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Address for correspondence:
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ul. Gustawa Herlinga-Grudzińskiego 1
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room 309
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Editorial

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One hundred years ago, in 1923, the first oncological journal in Poland was published: *Biuletyn Polskiego Komitetu Zwalczania Raka* (*Bulletin of the Polish Anti-Cancer Committee*). In 1928, the title was changed and a single, but significant word was added: *Nowotwory* (*Cancers*). For decades, this title has accompanied generations of Polish oncologists. This year marks the centenary of our common journal, *Nowotwory*. It is one of the world's oldest continuously published scientific journals in oncology.

Within this century, the journal has changed a lot. Today it is a colour bi-monthly journal which:

- is available in two language versions – in Polish and in English,
- is available online in open access for researchers all over the world,
- has increased its bibliometric parameters in recent years,
- is proud to receive more and more submissions, indexed in increasingly significant repositories of medical publications,
- is ambitious and focused on constant development.

It is not possible to list here all the people who have contributed to *Nowotwory* during these 100 years, by creating the journal, supporting and helping it – with their excellent papers, diligent reviews, careful editing, valuable advice, good translation, meticulous proofreading, high-quality printing, development of its user-friendly website, assistance in administration, financial help, and in many other ways. However, I want to thank each of them warmly.

By working at Nowotwory, we upkeep traditions of the Polish oncology and at the same time we shape the future of the journal itself and our milieu as a whole.

Wojciech M. Wysocki
editor-in-chief

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Original article

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Bone metastasis in head and neck squamous cell carcinoma – 5-year experience of an Indian Cancer Institute

Diptajit Paul[1], Sheeba Bhardwaj[1], Sumit S. Chatterjee[2], Abhirup Chanda[1]

[1]*Pandit BD Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India*
[2]*College of Medicine & JNM Hospital, Kalyani, India*

Introduction. Bone metastasis (BM), a common and awful complication of advanced malignancy, is comparatively infrequent in head and neck squamous cell carcinoma (HNSCC). Having a discouraging survival of around 6-months only, BM decreases the quality of life in such patients. We reported 13 cases of BM in HNSCC patients in respect to clinical patterns, treatment modalities and outcome.

Material and methods. This is a retrospective study conducted in a tertiary cancer institute of India. Records of all HNSCC patients reviewed and patients having BM were identified.

Results. Total 13 cases of BM were found over a 5-year period; 5 patients having synchronous BM and the rest had developed metastasis later. Monostotic and polyostotic diseases were found in 8 and 5 patients, respectively, bone exclusive disease was seen in 6 patients only. Overall median survival was 6.7 months.

Conclusions. Palliation seems to be the only option once BM is diagnosed in HNSCC. All of our patients received local palliative radiation, and systemic chemotherapy to increase survival. As there is no standardized treatment for such occurrence, more case series and prospective studies are welcomed.

Key words: bone metastasis, head and neck cancer, monostotic, polyostotic, radiotherapy

Introduction

Bone metastasis (BM) is a dreadful complication of advanced malignancy; incidence of bone involvement by cancerous cells depends mainly on the primary site. Nearly 90% cases of BM are seen in primary breast, prostate and lung cancer [1]. Other relatively less common primary sites include the thyroid, melanoma, kidney and gastrointestinal malignancies [1]. Overall, distant metastasis in primary head and neck carcinoma (HNC) is infrequent [2–4]. Involvement of the bone as a metastatic site, although second in order only after lungs, is relatively rare [3–5]. Few studies state a median overall survival of around 6 months in patients of BM with primary HNC [5, 6]. Advanced local disease burden, multiple metastatic sites and poor performance status (PS) of the patient limit the treatment options in such patients. In this article we report the clinical course of 13 cases of head and neck malignancy with bone metastasis.

The purpose of this study is to report a comparatively rare occurrence, i.e., bone metastasis in squamous cell head and neck carcinoma. Our main objectives were:

- to assess the patient's characteristics and etio-pathological factors,
- to describe the patterns of bone metastasis in HNC,
- to evaluate the treatment outcomes in them.

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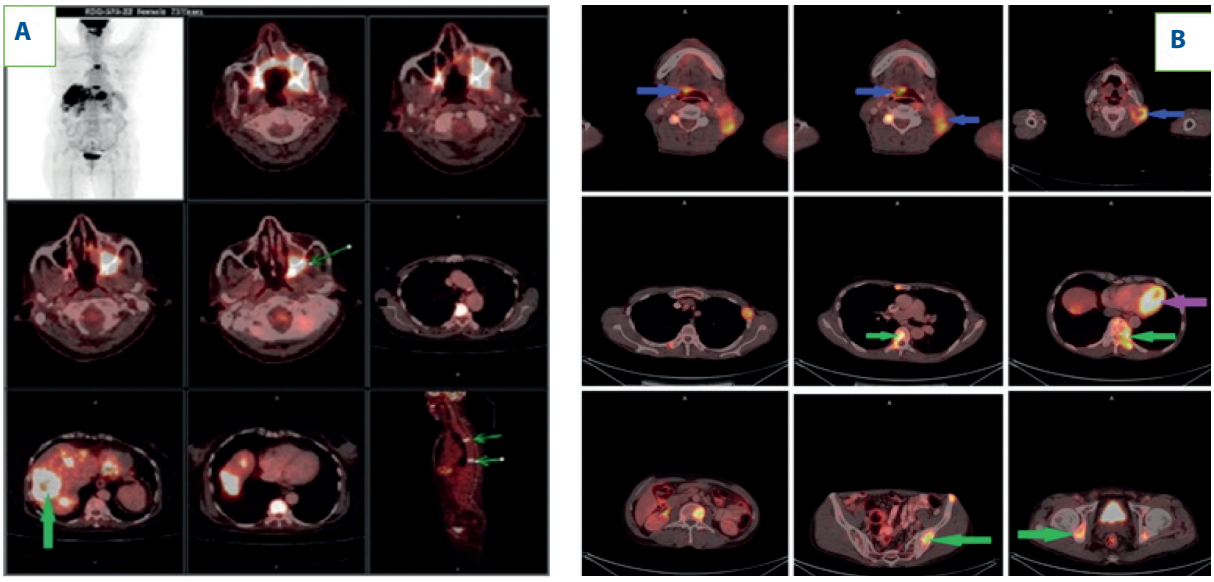

Figure 1. FDG-PET scan showing: (**A**) vertebral metastasis (D5 and D10, green arrow) in a patient with left maxillary sinus squamous cell carcinoma; (**B**) metastatic lesions in multiple pelvic bones, vertebra (green arrow) in a patient of base of tongue squamous cell carcinoma (blue arrow). The purple arrow indicates associated liver metastasis in the same patient

Material and methods

This is a retrospective analysis done in a tertiary cancer institute of India. Permission from the Institutional Review board was taken and informed consent was provided from the live patients as far as possible. Records of all patients of HNC registered in the institute over a period of 5 year were reviewed manually and patients having bone metastasis were identified. Only those patients were included in this series, in whom bone metastasis was confirmed either by histopathological proof (cytology or biopsy) or by imaging (bone scintigraphy or positron emission tomography [PET] scan) (fig. 1). Details of their records were evaluated using analytical software and compared with published literature.

Results

A total of 13 cases of squamous cell carcinoma of the head and neck region associated with bone metastasis are reported in this case series. Details of the patient's characteristics are illustrated in table I. The mean age of presentation was 64.3 years; the range was from 38 to 76 years. Male preponderance was seen in our case series, with male to female ratio being 3.3:1. Most of the patients were from a rural background. The mean duration of symptoms was 5.5 months.

Table II depicts the involved bones in all the patients along with different treatment received by them for primary as well metastatic lesions and final outcome. Bone metastasis was present in 5 out of 13 patients at initial presentation i.e., synchronous metastasis; while, the remaining 8 patients developed bone metastasis during the course of treatment. Overall, axial skeleton involvement by tumour spread was observed. The most commonly involved bone was vertebrae. Single bone involvement, i.e., monostotic metastasis was seen in only 5 patients (38.5%). Radical chemo-radiation to primary tumour was given to 3 patients, all of them were non-metastatic initially and had a good general condition. For metastatic bone lesions, all patients received palliative radiation therapy (RT); mostly to relieve pain and decrease the risk of complication (impending fracture, cord prolapse). Most common RT schedules was 20 Gy/5 fractions over 5 consecutive days. Salvage chemotherapy, to counter the overall local as well metastatic disease burden, in the form of either

Table I. Demographic profile of patients having bone metastasis with head and neck squamous cell carcinoma

Characteristics	Parameters	Number of patients
total patients		13
gender	male	10
	female	3
age	range	38–76 years
	mean	64.3 years
	median	68 years
background	rural	9
	urban	4
addiction	smoker	10
	alcoholic	7
ECOG performance status	0–1	1
	2	4
	3	8
presenting symptoms	difficulty in swallowing	6
	throat pain	5
	neck mass	4
	others	3

ECOG – Eastern Cooperative Oncology Group

Table II. Treatment profile and outcome in patients of bone metastasis with primary head and neck carcinoma

Involved metastatic bone(s)	Duration from primary to bone metastasis (in months)	Primary treatment received		Treatment for bone metastasis		Outcome
		RT	chemotherapy	RT	chemotherapy	
lumbar vertebrae	12 months	70 Gy/35 fr	NACT – TPF CCT – cisplatin	20 Gy/5 fr	salvage – oral Mtx	death
multiple (bilateral pelvic bones, femurs, scapula and sternum)	3 months	20 Gy/5 fr	salvage – TPF	20 Gy /5 fr	salvage – TPF	death
multiple (dorso-lumbar vertebrae, right acetabulum and femur, few bilateral ribs)	at diagnosis	20 Gy/5 fr	salvage – oral gefitinib	20 Gy/5 fr	salvage – oral sefitinib	death
multiple (cervico-dorsal vertebrae, right mandible and occipital condyle)	at diagnosis	20 Gy/5 fr	nil	20 Gy/5 fr	nil	death
right femur	at diagnosis	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – oral Mtx	8 Gy single session	salvage – oral Mtx	PR (residual disease)
D5 and D10 vertebrae and bilateral 6th ribs	at diagnosis	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – TPF f/b – oral Mtx	20 Gy/5 fr	salvage – TPF f/b – oral Mtx	PR (residual disease)
multiple pelvic bones, both femur, multiple cervical, dorsal and lumbar vertebrae, left scapula and sternum	at diagnosis	20 Gy/5 fr	salvage – oral Mtx	20 Gy/5 fr	salvage – oral Mtx	death
multiple vertebrae, ribs	3 months	20 Gy/5 fr f/b supplementary 20 Gy/5 fr	salvage – oral Mtx	8 Gy single session	salvage – oral Mtx	death
left femur	8 months	66 Gy/33 fr	CCT – cisplatin salvage – TPF f/b oral gefitinib	20 Gy/5 fr	salvage – TPF f/b oral gefitinib	PR (residual disease)
single vertebrae	5 months	66 Gy/33 fr	NACT-TPF – CCT – cisplatin	20 Gy/5 fr	salvage – oral cyclophosphamide	PR (residual disease)
multiple pelvic bones, sacrum	4 months	20 Gy/5 fr	salvage – oral Mtx	20 Gy/5 fr	salvage – oral Mtx	death
scapula	5 months	44.4 Gy/12 fr (quad shot regimen)	salvage – oral gefitinib	8 Gy single session	salvage – oral gefitinib	death
multiple vertebrae, pelvic bones	at diagnosis	20 Gy/5 fr	salvage – cisplatin	8 Gy single session	salvage – cisplatin	death

CCT – concurrent chemotherapy; f/b – followed by; fr – fractions; Gy – Gray; Mtx – methotrexate; NACT – neoadjuvant chemotherapy; PR – partial response; RT – radiotherapy; TPF – taxane, platinum, 5-fluorouracil

an oral metronomic or intravenous combination regimen, was advised to all the patients according to their general condition and disease status.

A summary of all the cases was illustrated in tabulated format (tab. III). The involvement of the oropharyngeal structure (tonsil, base of tongue, soft palate and lateral pharyngeal wall) was seen in 7 out of 13 patients (fig. 2). Eight patients were in locally advanced stage initially, the rest had metastatic disease. The median survival time was 6.7 months. Four patients were alive at the time of reporting this series; however, they have residual disease and were on oral metronomic agents.

Discussion

The development of bone metastasis in any malignancy is associated with poor survival outcome and poses a therapeutic challenge for the treating oncologist. BM usually leads to a dismal prognosis and affect patients' quality of life [7, 8]. Once BM is diagnosed, palliative treatment of symptoms becomes the desired treatment. On average, 20% of cases of head and neck squamous cell carcinoma metastasize to distant organ throughout the time of the disease's course [2–4, 9]. Bone is the second-most frequent organ involved by metastasis, the first being the lungs, and it accounts for nearly 15–39% of distant metastases

Table III. Summary of important parameters in bone metastasis patients with primary head and neck squamous cell carcinoma

Primary site – subsite	Histopathological grade (differentiation)	TNM stage at presentation	Type of bone metastasis	Bone-exclusive metastasis	Survival after bone metastasis diagnosed
oropharynx – tonsil	MDSCC	T3N2M0 (IVA)	monostotic	no (lung, liver)	5 months
oropharynx – base of tongue	PDSCC	T3N3M0 (IVB)	polyostotic	yes	3 months
oropharynx – tonsil and soft palate	PDSCC	T4N2M1 (IVC)	polyostotic	yes	5 months
oropharynx – tonsil	MDSCC	T4N1M1 (IVC)	polyostotic	yes	2 months
hypopharynx – post cricoid region	MDSCC	T3N2M1 (IVC)	monostotic	no (abdominal lymph nodes, ascending colon)	>24 months
para nasal sinus – left maxillary sinus	MDSCC	T4N0M1 (IVC)	polyostotic	no (liver)	6 months
oropharynx – base of tongue	PDSCC	T4N3M0 (IVB)	polyostotic	no (lung)	3 months
larynx – supraglottis	PDSCC	T3N2M0 (IVA)	polyostotic	yes	4 months
oral cavity – anterior tongue	MDSCC	T3N1M0 (III)	monostotic	yes	9 months
hypopharynx – posterior pharyngeal wall	PDSCC	T2N2M0 (IVA)	monostotic	no (liver)	7 months
oropharynx – tonsil and base of tongue	MDSCC	T4N3M0 (IVB)	polyostotic	no (lung, liver)	5 months
oropharynx – lateral pharyngeal wall	PDSCC	T3N2M0 (IVA)	monostotic	no (lung)	8 months
hypopharynx – right pyriform sinus	PDSCC	T3N2M1 (IVC)	polyostotic	yes	4 months

MDSCC – moderately differentiated squamous cell carcinoma; PDSCC – poorly differentiated squamous cell carcinoma

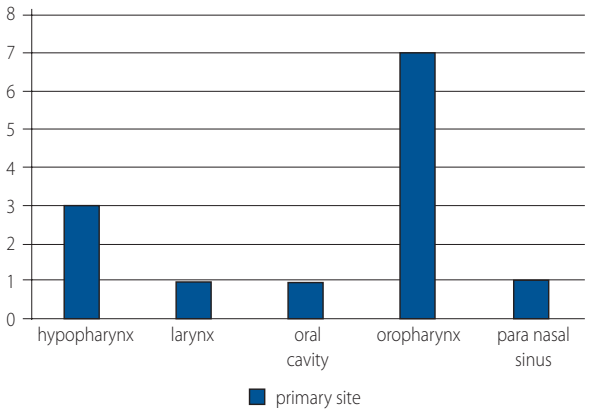

Figure 2. Distribution of all patients according to primary site

cases [3–5, 10, 11]. Nowadays, in Western countries, routine use of fluoro-deoxy-glucose positron emission tomography (FDG-PET) scan and bone scintigraphy as part of metastatic work up in HNSCC has increased the detection rate of clinically relevant BM [11, 12]. Primary HNC having bony involvement has a relatively shorter survival compared to that from primary breast and prostate malignancy [5–7].

The frequency of osseous dissemination in HNC depends greatly upon the primary tumor size (T) and regional nodal (N) involvement. T and N staging also affects the prognosis of such patients [13]. It is reported that the primary site (hypopharynx *vs.* others) and size (less in T1 tumors), tumor grade (well *vs.* moderately *vs.* poorly differentiated), nodal status (more in N3 node and highly prevalent in disease with extra-capsular extension), prognostic stage (higher incidence in stage IV disease than others) are contributory risk factors for the development of distant bone metastasis [4, 14]. As far as the primary site of the tumor is concerned, the prevalence of distant metastasis, bone as well as other organs, is highest in the tumor of the hypopharynx, followed by oropharynx (base of tongue) [4, 15]. Bhandari et al. [16] reported that among different primary sites of head and neck tumors, the hypopharynx is more likely to develop distant metastases with a probability of 20.5–60% and thus has a poorer prognosis. Outcomes in metastatic HNSCC also have a significant connection with old age, poorly differentiated tumors, higher nodal stage, race (more in black Afro-Americans) and multiple metastatic sites [14, 17].

Our study revealed that most of the cases have high tumors (T3 and T4 cases mostly, only 1 patient had T2 disease) and nodal stage (≥N2 in 10 patients) at the time of presentation. Except a single case, all the patients' neck nodes revealed tumor infiltration and were stage IV disease. This correlates well with other studies [4, 13, 14]. In our study, most patients had primary lesion in the oropharyngeal region, which is not matched with the global documentation of higher metastatic cases in hypopharyngeal cancer [4, 15]. This is most probably due to the relatively higher incidence of carcinoma oropharynx in our institution. In our study, distribution of MDSCC and PDSCC are nearly equal, 6 and 7 cases respectively. Most patients presented in advanced age with the median age being 67 years.

In general, the axial skeleton is the most prevalent site of bone metastasis involving the spine, pelvis and ribs frequently; the lumbar spine is the single most frequent site as documented in literature [1, 18]. Involvement of bone from primary HNSCC is thought to be the result of a systematic spread of tumour cells and the site distribution matches the red marrow distribution in the skeletal system [13, 19, 20]. The patient may present with pain originating from the bone as well as associated skeletal-related events (SREs) such as fractures, cord compression, and, obviously, hypercalcemia. Grisanti et al. [21] reported skeletal related events (SRE) were in 9% of nasopharyngeal cancer cases (NPC) and in 27% of non-NPC patients. As a result, subsequent median survival decreased from 25 months in nasopharyngeal cancer patients to 6 months in non-NPC patients, respectively [21]. They also opined that bone-directed treatments (bisphosphonates and denosumab) and radiotherapy are good options in improving survival for these patients.

Radiological changes of BM from HNSCC are variable. Skeletal metastasis invariably incites the process of bone resorption and bone formation, and depending upon the dominant process, radiologic appearance can be lytic, sclerotic or mixed type. Al-Bulushi et al. [12] and Basu et al. [19] recorded that more than 80% of cases of BM showed an osteolytic lesion; while Nakanishi et al. [10] and Kim et al. [20] documented osteoblastic and inter-trabecular types in nearly 60% of cases of their analyses. Prognosis in metastatic disease is determined by multiple factors. In a large case series over an 11-year period, single site BM, a good PS (ECOG 0-1) and a systemic chemotherapy receiver were found to be independent factors for comparatively prolonged survival; yet the median survival remained 11 months in that analysis [22]. It is obvious that a patient with favourable general condition (good PS) is likely to have a lower chance of lung infection and a greater stamina to tolerate more aggressive systemic therapy. A comparatively fair PS also suggests that the BM may not be that extensively distributed so as to hamper daily activities [23–25].

Recent published articles have mentioned that neither metastasis of monostotic origin nor bone-exclusive metastasis are rare in HNC; with the former having a frequency of 24–50% and the latter of 24–46% [12, 19, 20]. Suzuki et al. [5] found favourable prognosis in patients with bone-exclusive and monostotic metastases compared with patients with multi-organ or polyostotic metastases, with an average survival time of 18.2 months and 5.7 months, respectively.

Bony dissemination as a result of distant metastasis in HNC are crucial in clinical practice because they serve as a major cause of misery in such patients, such as severe refractory pain, pathological fractures, spinal cord compression and hypercalcemia. Palliation with the help of both radiation and salvage chemotherapy is the routine therapeutic strategy for patients with HNSCC who have distant organ involvement; platinum-based systemic chemotherapy has been reported to improve outcomes to a certain degree [6, 26–29]. Radiotherapy to the involved bone, either single session or multi-fractionation regimen, is usually employed in all BM patients, along with systemic chemotherapy or bone directed treatment (zoledronic acid) [21, 26]. Once BM develops in these patients, median survival time becomes significantly less [2–4].

The management strategy of such patients having bone metastases, requires a multidisciplinary team from different fields including but not limited to medical and radiation oncologists, orthopedicians, neuro-vascular surgeons, interventional radiologists and pain specialist to dispense the best therapeutic approach, appropriate measures to prevent further damage, and the treatment of SREs. A few classes of drugs like bisphosphonates and denosumab, have bone-directed mechanism of action and revealed to decrease the risk of SREs remarkably in patients having bone metastases from common solid primaries like prostate, breast and lung cancer, and multiple myeloma [30]. The addition of zoledronic acid to chemotherapy in patients with nasopharyngeal carcinoma having distant osseous involvement was correlated with a lower rate of symptomatic skeletal events and better survival in comparison to chemotherapy alone [31]. Patel et al. [32] showed that surgery and radiation therapy, when used in patients with distant metastatic disease, can improve survival. Operative intervention, in terms of decompression surgery in spinal cord compression cases or internal fixation in pathological fractures, can be performed in BM patients when non-surgical therapies have failed. Compared with lung metastases and locoregional recurrence, systemic chemotherapy is more effective in bone involvement from HNSCC. This can be justified by richer blood supply of bone marrow compared with the lung and local area. Sakisuka et al. [22] reported the statistically significant prognostic influence of systemic chemotherapy in HNC patients with BM; unfortunately, this influence is limited on survival. This was also pointed out by Suzuki et al. [5] that neither chemotherapy nor radiotherapy could significantly prolong the overall survival of HNC patients with BM. Therefore, the adverse effects of adding systemic chemotherapy in patients of BM from HNSCC should be carefully looked at and the decision should be taken on an individual basis.

In our study, most patients presented in advanced stage and received palliative radiotherapy to the primary site and bone metastasis. Incidence of synchronous bone metastasis and bone-exclusive metastasis were 38.5% and 46%, respectively in our analysis. Both of these values are similar to analysis done by another Asian country [22]. Around 40% of cases were monostotic metastases and the rest showed polyostotic metastasis. Median survival for the patients with solitary bone metastasis was 11 months, while in patients with multiple bone metastases it was only 4 months. The overall median survival value closely matched with the other published articles [5]. Nine patients expired due to the progression of the disease; surprisingly one patient, with maintenance oral metronomic chemotherapy, is still regularly followed up with more than 2 year survival.

Conclusions

Bone metastasis in primary HNSCC is an occurs infrequently. Palliation is the only option after BM occurs in these patients. Survival is usually discouraging. However, high palliative radiotherapy to both the local and metastatic site as well as systemic chemotherapy can improve their quality of life as well as survival. More case series and prospective trials in this topic will highlight the standard treatment guidelines for these patients.

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Diptajit Paul
Pandit BD Sharma Post Graduate Institute of Medical Sciences
Rohtak, Haryana
124001 Rohtak, India
e-mail: diptajitpaul.91@gmail.com

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The prototype of EPID-based *in vivo* dose verification for VMAT treatments in patients with prostate cancer

Krzysztof Ślosarek[1], Adam Gądek[1], Marta Reudelsdorf-Ullmann[1], Łukasz Sroka[1], Janusz Winiecki[2, 3]

[1]*Radiotherapy Planning Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*
[2]*Medical Physics Department, Oncology Center in Bydgoszcz, Bydgoszcz, Poland*
[3]*Department of Oncology and Brachytherapy, Collegium Medicum in Bydgoszcz, Nicholas Copernicus University in Toruń, Bydgoszcz, Poland*

Introduction. The volumetric modulated arc therapy technique (VMAT) is now widely used in radiotherapy. Verification of the dose delivered to the patient is performed prior to the treatment (pre-treatment mode). However, during the therapeutic session, only the patient's position is verified and monitored. AnEPID's (electronic portal imaging device) matrices can measure the intensity of radiation passing through the patient, but the calculation of the dose distribution from this measurement is limited due to the lack of reliable algorithms and software. Therefore, it seems promising to develop a method to estimate the dose in the patient's body based on the measured calibration units (CU) values.

Material and methods. The material consists of 53 patients treated for prostate cancer with the VMAT technique. The CU signal is measured during the treatment and its value is then transformed according to the self-developed algorithm into a dose. This delivered dose is then compared with the planned dose in the target.

Results. The performed measurements of the CU and preliminary calculations indicate that it is possible to estimate the dose that the patient receives during the therapeutic session. The mean difference between the prescribed and measured dose values is less than 1%, however, there are differences of 17%.

Conclusions. The proposed method can be used in clinical practice for actual dose estimation. The uncertainty of the proposed method was estimated at 5%. In the event of differences above 10%, the treatment realization should be verified by additional tests including patient positioning and technical tests of accelerator, such as verification of kV and MV isocenter compatibility.

Key words: EPID, verification, CU values, *in vivo*

Introduction

An important milestone in improving the quality of radiotherapy worldwide was the development of the multi-leaf collimator (MLC). The original intention of the MLC was to define the shape of the therapeutic beam only, but it significantly increased the protection of critical organs. The full use of all the possibilities of MLC was possible thanks to the concept of inverse planning proposed by Thomas Bortfeld (at the turn of the 20th and the 21st centuries), which led to the implementation of dynamic radiotherapy techniques (IMRT, VMAT).

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Dynamic techniques were introduced primarily to increase the protection of critical organs, but their capabilities also allowed for the generation of intentional inhomogeneities in the irradiated area (in particular in the target) [1–9].

Contemporary techniques used in radiotherapy are characterized by a very high conformality. This means that the dose is delivered very precisely, using steep dose gradients between the target area and the surrounding tissues. Any abnormality (e.g., incorrect patient positioning or changing anatomical conditions as a result of bladder filling) may result in incorrect irradiation. Therefore, it is essential to use the IGRT technique [10–12]. Accurate positioning of the patient and precise reconstruction of the therapeutic position in each fraction is a necessary condition for treatment. The verification of the positioning is mainly carried out on the basis of kV imaging, before or after irradiation (sometimes also during a therapeutic session). Imaging methods allow for checking the geometry of the irradiation. The methods make it possible to increase the local tumor control probability (TCP). Each geographical error will reduce the TCP and increase the probability of complications [13].

Unfortunately, the success of radiotherapy depends not only on the precise positioning of the patient. Another issue is the compliance of the delivered dose with the planned one [14–18]. Before the era of dynamic techniques, *in vivo* dosimetry was widely used in radiotherapy for dose monitoring [19–21]. Dynamic techniques have made this method of dose verification very difficult to use as the dose at the measuring point changes dynamically. The typical dosimeters used, i.e., thermoluminescent ones, unfortunately cannot cope with measurements in which the beam intensity changes and the dose differs at the neighboring points. The known methods of *in vivo* measurement were burdened with very high measurement uncertainty. Modulation of dose distribution made it necessary to verify the dose for the entire irradiated plane, not only in the beam central axis (CAX). Due to technological reasons, the verification of dynamic techniques is currently carried out without the participation of the patient and is limited to checking whether the therapeutic device implements the treatment plan correctly [22–29].

During more than twenty years of the use of dynamic techniques in radiotherapy, many recommendations for quality control have been developed [30–34]. However, they only consider pre-treatment verification without the patient. It is assumed that if the plan is correctly implemented on the measuring phantom, it will be correctly performed with the patient. Increasingly, an independent system for calculating the dose distribution (number of monitor units) is used instead of the measurement. In many countries, checking the dose distribution before the first fraction is a formal and legal requirement [35, 36].

Recently, there has been a rapid development of systems for detection of the fluence of megavoltage radiation. For example, EPID (electronic portal imaging devices), which have been used in radiotherapy for many years, are used for this purpose [37]. They appeared as additional equipment for accelerators before the appearance of the devices dedicated to imaging and IGRT implementation, known to us today. Over time, they have become an integral part of treatment units. EPID and CBCT systems, as imaging tools, are used to verify the patient's position during a therapeutic session and to assess the repeatability of treatment in subsequent fractions [38-44]. Many years ago, attempts were made to correlate the signal read by EPID expressed in so-called calibration units (CU) with the dose during the therapy session [45]. Currently, the literature on the use of this device (EPID) for dose estimation and distribution is very extensive [46–52]. Numerous attempts have been made to calculate the dose in a patient (in space) from the measurement of the signal in a plane, in matrix of semiconductor detectors [46, 53, 54]. The proposed algorithms are usually very complicated and have unit-related limitations (e.g. they relate to a specific therapeutic accelerator) that make their application difficult. They are used only in radiotherapeutic centers that have great scientific and experimental potential. Therefore, the question arises whether they have matrix semiconductor detectors integrated with the accelerator (EPID), it is possible to estimate the dose at the point, placed in the patient.

Aim

The aim of this study was to create a method of estimating the dose at the target area (tumor) received by a patient during a therapeutic session in the VMAT technique. The parameter, which is measured directly, is the signal recorded by the EPID matrix directly behind the patient (acquired image). This method of dose measurement is often called transit dosimetry. On its basis, withreference to the data obtained in the phantom experiment, the average dose received by the patient in the tumor area will be estimated. A low level of complexity of the method is assumed in order to enable its popularization in other radiotherapeutic centers. The parameter describing the quality of the procedure will be the deviation of the estimated dose delivered to the patient (from EPID), compared to the expected value read from the treatment planning system (TPS). As the measurement is performed in real time, it can be considered an *in vivo* method.

Material and methods

The experiment was carried out on Edge, a C-Arm biomedical accelerator (varian medical system, Palo Alto, US) equipped with an aS 1200 EPID detector. We limited the study to 6 MV FFF therapeutic beams only. The control group consisted of patients with diagnosed prostate cancer who underwent radiotherapy at the Radiation Therapy Department of Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, in Poland. Radiotherapy planning was performed using TPS Eclipse v.16.1 (varian medical systems, Palo Alto, USA).

The measurement system was calibrated using the TMR method. The purpose of the procedure was to correlate the CU value read by the EPID with the actual absorbed dose deposited in the patient's body at the isocentric point. The influence the distance of the matrix from the phantom bottom-surface (DEP) and the dose deposited in the isocenter (D_{iso}) have on the value of the signal recorded by the EPID was checked.

During the experiment the EPID (detector) was positioned at a constant distance of 160 cm from the source (source imager distance – SID). It should be noted here that the dose estimation at the isocenter is performed only for the VMAT technique with full gantry rotation around the patient (phantom). Due to the rotation of the gantry, the distance DEP fluctuates as a function of the arm position and depends on the dimensions of the patient (phantom).

First, the linearity of the EPID response (CU reading) was checked against the dose deposited in the isocenter. The check was done using a phantom made of PMMA plates with dimensions of 30 x 30 cm^2 and a thickness of 1 cm, which formed a cuboid with the dimensions 30 x 20 x 20 cm^3. The dose prescription point was always located in the center of the phantom, at the isocenter, at a depth of 10 cm (SSD = 90 cm). Measurements were performed for a 6 MV-FFF beam with dimensions of 10 x 10 cm^2, with a 0° gantry position. The CU readings were performed at the SID = 160 cm position, i.e., at a distance of 50 cm below the lower surface of the phantom (the influence of the therapeutic table was considered negligible). The dose value at the isocenter varied from 0.5 Gy to 5.0 Gy.

In the next stage, it was checked what influence DEP distance has on the value of the signal recorded by EPID. The dose at the bottom surface of the phantom D_{out} can be calculated as a function of D_{iso} and the phantom thickness AP using the TMR function. We treat the point on the lower surface of the phantom where D_{out} is defined as the source of the radiation recorded by the EPID.

It is obvious that for different phantom thicknesses there is a relationship: if $AP_1 > AP_2$ then $DEP_2 > DEP_1$. With a fixed D_{out} value, CU_1 will be greater than CU_2. This is in line with the principle that an increase in the distance between the radiation source and the detector reduces the intensity of the recorded radiation. Figure 1 shows the assumptions of this measurement.

It should be noted that the accelerator arm rotates during the procedure, which means that the DEP in the case of a real patient, as well as the depth of the isocentric point are not constant in time (fig. 2).

The dependence of CU on the DEP distance was investigated using the possibility of adjusting the thickness of the plate phantom (AP). The AP thickness was varied in the range of 6–30 cm, which gives the DEP a variation range of 45–57 cm. Using the TMR function, the dose D_{iso} was prescribed in such a way as to maintain a constant D_{out} value for each set of AP and DEP distances.

It should be noted that in the phantom experiment the depth of the dose prescription d (d = 0.5 AP) is similar to the equivalent path length d_{EPL} [55], as the density of the phantom material is similar to the density of water. The physical depth d (or d_{avg}) is needed to determine DEP and d_{EPL} to calculate D_{out} for a known D_{iso}. In the case of the PMMA phantom, these two values are equal. However, in the case of a real

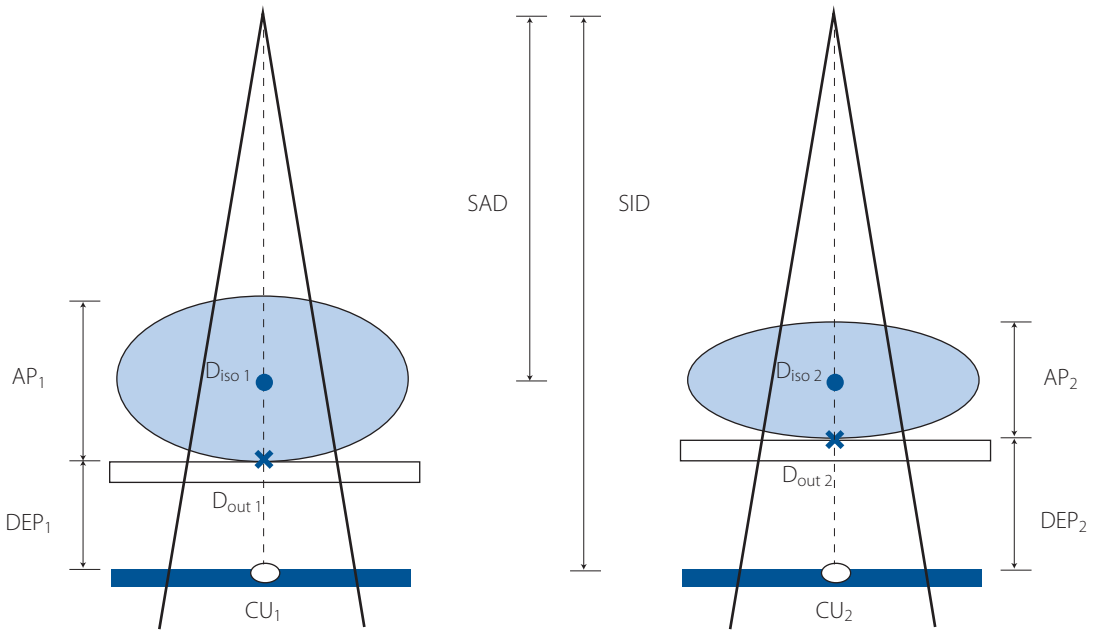

Figure 1. The method of investigating the relationship between the CU value and the D_{out} for different patient thicknesses (phantom dimensions). Explanation of symbols in the text

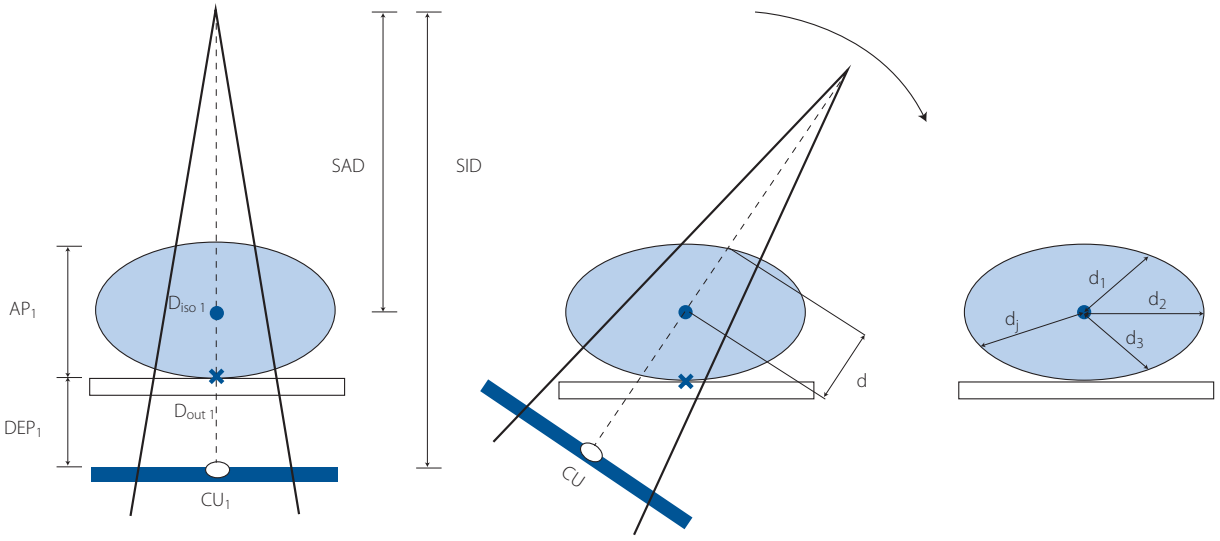

Figure 2. The method of D_{iso} determination: SAD – source axis distance, defines the position of the isocenter, the point at which the dose was prescribed; d_1, d_2, d_3, and d_4 – depths of isocenter for selected angles (gantry positions). The dose at the isocenter (D_{iso}) is dependent on the average depth (d_{avg})

patient, the radiological depth differs from the geometric depth due to the non-uniform density. In calculations for actual patients at full gantry rotation, the mean geometric depth d_{avg} and the mean $d_{EPL,\,avg}$ should be used. The values of d_{avg}, $d_{EPL,avg}$ and D_{iso} can be read from the treatment plan. D_{out} can be derived knowing the DEP and the CU value read from the EPID matrix. It was assumed that this correlation can be derived as follows:

$$D_{out} \sim CU \tag{1}$$

$$D_{out} \sim \frac{1}{DEP^2} \tag{2}$$

$$D_{out} \sim \frac{W1 \times CU}{W2 \times DEP^2 + W3} - W4 \tag{3}$$

Formula (3) is an empirical formula resulting from the reflections of researchers. So we get:

$$CU = \frac{(D_{out} + W4) \times (W2 \times DEP^2 + W3)}{W1} \tag{4}$$

Formula (4) will be used to calculate the coefficients W1, W2, W3, and W4 in phantom measurements. The values will then be used to calculate D_{iso} in the patient during transit dosimetry.

In the case with a real patient, the EPID detector records the CU value during a therapeutic session. Thus, the D_{out} at surface in the first step and then the D_{iso} within the body can be calculated using the mean depth value and the TMR value.

To calculate the dose at the isocenter point in the patient (D_{iso}^{EPID}), the following formula is used:

$$D_{iso}^{EPID} = D_{out} \times \frac{TMR(2d_{EPL})}{TMR(d_{EPL})} \tag{5}$$

and considering that DEF = SID–SAD + d_{avg} = 60 + d_{avg}, we get:

$$D_{iso}^{EPID} = \frac{W1 \times CU + W3}{TMR(d_{EPL})} \times \frac{TMR(2d_{EPL})}{TMR(d_{EPL})} \tag{6}$$

where:

- CU – mean value of the signal registered in the central part of the EPID matrix, a set of points located at a distance of no more than 1 cm from CAX,
- d_{avg} [cm] – average depth of the dose prescription point (isocenter), value determined from the treatment planning system resulting from the rotation of the head around the patient,
- SID – source imager distance (consider fig. 1 and fig.2).

The deviation between the D_{iso}^{EPID} dose value (calculated from the CU measured during the therapeutic session) and the D^{TPS}_{iso} dose in the isocenter (calculated in the treatment planning system) was calculated using the formula:

$$\%\Delta = \frac{D_{iso}^{EPID} - D_{iso}^{TPS}}{D_{iso}^{TPS}} \times 100\% \tag{7}$$

In order to verify the correctness of the model, calculations of the dose distribution were performed for

a cuboid-shaped polystyrene phantom in the TPS system. The phantom was then irradiated by setting the calculated number of MU_{PMMA}. EPID recorded radiation passing through the phantomCU_{PMMA}. The PMMA phantom was then changed to a CIRS Thorax (lungs) and the exposure was repeated with the same settings (including MU_{PMMA}). This time CU_{CIRS} was registered. For both cases (CU_{PMMA} and CU_{CIRS}) the D_{iso}^{EPID} was determined. Two phantoms with different density homogeneity were used. The PMMA phantom has uniform densities throughout the volume. The CIRS phantom has a very heterogeneous density in the tested volume (lung tissue, bone, soft tissue). If dose was calculated for of PMMA phantom but irradiated was phantom CIRS (slightly different in density) the difference in the measured EPID signal should be "pronounced". And the described method is to ensure, above all, the detection of a significant error.

The clinical material consists of 53 patients treated for prostate cancer. The VMAT technique (full rotation) was used, a fractionation of 5 fractions at 7.25 Gy (isodose 98%) per fraction, up to a total dose of 36.25 Gy. Dose distribution calculations were performed using Eclipse treatment planning system (Varian Medical Systems) with the Acuros v.16.1 algorithm. Imaging examinations dedicated to treatment planning were performed on a Somatom go.Open Pro-/S or Somatom Definition AS CT-scanners from Siemens AG Germany. The treatment was carried out on the Edge v.2.7 accelerator (Varian Medical System), equipped with the EPID aS 1200 detector. 6 MV-FFF beams were used for all patients.

Results

Phantom measurements

Figure 3 shows the relationship between the dose (D_{out}) and the CU value for different DEP values (40, 50, and 60 cm). In the dose range: 0.24 Gy it is a linear relationship, the R^2 coefficient is equal to unity. Thus, we consider the measured CU signal to be directly proportional to the radiation dose.

Table I shows the correlation between CU and dose D_{out}. For selected clinical situations (differing in the D_{out} and DEF values), the CU measurement was performed and then compared with a value calculated in accordance with formula 4.

Analyzing table I, it can be seen that the dispersion of differences %Δ between the calculated and measured CU value ranges from –1.92% to 3.17%. Therefore, the uncertainty of this method can be assumed to be ≈5% (3.17 – (–1.92) = 5.09). The Wilcoxon test for these sets showed no statistically significant differences ($p > 0.05$).

Validation

As part of the method validation, the treatment plan was prepared for PMMA homogeneous phantom, which was then irradiated. We recorded the output signal with EPID and then the PMMA phantom was replaced with the CIRS Thorax phantom. It was then irradiated with the same beam parameters as a homogeneous phantom.

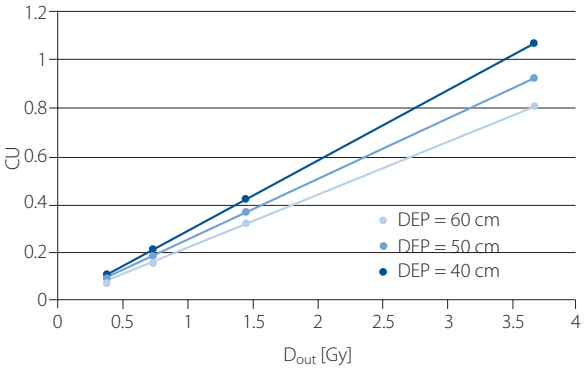

Figure 3. Dependence of the CU value on the dose (D_{out}) and the DEP value, for the 6 MV-FFF beam, with a size of 10 x 10 cm, SID = 160 cm

Table I. Deviation of the calculated CU value from the measured value for selected clinical situations

DPE (cm)	D_{out} (Gy)	CU measured	CU calculated	%Δ
60	0.367	0.080	0.080	0.10%
60	0.734	0.161	0.160	–0.47%
60	1.451	0.322	0.316	–1.92%
60	3.670	0.806	0.798	–0.93%
50	0.367	0.092	0.095	3.17%
50	0.734	0.184	0.190	2.85%
50	1.451	0.369	0.374	1.18%
50	3.670	0.924	0.944	2.10%
40	0.367	0.107	0.107	0.09%
40	0.734	0.214	0.213	–0.35%
40	1.451	0.428	0.421	–1.81%
40	3.670	1.072	1.063	–0.85%

The reconstructed D_{iso}^{EPID} dose value for the PMMA phantom differed from the ordered D_{iso} by –5.39%, while the replacement of the phantom with the CIRS caused a significant difference of 164.44% (!) of the expected value.

Measurements with the patient

For each patient, the CU measurements were performed using the EPID device during all fractions. The detector was always set at SID = 160 cm. The basic parameters of the treatment plan for the patients are presented in table II.

The average number of arcs is 3. The minimum number of MUs for a plan is 1803 MU and the maximum is 4232 MU, which gives an average value of 2966 MU.

The mean difference between the planned dose (D_{iso}^{TPS}) and the measured one (D_{iso}^{EPID}) for the 53 patients analyzed is less than 1%, the maximum noticed difference is 17%. In 64% of the analyzed cases, the difference between the planned

Table II. Basic parameters describing treatment plans included in the experiment

	Number of arcs	sum of MU's	d_{avg} [cm]	$d_{EPI, avg}$ [cm]
average	3	2966	17.3	15.9
max	4	4232	19.6	18.0
min	2	1803	14.6	13.3

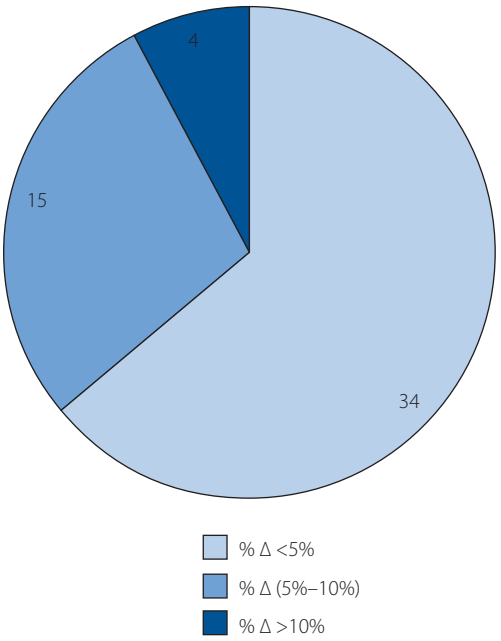

Figure 4. The number of cases for the deviation between the planned and measured dose using the proposed method based on EPID measurements. For over 60% of cases, the difference was less than 5%

and measured dose was lower by 5%. In 28% of cases, the difference ranged from 5–10%, in the remaining 7% (four patients) it exceeded 10% (fig. 4).

Since in a few cases the difference %Δ exceeded 10%, the relationship between the complexity of the plan and the investigated parameter %Δ was analyzed. Plan complexity was defined as the number of monitor units per arc. No such correlation has been found.

The mean difference between the planned dose and the measured dose is 0.9%. However, the maximum values of the differences were 17%. Statistical tests (Wilcoxon) did not show a statistical significance between the set of doses in the ISO, both the planned and measured one.

Discussion

The proposed method of dose verification does not require any additional procedures. It does not extend the time of the patient's preparation for the therapeutic session and the total time spent in the therapeutic room. The method allows to estimate the actual dose that the prostate cancer patient receives during the VMAT therapy. We denote the uncertainty of the method as 5%. Reducing this uncertainty in the future can be achieved by introducing into the formulas dependencies on the dimensions of the fields, which change significantly in dynamic techniques. Undoubtedly, the lack of this value in the calculation method affects the results. Discrepancies may occur when the dose prescription point does not coincide with the beam CAX. As described, the CU is read from the center of the matrix through which the CAX passes. We suspect that the method may be less accurate if the dose prescription point is in the area of significant heterogeneities, where small absolute differences between calculated dose and the measured one translate into relatively large percentage differences.

The phantom experiment has shown that using the wrong treatment plan or irradiating the wrong patient will result in differences that far exceed the uncertainty of the method. Such large differences, in this case, are explained by significant differences in the geometry of the phantoms and their density.

However, for over fifty patients, the sets of planned and measured doses do not show a statistically significant difference. The average error is around 1%.

In 4 out of 53 cases, the differences in planned and measured doses were greater than 10%. This happened despite the fact that each patient had IGRT applied, so it is necessary to assume the correct reconstruction of the therapeutic position (geometry). As already mentioned, we found no correlation between the number of MUs per arc and the %Δ. However, it is true that with a %Δ greater than 10%, the number of MUs per arc was as much as 20% higher than where %Δ was less than 5%. Therefore, although this has not been clarified, it is worth considering the complexity of the treatment plan when assessing the differences between calculated and measured doses.

Of course, this method can be considered complementary to the verification process, but in its current form it cannot be considered as an *in vivo* method in the VMAT technique. However, combining it with the treatment repeatability assessment presented in [39], it can be successfully used to verify the dose delivered during a therapeutic session.

Conclusions

The developed method of comparing the dose in a patient measured by EPID and the planned one can be used in clinical practice to estimate the dose that a patient receives during therapeutic sessions. The uncertainty of the method is at the level of 5%. Unfortunately, there are situations where the differences between the planned and measured dose are greater than 10%. In this case, the first step is to assess the complexity of the treatment plan (e.g. the number of monitor units per arc).

Conflict of interest: none declared

Adam Gądek
Maria Sklodowska-Curie National Research Institute of Oncology
Gliwice Branch
Radiotherapy Planning Department
Wybrzeże Armii Krajowej 15
44-102 Gliwice, Poland
e-mail: adam.gadek@io.gliwice.pl

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The challenges of oncogerontology

Krzysztof Jeziorski[1, 2]

[1]*Department of Gerontology, Public Health and Didactics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland*
[2]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Oncogerontology is a term that describes an interdisciplinary discipline dealing with the broadly understood relationship between oncology and human aging. The problems that pose a challenge for oncogerontology include, among others, the deteriorating cancer epidemiological situation, as well as the impact of the COVID pandemic on this situation, age restriction of screening tests in the elderly and the inequalities for older patients in accessing medical services and their participation in clinical trials. Data from the National Cancer Registry show an increase in the incidence and mortality of malignancies, especially in the elderly population. The epidemiological situation of cancer in Poland has been negatively affected by the COVID pandemic. New EU recommendations increase the number and quality of screening tests in the elderly. This group of patients has limited access to some oncological services and clinical trials. Artificial intelligence is an opportunity to improve diagnostics, therapy and oncology care in older patients.

Key words: cancer epidemiology, COVID pandemic, screening tests, clinical trials, artificial intelligence

Introduction

Oncogerontology is a new term that describes an interdisciplinary discipline dealing with the broadly understood relationships between oncology and human aging. Geriatric oncology is not a synonym for this term, but an integral part of oncogerontology. Problems related to geriatric oncology have been described in an excellent way in the recent series of publications by Kenig and co-authors in *Nowotwory. Journal of Oncology* started in 2019 [1].

The problems that pose a challenge for oncogerontology include, among others, the deteriorating epidemiological situation regarding malignant neoplasms in the elderly, as well as the impact of the COVID pandemic on this situation, age restrictions in screening tests for the elderly and inequalities for older patients in accessing medical services and their participation in clinical trials.

Epidemiology of cancer in the elderly

From a demographic point of view, the elderly population is divided into a third age group: 65–79 years and a fourth age group at 80 years and older [2]. Generally, the main cause of death in Poland among people over 65 years of age are: cardiovascular diseases (46%), followed by malignant tumours (23%), but in the third age group, cancer is almost as common a cause of death as cardiovascular diseases (35% *versus* 36%). By contrast, in the fourth age group, deaths from cardiovascular diseases predominate with cancer-related deaths accounting for 14% of all causes of death [2].

There are two interesting trends in cancer epidemiology in Poland. Since 2016, prostate cancer has been the most common cause of incidence of malignant tumours in men instead of lung cancer; in women for about 10 years, lung cancer has been the main cause of cancer mortality instead of breast

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cancer. Data from the National Cancer Registry show an increase in the incidence and mortality of malignancies, including the elderly population [3]. Data from the International Agency for Research on Cancer show that cancer mortality in Poland will increase in the coming years. Compared to 2018, in 2025 the increase in mortality from breast cancer and cervical cancer is estimated to be 8.3% and 6.7%, respectively. In the same period, the estimated increase in mortality from colorectal cancer is 11.9% in women and 17.1% in men [4].

Santucci et al. noted the growing difference in malignant cancer mortality between Western and Eastern Europe, to the detriment of Eastern Europe. This epidemiological gap is mainly caused by differences in lifestyle patterns – mainly smoking and alcohol abuse in Eastern Europe [5].

Since the development of cancer in adults takes several years, the effectiveness of health education on cancer in older people is limited from an epidemiological point of view. This education should be implemented as early as possible.

Epidemiology of cancer and COVID

The epidemiological situation of cancer in Poland has been negatively affected by the COVID pandemic, as presented in several publications.

Patt and co-authors showed that the COVID pandemic not only reduced the number of cancer cases detected, but also delayed the implementation of treatment [6]. In addition, the work of Koczkodaj et al. points out that COVID-19 has been a long-term factor that has negatively affected the epidemiology of malignant tumors, especially breast cancer, cervical cancer and colon cancer and the screening of these diseases [7]. Despite the end of the lock-down, the proportion of patients in screening tests is still lower than before the outbreak of the pandemic.

Similar conclusions emerge from the work of Olszewski et al. [8]. The authors used the infodemology technique (Google Trends) to collect data on the interest in screening during the COVID-19 pandemic. During the first months of the pandemic, the interest in performing screening tests by the respondents decreased, which could lead to increased cancer incidence and mortality. After six months, the interest in these tests returned to pre-pandemic states.

Screening procedures

In view of the increase in cancer incidence and mortality, particularly among older people, the question arises whether the upper age limit for early detection of selected tumour diseases for which screening is carried out should be extended. However, the main goal of cancer prevention is to prevent deaths. Early detection of older people is advantageous if life expectancy is more than 5 years. When formulating guidelines, it is recommended to analyse life expectancy, the degree of efficiency and the coexistence of other diseases.

Recently published European Union screening recommendations emphasize increasing the number and quality of screening tests as the COVID-19 pandemic has had a negative impact on prevention, detection and diagnosis. By focusing on early-stage cancer detection, the proposed recommendation aims to increase the number of screening tests to cover more target groups and more types of cancer. The new recommendations also extend organized population screening for cancer to include cancers of the lung, prostate and, under certain circumstances, the stomach [9].

The recommendations aim to increase the number of screening tests for breast, colorectal and cervical cancer in order to meet the target set in the European Action Plan for the Control of Cancer of 90% of eligible respondents to have such screenings carried out by 2025. In addition, targeted screening should be extended to other types of cancer, in particular prostate, lung and stomach cancer [9].

Recommendations:

- expand the target group of breast cancer screening to women aged 45–74 (compared to the current age group 50–69),
- indicate that cervical cancer screening should be performed for human papillomavirus (HPV) in women aged 30–65 years at least every 5 years, taking into account HPV vaccination status,
- call for colon cancer screening in people aged 50–74 using the stool immunochemical method to determine any follow-up tests in the form of endoscopy/colonoscopy.

Based on the latest findings and methods, the recommendations extend structured screening to include three additional types of cancer:

- lung cancer in current heavy smokers and ex-smokers aged 50–75 years,
- prostate cancer test in men up to 70 years using a prostate antigen test and magnetic resonance imaging (MRI) as a follow-up examination,
- screening for the presence of *Helicobacter pylori* and monitoring of premalignant gastric lesions in sites with high a incidence of gastric cancer and mortality.

The recommendations pay particular attention to equal access to early detection, to the needs of certain socio-economic groups, people with disabilities and people living in rural or remote areas, in order to make the idea of cancer prevention a reality across the EU [9].

Inequality in accessing medical services for the elderly

Another challenge for oncogerontology is unequal access for older patients compared to the younger group as regards oncological procedures and participation in clinical trials. Elderly oncological patients have limited access to oncological services:

- diagnostics,

- treatment,
- screening,
- clinical tests.

This situation results from the sometimes prevailing belief that elderly patients may not tolerate some diagnostic and therapeutic procedures. This is reflected in the conscious resignation from some diagnostic procedures burdened with increased risk or choosing a sub-standard treatment procedure in oncology, especially in the systemic treatment of neoplasms: using less aggressive and less effective chemotherapy programs, and in multi-drug regimens, reducing the dose of drugs for fear of the occurrence of side effects of these medications, ultimately leading to a deterioration in treatment outcomes and, in particular, patient survival.

The situation of suboptimal diagnostics and therapy of cancer patients is best illustrated by the work of Malik et al., who showed that breast cancer patients over 71 years of age received not only limited diagnosis, but also suboptimal oncological treatment. The authors showed that 51% of patients (383 patients), aged 71 and above, did not receive sufficient perioperative treatment (chemotherapy, radiotherapy or hormone therapy). In this group of patients, fewer axillary lymph node biopsies and mastectomies were performed [10].

The participation of older patients in clinical trials is also limited, which is puzzling, as patients aged 70 years and above account for 42% of the total cancer population, but they are under-represented in clinical trials, as their total share is only 24%. In a French study published in 2016, Le Saux et al. compared two periods: 2001–2004 and 2011–2014. The share of elderly cancer patients in France was only 19.3% (366 studies) in the first period and in the second period it significantly increased to 46.7% (718 studies) [11].

One of the latest studies published in 2022 on the participation of older people in 11 early-stage studies supervised by the French National Cancer Institute, found that patients aged 70 years and older were underrepresented in clinical trials from 2015 to 2016 compared to patients under 70 years of age (17.7% *vs.* 82.3%, respectively). Interestingly, patients aged 70 years and older were willing to participate in clinical trials, but did not receive such a suggestion [12].

There are three groups of factors that determine the unequal access of older people to clinical trials:

- research protocol: its structure, especially the criteria for inclusion of the patient into the study,
- patient motivation and their comorbidities,
- motivation and financial aspects of the sponsor.

The clinical trial protocols so far preferred randomized trials. However, it turns out that randomized trials are not the preferred method of answering research questions in the elderly, and alternative options should be used in this age group: prospective cohort studies or retrospective assessment from national registries [13].

Changes to the design of the trial report should include:

- a change in study endpoints: instead of assessing: response rate (RR), overall survival (OS) and progression-free survival (PFS) other parameters such as: quality of life, treatment toxicity, maintenance of functional independence, and disease-specific survival should be assessed [14],
- loosening the inclusion / exclusion criteria,
- decentralization of clinical trials by using: telemedicine, telephone consent, video contact, virtual treatment assessment,
- preparation of information about the research program in a manner adapted to the patient's age: larger letters, properly prepared audiovisual materials for the visually impaired and hearing impaired people [15],
- participation by a geriatric trained nurse in the research team.

Many studies indicate that older patients:

- want to participate in clinical trials, even if the final result is negative or indifferent [16],
- they are not actively looking for research in which they could participate, because nobody informs them about this possibility and they don't know how to do it themselves [17],
- they are less likely to participate in studies in which the therapeutic arm has significant side effects that may potentially be detrimental to their quality of life [18].

Artificial intelligence

A new challenge in oncogerontology is artificial intelligence. The reasons for the use of artificial intelligence in the oncology of older people include: high mortality rates, concomitant diseases and their negative impact on quality of life, limited access to medical services, especially for those living in agricultural areas, the need for long-term care of older people.

Despite many problems associated with the use of artificial intelligence (AI) in medicine, particularly in oncology, AI will facilitate imaging and histopathological diagnostics. AI enables not only imaging and histopathological diagnostics, but also their integration with other data such as molecular and biochemical markers. Moreover, AI helps in predicting the results of treatment: response to treatment, toxicity and mortality.

Conclusions

1. Health education about cancer should be carried out at an early stage of education in order to reduce the risk of cancer among older people.
2. Elderly patients should have access to oncology services and participation in clinical trials like younger patients.
3. Artificial intelligence is an opportunity to improve diagnostics, therapy and oncology care in older people.

From the editor

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Krzysztof Jeziorski
National Institute of Geriatrics, Rheumatology and Rehabilitation
Department of Gerontology, Public Health and Didactics
ul. Spartańska 1
02-637 Warszawa, Poland
e-mail: krzysztof.jeziorski@spartanska.pl

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Radiotherapy in the combined treatment

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Radiotherapy and immunotherapy

Ewa Sierko[1, 2]

[1]*Radiotherapy Department 1, Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland*
[2]*Department of Oncology, Medical University of Bialystok, Bialystok, Poland*

Radiation therapy is one of the standard treatment methods for cancer patients. Apart from killing cancer cells, it produces a modulation effect on local and systemic disease. Recently, immunotherapy, aiming mainly to immune checkpoint blockade, has become widely used in many clinical situations. Experimental and clinical studies indicate that the combination of both radiation therapy and immunotherapy may be beneficial in the cancer patient population in different clinical scenarios. Durvalumab maintenance therapy after radiochemotherapy in stage III non-small-cell lung cancer (NSCLC) patients was introduced to standard clinical care. The paper discusses the pathogenesis of the mutual interaction between radiation therapy and immunotherapy, as well available preclinical and clinical data concerning this promising treatment combination.

Key words: radiation therapy, radiotherapy, immunotherapy, checkpoint inhibitors, cancer

Introduction

Radiation therapy (RT) plays an important role in cancer patients' cure, the prolongation of their lives and the alleviation of cancer-related symptoms. The death of cancer cells due to DNA damage (e.g. apoptosis, autophagy) during cell division or in interphase (e.g. lymphocytes) is the main mechanism of RT. Recent evidence revealed that the efficacy of RT results from the optimal immune response triggered in irradiated tissue. Experimental studies demonstrated that mice lacking T and B cells required a higher radiation dose to achieve the same antitumor effect as mice harboring a properly active immune system. [1]. Additionally, preclinical studies demonstrated reduced RT efficacy in natural killer cells (NK) or macrophages or dendritic cells (DC) – deficient animals [2]. Furthermore, interferon gamma (IFN-γ) was documented to serve as the main factor in CD8+T cells activation, as key effectors in response to RT [3, 4].

Cancer cells accumulate genetic alterations and loss of normal regulatory processes. This results in expression of the neoantigens, differentiation antigens, and/or cancer nuclei antigens, which may lead to presentation of the peptides through binding to major histocompatibility class I (MHC I) molecules on the surface of cancer cells [5, 6]. Such cancer-specific antigens may be recognized by CD8+ T cells produced spontaneously in cancer patients [7], and thus cancer cells may be distinguished from normal cells. Recent studies revealed that at the tumor bed, cancer cells rely on different normal cells and recruit accessory cells to support progression of the tumor [8]. Accessory cells include cells forming hematogenous and lymphatic vasculature, tissue stroma components (among them – tissue-specific mesenchymal support cells, soluble and insoluble matrices), as well as myeloid and lymphoid-lineage cells [5, 8]. Reciprocal interaction between cancer cells, accessory cells, and their mediators, as well as extracellular matrix components exists and is a dynamic process [5]. During the early phase of cancer development, cancer cells are visible to the immune system (through cancer-specific antigens and proinflammatory "danger" signals, and most

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of them are eliminated (cancer immunosurveillance). Further, the process is not so successful, and the tumor cells may enter the equilibrium phase, where they may be either maintained chronically or immunologically sculpted by immune "editors" to produce new populations of tumor variants [9]. Finally, during the escape phase, cancer cells are invisible to the immune system and this is clinically visible phase of cancer progression [9]. Well designed studies in mice revealed that the continued deletion of cancer cells expressing T cell targets (immune editing) may enable cancer cells to avoid attacking the immune system [9]. There are multiple other factors contributing to the cancer cells escape from immunosurveillance: cancer cells variability (e.g. proteasome dysfunction, loss of classic MHC I molecules, presence of ligand 1 for programmed cell death (PD-L1), immunosuppressive activity of tumor matrix, presence of cells promoting escape phase (e.g. myeloid-derived stem cells, M2 macrophages, regulatory T cells – Treg, fibroblasts), soluble in tumor extracellular matrix suppressive factors, e.g. adenosine, transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF) [5, 6].

Immune responses in tumors reflect a series of carefully regulated events [6]. Both innate and adaptive immunity contributes to the immune system's optimal activity. The difference between them is based on antigen specificity. Innate immunity, composed mainly from DC, myeloid cells/macrophages and NK, serves as an early warning system and the gatekeeper to T cell activation [6]. The specialized receptors located on the innate immunity cells recognize potential danger targets, which should be eliminated by the host. Pathogen associated molecular patterns (PAMPs) or signals indicating tissue damage ("danger") – danger-associated molecular patterns (DAMPs) are recognized by the innate system, which leads to an immune response [10]. Cells of the innate system play a role in the early phase of the multistep inflammation process and facilitate a full and robust immune adaptive response. The adaptive immunity consists primarily of B and T cells and provide different specificity of the immune system through B and T cell receptor activation [6, 11].

Radiation therapy and innate immunity

At the tumor burden, innate immunity allows for detection of signals indicating the presence of cell damage or danger (fig. 1) [12]. Radiation induces both cancer and normal cells leading to release of specific danger signals that consequently activate multiple inflammatory pathways in innate immune cells. The danger signals include, among others, high-mobility group box protein-1 (HMGB1), calreticulin, complement, heat shock protein 70 (hsp70), cytosolic DNA, and adenosine triphosphate (ATP) [2]. These molecules are sensed by the innate immune cells, such as macrophages, DC *via*: toll-like receptor 4 (TLR-4), cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING), CD47 and NLR family pyrin domain containing protein 3 (NLRP3). These lead to the release of mediators, such as cytokines and chemokines, which trigger an immune response [2].

Damaged cells release HMGB1protein, which binds to TLR-4 on the macrophages and DC. The innate immune cells are characterized by high levels of the receptor. The TLR-4 is the main receptor for bacterial lipopolysaccharide (LPS) as well. Similarly to LPS, HMGB1 stimulates innate immune cells

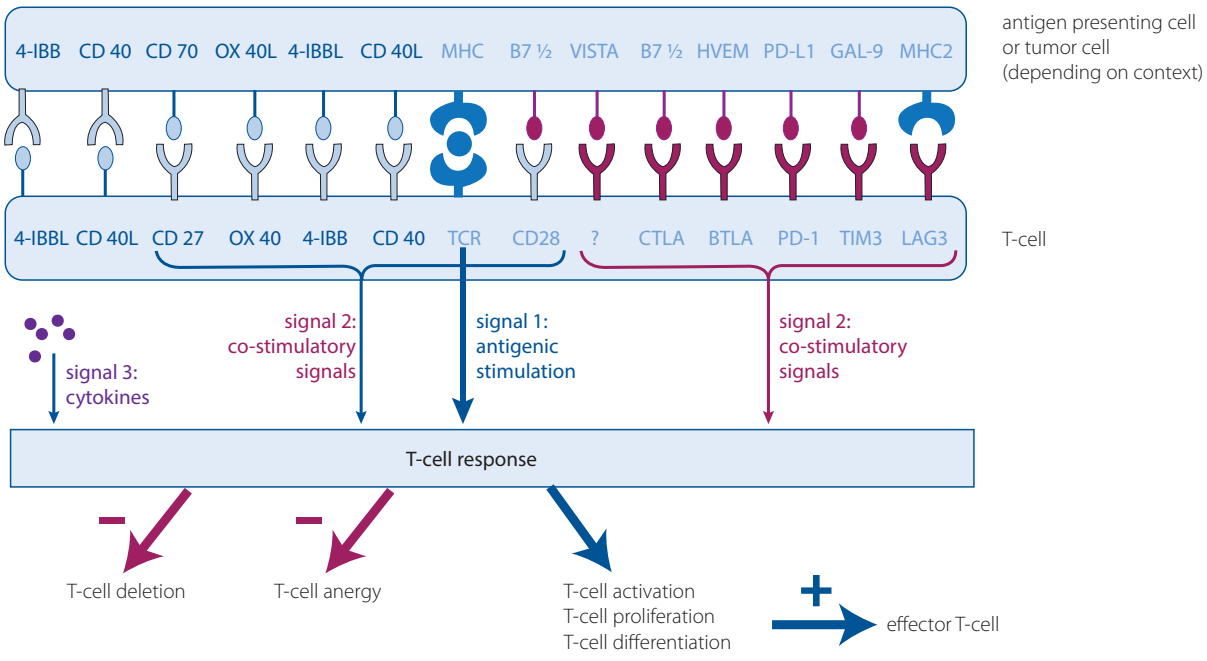


Figure 1. Innate immunity and radiation therapy

to cytokine release and upregulation of different molecules, like MHC, CD80, CD86, which leads to T cell activation [2]. Following radiation damage, cells express calreticulin on their surface, which is a phagocytic signal for macrophages and DC. The former cells engulf the dead cells and subsequently may present tumor antigens [13]. Recently, cytosolic DNA was indicated as a critical inflammatory signal induced by radiation [12,14]. Direct and indirect, radiation damage of nuclear and mitochondrial DNA causes DNA fragment formation in the nucleus and in the cytosol. Cytosolic DNA fragments are recognized by an intracellular protein called cyclic GAMP synthase (cGAS) that leads to cGAMP synthesis. It activates the endoplasmic reticulum-bound STING pathway leading to the activation of IFN-regulatory factor 3 (IRF3), and subsequent INF production [15, 16]. Innate immune cells, like macrophages and dendritic cells, are highly abundant in cGAS and STING, which are required for optimal production of type I INF. Synthesis of type I INFs after RT is the prerequisite for inducing the anti-tumor cytosolic CD8+ T cell response, since it induces tumor associated antigens presentation on T cells [16–19]. A recent elegant study demonstrated that DNA exonuclease – 3'repair exonuclease 1 (Trex1) regulates RT-induced activation of cGAS-STING-IFN pathway through cleaving cytosolic DNA formed after radiation exposure [20]. It was revealed that sensitivity of radiation in part depends on Trex1 levels. Namely high levels of Trex1 prevent RT-induced INF production [20].

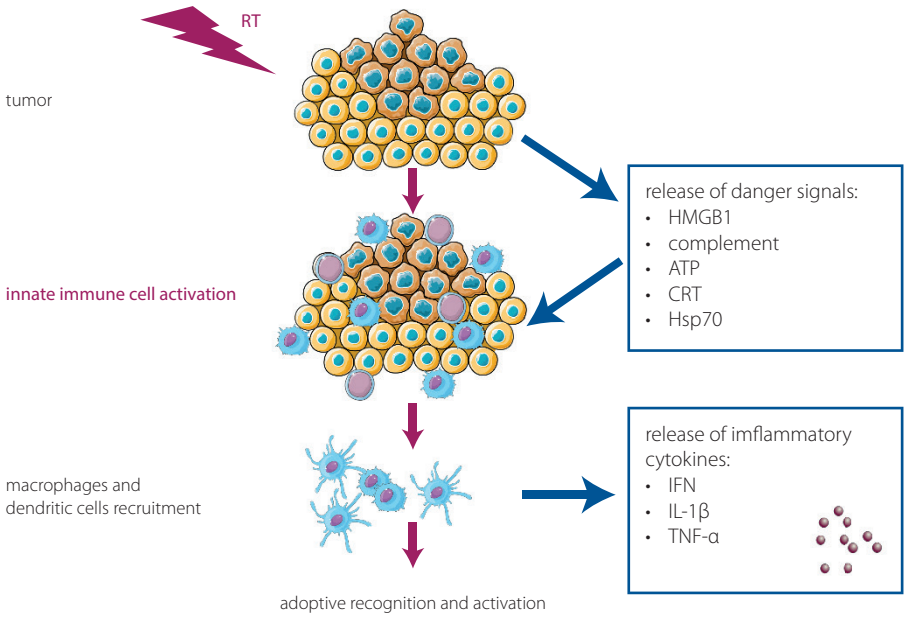
Radiation therapy and adaptive immunity

Cancer antigens are presented to T cells both at tumor burden or in draining lymph nodes mainly by extremely efficient DC. After antigen recognition and capture, DC migrate to draining lymph nodes along with free tumor associated antigens (TAA). Soluble TAA are captured by DC localized at lymphatic tissue. At the lymphoid tissue DC present captured antigens, in the form of peptide-MHC I or MHC II molecule complexes, to naive (antigen inexperienced) T cells (first signal). Additional co-stimulation should proceed through CD80, CD70 and/or 4-1BB (second signal) as well trough cytokines e.g. interleukin 12 (IL-12), type I IFN, IL-15 (third signal) (fig. 2). Naive CD8+ T cells differentiate into cytotoxic T lymphocytes (CTLs) exerting antitumor activity, whereas naive CD4+ cells differentiate into helper cells (T_H) or to Treg – Treg, which role is to decrease the immune response [21, 22].

Immunologic synapse (adaptive response)

T cells migrate through blood and lymphatic vessels to the tumor microenvironment, where they face numerous barriers, like intrinsic regulators (e.g. CD28 – CTLA-4 or PD-1 – PD-L1 systems – called check point regulators), extrinsic factors (Treg, Breg, myeloid cells), pro-tumor inflammatory microenvironment, tissue microenvironment-related DC inhibition, immune evasion of tumor target, tissue-specific alteration, like the presence of fatty cells, desmofibrosis [23]. The killing of cancer cells via T cells release leads again to endogenous tumor-associated antigen (TAA) release and further DC activation, closing so-called "cancer-immunity cycle" [5, 6].

Radiation therapy causes the death of cancer cells due to DNA damage (e.g. apoptosis, autophagy) during cell division or in interphase (e.g. lymphocytes) [24]. In this way it essentially contributes to an exacerbation of the immune system response. Radiation leads to TAA and DAMPS release from cancer cells, deletion of anergic T cells and Treg, incre-



HMGB1 – high-mobility group box protein 1, ATP and adenosine triphosphate; CRT – calreticulin; Hsp70 – heat shock protein 70; IFN – interferon; IL-1β – interleukin 1β; TNF-α – tumor necrosis factor α; RT – radiation therapy

Figure 2. Immunologic synapse (adaptive response)

ases in antigen processing, and increases in the expression of death receptors, an increase of cytokine and chemokine production as well as stimulation of immune cell circulation through the bloodstream [5]. On the other hand, stereotactic radiation therapy (SRT)/ stereotactic body radiation therapy (SBRT) contributes to a diminished number of lymphocytes within the tumor burden, myeloid-derived stem cells increase within the tumor and in the bloodstream, Treg increase, all of which leads to immunosuppression and resistance to immunotherapy [24].

In 1953, for the first time an "abscopal effect" of RT was described. Namely, after RT delivery to one site, the systemic response arises and nonirradiated tumors, being located far away from radiation fields diminished in size or disappeared [25]. From that time such cases were documented in the literature, particularly after hypofractionated regimens [26]. However, in real clinical practice this phenomenon is not frequently observed, probably due to existing, dominant immunologic tolerance mechanisms [24]. Many studies demonstrated that combining RT and immunotherapy increases the antitumor response [24, 27].

Combination of RT and immunotherapy

Currently two concepts between an interplay of RT and immunotherapy exists:

- RT acts as a vaccine, and increases/stimulates the abscopal effect. This is an issue in cancer metastatic setting,
- RT contribution to immunologic modulation in case of radical treatment [26, 27].

It should be stressed that the maximal effect is seen when patients' immunological system is well-functioning. Thus, frail patients are less likely to respond to RT combined with immunotherapy.

Influence of RT dose on immunologic response

Preclinical studies demonstrated that the best effect of combining checkpoint inhibitors with RT is achieved when hypofractionation is used compared to conventionally fractionated RT [28]. However, data from preclinical studies and early clinical experience are not uniform. Brooks et al. [29] demonstrated that a single fraction of 30 Gy resulted in higher CD8+ T cells infiltration and better tumor response than a single 5 Gy fraction, single 20 Gy fraction or 10 x 3 Gy fractionation regimen.

In a PEMBRO-RT phase III trial, SBRT administration (3 x 8 Gy) to the non small-cell lung cancer (NSCLC) metastatic sites combined with pembrolizumab increased relative responses compared to pembrolizumab alone (36% *vs.* 18%) [30]. Of note, the patients were irradiated to the lung tumors or lymph nodes metastases. On the other hand, Luke et al. [31] demonstrated that SBRT administration to 2–4 metastatic sites (30–50 Gy/3–5 fractions) and subsequent pembrolizumab therapy resulted in only a 13% relative response rate. Interestingly, in the study increased expression of 4 preselected IFN-γ genes in postradiation biopsy samples significantly corelated with observed responses in non-irradiated metastatic lesions [31].

The experimental study implies that fractionated RT (8 Gy) induces a better antitumor immune abscopal effect when compared to a single RT dose (20 Gy) [32]. The study, performed by Vanpouille-Box et al. [20], demonstrated that after 3 x 8 Gy-fraction regimen, double strand DNA fragments are present in the cell cytoplasm, whereas a 20 Gy dose produces no such effect [20]. Doses above 12–18 Gy induces the activity of DNA exonuclease Trex1 in cancer cells and attenuates their immunogenicity by degrading DNA that accumulates in the cytosol upon RT [20]. Contrary, RT used at immunogenic doses (oscillating around 8 Gy per fraction) leads to the accumulation of cytosolic double-stranded DNA (dsDNA) in cancer cells, which activates type I IFN (IFN-I) *via* the cGAS/STING pathway [20, 33]. The abscopal effect in mice is seen when a high dose of RT (but not too high) is combined with anti-CTLA-4 and anti-PD-L1 treatment (tab. I) [20].

Interestingly, Menon et al. [34] demonstrated that the addition of low-dose radiation (to tumors nonirradiated with high-dose) to SBRT combined with immunotherapy increases the systemic response rates of metastatic disease. Furthermore, the addition of very low radiation (2 x 1 Gy) to secondary tumors delivered with immunotherapy and high-dose RT to primary tumors (3 x 12 Gy), the so-called RadScopal technique, enhances systemic antitumor immune responses through overcoming the inhibitory tumor stroma [35].

Is what is irradiated important?

Distinct results were obtained in different trials combining treatment with immunotherapy and SBRT delivered to the lymph nodes/lung tumors in the PEMRO-RT trial resulting in doubling of the response rate of combined treatment [30], whereas SBRT to different tumor sites included a substantial number of bony sites (25% of irradiated lesions) did not result in high response rate [31]. Thus, the type of irradiated site may by important to induce immunogenic cell death and durable antitumor immunity.

MacGee et al. [36] revealed that SBRT delivered to parenchymal sites (lung, liver) induces systemic immune changes, including a decrease in the total number of NK and cytotoxic ($CD56^{dim}CD16^{+}$) NK cells, an increase in TIM-3+ NK cells, and an increase in activated memory CD4+ and CD8+ T cells. On the other hand, SBRT administered to non-parenchymal sites (the bones, central nervous system) did not induce such changes. By comparing the immune response after RT to different organs, the data suggest that SBRT induces systemic immunologic changes dependently upon the irradiated site. Based on the forementioned data, a question raises, if all or some metastatic sites should be irradiated to most efficiently increase the chance of immunogenic cell death and to achieve the best effect of combined RT and immunotherapy [29]. Brooks et al. [29] propose delivering SBRT to all or multiple lesions

Table I. Influence of radiation does on immune response

	Radiation dose per fraction (Gy)		
	≤2	4–10	>10
tumor cells	• cancer cell apoptosis • not effective in boosting TAA and DAMPs generation	• cancer cell death • no immunosupression	• cancer cell necrosis • tissue damage • increased cancer cell killing • increased TAA and DAMPs release
immune response	• no change in DCs phenotype and function • increased immunosuppresion • increased number of MDSC, TGF-β, TAM M2 at the tumor burden • immune adjuvant effects • increased number of CD8+ and CD4+ T cells • some TAMs repolarize toward M1 phenotype • lack of efficient antitumor response	• MHC-I up-regulation • DCs capture TAA • promotion of DCs migration tom the lymph nodes • MDSCs, Treg, M2-phenotypic traits decrease • macrophage increase • transient induction of proinflammatory microenvironment	• MHC-I up-regulation and expression on DCs • increased maturation of DCs, APCs • increased Type-I IFN production by DCs • increased number of CD45+ cells and CD8+ T cells • hipoxia-driven immunosuppresive microenvironment • increased number of MDSCs, tolerogenic TAMs M2, Tregs, TGF-β • triggering of innate and adaptive response

TAA – tumor associated antigen; DAMPs – damage and molecular patterns; DCs – dendritic cells; MDSCs – myeloid-derived stem cells; TGF-β – transforming growth factor beta; TAM M2 or -M1 – tumor associated macrophages-M2 or -M1; MHC-I – main histocompatibility complex I; Treg – regulatory T cell; APCs – antigen presenting cells; Type-I IFN – interferon type I; Gy – grey

to enhance the probability of immunogenic cell death. Future trials directed to assess the efficacy of SBRT/ immunotherapy should address the issue of number and localization of irradiated lesions as well as define biomarkers of the immunologic cell death [37].

The main effector cells of the immune system are lymphocytes. Radiation therapy volumes including large vessels, the heart, lymphatic structures (e.g. lymph nodes, the spleen, bone marrow, thymus in children) may lead to transient or persistent lymphopenia [38]. Numerous clinical trials demonstrate that lymphopenia correlates with decreased overall survival [39]. There is no data on radiation dose/lymphatic organ volume ratio to guide the safety of RT to lymphatic sites, thus the as low as rationally allowed (ALARA) rule should be used. In so-called "lymphocyte spraying RT", modern imaging methods and sophisticated RT techniques should be used to spare lymphatic organs and bone enriched with bone marrow as much as possible [38, 39]. Utilization of functional imaging, like positron emission tomography (PET) with different tracers, magnetic resonance imaging (MRI) or spectroscopy (SPECT) allow to identify active and inactive volumes of bone marrow, which may help for optimal RT planning to reduce the active volume of the tissue in the radiation volume [39].

Another conception of improving the efficacy of SBRT/ immunotherapy combination is based on partial tumor irradiation. An example is the SBRT-PATHY trial, where SBRT (1–3 fractions, 10–12 Gy each) was delivered to exclusively hypoxic segment of bulky tumors [40]. Such treatment resulted in better SBRT outcomes by exploiting both bystander and abscopal effects [40]. The addition of immunotherapy to such RT might further improve survival. To date, no data exists on such combination efficacy.

Recently, a ultrarapid ultrahigh dose rate FLASH RT was introduced. It delivers very high doses of radiation (8–20 Gy) in less than 1 second(s) [26, 38]. FLASH produces changes in the immunologic microenvironment in both tumor and normal tissues and allows for normal tissue sparing. Furthermore, spatially fractionated radiation therapy (SFRT), the intentional use of heterogeneous doses of radiation to different subvolumes within the same tumor (high dose peaks separated by low dose areas) [26, 38]. Early studies revealed that FLASH induces the release of TNF-α, which correlates with a complete clinical response [26, 38]. The introduction of the novel technologies in combination with immunotherapy is interesting, but requires further thorough studies.

Tumor immunoreactivity

Many studies revealed that the patients who most benefit from immunotherapy are those with cancers that have a high mutational burden [41, 42]. These are for example skin melanomas or microsatellite-instability-high colorectal cancers. Sensitivity of such tumors results from formation of immunogenic, tumor-specific mutant neoantigens [41]. On the other hand, some tumors do not respond to immunotherapy, like: estrogen receptor-positive breast cancer, prostate cancer. These tumors are characterized by limited mutational burden. Cancer cell clones with high mutational burden may be eliminated during progression of the disease as a result of cancer immunoediting, leading to the outgrowth of tumor cell clones with reduced immunogenicity. It was documented that RT-induced neoantigens broaden the immunotherapeutic window of cancers with low mutational loads [41]. As mentioned earlier, the cancer subtype matters in terms of immunoreactivity. Microsatellite-instability-high colorectal cancers are characterized by high mutational burden, contrary to other subtypes of colorectal cancers. Triple negative and HER positive breast cancers are enriched with lymphocyte infiltrations and are characterized

by higher immunogenicity, contrary to estrogen receptor/progesterone receptor positive breast cancers [43].

Optimal timing and sequencing of SRT/SBRT and immunotherapy

Optimal sequence and timing of RT and immunotherapy combinations is the subject of numerous experimental and clinical studies [42, 44]. It should be taken into account that tumors are largely distinct in terms of primary site, histopathology, immunogenicity, and clinical stage. There are several therapeutic mechanisms exploited by immunotherapy. Currently, the most widely implemented is immune checkpoint blockade (ICB).

CTLA-4 blockade and RT

CTLA-4 inhibits an early stage T-cell development, thus contributing to maintaining immune tolerance. CTLA-4 inhibition prevent the downregulation of T-cell activity and reduce Treg activity [44]. Many experimental studies documented promising synergy between RT and anty-CTLA-4 inhibition in neoadjuvant, concurrent, and adjuvant settings [44]. However, to date the optimal sequence is elusive. In experimental studies adding CTLA-4 inhibitors after RT produced increased tumor response and improved survival (in primary and metastatic situations) [44]. CTLA-4 inhibitor administration before RT followed by OX40 inhibitor produced better effects than giving them after RT [45].

In clinical settings ipilimumab administration within 4 weeks after SRT due to melanoma brain metastases resulted in a higher response rate than giving the inhibitor after 4 weeks [46]. In a retrospective study (46 patients), it was observed that ipilimumab administration before or during SRT (single fraction of 21 Gy) for brain metastases produced the best survival benefit and lowest rate of recurrence [47]. Closer to the last dose of ipilimumab delivery of SRS to brain metastases (within 5.5 months) corelated with the best intracranial control [48]. Baker et al. [49] demonstrated that in stage III–IV, unresectable melanoma patients who received nonbrain RT, the longest median survival time was achieved when ipilimumab was administered after RT as maintenance therapy compared to induction delivery – before RT (39 *vs.* 9 months). Knisely et al. [50] reported similar outcomes in 77 melanoma brain metastatic patients after combining SRS and ipilimumab, irrespective of the sequence of administration of the two modalities. In IMCISION (NCT03003637), a non-randomized phase Ib/IIa trial, 32 head and neck squamous cell carcinoma patients were treated with 2 doses (in weeks 1 and 3) of ICB using nivolumab (NIVO MONO, n = 6) or nivolumab plus a single dose of ipilimumab (COMBO, n = 26) prior to surgery [51]. A major pathological response was achieved in 35% of patients after COMBO ICB, whereas after NIVO MONOs – the rate was only 17% [51].

In a prospective trial, enrolling 24 locally advanced melanoma patients, ipilimumab was delivered at 3 mg/kg every 3 weeks for four doses in conjunction with RT (the median dose was 40 Gy). In inoperable patients undergoing neoadjuvant/definitive combined treatment, the objective response rate was 64%, with 4 of 10 evaluable patients achieving a radiographic complete response. An additional 3 patients in this cohort had a partial response and went on to surgical resection [52]. Furthermore, in the second cohort, where the high-risk of recurrence melanoma patients received the combined treatment postoperatively, as adjuvant therapy, the 6-, 12-, and 24-month relapse-free survival was 85%, 69%, and 62%, respectively (with 2 years of follow-up) [52].

In a prospective phase I trial, conducted by the Gynecology Oncology Cooperative Group enrolling 34 cervical cancer patients in clinical stage IB2 to IVA with positive pelvic lymph nodes (LNs), para-aortic LNs, or both, ipilimumab was administered after definitive radiochemotherapy. Treatment was well tolerated, and the 12-month overall survival (OS) was 90%, and progression-free survival (PFS) was 81% [53].

PD-1 blockade and RT

PD-1 present on the mature T lymphocytes inhibits the activation of T cells. It binds with PD-L1 and PD-L2 expressed on tumor cells and antigen-presenting cells. Nivolumab, pembrolizumab, and cemiplimab are PD-1 inhibitors currently used in the clinic [42].

In murine breast cancer model Verburgge et al. [54] observed that PD-1 inhibition given concurrently with RT enhances its efficacy. Furthermore, SBRT delivered 1 day before PD-1 blockade resulted in increased PD-1 blockade antitumor response [55].

A pooled analysis of the phase II PEMBRO-RT trial (NCT 02492568) and phase I and II MD Anderson Cancer Center (MDACC) trial (NCT02444741) revealed that in metastatic NSCLC patients adding radiotherapy to pembrolizumab immunotherapy increased outcome responses [56]. Pembrolizumab was administered intravenously (200 mg every 3 weeks) with or without RT in both trials. In the PEMBRO-RT trial, the first dose of pembrolizumab was given sequentially less than 1 week after the last dose of SBRT (3 x 8 Gy), whereas in the MDACC trial, pembrolizumab was given concurrently with the first dose of RT (4 x 12.5 Gy or 15 x 3 Gy). Only unirradiated lesions were measured for response. Median PFS was 4.4 months with pembrolizumab alone *versus* 9.0 months with pembrolizumab plus RT (p = 0.045), and median OS was 8–7 months with pembrolizumab *versus* 19.2 months with pembrolizumab plus RT (p = 0·0004) [57]. In a phase II NICOLAS trial, 79 stage IIIA–B unresectable treatment-naive NSCLC patients underwent standard, definitive radiochemotherapy plus nivolumab and subsequent nivolumab monotherapy as maintenance setting [58]. The 1-year PFS was 53.7% and the median PFS was 12.7 months. At an extended follow-up (median 32.6 months) median OS was 38.8 months and a 2-year OS rate was 63.7% [58]. Secondary analysis of results from the KEYNOTE-001 trial revealed that patients who

Table II. Phase III pending trials involving PD-1 inhibition and radiation therapy

Clinicaltrials.gov identifier [reference]	Setting	Treatment	Endpoint
NCT03700905 [60]	postoperative head and neck cancer	nivolumab or nivolumab plus ipilimumab after surgical resection and adjuvant RT or RT-CT	DSF
NCT04365036 [61]	early stage natural killer/T-cell lymphoma	toripalimab and induction CT followed by RT with concurrent toripalimab vs induction CT followed by RT	PFS
NCT04221945 [62]	locally advanced cervical cancer	CH-RT with or without concurrent pembrolizumab	PFS, OS

RT – radiation therapy; CT – chemotherapy; RT-CT – concurrent radiochemotherapy; DFS – disease free survival; PFS – progression free survival; OS – overall survival

had received RT before pembrolizumab administration had longer PFS and OS than those undergoing pembrolizumab therapy alone [59]. Multiple studies (mainly phase I and II) testing various sequencing of RT and anti-PD-1 combinations have been published or are ongoing, among others in: in head and neck, cervical, lung, gastrointestinal, genitourinary, breast cancer patients as well as in the central nervous system or hematologic malignancies [42]. Ongoing phase III clinical trials are presented in table II.

PD-L1 blockade and RT

Increased PD-L1 expression on cancer cells allows tumors to evade the immune system. RT increases the expression of PD-L1 in the tumor microenvironment and on CD8+ T-cells [42].

In experimental models, concurrent administration of the PD-L1 inhibitor and RT led to improved survival compared to sequential treatment [63]. A study in a murine pancreatic cancer model demonstrated that adding anti-PD-L1 antibody to high-dose RT significantly improved tumor response and the delay of 7 days between RT and receipt of PD-L1 inhibition abolished the radiosensitization effect [64]. Durvalumab, atezolizumab, and avelumab are PD-L1 inhibitors currently used in the clinic.

The efficacy of combining durvalumab as maintenance therapy after concomitant chemoradiation in clinical stage III NSCLC patients was demonstrated in an elegant phase III PACIFIC trial. Namely the 12-month PFS rate was 55.9% *versus* 35.3%, and the 18-month PFS rate was 44.2% *versus* 27.0%. The response rate was higher with durvalumab than with the placebo (28.4% *vs.* 16.0%; $p < 0.001$), and the median duration of response was longer (72.8% *vs.* 46.8% of the patients had an ongoing response at 18 months) [65]. Of note, subgroup of patients who received durvalumab within 14 days after completing radiochemotherapy had increased survival compared to those who were randomized after this period. Furthermore, durvalumab significantly prolonged OS, as compared with the placebo ($p = 0.0025$) [66]. Estimated 5-year rates for durvalumab and placebo were 42.9% *versus* 33.4% for OS and 33.1% *versus* 19.0% for PFS [67]. Such spectacular results led to incorporating a new benchmark for standard of care in this setting.

Another, phase III randomized study (PACIFIC-4) examines the efficacy and safety of durvalumab with SBRT versus placebo with SBRT in patients with unresected clinical stage I/II lymph node-negative (T1 to T3N0M0) NSCLC [68]. An interesting randomized phase II study (NCT04786093) is ongoing, which is designed to determine the impact of SBRT and durvalumab on quality-of-life and oncologic outcomes in patients with advanced NSCLC. Durvalumab and SBRT, with each fraction of RT given every other day on a standard stereotactic ablative RT schedule or every four weeks on the personalized ultra-fractionated stereotactic adaptive RT (PULSAR) schedule [69].

A randomized, phase III CALLA study to determine the efficacy and safety of durvalumab plus chemoradiotherapy versus chemoradiotherapy alone as a treatment in locally advanced cervical cancer patients is active (NCT03830866) [70]. The results (PFS) are awaited.

Toxicity and tolerability of ICB and RT

In most cases RT and immunotherapy are characterized by a distinct toxicity profile.

Meta-analysis of results obtained in 51 studies showed comparable grade 3–4 toxicity in using ICB plus RT compared to ICI alone in CNS melanoma metastases, NSCLC, and prostate cancer. The author concluded that ICIB plus RT is safe for future clinical trials in these cancers [71]. Additionally, a pooled analysis of trials in the US Food and Drug Administration Database revealed that immune checkpoint inhibitors given within 90 days following RT did not appear to be associated with an increased risk of serious adverse effects [72].

RT combination with other forms of immunotherapy

Apart from immune checkpoints inhibitors, which are the most frequently applied during clinical practice, many other options of immunotherapy combined with RT are currently tested [44]. One of the options are combinations of RT with cancer vaccines, e.g. dendritic cell vaccine (Sipuleucel-T), viral vaccines (rV-CEA/TRICOM or rV-PSA/rV-B7), or protein and peptide vaccines (Vitespene/Oncophage) [44]. Administration of RT with adoptive immunotherapy (T-cell therapy, CAR-T cell therapy, or NK cell therapy) is under early clinical investigation as well

[44]. Inclusion of cytokines (TGF-β, TNF-α, GM-SCF, IL-2, Il-7 and IL-15) to stimulate the innate and adaptive immune cells along with RT is also an interesting option, however cytokine toxic side effects may limit their usage in combination treatment with RT [44].

RT and steroids

Glucocorticosteroids are potent immune suppressants. They trigger T cell apoptosis and may increase the number of Treg. Since the purpose of RT is to stimulate the immune system to act against tumor cells, steroids may prevent this function and abolish the production of new T cells and their priming and activation. In clinical studies with ipilimumab in melanoma patients undergoing SRS, steroids were given prophylactically to avoid brain edema [73–75]. Patients receiving steroids have had lower median survival rates than those who were not given the regimen. However, administering steroids during RT did not interfere with the treatments results, since T cells may already be activated. This needs to be more precisely explained in dedicated studies. The optimal interval between steroid usage and beginning of immunotherapy should be also assessed.

Currently it is recommended to avoid usage of steroids before administration of RT combined with immunotherapy. However, there is an indication that using steroids can mitigate side effect of immunotherapy [76].

Conclusions and future perspective

Despite the encouraging results of many experimental and clinical studies on the combination of radiation therapy and different types of immunotherapy, there is a lack of uniform recommendation concerning the optimal composition of the two modalities in different clinical scenarios (primary or metastatic settings). There is a need to analyze the optimal combinations of RT and immunotherapy in terms of their influence on particular tumors, tumor microenvironment, and immune response. The influence of histopathology, the biological characteristics of the tumor, its localization, primary or metastatic site irradiation, RT delivery to one or multiple sites, the type of site undergoing irradiation (e.g. bone or lung tissue), optimal sequence of the combined therapy, the duration of immunotherapy, the total and fractional radiation dose, etc. should be widely studied. There is a need to find predictive factors (e.g. total mutation burden, total lymphocyte count, p53 status, calreticulin expression, Trex1 level or activity of STING) that allow for the best choice of proper treatment options for the individual patient.

Conflict of interest: none declared

Ewa Sierko
Radiotherapy Department 1
Maria Sklodowska-Curie Bialystok Oncology Center
ul. Ogrodowa 12, 15-027 Białystok
Poland
e-mail: esierko@onkologia.bialystok.pl

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The role of stereotactic body radiotherapy in the management of oligometastatic soft tissue and bone sarcomas

Konrad Zasadziński[1], Mateusz J. Spałek[1, 2]

[1]*Department of Radiotherapy I, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Sarcomas are a highly heterogeneous group of rare malignancies. Historically, metastatic disease was considered incurable and was an indication for a palliative approach. Modern local therapies have led to a paradigm shift, making long-term disease-free survival possible for selected groups of metastatic sarcoma patients. Oligometastatic and oligoprogressive disease constitute such indications. Although the administration of stereotactic radiation therapy (SBRT) for sarcoma metastases has been continuously rising over the past years, the evidence for such treatment is relatively scarce, lacking in larger prospective randomized clinical trials, and there is no consensus regarding strict indications, patient selection, and the time order of multimodal treatment. In this article, we discuss available clinical data regarding the efficacy and safety of SBRT in oligometastatic and oligoprogressive sarcoma, highlighting its indications in specific organ sites, as well as the possible limitations of this treatment modality.

Key words: stereotactic body radiotherapy, sarcoma, metastases, hypofractionation, radiotherapy

Introduction

Soft tissue and bone sarcomas (STBS) comprise a heterogeneous group of rare diseases that require treatment in specialized tertiary centers. The only curative method of treatment for localized spindle cell STBS is surgery, often combined with perioperative radiotherapy and chemotherapy whereas disseminated disease is an indication for systemic therapy [1–3].

Some patients with STBS present an intermediate state between localized and fully disseminated disease, so-called oligometastatic disease (OMD). The idea of OMD originates from the work by Hellmann et al. This classical definition covers up to three to five distant metastases amenable for medical imaging detection and involving one or two organ systems [4]. One of the modern definitions proposed by the European Society for Radiotherapy and Oncology (ESTRO), and the American Society of Radiation Oncology also use the numerical concept of one up to five metastatic lesions that can be safely controlled by local therapies [5]. Adopting this concept potentially rationalizes a curative treatment approach in patients with OMD, involving a definitive local treatment of single distant metastases, with the prerequisite of early and complete local control of the primary tumor. Furthermore, some macrometastases still present after systemic treatment might be successfully eliminated with the use of modern local ablative techniques.

Historically, the only potentially curative approach for distant sarcoma metastases that offered satisfactory local control

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was metastasectomy, applied only in selected patients eligible for surgery. The emergence of new local therapies, such as stereotactic body radiotherapy (SBRT), thermal, chemical, and radioablation has led to a paradigm shift in metastatic STBS treatment [6]. Initiating such a treatment pathway is possible only after a thorough consideration of multiple interacting factors, such as locoregional spread, tumor burden, involvement of organs, time setting (synchronous or metachronous metastases), and biological features, including tumor grade.

Moreover, even in the case of disseminated disease, modern systemic treatment frequently enables long-term disease control. In the past, any signs of disease progression caused treatment change or withdrawal. Nowadays local ablative therapies such as SBRT for progressive metastases may allow continuing the current effective line of systemic therapy after eliminating treatment--resistant clones. This concept is called oligoprogressive disease (OPD) [7]. The clinical benefit of such an approach was a matter of some retrospective studies and case reports [8–13]. The role of SBRT and other therapies in OPD is intensively investigated in various cancers, especially those susceptible to immunotherapy.

Concepts of OMD and OPD were summarized in consensus guidelines proposed jointly by ESTRO and the European Organisation for Research and Treatment of Cancer. This article contains a decision tree for OMD and OPD with relevant definitions [14].

Available clinical data, although relatively scarce, suggests highly promising advantages of SBRT in sarcoma patients with OMD:

- excellent local control rates and a potentially improved overall survival,
- good tolerability,
- a delay or even complete avoidance of systemic therapy,
- early prevention of tumor-related complications with avoidance of emergency/salvage surgery [15].

However, some of these features may reversely adversely influence clinical outcomes in many cases, raising some reasonable concern about overtreatment. The same advantages and risks are related to the SBRT for OPD with even less evidence.

Although the administration of SBRT for STBS OMD and OPD has been continuously rising over the past years, the evidence for such treatment is relatively scarce, lacking in larger prospective randomized clinical trials, and there is no consensus highlighting strict indications, patient selection, and the order of treatment in a multimodal setting.

In this article, we discuss available clinical data regarding the use of SBRT in STBS OMD and ODP and directions for further investigations.

Clinical data

Lung metastases

The lungs are the most common site of distant sarcoma metastases due to the hematogenous pattern of spread [16]. About 20% of patients with soft-tissue sarcoma and 40% of patients with bone sarcoma develop lung metastases during the course of the disease [17]. The first SBRT approaches for STBS lung metastases relied on the analogy to early-stage non-small cell lung cancer treated with SBRT with excellent clinical outcomes, comparable to the invasive surgical approach [18]. All the discussed studies were summarized in table I.

The first retrospective single institution SBRT study published by Dhakal et al. involved 52 patients with STBS pulmonary metastases [19]. Among them, 15 received SBRT for 72 lung lesions. The authors reported the most common fractionation regimen as 50 Gy in ten fractions. Three-year local control after SBRT was reached by 82% of patients who received SBRT, whereas the median overall survival in the SBRT group was significantly higher than survival in those who did not undergo SBRT (2.1 years *vs.* 0.6 years, $p = 0.002$). Moreover, no patients experienced severe toxicity of SBRT.

The abovementioned findings have been confirmed by several other trials over the following years [20, 21]. Bauman et al. published two manuscripts reporting the results of SBRT for STBS lung metastases using more aggressive fractionation regimens, namely 50 Gy in five and four fractions delivered by CyberKnife or conventional linear accelerators. In the first study, the authors analyzed a cohort of thirty consecutive STBS patients who received SBRT to 39 lung metastases [20]. Then the patients were monitored using CT or PET/CT scans every three months after SBRT. Local control at 12 and 24 months reached 94% and 86%, respectively. Overall survival (OS) at 12 and 24 months was 76% and 43%, respectively. The authors did not find an influence of SBRT technique, fractionation, target volume site, histopathology, and diameter on local control and survival. The treatment tolerance was good. The second study reported the results of a pooled analysis of 44 patients with 56 lung metastases who received SBRT and provided similar results to the previous one [21].

A small retrospective study on 16 patients with 25 lesions treated with SBRT also confirmed very good local control with a favorable toxicity profile of such irradiation, namely 94% at 43 months [22].

Excellent results of SBRT for lung metastases were found in another retrospective study performed by Navarria et al. [23]. The authors analyzed a cohort of subsequent 28 patients with soft tissue sarcomas who underwent SBRT for 51 lung metastases not eligible for surgery. Various fractionation regimens were used, namely 30 Gy in one fraction, 60 Gy in three fractions, 60 Gy in eight fractions, and 48 Gy in four fractions. All patients were irradiated using volumetric modulated arc therapy in a conventional linac. The patients were followed-up every three months after SBRT. The median follow-up was 21 months. Five-year local control was 96%. Overall survival at two and five years was 96.2% and 60.5%, respectively. No grade 3 or higher toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.0 were observed.

Table I. The summary of studies on stereotactic body radiotherapy for sarcoma lung metastases

Study	Study design	Number of patients	Number of lesions	Median lesion size	The most common fractionation regimen	Local control rate	Overall survival	Toxicity
Dhakal et al., 2012 [19]	retrospective single center	52	74	nd	50 Gy in 10 fr.	3 y: 82%	median: 2.1 years *vs.* 0.6 years in control group (no SBRT)	no grade 3 or higher
Baumann et al., 2016 [20]	retrospective multicenter	30	39	2.4 cm	50 Gy in 4–5 fr.	1 y: 94% 2 y: 86%	1 y: 76% 2 y: 43%	no grade 3 or higher
Baumann et al., 2020 [21]	retrospective multicenter pooled analysis	44	56	2.0 cm	50 Gy in 4–5 fr.	1 y: 96% 2 y: 90%	1 y: 74% 2 y: 46%	no grade 3 or higher
Mehta et al., 2013 [22]	retrospective single center	16	25	nd	36–54 Gy in 3–4 fr.	43 m: 94%	4 y: 72%	no grade 2 or higher
Navarria et al., 2015 [23]	prospective observational	28	51	6.5 cm^3	30 Gy in 1 fr 60 Gy in 3 fr. 60 Gy in 8 fr. 48 Gy in 4 fr.	5 y: 96%	2 y: 96.2% 5 y: 60.5%	no grade 3 or higher
Frakulli et al., 2015 [24]	retrospective single center	24	68	nd	30-60 Gy in 3–8 fr.	1 y: 88.2% 2 y: 85.9%	1 y: 73.1% 2 y: 66.4%	no grade 3 or higher
Soyfer et al., 2017 [25]	retrospective single center	22	53	nd	24–60 Gy in 3–4 fr.	95 m: 96%	5 y: 50%	1 grade 3 no grade 4
Lindsay et al., 2018 [26]	retrospective single center	44	117	2.1 cm	36–50 Gy in 5–12 fr.	14 m: 95%	2 y: 82% 5 y: 50%	1 grade 3 no grade 4
Navarria et al., 2022 [27]	prospective phase 2 single arm clinical trial	44	71	2.0 cm	30 Gy in 1 fr. 60 Gy in 3 fr. 48 Gy in 4 fr.	1 y: 98.5% 5 y: 93.1%	1 y: 88.6% 5 y: 48.2%	no grade 3 or higher

fr. – fractions; m – month(s); SBRT – stereotactic body radiotherapy; y – year(s)

Another retrospective study was conducted by Italian researchers that included STBS patients who were treated with SBRT for lung metastases [24]. The authors identified 24 patients who underwent irradiation for 68 lung lesions not suitable for surgery. The patients received total doses between 30 and 60 Gy given in three up to eight fractions. Two-year local control was high and reached 86% whereas two-year overall survival was 66%. No significant toxicities of SBRT were reported.

Similarly designed studies were performed by Soyfer et al. and Lindsday et al. [25, 26]. The cohort from the first study comprised 22 patients with 53 STBS lung metastases who received SBRT [25]. After a long follow-up of 95 months, no progressive disease in all treated lesions was observed. Five-year overall survival was 50%. Treatment tolerance was described as very good. The second study analyzed a group of 44 patients with STBS lung metastases treated with SBRT [26]. Follow-up time was shorter than that presented in the first mentioned study – namely 14.2 months. The local control rate was 95%. Two- and 5-year overall survival was 82% and 50%, respectively. The most frequent side effects included radiation pneumonitis, cough, rib fracture, pain, dermatitis, and dyspnea.

The only prospective clinical trial on SBRT for STBS lung oligometastases was performed by Navarria et al. [27]. The authors enrolled adult patients with up to four inoperable STBS lung metastases. The allowed fractionation regimens included 30 Gy in one fraction for peripheral lesions ≤1 cm, 60 Gy in three fractions for peripheral lesions between 1.1 and 2 cm, 48 Gy in four fractions for peripheral lesions over 2 cm, and 60 Gy in eight fractions for central lesions. The proportion of progression-free treated lesions at 12 months was chosen as the primary endpoint of this study. Forty-four patients with 71 lung metastases met the inclusion criteria and received SBRT for metastatic lesions. Twelve-month local control was 98.5%. The median disease-free survival reached 12 months whereas the median overall survival was 49 months. Age, grade of STBS, the interval from diagnosis to disease dissemination, and the number of lung metastases were prognostic for survival. No significant pulmonary toxicity was reported.

Based on the described results, we may presume the high efficacy and favorable toxicity profile of SBRT for STBS lung metastases. However, the crucial issue is the identification of patients who are the best candidates for local therapy. Tanadini-Lang et al. calculated a nomogram predicting overall survival after SBRT for lung metastases from various cancers that could be helpful to choose the most appropriate candidates for lung SBRT [28]. The cohort consisted of 715 patients treated with SBRT for 964 pulmonary metastases, including 49 patients with STBS.

Diagnosis of STBS moderately worsened the probability of two-year survival as compared with renal cell cancer and colorectal cancer but less affected survival than the diagnosis of breast cancer, non-small cell lung cancer, esophageal cancer, melanoma, and other analyzed malignancies. Importantly, the authors concluded that long-term overall survival after SBRT for pulmonary metastases in this heterogeneous cohort was similar to survival achieved after metastasectomy. Thus, patients with STBS OMD seem to be excellent candidates for SBRT in the case of pulmonary metastases.

Various sites

Despite the lack of strong scientific evidence, SBRT seems to be also an effective local treatment for non-pulmonary metastases localized to various sites. An example of an SBRT plan in a patient with oligoprogressive myxoid liposarcoma during systemic treatment was presented in figure 1. This patient received 35 Gy in five fractions prescribed to covering 80% isodose. Irradiation was combined with hyperthermia.

The largest retrospective study on SBRT in STBS was published by a team from our institute [15]. We aimed to investigate the use and outcomes of SRT in this group of tumors, identify the patients who benefit the most, and check if there is any dose-response relationship. The cohort consisted of consecutive adult patients with primary, recurrent, or metastatic STBS treated with linac-based SBRT. SBRT was defined as highly conformal radiotherapy delivered in ten or fewer fractions using daily image guidance, and a biologically effective dose no lower than 50 Gy. We identified 141 patients who underwent 233 SBRT procedures. The median follow-up was 21 months. Local progression after SBRT occurred in 15 patients. We found that OMD, lung metastases, and soft tissue sarcomas get the highest benefit from SBRT.

In a relatively large retrospective study from Karolinska University Hospital, Stragliotto et al. reported the results of SBRT for 136 STBS metastases in 46 patients [29]. This cohort differed from the cohort published by our team in fractionation regimens allowing total doses closer to the palliative ones, for example, 20 Gy in five fractions or 10 Gy in one fraction. In both studies, local control was very high, namely 88% in the Swedish and 95% in the Polish cohort. Importantly, the authors reported serious complications of SBRT, namely one colon perforation and contracture of the hip region. This study also highlighted the true benefit of SBRT, reporting 13 patients (31%) as long-term survivors who lived longer than three years after treatment.

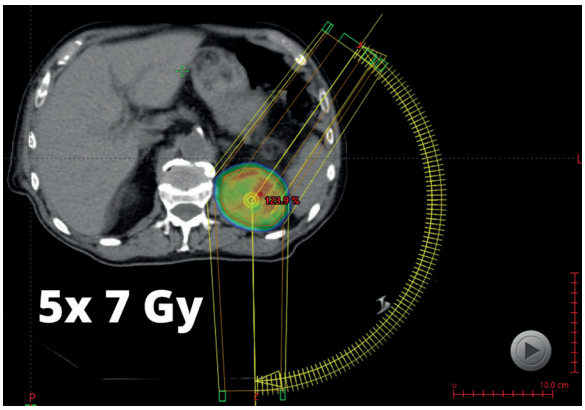

Figure 1. Stereotactic body radiotherapy for oligoprogressive myxoid liposarcoma

Another retrospective study focused on patients with metastatic or recurrent osteosarcomas and Ewing sarcomas [30]. The authors analyzed a retrospective cohort of 14 patients with osteosarcomas and Ewing sarcomas who underwent SBRT for 27 lesions, mostly bone and lung metastases. The role of SBRT in this analysis was divided into definitive (n = 14) and palliative (n = 13). In those who were treated with definitive intent, the median follow-up reached two years with two-year estimated local control as high as 85%. Those who received palliative SBRT had significantly shorter 0.2 years of median follow-up. However, local control was also good despite lower doses used in this arm. Three clinically significant toxicities were observed in patients who were irradiated concomitantly with chemotherapy or underwent reirradiation.

Limitations

The main limitation of SBRT is the lack of convincing scientific evidence, namely results of prospective randomized clinical trials that confirm its non-inferiority to surgery. However, the only available single-arm prospective clinical trial showed excellent local control with minimal toxicity of SBRT. Furthermore, we may assume at least similar efficacy based on trials with early non-small cell lung cancer.

Another problem is the choice of an optimal fractionation regimen. The heterogeneous group of STBS covers a wide spectrum of radiosensitivity, from extremely radioresistant chondrosarcomas up to the highly radiosensitive Ewing sarcoma and myxoid liposarcoma [31–33]. Moreover, even within the same pathological subtype, the radiosensitivity may vary [34]. Moreover, data regarding stereotactic reirradiation in this group of patients are scarce. Thus, the choice of fractionation should be individualized, considering many factors, among others, predicted radiosensitivity, site, previous irradiation, concomitant systemic treatment, and performance status.

Finally, there is the fear of late complications, especially in patients who are believed to be long-term survivors. This issue may be answered by data collection in prospective registries of all STBS patients who are treated with SBRT.

Conclusions

Despite limited high-quality evidence, SBRT is a viable method of treatment for OMD and OPD STBS. Its excellent local efficacy, favorable toxicity profile, and wide availability make it a real alternative to more invasive surgical approaches. Data regarding the role of SBRT in rare diseases should be collected

in prospective registries. The ongoing international project may answer the unsolved questions regarding the true benefit of SBRT in oligometastatic cancers [35]. Further investigations should focus on the development of new predictive factors, models of patient selection for SBRT in STBS, biologically-guided treatment, and combined therapy.

Conflict of interest: none declared

Mateusz J. Spałek
Maria Sklodowska-Curie National Research Institute of Oncology
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: mateusz.spalek@pib-nio.pl

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Editorial

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I am very happy to inform you that *Nowotwory. Journal of Oncology* has launched a new thematic section entitled ***Cancer prevention and public health***.

Prophylaxis is one of the most crucial elements of public health. We can see this trend very clearly on the cancer prevention example – about 90–95% of all malignancies are related to highly preventable risk factors such as: tobacco smoke, poor diet, low physical activity or alcohol consumption. Effective health education and preventive actions contribute significantly to cancer burden decrease. What is more, further research on this subject is very much needed. I am convinced that this new section will become a platform for showcasing high quality studies, while also providing a space for scientific discussion that will result in new ideas and initiatives being forged.

I warmly encourage you to read the first thematic article entitled *The role of health literacy and health education in the prevention and course of neoplastic diseases* by Dominik Olejniczak and Agata Olearczyk. I would also like to take this opportunity to kindly invite you to submit papers on cancer prevention and public health for upcoming issues.

Paweł Koczkodaj
Section Editor
Cancer prevention and public health

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The role of health literacy and health education in the prevention and course of neoplastic diseases

Dominik Olejniczak, Agata Olearczyk

Public Health Department, Medical University of Warsaw, Warsaw, Poland

The idea of health literacy is a relatively new term in contemporary health promotion, especially in Poland, where it has only recently started to be used. It was created as a result of the need to name a certain set of conditions and competences that could realistically determine the health of individuals and populations. This applies to both healthy people, including those at high risk of disease (the use of health literacy in prevention), as well as sick people (the use of health literacy in the course of a disease), including people suffering from oncological diseases.

Key words: health literacy, health education, health promotion, neoplastic diseases

Introduction

The idea of health literacy is a relatively new term in contemporary health promotion, especially in Poland, where it has only recently started to be used. It was created as a result of the need to name a certain set of conditions and competences that could realistically determine the health of individuals and populations. This applies to both healthy people, including those at high risk of disease (the use of health literacy in prevention), as well as sick people (the use of health literacy in the course of a disease), including people suffering from oncological diseases.

The sources of this term can be found in the Ottawa Charter from 1986, where the starting point for health literacy is the phrase "developing individual skills" [1].

Taking into consideration the Ottawa Charter and comparing the scope of health literacy with the components of health promotion, health education should be considered the most important element for generating this skill.

Health education is a key tool in ensuring the goals of health promotion are met. The original one focused only on providing society with knowledge about health (often selective, encyclopedic). Currently, the concept of modern health education encourages society to engage and proactively participate in the achievement and enhancement of well-being. This also fits in with the objectives and definitions of public health, which indicates a strong relationship between these areas and health literacy. Recalling Winslow's definition that "public health is the science and art of preventing disease, prolonging life and promoting physical and mental health and well-being through organized community efforts for the sanitation of the environment, the control of community infections, the education of the individual in principles of personal hygiene, the organization of medical and nursing service for the early diagnosis and preventive treatment of disease and the development of the social machinery which will ensure to every individual in the community a standard of living adequate for the maintenance of health", a relationship can be noticed between "community involvement" and health literacy, which will be discussed later in the article [2].

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Health education

Returning to health education, Woynarowska defined it as "a lifelong process of teaching people how to live in order to maintain and improve their health and that of others, and in the event of a disease or disability, actively participate in its treatment, cope with and reduce the negative effects" [3].

Andruszkiewicz and Banaszkiewicz write about health education as follows: "Health education can be directed towards an individual or a group of people. In both strategies, the essence of actions is to develop the ability to make the right decisions in solving health problems" [4]. Dudkiewicz and Kamińska, on the other hand, say about health education that: "It is a process in which people learn to take care of their own health and the health of the society in which they live. Health education covers: knowledge about social, political and environmental factors influencing health; knowledge about health related to the functioning of one's own body; the ability to prevent and cope with difficult situations; knowledge and skills related to the use of the healthcare system" [5]. The above-mentioned definitions will allow for a precise evaluation of the programs submitted for analysis, in terms of achieving the objectives of health education in the context of assessing the needs and capabilities of the chosen target groups and selected tools.

Effective health education creates opportunities to engage society in health matters by building key skills aimed at health described in the literature as "health literacy".

From the point of view of pro-health behaviors and activation of the society in acquiring and maintaining healthy habits, health literacy is a key skill. It is a concept whose importance has been appreciated by the gratest authorities in the field of health promotion around the world, including Kickbush. It says that health literacy consists of:

1. information and knowledge about health,
2. understanding the social components of health,
3. ability to negotiate with the environment, understanding and balancing the risk of individual and social behavior,
4. coping skills,
5. care delivery skills,
6. ability to use the healthcare system,
7. moving from fatalistic acceptance of health issues to the implementation and use of health knowledge [6].

Taking into account building knowledge about health, especially oncological diseases, the role of so-called therapeutic education should be recognized. When discussing the concept of therapeutic education, the starting point should be broadly understood health education – one of the components of health promotion. It is worth emphasizing that health education should be treated as a process, a series of planned activities, and not as an individual or incidental transfer of knowledge. Only continuous, consistently implemented health education, also in terms of slightly broader scope than therapeutic education, can bring results, both in primary, secondary and tertiary prevention, which is particularly important in the case of neoplastic disease.

Therapeutic education

Health education is also an integral part of therapy, especially in chronic diseases – e.g., oncological diseases, hence the concept of therapeutic education emerged. As in the case of health education, there are many definitions of this concept as well. Nevertheless, it should be talked about as an immanent element of the treatment process, taking into account in a special way the empowerment of the patient and their adaption as regards functioning in the new reality – the existence of the disease.

The effectiveness of therapeutic education has been scientifically proven, and its application particularly applies to chronic diseases, such as, inter alia, metabolic diseases – e.g. diabetes, respiratory diseases – e.g. asthma, neoplastic diseases as well as dermatological diseases – e.g. atopic dermatitis. It was the growing number of people with chronic diseases that forced the creation of tools that would facilitate an increase in the patient's independence during the course of their disease. Therefore educational content should be in line with the specificity of a given diseases entity and its impact on the patient.

Effective implementation of therapeutic education should be preceded by a precise assessment of health needs, including the patient's educational needs. This is important because a therapeutic education program will bring the desired results only if it is adjusted to the needs and capabilities of the patient (e.g. to the perceptual and cognitive abilities dependent on or resulting from age, health status or education level).

The main goals of therapeutic education include building a high level of competences and skills in the field of broadly understood health, obtained through the proper use of information sources, allowing for minimizing the occurrence and impact of health risk factors on the individual and the environment of living, in order to improve or avoid worsening the current state of health. In English-language literature (although also in Polish), this competence is called health literacy. By acquiring such skills, another goal of therapeutic education can be achieved, which is building the independence and self-sufficiency of the patient, in order to improve their quality of life with the disease.

Another goal of therapeutic education is to build self-treatment skills. The English-language literature provides many equivalents for this concept, incl. self-treatment and self-care. The self-treatment concept (successfully functioning in countries with a high level of education) concerns the independent, self-use of medications by chronically ill people. Such people are usually better educated in terms of their disease entity than patients treated on an ad hoc basis. This often happens as a result of effective therapeutic education. The competences acquired in this way allow even the self-regulation of doses of some medications to a limited extent

(for example, adjusting the dose of an anticoagulant based on the results of tests performed by so-called cardiological patients with implanted valves). At the same time, the concept of self-care extends the discussed area by, for example, ability to care for a diabetic foot or proper hygiene of the stoma belt. Mastering these skills affects quality of life, giving a sense of real agency to the situation and the course of the disease, which is an obvious reference to the sense of coherence [7].

It is worth noticing that therapeutic education, referring to the definition of health education, should be a process – planned and based on the concept of EBM and EBH (respectively: evidence-based medicine and evidence-based health). If there is such possibility, its assumptions should be implemented by the therapeutic team from the moment of diagnosis, which is often a critical moment for the patient.

Failure to implement therapeutic education may lead to serious consequences, not only physical – such as the lack of self-care skills or its improper implementation, resulting in e.g. infection of a wound or failure to regulate diabetes. There may also be psychological consequences, such as the lack of acceptance of a chronic disease, which may increase the risk of secondary health issues, for example depression.

It can be stated with certainty that striving to increase the patient's independence, especially in the course of oncological diseases – in view of the growing burden on health care systems – is currently one of the main challenges for public health policy, and, in particular, for health promotion (including health education) not only in Poland, but also around the world.

Health literacy – concept development

Returning to health literacy, the concept itself began to develop intensively in the late 1990s. It was then that an attempt was made to define the concept. Kickbush states that health literacy covers information and knowledge about health, but also understanding the social components of health and the skills, as it is put, to negotiate with the environment, understand and balance the risks of individual and social behaviors, coping skills, the ability to deliver care, use of available health services and implementation of health knowledge [8]. It is worth underlining, that the definition of Kickbush strongly emphasizes the social dimension of health, which suggests the direction in which to go in order to define the concept as fully as possible.

Nutbeam underlines that health literacy is one of the most important challenges and tasks for public health in the 21st century. He states that health literacy is closely related to individual, cognitive and social skills, which constitutes the ability of individuals to access information, as well as understand and use it in order to promote and maintain good health [9]. In Nutbem's deliberations, one can observe a reference to the sense of coherence, therefore it can be concluded that coherence and health literacy are related and interdependent. Nutbeam included three elements among the abovementioned skills:

1. Improving self-sufficiency in the implementation of specific health tasks

This is an element that fits in with the idea of building social responsibility for one's own health. A certain self-sufficiency in this respect is possible only with a sufficiently high level of health awareness and perception. Generating responsibility for one's own health is determined by the individual's perception of health as a value – an individual resource that needs to be achieved and maintained. In the process of building responsibility for one's own health, it should be emphasized that losing it may also have an impact on the living environment of an individual. In the case of neoplastic diseases, at the stage of their prevention, one can talk about increasing one's knowledge about risk factors, and – in terms of secondary prevention – about regular preventive examinations, especially in cases of high-risk medical or family history.

2. Increasing knowledge and understanding of the importance of health determinants

A reference to the definition of health promotion can be observe here, consisting in assigning a special rank to knowledge about the health determinants. The resulting possibility of increasing control over some of them should be the basis for building health literacy. This, in turn, leads to the achievement of the goals of health literacy.

3. Changing attitudes and motivations in relation to health behaviors

Changing health behaviors and attitudes towards health is a long-term process that is not easy to implement [10]. It is associated with difficulties in finding motivation to change negative behaviors. Activities for health can only bring effects if they are implemented consistently and in accordance with the ideas of evidence-based medicine.

In Poland, the concept of health literacy was initially translated as "the ability to read / perceive health". However, with a deeper understanding of the meaning of the concept, slightly more accurate expressions began to be used, such as "health alphabetism", "health literacy", or, which seemed to be the most accurate translation, "health competence" [11].

The proper and complete definition of health literacy is somewhat difficult, because it is a broad concept, encompassing a whole range of behaviors, competences and individual skills.

Taking into account the existing definitions of health literacy and comparing them with the multidimensionality of the concept, it can be proposed to define it as a set of competences and skills in the field of broadly understood health, obtained through the proper use of information sources, allowing to minimize the occurrence and impact of health risk

factors on the individual and the living environment in order to improve and maintain good health.

As can be deducted, the level of health literacy is positively correlated with the level of education and health potential. The sense of coherence is important as well. It can also be concluded that the level of health literacy among citizens is the higher the earlier health education begins, which includes not only elements of lifestyle, but also the ability to navigate the healthcare system, or the so-called critical health literacy.

Health literacy in health promotion

From the point of view of health promotion, it is important to use health literacy in practice and place it in projects that pursue the goals of health promotion. Health literacy accompanies health promotion practically at every stage: from the assessment of health needs (a low level of health literacy is evidently a health need), to the evaluation of changes in the level of health literacy among target groups.

Health literacy is still an insufficiently recognized and underestimated issue in Poland, especially in the prevention of diseases, including neoplastic diseases. This may result from some shortcomings in the Polish-language literature and the inability to use it in practice. In order to facilitate the understanding of the meaning of health literacy, one should go back to the perception of health not in the way of salutogenetic concept (which is focued on presence of health) but in the opposite way – from the point of health's absence. Referring to Lalonde's fields (modern health promotion seems to be departing from this concept), which say that lifestyle impacts health in about 50%, it can be concluded that the level of health education, manifested by the type of health-related behaviors, has a decisive influence on individual's health. The level of an individual's education is also determined by many factors. In the era of universal access to data sources (e.g. the internet), not always of evidence-based nature, it depends on the ability to search, select and interpret information related to health. This is where health literacy is used, and more precisely one of its part – the aforementioned critical health literacy. The ability of an individual to make evidence-based decisions about health is one of the measures of health literacy and should be analyzed when assessing health needs for selected groups of the population. The level of this skill can provide an answer to the question about the health potential of the group, and thus facilitate the decision e.g. about the selection of the information flow channel, or, in the case of direct education, about the selection of appropriate teaching methods and about choosing the material with the proper scope and adequate level adjusted to the group's needs and capabilities. Appreciating the importance of the assessment of health needs as an integral part of the implementation of the health promotion program, it is noticeable how important the inclusion of the level of health literacy in such an assessment can be.

By implementing activities and interventions aimed at building broadly understood health awareness in relation to the evaluation phase, it can be argued that, in addition to checking the substantive knowledge (e.g. on a given disease unit), the evaluation should also include examining the level of health literacy, expressed by skills [12].

Bearing in mind the above statement, it can certainly be concluded that the health education of society should be directed to a lesser extent at specific health problems and at providing encyclopedic knowledge, but above all, at stimulating people to acquire it on their own. This fits in with the idea of so-called modern health education, which involves stimulating the society to be active and creating conditions for changing health behaviors, instead of merely providing "dry" theoretical knowledge [3].

It is therefore visible that the degree of public involvement in pro-health initiatives is also a measure of the level of health literacy. We can also reverse the situation and put forward a thesis that the low level of health literacy significantly hinders the involvement of citizens in social life and joint care for increasing access to the healthcare services and safety, and thus the implementation of the idea of health promotion and public health [9].

Regarding the procedure in the prevention of diseases, including neoplastic diseases, one should focus on the issue of using the internet as a source of knowledge about health, which is now a common practice both in Poland as well as worldwide [13, 14]. In the era of universal access to information, it seems natural to search for information online, especially in terms of health. Also in an era of inefficient healthcare infrastructure, patients often use information from websites to try to assess their own health, as well as to interpret the observed symptoms, ending with treatment methods. Keeping in mind that a lot of information available in the discussed source is not evidence based, , health literacy and the ability to apply it in practice, i.e. through the selection of online sources, return to the force.

It can therefore be concluded that building health literacy is one of the main challenges for contemporary health promotion and public health. As one of the elements conditioning social commitment, it significantly facilitates the achievement of health goals in various thematic areas. It should be emphasized that a certain developed scheme of action, which is allowed by the appropriate level of health literacy, can be used to counteract many different health problems. It seems much more beneficial to educate society on how to deal with health issues through the use of a certain proven scheme, than saturating educational content with substantive information. The idea is to generate society's ability to inter alia, the independent search for evidence-based information on given health problems.

One of the necessary conditions for building a high level of health literacy is the so-called information society. It has to

do with access to data, information – in this case about health. In order to define a given society as informational, three conditions must be met:

- the existence of databases, information (including resources contained, for example, on the internet),
- access to the databases in question,
- society's ability to use these databases [15].

In information societies, due to free access to the information, there are more favorable conditions for the development of health literacy, but there are also more threats. They are created by a large number of sources that provide a significant amount of information that an individual may have problems to classify as substantive and trustworthy [16].

Thus, it can be seen that building an information society should go hand in hand with generating health literacy in the community. In an era of dynamic technological development and popularization of access to the internet, i.e., the main source of information about health, it is this medium that should focus on building health competences. It is visible, therefore, that health literacy is a broad concept and there are many ways to nurture this skill. The basis, however, seems to be the information society, i.e., building the idea of e-Health in a broader perspective. This idea offers opportunities when it comes to the health potential of the society, for example by computerization of the healthcare system, like the electronic registration system. This has a positive effect, for example, on access to services and waiting times for appointments.

In terms of access to services, health literacy is used, for example, when searching for medical facilities in which the waiting time for a visit to a specialist is the shortest, i.e. it is manifested by lack of "attachment" to one facility. However, this is related, firstly, to the fact that the choice of the medical facility in which the patient wants to be treated is his or her right (some patients in Poland are still convinced of the regional limitation in delivering medical services through public system, which shows gaps in basic knowledge about healthcare system in general), and secondly, the ability to find a facility in which the waiting time for an appointment may be shorter. It should also be emphasized that behavior consisting in canceling scheduled medical appointments, where the patient can't be present, is also a component of health literacy, expressed in pro-social behavior, i.e., freeing space for another patient – the ability to be sensitive to the health needs of other member of the local community.

Building a high level of health literacy is accompanied by many dependencies and changes. It is a slow and long-term process, but it is worth investing in its development. This facilitates the implementation of the idea of making people responsible for their own health, which is also an activity toward improving the functioning of the healthcare system. It may be manifested, for example, by a greater tendency to implement secondary prevention by carrying out regular preventive health check-ups.

The need for social responsibility for health is also emphasized by the World Health Organization (WHO), inter alia in the Jakarta declaration of 1997 [17]. Special attention should also be paid to health literacy in the context of different groups of the population. This mainly concerns school-age adolescents and pregnant women, as well as young mothers, and groups at higher risk of developing a given disease (e.g. cancer). In case of adolescents, it is about searching for information on risky health behavior, including intoxication with psychoactive substances.

For young people, the Internet is a source of information about methods of intoxication, or about the way of using various types of substances, ranging from designer drugs, to medications (mainly from the OTC group), to induce intoxication. The sources of such information are most often internet forums and closed groups of social networking sites. These sources contain a type of instruction, but do not indicate health consequences, creating a false sense of security [18].

Conclusions

Summing up, the construction of high-level health literacy and the implementation of all ideas and projects serving it should be considered a priority task for central and local authorities. With the support and involvement of international institutions such as the European Union or the World Health Organization, it is possible to achieve visible health effects faster, also in terms of cancer prevention. Local communities can benefit from it, and it can also translate into economic effects in the form of increasing the efficiency of the system, for example in the context of the rational use of resources, or reducing costs due to the earlier detection of health problems.

It is also worth noting that building health promotion strategies on each level (whether at a local of central level) related to oncological diseases, including high level of health literacy, should be treated as a priority, because no healthcare system will function properly without conscious and well-educated patients.

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Dominik Olejniczak
Medical University of Warsaw
ul. Żwirki i Wigury 61
02-091 Warszawa, Poland
e-mail: dolejniczak@wum.edu.pl

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Editorial

Photo: archives

Starting this year 2023, we are launching a new section of *Nowotwory. Journal of Oncology*, the official journal of the Maria Sklodowska-Curie National Research Institute of Oncology and the Polish Society of Oncology, entitled ***Cancer epidemiology,*** which I have the honor to edit.

The *Cancer epidemiology* section aims to publish research that gives new insights into the distribution of cancer incidence and mortality, time trends, and prognosis. We also encourage papers on etiology, survivorship, and surveillance of cancer incidence. Both descriptive and analytical epidemiology research is welcome.

In the presented issue, you will find a paper entitled *Morbidity and mortality trends of the most common cancers in 1990–2019. Poland's position compared to other European countries* written by the team of professor Joanna A. Didkowska, Head of the National Cancer Registry. In the upcoming issues in the *Cancer epidemiology* section, you will find papers on lung cancer and environmental exposure by Dr. Mark Parascandola from the American National Institutes of Health in Bethesda; on cancer mortality among the elderly in Poland by Dr. Dana Kristjansson from the Norwegian Institute of Public Health in Oslo; and many more. We are also planning to publish, once yearly, the digest from the National Cancer Registry with the latest data on cancer incidence and mortality in Poland.

I wish you interesting and pleasant reading, and cordially invite everyone interested in the topic, to submit work.

Marta Mańczuk
Section Editor
Cancer epidemiology

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Cancer epidemiology

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Morbidity and mortality trends of the most common cancers in 1990–2019. Poland's position compared to other European countries

Marta J. Miklewska[1, 2], Klaudia Barańska[1, 3], Urszula Wojciechowska[1], Urszula Sulkowska[1], Jerzy E. Tyczyński[1], Joanna A. Didkowska[1, 4]

[1]*Polish National Cancer Registry, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Dietetics, Institute of Human Nutrition Sciences, Warsaw University of Life Sciences, Warsaw, Poland*
[3]*Faculty of Biomedical Engineering, Silesian University of Technology, Zabrze, Poland*
[4]*Department of Epidemiology and Cancer Prevention, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction. The purpose of the study was to evaluate the trends in morbidity and mortality of the selected cancer sites in Poland against other European countries.

Material and methods. Countries for analysis were selected based on geographical location. Estimates of age-adjusted incidence and mortality rates were calculated using the new European 2013 standard population. Lung, colorectal, breast, and prostate cancers were chosen. Time trends for age-standardized rates were analyzed using Joinpoint Regression software.

Results. Poland differed from other analyzed countries mainly in terms of cancer mortality. Poland is a country with one of the smallest amounts of current expenditures on health care per capita, which translates into one of the highest levels of cancer mortality in both women and men.

Conclusions. Compared to other countries, Poland's cancer outcomes on population level are unsatisfactory. The situation may improve with the introduction of educational and screening programs.

Key words: mortality, morbidity, Europe, neoplasms, Poland

Introduction

Poland is a country that differs from other European countries in terms of low morbidity (breast, prostate, and colorectal cancer) and higher mortality. In 1989, after decades of being a part of the so-called "Eastern bloc" influenced by the USSR, Poland was the very first country from Central and Southeastern Europe to adopt economic reforms and separate itself from the centrally planned economic system. In the Soviet model of health care (the so-called Semashko model – named after the first Minister of Health in the USSR [1]) every citizen was guaranteed universal access to healthcare and medical services, funded by the state budget. The model was replaced with a mandatory health insurance system (the National Health Fund [NFZ] – the payer in the system), complemented by financing from central and local budgets. In Poland and other countries of the region, the perception of health

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by an individual has changed since the end of dependence on the Soviet Union [2, 3].

Incidence and mortality rates are influenced by risk factors that vary not only by the type of cancer but also by geographical location, ageing and growth of the population, sex and reproductive patterns, or factors associated with socioeconomic development [4]. In this paper, factors that may influence the different course of trends in morbidity and mortality have been evaluated, as well as, most importantly, national-level activities such as screening and preventive programs. For many years, lung, colorectal, prostate, and breast cancers have presented as the most common types of cancer in Poland (45.6% of all incident cases in 2019) and in Europe (49.5%) [5, 6].

The purpose of the analysis was to evaluate the trends in morbidity and mortality of the cancer sites mentioned above in Poland against European countries located in the same region and with a similar economic history, and, as a context, countries with a long history of democracy and a market-based economy.

Material and methods

Selection of countries

Countries for analysis were selected based on geographical location – Central and Western European Countries were chosen. An additional inclusion criterion was the existence of a national cancer registry. The final list of countries included in analysis is as follows: Austria, Czechia, Denmark, Estonia, Latvia, Lithuania, Poland, Slovakia, Slovenia, and Sweden.

Selection of sites

The neoplasms for analysis were selected based on the most common incidence and mortality in the Polish and European populations. Lung (ICD-10 C34), colorectal (C18–C21), breast (C50), and prostate (C61) cancers were chosen. Data for all cancer sites combined was also used in the analysis. For all sites, incidence data included C00–C97 neoplasms.

Data sources

Data was provided for all populations separately by sex. All data for the analysis presented was obtained from June to November 2022. The authors sent a request for data to institutions that oversee cancer data collection in the selected countries (see below for details).

Poland

Data on incidence was collected from the Polish National Cancer Registry [7] (1990–2019) and data on mortality from Statistics Poland [8] (1990–2019).

Austria

Data for Austria (1990–2019) was sent at the request of the Authors. Indicated data source was The National Statistical System of Austria [9].

Czechia

Incidence and mortality data (1990–2018) for single or grouped sites (C18–C21, C34, C50, C61) was retrieved from the official web portal on Epidemiology of Malignant Tumors in Czechia (SVOD) [10]. The SVOD project did not contain data about all cancer sites as a group. All cancer incidence data (1990–2016) was obtained from the European Cancer Information System (ECIS) [9], whereas mortality data (1990–2016) from the International Agency for Research on Cancer (WHO Cancer Mortality Database) [10].

Denmark

Incidence and mortality data in Denmark (1990–2019) was retrieved from the NORDCAN (Association of the Nordic Cancer Registries) database [11].

Estonia

Incidence and mortality data in Estonia (1990–2019) was collected from the ANDMEBAAS Health Statistics [12] and the Health Research Database and from the International Agency for Research on Cancer (WHO Cancer Mortality Database) [13] (1990–2018).

Latvia

Incidence data in Latvia (1996–2017) was retrieved from the register of patients with particular diseases regarding patients with oncological diseases from The Centre for Disease Prevention and Control of Latvia. Mortality data (1996–2017) was calculated based on the number of deaths from the Database of Causes of Death of Inhabitants of Latvia, The Centre for Disease Prevention and Control of Latvia. Data for the Latvian population was sent on request (the Central Statistical Bureau of Latvia was indicated as the source).

Lithuania

Data for Lithuania was collected from the European Cancer Information System (ECIS) [14] (1993–2012) and the International Agency for Research on Cancer (WHO Cancer Mortality Database) database [13] (1996–2019). Morbidity was excluded from the rate of change comparisons due to the short observation period (1993–2012).

Slovakia

Morbidity data for Slovakia was retrieved from the National Health Information Centre (NHIC) [15] (1990–2010), European Cancer Information System (ECIS) [14] and the International Agency for Research on Cancer (WHO Cancer Mortality Database) [13] database for mortality rates (1996–2019). Morbidity was excluded from the rate of change comparisons due to the short observation period (1990–2010).

Slovenia

Incidence and mortality data in Slovenia were acquired using data from The Cancer Registry of the Republic of Slovenia (CRS) [16] (1990–2018).

Sweden

Incidence and mortality data for Sweden was taken from the NORDCAN (Association of the Nordic Cancer Registries) [11] database (1990–2019).

Statistical analysis

Estimates of age-adjusted incidence and mortality rates standardized using the new European standard population (ASR-European, new E-ASR) from 2013 were used for all countries [17]. If the rates with the European standardization of 2013 were not found in the databases of countries, the data were recalculated by the authors based on the epidemiological and demographic data contained in the databases (Estonia, Latvia, Lithuania). Time trends for age-standardized rates were analyzed using Joinpoint Regression software (version 4.9.1.0) [18]. Annual percent change (APC) and average annual percent change (AAPC) were calculated. The minimum number of observations between two joint points was set at 5. The minimum number of observations from a joint point to either end of the data was set at 3 or 5. It depended on the number of years taken for analysis. The models were restricted to a maximum of 3 joint points. The error option which has been chosen was constant variance (homoscendasticity). P values < 0.05 were considered statistically significant.

Results

A comparison of the morbidity and mortality trends of the sites analyzed in the selected countries is presented in figure 1. Dots represent a point in time at which a trend change (joinpoint) occurred. Figure 2 represents the annual per cent change (APC) of the latest identified linear segment (trend) in incidence and mortality by neoplasm location in the selected countries calculated with the joinpoint regression method. A detailed table with APC values for each period was included in the supplement to the paper.

All sites

Panel A in figure 1 presents morbidity and mortality time trends for all cancer sites. Most countries noted an increase in the incidence among women since the beginning of the observation period, except for Austria. Among men, decreasing trends in incidence of the last observed period were recorded in Austria, Estonia, and Slovenia, but none of them was statistically significant (fig. 2, panel A).

The following patterns of morbidity were observed. The first one is represented by Poland, Czechia, Latvia, Sweden in both sexes and among women in Estonia, Slovenia – raising trends with periodic pace changes. The second pattern applies to Austria (both sexes) and Estonia, Slovenia (men) – the most recent segment of the trend is decreasing, the previous periods show an upward trend. The last curve presenting data from Denmark for women and men remained without change for the last 10 years (fig. 1, panel A). In Poland, the APC for morbidity among men (0.27% annually – fig. 2, panel A) was lower than for women (1.01% annually – fig. 2, panel A).

Overall cancer mortality decreased in both sexes in almost all countries. Only in Latvia was there a statistically significant mortality increase among women (0.14% annually – fig. 2, panel A). The smallest gap between mortality rates among men and women occurred in Sweden and Denmark, where the rates were also the lowest. These countries also had the highest APC rates of mortality decline. In Poland, a greater mortality reduction was observed among men (–1.28% annually – fig. 2, panel A) than in women (–0.59% annually – fig. 2, panel A).

Colorectum

Panel B in figure 1 shows data on colorectal cancer. In half of the countries, there was a downward trend of morbidity in men. An upward trend was observed in the Baltic States (Estonia, Latvia, and Lithuania), Slovakia, and Sweden, but at the same time, Sweden had the lowest incidence rate in men among all analyzed countries. In Poland, the decreasing incidence trend among men was observed from 2015, and APC was not statistically significant. An incidence decrease in women was observed only in 4 countries: Austria, Czechia, Slovenia, and Poland. The longest downward trend was noted in Austria (since 1998).

In all countries, except Poland and Estonia (only among men), a decreasing trend in cancer mortality was observed. The lowest mortality rates for both sexes were noted in Sweden. One of the highest values for the mortality rate in both sexes was observed in Poland compared to other analyzed countries. Similar values as in Poland were noticed in the Baltic States.

For both morbidity and mortality, higher values of standardized rates were observed among men than women.

Lung

In all analyzed countries, the morbidity and mortality rates have been decreasing among men over the years. The mortality trend shows the largest decrease. Among women, trends in morbidity and mortality tended to increase most of the time. Referring to the last observed period based on joinpoints, Denmark showed an outlier among women (decreasing curves for morbidity and mortality), also in Sweden the same tendency for mortality was observed (fig. 1, panel C). The highest APC rate of incidence increase in women was observed in Slovenia. Poland ranked second in terms of the increase in lung cancer mortality in women (2.46% annually – fig. 2, panel C) in the last observed period but had the highest standardized rate in the last analyzed year (38.9/100,000 – fig. 1, panel C). The trend line of morbidity and mortality within sex showed the same tendency – decreasing in men and increasing in women.

The values for morbidity and mortality rates were similar which distinguished them from other cancer trends, in which

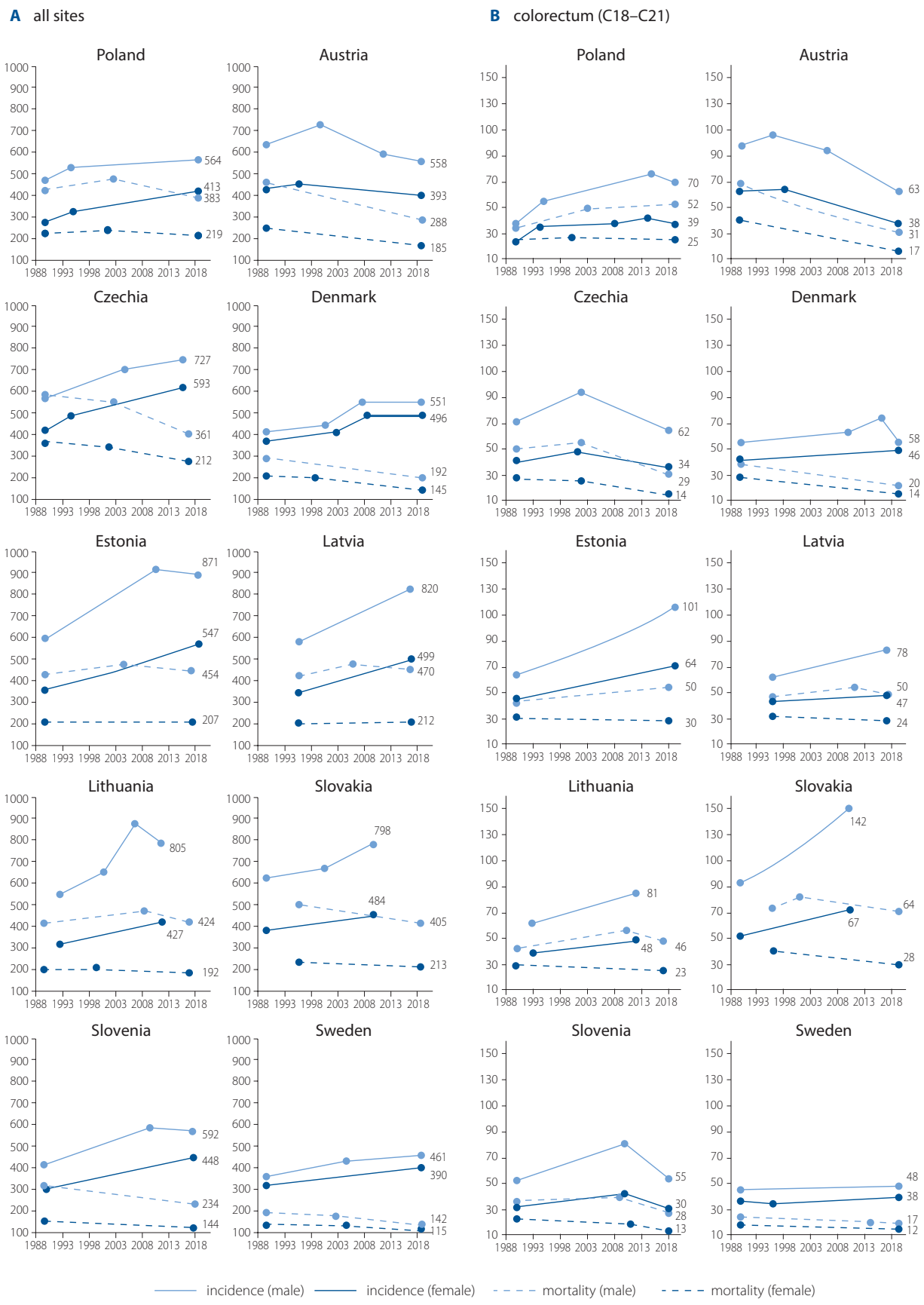

Figure 1. Joinpoint analysis of trends in incidence and mortality among men and women from 1990 to 2019 as per data availability

The values at the last point in the graph represent the actual age-standardized rate in the last observed year. Incidence and mortality in men (light blue) refer to C61 cancer, while incidence and mortality in women (dark blue) refer to C50 cancer.

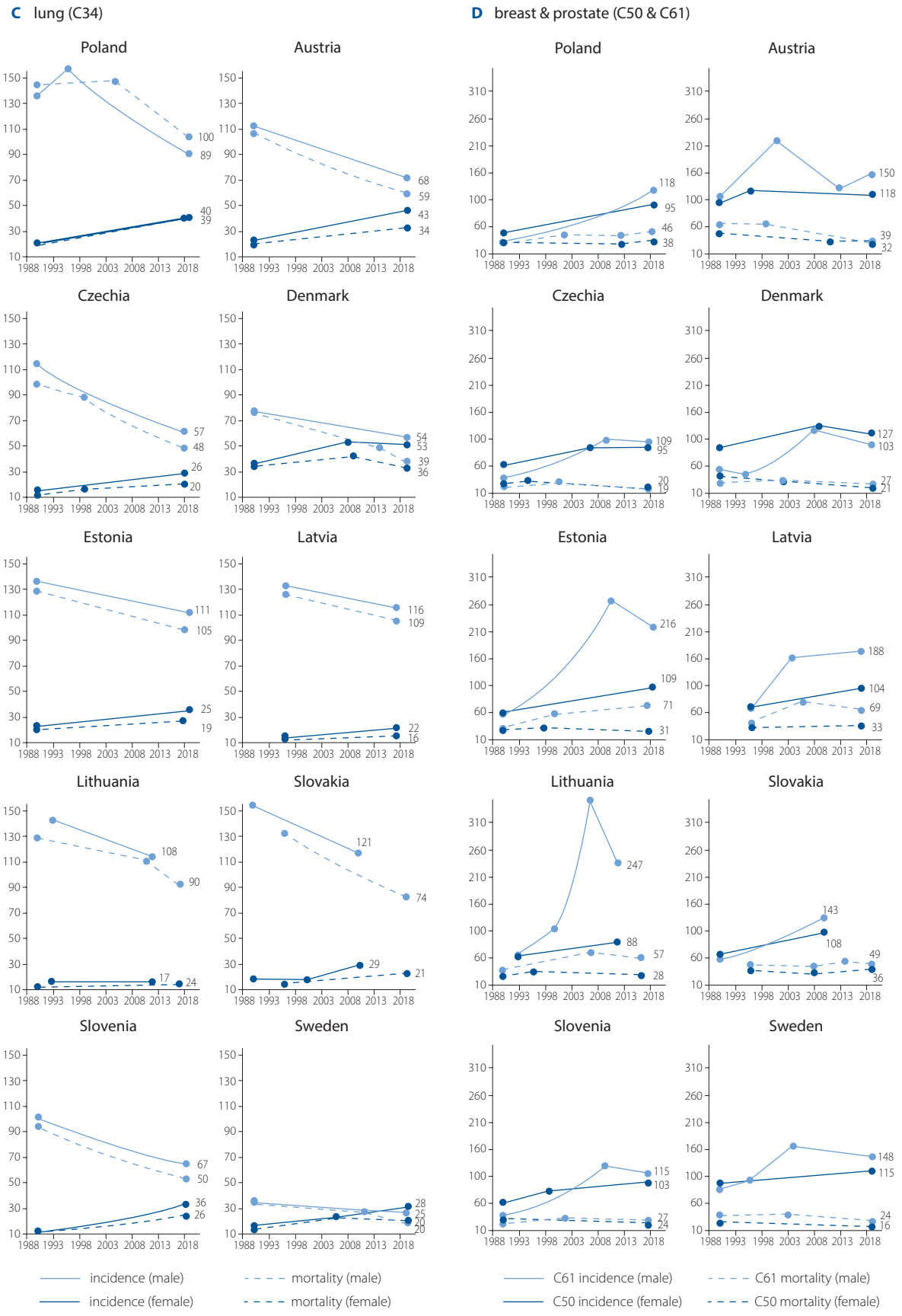

Figure 1. cont. Joinpoint analysis of trends in incidence and mortality among men and women from 1990 to 2019 as per data availability

The values at the last point in the graph represent the actual age-standardized rate in the last observed year. Incidence and mortality in men (light blue) refer to C61 cancer, while incidence and mortality in women (dark blue) refer to C50 cancer

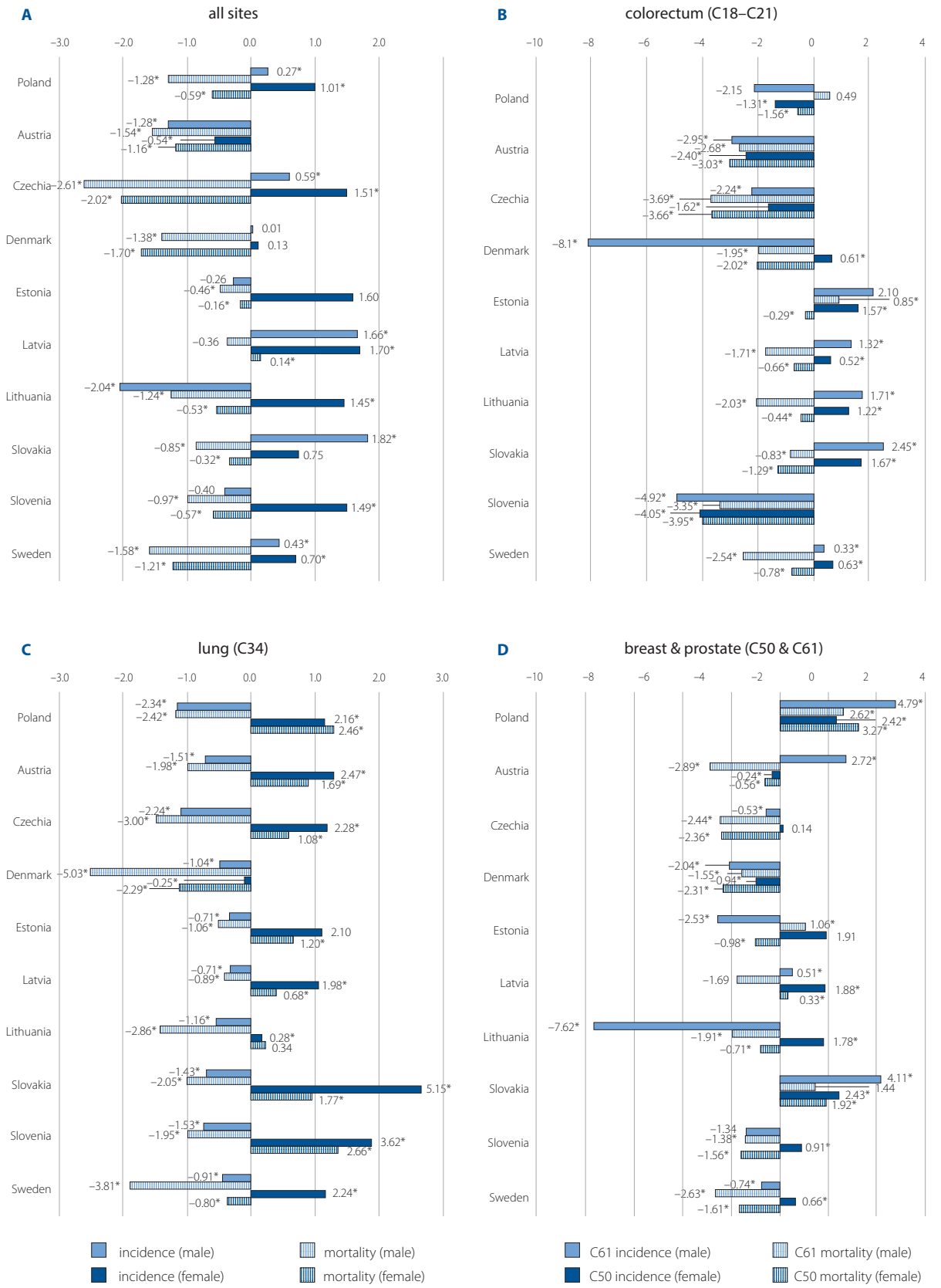

Figure 2. The annual percent change (APC) of the last linear segment identified (trend) in incidence and mortality by neoplasm location in selected countries calculated with the Joinpoint Regression method*

* – indicates that the APC is significantly different from zero at the alpha = 0.05 level. Incidence and mortality in men (light blue) refer to C61 cancer, while incidence and mortality in women (dark blue) refer to C50 cancer

Table I. Comparison of GDP and current healthcare expenditure [20] with mortality in selected countries in 2019

	% of gross domestic product (GDP)	PPS per inhabitant	Mortality, males [E-ASR]	Mortality, females [E-ASR]
Sweden	10.9	3968	142	115
Austria	10.4	4078	288	185
Denmark	10.0	3915	192	145
EU	9.9	3207	–	–
Slovenia	8.5	2361	234[b]	144[b]
Czechia	7.8	2443	361[a]	212[a]
Lithuania	7.0	1949	424[a]	192[a]
Slovakia	7.0	1565	405	213
Estonia	6.7	1792	454[b]	209[b]
Latvia	6.6	1457	470[a]	212[a]
Poland	6.5	1636	383	219

a – 2017; b – 2018

the mortality in both sexes tended to be lower than the morbidity. The unique case was Poland where mortality was higher than morbidity among men since 1999.

Breast and prostate

Breast

All countries, except Austria and Denmark, experienced an increase in breast cancer incidence during the period covered by the analysis. The fastest statistically significant increase of the APC was in Poland (2.42% annually). At the same time, Poland, Slovakia, and Latvia were the only countries where an increase in mortality was observed. Moreover, the highest statistically significant increase in mortality was observed in Poland (3.27% annually).

Prostate

The largest significant increase in the incidence of prostate cancer was observed in Poland (4.79% annually – fig. 2, panel A) with the greatest increase in mortality (2.62% annually). In other analyzed countries, except Latvia, a pattern was noticed in which a rapid increase in the incidence was followed by a sharp decrease.

All countries except Poland, Estonia, and Slovakia recorded a reduction in prostate cancer mortality. The lowest prostate cancer mortality rates in the last analyzed year were in Czechia (26.6 per 100 000) and the highest in the Baltics.

Discussion

Compared to other countries, Poland's cancer outcomes on population level are unsatisfactory. With lower morbidity (except for lung cancer), it had higher mortality.

The gross domestic product (GDP) level has been a factor that has differentiated the health status of societies in the world for many years [19]. This dependence is also visible in Europe, especially in the countries of Central and Eastern Europe when compared with the "old" European Union.

Table I presents the GDP and current healthcare expenditure of the analyzed countries for the year 2019, compared to data on cancer mortality for the same year. There was a considerable difference between the Nordic countries and Austria and the rest of the analyzed countries. Compared to other European countries and the European average, the current expenditure on health care in Poland was comparatively low and the percentage of GDP spent on health was the lowest. The presented data showed negative correlations between GDP and mortality in both sexes.

The funds allocated to health care translate beyond current healthcare expenditure into ways and possibilities of planning long-term healthcare costs expenditure (such as preventive, curative, rehabilitative and long-term care) [21]. The way these funds are allocated is of utmost importance for the health of citizens. The cheapest and most effective action to reduce the health burden of societies is disease prevention. It has been estimated that up to half of the cancer burden is preventable [22, 23]. Two strategies – disease prevention and prevention of premature death – should form the basis of cancer health policy. Health education brings the greatest benefits, as exemplified by the implementation of the European Code Against Cancer (in Western Europe, the first edition of ECAC was presented in 1987) [24].

The spectacular success of primary prevention is demonstrated by the reduction of tobacco smoking and, consequently, a decrease in lung cancer incidence. The introduction of primary prevention in the form of educational campaigns informing about the harmful effects of smoking had a huge impact on the number of lung cancer cases and deaths among

men in developed countries [25, 26]. Throughout the observed periods, morbidity and mortality in women have been increasing in most countries – the only exception is Denmark.

An interesting case is Sweden, where, due to the decreasing incidence trend among men and increasing among women, in the last observed year the incidence rate was higher among women than among men. The phenomenon of the lack of success in reducing smoking among women is mainly psychological [27]. There are no population screening programs introduced for lung cancer, although attempts are being made to implement them [28]. It seems that the greatest emphasis should be placed on supporting women in quitting smoking.

The second type of cancer prevention is early detection of precancerous conditions (secondary prevention), which is possible thanks to the introduction of the policy of preventive examinations. The observed changes in morbidity and mortality in Central European countries are likely the result of different health policies, which is apparent in the timing of the implementation of screening programs. In most countries, screenings for colorectal and breast were implemented, except for Slovakia where such programs have not been introduced at all. PSA screening towards prostate cancer is controversial because of low specificity for prostate cancer detection in symptomatic patients [29].

Many studies have shown that healthy lifestyle factors are associated with a lower risk of developing colorectal cancer [30]. This observation has been implemented in the recommendations of the European Code Against Cancer (ECAC). Simultaneously, ECAC recommends a second form of prevention for this neoplasm – screening for the early detection of polyps in the intestine, which reduces the risk of both subsequent cancer development and death [31]. Colorectal cancer screening was introduced at the earliest in Czechia – In 2000 [32]. The time trends showed a shift in the trend from ascending to descending in the incidence (men and women) and mortality (men) already in 2002, which suggests that there may have been educational campaigns undertaken earlier. A clear effect of the screening implementation could be seen in Austria (introduction date 2002), Slovenia (2009), and Denmark (2014) [32], where there was a reduction in mortality after the introduction of screening. In Sweden, no clear differences in morbidity and mortality trends were observed after the introduction of screening (2008) [32], however, in this country, mortality from the beginning of the observed period had a downward trend and the mortality rate value in the last year of observation was the lowest among all the countries surveyed. Poland introduced a screening test policy in 2012 [32]. Poland and Estonia were the only ones in the analyzed group to have growing trends in colorectal cancer mortality, while in Estonia the screening program was introduced only in 2016. The European Union study in 2019 showed that Denmark, Austria, Slovenia, and Czechia reported the highest percentage of people (in the 50–74 age group) ever screened for colorectal cancer [33]. In these countries, more than two-thirds of respondents took part in preventive examinations. In Poland, about 80% of respondents reported that they had never taken part in such a program [33]. It was the worst result among the countries analyzed in this paper. The low level of health literacy has a direct impact on colorectal cancer in Poland. In January 2022, screening for colorectal cancer was abandoned in Poland – the effects of this decision may be observed in the following years, but it can be expected that it will contribute to an increase in mortality among Poles.

Screening with mammography and breast self-examination can help detect breast cancer at an early stage and reduce mortality [34]. The earliest screening program was introduced in Sweden in 1986 [32]. The morbidity and mortality trends in Sweden since this year did not change over time, remaining at the same level, and Sweden had the lowest mortality rate from breast cancer in the last observed year. The second country with a low mortality rate was Czechia, which introduced screening in 2002 [32]. Even by 2001 a decline in mortality rates began, maintaining that trend throughout all subsequent years of observation. In the following year, an increase in morbidity was observed, which persisted for the next 5 years. Subsequently, the incidence rate stabilized at around $100/10^5$. Screening programs have also been introduced in Estonia (2003), Slovenia (2008), Denmark (2008), and Austria (2014) [32]. In these countries, a reduction in mortality caused by breast cancer was noted, although in the case of Austria, due to the short time that had passed since the start of the intervention, this effect cannot be linked to the introduction of screening. A particularly substantial increase in incidence was noted in Denmark, where the rates increased from $137/10^5$ in 2008 (start of screening) to $166/10^5$ in 2009. In Poland, screening was introduced in 2006, but despite the increase in morbidity, a decrease in mortality was not observed. The increase in the mortality rate was the highest in the entire study group (3.27% annually). The other two countries where an increase in mortality was observed were Latvia and Slovakia, but in these countries, the APC was at a much lower level (fig. 2, panel D). Among the countries analyzed in 2019, Poland, Slovakia, and the Baltic countries were below the average European proportion of women having mammography, but at the same time, over 80% of women reported having taken part in screening examinations at least in the last 2 years [33]. In 2016 in Poland, paper invitations to breast and cervical cancer screening stopped being shipped, and an important communication channel with women was lost. The effect of this action has not yet been considered in this analysis.

In the last decade of the 20^{th} century, in some developed countries prostate cancer screening was introduced through the PSA test. The analysis of trends in the discussed countries indicates that the introduction of the PSA test is reflected in the growing incidence rate. The clearest peak of growth

could be seen in the incidence in Lithuania, where in 2006 a program of preventive examinations was started [35]. Large increases in incidence were also noted in Estonia (no population-based program but increased PSA testing [36]) and Austria (intensive screening program in 1990–2002 [37]). In Sweden, Slovakia, and Czechia a population program was conducted until 2003 [38, 39] and in Denmark until 2009 [40].

Currently, doubts are raised that conducting population studies using PSA tests is unjustified and can lead to overdiagnosis [41, 42]. In Poland, there were no population-based screening programs using the PSA test. However, a study was conducted on participation in PSA levels in men participating in the PolSenior population study. It has been shown that about 60% of older men have never had a PSA test. Among younger men (55–59 years), the percentage was 72.2%, and the respondents were more often functionally independent, better educated and married with higher than average personal income and a healthy lifestyle (nonsmoker) [43]. Considering that Poland was the only country with a significant increase in prostate cancer mortality among the analyzed countries, it can be concluded that the effectiveness of treatment is lower in Poland than in other countries. In 2021 the European Commission presented Europe's Beating Cancer Plan focused on four key action areas: prevention, early detection, diagnosis and treatment, and improving quality of life. The European plan assumes that by 2025, 90% of the European Union population that is affected by breast, cervical, and colon cancer will have access to breast, cervical, and colon cancer screening programs co-financed by EU funds [44].

Conclusions

The challenge for Europe is to provide equal access to health care for all citizens. Wide disparities in cancer screening exist across European countries and even between specific regions within a country. One of the fundamental recommendations proposed by The Lancet Oncology European Groundshot Commission is the implementation of screening programs, which has real effects in reducing the burden of cancer and in slowing down or reversing the upward trend in cancer mortality [45]. Screening programs do not include lung cancer, but in this case, due to primary prevention, the rates among men are decreasing through the years.

Compared to Western countries, Poland fares worse both in terms of morbidity and mortality. Poland is a country that has one of the smallest amounts of current expenditures on health care, which translates into one of the highest mortality rates in both women and men. Screening and educational programs in Poland should be supported. On the whole, European education on lung cancer among women should be promoted.

Limitations

A limitation of the study is the unequal amount of available data, especially in the case of Latvia, Lithuania, and Slovakia. Not all data comes from national institutions. Some were taken from the European and WHO databases. Therefore, it was difficult to assess to what extent the analyzed data represented the continuing trend in the following years.

Conflict of Interest: none declared

Marta J. Miklewska
Maria Sklodowska-Curie National Research Institute of Oncology
Polish National Cancer Registry
ul. Wawelska 15B,
02-034 Warszawa, Poland
e-mail: marta.miklewska@pib-nio.pl

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Intraoperative touch imprint cytology of sacro-coccygeal chordoma

Gabriele Gaggero[1], Veronica Parrella[2], Antonio Guadagno[1], Bruno Spina[1]

[1]*UO Anatomia patologica ospedaliera, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Policlinico San Martino, Genova, Italy*
[2]*Division of Anatomic Pathology, Department of Integrated Surgical and Diagnostic Sciences, Scuola di Scienze Mediche e Farmaceutiche, Università di Genova, Genova, Italy*

Chordoma is a neoplasm that originates from the notochord, usually in the sacrum, clivus or vertebrae, and although it grows slowly it can lead to local recurrences and metastases; the treatment of choice is radical surgery. Pre-operative diagnosis is therefore very important and is based on microscopic features: physaliphorous cells in a chondromyxoid matrix and immunohistochemical positivity for brachyury. Such main features are usually seen histologically on a biopsy and sometimes on fine needle aspiration cytology (FNAC), but is only rarely reported intraoperatively [1]. A 56-year-old woman presented with an expansive sacrococcygeal mass of 15 cm in diameter. Radiology showed a lesion of multiloculated appearance, hyperintense in T_2 and hypointense in T_1, suspected to be a chordoma. During surgery, a biopsy was sent for rapid pathological examination to quickly decide whether to proceed with a radical excision: the sample was too small for histology on frozen sections, and it was therefore decided to examine it cytologically with the touch imprint. Microscopy showed cells of medium and large size, also in aggregates, with vesicular and sometimes nucleated nuclei and granular cytoplasms even pigmented; these elements were loosely distributed in a myxoid matrix (fig. 1A–1C). Such cytological features were consistent with a chordoma [1]. After surgery, the intraoperative diagnosis was confirmed: both histology and immunohistochemistry (cytokeratins AE1/AE3+; EMA+; S100+; brachyury+; CK7–; CK20–) were consistent with a chordoma (fig. 1D–1F), making it possible to exclude the main differential diagnoses (chondrosarcoma, metastatic carcinoma, myoepithelial tumors, myxopapillary ependymoma, ecchordosis physaliphora) [2]. Finally, it is noteworthy that the neoplastic cells from the touch imprint were also brachyury-positive, demonstrating its applicability on cytological samples.

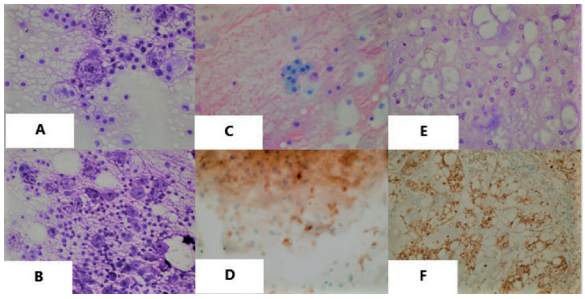

Figure 1. Main microscopic features of chordoma. **A**, **B** – intraoperative touch-imprint shows large cells with central nuclei, a high nuclear/cytoplasmic ratio and a myxoid matrix (toluidine blue staining, 40x and 20x); **C** – intraoperative touch-imprint shows epithelial-like cell types arranged in cords and clusters (PAP staining, 20x); **D** – brachyury immunohistochemical positive staining on cytology (20x); **E** – histology confirmed epithelioid cells with a central nucleus, granular cytoplasm, physaliphorous cells and myxoid matrix (H&E, 40x); **F** – brachyury immunohistochemical staining on histology (10x)

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An accidental diagnosis of a gigantic gastric GIST in a patient with severe COVID pneumonia

Krzysztof Rostkowski[1], Andrzej Komorowski[2, 3], Krzysztof Korneta[1, 2], Sławomir Bednarz[1, 2]

[1]*St. Queen Jadwiga Clinical Provincial Hospital No. 2 in Rzeszow, Rzeszow, Poland*
[2]*Department of Surgery, College of Medicine, Univeristy of Rzeszow, Rzeszow, Poland*
[3]*Department of General Surgery, Edmund Biernacki Specialist Hospital, Mielec, Poland*

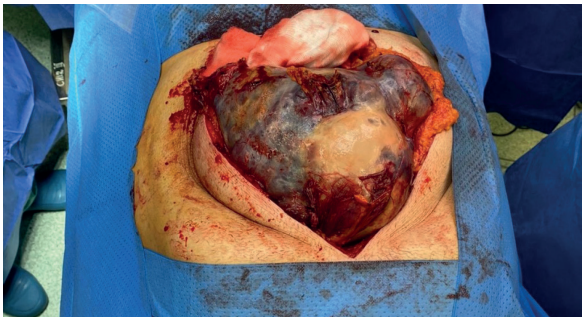

Figure 1. Intraoperative view after laparotomy

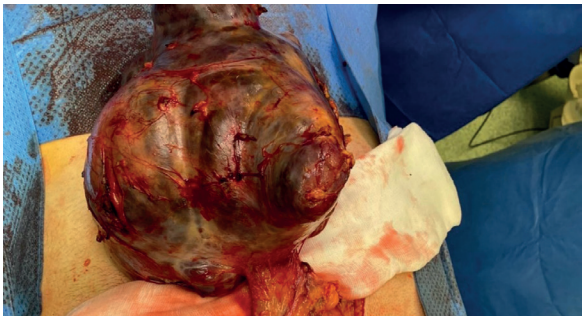

Figure 2. The tumor arising from the stomach after dissection is clearly seen

A 58-year-old male was admitted to the internal medicine ward during the COVID pandemic due to the progression of respiratory failure related to a COVID-19 infection. Upon performing a chest CT scan, apart from the typical COVID-related pneumonia, part of a large abdominal tumor filling the upper abdominal compartment was noted. Once the respiratory symptoms were under control and the patient became stable, the abdominal CT was performed showing a borderline resectable tumor of uncertain origin. Two months after discharge from the internal medicine department, the patient was admitted to a surgical ward. A laparotomy was performed during which a gigantic tumor arising from the greater curvature of the stomach was seen (fig. 1, 2). A partial gastric wall resection *en bloc* with the tumor was performed. The patient made an uncomplicated recovery and was discharged 4 days after surgery. On the histopathology report, a 24 cm x 21 cm x 15.5 cm gastrointestinal stromal tumor arising from the gastric wall was diagnosed. Immunohistochemistry reported that the tumor cells were positive for CD117, CD34 and negative for SMA, desmin and cytokeratine. The risk stratification was established at 12%. Surgery is the mainstay of GIST treatment. The diagnosis is usually made by imaging and endoscopic studies. The objective of the operation is R0 resection but multivisceral resection and surgery with major functional sequelae are discouraged [1]. Abdominal surgery in a patient with active or recent COVID infection has a higher risk of pulmonary complication and higher mortality [2].

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