range; categorical data were presented with the frequency. The diagnostic accuracy of US was defined by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (PNV). Graph-Pad 5 software (GraphPad Co. La Jolla, CA-USA) was used to analyse statistical data.

TABLE 3. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ultrasound vs. fine-needle aspiration biopsy

Imaging method	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)
US	55.7	95	68.75	91.7

Results

Ninety percent of patients presented lymph nodes of ≤ 2 cm in size at US examination; in 129 of them the size was < 1.5 cm (Table 2). The prevalent lymph nodal stations were the axillary and inguinal (40 % in both cases). Of the 480 patients included in the study (Figure 1), 336 (70%) presented features suggesting recurrence (US+) at the US examination; in the remaining 144 patients (30%) the US pattern appeared non-suspicious, suggesting a reactive or inflammatory lymphadenopathy (US-). The absence, attenuation or dislocation of the chillum was the most frequent characteristic among positive lymph nodes; the round morphology of lymph nodes was the most important prognostic factor for the metastatic involvement.

The FNAB examination produced adequate cell material in nearly all cases - in 5 cases inadequate material at the first sampling made it necessary the repetition of the procedure, none at the second sampling. Neither complications nor significant sequel were reported. Upon cytological verification, 231 (68.8%) of the 336 US+ classified cases received confirmation and, therefore, represent the "true positives" (TP) for the test, whereas the remaining 105 (31.2%) with negative cytological reports, represent the "false positives" (FP). In the group of the 144 US- classified patients, 132 (91.7%) tested negative for neoplasm upon cytological examination and 12 (8.3%) tested positive, therefore representing the US "true negatives" (TN) and US "false negatives" (FN), respectively. According to these results, the sensitivity of US compared to cytological examination is 95%, with a specificity of 55.7%; the negative predictive value and the positive predictive value are equal to 91.7% and 68.8% respectively (Table 3).

FNAB positive patients (N = 243–231 US TP and 12 US FN) underwent surgical exeresis of the lymph node; definitive histological and cytological results were eventually compared. Of these, 237 (97.5%) received confirmation from the definitive histological examination, whereas in 6 cases (2.5%) the definitive histological examination resulted negative for neoplasm. Specifically, in the US- and FNAB+ cases, the histological examination highlighted the presence of micrometastases or isolated tumour cells (ITC) of the lymph node, a condition which is generally harder to detect under US examination.

During the subsequent clinical and instrumental follow-up (average of 18 months, range of 12-40 months) no relapse in the same lymph node in none of the 132 TN patients (US- and FNAB-) was reported. In the group of 105 FP (US+ and FNAB-), 14 patients – representing 13.3% of this specific group and 4.2% of the suspicious US examination – had subsequent final evidence of lymph node metastases in the same location, four of whom after more than one year following FNAB.

Discussion

Our study demonstrates that US, utilizing FNAB as a reference standard, is a sensitive method in the evaluation of lymph node metastatic involvement in skin tumours. Specifically, not only has US examination proved to be a valuable method for preoperative melanoma staging[21], but it is also a valid technique for assessing metastatic lymph nodes during the melanoma follow-up.

The high sensitivity observed in our cohort is also due to the wide neoplastic involvement of the lymph nodes as highlighted by the histological examination. All the US false negatives are in fact due to presence of micrometastasis and/or isolated tumour cells, findings that are more difficult to identify with US.

On the basis of the results, we can also infer that US is relatively inefficient in differentiating between inflammatory-induced and a neoplasm-induced structural alteration (55.7% specificity). Indeed, 105 out of 336 (31%) patients who were considered suspicious at the US examination, tested negative at the cytological examination. This finding suggests that US, either two-dimensional or combined with Doppler techniques for the study of lymph node vascularisation, does not seem to be conclusive in differentiating inflammatory-induced structural alteration from neoplasms. To this end, the need for technological improvements, new cultural acquisitions and the use of contrast-

enhanced US is evident, with the possible use of other imaging techniques (i.e. computed tomography, magnetic resonance imaging).

A review of relevant literature shows that there have been many studies evaluating the ability of US in identifying lymph node metastases from skin tumours, especially melanoma. Considerable differences in the reported sensitivity and specificity values emerge from the results; these differences are ascribable to the wide variety of the study designs and the methods employed.[14,15,22-24] Our results do not seem to be in accordance with the ones by other authors about the ability of US in evaluating lymph nodes. Specifically, Moehrle *et al*. report a US accuracy value close to 100% (100% sensitivity and 96% specificity), using few carefully-selected suspicious criteria on US. Moreover, a much smaller population was evaluated in said publications, generally analysing lymph nodes of larger sizes which is a decisive variable in highlighting the structural and architectural modification of the lymph nodes.[25] In addition, other authors report a much lower sensitivity value (21 to 34%) [23,24]; this represents a further example of the variability of the factors influencing the results and makes it difficult to compare the results from other studies.

As regards the follow-up of 105 patients suspicious upon US and with negative cytology reports, the presence of metastatic recurrence in the same lymph node location was detected after the first sampling in 14 cases (13.3%). The evidence of recurrence at FNAB in the same lymph node stations does not represent per se a valid parameter for the certification of the initial positivity of that lymph node; nevertheless, it clearly suggests that the number of correct diagnoses could be greater (72% of US+ cases).

It should be highlighted that performing a FNAB procedure there are significant probabilities of encountering areas not yet affected by the disease, especially lymph nodes of small sizes, as is the case with our cohort. Said element acquires a great significance, considering that in all our study cases the presence of lymphocytes in the material examined was documented, thus, confirming a correct execution of the cytological sample collection.

This evidence opens a discussion concerning the optimal methods for monitoring and the need for integrated diagnostic procedures in cases with suspicious US and negative cytology reports.

When comparing the results from US-guided FNAB with histology in pre-surgical assessment of the sentinel lymph node, some studies reported a positive predictive value greater than 65%.[15,26]

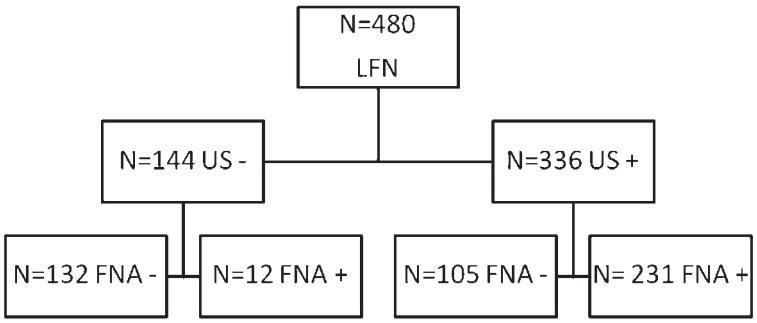

FIGURE 1. Flow-chart describing lymph-nodes analysed by ultrasound and FNAB cytology.

LFN = lymph-nodes investigated; US- = ultrasound negative for lymph-node metastasis; US+ = ultrasound positive for lymph-node metastasis; FNAB = fine-needle aspiration biopsy; FNAB- = FNAB negative for lymph-node metastasis; FNAB+ = FNAB positive for lymph-node metastasis

Another article reports a 100% FNAB sensitivity and specificity in a cohort of only 50 patients when compared to surgical biopsy.[16] Other authors report FNAB values of sensitivity, specificity and positive predictive value of 90.9%, 67.2% and 82.6%, respectively. Besides, such cohort does not only refer to dermatological neoplasm and the inadequate samplings were discarded for statistical purposes.[27] These results contrast slightly with those we obtained, but the methodological differences make it difficult to properly compare the data.

In our series, the number of inadequate samples (1%) is greatly inferior to the values reported in relevant literature (10% according to Basler *et al*.).[16] This could be partly ascribable to the considerable specialization of the operators (sample taker and cytologist), as well as to the systematic sampling procedure of at least two different areas of the target lymph node; furthermore it is certainly also ascribable to the methods employed and the wide use of immunocytochemistry and special staining.

Moreover, the percentage of FNAB false positives as compared with histological results is very low, confirming the clinical significance of the positive result of fine needle aspiration.

Our study has methodological strong points, considering the high number of cases and the presence of a single operator which allows us to avoid the problem of inter-operator variability, which would otherwise occur; however, resorting to the cytological gold standard (imposed by the absence of histological verification of the lymph nodes with a negative histological report, for clearly ethical reasons) represents a limit of the study. It should be noted that the results have to be interpreted within a low-risk lymph node recurrence population like ours, mainly composed of melanomas in

their early stages. Moreover, the level of diagnostic accuracy was obtained by a highly skilled operator. However, the specific characteristics of our population represent also a limit of the study since the cohort was selected on the basis of a suspicious metastatic involvement of superficial lymph nodes.

These elements have to be considered in the generalization of results.

Conclusions

On the basis of the above, taking into consideration the great number of our records and in light of the difficulty in making a comparison with the cohort of other authors, we think that US, performed by expert operators, is of considerable value in excluding (except for micrometastases and ITC) the neoplastic involvement of superficial lymph nodes in the follow-up of patients with skin tumours. On the contrary, in about one third of the cases classified as suspicious upon US, the FNAB cytology demonstrates the absence of neoplastic cells; this highlights the existence of a fair number of false US positives, a diagnostic error determined by a difficult differential diagnosis between the inflammatory changes and the tumour.

A few of these patients showed later recurrence in the same lymph node location, thus suggesting the existence of a considerable percentage of false FNAB negatives, rightly related to a not yet massive neoplastic involvement of the lymph node. It is an empirically plausible element, given the small dimensions of the lymph nodes in our cohort. Hence the suggestion, limited to this group of patients, is for at least a closer clinical/US follow-up, even if this results in an inevitable increase in cost.

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case report

Minimally invasive CT guided treatment of intraspinal synovial cyst

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Background. Intraspinal synovial cysts of vertebral facet joints are uncommon cause of radicular pain as well as neurological deficits. They can be managed both conservatively and surgically.

Case report. A 77-year old polymorbid patient presented with bilateral low back pain which worsened during the course of time and did not respond to the conservative treatment. A diagnosis of intraspinal synovial cyst was made using the magnetic resonance imaging (MRI). Percutaneous computed tomography (CT) guided injection with installation of local anesthetic together with corticosteroid and rupture of the cyst was successfully used. A month after the procedure his pain improved, the usage of analgesics diminished and his over-all quality of life improved.

Conclusions. Percutaneous CT guided lumbar synovial cyst treatment is safe and reliable alternative to the surgical treatment in polymorbid patients with radiculopathy who are not able to tolerate general anesthesia and operation.

Key words: intraspinal synovial cyst; polymorbid patient; radiculopathy; pain; percutaneous CT guided treatment

Introduction

Radicular pain in lumbar region is a symptom which can have many causes such as herniated nucleus pulposus, migrated disc fragment, lumbar stenosis, facet joint syndrome, malignancy and/or infection.[1,2] Intraspinal synovial cysts are among uncommon causes.[1]

The incidence of lumbar synovial cysts in symptomatic patients is 0.65-2.3% according to a diagnostic method.[2] Recent reports in literature show that true incidence of the lumbar intraspinal synovial cysts is higher. Higher incidence reflects the improved diagnostic methods.[3] The disease is more common in older population and in women and is supposed to be related to degenerative changes of the lumbar spine.[1,4]

Cysts may be asymptomatic but they usually cause radicular pain, neurogenic claudication, motor deficits, sensory and reflex disturbances or even cauda equina syndrome.[1] Diagnosis is based on different imaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT) and/or CT myelography.[1,5]

Case report

A 77-year-old patient presented with back pain in the lumbar region and both legs. Lumbar pain started 3 years ago and was primarily described as blunt and propagating along the left lower extremity. Nature of pain changed a year before the presentation into prickling in nature and spontaneous. Symptoms interfered with his daily routine. A similar type of pain affected his right lower limb. According to visual analogue scale (VAS) he evaluated his pain as 8/10. This was improved by bed rest and usage of analgesics and described as VAS 4/10.

The patient had a complete occlusion of left internal carotid artery, both vertebral arteries and 70% stenosis of right internal carotid artery. He had already suffered two myocardial infarctions

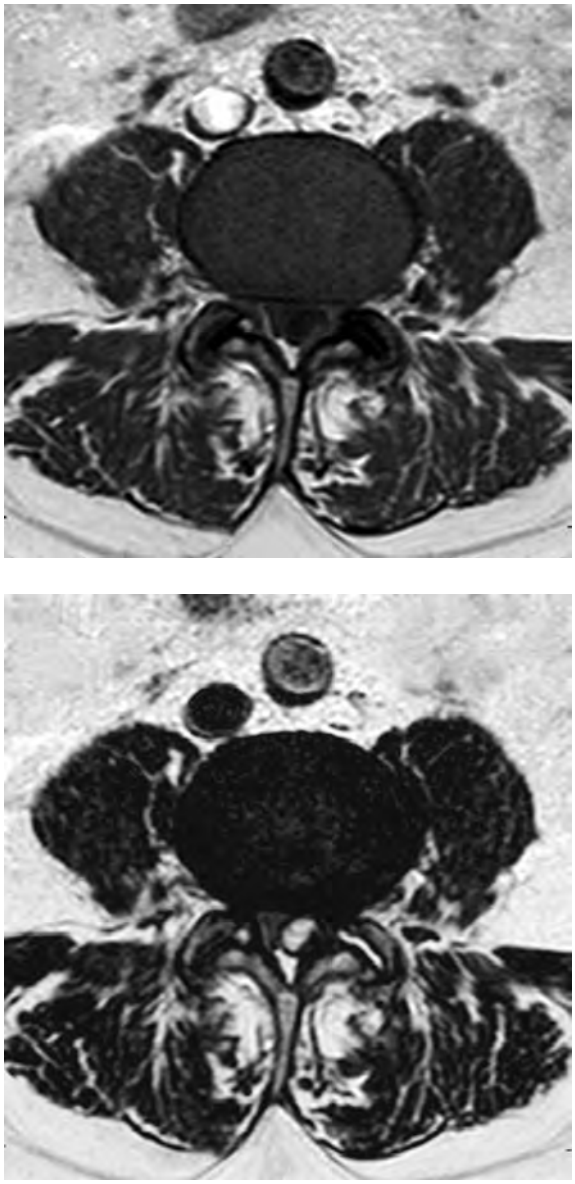

FIGURE 1. Baseline (preoprocedural) MRI in an axial plane at the level of the L4-L5 lumbar segment. Hypointense well delineated cystic formation compressing dural sac from the left dorsolateral side is seen on T1 SE image (A). The cyst that is hyperintense on T2 FSE image shows continuation with the left facet joint (some fluid can also be seen in the degenerated facet joint) (B).

as well as an ischemic stroke. His other comorbidities included chronic atrial fibrillation, congestive heart failure, peripheral arterial occlusive disease, arterial hypertension, hyperlipidemia, hypercholesterolemia, benign prostatic hyperplasia and chronic renal insufficiency.

MRI revealed well delineated intraspinal cystic formation compressing dural sac from the left dorsolateral side at the level of fourth and fifth lumbar facet joint. The dural sac was significantly compressed and displaced by the cyst filling more than half of the normal canal. The communication of the cyst with the left facet joint was seen. Presence of the fluid within the degenerated facet joint was additional finding that supported the diagnosis of intraspinal synovial cyst (Figure 1).

Due to complex medical history the decision for non-surgical, percutaneous CT -guided intervention was made. Standard monitoring (electrocardiogram, non-invasive blood pressure measurement and pulse oximetry) was used. An intravenous line was inserted. The patient received cefazoline 2 g and paracetamol 1 g 30 minutes before the start of the procedure and was placed in the prone position on the CT scanner's table. The procedure was performed under strict aseptic conditions by using CT scanner with 82 cm gantry opening (Sensation Open, Siemens Healthcare, Erlangen, Germany). The scanner with STRATON X-ray *tube* technology *enables an* acquisition of *40 slices. T*he *wide gantry opening* ensures an easy patient access. The following CT protocol was used for CT guidance: low dose scans (120 kV, 112 mAs) with rapid 360^0 gantry rotation speed (1 second) and 0.6 mm section collimation (slice thickness). A puncture point (overlying the left L4-L5 facet joint) was selected on axial CT scan. Local infiltration with 2% lydocaine 2 ml was used.

A 22 gauge (G) atraumatic spinal needle (RapID Portex, Smiths Medical, London, United Kingdom) was advanced forward targeting the joint. The position of the needle was confirmed with subsequent CT scans. After the insertion of the needle into the facet joint space, iodine contrast media iohexol (Omnipaque 300 mg/mL, GE Healthcare, Amersham, United Kongdom) 10 ml was instilled. A communication between the joint space and the intraspinal cyst was proved, confirming the diagnosis of the synovial cyst. A mixture of local anaesthetic 1% lydocaine 1 ml and methylprednisolone 125 mg was injected into the lumen of the cyst. Additional sterile saline was installed in order to distend and rupture the cyst. The patient described pain in the spinal region and both legs during this part of the procedure, which partially responded to intravenous 0.05 mg of alfentanyl application. The loss of resistance suggested the rupture of the cyst and this was confirmed by CT scan (Figure 2). At the moment of the rupture the pain disappeared. The procedure was terminated by this event. The patient was haemodinamically stable during the procedure.

Immediately following the procedure a sterile dressing was placed over the skin entry. The pa-

tient was observed and monitored in recovery unit for two hours. A strict body rest was maintained during this period of time. The patient did not require any additional analgesics. He was discharged next day. Instructions about the wound care and observation were given to him.

A short-term follow-up with the referring physician as well as with the patient himself revealed the partial relief of radicular symptoms a month after the procedure. His pain still persists but is described as blunt and without propagation. Prickling pain in both his lower extremities disappeared. His only pain therapy is weak opioid before sleep.

Discussion

As already mentioned, intraspinal synovial cysts are uncommon cause of radicular pain and are located on the internal and posterolateral side of the spinal canal.[1] Intraspinal synovial cysts are continuous with the facet joints and lined with epithelial lining. They are typically located posterior to the thecal sac; this is thought to be related to the presence of ligamentum flavum which represents a barrier to anterior cyst formation.[3] Majority of these cysts occur in the segments of lumbar spine with the predilection for the fourth and fifth lumbar vertebra as described in our patient.[1,4-6] Cysts in the cervical spine are uncommon and those in the thoracic spine are even more rare.[1]

Pathogenesis of synovial cysts is not well understood. A chronic degenerative process causes the protrusion of the synovial membrane through the defects of the joint capsule. Consequently formation of the cavity filled with synovial fluid occurs.[1,2,5] Therefore, the pathognomic imaging finding is a direct communication between the cyst and the facet joint.[3,5] This was clearly demonstrated in our case as well. Imaging with iodine contrast media proved the communication between the cyst and facet joint and, thereby, confirmed the diagnosis. This theory is also supported by the fact that most of the patients with synovial cysts suffer from facet joint osteoarthritis and disk degeneration.[2]

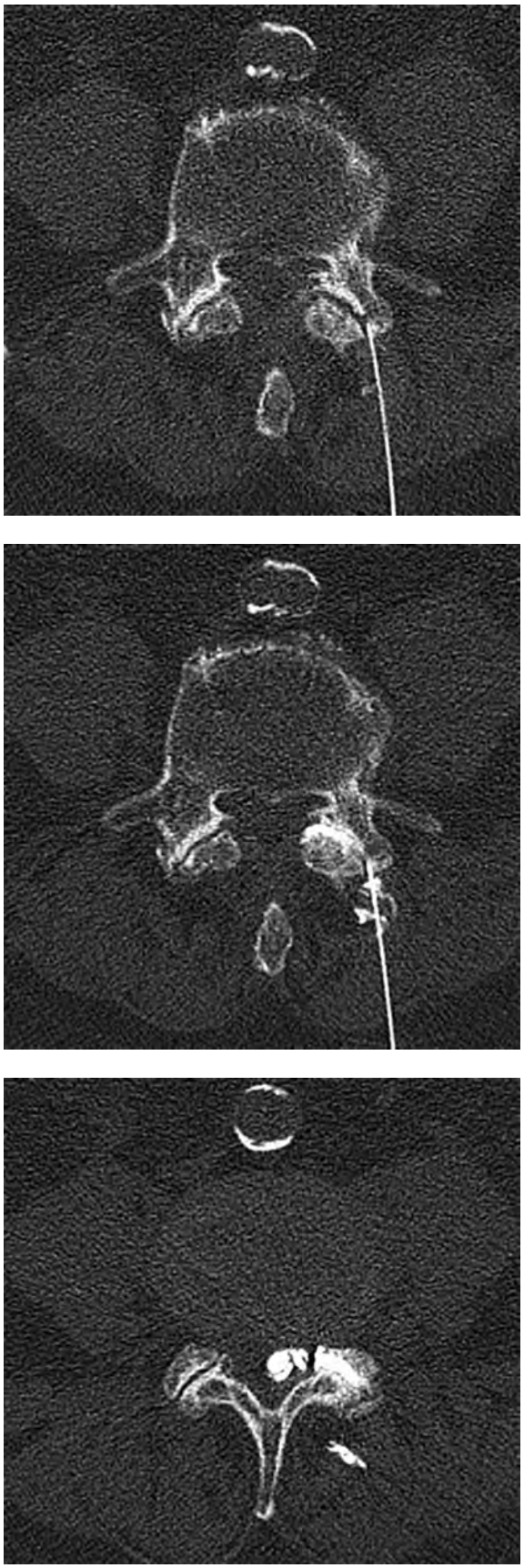

FIGURE 2. Intraprocedural CT in an axial plane at the level of the L4-L5 lumbar segment. A 22G needle that has entered a posterior part of a target facet joint can be seen (A). Iodine contrast media instilled through the needle has filled the facet joint, confirming the needle tip position inside the joint (B). Continuous contrast instillation resulted in intraspinal contrast opacification of the cyst (confirming the diagnosis of intraspinal synovial cyst) (C). A loss of resistance was felt at the time of cyst rupture. The procedure was terminated at that point.

Since the cysts arise at the most unstable segments of the spine, instability is a pivotal factor. Another theory implicates trauma to the spine.[1] Our patient had no history of previous spinal trauma. Diagnostic imaging of lumbosacral region revealed degenerative changes.

The clinical presentation of the intraspinal synovial cysts depends on the size, site and relationship to the adjacent structures. Cysts may be asymptomatic but they usually cause radicular pain, neurogenic claudication, motor deficits, sensory and reflex disturbances or even cauda equina syndrome.[1] The most common presentation is a radicular pain.[7] All these presentations develop gradually; the acute onset of symptoms may be associated with a sudden cyst distension and/or compression of parts of nervous system, usually caused by intercystic haemorrage.[1] Our patient suffered from bilateral low back pain. He also experienced weakness in both lower extremities, which besides the pain interfered with his general activities and ability to walk. All symptoms progressed during the course of time. No other neurological deficits were described by the patient or clinicians.

The diagnosis of intraspinal synovial cysts is based on MRI, CT or CT myelography.[1,5,8] The latter is used when MRI is not available or cannot be performed.[1] A typical synovial cyst is defined as round or ovoid collection arising from the facet joint. It is composed of varying types of fluid.[3] According to MRI evaluation in our case, the cyst contained a fluid with a density similar to clear fluid (the signal was similar to cerebrospinal fluid). However, due to the viscosity of the fluid, the aspiration with 22 G needle was not possible.

Intraspinal synovial cysts can resolve spontaneously, but they usually require the treatment. The treatment (besides surgical) includes bed rest, analgesics, physical therapy, transcutaneous electrical stimulation (TENS), as well as minimal invasive methods such as epidural/intraarticular corticosteroid injections with or without rupture of the cyst and CT or endoscopy guided aspiration of the cyst.[1,2] The conservative treatment was used in our case, but the symptoms worsened during the course of time. Therefore, the interventional treatment became an option.

Non-surgical interventions include installation of corticosteroids and/or local anesthetics. The aim is to prevent the recurrence of the cyst and inflammation.[3]

The rupture of the cyst can be achieved with the additional injection of normal saline. An immediate complete relief is described by the majority of patients. According to reports of some authors, significant long term effect cannot be achieved.[3,7] A retrospective study conducted by Martha *et al.* confirmed a sufficient symptomatic improvement in 46% of treated patients as well as avoidance of the surgical treatment. A cyst rupture was described in all of them. Patients, who underwent surgical procedure after the minimal invasive procedure, reported the significant improvement in disability, back and leg pain.[9] Another retrospective study proved pain relief to be associated with the rupture of the cyst.[6] In case of the severe degenerated facet joint with a very narrow joint space, the posterior facet puncture could be challenging. An alternative approach can be used in such cases. The cyst can be punctured directly through vertebral lamina. The later approach is commonly used in ganglion cysts that have no connections with facet joints.[1]

The advantage of CT over fluoroscopy is direct, reliable puncture of the cyst without dural violation and was a method of choice in our case as well. Another advantage of the procedure is that it can be repeated if necessary. Common risks include infection, bleeding or damage to nervous structures.[3,7] None of the complications occurred in our case; the patient received antibiotic prophylaxis and the procedure was performed under strict aseptic conditions. His therapy with warfarine was stopped and changed into low molecular weight heparine to minimize the possibility of bleeding.

Surgical treatment includes different procedures (laminectomy, facetectomy, flavectomy together with cyst excision and microsurgical procedures). The aim of these procedures is a complete resection of the cyst as well as the treatment of concomitant disease.[1,2,10] The surgical treatment is the most effective treatment option with very rare instances of recurrence of the cyst.[3,11]

However, the optimal treatment strategy of synovial cysts remains controversial.[1,4] The surgical treatment can be recommended when conservative methods (bed rest, analgesics, physiotherapy) fail to alleviate symptoms or as soon as neurological deficits appear. Older and high risk patients may also benefit from percutaneous interventions.[1-3,10,11] Our patient was not able to tolerate the surgical procedure due to all his comorbidities, especially his cardiac and vascular disease.

Conclusions

Percutaneous CT- guided lumbar synovial cyst treatment is safe and reliable alternative to the

surgical treatment in polymorbid patients with radiculopathy unable to tolerate general anesthesia and operation.

Acknowledgement

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research article

Increased expression of SHP-1 is associated with local recurrence after radiotherapy in patients with nasopharyngeal carcinoma

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Background. Nasopharyngeal carcinoma (NPC) is a major cancer in southern China. Src homology phosphatase-1 (SHP-1) is a tyrosine phosphatase that regulates growth, differentiation, cell cycle progression, and oncogenesis. We determined the clinical significance of SHP-1 expression in the tumours of NPC patients from southern China who were treated with radiotherapy.

Patients and methods. SHP-1 expression was determined by real-time polymerase chain reaction (PCR) and western blotting of NPC tissue samples of 50 patients and nasopharyngeal tissues of 50 non-NPC patients who had chronic nasopharyngeal inflammation. SHP-1 expression was measured in NPC tissue samples of 206 patients by immunohistochemistry and survival analysis was performed.

Results. The tumours of NPC patients had significantly increased expression of SHP-1 at mRNA and protein levels relative to patients with chronic nasopharyngeal inflammation. Survival analysis of NPC patients indicated that SHP-1 expression was significantly associated with poor local recurrence-free survival (p = 0.008), but not with nodal recurrence-free survival, distant metastasis-free survival, or overall survival.

Conclusions. SHP-1 appears to be associated with radiation resistance of NPC cells and can be considered as a candidate marker for prognosis and/or therapeutic target in patients with this type of cancer.

Key words: SHP-1; nasopharyngeal carcinoma; real-time quantitative PCR; Western blotting; immunohistochemistry; radiation resistance

Introduction

Nasopharyngeal carcinoma (NPC) is one of the most common tumours of the head and neck in China and is a major cancer in southern China, northern Africa, and certain other geographic regions.[1] Non-keratinizing undifferentiated carcinoma is the most common of the three forms of NPC.[2] This form is sensitive to radiation, and radiotherapy (RT) has been the main treatment for NPC because radical resection is typically not possible.[3]

In recent years, the 5-year survival rate of patients with locally advanced NPC after RT alone is about 50% and the 5-year survival rate after concurrent chemoradiation is about 70%.[4-9] However, due to the presence of tumour cell heterogeneity, surviving cell sub-lines that are resistance to RT can lead to local recurrence and distant metastasis, a major cause of treatment failure and patient death.[4-9] This was confirmed by our recent study which compared treatment of NPC with intensity modulated radiation therapy (IMRT) and two-di-

mensional conventional radiotherapy (2D-CRT).[10] Thus, identification of the mechanisms underlying radiation resistance in NPC may help to improve radiotherapy outcome.

Previous research has shown that NPC is characterized by a subset of cells with low radiation sensitivity and another subset with high radiation sensitivity.[10,11] This difference in radiation sensitivity is related to cellular oxygen consumption, repair capacity after RT-induced DNA damage, apoptosis, and cell cycle distribution.[10,11]

Recent studies of Src homology phosphatase-1 (SHP-1), which is strongly expressed in hematopoietic cells, indicate that this tyrosine phosphatase plays important roles in controlling cell proliferation and tumour cell cycle distribution. SHP-1 regulates the cell cycle of tumour cells *via* regulating the expression of CDK2, p27, and cyclin D1, suggesting that it may be a potential tumour marker or therapeutic target.[12] In prostate cancer cells, SHP-1 induction blocks the JAK/STAT3 signal transduction pathway, making tumour cells more sensitive to chemotherapy; knockdown of SHP-1 blocks the IL-6-mediated JAK/STAT3 dependent tumour cell proliferation, thereby inducing tumour cell apoptosis.[13,14] In prostate cancer cells, silencing of SHP-1 expression inhibits the expression of CDK2, CDK6, and cyclin E, resulting in retention of cancer cells in G0/G1 phase.[15] Thus, SHP-1 appears to have different roles and mechanisms in regulation of the cell cycle and cell proliferation in different types of tumours. There have been no reports on the effects of SHP-1 regulating the cell cycle and proliferation of NPC cells, and no reports of the effect of SHP-1 on the regulation of cell radiosensitivity.

The purpose of the present study was to study the clinical significance of SHP-1 expression in radiation resistance of the tumour cells of patients with NPC.

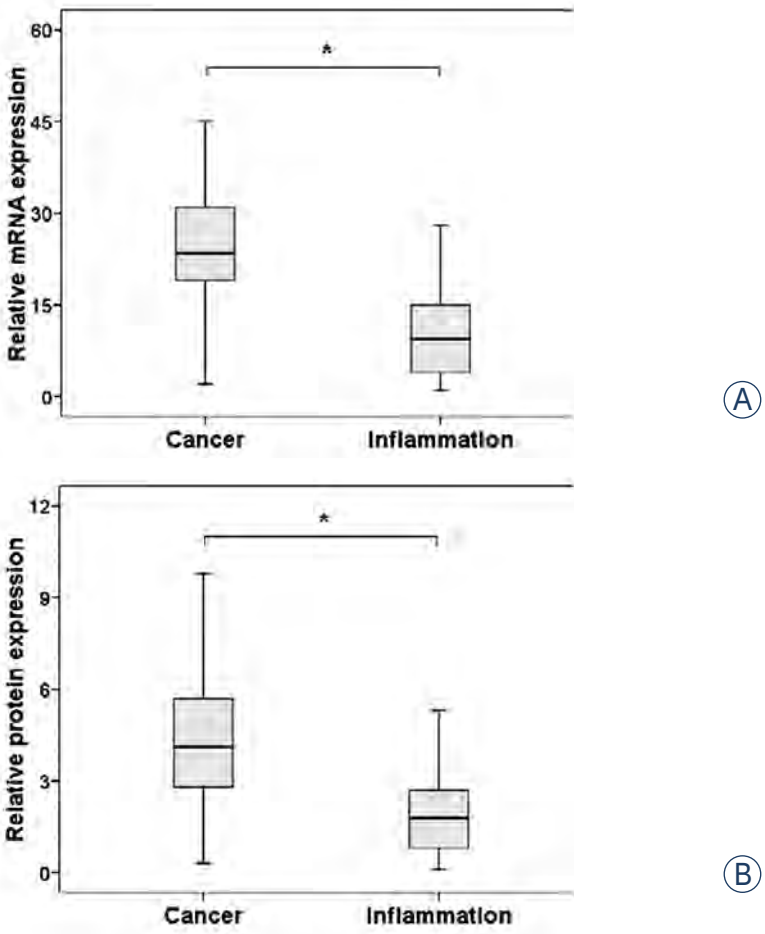

FIGURE 1. Expression of SHP-1 mRNA (A) and protein (B) in the tumor tissues of patients with nasopharyngeal carcinoma and the inflammatory tissues of patients with chronic nasopharyngeal inflammation. *p<0.05, Mann-Whitney U test.

Patients and methods

Patients and follow-up

This study was approved by the Ethical Committee of our hospital. All patients provided written informed consent for inclusion and for all procedures. A total of 206 consecutive patients with untreated, non-metastatic NPC who received curative RT at our centre from July 2003 to June 2006 were eligible for inclusion in this retrospective study. The inclusion criteria were: (*i*) histological diagnosis of NPC; (*ii*) tumour stage of T1-4, N0-3, and M0; (*iii*) Eastern Cooperative Oncology Group (ECOG)/World Health Organization (WHO)/Zubrod performance score less than 4[16]; and (*iv*) treatment with curative RT. The exclusion criteria were: history of another malignancy within the past 5 years; lack of full capacity for making medical decisions; severe comorbidities or active infection; concurrent immunotherapy or hormone therapy for another disease; and pregnancy or lactation.

Pretreatment staging of tumours was performed by complete physical examination, fiberoptic nasopharyngoscopy, magnetic resonance imaging (MRI) of the head and neck, chest radiography, abdominal and cervical ultrasonography, and dental assessment. Technetium-99m-methylene diphosphonate (Tc-99-MDP) whole-body bone scanning was performed for patients with stage T3-4 or N2-3 disease. Staging of patients was according to the 2002 AJCC/UICC system.[3]

A thorough clinical assessment, including physical and laboratory examinations, contrast-

TABLE 1. Demographic and clinical characteristics of NPC patients whose tumors tested positive or negative for SHP-1 prior to radiotherapy based on immunohistochemistry results

Characteristic	N	SHP-1(+)	SHP-1(-)	P
All	206	104 (50.5%)	102 (49.5%)	
Gender				0.357
Male	147	71 (48.3%)	76 (51.7%)	
Female	59	33 (56%)	26 (44%)	
Age (years)				0.726
<60	166	85 (51.2%)	81 (48.8%)	
≥60	40	19 (47%)	21 (53%)	
ECOG performance score[a]				0.329
0~1	197	101 (51.3%)	96 (48.7%)	
≥2	9	3 (33%)	6 (67%)	
Histological type[b]				**0.770**
Type 1	2	1 (50%)	1 (50%)	
Type 2.1	28	16 (57%)	12 (53%)	
Type 2.2	176	87 (49.4%)	89 (50.6%)	
T stage				**0.967**
T1	19	11 (58%)	8 (42%)	
T2	92	45 (49%)	47 (51%)	
T3	60	31 (52%)	29 (48%)	
T4	35	17 (49%)	18 (51%)	
N stage				**0.351**
N0	23	15 (65%)	8 (35%)	
N1	64	30 (47%)	34 (53%)	
N2	108	52 (48.1%)	56 (51.9%)	
N3	11	7 (64%)	4 (36%)	
Clinical stage[c]				**0.873**
I	11	7 (64%)	4 (36%)	
III	50	25 (50%)	25 (50%)	
III	103	51 (49.5%)	52 (50.5%)	
IV	42	21 (50%)	21 (50%)	
IVa	31	14 (45%)	17 (55%)	
IVb	11	7 (64%)	4 (36%)	
RT technique				**0.577**
2D-CRT	102	49 (48.0%)	53 (52.0%)	
IMRT	104	55 (52.9%)	49 (47.1%)	
Chemotherapy				
Neo-adjuvant Chemotherapy	72	40 (55%)	32 (46%)	0.309
Concurrent Chemotherapy	71	33 (47%)	38 (53%)	0.464
Adjuvant Chemotherapy	116	62 (53.4%)	54 (46.6%)	0.399

[a] Patients with Eastern Cooperative Oncology Group (ECOG) performance score ≥ 4 were excluded;

[b] 2005 World Health Organization (WHO) Classification: type 1, keratinizing squamous cell carcinoma; type 2.1, nonkeratinizing carcinoma, differentiated subtype; type 2.2, nonkeratinizing carcinoma, undifferentiated subtype;

[c] 2002 American Joint Committee on Cancer (AJCC) staging system;

RT = radiotherapy; 2D-CRT = 2-dimensional conventional radiotherapy; IMRT = intensity-modulated radiotherapy

enhanced MRI, and fiberoptic nasopharyngoscopy was performed 4 weeks after completion of RT, and at 3-month intervals for the next two years. Thereafter, follow-up visits were scheduled every 6 months or as needed clinically, until at least 5 years after completion of RT or until patient death.

NPC tissues

For real-time quantitative PCR and western blotting, we collected 50 tumour samples from randomly selected NPC patients (n = 206) and 50 nasopharyngeal samples from randomly selected non-NPC patients who underwent fiberoptic nasopharyngoscopy for chronic nasopharyngeal inflammation at the Department of Otorhinolaryngology from July 2010 to June 2011. These 100 patients included 64 men and 36 women and the median age was 55 years (range: 28–76 years). After resection, fresh tissues were immediately frozen in liquid nitrogen and stored at -80°C.

Cancerous and inflammatory tissue samples were used for histological examination and assessment by immunohistochemical staining. Tissue samples collected from all participants were formalin-fixed, paraffin-embedded and stored at room temperature. For pathological evaluation, 5-mm thick tissue sections were cut from blocks containing representative tumour regions and then Hematoxylin and eosin stained slides were reviewed by a pathologist.

RNA extraction and quantitative real-time PCR

Total RNA was extracted using the TRIzol reagent (Invitrogen, Carlsbad, CA) according to the manufacturer's protocol. Then, 2 mg of RNA was reverse transcribed into first-strand cDNA by M-MLV Reverse ranscriptase (Promega, Madison, WI) according to the manufacturer's instructions. SHP-1 and GAPDH (housekeeping gene) were amplified by quantitative real-time PCR using the following primers: SHP-1 forward: 50-TATGCGTAGCCTGTTAGGTGCC-30, reverse: 50-GGTCTTACCGCGATGAATTTCT-30; GAPDH forward: 50-TGTTCGACACTCCTCCGTCAGC-30, reverse: 50-CAAATCCCCCAATACGACGTT-30. Gene-specific amplification was performed in an ABI 7900HT real-time PCR system (Life Technologies, Carlsbad, CA) with a 15 ml PCR mix that contained 0.5 ml of cDNA, 7.5 ml of SYBR Green PCR Master Mix (Invitrogen), and 200 nM of primer. The mix was preheated at 95°C for 10 min and then amplified in 45 cycles of 95°C for 30 sec and 60°C for 1 min. The resolution curve was measured at 95°C for 15 sec, 60°C for 15 sec, and 95°C for 15 sec. The threshold cycle (Ct) value of each sample was calculated, and the expression of SHP-1 mRNA relative to GAPDH was determined by the $2^{-\Delta\Delta}$Ct method.

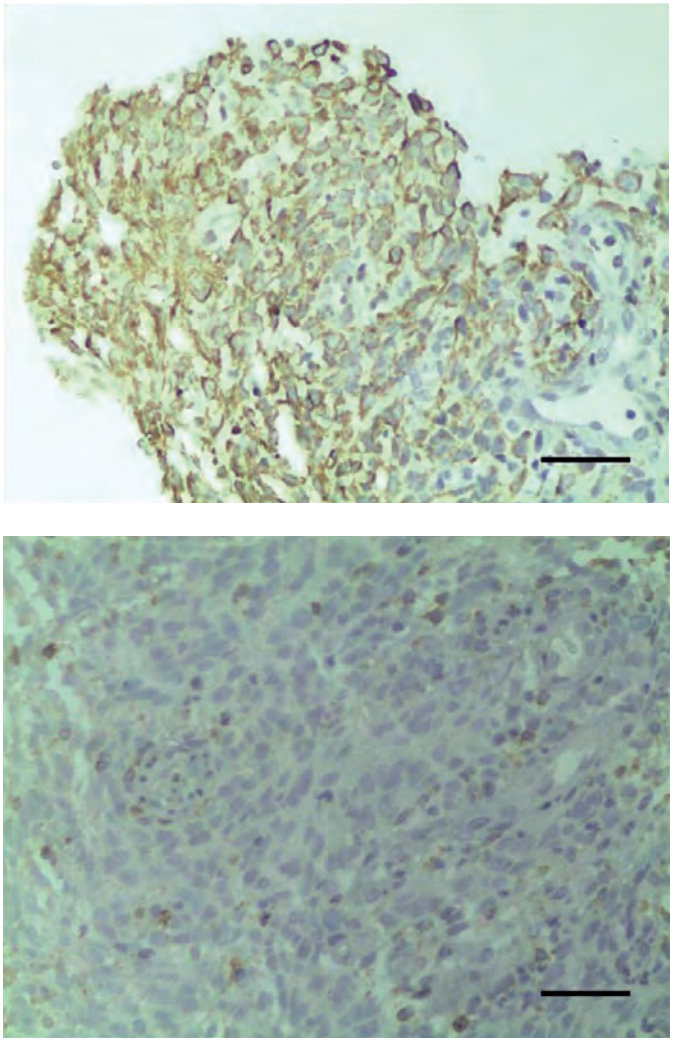

FIGURE 2. Representative results of immunohistochemistry (×400). Scale bar: 50 mm. A – SHP-1-positive NPC patient. B – SHP-1-negative NPC patient.

Western blotting analysis

Homogenized tissues were lysed in RIPA lysis buffer, and lysates were harvested by centrifugation (12 000 rpm at 4°C for 30 min). Protein samples (20 mg) were separated by electrophoresis (12% SDS-PAGE), transferred to a polyvinylidene fluoride membrane, and the membrane was placed in 5% nonfat milk for 1 h and incubated with a sheep anti-human SHP-1 antibody (1:1,000, R&D Systems,

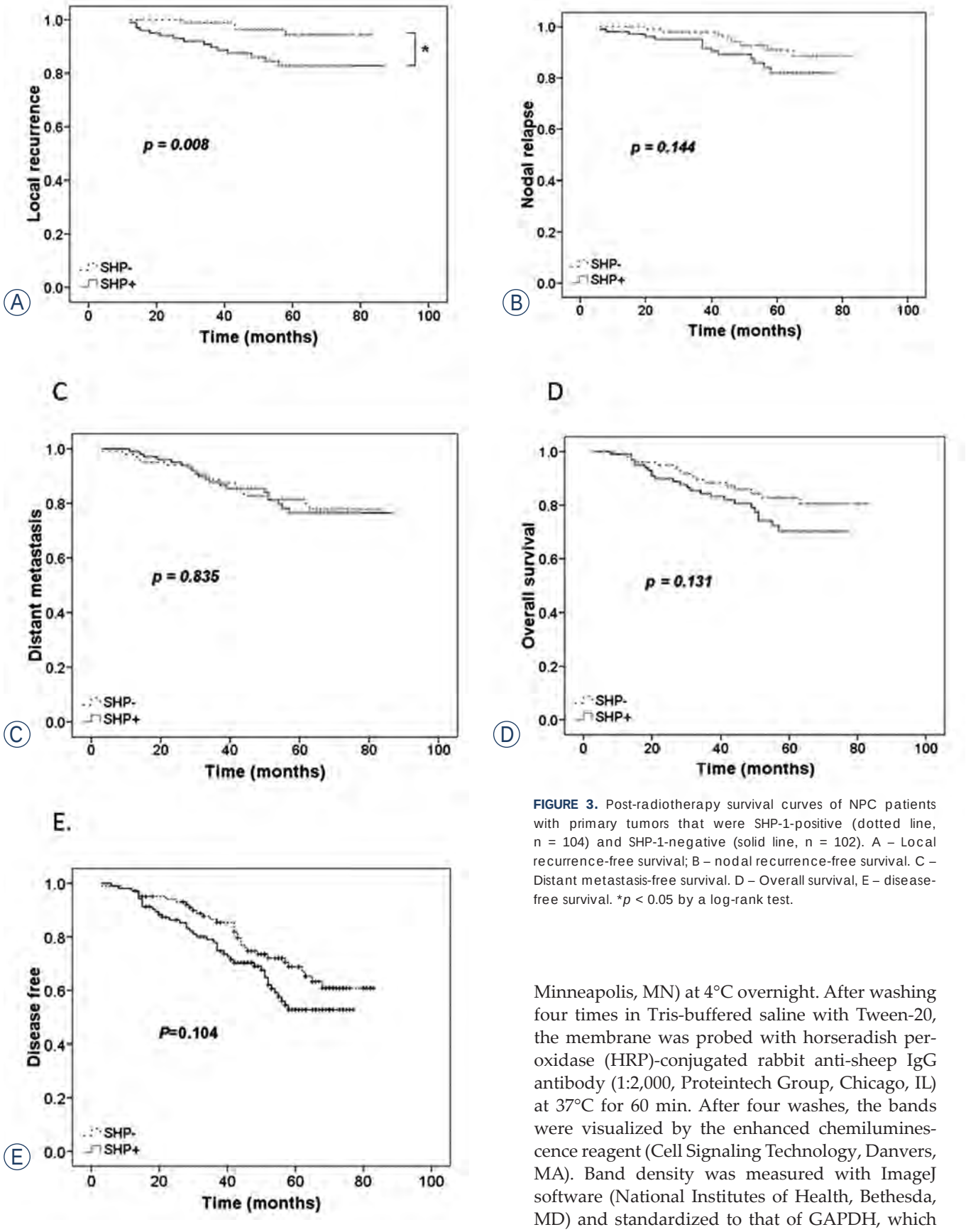

FIGURE 3. Post-radiotherapy survival curves of NPC patients with primary tumors that were SHP-1-positive (dotted line, n = 104) and SHP-1-negative (solid line, n = 102). A – Local recurrence-free survival; B – nodal recurrence-free survival. C – Distant metastasis-free survival. D – Overall survival, E – disease-free survival. *$p < 0.05$ by a log-rank test.

Minneapolis, MN) at 4°C overnight. After washing four times in Tris-buffered saline with Tween-20, the membrane was probed with horseradish peroxidase (HRP)-conjugated rabbit anti-sheep IgG antibody (1:2,000, Proteintech Group, Chicago, IL) at 37°C for 60 min. After four washes, the bands were visualized by the enhanced chemiluminescence reagent (Cell Signaling Technology, Danvers, MA). Band density was measured with ImageJ software (National Institutes of Health, Bethesda, MD) and standardized to that of GAPDH, which

TABLE 2. Multivariate analysis of prognostic factors associated with overall survival of patients with nasopharyngeal carcinoma

	Simple OR (95% CI)	P	Multi OR (95% CI)	P
Gender				
Male	Ref		Ref	
Female	0.29(0.07-1.24)	0.094	0.23(0.05-0.98)	0.047
Age (years)				
<60	Ref			
≥60	1.1(0.36-3.31)	0.870		
ECOG				
0~1	Ref		Ref	
≥2	2.67(0.62-11.55)	0.190	4.8(1.09-21.25)	0.039
Histology type				
Type 1, 2.1	Ref			
Type 2.2	0.46(0.16-1.27)	0.132		
T stage				
T1-T2	Ref			
T3-T4	1.88(0.74-4.78)	0.186		
N stage				
N0-N1	Ref			
N2-N3	1.43(0.54-3.75)	0.472		
Clinical stage				
I-II	Ref		Ref	
III-IV	7.17(0.96-53.76)	0.055	8.87(1.17-67.23)	0.035
RT technique				
2D-CRT	Ref			
IMRT	1.83(0.72-4.65)	0.203		
Chemotherapy				
New Adjuvant	1.65(0.67-4.07)	0.274		
Concurrent	1.72(0.7-4.24)	0.237		
Adjuvant	0.64(0.26-1.57)	0.326		
SHP-1				
Negative	Ref		Ref	
Positive	3.95(1.31-11.91)	0.015	4.16(1.37-12.65)	0.012

OR = Odds ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy; 2D-CRT = 2-dimensional conventional radiotherapy; IMRT = intensity-modulated radiotherapy

was measured with a mouse anti-human GAPDH monoclonal antibody (Wuhan Boshide, Wuhan, China).

Immunohistochemistry

After deparaffinization with dimethylbenzene, tissue sections were rehydrated in 100%, 95%, 90%, 80%, and 70% ethanol. After three washes in phosphate-buffered saline (PBS), slides were boiled in antigen retrieval buffer that contained 1 mM EDTA (pH = 8.0) for 15 min in a microwave oven, and then rinsed in peroxidase quenching solution (Invitrogen, USA) to block endogenous peroxidase. Sections were then incubated with a sheep anti-human SHP-1 polyclonal antibody (1:200) at 4°C overnight and then with an HRP-conjugated rabbit anti-sheep IgG antibody (1:200) at room temperature for 30 min. Finally, a 3,3′-diaminobenzidine (DAB) solution was added, followed by counter-

TABLE 3. Univariate analysis of prognostic factors associated with overall survival of patients with nasopharyngeal carcinoma stratified by SHP-1 expression

	SHP- OR (95% CI)	P	SHP+ OR (95% CI)	P
Gender				
Male	Ref		Ref	
Female	0.03(0-551.31)	0.489	0.31(0.07-1.37)	0.121
Age (years)				
<60	Ref		Ref	
≥60	1.3(0.13-12.48)	0.822	1.08(0.31-3.84)	0.901
ECOG				
0~1	Ref		Ref	
≥2	6.15(0.64-59.51)	0.117	2.28(0.3-17.36)	0.426
Histology type				
Type 1, 2.1	Ref		Ref	
Type 2.2	0.15(0.02-1.09)	0.060	0.7(0.2-2.49)	0.584
T stage				
T1-T2	Ref		Ref	
T3-T4	0.93(0.13-6.58)	0.938	2.46(0.84-7.2)	0.100
N stage				
N0-N1	Ref		Ref	
N2-N3	0.66(0.09-4.73)	0.683	1.84(0.58-5.78)	0.299
Clinical stage				
I-II	Ref		Ref	
III-IV	1(0.1-9.6)	0.998	36.99(0.38-3588.19)	0.122
RT technique				
2D-CRT	Ref		Ref	
IMRT	1.16(0.16-8.27)	0.879	1.95(0.67-5.71)	0.224
Chemotherapy				
New Adjuvant	5.9(0.61-56.96)	0.125	1.12(0.4-3.13)	0.836
Concurrent	1.62(0.23-11.48)	0.631	2(0.73-5.52)	0.180
Adjuvant	0.75(0.11-5.36)	0.778	0.55(0.2-1.52)	0.251

OR = Odds ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy; 2D-CRT = 2-dimensional conventional radiotherapy; IMRT = intensity-modulated radiotherapy

staining with hematoxylin. For negative controls, adjacent sections were processed as above, except they were incubated overnight at 4°C in blocking solution without the primary antibody. The intensity of SHP-1 immunostaining was evaluated for all samples under double-blinded conditions. The percentage of positive staining was scored as 0 (0–9%), 1 (10–25%), 2 (26–50%), or 3 (51–100%), and the intensity as 0 (no staining), 1 (weak staining), 2 (moderate staining), or 3 (dark staining). The total score (0 to 9) was calculated as the product of intensity and extent. The expression of SHP-1 was defined as: SHP-1(-) (negative, score 0-3), SHP-1(+) (positive, score 4–9).

Statistical analysis

Overall survival (OS) was defined as the time from RT to death or last follow-up. Disease-free survival (DFS) was defined as the time from RT to the time of recurrence or distant metastasis (with confirmation by histopathology or imaging), or death. Local recurrence-free survival (LRFS) and nodal recurrence-free survival (NRFS) were also determined.

Distant metastasis-free survival (DMFS), survival in the absence of remote metastasis in organs (lung, bone, brain, liver), was also assessed. Categorical data are presented as counts and were compared with the Chi-square test. Continuous data are presented in boxplots and comparisons were performed with the Mann-Whitney U test. Data are presented as Survival curves and compared with the log-rank test. All data were analysed with SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, US). A p-value less than 0.05 was considered statistically significant.

Results

Characteristics of NPC patients

Table 1 shows the characteristics of the 206 NPC patients, which we divided into two groups based on tumour expression of SHP-1 as described in the Patients and methods. These two groups were similar in terms of demographics, ECOG performance score, histological type, TNM staging, AJCC clinical stage, and also with regard to type of RT (2D-CRT or IMRT) and chemotherapy that was given.

Expression of SHP-1 mRNA and protein in tumours and control tissues

We determined the levels of SHP-1 mRNA and protein in the 50 NPC tumour tissues and 50 non-NPC nasopharyngeal tissues (controls) by real time RT-PCR and immunohistochemistry. The control samples were from randomly selected non-NPC patients who underwent fiberoptic nasopharyngoscopy for chronic nasopharyngeal inflammation. Figures 1A and 1B show that the median expression of SHP-1 mRNA and protein was significantly higher in the cancer tissues than in the inflammatory nasopharyngeal tissues ($P < 0.001$ for both comparisons).

We also performed immunohistochemical analyses of paraffin-embedded NPC tissue of all 206 patients. Figures 2A and 2B show representative immunohistochemistry results of an NPC tissue that was positive for SHP-1 and an NPC tissue that was negative for SHP-1 expression, respectively.

Multivariate analysis of prognostic factors for OS of NPC patients

Next, we performed multivariate analysis of prognostic factors associated with OS of patients with NPC (Table 2). The results indicate that female gender was independently associated with improved OS (OR: 0.23, 95% CI: 0.05-0.98, $p = 0.047$), but that ECOG status of 2 or higher (OR: 4.8, 95% CI: 1.09-21.25, $p = 0.039$), clinical stage III-IV (OR: 8.87, 95% CI: 1.17-67.23, $p = 0.035$), and positive SHP-1 expression (OR: 4.16, 95% CI: 1.37-12.65, $p = 0.012$) were independently associated with poor OS.

Univariate analysis of the prognostic factors for OS of NPC patients stratified by SHP-1 expression

The results of this univariate analysis indicate that none of the analysed factors were associated with OS ($p > 0.10$ for all comparisons) (Table 3).

Survival analysis

The follow-up was closed in October 2011. The median follow-up time for the entire cohort was 58 months (range: 16–82 months). Figure 3 shows the results of survival analysis of NPC patients who tested positive and negative for tumour expression of SHP-1. SHP-1-positive patients had significantly poorer local recurrence-free survival ($p = 0.008$, log-rank test, Figure 3A). However, the two groups had similar nodal recurrence-free survival ($p = 0.144$, Figure 3B), distant metastasis-free survival ($p = 0.835$, Figure 3C), overall survival ($p = 0.131$, Figure 3D), and disease free survival ($p = 0.104$, Figure 3E).

Discussion

The results of this retrospective study indicate that the tumours of NPC patients had significantly increased expression of SHP-1 at the mRNA and protein levels relative to inflammatory nasopharyngeal tissues of non-NPC patients. In addition, our survival analysis of NPC patients after RT indicated that SHP-1 expression was significantly associated with poor local recurrence-free survival, but not with nodal recurrence-free survival, distant metastasis, overall survival, or disease free survival.

Previous RT studies indicated that some subsets of tumour cells have low radiation sensitivity and that others have sensitivity. For example, a recent microarray study of NPC patients indicated that at least 2 ectopically expressed genes had roles in the prognosis of NPC patients after RT.[17] Radiation sensitivity is believed to be related to cell cycle regulation[10,11], and SHP-1 plays an important role in cell cycle regulation.[18] In particular, cells in S phase

are relatively resistant to radiation, cells in G0-G1 are somewhat sensitive to radiation, and cells in G2-M are most sensitive to radiation.[19]

Numerous other cell cycle factors also have important roles in tumorigenesis.[20] In particular, several cyclin-dependent kinases (CDKs), coupled with cyclin D, cyclin E, and CDC25A, positively regulate the transition from G1 to S, and other CDKs, coupled with cyclin B and CDC2, positively regulate the transition from G2 to M. Following DNA damage, ATM/ATR/CHK2 negatively regulates the transition from G2 to M and the transition from G1 to S *via* the p53 induction of p27 and p21. ATM/ATR/CHK2 also negatively regulates the transition from G2 to M by direct inhibition of CDC25A and CDC25B/C. CDK4, CDK6, and cyclin D is negatively regulated by p16 and p15. Signal transduction pathways, including PI3K/AKT/mTOR, Ras/MAPK, and JAK/STAT, trigger cell proliferation, survival, and apoptosis.[21] SHP-1 regulates the cell cycle of tumour cells by regulating the expression of CDK2, p27, and cyclin D1.[22] Knockdown of SHP-1 inhibits the G1/S transition in prostate cancer cells[15] and plasma SHP-1 methylation was reported as a biomarker for prognosis of patients with non-small cell lung cancer.[23] In addition, analysis of SHP-1 expression by immunohistochemistry in a breast tissue microarray indicated that expression of SHP-1 correlated with conventional pathologic parameters of tumour aggressiveness and with reduced patient survival.[25] However, there have been no previous reports on the role of SHP-1 in NPC. Our immunohistochemical staining results indicated that SHP-1 was present in the nucleus and cytoplasm of SHP-1-positive NPC cells, but the significance of the intracellular distribution of SHP-1 is unknown at present.

Tyrosine kinases are major targets for anticancer drug development. Many tyrosine kinase inhibitors and antibodies are in clinical trials or are already approved for treatment of various cancers.[25] However, there has been limited progress in the development of drugs that target tyrosine phosphatases. A recent phase I study examined the efficacy of sodium stibogluconate in inhibition of SHP-1 and SHP-2 from the peripheral blood leukocytes of patients with melanoma and some other cancers (ClinicalTrials.gov, Identifier NCT00498979), but the results have not yet been reported. As a key regulator of intracellular phosphorylation and cell cycle progression, SHP-1 may have potential as a prognostic indicator or drug target.[26]

This study is the first to provide evidence that SHP-1 may play a role in the radiation resistance of NPC cells. Nonetheless, several limitations should be noted. First, at this stage, we are unable to provide molecular details of the role of SHP-1 in radiation sensitivity. It remains to be determined whether SHP-1 is acting as an oncoprotein or as a tumour suppressor. Second, all tumour tissues were obtained before radiotherapy. It would also be informative to sample tissues after radiotherapy. Third, we used inflammatory tissues of non-NPC patients who had chronic nasopharyngeal inflammation as negative controls. It would have been better to use adjacent normal tissue of NPC patients or tissues after RT of NPC patients as negative controls.

Conclusions

Our results indicate that SHP-1 expression was higher in the tumours of patients with NPC than in the nasopharyngeal tissues of non-NPC patients who had chronic nasopharyngeal inflammation. In addition, survival analysis indicates that NPC patients who were positive for tumour expression of SHP-1 were more likely to experience local recurrence. This is the first report of an association of SHP-1 expression with a clinical outcome of NPC patients.

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research article

Evaluation of undiagnosed solitary lung nodules according to the probability of malignancy in the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines

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Background. This study retrospectively investigated the clinical significance of undiagnosed solitary lung nodules removed by surgical resection.

Patients and methods. We retrospectively collected data on the age, smoking, cancer history, nodule size, location and spiculation of 241 patients who had nodules measuring 7 mm to 30 mm and a final diagnosis established by histopathology. We compared the final diagnosis of each patient with the probability of malignancy (POM) which was proposed by the American College of Chest Physicians (ACCP) guidelines.

Results. Of the 241 patients, 203 patients were diagnosed to have a malignant lung tumor, while 38 patients were diagnosed with benign disease. There were significant differences in the patients with malignant and benign disease in terms of their age, smoking history, nodule size and spiculation. The mean value and the standard deviation of the POM in patients with malignant tumors were 51.7 + 26.1%, and that of patients with benign lesions was 34.6 + 26.7%. The area under the receiver operating characteristic (ROC) curve (AUC) was 0.67. The best cut-off value provided from the ROC curve was 22.6. When the cut-off value was set at 22.6, the sensitivity was 83%, specificity 52%, positive predictive value 90%, negative predictive value 36% and accuracy 77%, respectively.

Conclusions. The clinical prediction model proposed in the ACCP guidelines showed unsatisfactory results in terms of the differential diagnosis between malignant disease and benign disease of solitary lung nodules in our study, because the specificity, negative predictive value and AUC were relatively low.

Key words: inflammatory lung nodule; undiagnosed lung nodule; surgical resection; non-small cell lung cancer; solitary pulmonary nodules; computed tomography

Introduction

The recent prevalence of computed tomography (CT) scans in daily medical practice permits the identification of a large number of small, peripheral, undefined pulmonary lesions. The introduction of spiral CT has provided a technique with a high sensitivity for the detection of small lung cancers.[1,2] The clinical characteristics of benign solitary pul-

TABLE 1. The characteristics of 241 patients who underwent surgical resection for an undiagnosed solitary lung nodule

	Malignant tumor (n = 203)	Benign disease (n = 38)	P
Mean age	68.6	65.3	0.029
Male (%)	122 (60)	25 (66)	0.509
Smoker (%)	132 (65)	17 (45)	0.018
Past history of cancer (%)	90 (44)	12 (32)	0.144
Mean tumor diameter (mm)	17.5	14.6	0.025
Spicula (%)	122 (60)	11 (29)	<0.001
Tumor in upper lobe (%)	66 (33)	18 (47)	0.078

monary nodules, such as inflammatory pulmonary nodules, have not been fully investigated, and it is not always easy to distinguish between benign and malignant nodules using recent advanced radiographic modalities. Bronchoscopy under fluoroscopic guidance has come into wide use as a simple, safe and readily available sampling technique. However, the diagnostic yield of bronchoscopy for peripheral pulmonary lesions has been reported to be limited, because the identification of accessible bronchial routes to reach small peripheral pulmonary nodules is often difficult, and small peripheral pulmonary lesions may not be visible under fluoroscopic guidance.[3] Furthermore, it is not always easy to obtain a sufficient amount of specimen to completely rule out malignancy. For these reasons, radiological evaluations, including observational CT, should be repeated.

Alternatively, surgical resection can be selected to decide on the course of treatment. The American College of Chest Physicians (ACCP) proposed evidence-based clinical practice guidelines based on a systematic literature review and discussion with a large multidisciplinary group of clinical experts and other stakeholders.[4] This study retrospectively investigated the clinical significance of undiagnosed solitary pulmonary nodules (SPN) that were removed by surgical resection, and reviews whether using the probability of malignancy (POM) proposed in the ACCP evidence-based clinical practice guidelines is appropriate.

Patients and methods

Pulmonary resections for lung nodules were performed in 759 patients between 2006 and 2010 in the Second Department of Surgery of the University of Occupational and Environmental Health. Among them, the clinic pathological data of 241 consecutive patients who underwent surgical resection to make a differential diagnosis of malignancy or non–malignancy were reviewed.

The preoperative assessments included chest radiography and CT of the chest, upper abdomen and brain. Whole lung CT scans were obtained with a 32-detector row CT scanner (Aquilion 32, Toshiba Medical Systems) or a 64-detector row CT scanner (Aquilion 64, Toshiba Medical Systems) using the following technique: 1 mm collimation, 0.5 second rotation time, 2 mm thick reconstructions, pitch (ratio of table travel per rotation to total beam width) of 27 or 53,120 kV. Automatic tube current modulation (z-axis modulation with Real E.C. technique, Toshiba Medical Solutions) was used with the noise level set at10 SD. Bronchoscopy was routinely performed to obtain a pathological diagnosis by a trans-bronchial lung biopsy. The patients' records, including their clinical data, preoperative examination results, details of surgeries, and histopathological findings were also reviewed. Positron emission tomography (PET) scans were not routinely performed. We evaluated the probability of malignancy (POM) score for each undiagnosed solitary lung nodule according to validation of the Mayo Clinic Model on ACCP evidence-based Clinical Practice Guidelines.[5,6] The Mayo Clinic Model used a multiple logistic regression analysis to identify the following six independent predictors of malignancy: older age; a history of smoking; a history of an extrathoracic cancer; larger nodule diameter; upper lobe location; and the presence of spiculation. The prediction model is described by the following equations:

Probability of malignancy = ex / (1+ ex)

x = - 0.6827 + (0.0391 × age) + (0.7917× smoke) + (1.3388 × cancer)

+ (0.1274 × diameter) + (1.0407 × spiculation) + (0.7838 × location)

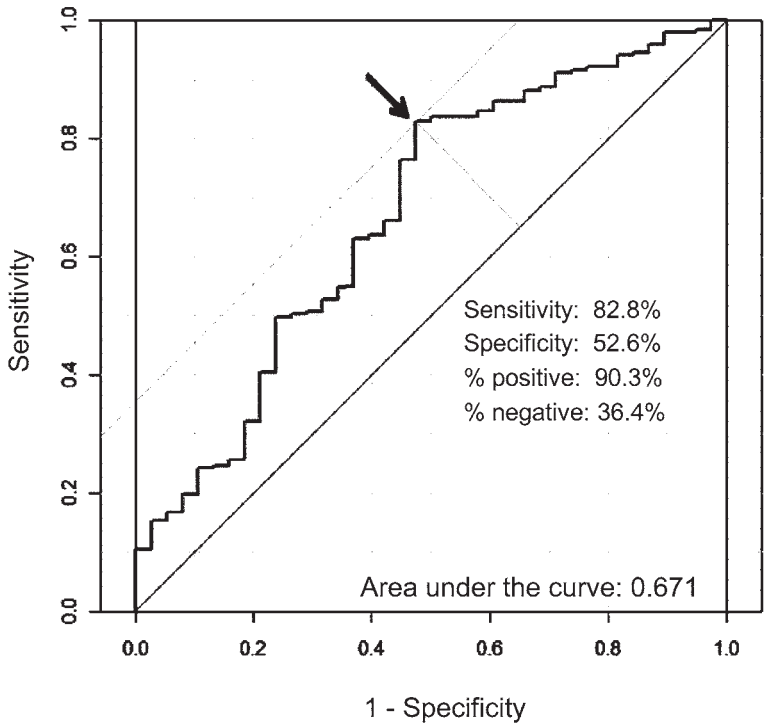

FIGURE 1. The Receiver Operating Characteristic Curve (ROC) for the prediction model of the ACCP guidelines. The area under the ROC curve was 0.67, and the best cut-off value provided from the ROC curve was 22.6.

where e is the base of the natural logarithm, age indicates the patient's age in years; smoke indicates smoking history (1 = current or former smoker, 0 = never smoker); cancer indicates a history of an extrathoracic cancer 5 or more years before nodule identification (1 = yes, 0 = no or not specified); diameter indicates the largest nodule measurement in mm, reported on initial chest x-ray or CT; spiculation indicates mention of nodule spiculation on any imaging test report (1 = yes, 0 = no or not specified); and upper is the location of the nodule within the upper lobe of either lung (1 = yes, 0 = no). The ACCP evidence-based Clinical Practice Guidelines recommends that patients should be classified into the low risk category when the POM is less than 5%, moderate risk when the POM is 5 to 60 %, and high risk when the POM is more than 60%.[6,7]

A receiver operating characteristic (ROC) analysis (LABROC5 program by Metz *et al.*, University of Chicago, IL, USA) was used to compare the observer performance in discriminating between malignant and benign cases. The accuracy of the detection was quantified by using the area under the ROC curve. The comparison between two groups was performed using Student's t-test or the Mann–Whitney test. P values < 0.05 were considered to indicate a significant difference.

The investigators followed recommendations of the Helsinki Declaration.

Results

The characteristics of the 241 patients are shown in Table 1. A total of 203 patients were diagnosed to have malignant lung tumors, while 38 patients were diagnosed with benign disease. In patients with malignant disease, 178 cases were diagnosed as primary lung cancer (143 cases of adenocarcinoma, 25 cases of squamous cell carcinoma, 5 cases of large cell carcinoma, 2 cases of small cell carcinoma, and 3 cases with other pathological types) and 25 cases were diagnosed as metastatic lung tumors. In the patients with benign disease, 13 cases were diagnosed as nonspecific inflammatory nodules, 11 cases as tuberculomas, 6 cases as hamarthomas, 4 cases as cryptococcosis, 3 cases as intrapulmonary lymph nodes and 1 case of atypical adenomatous hyperplasia. The mean age was 68.6 years in patients with malignant tumors and 65.3 years in the patients with benign disease, indicating that the patients with malignant tumors were significanty older than the patients with benign disease (p = 0.029). The former and current smokers were significantly more likely to be in the malignant tumor group (65% of subjects with malignant tumors) than to have benign disease (45% of subjects with benign disease) (p = 0.018).

Although 44% of patients with malignant tumors had malignancy in the histological evaluation of surgical specimen, 32% of patients with benign disease had malignancy in the postoperative histological evaluation. The mean tumor diameter was significantly larger in patients with malignant tumors (17.5 mm) than that of patients with benign disease (14.6 mm) (p = 0.025). Regarding spiculation, 122 malignant tumors (60%) showed spicules (55.2%), whereas 11 benign lesions (29%) had them. Malignant tumors had spicules significantly more frequently than did benign lesions (p < 0.001). No significant differences were observed in the patient gender, history of extra thoracic malignancy, or tumor location.

The mean value and the standard deviation of the POM in patients with malignant tumor were 51.7 + 26.1%, and that of patients with benign lesions were 34.6 + 26.7% (Table 2). According to the classification of the ACCP guidelines, the low risk group, moderate risk group and high risk group in

TABLE 2. The comparison of the probability of malignancy between malignant tumor and benign disease

	Malignant tumor (n = 203)	Benign disease (n = 38)	P
Mean probability of malignancy	51.7	34.6	p < 0.001
Low risk group (%)	3 (1)	4 (10)	
Median risk group (%)	112 (55)	25 (66)	
High risk group (%)	88 (43)	9 (24)	

patients with malignant tumors included 3 (1.5%), 112 (55.2%), and 88 (43.3%) patients, respectively. There were 4 patients (10.5%) who were at low risk, 25 (65.8%) at medium risk and 9 (23.7%) at high risk among the patients with benign lesions.

The ROC curve of the POM is indicated in Figure 1. The area under the ROC curve (AUC) was 0.67. The best cut-off value provided from the ROC curve was 22.6. When the cut-off value was set at 22.6, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 83%, 52%, 90%, 36% and 77%, respectively.

Discussion

The incidental finding of a pulmonary nodule on CT is becoming an increasingly frequent event, and the management of these nodules has become an important issue.[1,8] The most important concern is the differential diagnosis of benign disease from lung carcinoma. The optimal management of these SPN remains unclear. Minimizing the risk of unnecessary surgery should be considered, especially in patients with benign disease. However, it is not always easy to make a diagnosis preoperatively. The size of the nodule is a significant determinant of the diagnostic yield in bronchoscopy when evaluating lung nodules.[3] The yield of bronchoscopy is particularly low for lesions ≤ 2 cm that are located in the outer third of the lung. In a recent review article, the sensitivity of conventional bronchoscopy for peripheral bronchogenic carcinoma < 20 mm was reported to be 34%, and was 63% for peripheral bronchogenic carcinoma > 20 mm.[4]

High resolution CT can evaluate the detailed characteristics of lung nodules, such as their size, morphology, and type of opacity. The risk for malignancy increases at a rate proportional to the diameter of the nodule.[9] Solitary nodular shadows with pleural indentation and spicule formation are common radiological features of NSCLC. Wadahi *et al*. reported that the risk for malignancy in incidental or screening-detected nodules was approximately 20 to 30% in nodules with smooth edges; in nodules with irregular, lobulated, or spiculated borders, the rate of malignancy was higher, but varied across studies from 33 to 100%.[10] In our study, there was statistically significant relationship between the tumor diameter and spiculation. Nodules that were pure ground-glass opacities (GGO), or predominately GGO were more likely to be malignant than solid nodules.[8,11]

FDG-PET scanning has been used to differentiate malignant solid lung nodules from benign nodules according to the basic concept that malignant pulmonary nodules have higher glucose metabolism. A recent review calculated the sensitivity and specificity of FDG-PET scanning to be 94.2% and 83.3%, respectively, for the identification of malignant pulmonary nodules.[5,10] False-positive results are usually observed in lung nodules with an infectious or inflammatory etiology, such as due to tuberculosis, histoplasmosis, or rheumatoid nodules. Chun *et al*. reported that the maximum SUV uptake was significantly higher in patients with inflammation than in those with malignancy in part-solid nodules.[12]

In CT-guided percutaneous lung biopsy, the lesion size was also a determining factor for the diagnostic accuracy, and the sensitivity for malignancy was 76-88%.[13,14] However, pneumothorax was the most common complication and occurred in 20-40% of patients.[15] Tomiyama *et al.* reported severe complications in 9783 biopsies as follows; 0.061% with air embolism, 0.061% with tumor seeding at the site of the biopsy route, 0.10% with tension pneumothorax, 0.061% with severe pulmonary hemorrhage or hemoptysis, and 0.092% with haematothorax.[16] The procedure is a safe and useful method, but it should be performed by appropriately trained and experienced physicians.[17]

After the use of a non-surgical approach such as bronchoscopy, or transthoracic needle aspiration/biopsy, the next step is to perform a radiological follow-up, since the evaluation of temporal changes in a small nodule may contribute to differentiating a malignant tumor from benign pathology.[18,19]

Alternatively, the diagnosis of a lung nodule may require surgical resection, after taking into account the benefits of a definitive diagnosis and treatment when compared with the surgical risk. Thoracoscopic resection is a minimally-invasive procedure for an undiagnosed solitary pulmonary nodule; it is useful for a definitive diagnosis not only to treat benign lesions, but also to plan the proper surgical procedure in case of malignancy.[20,21] In patients with indeterminate lung nodules in the peripheral third of the lung, thoracoscopy should be recommended to perform a diagnostic wedge resection.[5]

There are several algorithms for the diagnostic prediction to manage solitary lung nodules.[9,22,23] The Mayo Clinic model expressed the probability of malignancy using independent predictors of three clinical and three radiographic variables.[9] Herder *et al*. reviewed and calculated the prediction of malignancy based on the Mayo Clinic model together with a PET scan.[23] They demonstrated that the prediction model improved the AUC after the addition of the results of PET scans. Michael *et al*. identified the following four independent predictors of malignancy by using multivariate logistic regression analysis: positive smoking history; older age; larger nodule diameter; and quitting smoking.[24] Each prediction model included the clinical and radiographic characteristics of lung cancer and seemed to provide good accuracy and calibration. In our study, a significant difference was found for the POM according to the calculation of the Mayo Clinic model, and the clinical prediction model was proven to have external validity. The AUC in our study was 0.67, which was low in comparison with those reported by other investigators (AUC 0.79 by Herder, AUC 0.83 by Swensen).

According to the ACCP guidelines, patients with a POM higher than 5% are classified into an intermediate–high risk group, and they are recommended to undergo additional tests, including PET, contrast-enhanced CT, transthoracic fine-needle aspiration biopsy or bronchoscopic biopsy, or video-assisted thoracoscopic surgery. The clinical prediction model proposed in the ACCP guidelines is an overestimated model, with few patients being categorized into the low risk group in the present study. While the POM overestimation model might result in unnecessary surgery or biopsy in some patients with benign nodules (a false positive diagnosis), underestimation models might lead to a delayed diagnosis and missed opportunities for a surgical cure in patients with malignant nodules (a false negative diagnosis). Schultz *et al*. proposed that clinicians should be mindful of the prevalence of malignant nodules in their practice setting.[25]

In the present study, we retrospectively reviewed the clinic pathological data of patients who had nodules measuring 7 mm to 30 mm and a final diagnosis established by histopathology. Therefore, the effect of "work up bias" should be considered in the evaluation of the prediction model.[26] Patients with a positive test result are likely to undergo a procedure for tissue pathologic verification, resulting in a disproportionately large share of patients undergoing verification having a positive test. For this reason, sensitivity (positive test when disease is present) appears to be high. Although the specificity, negative predictive value, and AUC were relatively low in our study, the clinical prediction model proposed in the ACCP guidelines have validity to prevent a false negative diagnosis. We consider that this model should not be used as a stand alone test, but that the model can help to adjust the diagnostic work-up. Further investigations should be necessary to evaluate the benefits of the clinical prediction model of ACCP guidelines in various cohorts as follows; all population having a mass screening CT, or high risk groups such as elderly, smokers or patients with history of cancer.

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research article

Results of photon radiotherapy for unresectable salivary gland tumors: is neutron radiotherapy's local control superior?

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Background. The results of RTOG-MRC randomized trial of photon (n=15) versus neutron (n=17) therapy in the 1980's reported an improved local control (LC) with neutron radiotherapy for unresectable salivary gland tumors. Due to increased severe toxicity with neutron radiotherapy and the paucity of neutron-therapy centers, we analyzed our institution's results of photon radiotherapy for unresectable salivary gland tumors.

Patients and methods. From 1990 to 2009, 27 patients with unresectable salivary gland cancer underwent definitive photon radiotherapy at our institution. Nodal involvement on presentation was found in 9 patients. Median dose of radiotherapy was 70 Gy. Chemotherapy was given to 18 patients, most being platinum-based regimens. Local control (LC), locoregional control (LRC), distant metastasis-free survival (DMFS), overall survival (OS), and toxicity outcomes were assessed.

Results. With a median follow-up of 52.4 months, the 2/5-year actuarial LC was 69% (95%CI ± 21.0%)/55% (± 24.2%), LRC was 65% (± 21.4%)/47% (± 21.6%), and DMFS was 71% (± 21.8%)/51% (± 22.8%), respectively using competing risk analysis. The median OS was 25.7 months, and the 2/5-year OS rates were 50% (± 19.0%)/29% (± 16.6%), respectively. Higher histologic grade was significant for an increased rate of DM (intermediate grade *vs.* low grade, p=0.04, HR 7.93; high grade *vs.* low grade, p=0.01, HR 13.50). Thirteen (48%) patient's experienced acute grade 3 toxicity. Late grade 3 toxicity occurred in three (11%) patients.

Conclusions. Our data compares favorably to neutron radiotherapy with fewer late complications. Photon radiotherapy is an acceptable alternative to neutron radiotherapy in patients who present with unresectable salivary gland tumors.

Key words: photon; neutron; radiotherapy; salivary gland cancer; IMRT

Introduction

Salivary gland tumors are rare, with the annual worldwide incidence ranging from 0.05-2 per 100,000. A small but appreciable rise in incidence in the United States has occurred from 6.3% in 1974 to 8.1% in 1999.[1] Salivary gland tumors are a heterogeneous group of tumors consisting of a diverse range of histologies. Initially it was felt that salivary gland tumors were radioresistant, although multiple-studies have demonstrated improved local control in high-risk patients with post-operative radiotherapy (RT). Therefore, the standard treatment approach for salivary gland tumors be-

came surgery with the addition of post-operative radiotherapy for patients at high risk of locoregional recurrence.

Dismal local control has been reported for definitive radiotherapy using photon beam RT alone. The low LET of photon RT for these superficial tumors most likely accounted for the poor local control.[2] On the contrary, neutron beam RT had a superior radiobiological effectiveness (RBE) versus photon beam, with reports by Batterman *et al.* providing some of the earliest evidence for its use with unresectable salivary gland tumors.[3] Based upon these results, as well as numerous non-randomized studies, the RTOG-MRC performed a landmark phase III trial comparing photon and neutron RT for unresectable salivary gland tumors. This small randomized study consisted of a cohort of 32 patients who received photon radiotherapy of 55-70 Gy or fast neutron therapy. The neutron arm had a 2-year local regional control (LRC) rate of 67% in comparison to only 17% for photon-based RT. The study was closed early due to the large difference in efficacy between the two arms. As a result, neutron RT was established as the preferred treatment modality for unresectable salivary gland tumors. In their 10-year update the authors report the 5-year local control (LC) rate was 56% and 17% for neutron and photon RT, respectively. Despite improvement in LC, there was no improvement in overall survival. Furthermore, they did report that neutron therapy resulted in more severe toxicity.[4,5]

Currently, there are few centers that offer neutron RT. Due to the logistical difficulty in sending patients for neutron therapy, and the increased severe toxicity, we aimed to assess our institutions experience with photon RT since the routine implementation of more advanced radiotherapy techniques, imaging, and systemic therapies.

TABLE 1. Baseline characteristics

		N	%
Gender	Male	12	44.4
	Female	15	55.6
Age	Median	55	
	Range	34 - 92	
Year of RT	1990-1995	9	33.3
	1995-2000	9	33.3
	2000-2005	4	14.8
	2005+	5	18.5
Subsite	Minor	19	70.4
	Major	8	29.6
Histology	Adenoid Cystic	10	37.0
	Mucoepidermoid	6	22.2
	Myoepithelial	0	0
	Adenocarcinoma	6	22.2
	Other	5	18.5
Grade	Low	2	7.4
	Intermediate	3	11.1
	High	17	63.0
	Unknown	5	18.5
T-stage	T1	1	3.7
	T2	2	7.4
	T3	6	22.2
	T4a	14	51.9
	T4b	4	14.8
Primary tumor size (cm)	Median	5	
	Range	3 - 12	
LN involved	Yes	9	33.3
	No	16	59.3
	Indeterminate	2	7.4
Recurrent Disease		3	11.1
Chemotherapy	Yes	18	66.7
	No	9	33.3

Patients and methods

Between January 1990 and December 2009, 27 patients with primary unresectable salivary gland cancer were diagnosed and treated at Memorial Sloan-Kettering Cancer Center. The records of these patients were reviewed. Table 1 shows baseline characteristics for our cohort.

All patients underwent a complete history and physical examination along with staging imaging, including computed tomography (CT) and magnetic resonance imaging (MRI). More recently, positron-emission tomography (PET) was used. All patients were staged according to the American Joint Committee on Cancer staging 7th edition.

No patients received prior treatment and none had distant metastasis (DM) at presentation. The median follow up was 52.4 months. CT simulation with intravenous contrast was performed on all patients, and beginning in 2005 was often fused to diagnostic MRI imaging for improved target delineation. All patients received photon based RT at Memorial Sloan-Kettering Cancer Center. Twenty-one of the

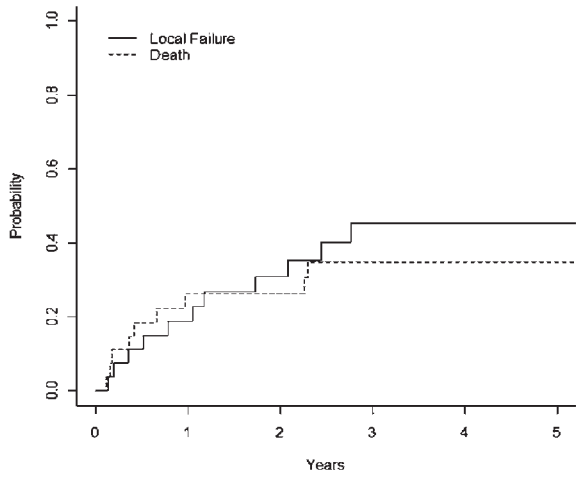

FIGURE 1. Local failure cumulative incidence for entire cohort with death as the competing risk.

due to the small sample size. Two-sided *P* values ≤0.05 were considered statistically significant. Statistical analysis was performed using R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

As shown in Figure 1, among our cohort the 2- and 5-year LC rates using competing risk analysis were 69% (95%CI ± 21.0%) and 55% (± 24.2%) respectively. There were 12 patients who experienced a local recurrence. All local recurrences occurred within the first 3 years after treatment.

A univariate analysis was conducted to determine predictors of local recurrence shown in Table 2, and found that neither histology, lymph

TABLE 2. Univariate analysis for local failure

Variable	HR	P-value
T-Stage	0.81	0.7
N-Stage	0.61	0.46
Histology (adenoid cystic vs. other)	1.34	0.59
Grade		
Low	1.00	Reference
Intermediate	4.41	0.09
High	5.60	0.15
BOS Location	1.8	0.7
Major vs. Minor	0.83	0.78
Chemotherapy	1.60	0.45

27 patients received 70 Gy, and the remaining six patients received between 60 and 68.4 Gy.

Target delineation for patients treated with 3D-CRT and IMRT were defined as follows. The gross target volume (GTV) was based upon the primary site. All gross disease was included in the GTV70, as well as any involved lymph nodes, or nodes ≥ 1cm in the short axis. The clinical target volume (CTV) 70 was a 5 mm expansion, and included any additional suspicious lymph nodes <1 cm. The planning target volume (PTV) 70 generally was an additional 3-5 mm expansion. The high-risk subclinical regions were treated to 60 Gy. An additional region was treated to 50 Gy; for node positive patients ipsilateral levels Ib-V were included, and node-negative patients levels Ib-IV were treated. The exception to the nodal coverage was adenoid cystic histology which we did not include elective neck coverage secondary to the low incidence of lymphatic spread. The base of the skull was also prophylactically treated in patients at high risk of tumor spread secondary to perineural invasion. Eleven patients received RT to nodal regions. Five patients also received electrons to the primary site. A total of 9 patients received IMRT, and 18 were treated with 3D-CRT. Chemotherapy was given at the discretion of the treating medical oncologist.

Patients were followed routinely with CT, MRI, or PET scan depending on the degree of suspicion for local or distant recurrence. Imaging was performed usually every 3 to 6 months post-treatment to assess for response to therapy. Recurrent disease was biopsied in all cases for pathologic confirmation. DM was determined by imaging evidence, and biopsies were performed only if there was question to the radiographic certainty. Grading of toxicities was performed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Unresectability was a clinical decision made in conjunction with a head and neck surgical oncologist, radiation oncologist, and medical oncologist. All but two patients were deemed unresectable secondary to advanced stage disease, extensive volume of disease, and proximity to nearby critical structures that would results in excessive surgical morbidity (*i.e.* cranial nerves, orbit, base of skull, nasopharynx, etc). Two patients were deemed unresectable secondary to poor performance status and multiple comorbidities.

Actuarial likelihood estimates, univariate hazard ratios, and 95% confidence intervals (95% CI) for LC, LRC, and DMFS were analyzed using the competing-risk method, with death as the competing risk. Multivariate analyses were not performed

node involvement, use of chemotherapy, and proximity to base of skull were significant. Histologic grade trended towards significance for higher histologic grades having a detriment in LC (intermediate grade vs. low grade, p=0.09, HR 4.41; high grade vs. low grade, p=0.15, HR 5.60).

The LRC rates using competing risk analysis at 2- and 5-year were 65% (± 21.4%) and 47% (± 21.6%), respectively (Figure 2). The median time to locoregional failure was 2.1 years, and all events occurred prior to 3 years post-treatment. A total of 14 patients experienced a locoregional failure. A univariate analysis was performed and did not show that T-stage, N-stage, histology, major versus minor salivary gland origin, or chemotherapy use were predictive for LRC. Base of skull location (p=0.09, HR=2.37), and histologic grade (intermediate grade *vs*. low grade, p=0.08, HR 4.40; high grade *vs*. low grade, p=0.14, HR 5.60) trended for worse LRC.

The DMFS rates at 2- and 5-year using competing risk analysis were 71% (± 21.8%) and 51% (± 22.8%), respectively (Figure 3). A total of 14 patients developed DM, and all events occurred at less than 3 years post-treatment. A univariate analysis was performed and did not show that T-stage, N-stage, Histology, major versus minor salivary gland location, or base of skull location were prognostic for DM. Higher histologic grade was significant for an increased rate of DM (intermediate grade *vs*. low grade, p=0.04, HR 7.93; high grade *vs*. low grade, p=0.01, HR 13.50). The median overall survival was 2.14 years (25.7 months), with a 2 year survival rate of 50% (± 19.0%) and 5 year overall survival of 29% (± 16.6%) (Figure 4). At time of analysis, 21 of 27 patients had died. The 10-year overall survival rate was 16.6% (± 15.8%) and only 3 patients had lived this long in our cohort.

Thirteen (48%) patient's experienced acute grade 3 toxicity. Of these patients three patients experienced more than 1 type of acute grade 3 toxicity. Most grade 3 toxicity consisted of mucositis and dysphagia. No patients experienced acute grade ≥4 toxicity. Fifteen patients experiences acute grade 2 toxicity, which primarily consisted of mucositis, skin irritation, dysphagia, fatigue, and xerostomia. Late grade 3 toxicity occurred in three (11%) patients consisting of dysphagia in two patients, and the third patients experienced both grade 3 mucositis and hearing loss. Five patients had grade 2 late toxicity consisting of xerostomia in four patients, and trismus in 1 patient. No late grade ≥4 toxicity occurred.

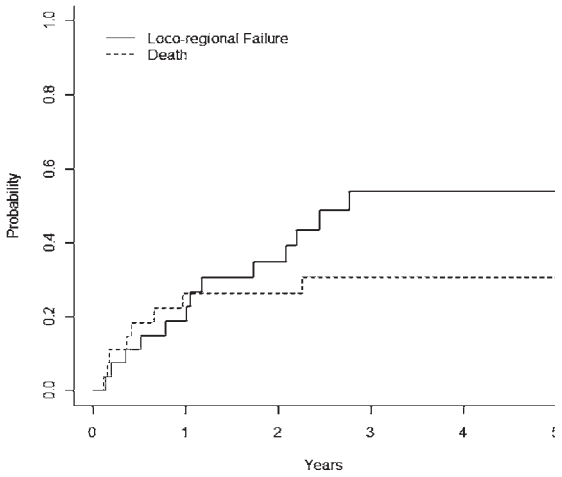

FIGURE 2. Loco-regional failure cumulative incidence for entire cohort with death as the competing risk.

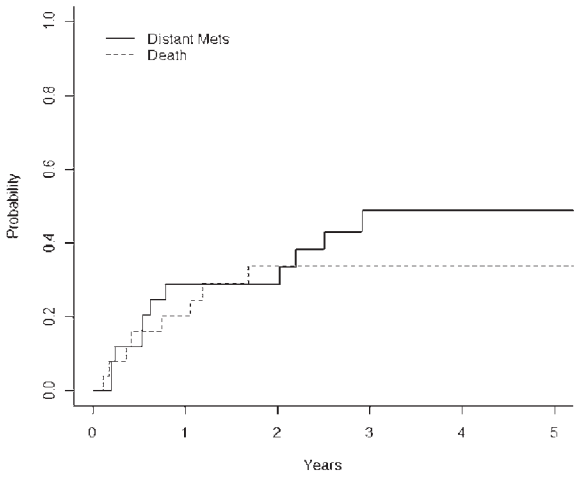

FIGURE 3. Distant-metastasis cumulative incidence for the entire cohort with death as the competing risk.

Discussion

Current level 1 evidence suggests a superior LC for neutron RT compared to photon RT. The data that supports this however is derived from patients treated over twenty years ago, and numerous advances have occurred in the field of radiation oncology, systemic chemotherapy options, and imaging techniques. In addition, during this time period the number of centers offering fast neutron RT have diminished to now only three in the United States. With each facility costing over 20 million dollars, and the limited utility of neutron therapy in oncology, it is unlikely that more centers will be starting up. For these reasons when a radiation oncologist is faced with decision of how to treat a patient with an unresectable salivary gland cancer,

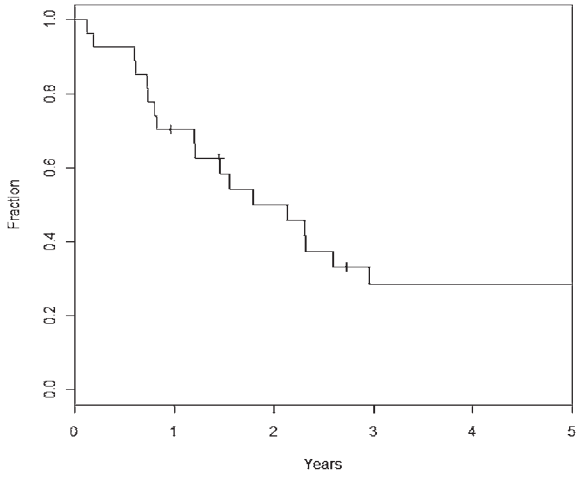

FIGURE 4. Kaplan Meier for overall survival of entire cohort.

they must pose the question of referring them to a neutron facility (assuming the patient can afford and is willing to travel).

The spark for neutron radiotherapy began in the 1930's and since that time a plethora of clinical and laboratory research has been conducted to evaluate its utility in oncology. Salivary gland tumors in general have long doubling times which make them particularly sensitive to high LET RT, one of the reasons why neutron RT was appealing to test in this tumor type. Based upon over 600 patients that were aggregately pooled and reported in the discussion in the RTOG-MRC trial there was a 26% LC rate in the pooled photon RT studies when compared to 67% in the pooled neutron studies. This was consistent with their randomized phase III trial results comparing neutron with photon/electron RT showing 2- and 5-year LC rates for neutron RT of 67% and 56%, respectively. From these results neutron RT was recommended as the preferred treatment modality.[5]

In a more modern cohort we report here comparable 2- and 5-year LC rates of 69% and 55%, respectively. Furthermore, despite the RTOG-MRC and our study including only unresectable patients, where both had similar tumor size; RTOG-MRC trial neutron arm had a median tumor size of 6 cm (range of 3-9 cm), and in our cohort median tumor size of 5 cm (range 3-12 cm). In addition we had an identical rate of lymph node involvement compared to the photon arm in the RTOG-MRC trial (33%).

Importantly, the RTOG trial did not show that neutron RT was associated with an improvement in OS. Being that the trial was small (n=25 analyzable patients) it is unlikely that it would be able to show an OS with such a small cohort. Other studies have attempted to replicate the results of the RTOG-MRC study. Huber *et al*. compared neutron radiotherapy, photon radiotherapy, and mixed beam radiotherapy for the treatment of 75 patients with inoperable, recurrent, or incompletely resected adenoid cystic carcinoma of the head and neck.[6] In this study, the actuarial 5-year LC was 75% for neutrons, and 32% for both mixed beam and photons. Similar to the RTOG-MRC study, LC did not translate into a survival benefit.

In the 1980's retrospective series of photon/electron based RT had LC rates that ranged from 6.5% in Vikram *et al*.[7], to most reports of 20-40%. Vikram *et al*. highlighted that definitive RT is feasible, but primarily should be reserved for palliation. All of these series had less than 50 patients and doses were often suboptimal by today's standards (<60 Gy). Wang *et al*. from Harvard analyzed 24 patients treated from 1980 to 1989 with unresectable salivary gland lesions.[8] All of the patients were irradiated with either a ^{60}CO or 4-6 MV photon linear accelerator and hyperfractionated photons, twice daily, with 1.6 Gy per fraction for a total of 65-70 Gy. Furthermore, various boost techniques such as intraoral cone and interstitial brachytherapy were employed. With a median follow up of 43 months, overall 5-year actuarial local control survival rates were 85% and 83% respectively. Most impressively, parotid lesions displayed a 100% 5-year actuarial LC rate at the primary site. It should be noted that almost half of the lesions were low stage (T1-T2), contributing to their excellent outcomes.

Since 2000, there have been select publications on the use of photon RT for unresectable salivary gland tumors. One of the largest series originates from the Netherlands, and included 386 patients treated with RT treated from 1984-1995, of which only 40 were treated with definitive RT without upfront surgery.[9] They reported complete, partial, and <50% response rates 3–6 weeks after RT of 38%, 30%, and 30%, respectively. In addition, they demonstrated a dose–response relationship with a 50% LC rate at 5 years for doses ≥66 Gy *vs*. 0% for < 66 Gy (p=0.0007). Twenty-three of the 27 patients in our cohort received ≥66 Gy, likely contributing to our improved results over historic studies. Chen *et al*. reported on 45 definitively treated patients between 1960 and 2004, with a median dose of 66 Gy (range, 57–74 Gy).[10] The 5- and 10-year rate estimates of LC were 70% and 57%, respectively. Their excellent outcomes likely relate to half of the patients had T1 or T2 tumors, and none had lymph node involvement at presentation. One-third of our

cohort had involved lymph nodes, and only 3 of the 27 had early stage disease, and 18 had T4 disease.

Combined modality therapy with concurrent chemo-radiotherapy has shown promising outcomes. A study by Katori *et al*. evaluated 17 patients with advanced salivary gland cancer who received cisplatin, pirarubicin, and cyclophosphamide, and found that 4 patients had a complete pathologic complete response.[11] The authors reported a 5-year OS of 70%. Most recently, Rosenberg et al. published the results of 15 patients treated with chemo-radiotherapy, of which 7 patients had unresectable salivary gland cancer treated with definitive chemo-radiotherapy.[12] For the whole cohort 2-year OS was 67%, LC 76%, and DMFS 70%. However, among definitively treated patients, only two patients did not develop a local, regional, or distant failure. Due to the inherent bias for higher risk patients to receive chemotherapy, it is not surprising chemotherapy did not show a benefit for any outcomes measured.

A key component regarding the RTOG-MRC trial pertains to the increased "severe or greater" toxicity in the neutron arm. They reported 26 events of "severe or greater" toxicity in the neutron arm, compared to only 10 events in the photon/electron arm. Overall there were 9 patients (69%) in the neutron arm compared to 4 patients (33%) in the photon arm (p=0.07) experiencing severe or greater toxicity. The high toxicity of neutron therapy has been shown by others as well. Douglas *et al*. reported numerous severe complications in their cohort; temporal lobe necrosis, cervical cord myelopathy with resultant paralysis, osteoradionecrosis of the mandible, palatal fistula, severe trismus, and complete loss of vision in the left eye.[13] We report 13 (48%) patient's experienced acute grade 3 toxicity, which would correlate with severe toxicity. In addition, late grade 3 toxicity occurred in only three (11%) patients. Importantly, no grade ≥4 toxicity occurred. With late toxicity generally being the primary predictor of long-term quality of life, we report markedly lower toxicity in our series with similar LC rates.

There are several limitations of our current study. The retrospective methodology of our study is inherent to bias. Despite this being a relatively large series for this rare disease, the small number of patients limits the ability for robust multivariate analyses. Furthermore, historical comparisons to RTOG-MRC trial have potential confounding variables due to difference in treatment year, histologies and subsites of the head and neck involved, and other high risk features that may be imbalanced from our cohort.

Conclusions

We show comparable 2- and 5-year LC rates with photon based RT compared to the historic results from fast neutron radiotherapy in the RTOG-MRC trial. Additionally, we report markedly lower grade 3 (severe) toxicity rates in only 11% of patients, and no grade ≥4 toxicity occurred. Due to the lack of available neutron centers, the authors believe that when treating to doses ≥70 Gy, and with the addition of chemotherapy and IMRT techniques, photon RT is a reasonable alternative. A modern randomized trial is warranted to reassess the superiority on local control of neutron radiotherapy for unresectable salivary gland tumors.

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research article

Balloon aortic valvuloplasty (BAV) as a bridge to aortic valve replacement in cancer patients who require urgent non-cardiac surgery

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Background. Balloon aortic valvuloplasty (BAV) is a percutaneous treatment option for severe, symptomatic aortic stenosis. Due to early restenosis and failure to improve long term survival, BAV is considered a palliative measure in patients who are not suitable for open heart surgery due to increased perioperative risk. BAV can be used also as a bridge to surgical or transcatheter aortic valve implantation (TAVI) in haemodinamically unstable patients or in patients who require urgent major non-cardiac surgery.

Patients and methods. We reported on 6 oncologic patients with severe aortic stenosis that required a major abdominal and gynaecological surgery. In 5 cases we performed BAV procedure alone; in one patient with concomitant coronary artery disease we combined BAV and percutaneous coronary intervention (PCI).

Results. With angioplasty and BAV we achieved a good coronary artery flow and an increase in aortic valve area without any periprocedural complications. After the successful procedure, we observed a hemodynamic and symptomatic improvement. As a consequence the operative risk for non-cardiac surgery decreased and the surgical treatment of cancer was done without complications in all the 6 cases.

Conclusions. BAV can be utilized as a part of a complex therapy in severe aortic stenosis aimed to improve the quality of life, decrease the surgical risk for major non-cardiac surgery or as a bridge to surgical or transcatheter aortic valve implantation.

Key words: aortic valve stenosis; balloon dilatation; angioplasty; heart valve prosthesis implantation; elderly; comorbidities; coronary artery disease

Introduction

Aortic stenosis in high risk patients

Calcific stenosis of the aortic valve (AS) is the most common acquired valve disorder in the Western world.[1] It is a degenerative, atherosclerosis-like chronic inflammatory process that leads to lipid and calcium accumulation into the valve leaflets. It leads to leaflet sticking, limitation of movement and narrowing of the aortic valve area (AVA). The disease progresses slowly and the prevalence is increasing with aging of the population. Moderate AS is present in 2 to 7% of the population over 65 years and severe AS is present in 5 to 7% of the population over 80 years and in 10 to 15% over 90 years.[1-3] Patients may be asymptomatic for several years and become symptomatic only in the last stage of the disease when the average survival is around 2 years with high risk for sudden cardiac death.[4] So far no reliable data exist on prevalence of AS in patients with cancer but this coincidence is not rare in clinical practice.

Surgical aortic valve replacement (SAVR) is considered the treatment of choice in patients with severe, symptomatic AS regardless of age.[5,6] The surgical risk in elderly patients with multiple co-

morbidities can be very high and the presence of concomitant coronary artery disease (CAD) with the need for additional coronary artery bypass may duplicate the risk.[7-9] Therefore approximately one third of such patients might not be surgically treated and are left to the natural history of the disease.[4]

Aortic stenosis in cancer patients

The decision for SAVR is particularly complex in cancer patients where cancer prognosis and possible perioperative complications raise concerns. Thus, one of the common reasons for declining surgery in patients with severe aortic stenosis is cancer.[4]

Two studies were published on the latter, where in the first study the authors observed greater increased perioperative mortality and morbidity in chronic lymphocytic leukaemia patients after an open heart surgery, due to infectious complications.[10] The second study did not prove this kind of phenomena, but, the authors included patients with solid tumours, who may have less compromised immunity than patients with haematological malignancies.[11] Yusuf *et al*. recently analyzed a group of 48 cancer patients with severe AS where 13 patients underwent SAVR and the others were managed medically. He demonstrated that cancer patients with severe AS who underwent SAVR had longer survival, regardless of cancer status or presence of metastasis.[11]

Balloon aortic valvuloplasty

Balloon aortic valvuloplasty (BAV) was introduced in 1986 as the first less invasive, percutaneous treatment option for treatment of AS (Figure 1).[12]

Unfortunately, early restenosis of the dilated valve with symptom recurrence and poor long term survival limits the use of this procedure.[13-17] Today BAV is considered a palliative measure in patients with increased perioperative risk or a bridge to open heart surgery in haemodinamically unstable patients or in patients who require urgent major non-cardiac surgery, like oncologic patients. In case of concomitant coronary artery disease (CAD), valvuloplasty and coronary angioplasty (PCI) may be performed safely during the same procedure.[18,19] In the last few years new therapeutic options are being developed such as transcatheter aortic valve implantation (TAVI) where BAV plays an important role in preparing the stenotic aortic valve for the aortic valve prosthesis implantation.[20-23] Furthermore, in high risk patients where SAVR is not an option BAV can be used as a bridge to TAVI.

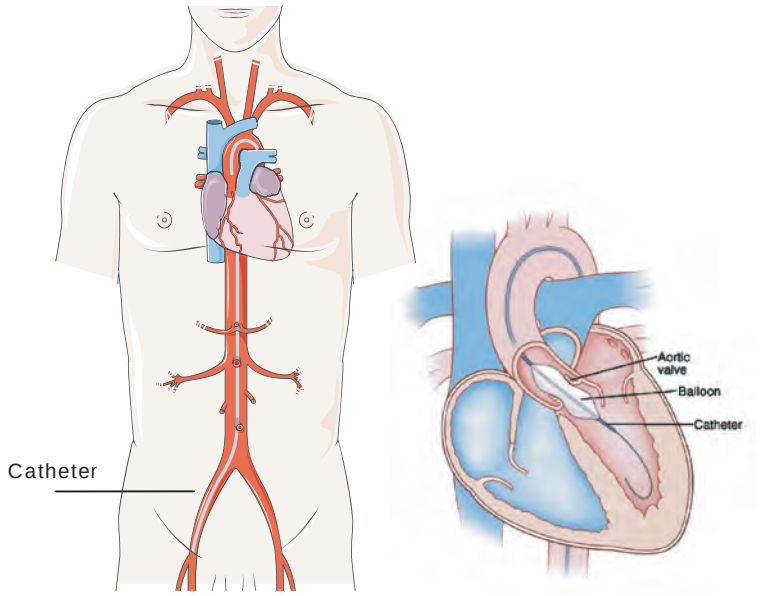

FIGURE 1. Balloon aortic valvuloplasty (BAV): The balloon catheter is advanced via femoral artery to the left ventricle and placed into the stenotic aortic valve where the balloon is inflated.

In this paper we report experiences of a single institution in percutaneous treatment of aortic stenosis in oncologic patients undergoing urgent non-cardiac surgery.

Patients and methods

We retrospectively reviewed all the patients who were treated with BAV in the Department of Cardiology, Division of Internal Medicine, University Medical Centre Ljubljana from June 2009 to April 2011. We included in the present study only the high risk patients who presented with carcinoma and required the procedure before urgent major tumour excision.

Inclusion criteria for BAV were:
- severe AS,
- increased perioperative risk defined with Logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation calculated at http://www.euroscore.org/) > 20%,
- indication for urgent major tumour excision

Description of the procedure

Before and after BAV patients underwent invasive and non invasive cardiac diagnostic studies to evaluate the severity of aortic stenosis and left ventricular function. Informed consent was

TABLE1. Baseline clinical characteristics and results of the procedure for each patient

Patient number	1.	2.	3.	4.	5.	6.
Age (year)	73	87	79	80	77	82
Gender	F	F	M	M	F	F
Logistic EuroSCORE (%)	5.22	12.8	5.6	28.9	5.8	15,9
Comorbidities	AH, HLP	AH	AH,DM,CKD,PH, ACI stenosis, HLP	PH, HF	ACI stenosis AH,HLP	CKD-HD,AH
CAD	NO	NO	1 VD: S/P PCI D1	NO	1 VD: M1	NO
Carcionoma/stage	Colon T3 N0 M0	Rectum T4 N1 M0	Colon T3 N0 MX	Rectum T3 N1 M0	Gastric T3 N0 MX	Vulva T1b N0 M0
Suregery after BAV	Hemicolectomy	APE and right adnexectomy	Colon resection	Abscess drainage, ileum resection	Gastric resection	Vulva resection
Procedure	BAV	BAV	BAV	BAV	BAV and PCI M1	BAV
LVEF (%) before BAV	80	60	50-55	20-25	60	60
LVEF (%) after BAV	85	60	55	20-25	70	60
AVA before (cm2)	0.9	0.8	0.67	0.45	0,7	0,5
AVA after (cm2)	1.0	1.1	0.7	0,55	0,75	0,6
Peak grad before (mmHg)	60	75	65	51	71	90
Peak grad. after (mmHg)	53	54	47	40	60	75
Mean gradiet before	42	53	40	55	53	50
Mean gradiet after	33	50	30	40	42	40
Periprocedural Complications	NO	NO	LBB, TnI	NO	NO	Catheter stuck in femoral a.
Days of hospitalisation	9	2	8	1	13	1
Follow up - period months	10.5-†	29	29	3-†	23	14

ACI = internal carotid artery; APE = abdominoperineal resection; AH = arterial hypertension; BAV = balloon aortic valvuloplasty; CAD = coronary artery disease, CKD = chronic kidney disease; DM = diabetes mellitus; D1 = first diagonal coronary artery; F = female; HD = haemodialysis; HF = heart failure; HLP = hyperlipidemia; LBB = left bundle branch block; M = male; M1 = first marginal coronary artery; PCI = percutaneous coronary intervention; PH = pulmonary hypertension; TnI: troponin I; 1 VD = one vessel disease; † = has died during the follow up

obtained from all the involved patients and their relatives. The procedure was performed in our cardiac catheterisation laboratory in local anaesthesia. Via percutaneous transfemoral approach a balloon catheter (18–23 mm x 4.0 cm) was introduced and positioned across the stenotic aortic valve (Figure 1). Aortic valvuloplasty was performed with balloon inflation (25–30 ml, 3–4 atm) with the aim to increase AVA and reduce transaortic pressure gradient. Before and after the valvuloplasty the peak to peak pressure gradient was measured with the pigtail catheter. The goal of the procedure was a reduction of the pressure gradient by at least 50% and if necessary, the balloon inflation could be repeated. Before valvuloplasty a coronary angiography was performed and in case of CAD, angioplasty was also done during the same procedure.

Results

Among 230 patients who underwent BAV since June 2009, we performed the procedure in 6 high risk patients who presented with severe aortic stenosis and required an urgent non-cardiac surgery. Baseline characteristics and the procedure results are displayed in Table 1. The patients were at high risk for surgery with mean age of 79.7 years and mean logistic EuroSCORE of 12.37%. Five of them suffered from gastrointestinal and one from gynaecological carcinoma. In one patient we observed concomitant obstructive CAD that was resolved with PCI and implantation of two coronary stents, in the rest of the patients only BAV was done.

Echocardiographic assessment before and after BAV showed a significant increase in AVA (from

0.67 to 0.78 cm^2; $p<0.05$) accompanied by a decrease in peak and mean transvalvular pressure gradients (from 68 to 54 mmHg; $p<0.05$ and from 48 to 39 mmHg; $p<0.05$ respectively). No significant change in left ventricular systolic function evaluated with left ventricular ejection fraction (EF) was noted (EF from 56.0% to 58.8%; $p = 0.16$). We did not observe any periprocedural death and any severe periprocedural complication. In one case the balloon catheter got stuck in left femoral artery and was removed surgically. In another patient with a known coronary artery disease, we observed a new onset of left bundle branch block with troponin elevation. In this patient we repeated coronarography and we excluded new lesions on coronary arteries. The average duration of hospitalization was 5.7 days. Soon after the percutaneous procedure the patients underwent surgery: 4 patients gastrointestinal tract resection, one abdominoperineal resection and right adnexectomy and one vulvar resection. The surgery was successful in all six cases without cardiovascular complications.

The median follow up period was 18.5 months. Successful procedure was associated with early symptomatic improvement with the decrease of New York Heart Association (NYHA) functional status from 3.2 to 2.5 and in a decrease in number of hospitalizations for cardiovascular causes. Two patients died, one 3 moths after BAV and one 10.5 months after BAV. The causes of both deaths were not related to the procedure.

Discussion

BAV procedure was originally proposed as an alternative to SAVR for severe, symptomatic AS, but it was rapidly neglected secondary to high restenosis rates and lower survival at follow up compared to SAVR.[12-17] However, BAV might be a reasonable approach to offer symptomatic relief and improvement of the quality of life in selected high risk patients when SAVR or TAVI are not an option. The new guidelines support this statement (recommendation Class IIb) and suggest this percutaneous treatment also as a bridge to SAVR or TAVI in haemodinamically unstable patients or in patients who require urgent major non-cardiac surgery.[5,6]

Soon after BAV we often observe an improvement of hemodynamic conditions; an increase of cardiac output, a reduction of pulmonary pressure and improvement of other heart failure clinical presentations.[24,25]

However, the effects of BAV are transient and usually last from three to six months. Therefore, the timescale between BAV and potentially planned non-cardiac surgery should be optimized. Patients with calcific AS often suffer also for CAD that aggravates their symptoms and contributes to the increase of surgery risk. We proved the BAV combined with PCI has no higher complication rate comparing to BAV as a single procedure.[19]

In the upper paper we describe 6 oncologic patients that underwent major abdominal and gynaecological surgery soon after BAV; in one case we combined BAV and PCI. In our cases surgery was performed without major cardiovascular complications.

Advances in cancer therapy have lead to improved survival and cancer is increasingly being recognized as a chronic disease.[26] A recent study demonstrated that cancer patients with non-treated severe AS had worse survival in comparison to patients where the stenotic valve was surgically replaced.[11] This suggests that AS is a condition that needs to be managed in oncologic patients as well. In selected, high risk carcinoma patients BAV may be used as bridge to TAVI and in case there is no carcinoma relapse in a year after non-cardiac surgery, may be implanted percutaneously.

Conclusions

BAV is a feasible and safe palliative treatment for high risk patients with severe, symptomatic AS. It may be also a therapeutic bridge to SAVR or TAVI or in case of urgent non-cardiac surgery. Treatment of aortic stenosis in oncologic patients is a challenge. Percutaneous methods such as BAV should be considered as one of the treatment options in an individualized therapeutic plan that should be discussed by cardiac-oncologic team.

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research article

Semirigid thoracoscopy: an effective method for diagnosing pleural malignancies

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Background. Thoracoscopy with a semirigid instrument is a recent technique for diagnosing pleural diseases. The purpose of this study was to report diagnostic yield and complications of the method.

Patients and methods. Patients with pleural effusion of unknown origin and/or pleural irregularities suspicious for pleural malignancy were included after less invasive means of diagnosis had failed. All procedures were performed under local anaesthesia with intravenous sedation/analgesia with a single point of entry with a semirigid thoracoscope (Olympus LTF-160). Data were collected prospectively between 2008 and 2012.

Results. One hundred fifteen thoracoscopies were performed on 111 patients. The median age was 65 years (range 28–86 years), 14.4% were female and 85.6% male. Seventy-three (65.8%) patients had malignant pleural disease (malignant mesothelioma, metastatic cancer) and 38 (34.2%) had benign disease. The sensitivity, negative predictive value, and accuracy of the procedure for malignancy were 96.0%, 93.0%, and 97.4% respectively. Pleurodesis was carried out in 34 patients; in 32 (94.1%) it was assessed as successful after 1 month. There were 24 adverse events: three empyemas/pleural infections, three bronchopleural fistulae after chest tube placement and lung re-expansion, five patients had excessive pain after pleurodesis, six patients had sedation-associated hypotension, and seven patients had self-limited fever after plerodesis. One patient died 11 days after a procedure for advanced carcinoma.

Conclusions. Semirigid thoracoscopy is an accurate and safe method for evaluation of pleural diseases and useful for therapeutic talc pleurodesis.

Key words: flex-rigid pleuroscopy; pleural biopsy; pleural effusion; safety; thoracoscopy

Introduction

Pleural effusion and pleural irregularities are frequent causes for referral for diagnostic evaluation.[1-3] However, obtaining an accurate diagnosis sometimes represents a considerable challenge, even though changes in the pleural space are radiologically obvious.[3,4] Approximately 25% of pleural abnormalities remain unexplained after repeated thoracenthesis and/or closed pleural biopsies.[1-3]

The role of medical thoracoscopy is well established in the diagnostic process for the pleural cavity, although the majority of published data on diagnostic yield and safety have been obtained from studies with rigid instruments.[1-3,5] Rigid thoracoscopy has certain advantages, including a spacious and readily available entrance to the pleural cavity, which enables good sampling and several therapeutic approaches, in which adhesiolysis and talc poudrage are most widely used.[6] However, the angle of view is limited and a second entry point is sometimes needed for thorough inspection and sampling. It also requires sufficient pleural space for insertion, which should be at least 10 cm in depth and 10 cm in length or width, which could represent an obstacle in the case of thick adhesions.[7] The second entry channel can be an additional risk for tumour seeding in cases of malignancy.[8]

The semirigid thoracoscope was recently developed and initial experiences with it show that the

method is easy to use and could overcome some of the disadvantages of rigid thoracoscopy.[9-11] The initial published experiences have proven the new technique to be safe, well-tolerated, and effective in evaluating pleural effusion of unknown origin.[9,11-14] The angle of view is extended in all directions because of the flexible tip and offers a better overview of the pleural cavity. However, the main concern is the flexible forceps, which lack mechanical power in the sampling process and delay the entire procedure.[10,15]

Studies with new semirigid instruments are therefore needed to define their value. The purpose of our report is to contribute additional data about the diagnostic accuracy and safety of semirigid thoracoscopy in the diagnosis of unilateral pleural effusion with a focus on predictive values for pleural malignancy.

Patients and methods

Patients

The study period was carried out between 2008 and 2012 with follow-up until February 2013. The patients included were at least 18 years old with unilateral pleural effusion of unknown origin and/or pleural irregularities suspicious for pleural malignancy, and they were candidates for thoracoscopy after less invasive means of diagnosis had failed. We excluded patients with uncontrolled bleeding tendency, unstable cardiovascular status or severe heart failure, ECOG performance status 4, and persistent hypoxemia after evacuation of pleural fluid.

The procedure was explained to patients verbally and in writing, and signed informed consent was obtained before the procedure. The data collection for purpose of this study was approved by the Institutional Ethics Committee.

The study was conducted at a single centre, prospectively by a predefined set of data to be collected.

Procedure technique

Semirigid thoracoscopy was performed using an Olympus LTF-160 autoclavable thoracoscope (Olympus Tokyo, Japan). We obtained biopsy samples using flexible FB-55CD-1 Olympus forceps with a cusp outer diameter of 2.4 mm and length of 3.5 mm.

The procedures were performed in the endoscopy suite through the single point of entry technique. Patients were placed in the lateral decubitus position with the affected side of the thorax upwards. Continuous visual monitoring and measurements of blood pressure, pulse rate, and haemoglobin saturation were performed. Topical anaesthesia was achieved using 2% lidocaine. Patients received intravenous fentanyl and midazolam for analgesia and sedation. Supplemental oxygen was given through a nasal catheter.

All patients had a chest CT-scan before the procedure and chest ultrasound was performed on the spot for selection of the entry site. Pneumothorax was introduced under C-arc fluoroscopic control and the thoracoscope was typically inserted through selected intercostal space. All pleural fluid was removed after insertion and the pleural space was thoroughly inspected, biopsies were taken, and talc plurodesis performed where indicated (4 g of sterilized talc, Novatech, France). Pleurodesis was avoided in patients with an inconclusive macroscopic appearance or with signs of lung entrapment. A 24F chest tube was placed at the end of the procedure and a chest radiograph was obtained afterwards.

Histopathology techniques

Biopsy specimens were immediately fixed in 4% neutral buffered formalin. Paraffin embedded tissue sections were HE stained and evaluated. In the case of neoplastic morphology, immunohistochemistry was performed using various antibodies on an automated platform (Benchmark XT, Ventana, Tucson, Arizona).

Follow up

Non-specific pleuritis was accepted as the final diagnosis after 12 months of follow-up when no other definitive diagnosis was made during that time.

Data analysis

Descriptive statistical methods were used for data analysis (range, mean, standard deviation).

Results

One hundred twenty-three patients were referred for semirigid thoracoscopy during the study period. In 12 (9.8%) of them we were unable to induce pneumothorax because of fibrothorax or extensive adhesions. Data were evaluated from 115 procedures on 111 patients; one patient had thoracosco-

TABLE 1. Clinical and demographic characteristics of the 111 patients that underwent semirigid thoracoscopy

Variables	*n* (%)
Patients	111
Procedures	115
Median age (years)	65.0 (range 28–86)
Male	95 (86.6%)
Female	16 (14.4%)
Smoking status	
Current and previous	67 (60.4%)
Non-smoker	44 (39.6%)
Asbestos exposure	
Yes	36 (32.4%)
No	75 (67.6%)
Size of effusion	
1/3 hemithorax or less	54 (46.9%)
2/3 hemithorax	50 (43.5%)
Massive	11 (9.6%)
Side	
Left	52 (45.2%)
Right	63 (54.8%)
Performance status	
ECOG 0*	4 (3.6%)
ECOG 1	77 (69.4%)
ECOG 2	20 (18.0%)
ECOG 3	10 (9.0%)

*ECOG = Eastern Cooperative Oncology Group

TABLE 2. Final diagnosis, complications, diagnostic yield, and other features of patients undergoing semirigid thoracoscopy procedures

Variables	*n* (%)
Malignant disease	73 (65.8%)
Mesothelioma	48
Secondary carcinoma	24
Lymphoma	1
Benign disease	38 (34.2%)
Non-specific pleuritis	20
Asbestos pleuritis	12
TBC pleuritis	2
Rheumatoid pleurisy	1
Hemothorax	1
Number of biopsies per patient	11.2 (±3.2)
Pleural adhesions / loculations	64 (55.7%)
Trapped lung	17 (15.3%)
Talc pleurodesis	34 (29.6%)
Median duration of chest tube drainage after procedure (days)	2 (range 0–22)
Complications	
Major	6
Minor	18
Mortality at 30 days	1
Overall diagnostic accuracy (%)	97.4%
Sensitivity for malignancy (%)	96.0%
Positive predictive value for malignancy (%)	100%
Negative predictive value for malignancy (%)	93.0%

py on both sides on two occasions and in three patients thoracoscopy was repeated on the same side. The clinical and demographic data of the patients included are presented in (Table 1).

The mean follow-up was 22.3 (± 12.1) months after the procedure.

Seventy-three (65.8%) patients had malignant pleural disease and 38 (34.2%) benign disease (Table 2). Most of the pleural malignancies were malignant mesotheliomas, followed by secondary carcinomas with origins in the lung (n = 13), breast (n = 3), head and neck (n = 3), or rectum (n = 1), or of unknown origin (n = 4). Benign diagnoses included non-specific pleuritis, asbestos pleuritis, tuberculous pleuritis, rheumatoid pleurisy, and one case of hemothorax. The patient with hemothorax had no history of physical trauma, but received anticoagulant treatment at the time of presentation.

Overall diagnostic accuracy, sensitivity, and positive and negative predictive value for malignancy were 97.4%, 96.0%, 100%, and 93.0% respectively.

Five patients had clinical presentations that did not entirely match with the diagnostic findings from thoracoscopy. One patient underwent a surgical diagnostic procedure in which the diagnosis of non-specific pleuritis was confirmed. Three patients had repeated thoracoscopy at clinical deterioration several months later. Two of them were diagnosed with mesothelioma on a second occasion and one still had non-specific pleuritis, which was the final diagnosis after follow-up. One patient with suspicion for malignant mesothelioma had severe comorbidity and was treated conservatively

thereafter. Diagnosis of malignant mesothelioma was confirmed at autopsy after his death.

Talc pleurodesis was carried out in 34 patients with macroscopically obvious malignant pleural disease and without evidence of trapped lung during the same procedure. Thirty-two of them (94.1%) were assessed as successful after 1 month.

Six serious adverse events were recorded in four patients. There were three serious adverse events associated with infection. The first patient presented with fever, malaise, and chest pain 1 week after the procedure with pleurodesis. Empyema caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) was found. The patient recovered after chest-tube drainage and antibiotic treatment. In another two patients the signs of pleural infection were associated with trapped lung, subsequent bronchopleural fistula, and prolonged chest drainage (up to 22 days). No pathogens were isolated from pleural space or other samples (hemocultures, urine, sputum) and both patients recovered within a few days of antibiotic treatment. In the fourth patient there was prolonged air leak due to bronchopleural fistula, extensive subcutaneous emphysema, and prolonged chest-tube drainage, without signs of infection.

Among the minor adverse events were seven cases of transient self-limited fever (38ºC or more). Additional analgesia was required in five patients postoperatively after talc poudrage. Six patients had a transient hypotensive period associated with sedation during the procedure, which was reversed by application of plasma-expander.

Seventeen patients (five malignant mesothelioma, four secondary carcinoma, eight non-specific pleuritis) had trapped lungs and re-expansion was not achieved by chest tube drainage immediately after the procedure. Three cases were complicated by bronchopleural fistula, mentioned above.

One patient died 11 days after a procedure for advanced carcinoma.

Discussion

Rigid thoracoscopy has been a valuable method for evaluating and treating unilateral pleural effusion for more than a century.[16,17] It is used to avoid surgical exploration of the pleural space after cytological examination of pleural fluid and/or after closed needle biopsy of pleura has failed to retrieve diagnostic material.[5] The new, semirigid instrument has already proved its safety and accuracy in phase II studies, but the level of evidence is still limited in comparison to rigid thoracoscopy.[9,11,12] In a previous pilot study we evaluated both techniques for diagnostic value and found comparable diagnostic yields.[15] Although the biopsy specimens were smaller in the semirigid technique arm, the quality of the samples, interpretability, and immunohistochemistry staining allowed accurate pathological diagnoses. With that experience, we assume that a large multicentric randomized study including hundreds of patients would be required to establish the non-inferiority of the semirigid technique with sufficient power.

Our series of 115 semirigid thoracoscopies is the largest analysed and reported so far. We have confirmed the high diagnostic yield, which is comparable to our previous data from historic cohorts obtained with a rigid instrument and which was between 91.5% and 94%.[16,18,19] The majority of patients referred had pleural malignancy: either malignant mesothelioma or metastatic cancer. In this study the prevalence of malignancy was 65.8% compared to 55.2% and 62.4% from our previously published data.[18,19] The high percentage of malignant mesothelioma patients in comparison to patients with secondary carcinoma in our sample is a reflection of the inherent low diagnostic yield of less invasive diagnostic techniques for diagnosing malignant mesothelioma and their low ability to establish a reliable subtype diagnosis and stage, which decisively influences the treatment and prognosis of malignant mesothelioma patients.[7,16,20-22]

Non-vascularized pleural adhesions and/or loculations that could impede the range of vision and pleural fluid removal were present in a large percentage of our patients. We were able to use the semirigid instrument for fenestration and removal of the fluid and thus achieve a wider range of inspection and favourable conditions for successful pleurodesis. An additional contribution to the wide range of visibility in the pleural cavity is the flexible tip, which enables inspection of the pleural area around the entry point and better maneuverability in partly septated pleural space without establishing a secondary entry port.

Procedures were well tolerated and patients did not report pain at the site of the insertion. There were no premature terminations of the procedure because of pain, intolerance, or hemodynamic instability. Large volumes of pleural fluid were safely aspirated, but some patients experienced coughing and chest discomfort after lung re-expansion with a chest tube. However, there were no cases of re-expansion pulmonary oedema. Additional intravenous anaesthesia was required in five patients after

pleurodesis. All cases of serious adverse events underwent detailed analysis. Patients with pleural infection recovered after chest-tube drainage and antibiotic treatment. Trapped lung was regarded as a characteristic of the existing pleural disease, which was complicated by prolonged air leak in three patients.

The role of thoracoscopy for patients with undiagnosed unilateral pleural effusion is therefore important for several reasons.[23] It has a high diagnostic yield and good safety profile, and is well tolerated. It does not require general anaesthesia and mechanical ventilation because many patients have severe co-morbidity that could make such a procedure too risky.[24] It enables early palliative measures such as complete removal of pleural fluid, especially where mechanical intervention is required to fenestrate loculized effusion and to perform pleurodesis in incurable patients. Semirigid thoracoscopy has several potential advantages, among which the most prominent is easy and more extensive maneuverability without application of excessive force to the ribs during navigational efforts. Comprehensive examination of the pleural space enables better selection of biopsy sites, which is reflected in a high diagnostic yield. Pleurodesis with talc insufflation under direct supervision is feasible and effective. There may also be some disadvantages such as a narrow working channel and especially weak and bendable biopsy forceps, which could slow down the biopsy process and thus the entire procedure.[15] New biopsy techniques are needed to simplify the biopsy process, and biopsy with an electrocautery knife or cryobiopsy might be among these.[25]

Semirigid thoracoscopy is an effective and safe method for diagnosing and to some extent treating pleural disorders. The method is still under development, where further improvements might be expected. However, additional studies are needed to compare rigid and semirigid thoracoscopy and establish their relation and indications for each technique. We view both techniques more as complementary than competing, but further development may provide an answer to this issue.

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research article

Glioblastoma patients in Slovenia from 1997 to 2008

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Background. Glioblastoma is the most common primary brain tumour. It has a poor prognosis despite some advances in treatment that have been achieved over the last ten years. In Slovenia, 50 to 60 glioblastoma patients are diagnosed each year. In order to establish whether the current treatment options have any influence on the survival of the Slovenian glioblastoma patients, their data in the period from the beginning of the year 1997 to the end of the year 2008 have been analysed.

Patients and methods. All patients treated at the Institute of Oncology Ljubljana from 1997 to 2008 were included in the retrospective study. Demographics, treatment details, and survival time after the diagnosis were collected and statistically analysed for the group as a whole and for subgroups.

Results. From 1997 to 2008, 527 adult patients were diagnosed with glioblastoma and referred to the Institute of Oncology for further treatment. Their median age was 59 years (from 20 to 85) and all but one had the diagnosis confirmed by a pathologist. Gross total resection was reported by surgeons in 261 (49.5%) patients; good functional status (WHO 0 or 1) after surgery was observed in 336 (63.7%) patients, radiotherapy was performed in 422 (80.1%) patients, in 317 (75.1%) of them with radical intent, and 198 (62.5 %) of those received some form of systemic treatment (usually temozolomide). The median survival of all patients amounted to 9.7 months. There was no difference in median survival of all patients or of all treated patients before or after the chemo-radiotherapy era. However, the overall survival of patients treated with radical intent was significantly better (11.4 months; $p < 0.05$). A better survival was also noticed in radically treated patients who received additional temozolomide therapy (11.4 *vs.* 13.1 months; $p = 0.014$). The longer survival was associated with a younger age and a good performance status as well as with a more extensive tumour resection. In patients treated with radical intent, having a good performance status, and receiving radiotherapy and additional temozolomide therapy, the survival was significantly longer, based on multivariate analysis.

Conclusions. We observed a gradual increase in the survival of glioblastoma patients who were treated with radical intent over the last ten years. Good functional surgery, advances in radiotherapy and addition of temozolomide all contributed to this increase. Though the increased survival seems to be more pronounced in certain subgroups, we have still not been able to exactly define them. Further research, especially in tumour biology and genetics is needed.

Key words: glioblastoma; treatment; survival; surgery; radiotherapy; temozolomide

Introduction

Glioblastoma (GBM) is a WHO grade IV tumour arising from the astrocytes and represents the most common type of primary central nervous system (CNS) malignancies providing for well over one half of all gliomas.[1,2] GBM is characterised by a rapid growth and short time to progression in most treated patients. Its peak incidence is in the sixth and seventh decades of life with much lower incidence in younger age groups where low-grade gliomas predominate. It can also appear in the childhood, although the most frequent brain tumour in this period of life is meduloblastoma.[3-8]

Though the incidence of malignant gliomas is increasing among the elderly[8,9], the age-adjusted incidence of GBM in Slovenia remained comparatively low in the range of 2.3 to 3.0 per 100000 per year. This brought about around 50 new cases each year.[10]

GBM is one of the tumours least likely to be cured and causes quite severe physical as well as cognitive and psychological disabilities. Thus, it has a significant impact on the lives of affected patients, their caregivers and relatives, which is not to be underestimated.

By the introduction of a combined modality treatment, a statistically significant increase of survival in GBM patients was observed. This can in part be contributed to the addition of systemic therapy, but also to the improved quality of radiation therapy resulting in an increase of the total dose given.[9,11,12] There was a tendency to treat more patients who had only been deemed suitable for supportive care in the past.[13,14] Therefore palliative irradiation was applied to the tumour bed with a slightly higher dose than it was the case with metastatic brain tumours[15-17], and a less toxic systemic treatment was prescribed sequentially.[18,19]

Classically, younger GBM patients tended to fare better than older ones and, in some cases, patients over the age of seventy were treated palliatively and did not receive the same amount of treatment as younger ones. Likewise, although the performance status was one of the more important prognostic factors, it tended not to be taken into account when younger and older patients were treated. Therefore often even quite fit elderly patients received suboptimal treatment while severely ill younger patients were treated with aggressive regimens.[20-22]

The cause of gliomas is unknown though various theories has suggested a wide range of possible causes from nonionizing radiation to viral aetiology, none has as yet been proven, ionizing radiation aside. The sequence of mutations leading to the tumour is reasonably well known, with the key events in tumour genesis well documented.[23-30]

The diagnosis is usually established after a short period of complaints, headache being most frequent but not obligatory. In fact, only around 60% of patients report headache, less frequent are convulsions and focal neurological disturbances. On imaging, there is usually a contrast-enhancing tumour with varied signal surrounded by oedema. Neurosurgery should be applied for therapeutic and diagnostic purposes. A microscopic examination of the tumour specimen acquired by neurosurgery is necessary for a definite diagnosis.[31,32] Often, surgery is performed without the intention of resection or even reduction, the only goal being the biopsy and microscopic diagnosis, though some recent studies suggest that the extent of the tumour resection is one of the important factors influencing the survival of the patients. Therefore, a maximal safe tumour resection is mostly recommended.[33]

After surgery, the patients were typically treated with radiotherapy with or without systemic therapy.[9,34-38] Radiotherapy is usually performed at a dose level between 55 and 60 Gy applied at the tumour site with an additional 2 to 3 cm margin at preoperative MRI, 5 times weekly. Since 2004, concomitant radio-chemotherapy has been applied in the treatment of GBM patients. Usually, patients receive the same dose of radiotherapy, but with the addition of temozolomide in doses of 75 mg/m^2 daily during radiotherapy, followed by adjuvant temozolomide. These procedures are likely to produce an overall survival of 1 to 1.5 years with a 2-year survival of around 25% of the patients.[11,39]

In this paper, we are trying to review and evaluate the Slovenian GBM treatment results over 14 years along with the current treatment options while addressing some questions arising.

Patients and methods

Patients

In the retrospective study we analysed the treatments of glioblastoma patients at the Institute of Oncology in Ljubljana and their survival in the period from 1997 to 2008. There were included all glioblastoma patients treated with any other treatment modality but surgery alone and, for the period after 2000, there were included all patients fit enough for any therapy to be considered.

In Slovenia, most hospitals have neurology departments and internal medicine departments performing initial diagnosis of CNS neoplasms. Patients with unknown extra cranial primary were referred either to one of the two neurosurgical departments in Ljubljana and Maribor for surgical treatment or, in accordance with the imaging, if a brain metastasis was suspected and there was no immediate need for debulking surgery, to an appropriate diagnostic department.

After surgery, the microscopic examination of the tumour specimens was performed at one of the two pathology departments in Ljubljana and Maribor. Subsequently, all patients were discussed

TABLE 1. Characteristics of glioblastoma patients in Slovenia treated at Institute of Oncology Ljubljana from 1997 to 2008

Characteristics	Patients, n = 527 (%)
Age (years)	59 (SD 11.8)
Minimum	20
Maximum	85
Gender	
Males	321 (60.9)
Females	206 (39.1)
Performance status (WHO)	
0	84 (15.9)
1	252 (47.8)
2	103 (19.5)
3	86 (16.3)
4	2 (0.4)

TABLE 2. Treatment characteristics of glioblastoma patients in Slovenia referred to Institute of Oncology Ljubljana from 1997 to 2008

Treatment	Patients, n = 527 (%)
Surgery	
Gross total resection	261 (49.5)
Reduction	191 (36.2)
Biopsy	74 (14.0)
None	1 (0.2)
Radiotherapy	422 (80.1)
Palliative	105 (24.9)
Radical	317 (75.1)
None	104 (19.9)
Chemotherapy	198 (37.4)
Temozolomide	187 (94.9)
Concomitant	125 (66.8)
Adjuvant	62 (33.1)
Other (BCNU, PCV)	11 (5.1)
None	330 (62.6)

BCNU = carmustine; PCV = procarbazine, lomustine, vincristine

at multidisciplinary team meetings and the treatment strategy was outlined.

The vast majority of patients, with the exception of those deemed to be unfit to receive any further treatment, were referred to the Institute of Oncology for additional treatment. All patients in Slovenia were post-operatively treated in only one institution.

In the recent years patients deemed suitable for radiotherapy were treated either with 60 Gy in 30 fractions or with 59.4 Gy in 33 fractions over 6 to 7 weeks. Those intended for palliative irradiation received 35 Gy in 10 fractions or 30 Gy in 6 fractions over two weeks. All patients received radiotherapy at the linear accelerator, yet until 2005 some patients were treated at the old cobalt unit. Since 2004 all treatments were planned at 3D conformal (XiO and Eclipse). Prior to that, radical patients had been treated with plan done in one axial plane using Multidata TPS, without taking tissue inhomogeneity into account. All others had a simple depth dose calculation using in-house software. Since November 2004, the patients with good performance status were offered a possibility of concomitant chemo-radiotherapy with temozolomide followed by adjuvant chemotherapy over 6 or more cycles, depending on tumour response and toxicity.[40-48]

At progression, patients were repeatedly discussed at a multidisciplinary team meeting. If surgical treatment was possible, the patients were referred back to the neurosurgeon, or second-line systemic therapy was offered to the patients with good performance status. For patients relapsing after a period of more than a year, re-irradiation was considered, while others received supportive and symptomatic treatments.

Methods

The data were obtained from the hospital registry of the Institute of Oncology, from the Cancer Registry of Slovenia and from the treatment charts.

The data collected were the age of the patients at the diagnosis, the sex, the extent of neurosurgery, the performance status after surgery, the radiotherapy parameters (total dose, dose per fraction, number of fractions and treatment planning) and systemic therapy.

We calculated the overall survival from the day of diagnosis to the death of all patients or when censored. The Kaplan-Meier method was used for the estimation of overall survival and the log-rank test was used to compare survival distributions between samples. A p-value lower than 0.05 was considered as statistically significant. Statistical analysis was performed using SPSS statistical package (Release 19.0, IBM SPSS).

The investigators strictly followed recommendations of the Helsinki Declaration and of the

Council of Europe Convention on Human Rights and Biomedicine.

Results

Patients

In the period from the beginning of 1997 to the end of 2008, Cancer Registry of Slovenia registered 1145 patients with primary CNS tumours, 527 (46%) of them were GBM patients treated at the Institute of Oncology Ljubljana.

The patients' age ranged from 20 to 85 years, with median age of 59 years with a standard deviation (SD) of 11.8 years. The median age of patients slowly increased from 54 in 1997 to 63 in 2008 (Table 1).

During the period examined, the number of the glioma patients treated at the Institute of Oncology slightly increased. In 1997, 27 patients were treated and then the number slowly grew. It settled at around 55 patients per year.

Diagnosis and surgical treatment

All but one patient had the diagnosis confirmed by means of microscopic examination of surgically removed tumour samples. In one half of the patients (261 out of 527; 49.5%) the surgeons reported a gross total resection, in 191 (36.2%) patients the tumour was reduced and in 74 (14.0%) patients only diagnostic biopsy was performed (Table 2). The number of biopsies only was constantly low throughout the observed period.

The surgical results regarding the patients' performance status were good, with almost two thirds of the patients (336; 63.7%) having the WHO performance status of 0 and 1.

Radiotherapy

Most patients (422 out of 527; 80.1%) received some kind of radiotherapy, with either palliative or radical intent (317). Unfortunately, it was not possible for all 317 patients treated with radical intent to complete the radiotherapy. Some of them deteriorated during treatment. An equal number of patients received either palliative treatment or best supportive care.

In the patients receiving radiotherapy, the median tumour dose (TD) was 50 Gy, with SD of 10 Gy (range 2-67.5 Gy). In the patients irradiated with radical intent, the median TD was 56 Gy with SD of 8.4 Gy (range 2-65.7 Gy). In palliative patients, the median TD was 37.5 Gy with SD of 6.8 Gy (range 6-46 Gy), the most common fractionation being 35 Gy in 10 fractions and 45 Gy in 15 fractions. In patients receiving radical intent treatment, there was a trend for a gradual dose increase from 42 Gy through 50 Gy and 56 Gy to the now usual dose of 60 Gy. In total, the mean dose increased from 44.2 Gy in 1997 to 57.3 Gy in 2008.

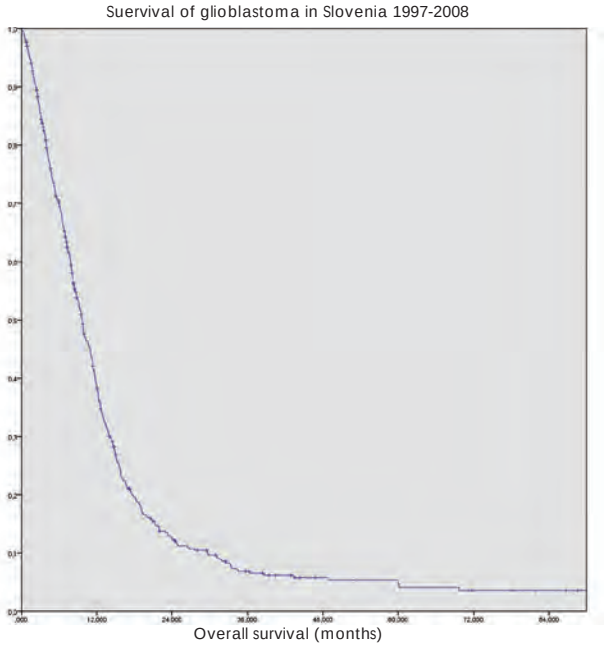

FIGURE 1. Overall survival of glioblastoma patients in Slovenia treated at Institute of Oncology Ljubljana from 1997 to 2008.

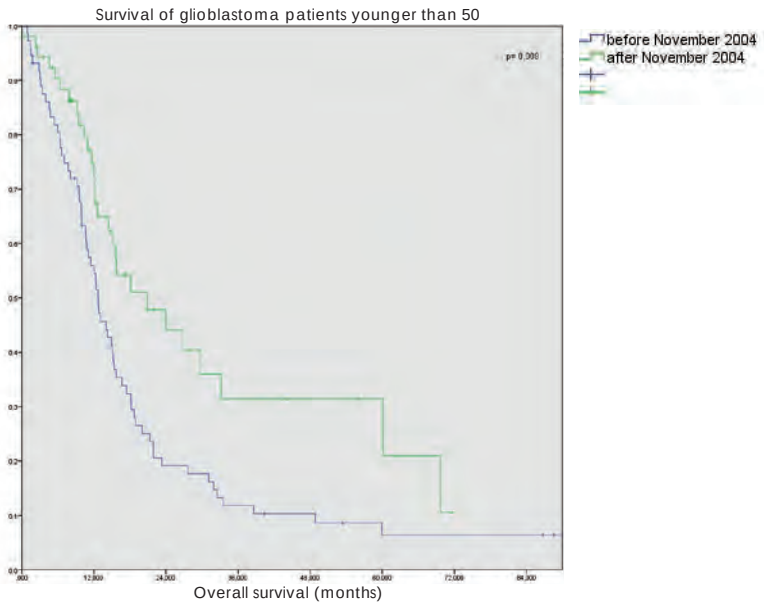

FIGURE 2. Overall survival of glioblastoma patients under 50-year radically treated at Institute of Oncology Ljubljana from 1997 to 2008.

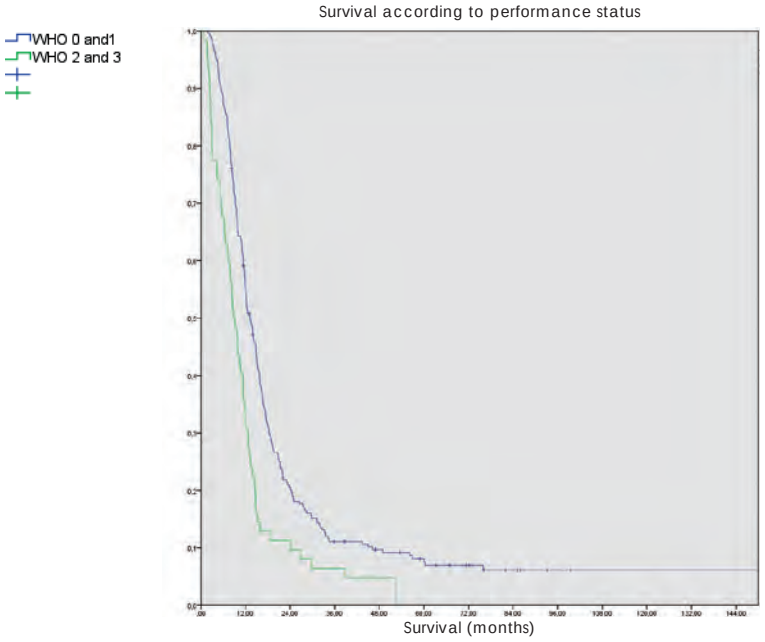

FIGURE 3. Overall survival of glioblastoma patients treated with radiotherapy at Institute of Oncology Ljubljana from 1997 to 2008 according to performance status.

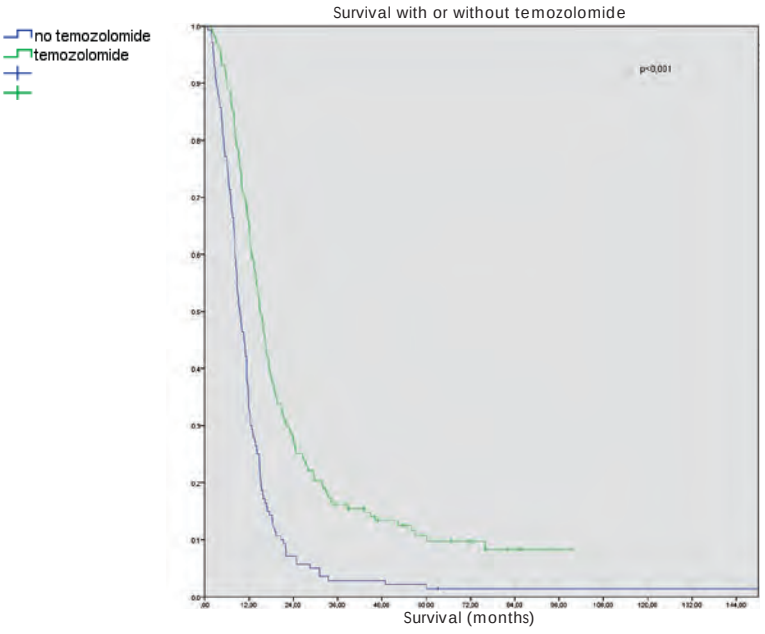

FIGURE 4. Overall survival of glioblastoma patients according the treatment with temozolomide at Institute of Oncology Ljubljana from 1997 to 2008.

Systemic therapy

From 1997 to the publication of EORTC study results in 2004, 301 glioma patients were seen at the Institute of Oncology Ljubljana. Two of them were enrolled in the trial and received concomitant chemo-radiotherapy, 46 out of 301 (15.3%) received adjuvant chemotherapy with temozolomide and 10 out of 301 (3.3%) received other forms of chemotherapy (carmustine (BCNU) or procarbazine, lomustine, vincristine (PCV). Two hundred forty-three out of 301 (80.7%) patients received no systemic treatment. From the publication of the EORTC study results in 2004 to the year 2008, 266 glioblastoma patients were referred to the Institute of Oncology, one half of which (122; 54%) received concomitant chemo-radiotherapy followed by adjuvant chemotherapy with temozolomide. Over the last period, 16 (7.1%) patients received adjuvant temozolomide only, 1 (%) patient received BCNU only, and 87 (38.5%) patients received no systemic treatment (Table 2).

Survival

The overall median survival of the whole group was 9.7 months with standard deviation (SD) of 0.53 months (Figure 1).

There was no difference in median survival either of all patients or of all treated patients before and after chemo-radiotherapy era. However, the overall survival of the patients treated with radical intent radiotherapy was significantly longer ($p < 0.05$). Before the introduction of chemo-radiotherapy, the overall median survival of these patients was 11.4 months and afterwards it amounted to 13.1 months ($p = 0.014$).

The benefit of radical intent radiotherapy followed by chemotherapy was even more evident in the group of patients younger than 50 years with the median survival rising from 14.9 months to 24 months ($p = 0.009$) and with 26% patients surviving even more than 48 months (Figure 2).

Likewise, there was some survival benefit associated with more extensive surgery. The median survival of the patients with gross total resection of the tumour was 14.4 months, with partial surgical reduction 11.4 months and with biopsy only 8.4 months ($p = 0.088$).

The patients with good performance status after surgery had a median survival of 13.8 months, while those with a WHO performance status of 2 or 3 had a median survival of 9.8 months ($p < 0.001$).

In multivariate analysis, an age below 50 years, a gross total resection, a good performance status and chemo-radiotherapy all were associated with longer survival ($p < 0.05$).

In patients treated with radiotherapy, there was no difference in survival connected to the extent of surgery in the group of patients younger than 50 years, but in the older patient group, there was

a marked improvement of survival of those with gross total resection of the tumour ($p < 0.05$). In both age groups, the performance status after surgery was an important factor, even more so in the younger patients (Figure 3).

In the younger patients the effect of radiation techniques was more important. They greatly benefited from the introduction of more complex treatments and from the increase of the total dose with a median survival of 20.8 vs. 12.7 months ($p = 0.02$).

The survival was improved with the addition of temozolomide. While the median survival was only around 9 months in radically treated patients without chemotherapy, even the addition of temozolomide in adjuvant setting improved the median survival to 14 months, and the concomitant treatment followed by adjuvant temozolomide increased it to 16 months. In the age group under 50 years, the impact of concomitant treatment was even greater (16.7 months with adjuvant treatment *vs.* 20.8 months after concomitant treatment followed by adjuvant temozolomide). In the age group over 50 years, there was virtually no difference in survival regardless of temozolomide schedule (Figure 4).

In the group of patients treated with radiotherapy with a "radical" dose (317 patients), the extent of surgery played no significant role ($p = 0.179$). On the other hand, we found that in this group good performance status (WHO 0 and 1 *vs.* 2 and 3) after surgery ($p < 0.005$), radiotherapy planning (depth dose, 2D *vs.* 3D conformal) ($p = 0.015$) and the addition of temozolomide ($p < 0.005$) were statistically significant (Figure 5).

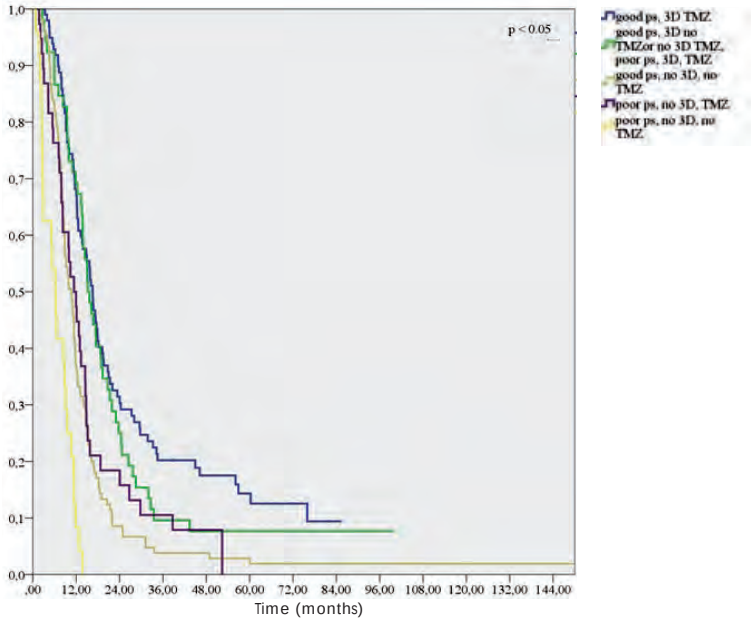

FIGURE 5. Overall survival of glioblastoma patients treated with radiotherapy at Institute of Oncology Ljubljana from 1997 to 2008 according to performance status, radiotherapy planning and addition of temozolomide.

Discussion

In our institution, the median survival of GBM patients since 1997 has risen similarly as elsewhere in the world. While the diagnosis of GBM remains one of the most unfavourable ones, there has been an increase of the overall survival and also of the time to progression observed in the patients treated for GBM in the last ten years.[49] Though the largest increase of survival was achieved by the inclusion of temozolomide in the initial treatment of GBM, there seems to be a subgroup of patients who benefited more than others.

In our analysis, we could confirm a gradual and modest increase in the overall survival of glioblastoma patients. Any potential changes in the time to progression were harder to detect, especially since our earliest patients were usually discharged from follow up after initial treatment or visited the clinic only once at the most after the completion of radiotherapy treatment and no imaging was performed. Some patients originated from other republics of the former Yugoslavia and for them even the overall survival was somewhat doubtful, so the overall survival in particular cases might have been more than calculated.

We observed a positive impact on survival after concomitant chemo-radiotherapy was introduced in 2004.[34] The survival increased most in the subgroup of younger patients with a maximal safe removal of the tumour, with a good post-operative performance status, receiving a dose of 56 to 60 Gy with 3D conformal radiotherapy as well as receiving concomitant and adjuvant temozolomide. Unfortunately, they were not cured. The majority of them progressed in due course. However, they were mostly exposed to some sort of treatment after progression. The salvage therapy seemed to work for the majority of those progressing after a prolonged progression-free survival.[50]

In the older age group, there was also an impact of combined modality treatment on survival. It is interesting that in our group the impact of concomitant treatment in this group was less pronounced. The patients receiving only adjuvant treatment seemed to fare no worse than those in the concomitant treatment group. This could probably be explained by the lesser toxicity of the former during initial treatment.[51,52]

In the present analysis, almost 10% of the patients treated with radical intent stayed alive for more than 3 years. This was somewhat more than usually reported. On average, they were younger patients, but still one third of them were over 50. On the other hand, one quarter of those who survived less than a year were under 50. Therefore, it appears unfair to deny the best possible treatment to patients just on the basis of their age and regardless of the patients' performance status.

A poor performance status after surgery was clearly linked with a poor prognosis, yet some patients, especially younger ones, had at least an average survival nevertheless. Thus, age seems to be more important in patients with a poor performance status than in overall GBM patients.

While it is clear from our results that there were clinical factors correlating with the longer survival of GBM patients, there is a need to find out other possible influences. The patients' age, extent of surgery and performance status after surgery might fail to identify patients suitable for a particular kind of treatment in the primary as well as in the secondary setting. In addition to the changes in radiotherapy planning and delivery, systemic therapy schedules and potential impact of salvage therapy, some exciting new possibilities are emerging in the field of molecular biology and genetics of GBM, including the biomarkers, which could help to determine the risks of a particular patient and to tailor his treatment accordingly.[53-56] Moreover, while targeted therapy is on the rise in other fields of oncology and vascular endothelial growth factor receptor (VEGFR) and integrin inhibitors are becoming available, we still do not know how to select patients for the application of these modalities and if there is a subgroup of patients who would benefit from a different initial approach than the one used today. All those questions will need to be answered in the near future.[57,58]

Conclusions

GBM remains a challenging issue for the patients, their immediate caregivers and for medical personnel. Since the introduction of temozolomide in early 2000s, there have been only minor advances. For some patients this treatment clearly seems to be rather advantageous and a larger proportion of patients than before survived over two years.

In this respect, Slovenia is no exception. Even more than elsewhere, neurosurgeons are performing extensive resections. Having only one oncology centre helps to assure an equal treatment of similar patients, yet a number of questions remain unanswered. For example, is it possible to select patients responding well to the current treatment and how can an alternative be offered to those not benefiting from it? Who are those patients and what is the alternative?

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research article

Individual radiosensitivity in a breast cancer collective is changed with the patients' age

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Background. Individual radiosensitivity has a crucial impact on radiotherapy related side effects. Our aim was to study a breast cancer collective for its variation of individual radiosensitivity depending on the patients' age.

Materials and methods. Peripheral blood samples were obtained from 129 individuals. Individual radiosensitivity in 67 breast cancer patients and 62 healthy individuals was estimated by 3-color fluorescence *in situ* hybridization.

Results. Breast cancer patients were distinctly more radiosensitive compared to healthy controls. A subgroup of 9 rather radiosensitive and 9 rather radio-resistant patients was identified. A subgroup of patients aged between 40 and 50 was distinctly more radiosensitive than younger or older patients.

Conclusions. In the breast cancer collective a distinct resistant and sensitive subgroup is identified, which could be subject for treatment adjustment. Preliminary results indicate that especially in the range of age 40 to 50 patients with an increased radiosensitivity are more frequent and may have an increased risk to suffer from therapy related side effects.

Key words: individual radiosensitivity; chromosomal aberrations; age; fluorescence *in situ* hybridization; radiotherapy; breast cancer

Introduction

The very demanding task of a radiotherapy is to kill all cancer cells and at the same time to spare the surrounding normal tissue. However, there is a spectrum of confounding parameters which can affect normal tissue tolerance. One parameter is the individual radiosensitivity of the patient.[1] By prediction of individual radiosensitivity and adjusting the dosing regimen side effects and adverse events could be avoided. Different techniques to determine individual radiosensitivity were used with varying degree of success.[2-5] Yet, chromosomal aberrations are generally known to have the potential to predict individual radiosensitivity.[1,6-10] Mostly lymphocytes are irradiated *in vitro* in the G0 phase and afterwards stimulated to proceed in cell cycle. The advantage of this approach is that chromosomal aberrations are a late endpoint in radiation damage processing. Chromosomal aberrations cover the entire ability of cells to recover from DNA damage and to process these damages. It includes: (i) DNA damage repair, (ii) mediating a proper signal transduction, (iii) achieving an appropriate cell cycle control and (iiii) induce cell death, if necessary. The analysis of this late endpoint could be favorable compared to assays detecting earlier endpoints like DNA-double strand breaks (γH2AX), apoptosis (sub-G1 peak, Annexin V or cleaved Caspase 3) or cell-cycle control (PI-flow cytometry).

Nevertheless, even if the individual radiosensitivity could be determined with great accuracy, it is not certain that a study allows proving the relation between radiosensitivity and side effect. There have been several studies with disappointing re-

sults. The reason is based on the observations of Jung *et al*.[11] that the probability to develop adverse events is defined depending on radiotherapy treatment. The treatment defined risk will be higher in the group of sensitive individuals than in the intermediate and resistant group. Nevertheless, also individuals in the intermediate group take the risk of developing side effects and because this group is normally much bigger than the sensitive one there will be more individuals suffering from side effects in the intermediate group than in the sensitive group. As a consequence, testing predictive assays individuals must be grouped prospectively in sensitive, intermediate and radio-resistant and side effects may be collected at different time points.[2]

Our aim was to determine the sensitive, intermediate and resistant groups of a breast cancer collective by a 3-color-fluorescence *in situ* hybridization approach (3-color-FISH) in a prospective study. Therefore the frequency of chromosomal aberrations in blood lymphocytes after *in vitro* irradiation with 2 Gy was detected. Additionally the influence of age on individual radiosensitivity was studied.

Material and methods

67 breast cancer patients and 62 healthy controls were included in the prospective study (Table 1). Patients were included into the study randomly. A peripheral blood sample was obtained from patients and healthy controls. The blood withdrawal was performed within one week before the beginning of radiotherapy. Blood samples were divided into two parts. One part was used to detect spontaneous aberrations, the other one was irradiated *in vitro* with 2 Gy on a 6 MV linear accelerator (Mevatron, Siemens, Germany). This study was approved by the ethics review committees of the Friedrich-Alexander-Universität Erlangen-Nürnberg (No. 2725), and informed consent was obtained from all patients and healthy volunteers. None of the patients used medications which are suspected to increase radiosensitivity.

Chromosomal aberrations were detected using 3-color FISH with whole chromosome painting of chromosomes 1, 2 and 4 as described earlier.[7,12] Heparinized blood samples of each patient were cultivated at 37°C for 48 h in RPMI 1640 medium with 1% penicillin-streptomycin, 1% glutamine, 2.5% phytohemagglutinin and 15% fetal calf serum. Cell division was stopped by adding colcemid (5µg/ml) 2.5 h before starting preparation of lymphocytes according to a standard technique as previously described.[13] Metaphase spreads were dropped on slides and preserved in 70% ethanol at -20°C before performing the 3-color FISH assay with whole chromosome painting of chromosomes 1, 2 and 4.[12] Chromosomes were counterstained with DAPI.[14]

A fluorescence microscope (Zeiss, Germany) was used to detect chromosomal aberrations, such as breaks, deletions, translocations, dicentrics, insertions and rings (Figure 1 A). 500 metaphases

TABLE 1. Patients characteristics

	129 individuals	
	67 breast cancer patients	62 healthy controls
mean age	57.2a (±12.9a)	56.3a (±14.2a)
stage 0 / I / IIA / IIB / IV	5 / 30 / 11 / 18 / 3	
Tis / T1 / T2 / T3 / T4	6 / 37 / 22 / 1 / 1	-
N0 / N+	44 / 23	-
M0 / M1	64 / 3	-
Dcis / no Dcis	37 / 30	-
mastectomy	9	-
breast-preserving	58	
single dose / total dose	1.8 Gy / 50.4 Gy	
body weight	78.8 kg (±15.4 kg)	
volume 20%-95% isodose	1460 ml (±870 ml)	-
dose*volume	6.8 Gy*dm³ (±4.5 Gy dm³)	

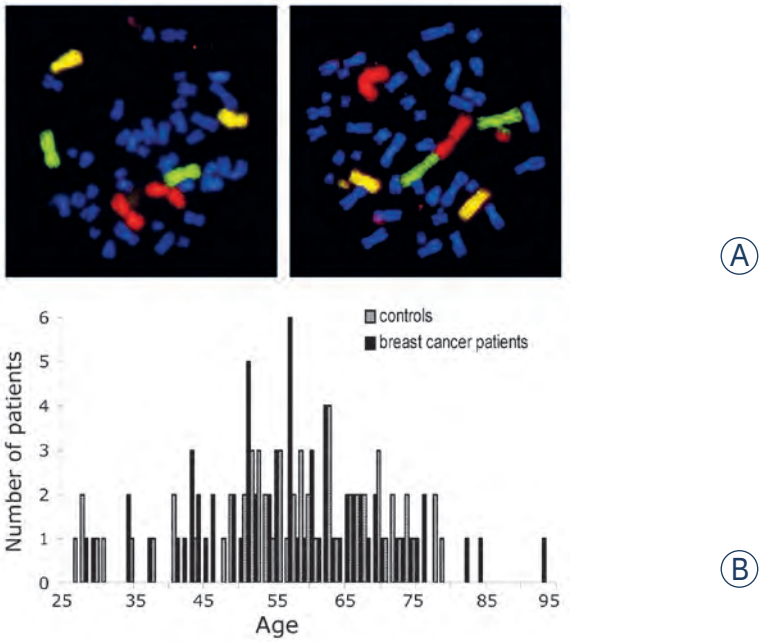

FIGURE 1: **A** – Three-color FISH painting of chromosomes 1 (red), 2 (green) and 4 (yellow). A metaphase without aberrations (left) and a metaphase (right) with a reciprocal dicentric chromosome and a break are displayed. The two aberrations were scored as 3 breaks. **B** – Frequency of patients and controls age distribution.

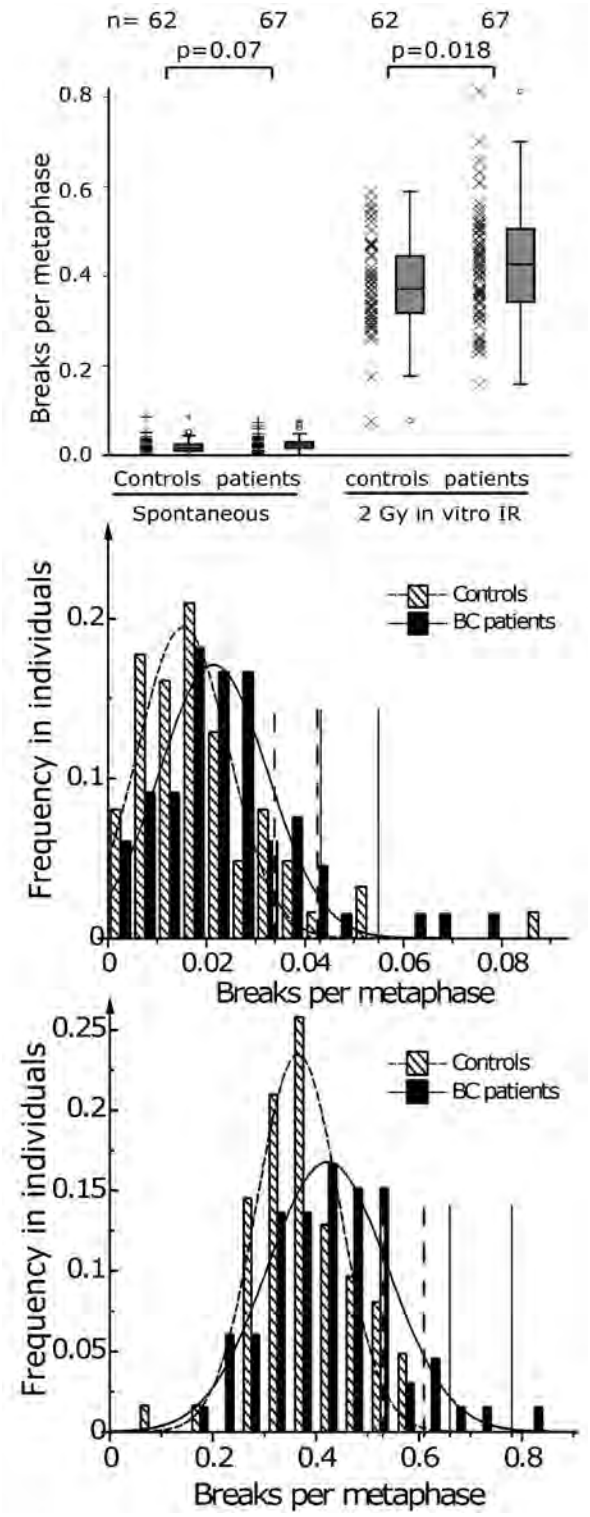

FIGURE 2. Individual chromosomal radiosensitivity as measured in *in vitro* and *in vivo* irradiated lymphocytes by three-color FISH. Chromosomal aberrations were scored as breaks per metaphase. Blood samples were derived from healthy individuals (controls) and breast cancer patients (BC patients). **A** – Breaks per metaphase of unirradiated samples (spontaneous) and after *in vitro* irradiation by a dose of 2 Gy (2 Gy *in vitro* IR) were shown as scatter plots and box plots. Frequency of breaks per metaphase fitted to a Gaussian distributions of **B** – unirradiated samples, **C** - after *in vitro* irradiation by a dose of 2 Gy

were scored for non-irradiated controls and 150 metaphases for 2 Gy *in vitro* irradiated slides.[15] Additionally the mitotic index was counted by using image analysis software (Biomas 3.3, MSAB, Erlangen, Germany).

Data analysis and statistics were performed using SPSS 16 for Windows (IBM Corp., Armonk, NY, USA). For comparing the results referred to the different groups, the Kolmogorov–Smirnov test and Lilliefors test were applied for testing normality and data were fitted by a Gaussian distribution. Standard deviations of the Gaussian distributions have been used to designate an individual's categorization. The cut-off values of 2 and 3 standard deviations are equivalent to the 95% and 99% confidence intervals. Different groups were compared using the two-sample t-test. Graphics were plotted with TechPlot for Windows 3.0.11 (SFTek, Dr. Ralf Dittrich, Braunschweig, Germany).

Results

Our intention was to study the individual radiosensitivity in a prospective collective of breast cancer patients. Three-color-FISH was used to estimate radiosensitivity (Figure 1 A). All aberrations in chromosomes 1, 2 and 4 were scored for themselves and additionally the breaks per metaphase were estimated according to the theoretically necessary number of breaks to form the aberrations: fragments equate to one break event, reciprocal translocations, simple dicentrics and rings equate to two break events and complex aberrations to as many breaks would be needed to cause this aberration at least. The 129 individuals in this study consisted of 67 patients suffering from breast cancer and 62 healthy individuals as controls. The median age of the breast cancer patients was 57.2a (±12.9a) and 56.3a (±14.2a) for the control individuals (Figure 1 B). The patients' clinical characteristics are described in Table 1. All patients got adjuvant radiotherapy and were irradiated with single doses of 1.8 Gy up to a total dose of 50.4 Gy. Blood was analyzed after *in vitro* irradiation with 2 Gy.

If possible, 650 metaphases per patient were scored, *i.e.* 150 metaphases from lymphocytes irradiated *in vitro* with 2 Gy and 500 metaphases from non-irradiated lymphocytes. Breaks per metaphase in the patients' group were slightly higher than in the group of healthy individuals. An *in vitro* irradiation with a 2 Gy dose leads to a distinct higher amount of breaks. Yet there was only a trend to an

increase of breaks in the patients' group compared to the controls (Figure 2 A).

Breaks per metaphases were classified and the normality of the distributions was tested by the Kolmogorov–Smirnov algorithm. All distributions were found to be normally distributed and Gaussian fits were performed. The average of the normal distribution of unirradiated blood samples was displaced to higher values by 23% in the breast cancer group compared to the healthy individuals group (Figure 2 B). The distributions of the blood samples after 2 Gy *in vitro* irradiation were changed similarly. The mean of the distribution was shifted by 12% to higher breaks per metaphase and the width of the distribution increased by 28% (Figure 2 C).

Additionally we studied the age dependence on the breaks per metaphase. A broad range of patients between 28 and 93 years was analyzed. All values of ten year intervals were summarized and the average was given as mean value. Breaks per metaphase did not increase with patients' age in the unirradiated group. In healthy controls breaks per metaphase increased with age (Figure 3 A). After *in vitro* irradiation by 2 Gy a linear regression indicated a marginal decrease of break events with advancing age of the patients and a distinct increase of the healthy controls breaks per metaphases (Figure 3 B). However, there was a distinct deviation of the 40 to 50 years data point from the linear regression and marked it as an outlier (Figure 3 B, C). Patients aged between 40 and 50 years have a significantly increased level of breaks per metaphase. After exclusion of the patients in this age range the linear regression matches the remaining data points and indicates an increase of breaks with advancing age by 0.01 breaks per metaphase per ten years.

Breaks per metaphases were fitted in a Gaussian distribution and patients were classified in resistant, intermediate and sensitive patients (Figure 4 A). In this way we defined a group of 49 intermediate patients, 9 resistant and 9 sensitive patients. A putative age dependency is displayed in Figure 4 B. Patients were divided into three groups which were supposed to reflect the patients' sensitivities best (Figure 4 C).

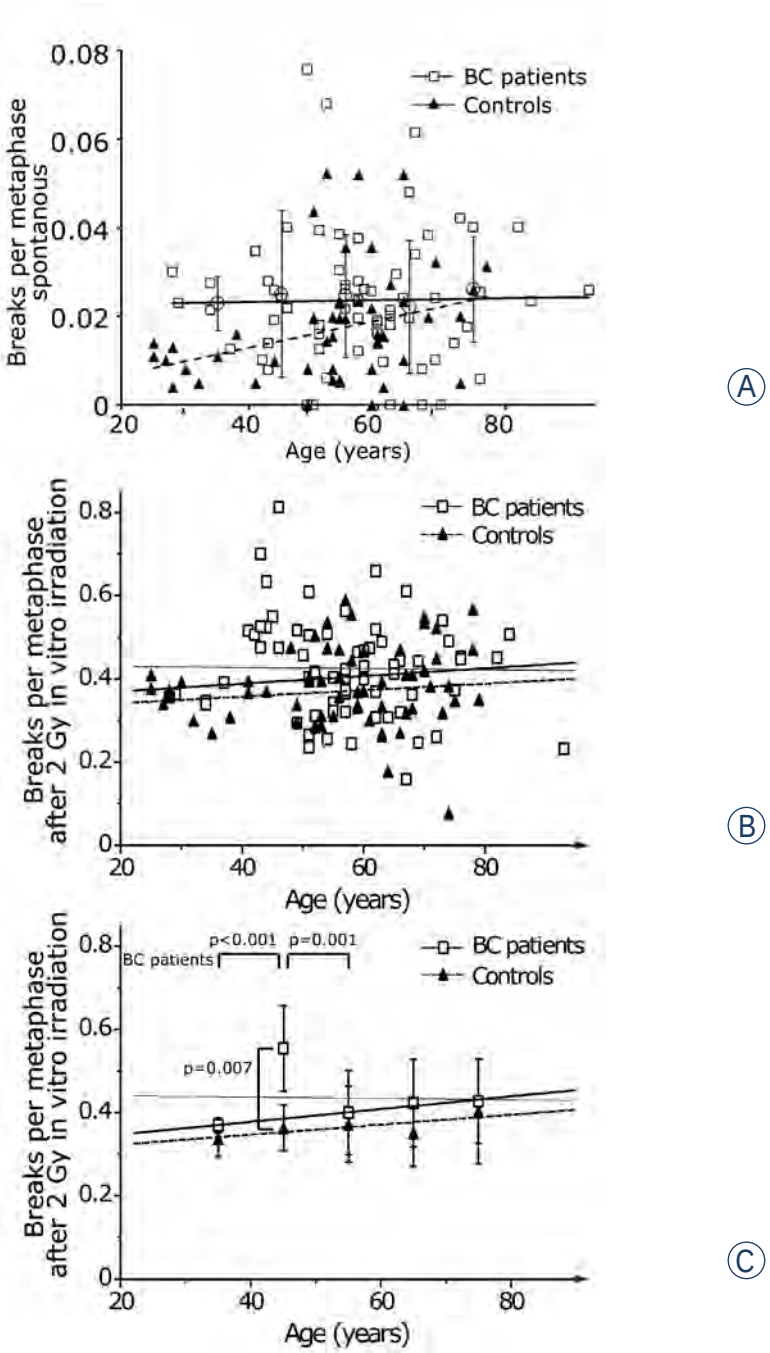

FIGURE 3. Breaks per metaphase in dependence of the patients (open square, continuous line) and healthy individuals age (filled triangle, dashed line). Ten year intervals were summarized and the average was given as mean value with its standard deviation. **A** – Unirradiated blood samples, **B** – samples after 2 Gy *in vitro* irradiation individual values and **C** – samples after 2 Gy *in vitro* irradiation mean values and standard deviation. B C – Thin line gives the linear regression including all patients values, thick continuous line gives the linear regression excluding the group aged 40 to 50 years.

Discussion

Chromosomal aberrations were detected in peripheral blood lymphocytes of 67 breast cancer patients and 62 healthy controls. Blood samples were taken before starting adjuvant radiotherapy using a 2 Gy *in vitro* irradiation. Breaks per metaphase were normally distributed with increased values of the breast cancer patients compared to controls.

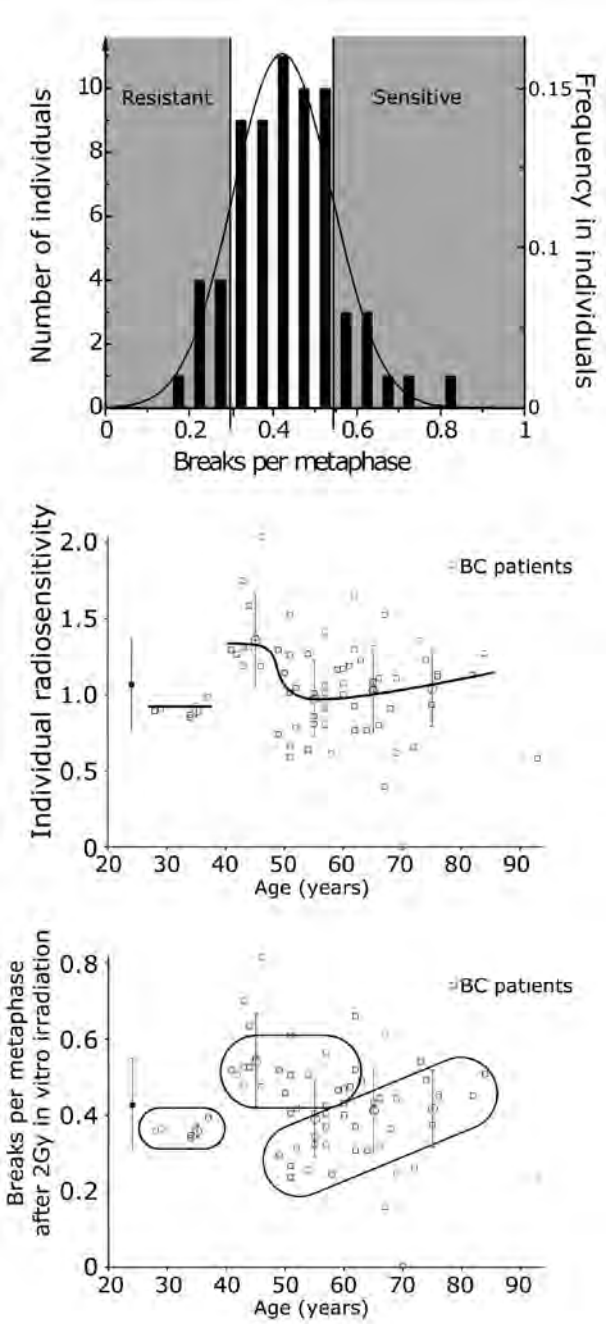

FIGURE 4. **A** - Classification of the breast cancer patients on the basis of the breaks per metaphase level after *in vivo* irradiation (2 Gy IR). **B** – Putative individual radiosensitivity dependent on breast cancers patients' age. **C** - Presumed classification of the breast cancer patients in three groups of different radiosensitivity.

It reflects that individuals with an increased probability of suffering from chromosomal aberrations or other mutations have an increased risk of cancer.[16,17] However, the main interest was not the comparison between the radiosensitivity of control individuals and cancer patients, but the grouping into radioresistant to sensitive cancer patients. These patient groups should be surveyed for the next years and it should be estimated whether in the sensitive group a higher portion of patients suffering from chronic side effects will be found[18,19].

The dose of 2 Gy given in the *in vitro* irradiation leads to a distinctly increased rate of breaks per metaphase. Breaks per metaphases fitted very well in a Gaussian distribution and were classified in resistant, intermediate and sensitive patients (Figure 4 A). The patients will be surveyed over the next years to gather the occurrence of late therapy side effects. However, the risk for developing radiation-induced late effects after conventional RT for breast cancer is low. Fibrosis and telangiectasia are still the most common late effects. Due to the low frequency and the time delay of occurrence of the adverse events it needs several years to quantify these late effects properly.[20] Therefore, we cannot compare the individual radiosensitivity in means of breaks per metaphase with late effects so far.

A further aspect of this study was the age dependency of radiosensitivity. There is a very limited increase of spontaneous chromosomal aberrations with advanced age. It is in contrast to a study comparing young healthy individuals (38.8 years) with older individuals (69.2 years) and a spontaneous increase of chromosomal aberrations by a factor of 5.[21] After a 2 Gy *in vitro* irradiation there is a discontinuous course of metaphase breaks per patient in dependence of age. Patients with age 40 to 50 are distinctly more sensitive. A putative age dependent radiosensitivity is displayed in Figure 4 B. Very young patients below age 40 have a low average radiosensitivity, patients between 40 and 50 years are extraordinarily sensitive and patients older than 50 are distinctly less sensitive. With further increasing age the sensitivity slowly increases (Figure 4 B). The reason for this may be that the cancer at different ages is acquired for different reasons. The very young patients have acquired the cancer by other mechanisms than the other groups, probably by an immature tissue. Patients between 40 and 50 are a group of sensitive individuals and may have acquired cancer because of genetic factors influencing the early onset of breast cancer. About 5-7 percent of all breast cancer patients have a familial breast cancer history. The most common mutations linked to an earlier onset of cancer are the BRCA 1 and 2 mutations and a large number of additional genes including STK11, CDH1, PTEN, TP53.[22] Genes related to an early onset of cancer are frequently related to an increased sensitivity to ionizing radiation and this may be the reason for the observed higher number of chromosomal

breaks. Individuals with a resistant or intermediate sensitivity do not acquire cancer before the age of 50 due to the lower mutation probability.

In Figure 4 C the three putative groups are marked. It must be assumed that patients in the sensitive group have an increased probability to suffer from therapy related side effects. However, the risk for radiation therapy related side effects in breast cancer are generally low, therefore only a limited increase in additional side effects will be expected. There are some publications that mention an increased risk in younger patients after radiotherapy and chemotherapy treatment.[23-25] It's worth bearing in mind that in this age group sensitive patients exists and therapy related side effects should be monitored carefully.

Conclusions

In the breast cancer collective a distinctly resistant and sensitive subgroup is identified by using 3-color-FISH after 2 Gy *in vitro* irradiation of peripheral blood lymphocytes, which could be subject for treatment adjustment. Especially in the range of age 40 to 50 there is an increased fraction of patients having an increased radiosensitivity. These patients have an increased probability to suffer from therapy related side effects.

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Authors' contribution

JA carried out the genetic analyses and drafted the manuscript.

UK participated in the genetic analyses and drafted the manuscript.

MS carried out the dose calculations and was involved in the preparation of the manuscript.

OO participated in the design of the study and was involved in the preparation of the manuscript.

RF participated in the design of the study and was involved in the preparation of the manuscript.

LD conceived of the study, and participated in its design and coordination and helped to draft the manuscript.

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research article

Evaluation of a software system for estimating planned dose error in patients, based on planar IMRT QA measurements

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Background. Intensity modulated radiation therapy (IMRT) dosimetry verification is routinely conducted *via* integrated or individual field dosimetry using film or a matrix of detectors. Techniques and software systems are commercially available which use individual field dosimetry measurements as input into algorithms that estimate 3D patient dose distributions on CT scan derived target volumes and organs at risk (OARs), thus allowing direct dose-volume histogram (DVH) analysis *vs.* treatment planning system (TPS) DVH. The purpose of this work is to present a systematic benchmarking technique to evaluate the accuracy and consistency of such a software system.

Methods. A MapCheck2 diode array and 3DVH™ software from Sun Nuclear were used for this study. Delivered planar dose was measured with the diode array as an input to 3DVH™ software that was used to estimate the 3D dose matrix. Accuracy of the output of 3DVH™ is tested by comparing measured planar doses over a range of depths to the same planes reconstructed by 3DVH™. Different fields from complex IMRT cases were selected and examined in this study. The sensitivity to depth of measurement was evaluated.

Results. The Gamma Index analysis, comparing calculated 3D dose with measured 3D dose with 2% and 2mm distance-to-agreement (DTA) criteria returned a pass rate of > 90% for all patient cases calculated by the treatment planning system and it returned a pass rate of > 96% in 9 out of 10 cases calculated by 3DVH™. Extracted computed dose planes with 3DVH™ software at different depths in the flat phantom passed all gamma evaluation analyses when compared to measured planes at different depths using MapCheck2.

Conclusions. Studying complex head and neck IMRT fields, it was shown that the 3D dose distribution predicted by the planned dose perturbation (PDP) algorithm is both accurate and consistent.

Key words: intensity modulated radiation therapy; quality assurance; 3D dosimetry; planar dosimetry; MapCheck; 3 dose-volume histogram

Introduction

The level of complexity and uniqueness of intensity modulated radiation therapy (IMRT) for each patient requires accurate and precise dosimetry verification and quality assurance (QA) technique(s).[1,2] QA usually can be carried out in the form of either composite or individual field dosimetry.[3] With the composite dosimetry approach, the composite dose distribution is measured in one or more selected phantom planes. For individual field dosimetry a flat phantom is used to measure the dose distribution in a plane perpendicular to the beam axis of each individual field.[3] The individual beam approach leads to useful information about the sources of discrepancy in the planning and delivery process of each individual field. The measurements could be done either using film or a matrix of detectors.[4-11] There are other techniques available that do not use a flat phantom.[12] Recently it was demonstrated that the individual beam approach may not be adequate in investigating the

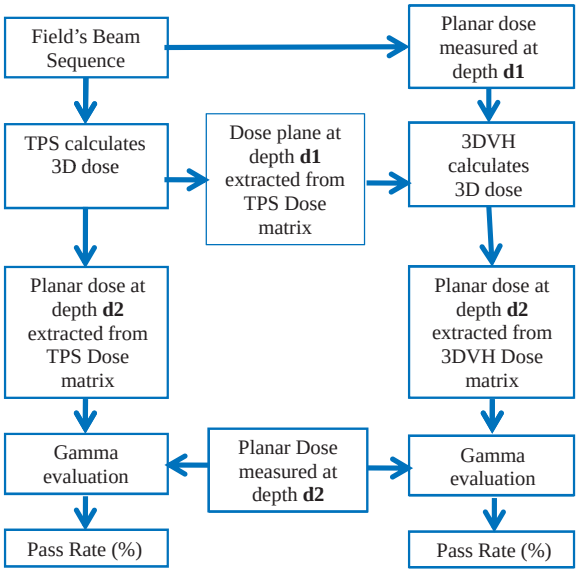

FIGURE 1. The flow chart of the benchmarking technique. Both treatment planning system (TPS) and 3DVH™ return a 3D dose matrix. The 3DVH™ dose matrix is reconstructed using the measurements and TPS data on a plane at depth d1. Additional measurement at a different depth of d2 is carried out. The new measurement at depth d2 was compared to the corresponding planar dose extracted from the calculated 3D doses in TPS and 3DVH™.

accuracy of dose delivery to individual organs at risk.[13,14] The conventional IMRT QA is performed for a plane normal to the beam axis using passing rates for Gamma index[15] or %/DTA composite;[16] as such, they do not provide much information about impact in 3D, *i.e.* the actual deliverable dose volume histograms of different organs. Therefore, obtaining a 3D dose distribution is desirable for an improvement in the sensitivity and specificity of IMRT QA analyses. A 3D dose distribution can be estimated in several ways such as: 1) measuring dose in a volume in a 3D dosimeter or 2) using a software system that estimates the 3D dose using phantom measurements and phantom calculations as input to guide a reconstruction algorithm.[17] Method 2 provides a volumetric planar dose distribution by modifying planned dose or reconstructing dose using measured planar dose and therefore we name it as a *virtual measurement* of the 3D dose distribution. This method may be useful if the accuracy of the algorithm is verified.

Currently there are several commercially available planar software systems that estimate 3D patient dose deviations based on inputs from 2D measurements such as the COMPASS system (IBA-Wellhofer), DOSIMETRYCHECK (Math Resolutions LLC), and 3 dose-volume histogram (DVH) (Sun Nuclear Corporation). Systematic benchmarking techniques must be developed in order to verify the accuracy of the algorithms behind them. Others have published studies on the accuracy of the planned dose perturbation algorithm (PDP) using planar measurement[18] and simulation.[17] In this investigation we developed another evaluation technique using measurements over a range of depths. The measured 2D dose matrices were used to compare to virtual measurements to verify the accuracy of the algorithm. Although the software system 3DVH™ is benchmarked here, the technique can be used for benchmarking other similar software systems as well.

Methods

In a systematic way, dose matrices were obtained in three different ways for inter-comparison: I) Using the treatment planning system in a homogeneous water phantom (3D dose), II) *via* multiple planar measurements over a range of depths, and III) *via* the 3DVH™ perturbation algorithm based on measurements and calculations from a single planar depth (3D dose). For methods II and III, a 2D diode array (MapCheck2 from Sun Nuclear, Melbourne, FL) was used for measuring the individual fields. For the PDP algorithm, two main components are used: 1) the 3D dose calculation exported from the treatment planning system (TPS) as the unperturbed planned dose $D(x,y,z)$ and 2) a modeling that perturbs the planned dose component $d(x,y,z)$ using QA phantom measurements vs. QA TPS calculations. In order to obtain a 3D perturbed dose matrix both the planar measurements at a certain depth and TPS calculated planar dose at the same depth are needed. If there is any dose differences found between the MapCheck measurement and the TPS dose calculation for each beam, the software uses those dose differences and projects them back into the TPS 3D dose calculation to obtain an estimate of the actual delivered 3D dose distribution.[18] A recent investigation verified accuracy of the PDP algorithm by introducing known errors and comparing the known effects versus the predicted effects.[17] In this work, we use similar strategy but use actual measurements at different depths to verify the 3DVH estimations at those depths.

The flow chart of the benchmarking technique is shown in Figure 1. The beam's multileaf collimator (MLC) segments for each field are used in the TPS to calculate a 3D dose matrix in a cubic water phantom for each field individually. The planar dose at depth d1 and d2 are extracted from the 3D dose ma-

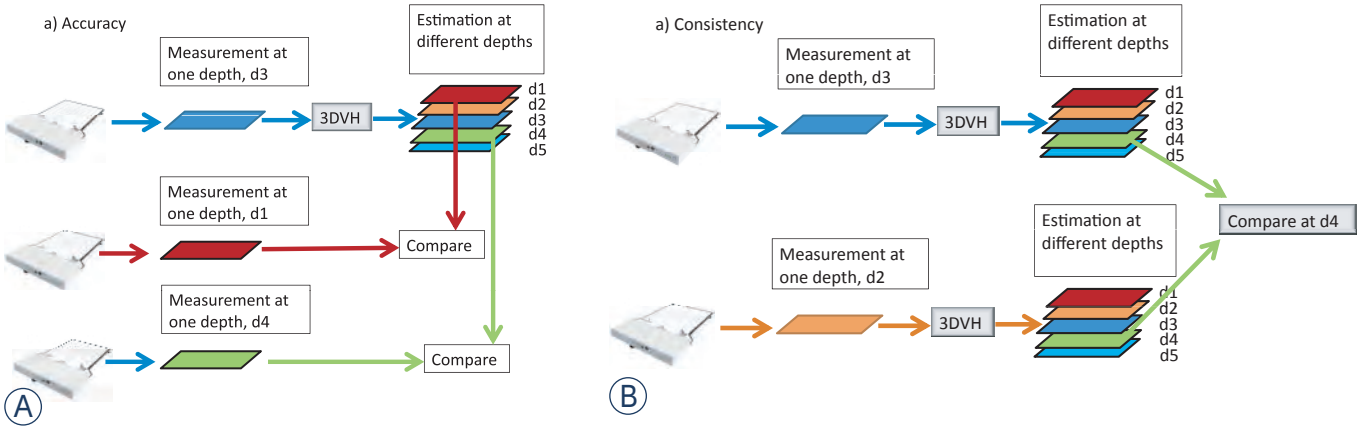

FIGURE 2. Schematic diagram of the experimental setup to benchmark 3 dose-volume histogram (DVH).

trix calculated by the TPS. The same programmed MLC segments are used to deliver and measure the planar dose at a depths d1 and d2 using MapCheck with rectangular solid water equivalent build up. The measured and TPS calculated planar doses at depth d1 are compared to calculate a 3D dose matrix using 3DVH™ software (Figure 2). Then, the planar dose at a different depth (such as d2, d3, or d4) was extracted from the 3D dose calculated by 3DVH™. For the measurements and calculations we kept the SSD fixed at 95 cm. Figure 2 also shows a schematic diagram of the experimental setup to benchmark 3DVH.

The MapCheck device calibration requires a relative array calibration and an absolute calibration. The array calibration is usually independent of the depth and can be done annually.[4] The absolute calibration at each depth is recommended to be done every time the MapCheck is set up for measurement.[19] We did the array calibration at depth 2 cm as recommended by manufacture and we did the absolute calibration for each depth separately.

Complex IMRT plans (three head and neck cases and one complex prostate case) were selected for the study. About twenty fields were randomly selected for checking the accuracy. For each field the 3D dose distributions were calculated in the TPS. Analytical anisotropic algorithm (AAA) dose computation algorithm was used in the Eclipse TPS (Varian Medical Systems, Palo Alto, CA).

Accuracy

The 3DVH™ dose matrices were calculated using the planar TPS and measurements at depth d1 = 5 cm. Comparisons of calculated planar dose matrices (from TPS and 3DVH™) were evaluated at depths d2 = 7 and 9 cm (Figure 2A). The gamma evaluation software returns the pass rate (%) using a distance to agreement of 2 mm and dose difference 2%.

Consistency

The 3DVH™ dose matrix calculated by measured data should be independent of the depth of measurements, that is the 3DVH™ dose distribution obtained with measurements at depth d1 = 7 cm should be almost identical to those obtained with measurements at depth d1 = 9 cm. The 3DVH™ code was run with measurements at depths d1 = 7 and 9 cm and the extracted planar doses were compared with measurements at depths d2 = 5 cm (Figure 2B).

An additional investigation of the consistency of the 3DVH algorithm was assessed by interrupting one of the IMRT fields half way through its delivery. Therefore half of the monitor units (MUs) were delivered (We simply pushed the beam off button when half of the beam MU was delivered). Using 3DVH™ the composite 3D dose and DVHs were calculated using beam measurements at different depths.

In this paper we have concentrated on field by field measurements. Recently there was also an investigation on the 3DVH accuracy based on cumulative/composite measurements.[18] In Ref.[18] the results were benchmarked with film and ion chamber. We also, as the last benchmark, did the same investigation but with MapCheck as the only measurement tool to finalize our study. A head and neck patient's fields were measured at a depth in 2 different ways: (I) measuring the individual fields at depth 5 cm with gantry angle set to zero and using these data in 3DVH™ to obtain a 3D dose distribution, and (II) Measuring a composite

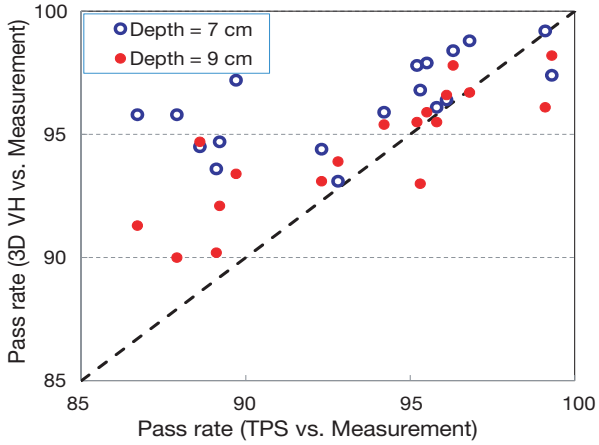

FIGURE 3. 3D doses were obtained using measurements and treatment planning system (TPS) planar doses at d1 =5 cm. The planar doses extracted at depths d2 = 7 and 9 cm from the calculated 3D doses are compared to measurements at corresponding depths. The gamma evaluation software returns the pass rate (%). The 3DVH™ estimates of dose are closer to the direct measurement than the original TPS calculation, as indicated by the points above the dotted line.

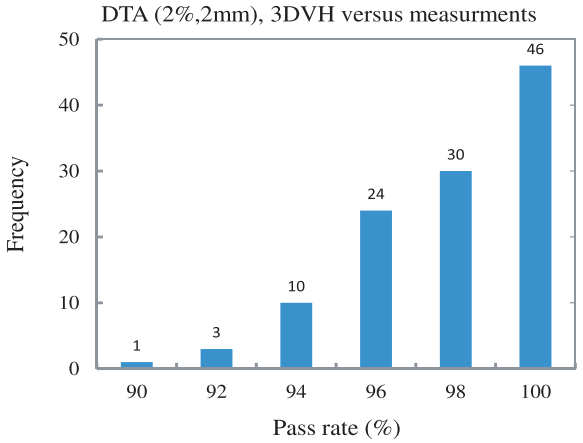

FIGURE 4. Bar chart of the pass rates obtained by comparing 3DVH™ outputs with measurements.

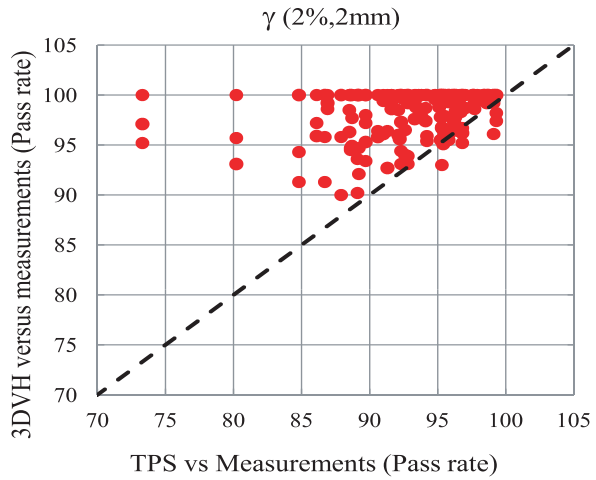

FIGURE 5. Comparison between treatment planning system (TPS) and DVH™ pass rate at 3 different depths. Again, the accuracy vs. measurement of 3DVH™ was an improvement over the original TPS dose.

planar dose distribution at depth 5 using MapPhan and actual gantry angle of each beam.

Results

Accuracy

In Figure 3, the pass rates calculated by comparing the measurements versus planar doses from the TPS and 3DVH™ are shown. In Figure 3, it is shown that there is a correlation between the pass rate of 3DVH™ dose planes and those from the TPS when the pass rate is high. Pass rates of greater than 90% are seen for the 3DVH™ data. On the other hand, comparing the measurements and TPS calculations leads to pass rates greater 86%. Most importantly, the 3DVH™ agreement *vs*. measurement is better than the TPS agreement as indicated by the vast majority (9 out of 10) of points residing above the dotted line on Figure 3; this is the goal of the perturbation software, that is, to be an improvement on the TPS prediction. The reason could be the MLC characterization in TPS that leads to differences between planned and delivered dose.

Similarly the measurement at d1 = 7 cm or d1 = 9 cm were used to run 3DVH™ and the results were compared with the measurements in other depths. A bar chart of all of the comparisons between 3DVH™ outputs and the measurements are shown in Figure 4. Approximately 90% of the data points have a pass rate of more than 96%. The comparison of these data with TPS is shown in Figure 5. Interestingly, when comparing to the TPS, the 3DVH™ results show a better agreement with measurements. This might be expected since 3DVH™ is calculated based on the delivered dose not calculated.

Consistency

The 3DVH™ planar dose code was run with measurements at depths d1 =7 and 9 cm and the extracted planar doses were compared with measurements at depths d2 = 5 cm (Figure 2B). The results are shown in Figure 6. There is a correlation between the data sets, however it seems there is a trend toward the depth dependence. In order to investigate this more, the beam delivery of one of the fields was interrupted half way through and all of the IMRT fields were measured at 3 different depths. The resulting DVH curves are shown in Figure 7. The DVH curves obtained from 3DVH™ at different depths overlap each other, showing a clear error in the delivery, as expected.

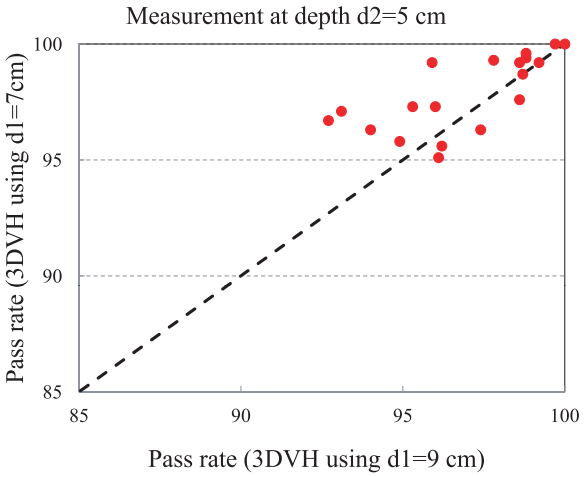

FIGURE 6. Two 3DVH™ dose matrices calculated using treatment planning system (TPS) and measured planar data at d1 = 7 and 9 cm. The extracted planar dose at d1 = 5 cm is compared with measurement. There is a correlation between both dose matrices.

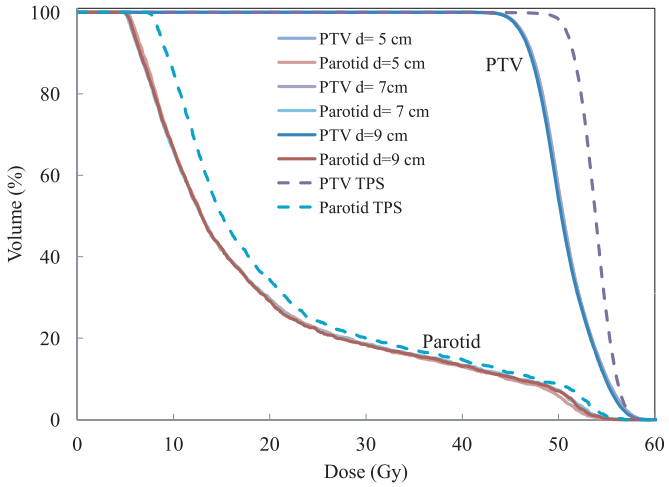

FIGURE 7. The dose-volume histogram (DVH) curves for different organs planned by the treatment planning system (TPS) (dashed lines) and calculated by 3DVH™ (solid lines). The input to 3DVH™ was measurements done by introducing a delivery error by interrupting the one of the beam's delivery half way through. The DVH curves from 3 different 3DVH™ files obtained at depths 5, 7, and 9 cm, three solid lines, are overlapped, indicating the consistency of the algorithm in detecting error.

The data from a composite calculation by 3DVH are compared with direct composite measurement by MapCheck in Figure 8. The gamma evaluation pass rate with 3 mm, 3% is about 96%. It is noted that MapCHECK/MapPhan has known inaccuracy for lateral beams due to measurement errors at these angles.[4] 3DVH™ allows 3D composite dosimetry that is not subject to these errors and which estimates a full volume rather than a single plane of dose.

Discussion

In Figure 3 it was shown that the dose matrices estimated by 3DVH are closer to direct measurements compare to the dose matrices calculated by TPS. The differences between delivered and calculated dose may come from MLC characterization in TPS (leading to calculation errors) or failure of MLCs in delivering the planned motions accurately.

In order to take out the effect of the consistency of MLC segment delivery on the results, we carried out the measurements in different days. Although MLC segment delivery errors are constrained by Linac manufacturer interlocks such that their magnitude cannot be large, it is also true, that small errors can add up to a large dosimetric error. For this study, we are focusing on systematic errors, and patient-specific errors (such as over-modulation leading to a very poor deliverability) that can be caught from just one fractional delivery.

The analysis done in Ref.[20] has shown that the spaces between diodes in comparison to films do not play a significant role in determining the final results of QA procedure.[20] The 3DVH software uses "Smarterpolation" as the interpolation technique, which means that it shapes the lines in between measurement point using the TPS plan's shape. We do not have any statistics or systematic study whether this may cause significant effect on the results. This should be addressed in future studies.

Regarding the inhomogeneity corrections, because 3DVH begins its calculation of patient dose from the starting point of the treatment planning system dose and only perturbs the dose based on measured errors, the dose already has the inhomogeneity information. The TPS has calculated the dose based on the heterogeneities in the CT scan.

It is seen in Figures 3 and 5 that some of the data points are below the diagonal line indicating lower pass rate with 3DVH in comparison to TPS. This research was designed to benchmark the 3DVH code on a single field basis. The 3DVH has been basically developed to obtain a composite dose error matrix from several single field measurements. An error in the setup or measurement can easily penetrate into other depths in single field analysis. Nevertheless, further investigation is needed for such cases.

Conclusions

A method was developed to investigate the accuracy and consistency of the software systems that

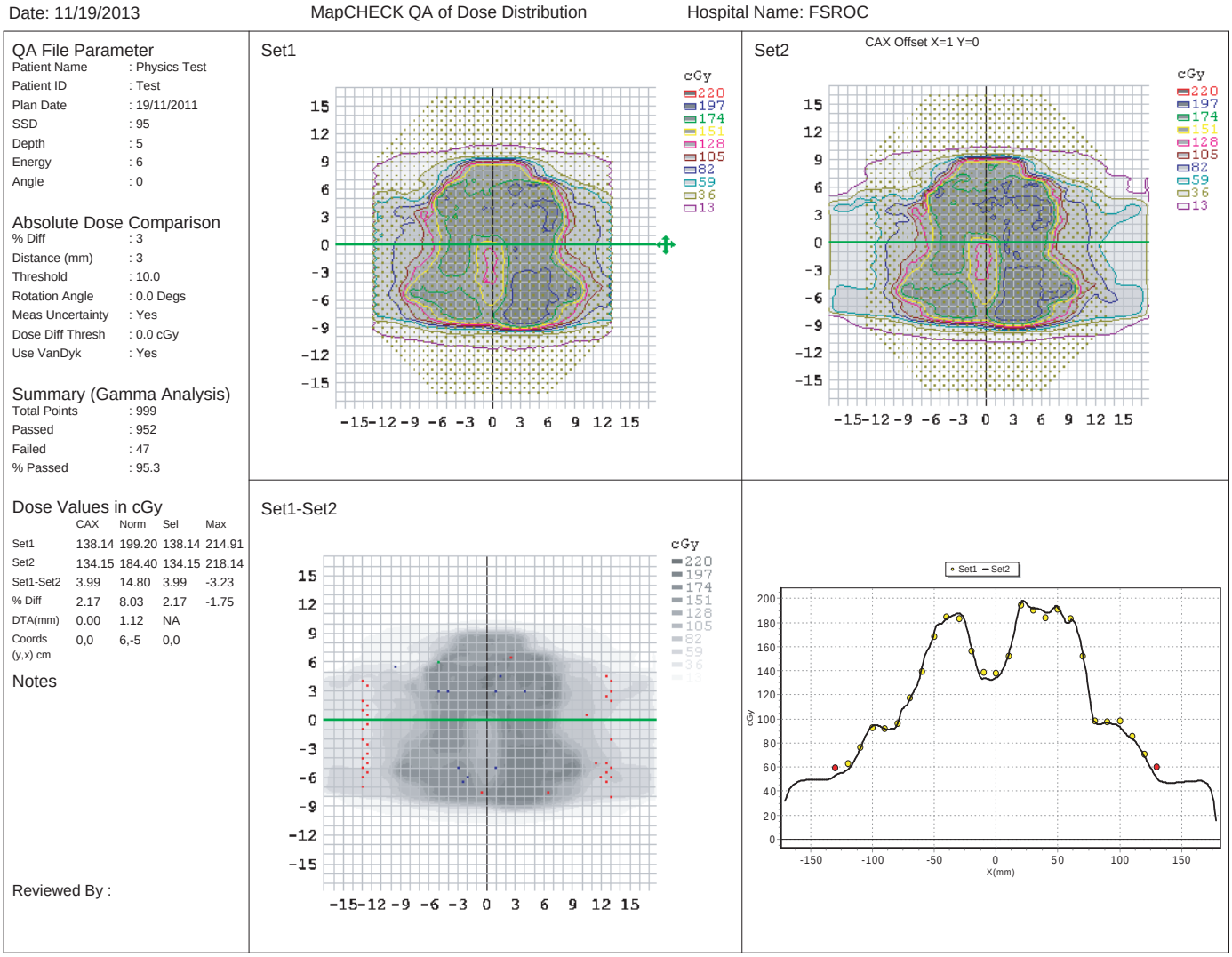

FIGURE 8. The composite measurement of a 9-field head and neck treatment planning system (TPS) case (set 1) is compared to the dose distribution obtained from 3DVH™ (set 2). The 3DVH™ software was run using individual field's measurement at fixed gantry angle of zero. The composite measurement was done by adding up individual field's measurement at their actual gantry angle. The resulted pass rate is 95.7%.

approximate the dose distribution in the patients based on planar measurements. The planar measurements can be carried out by film exposures or diode matrices (such as MapCheck). One of such software systems (3DVH™ from SunNuclear) was examined and it was found that:

The software results are independent of the depth of planar measurement, indicating the consistency of the results.

The 3D dose distributions obtained by 3DVH™ were closer to measurements compare to those from TPS, suggesting the accuracy of the software and usefulness of the software for *estimating* dose differences at other depths.

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research article

Impact of respiratory motion on breast tangential radiotherapy using the field-in-field technique compared to irradiation using physical wedges

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Background. This study aimed to evaluate whether the field-in-field (FIF) technique was more vulnerable to the impact of respiratory motion than irradiation using physical wedges (PWs).

Patients and methods. Ten patients with early stage breast cancer were enrolled. Computed tomography (CT) was performed during free breathing (FB). After the FB-CT data set acquisition, 2 additional CT scans were obtained during a held breath after light inhalation (IN) and light exhalation (EX). Based on the FB-CT images, 2 different treatment plans were created for the entire breast for each patient and copied to the IN-CT and EX-CT images. The amount of change in the volume of the target receiving 107%, 95%, and 90% of the prescription dose (V107%, V95%, and V90%, respectively), on the IN-plan and EX-plan compared with the FB-plan were evaluated.

Results. The V107%, V95%, and V90% were significantly larger for the IN-plan than for the FB-plan in both the FIF technique and PW technique. While the amount of change in the V107% was significantly smaller in the FIF than in the PW plan, the amount of change in the V95% and V90% was significantly larger in the FIF plan. Thus, the increase in the V107% was smaller while the increases in the V95% and V90% were larger in the FIF than in the PW plan.

Conclusions. During respiratory motion, the dose parameters stay within acceptable range irrespective of irradiation technique used although the amount of change in dose parameters was smaller with FIF technique.

Key words: breast cancer; radiotherapy; field-in-field technique; respiratory motion

Introduction

Most patients with early stage breast cancer are administered breast-conserving treatment consisting of wide excision and postoperative whole breast radiotherapy. This form of postoperative radiotherapy reduces the risk of local recurrence and results in a long-term survival similar to that obtained with mastectomy.[1-3]

In recent years, the field-in-field (FIF) technique has become a widely performed method of administering tangential whole breast radiotherapy, in addition to the use of physical wedge (PWs). Several studies have reported that the use of the FIF technique allows for the better control of dose homogeneity.[4-9] However, as the FIF technique requires the precise setting of the position of the multi-leaf collimators (MLCs) in order to reduce hot spots, there is concern that its use could significantly change the dose distribution to the target volume due to respiratory motion. The purpose of this study was to evaluate whether the FIF technique is more vulnerable to the impact of respiratory motion than irradiation using PWs.

Patients and methods

This planning study included 10 patients with early stage breast cancer, 6 with right-sided, and 4 with left-sided breast cancer. All patients had undergone breast-conserving surgery and implantation of 4 surgical clips on the tumor bed, 2 of which had been placed in the nipple side of the tumor bed and 2 on each medial and lateral side of the tumor bed.

CT acquisition

Computed tomography (CT) images were obtained using a scanner with 16 detector arrays (LightSpeed Xtra; GE Healthcare, Waukesha, WI, USA) while patients were in the supine position on a breast board with both arms above their heads. After radiopaque markers had been placed at the midline, the mid-axillary line, a site 1 cm below the infra-mammary fold, and at the level of the head of the clavicle, scanning was performed in 2.5-mm slices from the clavicle to the mid-abdomen during free breathing (FB). After the acquisition of the FB-CT data set, 2 additional CT scans were obtained during a held breath after a light inhalation (IN) and a light exhalation (EX). All CT images were transferred to Eclipse External Beam Planning 6.5 software (Varian Medical Systems Palo Alto, CA, USA). We fused the IN-CT and EX-CT images with the FB-CT images according to the spine. Images fusion was easy and very precise because the CT scans were obtained continuously without any movement of the body.

Simulation of radiotherapy planning

The remaining whole breast was contoured as the clinical target volume (CTV) with reference to the radiopaque markers. The planning target volume (PTV) was defined as the CTV with 5-mm margins except for the skin area. The evaluated planning target volume (PTVeval) was edited 5-mm of the build-up region from the skin surface of the breast. PTV defined on IN-CT and EX-CT was copied from FB-CT. The delineation was then moved and corrected on each CT slice, if necessary. The PTVeval on IN-CT or EX-CT was edited 5-mm of the build-up region from the skin surface of the PTV.

The FB-CT images were used as references for specifying the beam arrangement for developing a conventional PW plan and an FIF plan. After performing an initial calculation with a tangential 6-MV photon beam, the gantry angles and dorsal borders of the tangential field were adjusted such that the central lung distance (CLD) was < 2cm. CLD is defined as the distance between the deep field edge and the interior chest wall at the central axis.[10] Each patient's plan was normalized to a reference point set as the midpoint of the nipple and the posterior border of the field. None of the reference points was located on the lung parenchyma or the border between the lung and chest wall. The prescribed dose was 50 Gy in 25 fractions. The dose calculation algorithm used was according to the pencil-beam convolution method, and the Batho power-law method was used to correct for tissue inhomogeneities. After beam weighting had been optimized for each case, the medial field was copied as the subfield. The MLCs of the subfield were manipulated to shield the areas of the breast receiving doses ≥ 107% of the prescription dose on beam's eye view (Figure 1), with the beam weight of the subfield set at approximately one-tenth of the main field. If areas receiving a dose > 107% remained after recalculation of the dose distribution, the same process was repeated using a lateral field. All additional subfields were set not to shield the reference point.

After copying these fields to the IN-CT and EX-CT images for each patient, dose calculation was performed by inputting the same number of monitor units as for the FB-plan. The PW plan was then created by adding the PWs to the initial open field plan on the FB-CT images. The angles of the PWs

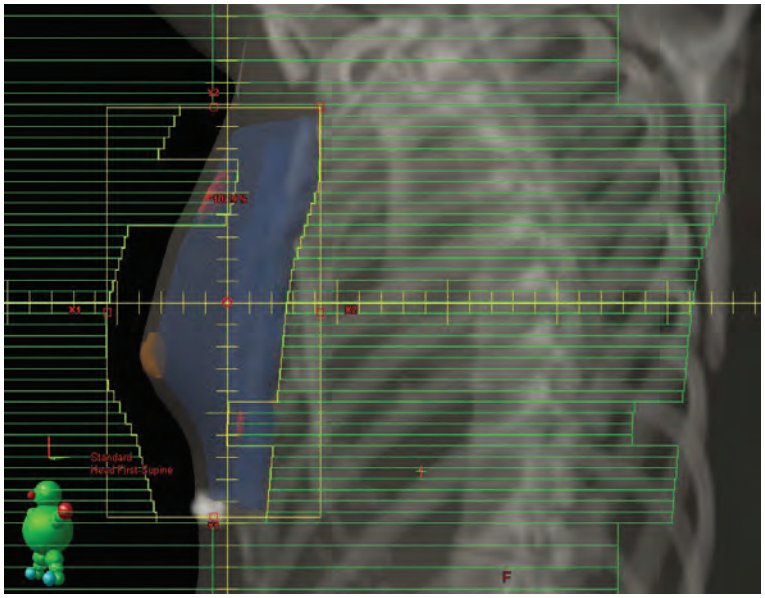

FIGURE 1. The additional subfield was designed to shield the hot region receiving ≥ 107% of the prescription dose. The evaluated planning target volume (PTVeval) is shown in dark blue, the nipple in brown, and the 107% isodose cloud in red.

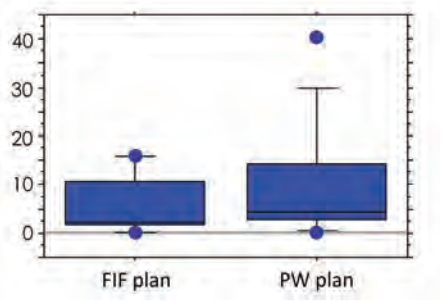

FIGURE 2. Comparison of amount of change of in the volume of the target receiving 107% (V107%) from the free breathing plan (FB-plan) to the light inhalation plan (IN-plan) for the field-in-field (FIF) and physical wedges (PW) plans.

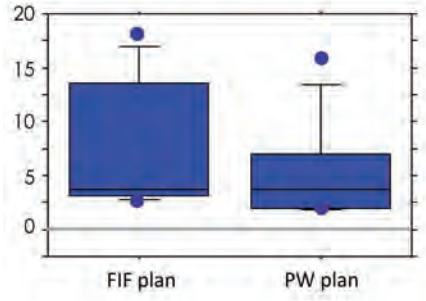

FIGURE 3. Comparison of amount of change in the volume of the target receiving 95% (V95%) from the free breathing plan (FB-plan) to the light inhalation plan (IN-plan) for the field-in-field (FIF) and physical wedges (PW) plans.

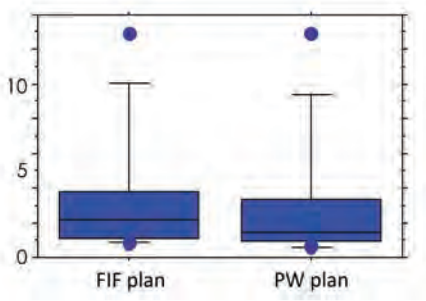

FIGURE 4. Comparison of amount of change in the volume of the target receiving 90% (V90%) from the free breathing plan (FB-plan) to the light inhalation plan (IN-plan) for the field-in-field (FIF) and physical wedges (PW) plans.

were ranged from 15° to 30°. This plan was also copied to the IN-CT and EX-CT images for each patient for dose calculation by inputting the same number of monitor units as for the FB-plan.

Evaluation

A dose-volume histogram (DVH) was calculated for each patient and the volumes of the PTVeval receiving 107%, 95%, and 90% of the prescription dose (V107%, V95%, and V90%, respectively) were calculated. The homogeneity index (HI) was defined as HI = (D2 - D98) / Dprescription, where D2 is the dose given to 2% of the PTVeval, D98 is the dose given to 98% of the PTVeval, and Dprescription is the prescription dose. The maximum, mean, and minimum doses delivered to each surgical clip were also calculated. The amount of change in the IN-plan and EX-plan from the FB-plan were evaluated for both the FIF and PW plans. Dosimetric parameters were compared using the Wilcoxon signed-rank test. A p value less than 0.05 was considered to indicate a statistically significant difference. The length of movement of each surgical clip from EX-CT to IN-CT in 3 directions (horizontal, anteroposterior, and craniocaudal) and three-dimensional vector displacement were measured.

Results

The median age of the patients was 54 years (range, 47 to 66 years). As shown in Table 1, which lists the displacement lengths of the clips in each direction, the average displacement length was the largest in the anteroposterior direction and the average three-dimensional vector displacement was 7.4mm.

No statistical differences were found regarding the amount of change for each surgical clip according to dose distribution between the IN-plan and FB-plan, or between the EX-plan and FB-plan.

The V107%, V95%, and V90% of the IN-plan were significantly larger in both the FIF and PW plans than those of the FB-plan (Table 2). The mean amount of change in the V107% of the FIF and PW plans was 5.7% (range, 0 − 16.0%) and 9.8% (range, -0.1 − 40.3%), respectively. The amount of change in the V107% was significantly smaller in the FIF than in the PW plan (p = 0.0069; Figure 2). The amount of change in the V95% in the FIF and PW plans was 7.3% (range, 2.7−18.1%) and 5.4% (range, 1.8−15.8%), respectively. The amount of change in the V90% in the FIF and PW plans was 3.6% (range, 0.7−13.0%) and 3.1% (range, 0.5−12.9%), respectively. The amounts of change in the V95% and V90% were significantly larger in the FIF than in the PW plan (p = 0.0125 and 0.0093, respectively; Figure 3 and Figure 4). These findings indicate that the increase in the V107% was smaller and the increase in the V95% and V90% was larger in the FIF than in the PW plan. The V95% and V90% of the FB-plan were slightly small. The dorsal borders of the tangential field were adjusted so that the central lung distance was < 2 cm on the FB plan. In some cases, the dorsal part of the PTVeval was out of the irradiation field. The plan was approved with a confirmation that the remaining mammary tissue was covered by the 95% isodose line. In the IN plan, the thoracic wall was moved to the anterior and was included to a greater extent in the irradiation field. Although the PTVeval parameters were better, the

TABLE 1. Displacement lengths of surgical clips from exhalation CT to inhalation CT

	Displacement length (mm)	Standard deviation	Minimum (mm)	Maximum (mm)
From lateral to medial	0.1	1.90	-3.3	4.2
From posterior to anterior	6.4	3.50	1.4	12.0
From caudal to cranial	2.7	2.40	-2.5	5.0
Three-dimensional vector	7.4	3.80	1.7	12.8

TABLE 2. Mean dose delivered to the evaluated planning target volume using the field-in-field and physical wedges plans during free breathing and light inhalation

		FB	IN	p value
FIF	V107%	0	5.7	0.0117
	V95%	91.0	98.9	0.0051
	V90%	96.2	99.7	0.0051
PW	V107%	0.9	10.7	0.0069
	V95%	93.7	99.0	0.0051
	V90%	96.7	99.8	0.0051

FB = free breathing; FIF = field-in-field; IN = light inhalation; PTVeval = evaluated planning target volume; PW = physical wedge; V107%, V95%, and V90% = percentage of PTVeval volume receiving ≥ 107%, ≥ 95%, and ≥ 90% of the prescription dose.

irradiated lung volume increased. No significant differences between the FIF and PW plans were found regarding other parameters, including the HI. No significant differences in V107%, V95%, and V90% were noted between the FB-plan and EX-plan in both the FIF and PW plans. No significant differences were found regarding the amount of change in any parameter.

Discussion

In a study of the effect of respiratory motion on breast tangential radiotherapy, Furuya *et al*. reported that movement along the anteroposterior direction significantly impacts dose distribution.[11] In the current study, the average length of movement of the surgical clips was 7.4 mm and largest movement was in the anteroposterior direction.

The FIF technique has been reported to be a useful method of breast tangential radiotherapy. Compared to the use of open-field irradiation with or without a PW, the use of the FIF technique allows for a reduction in the size of the high-dose region and the HI.[4-9] It has also been reported that it allows for the reduction of dosage to the contralateral breast.[9] However, as the FIF technique requires the precise setting of the position of the MLCs in order to reduce hot spots, there is a concern that its use could significantly change the dose distribution to the target volume because of respiratory motion. Despite this concern, a few reports have evaluated the effect of respiratory motion on breast tangential radiotherapy using the FIF technique. Nakamura *et al*. simulated each FIF and PW plan based on FB-CT for 20 breast cancer patients, and then moved the plans posteriorly and recalculated the dose.[12] They reported that the amount of change in the dose received by 98% of the PTV was smaller in the FIF than in the PW plan. However, as their simulation imitated respiratory motion, the deformation of thorax was not considered. To evaluate the effect of respiratory motion on an FIF plan, Bedi *et al*. created an FIF plan for 10 breast cancer patients on FB-CT images, copyied to the maximum inhalation and exhalation images obtained from four-dimensional CT.[13] They found that, compared to the reference plan, D2, the V95% and V90% of the PTV had been increased during the inhalation phase and D2, the V95% and V90% had been decreased during the exhalation phase, but identified no significant difference in any parameters. The FIF plan was not compared with the PW. In a study that performed scanning for 10 breast cancer patients during 3 different phases (FB, IN, and EX) and then created FIF and PW

plans, Frazier *et al*. reported that the V90%, V95%, and V100% for the ipsilateral breast were similar for each breathing position, but they did not statistically analyze their findings, or examine the difference in the amount of change with the use of the PW plan.[14] To the best of our knowledge, the current study was the first to compare the amount of change due to respiratory motion when using an FIF plan and a PW plan for breast tangential radiotherapy by examining 3 different CT phases. The results revealed that the V107%, V95%, and V90% of the IN-plan were significantly larger than those of the FB-plan in both the FIF and PW plans, while the increase in V107% was smaller and the increase in V95% and V90% was larger in the FIF than in the PW plan. Thus, the increase in the size of the "hot region" was smaller and the decrease in the size of the "cold region" was larger in the FIF plan than in the PW plan. However, no significant differences were found between the plans regarding the amount of change in the HI, which we hypothesized, may have been due to the small number of cases examined.

In conclusion, the results of this study indicate that the amount of change in dose parameters due to respiratory motion was smaller with the FIF technique than with irradiation using physical wedges, within an acceptable range.

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Ploščatocelični rak ustnega žrela in ustne votline pri mladih. Pregled literature

Majchrzak E, Szybiak B, Wegner A, Pienkowski P, Pazdrowski J, Luczewski L, Sowka M, Golusinski P, Malicki J, Golusinski W

Izhodišča. Čeprav je ploščatocelični rak glave in vratu (PCKGV) bolezen srednjega starostnega obdobja in starejših odraslih, so v zadnjem obdobju poročali o porastu incidence tega raka pri bolnikih mlajših od 45 let. V našem pregledu smo se osredotočili na epidemiologijo in etiologijo ploščatoceličnega raka glave in vratu pri odraslih starih manj kot 45 let.

Metode. Pregledali smo obstoječo literaturo, ki je obravnavala epidemiologijo in etiologijo ploščatoceličnega raka glave in vratu pri bolnikih mlajših od 45 let, ter razpravljali o možnostih zdravljenja in napovedi poteka bolezni.

Rezultati. Ploščatocelični rak glave in vratu pri mladih odraslih je povezan z višjo incidenco nekadilcev, nižjim razmerjem ženske-moški, večjim deležem rakov v ustni votlini in ustnem žrelu in manj z novimi primarnimi tumorji. Ob tradicionalnih dejavnikih tveganja, kot sta tobak in alkohol, so povzročitelji raka pri mladih odraslih nejasni. Dejavniki, ki bi lahko prispevali k tveganju za raka, vključujejo okužbo z visokorizičnimi podtipi človeškega virusa papiloma, vzrok pa so lahko tudi genetski dejavniki ali stanje imunske pomanjkljivosti. V primeru nadaljevanja obstoječih trendov, še posebej življenjskih navad, ki prispevajo k nastanku te bolezni, bi pričakovani porast incidence in smrtnosti pri mladih s ploščatoceličnim rakom glave in vratu lahko postal pomemben javnozdravstveni problem.

Zaključki. Upoštevajoč mladost in možne pozne stranske učinke tradicionalnih načinov zdravljenja ploščatoceličnega raka glave in vratu je potrebno načrtovati zdravljenje mladih odraslih individulno. Pri vsakem odločanju o zdravljenju je potrebno upoštevati kakovost življenja po zdravljenju.

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Zasevki drobnoceličnega raka pljuč v trebušni slinavki

Gonlugur U, Mirici A, Karaayvaz M

Izhodišča. Malo podatkov je na voljo glede incidence, klinične slike in napovedi poteka bolezni drobnoceličnega raka pljuč z zasevki v trebušni slinavki. Članek obravnava pregled literature na omenjeno temo, objavljene v angleškem jeziku.

Zaključki. Zasevki drobnoceličnega raka pljuč na trebušni slinavki redko povzročajo klinične simptome in funkcijske nepravilnosti. Računalniška tomografija je bistveno prispevala k večji prepoznavnosti zasevkov v trebušni slinavki. Potrebna je tudi histološka preiskava tkiva, saj radiološke preiskave ne razlikujejo zasevkov od primarnega tumorja trebušne slinavke. Zasevki na trebušni slinavki se pojavijo sorazmerno pozno v poteku bolezni drobnoceličnega raka pljuč. Komplikacije zaradi zasevkov so redke, najpogosteje se pojavlja akutni pankreatitis in obstruktivna zlatenica. Zgodnja kemoterapija podaljša preživetje bolnikov z zasevki drobnoceličnega raka pljuč v trebušni slinavki, tako pri bolnikih z akutnim pankreatitisom kot pri bolnikih z ekstrahepatično žolčno obstrukcijo.

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Vpliv rutinske slikovne diagnostike z 18F holinom pri bolnikih z rakom prostate. Pregled rezultatov dveh ustanov

Hodolič M, Michaud L, Huchet V, Balogova S, Nataf V, Kerrou K,Vereb M, Fettich J, Talbot JN

Izhodišča. 18-Fluoroholin (FCH) so začeli uporabljati aprila 2010 v Franciji, Sloveniji in treh drugih evropskih državah. Z njim dokažemo in opredelimo rak prostate ter mesto zasevkov raka prostate. Namen raziskave je bil primerjava razvoja slikovne diagnostike pri bolnikih z rakom prostate z uporabo novega radiofarmaka (FCH) v Franciji in Sloveniji ter vpliv nove slikovne diagnostike na odkrivanje zasevkov oz. ponovitve bolezni.

Metode. V dveh ustanovah, v Franciji in Sloveniji, smo pregledali število nuklearnomedicinskih preiskav,ki smo jih opraviliv petih četrtletjih po uvedbi FCH. Za vsako preiskavo FCH PET/CT smo zbrali klinične in biokemične podatke o bolniku ter morebitne že znane metastatske lezije v kosteh ali mehkih tkivih.

Rezultati. Opravili smo 688 nuklearnomedicinskih preiskav pri bolnikih z dokazanim rakom prostate; pri 77% bolnikov je FCH PET/CT preiskava bila narejena za ugotavljanje zasevkov po operativnem zdravljenju, pri 23% pa je bila preiskave narejene za spremljanje uspešnosti zdravljenja. Število preiskav s FCH PET/CT se je v petem trimestru povečalo za 220 % v primerjavi s prvim, izhodiščnim obdobjem, medtem ko se je število scintigrafij skeleta zmanjšalo za 42%, preiskav skeleta z (18-F)PET-om pa za 23%. PET/CT preiskava s fluorodeoksiglukozo (18F) (FDG) je ostala omejena le na nekaj bolnikov z rakom prostate neodzivnih na hormonsko zdravljenje. Delež negativnih rezultatov za dokaz zasevkov pri bolnikih z rakom prostate je bil značilno nižji pri uporabi FCH PET/CT (14 %) kot pri rezultatih scintigrafij skeleta (49 %), oz. pri rezultatih PET/CT skeleta z 18-F (54 %). Delež dokazanih kostnih zasevkov z uporabo FCH PET/CT je bil primerljiv, vendar smo s FCH PET/CT dokazali več zasevkov pri nižjih vrednostih prostate specifičnega antigena (PSA) v serumu, pa tudi odstotek nezanesljivih rezultatov preiskav je bil nižji. Z uporabo FCH PET/CT smo tako dobili le 4% nezanesljivih rezultatov, s scintigrafijo skeleta pa 28 % zaradi nizke specifičnosti te preiskave. Bistvena prednost FCH PET/CT je bil prikaz zasevkov v loži prostate (53% bolnikov) in zasevkov v mehkih tkivih (35% bolnikov).

Zaključki. V obeh ustanovah smo opazili hiter razvoj preiskav s FCH PET/CT in pomemben porast odkritega števila zasevkov raka prostate.

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Vloga ultrazvoka in ultrazvočno vodene aspiracijske biopsije s tanko iglo bezgavk pri bolnikih s tumorji kože

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Izhodišča. Prvi namen raziskave je bil določiti diagnostično natančnost ultrazvoka pri oceni v bližini površine telesa ležečih bezgavk med sledenjem bolnikov, ki so bili operirani zaradi tumorjev kože. Drugi namen je bil primerjati pozitivne citološke izvide s histološkimi izvidi.

Bolniki in metode. Med leti 2004 in 2011 smo pri 480 bolnikih naredili ultrazvočno vodeno aspiracijsko biopsija s tanko iglo sumljivo povečanih bezgavk. Razmerje med moškim in ženskim spolom je bilo 285 : 195; srednja starost bolnikov 57 let; najpogostejša vrsta tumorja je bil melanom. Najprej je izkušen radiolog opravil ultrazvočni pregled bezgavk in jih ocenil kot negativne ali pozitivne, nato smo naredili ultrazvočno vodeno aspiracijsko biopsija s tanko iglo. Bolnike s pozitivnim izvidom aspiracijske biopsije smo operirali, bolnike z negativnim izvidom pa sledili.

Rezultati. Velikost bezgavk je bila v 90 % primerov ≤ 2 cm. Izmed 336 (70 %) bolnikov s pozitivnim izvidom ultrazvoka je imelo pozitiven izvid ultrazvočno vodene aspiracijske biopsije 231 (68,8 %) bolnikov. Izmed 144 (30 %) bolnikov z negativnim izvidom ultrazvoka je imelo negativen izvid ultrazvočno vodene aspiracijske biopsije 132 (91,7 %) bolnikov. Občutljivost in specifičnost ultrazvočne preiskave je bila 95 % in 68,8 %; negativna napovedna vrednost je bila 91,7 % in pozitivna napovedna vrednost 68,8 %. Končni histološki izvid je potrdil pozitivni izvid ultrazvočno vodene aspiracijske biopsije pri 97,5 % limfadenektomiranih bolnikih.

Zaključki. Ultrazvok je občutljiva metoda za oceno v bližini površine telesa ležečih bezgavk med sledenjem bolnikov s tumorji kože. Potrjena je bila visoka pozitivna napovedna vrednost rezultatov citološke preiskave.

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Minimalno invazivno računalniškotomografsko vodeno zdravljenje intraspinalne sinovialne ciste. Prikaz primera

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Izhodišča. Intraspinalne sinovialne ciste, ki se pojavijo v povezavi s fasetnimi sklepi hrbtenice, so redek vzrok radikularne bolečine in nevroloških izpadov. Zdravljenje takšnih cist je lahko minimalno invazivno s pomočjo intervencijske radiologije ali kirurško.

Prikaz primera. Opisujeva 77-letnega bolnika z obojestransko lumboishialgijo in pridruženimi boleznimi. Lumboishialgija se je slabšala in ni več odgovarjala na konzervativno zdravljenje. Naredili smo slikovnodiagnostične preiskave in z magnetno resonanco ugotovili intraspinalno sinovialno cisto. Kot metodo izbora smo uporabili perkutano računalniško tomografsko (CT) vodeno punkcijo ciste z vbrizganjem mešanice lokalnega anestetika in kortikosteroida ter rupturo ciste. Mesec dni po posegu je bila pri bolniku bolečina manjša, zmanjšala se je uporaba analgetikov in izboljšala kakovost življenja.

Zaključki. Perkutano CT vodeno zdravljenje lumbalnih sinovialnih cist je varna in zanesljiva alternativa kirurškemu zdravljenju pri starejših in polimorbidnih bolnikih, kjer je kirurški poseg v splošni anesteziji zelo tvegan.

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Povišano izražanje SHP-1 je povezano z lokalno ponovitvijo bolezni po radioterapiji pri bolnikih z rakom nosnega žrela

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Izhodišča. Rak nosnega žrela je eden pomembnejših rakov v južni Kitajski. Src homologna fosfataza-1 (SHP-1) je tirozinska fosfataza, ki uravnava rast, diferenciacijo, delitev celic in onkogenezo. V prispevku smo določili pomen izraženosti SHP-1 v tumorjih bolnikov z rakom nosnega žrela iz južne Kitajske, ki smo jih zdravili z radioterapijo.

Bolniki in metode. Izraženost SHP-1 smo določili s polimerazno verižno reakcijo (PCR) v realnem času in analizo prenosa po Westernu v vzorcih tkiva raka nosnega žrela pri 50 bolnikih ter v tkivu nosnega žrela pri 50 bolnikih s kroničnim vnetjem nosnega žrela, a brez raka. Izraženost SHP-1 smo določili tudi imunohistokemično v vzorcih tkiva raka nosnega žrela pri 206 bolnikih in naredili analizo preživetja.

Rezultati. V tumorjih bolnikov z rakom nosnega žrela je bila izraženost SHP-1 na ravni mRNA in proteinov pomembno višja kot pri bolnikih s kroničnim vnetjem nosnega žrela. Analiza preživetja bolnikov z rakom nosnega žrela je pokazala, da je izraženost SHP-1 povezana s slabšim preživetjem brez ponovitve bolezni lokalno (p = 0,0008), ne pa tudi s preživetjem brez ponovitve bolezni področno, ali preživetjem brez oddaljenih zasevkov oz. celokupnim preživetjem.

Zaključki. SHP-1 smo videli povezano z odpornostjo celic raka nosnega žrela na obsevanje, zato bi SHP-1 lahko služila kot možnen napovedni kazalec in/ali terapevtska tarča pri bolnikih s to vrsto raka.

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Ocena verjetnosti za malignost pri nediagnosticiranih posameznih vozličih v pljučih kot jo opredeljujejo na dokazih temelječe klinične smernice Združenja ameriških pulmologov (ACCP)

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Izhodišča. Raziskava retrospektivno ugotavlja klinične značilnosti nediagnosticiranih kirurško odstranjenih posameznih vozličev v pljučih.

Bolniki in metode. Zbrali smo podatke o starosti, kajenju in predhodnih rakavih obolenjih bolnikov ter o velikosti vozličev, njihovem mestu in robni nazobčanosti. Obravnavali smo 241 bolnikov, ki so imeli vozliče velikosti od 7 do 30 mm in dokončno potrjeno histopatološko diagnozo. Pri vsakem bolniku smo primerjali končno diagnozo z verjetnostjo za maligno bolezen (VZM) po priporočilih Združenja ameriških pulmologov (ACCP).

Rezultati. Med 241 bolniki so imeli maligni pljučni tumor 203 bolniki, 38 bolnikov pa je imelo benigno bolezen. Ugotovili smo statistično značilne razlike med bolniki z maligno in benigno boleznijo v starosti, kajenju, velikosti vozličev in njihovi robni nazobčanosti. Povprečje in standardna deviacija verjetnosti za maligno bolezen pri bolnikih z malignim tumorjem je bila 51,7 % + 26,7. Površina pod krivuljo za ROC je bila 0,67. Najboljša mejna vrednost iz ROC krivulje je bila 22,6. Pri postavitvi vrednosti na 22,6 je bila občutljivost 83 %, specifičnost 52 %, pozitivna napovedna vrednost 90 %, negativna napovedna vrednost 36 % in natančnost 77 %.

Zaključki. V naši raziskavi klinični model napovedi verjetnosti za maligno bolezen – kot ga je predlagal ACCP – ni pokazal zadovoljivih rezultatov za razločevanje med maligno in benigno boleznijo posameznih vozličev v pljučih. Vrednosti za specifičnost, negativno napovedno vrednost in površina pod krivuljo za ROC so bile sorazmerno nizke.

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Rezultati zdravljenja neresektabilnih tumorjev žlez slinavk z radioterapijo s fotoni. Je lokalna kontrola po radioterapiji z nevtroni boljša?

Spratt DE, Salgado LR, Riaz N, Doran MG, Tam M, Wolden S, Katsoulakis E, Rao S, Ho A, Wong R, Lee NY

Izhodišča. Rezultati randomizirane raziskave RTOG-MRC, ki je v 80-ih letih preteklega stoletja primerjala fotone (n=15) z nevtroni (n=17), so pri zdravljenju neresektabilnih tumorjih žlez slinavk z radioterapijo z nevtroni pokazali boljšo lokalno kontrolo (LK). Zaradi povečane hude toksičnosti radioterapije z nevtroni in maloštevilnosti nevtronskih radioterapevtskih centrov smo analizirali rezultate zdravljenja neresektabilnih tumorjev žlez slinavk z radioterapijo s fotoni v naši ustanovi.

Bolniki in metode. Od 1990 do 2009 smo v naši ustanovi zdravili z radioterapijo s fotoni 27 bolnikov z neresektabilnim rakom žlez slinavk. Pri 9 bolnikih so bili ob predstavitvi najdeni področni zasevki. Srednja doza obsevanja je bila 70 Gy. Kemoterapijo, največkrat je vsebovala platino, je prejelo 18 bolnikov. Ocenjevali smo lokalno kontrolo, lokoregionalno kontrolo, preživetje brez oddaljenih zasevkov, celokupno preživetje in toksičnost.

Rezultati. Ob srednjem času sledenja 52,4 mesecev je bila 2 in 5-letna lokalna kontrola 69 % (95 % interval zaupanja [IZ] ± 21,0%) in 55 % (± 24,2 %), lokoregionalna kontrola 65 % (± 21,4 %) in 47 % (± 21.6 %) ter preživetje brez oddaljenih zasevkov 71 % (± 21,8 %) in 51 % (± 22,8 %); uporabljena je bila analiza konkurenčnih tveganj *(competing risk analysis)*. Srednje trajanje celokupnega preživetja je bilo 25,7 mesecev, 2 in 5-letno celokupno preživetje pa 50 % (± 19,0 %) in 29 % (± 16,6 %). Visok histološki gradus je bil statistično značilen kazalec povišane pojavnosti oddaljenih zasevkov (gradus II proti gradus I, p = 0,04, razmerje obetov [RO] 7,93; gradus III proti gradu I, p = 0,01, RO 13,50). Trinajst (48 %) bolnikov je imelo akutno toksičnost stopnje 3. Pozna toksičnost stopnje 3 se je pojavila pri treh (11 %) bolnikih.

Zaključki. Naši rezultati so primerljivi z rezultati radioterapije z nevtroni, ob manjšem številu poznih neželenih učinkih. Radioterapija s fotoni je sprejemljiva alternativa radioterapije z nevtroni pri bolnikih z neresektabilnimi tumorji žlez slinavk.

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Balonsko širjenje aortne zaklopke kot premostitveni poseg do zamenjave aortne zaklopke pri bolnikih, ki potrebujejo nujni ne-kardiokirurški operativni poseg

Kogoj P, Devjak R, Bunc M

Izhodišča. Balonsko širjenje aortne zaklopke (BAV) je perkutana možnost zdravljenja hude simptomatske stenoze aortne zaklopke. Ker prihaja po širjenju do zgodnjih restenoz, poseg ne vpliva na dolgoročno preživetje. BAV uporabljamo paliativno pri bolnikih, ki jih zaradi povečanega kirurškega tveganja ne moremo operirati na odprtem srcu. Takšno zdravljenje je tudi premostitveni poseg do kirurške zamenjave aortne zaklopke ali perkutane vstavitve aortne zaklopke (TAVI) pri hemodinamsko nestabilnih bolnikih ali pri bolnikih, ki potrebujejo nujno nekardiokirurško zdravljenje.

Bolniki in metode. V prispevku predstavljamo šest onkoloških bolnikov s hudo stenozo aortne zaklopke, ki so potrebovali nujno abdominalno in ginekološko kirurško zdravljenje. Pri vseh bolnikih smo opravili BAV, pri enemu bolniku s sočasno obstruktivno koronarno boleznijo pa smo v okviru istega posega opravili še koronarno angioplastiko.

Rezultati. Z uspešnim perkutanim zdravljenjem smo dosegli dober koronarni pretok in povečanje površine aortnega ustja ter posledično hemodinamsko in simptomatsko izboljšanje. Tako smo zmanjšali tveganje za kirurško zdravljenje raka, ki je v vseh šestih primerih potekalo brez zapletov.

Zaključki. BAV je varen poseg v okviru kompleksnega zdravljenja hude simptomatske aortne stenoze, ki izboljša kakovost življenja, zmanjša kirurško tveganje za nekardiokirurške operacije in omogoča premostitev do kirurške ali transkatetrske zamenjave aortne zaklopke.

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Torakoskopija s polupogljivim inštrumentom. Učinkovita metoda v diagnostiki malignih bolezni plevre

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Izhodišča. Torakoskopija s polupogljivim inštrumentom je novejša metoda v diagnostiki bolezni plevre. Cilj raziskave je bil natančneje opredeliti diagnostično učinkovitost in zaplete torakoskopije s polupogljivim torakoskopom.

Bolniki in metode. Torakoskopijo s polupogljivim inštrumentom smo opravili pri bolnikih z neopredeljenim plevralnim izlivom in/ali plevralnimi nepravilnostmi, ki so bile sumljive za maligno bolezen, in jih nismo uspeli opredeliti z manj invazivnimi preiskovalnimi metodami. Vse posege smo naredili v lokalni anesteziji in intravenski analgosedaciji s pomočjo polupogljivega torakoskopa (Olympus LTF-160). Vse preiskave smo naredili z enim vstopnim mestom. Podatke smo zbirali prospektivno med leti 2008 in 2012.

Rezultati. Napravili smo 115 torakoskopij pri 111 bolnikih. Srednja starost bolnikov je bila 65 let (razpon 28 do 86 let); med njimi je bilo 14,4 % žensk in 85,6 % moških. 73 (65,8 %) bolnikov je imelo maligno bolezen plevre (maligni mezotelioom, metastatski malignom), 38 (34,2 %) pa benigno bolezen. Občutljivost, negativna napovedna vrednost in natančnost metode za maligno bolezen so bile 96,0 %, 93,0 % in 97,4 %. Plevrodezo smo napravili pri 34 bolnikih; pri 32 (94,1%) je bila po enem mesecu ocenjena kot uspešna. Zabeležili smo 24 zapletov: 3 empieme oziroma okužbe plevralnega prostora, 3 bronhoplevralne fistule po plevralni drenaži in ponovnem razpenjanju pljuč, 5 bolnikov je imelo močnejše bolečine neposredno po plevrodezi, 6 bolnikov je imelo prehodno hipotenzijo v povezavi s sedacijo, 7 bolnikov pa je imelo prehodno povišano temperaturo po plevrodezi. En bolnik je umrl 11 dni po posegu zaradi napredovalega karcinoma.

Zaključki. Torakoskopija s polupogljivim inštrumentom je natančna in varna metoda za diagnostiko plevralnih bolezni, uporabna pa je tudi pri terapevtski plevrodezi s talkom.

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Bolniki z glioblastomom v Sloveniji od 1997 do 2008

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Izhodišča. Glioblastom je najpogostejši primarni možganski tumor. Kljub napredku v zdravljenja v zadnjem desetletju je napoved poteka bolezni pri bolnikih z glioblastomom še vedno slaba. V Sloveniji vsako leto na novo odkrijemo med 50 in 60 bolnikov. V prispevku analiziramo preživetje bolnikov z glioblastomom med leti 1997 in 2008.

Bolniki in metode. V raziskavo smo vključili vse bolnike, ki smo jih zaradi glioblastoma zdravili na Onkološkem inštitutu v Ljubljani med leti 1997 in 2008. Podajamo njihove demografske značilnosti, značilnosti zdravljenja in izračun preživetja za skupino kot celoto in podskupine.

Rezultati. Med letoma 1997 in 2009 smo na Onkološkem inštitutu zdravili 527 odraslih bolnikov z glioblastomom. Njihova srednja starost je bila 59 let, diagnoza je bila pri vseh, razen pri enem, potrjena histološko. Kirurg je pri 49,5 % bolnikov poročal o makroskopski odstranitvi tumorja. Po operaciji je bilo 64 % bolnikov v dobrem stanju zmogljivosti (po lestvici Svetovne zdravstvene organizacije 0 in 1) in smo jih 421 (80 %) še obsevali. Med njimi smo 317 (75%) bolnikov obsevali z radikalnim namenom in med slednjimi je še 198 (62%) bolnikov prejelo eno izmed oblik sistemske terapije (običajno temozolomid). Srednje preživetje vseh obravnavanih bolnikov je bilo 9,7 mesecev. Če upoštevamo le bolnike zdravljene z radikalnim namenom, je bilo srednje preživetje 11,4 mesecev pred obdobjem temozolomida, po njem pa 13,1 mesecev (p = 0,0014). Najbolj smo bili uspešni pri zdravljenju mlajših bolnikov v dobrem stanju zmogljivosti in če smo pri njih naredili obširno resekcijo tumorja. Med bolniki zdravljenimi z radikalnim namen so bili stanje zmogljivosti, način načrtovanja obsevanja in dodatek temozolomida statistično pomembni v multivariatni analizi.

Zaključki. V zadnjem desetletju vidimo postopno podaljševanje preživetja bolnikov z glioblastomom. K temu so pripomogli: kirurške tehnike z dobrimi funkcionalnimi rezultati, napredek obsevalnih tehnik in dodatek temozolomida. Agresivno zdravljenje je lahko koristno pri bolnikih vseh starostnih skupin, če ga dopušča splošno stanje zmogljivosti. Naša retrospektivni analiza nakazuje, da je bil način aplikacije temozolomida manjšega pomena pri starejših bolnikih. Prav tako nakazuje, da je pri določenih podskupinah bolnikov podaljšanje preživetja bolj izrazito. Te podskupine še ne moremo natančno opredeliti. Tako so potrebne dodatne klinične raziskave, predvsem na področju molekularne biologije in genetike tumorja.

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Radioobčutljivost bolnic z rakom dojke se spreminja s starostjo bolnic

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Izhodišča. Radioobčutljivost posameznika ima velik vpliv na radioterapijo, predvsem na njene stranske učinke. Zato smo v raziskavi proučevali razliko v radioobčutljivosti posameznikov, v skupini bolnic z rakom dojke in pri zdravih posameznikih ter jo primerjali s starostjo posameznikov.

Preiskovanci in metode. V raziskavo smo vključili 129 oseb, z rakom dojke je bilo 67 bolnic in zdravih prostovoljcev 62. Posameznikovo radioobčutljivost smo določali na vzorcih periferne krvi s 3 barvno fluorescentno in situ hibridizacijo.

Rezultati. Ugotovili smo značilno razliko v radioobčutljivosti, bolnice z rakom so imele večjo od zdravih prostovoljcev. Zaznali smo tudi dve podskupini po 9 bolnic s precej povišano in znižano radioobčutljivostjo. Poleg tega je imela skupina bolnic v starostnem obdobju med 40-50 let povišano radioobčutljivost v primerjavi s starejšimi in mlajšimi bolnicami.

Zaključki. Pri bolnicah za rakom dojke smo ugotovili specifični podskupini bolnic, ki so bile radioobčutljive in radiorezistentne, kar bi lahko izkoristili pri načrtovanju zdravljenja. Preliminarni rezultati nakazujejo, da so bolnice bolj radioobčutljive v starostnem obdobju od 40-50 let, zato lahko pri njih pričakujemo več stranskih učinkov radioterapije.

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Ovrednotenje programskega orodja za oceno planirane dozne napake pri bolnikih, na osnovi planarnih meritev IMRT QA

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Izhodišča. Dozimetrično preverjanje pri intenzitetno modulirani radioterapiji (IMRT) rutinsko izvajamo z uporabo filmske dozimetrije ali matrice detektorjev, bodisi integralno, bodisi za posamezno obsevalno polje. Komercialno so dostopne tehnike in programska orodja, ki na osnovi dozimetričnih meritev posameznih obsevalnih polj z uporabo algoritmov ocenijo tridimenzionalno porazdelitev doze v bolniku na skladovnici računalniško tomografskih (CT) rezov ter doze na pripadajočih tarčnih volumnih in rizičnih organih. S tem omogočajo neposredno analizo dozno-volumskega histograma (DVH) in njegovo primerjavo z DVH, dobljenim z načrtovalnim sistemom. Namen tega dela je predstavitev tehnike za sistematični primerjalni preizkus, s katerim ovrednotimo točnost in skladnost takega programskega orodja.

Metode. V raziskavi smo uporabili diodno polje MapCheck2 in programsko opremo 3DVH™, oboje izdelek Sun Nuclear. Izsevano dozo smo izmerili planarno z diodnim poljem, dobljene podatke pa obdelali s programom 3DVH™, s katerim smo ocenili tridimenzionalno dozno matriko. Točnost rezultatov 3DVH™ smo preizkusili s primerjavo izmerjenih planarnih doznih porazdelitev pri več različnih globinah z rekonstruiranimi porazdelitvami, dobljenimi s 3DVH™ pri istih globinah. V raziskavi smo izbrali in analizirali več različnih obsevalnih polj kompleksnega obsevalnega načrta IMRT. Ocenili smo občutljivost metode na globino, pri kateri smo opravili meritev.

Rezultati. Analiza indeksa gama, ki primerja izračunano tridimenzionalno dozno porazdelitev z izmerjeno dozno porazdelitvijo ob pogojih 2% odstopanja v dozi in 2 mm prostorskega odstopanja (distance-to-agreement, DTA), je pokazala več kot 90% ujemanje za vse obsevalne načrte, izračunane z načrtovalnim sistemom. Pri obsevalnih načrtih, izračunanih s 3DVH™, je bilo ob istih pogojih v 9 od 10 primerov ujemanje večje od 96%. Preseki dozne porazdelitve v planarnem fantomu, izračunani s 3DVH™, so pri analizi indeksa gama izkazali sprejemljivo ujemanje s planarnimi doznimi porazdelitvami, izmerjenimi pri različnih globinah z MapCheck2.

Zaključki. Proučevanje kompleksnih obsevalnih polj IMRT, izdelanih za obsevanje raka glave in vratu, je pokazalo, da je tridimenzionalna dozna porazdelitev, izračunana z algoritmom planarne dozne perturbacije (PDP) v programu 3DVH™, točna in skladna.

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Vpliv dihanja na tangencialno obsevanje dojk s tehniko polja v polju v primerjavi z obsevanjem s fizikalnimi klini

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Izhodišča. Namen raziskave je bil oceniti, ali je obsevalna tehnika polja v polju bolj občutljiva na vplive dihanja, kot je obsevanje s fizikalnimi klini.

Bolniki in metode. V raziskavo smo vključili deset bolnikov z začetnim rakom dojk. Računalniško tomografijo (CT) smo najprej naredili med prostim dihanjem, nato pa še dva CT posnetka med zadržanjem diha: po plitkem vdihu in po plitkem izdihu. Na osnovi CT preiskave med prostim dihanjem smo naredili za vsakega bolnika dva različna obsevalna načrta in ju preslikali na CT posnetke narejene po plitkem vdihu in po plitkem izdihu. Ocenili smo razlike v tarčnih volumnih, ki so prejeli 107%, 95% in 90% predpisane doze (V107%, V95% in V90%) med obsevalnim načrtom ob plitkem vdihu oz. izdihu na eni strani ter obsevalnim načrtom ob prostem dihanju na drugi strani.

Rezultati. Tarčni volumni V107%, V95% in V90% so bili značilno večji pri obsevalnem načrtu ob plitkem vdihu, kot so bili pri načrtu ob prostem dihanju pri obeh tehnikah (polja v polju in obsevanju s fizikalnimi klini). Velikost spremembe V107% je bila značilno manjša pri obsevalnem načrtu polja v polju kot pri načrtu s fizikalnimi klini, nasprotno pa je je bila velikost sprememb V95% in V90% značilno večja. Porast volumna V107% je bil manjši, porasta volumnov V95% in V90% pa večji pri obsevalnem načrtu polja v polju kot pri načrtu s fizikalnimi klini.

Zaključki. Ob dihanju dozni parametri ostajajo znotraj sprejemljivih meja ne glede na tehniko obsevanje (polja v polju in obsevanju s fizikalnimi klini), čeprav je velikost spremembe doznih parametrov manjša ob uporabi tehnike polja v polju.

Fundacija "Docent dr. J. Cholewa"
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Activity of "Dr. J. Cholewa" Foundation for Cancer Research and Education – a report for the last quater of 2013

The Dr. J. Cholewa Foundation for Cancer Research and Education is a non-profit, non-political and non-government organisation that unites individuals, professionals, institutions and other organisations in their effort to achieve optimal results in cancer research, education, treatment and prevention. It provides financial support for physicians and other experts interested in all the subjects associated with cancer, resulting in a number of successful initiatives and projects.

To honour the 20th anniversary of its activity the Foundation organized a symposium with the aim to present the most recent advances in cancer diagnostics and therapy primarily to general practitioners and others in everyday contact with people requiring relevant and up to date information about all aspects of cancer. The symposium took place on December 13th, 2013, and was co-organized with the Medical Faculty, University Clinical Center and Institute of Oncology, all in Ljubljana, Slovenia. The response to the symposium was positive both among the invited lecturers and ather participants, due to the positive feedback received it is hoped similar symposia will take place in the future on a regular basis.

The Foundation continues to provide regular financial support to "Radiology and Oncology", an international scientific journal that is edited, published and printed in Ljubljana, Slovenia. "Radiology and Oncology" publishes scientific research articles, reviews, case reports, short reports and letters to the editor about research and studies in experimental and clinical oncology, supportive therapy, experimental and clinical research in radiology, radiophyics, prevention and early diagnostics of different types of cancer. It is an open access journal available in pdf format and with an important Science Citation Index Impact factor. All the abstracts in "Radiology and Oncology" are translated in Slovenian and the journal can thus provide sufficient scientific information from various fields of high quality cancer research to interested lay public in Slovenia.

The Dr. J. Cholewa Foundation for Cancer Research and Education continues to provide financial and other means of support to all in Slovenia interested in the fight against cancer to organise scientific and other meetings of specific interest in different fields of cancer research and education.

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Bolezni imunskega sistema Redki: preobčutljivostna reakcija.
Bolezni dihal, prsnega koša in mediastinalnega prostora Zelo redki: laringospazem.
Bolezni kože in podkožja Občasni: fotosenzitivnost. Zelo redki: angioedem.

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ALIMTA je v kombinaciji s cisplatinom indicirana kot zdravljenje prvega izbora za bolnike z lokalno napredovalim ali metastatskim nedrobnoceličnim karcinomom pljuč, ki nima pretežno ploščatocelične histologije. ALIMTA je indicirana kot monoterapija za zdravljenje lokalno napredovalega ali metastatskega nedrobnoceličnega pljučnega karcinoma, ki nima pretežno ploščatocelične histologije pri bolnikih, pri katerih bolezen ni napredovala neposredno po kemoterapiji na osnovi platine. ALIMTA je indicirana kot monoterapija za zdravljenje drugega izbora bolnikov z lokalno napredovalim ali metastatskim nedrobnoceličnim pljučnim karcinomom, ki nima pretežno ploščatocelične histologije. **Odmerjanje in način uporabe:** *Odmerjanje:* ALIMTO smemo dajati le pod nadzorom zdravnika, usposobljenega za uporabo kemoterapije za zdravljenje raka. *ALIMTA v kombinaciji s cisplatinom:* Priporočeni odmerek ALIMTE je 500 mg/m^2 telesne površine (TP), dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21-dnevnega ciklusa. Priporočeni odmerek cisplatina je 75 mg/m^2 TP, infundiran v dveh urah približno 30 minut po zaključku infuzije pemetrekseda prvi dan vsakega 21 dnevnega ciklusa. Bolniki morajo prejeti zadostno antiemetično zdravljenje, pred in/ali po prejemanju cisplatina jih moramo tudi ustrezno hidrirati. *ALIMTA kot samostojno zdravilo:* Priporočeni odmerek ALIMTE je 500 mg/m^2 TP, dan kot intravenska infuzija v 10 minutah prvi dan vsakega 21 dnevnega ciklusa. *Režim premedikacije:* Da zmanjšamo incidenco in resnost kožnih reakcij, dajemo kortikosteroid dan pred dajanjem pemetrekseda, na dan dajanja pemetrekseda in naslednji dan. Kortikosteroid naj ustreza 4 mg deksametazona, danega peroralno dvakrat dnevno. Za zmanjšanje toksičnosti morajo bolniki dnevno jemati tudi peroralno folno kislino ali multivitaminski pripravek, ki jo vsebuje (350 do 1000 mikrogramov). V sedmih dneh pred prvim odmerkom pemetrekseda morajo vzeti vsaj pet odmerkov folne kisline, odmerjanje pa morajo nadaljevati ves čas zdravljenja in še 21 dni po zadnjem odmerku pemetrekseda. Bolniki morajo prejeti tudi intramuskularno injekcijo vitamina B12 (1000 mikrogramov) v tednu pred prvim odmerkom pemetrekseda in enkrat vsake tri cikluse zatem. Kasnejše injekcije vitamina B12 lahko dajemo isti dan kot pemetrekseda. **Kontraindikacije:** Preobčutljivost za zdravilno učinkovino ali katerokoli pomožno snov. Dojenje. Sočasno cepljenje proti rumeni mrzlici. **Posebna opozorila in previdnostni ukrepi:** Pemetreksed lahko zavre delovanje kostnega mozga, kar se kaže kot nevtropenija, trombocitopenija in anemija (ali pancitopenija). Mielosupresija običajno predstavlja toksičnost za omejitev odmerka. Pri bolnikih, ki pred zdravljenjem niso prejemali kortikosteroidov, so poročali o kožnih reakcijah. Uporabe pemetrekseda pri bolnikih z očistkom kreatinina < 45 ml/min ne priporočamo. Bolniki z blagim do zmernim popuščanjem delovanja ledvic naj se izogibajo jemanju nesteroidnih protivnetnih zdravil (NSAID), denimo, ibuprofena in acetilsalicilne kisline 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Vsi bolniki, ki jih lahko zdravimo s pemetreksedom, naj se izogibajo jemanju NSAID-ov z dolgimi razpolovnimi časi izločanja vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda. Poročali so o resnih ledvičnih primerih, vključno z akutno ledvično odpovedjo, s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki. Pri bolnikih s klinično pomembno tekočino tretjega prostora moramo razmisliti o drenaži izliva pred dajanjem pemetrekseda. Kot posledico toksičnosti pemetrekseda v kombinaciji s cisplatinom za prebavila so opažali hudo dehidracijo, zato moramo bolnike pred prejemanjem terapije in/ali po njej ustrezno hidrirati, prejeti morajo zadostno antiemetično zdravljenje. Občasno so v kliničnih študijah pemetrekseda, običajno ob sočasnem dajanju z drugo citotoksično učinkovino, poročali o resnih srčnožilnih dogodkih, vključno z miokardnim infarktom in možganskožilnimi dogodki. Odsvetujemo uporabo živih oslabljenih cepiv. Spolno zrelim moškim odsvetujemo zaploditev otroka v času zdravljenja in še 6 mesecev zatem. Priporočamo ukrepe proti zanositvi ali vzdržnost. Zaradi možnosti, da zdravljenje s pemetreksedom povzroči trajno neplodnost, naj se moški pred začetkom zdravljenja posvetujejo o shranjevanju semena. Ženske v rodni dobi morajo v času zdravljenja s pemetreksedom uporabljati učinkovito kontracepcijo. Poročali so o primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po zdravljenju s pemetreksedom. Poročali so o radiacijskem izpuščaju pri bolnikih, ki so se zdravili z radioterapijo pred tedni ali leti. **Medsebojno delovanje z drugimi zdravili in druge oblike interakcij:** Sočasno dajanje nefrotoksičnih zdravil (denimo, aminoglikozidov, diuretikov zanke, spojin platine, ciklosporina) lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Sočasno dajanje snovi, ki se tudi izločajo s tubulno sekrecijo (denimo, probenecid, penicilin), lahko potencialno povzroči zakasnjeni očistek pemetrekseda. Pri bolnikih z normalnim delovanjem ledvic lahko visoki odmerki nesteroidnih protivnetnih zdravil (NSAID-i, denimo, ibuprofen) in acetilsalicilna kislina v visokih odmerkih zmanjšajo eliminacijo pemetrekseda in tako lahko povečajo pojavnost neželenih učinkov pemetrekseda. Pri bolnikih z blagim do zmernim popuščanjem delovanja ledvic se moramo izogibati sočasnemu dajanju pemetrekseda z NSAID-i (denimo, ibuprofenom) ali acetilsalicilne kisline v visokih odmerkih 2 dni pred dajanjem pemetrekseda, na dan dajanja in še 2 dni po dajanju pemetrekseda. Sočasnemu dajanju NSAID-ov z daljšimi razpolovnimi časi s pemetreksedom se moramo izogibati vsaj 5 dni pred dajanjem pemetrekseda, na dan dajanja in še vsaj 2 dni po dajanju pemetrekseda.Velika različnost med posamezniki v koagulacijskem statusu v času bolezni ter možnost medsebojnega delovanja med peroralnimi antikoagulacijskimi učinkovinami ter kemoterapijo proti raku zahtevata povečano pogostnost spremljanja INR. **Kontraindicirana sočasna uporaba:** Cepivo proti rumeni mrzlici: tveganje za smrtno generaliziranо bolezen po cepljenju. **Odsvetovana sočasna uporaba:** Živa oslabljena cepiva (razen proti rumeni mrzlici): tveganje za sistemsko, potencialno smrtno bolezen. **Neželeni učinki** Klinične študije maligne plevralnega mezotelioma *Zelo pogosto:* znižani nevtrofilci/granulociti, znižani levkociti, znižan hemoglobin, znižani trombociti, nevropatija-senzorna, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, zaprtje, izpuščaj, alopecija, povišan kreatinin, znižan očistek kreatinina, utrujenost. *Pogosti:* dehidracija, motnje okusa, konjuktivitis, dispepsija. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, zdravljenje 2. izbora: *Zelo pogosti:* znižan nevtrofilci/granulociti, znižani levkocitit, znižan hemoglobin, diareja, bruhanje, stomatitis/faringitis, slabost, anoreksija, izpuščaj/luščenje, utrujenost. *Pogosti:* znižani trombociti, zaprtje, povišanje SGPT (ALT), povišanje SGOT (AST), srbenje, alopecija, povišana telesna temperatura. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA v kombinaciji s cisplatinom, zdravljenje 1. izbora: *Zelo pogosti:* znižan hemoglobin, znižani nevtrofilci/granulociti, znižani levkocitit, znižani trombociti, slabost, bruhanje, anoreksija, zaprtje, stomatitis/faringitis, diareja brez kolostomije, alopecija, izpuščaj/luščenje, povišan kreatinin, utrujenost. *Pogosti:* nevropatija-senzorična, motnje okusa, dispepsija/zgaga. Klinične študije nedrobnoceličnega pljučnega karcinoma - ALIMTA monoterapija, vzdrževalno in nadaljevalno zdravljenje: *Zelo pogosti:* znižan hemoglobin, slabost, anoreksija, utrujenost. *Pogosti:* znižani levkociti, znižani nevtrofilci, nevropatija-senzorična, bruhanje, mukozitis/stomatitis, povišanje ALT (SGPT), povišanje AST (SGOT), izpuščaj/luščenje, bolečina. Občasno so v kliničnih študijah pemetrekseda poročali o primerih resnih srčnožilnih in možganskožilnih dogodkov, vključno z miokardnim infarktom, angino pektoris, cerebrovaskularnim insultom in prehodnimi ishemičnimi atakami; primerih kolitisa ter o primerih intersticijske pljučnice z respiratorno insuficience, primerih edema, o ezofagitisu/radiacijskem ezofagitisu in o primerih sepse. Redkeje pa o primerih potencialno resnega hepatitisa in pancitopenije. Po uvedbi zdravila na trg so poročali o primerih akutne odpovedi ledvic s pemetreksedom samim ali v povezavi z drugimi kemoterapevtiki, primerih radiacijske pljučnice pri bolnikih, ki so jih zdravili z radiacijo pred, med ali po njihovem zdravljenju s pemetreksedom, primerih radiacijskega izpuščaja pri bolnikih, ki so se v preteklosti zdravili z radioterapijo, o primerih periferne ishemije, ki je včasih vodila v nekrozo okončin, redkih primerih bulloznih stanj, kot sta Stevens-Johnsonov sindrom in toksična epidermalna nekroliza, ki so bila v nekaterih primerih usodna in o redkih primerih hemolitične anemije. Poročali so o redkih primerih anafilaktičnega šoka. **Imetnik dovoljenja za promet** Eli Lilly Nederland B.V., Grootslag 1 5, NL 3991 RA, Houten, Nizozemska. Datum zadnje revizije besedila 12.11.2012. **Način izdaje zdravila:** H. SAMO ZA STROKOVNO JAVNOST.

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Sestava: En ml raztopine za infundiranje vsebuje 5 mg cetuksimaba in pomožne snovi. Cetuksimab je himerno monoklonsko IgG_1 protitelo. **Terapevtske indikacije:** Zdravilo Erbitux je indicirano za zdravljenje bolnikov z metastatskim kolorektalnim rakom z ekspresijo receptorjev EGFR in nemutiranim tipom RAS v kombinaciji s kemoterapijo na osnovi irinotekana, kot primarno zdravljenje v kombinaciji s FOLFOX in kot samostojno zdravilo pri bolnikih, pri katerih zdravljenje z oksaliplatinom in zdravljenje na osnovi irinotekana ni bilo uspešno in pri bolnikih, ki ne prenašajo irinotekana. Zdravilo Erbitux je indicirano za zdravljenje bolnikov z rakom skvamoznih celic glave in vratu v kombinaciji z radioterapijo za lokalno napredovalo bolezen in v kombinaciji s kemoterapijo na osnovi platine za ponavljajočo se in/ali metastatsko bolezen. **Odmerjanje in način uporabe:** Zdravilo Erbitux pri vseh indikacijah infundirajte enkrat na teden. Pred prvo infuzijo mora bolnik prejeti premedikacijo z antihistaminikom in kortikosteroidom najmanj 1 uro pred uporabo cetuksimaba. Začetni odmerek je 400 mg cetuksimaba na m^2 telesne površine. Vsi naslednji tedenski odmerki so vsak po 250 mg/m^2. **Kontraindikacije:** Zdravilo Erbitux je kontraindicirano pri bolnikih z znano hudo preobčutljivostno reakcijo (3. ali 4. stopnje) na cetuksimab. Kombinacija zdravila Erbitux s kemoterapijo, ki vsebuje oksaliplatin, je kontraindicirana pri bolnikih z metastatskim kolorektalnim rakom z mutiranim tipom RAS ali kadar status RAS ni znan. **Posebna opozorila in previdnostni ukrepi:** Pojav hude reakcije, povezane z infundiranjem, zahteva takojšnjo in stalno ukinitev terapije s cetuksimabom. Če pri bolniku nastopi blaga ali zmerna reakcija, povezana z infundiranjem, lahko zmanjšate hitrost infundiranja. Priporočljivo je, da ostane hitrost infundiranja na nižji vrednosti tudi pri vseh naslednjih infuzijah. Če se pri bolniku pojavi kožna reakcija, ki je ne more prenašati, ali huda kožna reakcija (≥ 3. stopnje po kriterijih CTCAE), morate prekiniti terapijo s cetuksimabom. Z zdravljenjem smete nadaljevati le, če se je reakcija izboljšala do 2. stopnje. Če ugotovite intersticijsko bolezen pljuč, morate zdravljenje s cetuksimabom prekiniti, in bolnika ustrezno zdraviti. Zaradi možnosti pojava znižanja nivoja elektrolitov v serumu se pred in periodično med zdravljenjem s cetuksimabom priporoča določanje koncentracije elektrolitov v serumu. Pri bolnikih, ki prejemajo cetuksimab v kombinaciji s kemoterapijo na osnovi platine, obstaja večje tveganje za pojav hude nevtropenije. Takšne bolnike je potrebno skrbno nadzorovati. Pri predpisovanju cetuksimaba je treba upoštevati kardiovaskularno stanje in indeks zmogljivosti bolnika in sočasno dajanje kardiotoksičnih učinkovin kot so fluoropirimidini. Če je diagnoza ulcerativnega keratitisa potrjena, je treba zdravljenje s cetuksimabom prekiniti ali ukiniti. Cetuksimab je treba uporabljati previdno pri bolnikih z anamnezo keratitisa, ulcerativnega keratitisa ali zelo suhih oči. Cetuksimaba ne uporabljajte za zdravljenje bolnikov s kolorektalnim rakom, če imajo tumorje z mutacijo RAS ali pri katerih je tumorski status RAS neznan. **Interakcije:** Pri kombinaciji s fluoropirimidini se je v primerjavi z uporabo fluoropirimidinov, kot monoterapije, povečala pogostnost srčne ishemije, vključno z miokardnim infarktom in kongestivno srčno odpovedjo ter pogostnost sindroma dlani in stopal. V kombinaciji s kemoterapijo na osnovi platine se lahko poveča pogostnost hude levkopenije ali hude nevtropenije. V kombinaciji s kapecitabinom in oksaliplatinom (XELOX) se lahko poveča pogostnost hude driske. **Neželeni učinki:** Zelo pogosti (≥ 1/10): hipomagneziemija, povečanje ravni jetrnih encimov, kožne reakcije, blage ali zmerne reakcije povezane z infundiranjem, mukozitis, v nekaterih primerih resen. Pogosti (≥ 1/100 do < 1/10): dehidracija, hipokalciemija, anoreksija, glavobol, konjunktivitis, driska, navzeja, bruhanje, hude reakcije povezane z infundiranjem, utrujenost. **Posebna navodila za shranjevanje:** Shranjujte v hladilniku (2 °C - 8 °C). **Pakiranje:** 1 viala z 20 ml ali 100 ml raztopine. **Način in režim izdaje:** Izdaja zdravila je le na recept-H. **Imetnik dovoljenja za promet:** Merck KGaA, 64271 Darmstadt, Nemčija.

Datum zadnje revizije besedila: december 2013.

Pred predpisovanjem zdravila natančno preberite celoten Povzetek glavnih značilnosti zdravila.

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Dent RAG, Cole P. In vitro maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95.

Chapman S, Nakielny R. *A guide to radiological procedures*. London: Bailliere Tindall; 1986.

Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.

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ODPIRANJE NOVIH MOŽNOSTI

Zdravljenje metastatskega karcinoma ledvičnih celic (mRCC), gastrointestinalnega stromalnega tumorja (GIST) in nevroendokrinih tumorjev trebušne slinavke (pNET)

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SUTENT 12,5 mg, 25 mg, 37,5 mg, 50 mg trde kapsule
Sestava in oblika zdravila: Ena kapsula vsebuje 12,5 mg, 25 mg, 37,5 mg ali 50 mg sunitiniba (v obliki sunitinibijevega malata). **Indikacije:** Zdravljenje neizrezljivega in/ali metastatskega malignega gastrointestinalnega stromalnega tumorja (GIST) pri odraslih, če zdravljenje z imatinibom zaradi odpornosti ali neprenašanja ni bilo uspešno. Zdravljenje napredovalega in/ali metastatskega karcinoma ledvičnih celic (MRCC) pri odraslih. Zdravljenje neizrezljivih ali metastatskih, dobro diferenciranih nevroendokrinih tumorjev trebušne slinavke (pNET), kadar gre za napredovanje bolezni pri odraslih (izkušnje z zdravilom Sutent kot zdravilom prve izbire so omejene). **Odmerjanje in način uporabe:** Terapijo mora uvesti zdravnik, ki ima izkušnje z uporabo zdravil za zdravljenje rakavih bolezni. *GIST in MRCC:* Priporočeni odmerek je 50 mg peroralno enkrat na dan, 4 tedne zapored; temu sledi 2-tedenski premor (Shema 4/2), tako da celotni ciklus traja 6 tednov. *pNET:* Priporočeni odmerek je 37,5 mg peroralno enkrat na dan, brez načrtovanega premora. *Prilagajanje odmerka*: Odmerek je mogoče prilagajati v povečanjih po 12,5 mg, upoštevaje individualno varnost in prenašanje. Pri GIST in MRCC dnevni odmerek ne sme preseči 75 mg in ne sme biti manjši od 25 mg; pri pNET je največji odmerek 50 mg na dan, z možnimi prekinitvami zdravljenja. Pri sočasni uporabi z močnimi zaviralci ali induktorji CYP3A4 je treba odmerek ustrezno prilagoditi. *Pediatrična populacija:* Uporaba sunitiniba ni priporočljiva. *Starejši bolniki (≥ 65 let):* Med starejšimi in mlajšimi bolniki niso opazili pomembnih razlik v varnosti in učinkovitosti. *Okvara jeter:* Pri bolnikih z jetrno okvaro razreda A in B po Child-Pughu prilagoditev odmerka ni potrebna; pri bolnikih z okvaro razreda C sunitinib ni bil preizkušen, zato njegova uporaba ni priporočljiva. *Okvara ledvic:* Prilagajanje začetnega odmerka ni potrebno, nadaljnje prilagajanje odmerka naj temelji na varnosti in prenašanju pri posameznem bolniku. *Način uporabe:* Zdravilo Sutent se uporablja peroralno, bolnik ga lahko vzame s hrano ali brez nje. Če pozabi vzeti odmerek, ne sme dobiti dodatnega, temveč naj vzame običajni predpisani odmerek naslednji dan. **Kontraindikacije:** Preobčutljivost na zdravilno učinkovino ali katero koli pomožno snov. **Posebna opozorila in previdnostni ukrepi:** *Bolezni kože in tkiv:* obarvanje kože, bolečine/draženje v ustih. Redko so poročali o primerih gangrenozne pioderme (običajno izgine po prekinitvi zdravljenja) ter o hudih kožnih reakcijah (multiforni eritem (EM), Stevens-Johnsonov sindrom (SJS) in toksična epidermalna nekroliza (TEN)). Če so prisotni znaki EM, SJS ali TEN, je treba zdravljenje prekiniti. *Krvavitve* v prebavilih, dihalih, sečilih, možganih; najpogosteje epistaksa; krvavitve tumorja, včasih s smrtnim izidom. Pri bolnikih, ki se sočasno zdravijo z antikoagulanti, se lahko redno spremlja celotna krvna slika (trombociti), koagulacijski faktorji (PT / INR) in opravi telesni pregled. *Bolezni prebavil:* poleg navzeje, diareje, stomatitisa, dispepsije, bruhanja in ezofagitisa tudi resni zapleti (včasih s smrtnim izidom), vključno z gastrointestinalno perforacijo. *Hipertenzija,* povezana z zdravljenjem; pri bolnikih s hudo hipertenzijo, ki je ni mogoče urediti z zdravili, je priporočljivo začasno prenehanje zdravljenja. *Hematološke bolezni:* zmanjšanje števila nevtrofilcev, trombocitov, anemija. *Bolezni srca in ožilja:* srčno-žilni dogodki, vključno s srčnim popuščanjem, kardiomiopatijo in motnjami v delovanju miokarda, v nekaterih primerih s smrtnim izidom. Sunitinib povečuje tveganje za pojav kardiomiopatije. *Podaljšanje intervala QT*: previdna uporaba pri bolnikih z znano anamnezo podaljšanja intervala QT, tistih, ki jemljejo antiaritmike, in tistih z relevantno, že obstoječo srčno boleznijo, bradikardijo ali elektrolitskimi motnjami. *Venski in arterijski trombembolični dogodki*; arterijski včasih s smrtnim izidom. *Dogodki na dihalih:* dispneja, plevralni izliv, pljučna embolija ali pljučni edem; redki primeri s smrtnim izidom. *Moteno delovanje ščitnice:* bolnike je treba med zdravljenjem rutinsko spremljati glede delovanja ščitnice vsake 3 mesece. *Pankreatitis*, tudi resni primeri s smrtnim izidom. *Hepatotoksičnost*, nekateri primeri s smrtnim izidom. *H*olecistitis, vključno z akalkuloznim in emfizemskim holecistitisom. *Delovanje ledvic:* primeri zmanjšanega delovanja ledvic, odpovedi ledvic in/ali akutne odpovedi ledvic, v nekaterih primerih s smrtnim izidom. *Fistula:* če nastane fistula, je treba zdravljenje s sunitinibom prekiniti. *Oteženo celjenje ran:* pri bolnikih, pri katerih naj bi bil opravljen večji kirurški poseg, je priporočljiva začasna prekinitev zdravljenja s sunitinibom. *Osteonekroza čeljustnic:* pri sočasnem ali zaporednem dajanju zdravila Sutent in intravenskih difosfonatov je potrebna previdnost; invazivni zobozdravstveni posegi predstavljajo dodatni dejavnik tveganja. *Preobčutljivost/angioedem*. *Motnje okušanja*. *Konvulzije:* obstajajo poročila, nekatera s smrtnim izidom, o preiskovancih s konvulzijami in radiološkimi znaki reverzibilnega posteriornega levkoencefalopatskega sindroma. *Sindrom lize tumorja*, v nekaterih primerih s smrtnim izidom. *Okužbe:* hude okužbe z ali brez nevtropenije (okužbe dihal, sečil, kože in sepsa), vključno z nekaterimi s smrtnim izidom. **Medsebojno delovanje z drugimi zdravili:** (Študije so izvedli le pri odraslih.) Zdravila, ki lahko zvišajo koncentracijo sunitiniba v plazmi (ketokonazol, ritonavir, itrakonazol, eritromicin, klaritromicin ali sok grenivke). Zdravila, ki lahko znižajo koncentracijo sunitiniba v plazmi (deksametazon, fenitoin, karbamazepin, rifampin, fenobarbital, *Hypericum perforatum* oz. šentjanževka). **Plodnost, nosečnost in dojenje:** Zdravila Sutent ne smemo uporabljati med nosečnostjo in tudi ne pri ženskah, ki ne uporabljajo ustrezne kontracepcije, razen če možna korist odtehta možno tveganje za plod. Ženske v rodni dobi naj med zdravljenjem z zdravilom Sutent ne zanosijo. Ženske, ki jemljejo zdravilo Sutent, ne smejo dojiti. Neklinični izsledki kažejo, da lahko zdravljenje s sunitinibom poslabša plodnost samcev in samic. **Vpliv na sposobnost vožnje in upravljanja s stroji:** Sutent lahko povzroči omotico. **Neželeni učinki:** Najbolj resni neželeni učinki (nekateri s smrtnim izidom) so odpoved ledvic, srčno popuščanje, pljučna embolija, gastrointestinalna perforacija in krvavitve (npr. v dihalih, prebavilih, tumorju, sečilih in možganih). Najpogostejši neželeni učinki (ki so se pojavili pri vsaj 20 % bolnikov v registracijskih preskušanjih) so: zmanjšan apetit, motnje okušanja, hipertenzija, utrujenost, prebavne motnje (npr. driska, slabost, stomatitis, dispepsija in bruhanje), sprememba barve kože/motnje pigmentacije in sindrom palmarno-plantarne eritrodisestezije. Med najbolj pogostimi neželenimi učinki so hematološke motnje (nevtropenija, trombocitopenija in anemija). Ostali zelo pogosti (≥ 1/10) neželeni učinki so: glavobol, epistaksa, bolečina v trebuhu/napihnjenost, zaprtje, glosodinija, izpuščaj, spremembe barve las, suha koža, bolečine v udih, vnetje sluznice, edemi. **Način in režim izdaje:** Predpisovanje in zdaja zdravila je le na recept, zdravilo pa se uporablja samo v bolnišnicah. Izjemoma se lahko uporablja pri nadaljevanju zdravljenja na domu ob odpustu iz bolnišnice in nadaljnjem zdravljenju. **Imetnik dovoljenja za promet:** Pfizer Limited, Ramsgate Road, Sandwich, Kent, CT13 9NJ, Velika Britanija. **Datum zadnje revizije besedila:** 21.3.2013
Pred predpisovanjem se seznanite s celotnim povzetkom glavnih značilnosti zdravila.

SAMO ZA STROKOVNO JAVNOST

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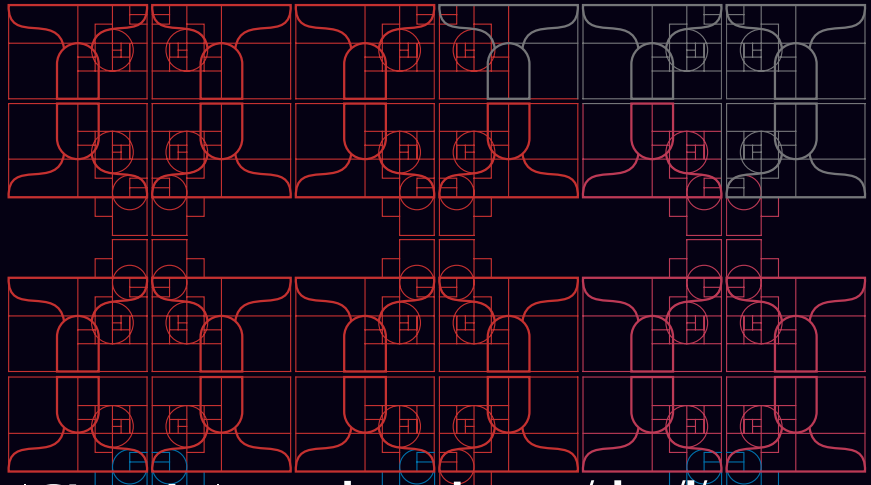

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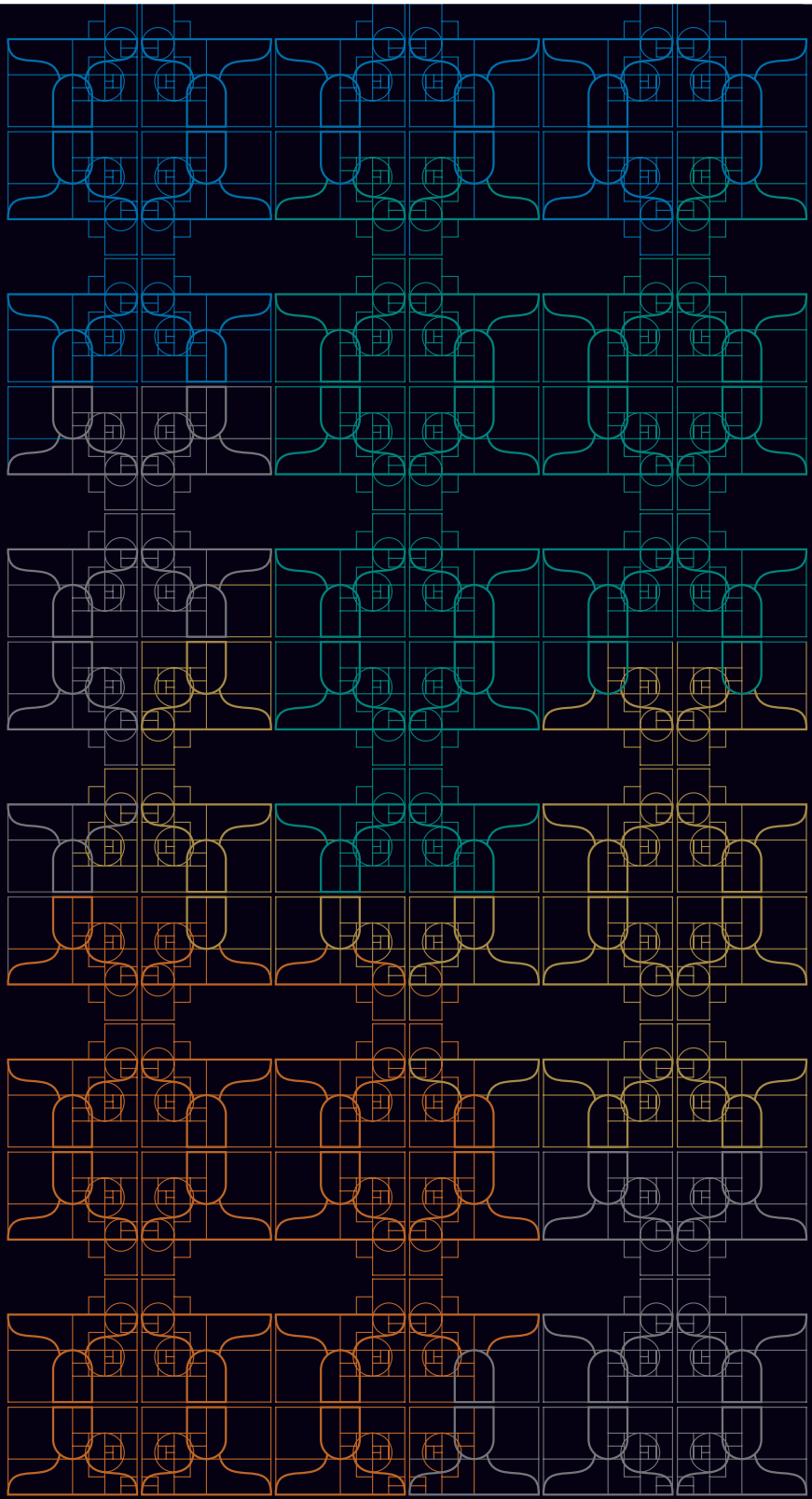

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