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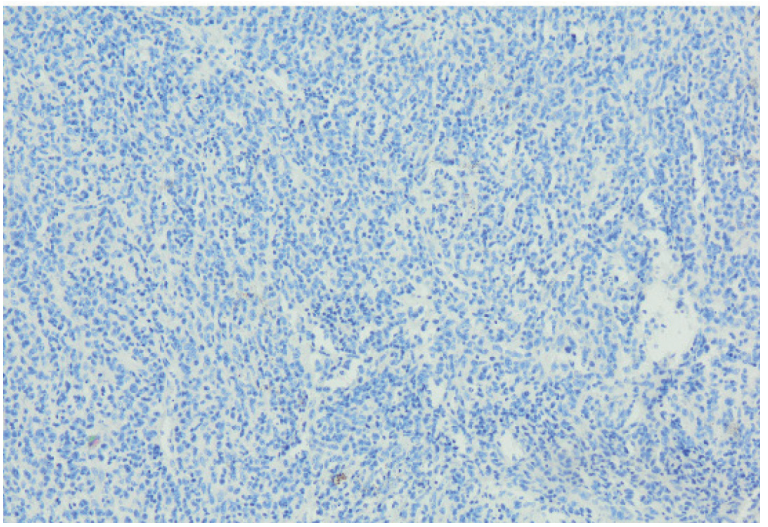

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Breast-conserving surgeries in HER-positive breast cancer patients are performed too rarely in Poland

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Breast cancer is the most common cancer among women in Poland and worldwide; after lung cancer it is the second highest cause of death among females with malignancies. HER2 positive breast cancer occurs in ca.15–20% of all cases. More often than other subtypes, it affects younger patients and more often spreads metastasises to internal organs. The new drugs against the HER2 receptor significantly improve patients' prognoses, regardless of the initial stage.
The authors of the study involved 1503 patients with HER2 positive breast cancer from all stages (I–IV); 482 patients received preoperative systemic therapy (chemotherapy or hormonal therapy), 385 trastuzumab. Among the 1219 females qualified to surgery, 734 (60%) underwent a mastectomy, 485 (40%) had breast conserving therapy with adjuvant radiotherapy, some of them had preoperative systemic treatment.

Key words: breast cancer, HER2 positive breast cancer, surgery, mastectomy, breast conserving therapy

Introduction

Breast cancer is the most commonly diagnosed cancer in women in Poland and worldwide. It is the second (after lung cancer) most common cause of cancer mortality. The prognosis depends, among other things, on the stage of the disease at the time of diagnosis, the biological subtype of cancer, the general clinical status of the patient, as well as access to different types of therapy [1].

Approximately 15–20% of all cases are HER2-positive cancers, overexpressing the HER2 receptor or amplifying the gene coding for this receptor protein. Compared to other subtypes, this biological subtype is diagnosed more commonly in young

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patients. The average age of diagnosis is approx. 50 years, so it is clearly lower than in the general breast cancer population. The predominant location of distant metastases in HER2-positive breast cancer is the liver and central nervous system [2]. Over the past few years, new HER2 inhibitors have significantly improved the efficacy of treatment of both early and advanced forms of the disease. The therapy now considered most active is the dual blockade of pertuzumab and trastuzumab, anti-HER2 monoclonal antibodies, combined with chemotherapy. This is the standard in preoperative care for HER2-positive breast cancer patients with a primary tumour diameter exceeding 2 cm or with metastases to axillary lymph nodes. The prognosis of patients is improved when a complete pathological response (i.e. the absence of invasive cancer cells in the post-operative specimen) is achieved as a result of preoperative treatment [3]. Effective neoadjuvant therapy increases the likelihood of breast-conserving therapy.

A question arises as to whether the increasing effectiveness of preoperative treatment, leading to downsizing of the primary tumour and downstaging of the tumour status, entails a real change in the proportion of breast cancer patients treated with conserving therapy in Poland. Therefore, this article presents data on the type of breast surgeries performed in HER2-positive breast cancer patients treated in selected national cancer centres between January 2014 and July 2017.

Material and methods

The study analysed retrospectively collected clinical data from 1503 HER2-positive breast cancer patients treated across 7 Polish cancer centres (Wielkopolskie Centrum Onkologii [*Greater Poland Cancer Centre*], Centrum Onkologii w Warszawie [*Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw*], Białostockie Centrum Onkologii [*Białystok Oncology Centre*], Mazowiecki Szpital Onkologiczny Wieliszew [*Masovian Oncological Hospital in Wieliszew*], Opolskie Centrum Onkologii [*Opole Oncology Centre*], Oddział Onkologiczny z Pododdziałem Hematologicznym Wojewódzkiego Szpitala Zespolonego w Koninie [*Department of Oncology with the Hematology Section at the Regional Polyclinical Hospital in Konin*], Szpital Uniwersytecki w Krakowie [*Krakow University Hospital*]) between January 2014 and July 2017. The doctors from the centres completed a questionnaire prepared and distributed by Roche, which included age as a categorised value (<40 years of age, 41–50, 51–65, 66–75, >75 years of age), patients' body weight, stage of the disease at the time of cancer diagnosis, and course of treatment including type of systemic treatment, surgery and adjunctive radiation therapy. All patient data was anonymous and gathered collectively, i.e. the responders stated how many patients in each centre meet the criteria of each question in the questionnaire. This method of data collection prevents tracking of the individual patients' survival status.

The questionnaire also asked the participating doctors for their opinion about potential qualification for therapies not reimbursed in Poland at the time concerned, provided that such therapies were feasible in specific patients. These therapies were meant to include the combination of trastuzumab and pertuzumab in preoperative treatment and in treatment of generalised disease, as well as the combination of trastuzumab and emtansine in the treatment of advanced breast cancer. This paper selectively presents the results of an analysis of data concerning the surgical treatment method.

All patients enrolled in the study were more than 18 years old and they were of good performance status (i.e. ECOG 0–2, Eastern Cooperative Oncology Group).

Results

More than ¾ of the study group were over 65 years of age, which is typical of the HER2-positive breast cancer population. The age structure of the study group is presented in figures 1 and 2.

The majority of the study group were patients with early breast cancer, accounting for 68% of the total group (331 patients with TNM stage I and 688 patients with TNM stage II, representing 22% and 46% of the total group, respectively). 327 patients (22%) had been diagnosed with stage III cancer, and 157 patients (10%) had been diagnosed with stage IV cancer. (tab. I). In the group of women with distant metastases at study entry, the majority (62%, n = 98) were patients with primarily generalised disease, while 38% of them (n = 59) had a relapse

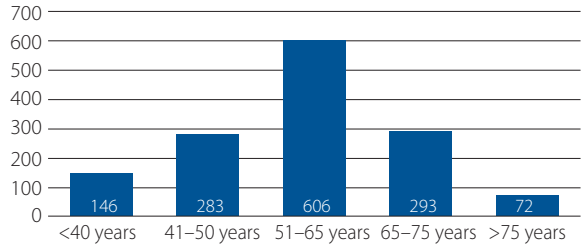

Figure 1. Classification of patients by the presented age categories, data for 1400 patients

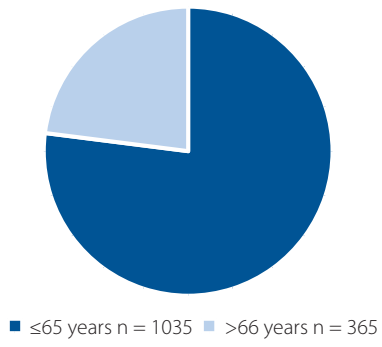

Figure 2. Classification of patients by two age categories, data for 1400 patients

of the disease after radical treatment. For the last mentioned subgroup of patients, the baseline advancement stage was unknown; therefore, the analysis classified them as stage IV.

Part of the patients (n = 482) received preoperative systemic treatment: chemotherapy, hormone therapy and trastuzumab therapy. Chemotherapy was used in more than half of the patients, and the proportion of patients treated in this way was higher in the stage III group than in the stage II group (68% and 50%, respectively). Trastuzumab was used in approximately 60% of patients, and its use was equally common in stage II and III patients.

Of all patients qualified for primary surgery or for systemic treatment followed by surgery (1219 patients in total), 734 (60%) underwent a mastectomy and 485 (40%) received conserving therapy (fig. 3).

Table I. Patient classification by breast cancer advancement stage (TNM), n = 1503 (100%)

Clinical advancement stage	Number of patients	%
I		22%
T1N0	331	
IIA	397	26.4%
T0N1	2	
T1N1	113	
T2N0	282	
IIB	291	19.4%
T2N1	248	
T3N0	43	
IIIA		6.9%
T3N1	103	
IIIB	170	11.3%
T1N2	30	
T2N2	37	
T3N2	31	
T4N2	72	
IIIC	54	3.6%
T1N3	14	
T2N3	19	
T3N3	8	
T4N3	13	
IV	157	10.4%
primary generalisation	98	
relapse	59	

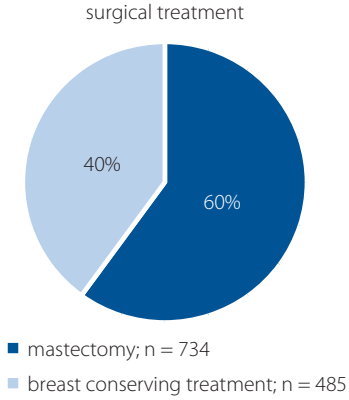

Figure 3. Breast surgery treatment methods, n = 1219

In the group of patients who underwent preoperative systemic treatment (n = 413), mastectomy was significantly more common in patients with a higher stage of disease at baseline. In stage II patients (n = 174), mastectomy was performed in 59% of the cases (n = 102) and conserving therapy was used in 41% of the cases (n = 72); whereas in stage III patients (n = 239), these methods of treatment were used in 83% (n = 199) and 17% (n = 40) of the cases, respectively (fig. 4). More than half of the patients (54%, n = 806) underwent primary surgical treatment. These were exclusively patients diagnosed with stage I and II of the disease. Also in this group, mastectomies was performed more frequently than breast-conserving therapy (54%, n = 433 and 46%, n = 373, respectively).

Discussion

Having analysed the data presented above, it should first be noted that the proportion of advanced cases of the disease is not as high as mentioned before in the report from the Polish Society for Research on Breast Cancer, where it was claimed to exceed 50% [4]. In contrast, the analysed material, involving a total of >1500 patients, showed that 2/3 of patients were diagnosed with stage I and II disease (1019 patients in total). Therefore, it could be expected that the proportion of patients receiving conserving therapy would be high in this group. That said, conserving therapy was performed in only 40% of patients out of 1219 patients qualified for surgery. It is worth highlighting, however, that conserving therapy was more common in patients with lower stages of the disease. Because the data was gathered collectively and analysed as a whole, individual patients' survival status could not be tracked. Since the questionnaire did not provide details about surgical qualification, it was not possible to determine the reasons for the relatively low proportion of patients who had conserving therapy administered. This proportion differs significantly from the level of 60–80% which is recommended by international scientific societies [5, 6].

However, the proportion of patients treated with a breast-conserving approach should not be indiscriminately accepted as an independent indicator of the quality of treatment of

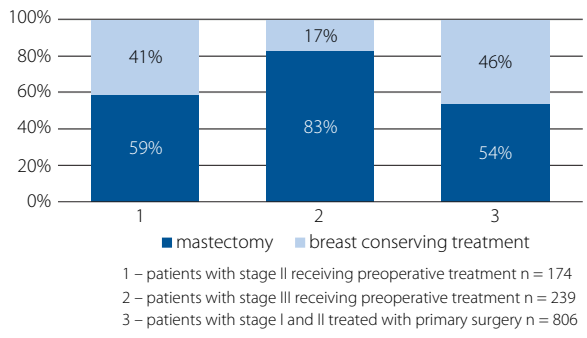

Figure 4. Surgical treatment methods according to advancement stage at baseline and preoperative systemic treatment, n = 1219

breast cancer patients in Poland. Current analysis from Australia and New Zealand indicates that in these countries also, where a modern and efficient healthcare system is implemented, the recommended values of the indicator mentioned above or other similar quality measures are not universally met and are often below the desired levels [7]. However, notwithstanding this observation, reference should be made to last year's ESMO recommendations, which clearly state that 'breast-conserving surgery is the primary surgical choice for breast cancer' [6]. In Poland, as indicated by the presented results, the proportion of breast-conserving procedures is still relatively low, despite the fact that in 2/3 of patients, the disease was diagnosed early.

Nonetheless, the observed proportion of conserving procedures, although not satisfactory, is twice as high as that observed in previous years. Data from 2005 to 2007 indicates that breast-conserving therapy was used in Poland at that time in approx. 21% of cases (with geographical variation ranging from 10% to 30%) [8]. From this perspective, significant progress can be observed.

It should also be noted that in the study period, the preoperative targeted therapy was not used in HER2-positive breast cancer patients in Poland. On 1 January 2017, this type of therapy started to be reimbursed from public funds under the drug programme of the National Health Fund. Since that time, trastuzumab combined with chemotherapy could be used in HER2-positive breast cancer patients if the size of the primary tumour was at least 2 cm or there were metastases to axillary lymph nodes. Since only a few months ago, the combination of trastuzumab and pertuzumab plus chemotherapy has been reimbursed, which is the combination recommended for neoadjuvant treatment of HER2-positive breast cancer by both the European and American oncology societies [6]. Before that time in Poland, patients received HER2 antibodies only after surgery, and if initial systemic treatment was required due to high stage at baseline, only chemotherapy was administered. It is possible that these limitations might have played a part in the reduced efficacy of preoperative treatment and might have resulted in higher incidences of mastectomy, although this is merely a hypothesis. Meta-analysis of 5 randomised clinical trials showed that the addition of trastuzumab to preoperative chemotherapy increased the likelihood of achieving a complete pathological response without increasing treatment toxicity; however this did not translate into reduced incidence of mastectomy [9].

The efficacy of treatment in breast cancer patients depends on, among other things, a well-organised and properly functioning breast cancer unit (BCU), and a structure which unites specialists across multiple diagnostic, treatment and broad patient care (psychological support, rehabilitation) fields. In Poland, the first accredited BCU was established in Szczecin in 2013, the second – in Kielce in 2015, and since 2017, the Senologic International Society has accredited 5 further units: Bydgoszcz (2017), Krakow (2017), Gdynia (2018), Warsaw (2018) and Opole (2019). The improved quality and efficacy of diagnostics and treatment within a BCU is linked to the close cooperation between specialists in different fields, who make collaborative decisions about different stages of patient management. Year-on-year, there is a growing number of accredited units that declare to perform at least 70% of breast-conserving surgeries in cancer patients. In recent years, BCUs in Poland have seen significant improvement in the availability and quality of oncoplastic procedures. Active units are subject to regular evaluation and, once specific criteria are met, reaccreditation.

In recent years, many European countries have seen a desired trend towards an increased number of conserving surgeries at the expense of mastectomies. Between 2005 and 2010, the number of mastectomies was observed to decrease by approximately 4% a year, whereas the average proportion of conserving surgeries accounted for 73% of the observed total surgeries. A different trend is observed in the USA, where the number of bilateral mastectomies increases – especially among younger patients, and the number of breast-conserving surgeries decreases, whereas the proportion of unilateral mastectomies remains stable. This phenomenon can be explained by, among other things, the increased popularity and availability of genetic tests and bilateral mastectomies being performed in breast cancer patients who are known carriers of *BRCA1/2* germinal mutations. It is also often mentioned that patients' preference to undergo a bilateral mastectomy is attributed to a sense of increased safety after both breasts are removed. Such a perception is quite common, as is the perception of greater efficacy of unilateral mastectomy compared to surgery that conserves the breast. It should be noted, however, that prognosis after conserving surgeries and mastectomy is comparable due to the increasing efficacy of adjuvant treatment [10]. In this context, it is extremely important that patients must be thoroughly informed about the benefits and possible complications of different procedures. The misconception among women that mastectomy is a less risky procedure compared to conserving therapy is alarming; it indicates the need to properly educate and inform the patient during the informed consent process.

In everyday practice, validated questionnaires, completed by patients before and after surgery (e.g. BREAST Q), may be helpful and provide a valuable source of information on the patient's motivation when selecting the type of surgery, as well as their level of satisfaction after surgery. Conclusions from the analysis of such data should be discussed by the entire team involved in the treatment and rehabilitation of breast cancer patients.

An increase in the number of breast-conserving surgeries depends, among others, on the stage of the disease, systemic treatment, and the availability of oncoplastic procedures carried out by highly qualified surgeons. In HER2-positive breast cancer patients, the addition of pertuzumab to chemotherapy

and trastuzumab has increased the proportion of complete pathological responses, making neoadjuvant treatment more effective [3]. The dual HER2 blockade has been reimbursed in Poland since 2019, and, consequently, it would be desirable to conduct studies into investigating the types of surgeries selected by patients and surgeons.

Conclusions

The presented data shows that the proportion of breast cancer patients treated with breast-conserving therapy is still relatively low in Poland. Breast-conserving procedures are performed in approx. 40% of patients and the data is mainly derived from referencing oncology centres. However, this proportion is twice as high as it was in the last decade.

The introduction of preoperative systemic therapy targeted at the HER receptor may significantly increase the incidence of breast-conserving procedures. Key importance is attached to interdisciplinary collaboration between BCUs and taking the utmost care when informing patients about their planned treatment.

Conflict of interest: none declared

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Testicular cancer risk incidence in perception of young men

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Introduction. Testicular cancer is the most frequently occurring malignant tumour in young men. Self-examination of testicles allows for early detection of the disease. The objective of this paper was to evaluate the level of knowledge concerning testicular cancer among young men.

Material and methods. The study was conducted among 296 students of the University of Warmia and Mazury in Olsztyn.

Results. The majority of students were never previously interested in the issue of testicular cancer. The students were not able to say at what age this type of cancer usually occurs nor did they know the risk factors or symptoms of the disease. Students of Medicine had much more knowledge about testicular cancer than the students from other fields. 91% of the examined men declared that doctors never informed them about the risk of developing testicular cancer and the importance of self-examination of the testicles. 72% of students of faculties other than medical, never searched for any information concerning testicular cancer on their own. Only 29% of students of all faculties perform self-examination of their testicles.

Conclusions. Young man do not have sufficient knowledge concerning testicular cancer and rarely self-examine their testicles. Therefore, it is justified to disseminate more broadly knowledge concerning testicular cancer and to encourage young men to undergo self-examination.

Key words: testicular cancer, self-examination of testicles

Introduction

Testicular cancer accounts for 1.6% of all malignant tumours among men [1]. However, in the age group between 20 and 44, every fourth malignant tumour is testicular cancer. The risk of developing this disease peaks between the age 25 and 30 years old, with about 70% of cases occurring before the age of 40 [1–3]. The incidence rate is still increasing; among young adults it is the highest and in the last 40 years in Poland the incidence rate has skyrocketed with more than a 3-fold increase [4].

The objective of this study was to evaluate the level of awareness of the risk of testicular cancer among young men.

Material and methods

All male students from the University of Warmia and Mazury in Olsztyn were invited to take part in the study. The

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students anonymously filled out a paper or an electronic questionnaire.

Statistical analysis

In order to compare the proportions in specific subgroups, the chi test[2] was performed. The significance level was adopted to be $p < 0.05$. The analysis was performed with STATISTICA software (version 13,3; Statsoft; Poland).

Results

296 students, aged between 20 and 32 (median age: 23 years), of various departments of the University of Warmia and Mazury in Olsztyn took part in the study. The participants were divided into groups depending on their field of study:

- Humanities (78 students: 26%),
- Mathematics (60 students: 20%),
- Life Sciences (59 students: 20%),
- Medical (99 students: 34%, including 50 students of the English Language) (tab. I).

About two thirds of the students of Humanities, Mathematics and Life Sciences (64%, 72% and 77% respondents respectively) had not previously been interested in the issue of testicular cancer. The students of the Faculty of Medicine, however, knew about the subject – this was declared by more than a half of the respondents (61% students of the Polish Language Faculty and 52% of the English Language Faculty respectively). The students of Medicine were more often interested in the issue of testicular cancer than students of other faculties (57% and 28% respectively; $p < 0.001$). People who knew somebody who had suffered from testicular cancer, often paid slightly more attention to this issue ($p = 0.09$) (tab. II).

Fewer than 25% of surveyed students correctly pointed out the age when testicular cancer occurs most frequently, whilst the students of Medicine were more often able to point to the correct age group (48% correct answers among the students of Medicine *vs.* 12% other students, $p < 0.001$).

The majority (68%) declared that they did not know the risk factors of testicular cancer (this rate was the highest among the students of mathematics – 95%). The persons who declared the knowledge of the risk factors, most frequently listed the environmental factors and those connected with the lifestyle (drinking alcohol and tobacco smoking). Nearly a half of the students of Medicine (45%) knew the risk factors (57% students of the Polish Language Faculty and 34% of the English Language Faculty). A significant difference in this respect was observed between the students of the Faculty of Medicine and other faculties ($p < 0.001$) (fig.1).

The question, "do you know the symptoms of testicular cancer?" was answered positively by 61% students of Medicine and only by 17% students of other faculties ($p < 0.001$). The students who declared that they knew the symptoms of testicular cancer mentioned mainly pain and enlargement/oedema of the testicle (57% respondents) as well as a tumour in the testicle (38% respondents).

Only 29% of all surveyed students declared that they perform testicular self-examinations – this rate was the lowest (15%) among the students of Humanities, and the highest (47%) among the Polish-language Medical students ($p < 0.001$). Self-examination of testicles was more often performed by

Table I. The Characteristics of the study group

Characteristics	N 296	% 100
Age: range: 20–32 years, mean age 23, ±2.2 years		
Faculties		
life sciences	59	20.0
humanities	78	26.3
mathematics	60	20.3
medicine – Polish language faculty	49	16.6
medicine – English language faculty	50	16.9
Are you a religious person?		
yes	198	66.9
no	98	33.1
Do you have a sexual relationship with a woman?		
yes	199	67.2
no	97	32.8
Do you have a sexual relationship with a man?		
yes	16	5.4
no	280	94.6
Does your partner touch your testicles?		
yes	117	39.5
no	179	60.5
Has a member of your family or a friend ever suffered from testicular cancer?		
yes	22	7.4
no	274	92.6

± standard deviation

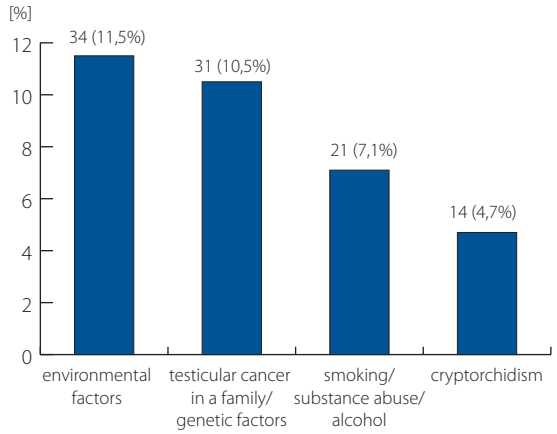

Figure 1. Factors affecting the development of testicular cancer as mentioned by the respondents

men whose friends or family members had testicular cancer (p = 0.02) and those who declared that their sexual partners touch their testicles (p = 0.009). The majority of students who examine their testicles declared that they knew how to perform a self-examination (80%) (tab. III).

The questionnaire showed that a definite majority of the surveyed students (91%) were never informed by doctors about the risk of developing testicular cancer and the necessity of regular self-examination of testicles (tab. II). In general, more than a half of all the respondents (58%) never looked for any information concerning testicular cancer (for students of Humanities, Mathematics and Life Sciences this rate was 72%). Such information was searched for by 73.5% of Polish-language students of Medicine and 52% English-language students of

Table II. The factors which determine an increase of interest in the issue of testicular cancer and self-examination of testicles among young men

Have you ever been curious to find out more about the issue of testicular cancer?					
	yes		no		
	N	%	N	%	p
Total	112	37.8	184	62.2	
Faculties					
– life sciences	21	35.6	38	64.4	<0.001
– humanities	18	23.1	60	76.9	
– mathematics	17	28.3	43	71.7	
– medicine – Polish language faculty	30	61.2	19	38.8	
– medicine – English language faculty	26	52.0	24	48.0	
Has a member of your family or a friend ever suffered from testicular cancer?					
yes	12	10.7	10	5.4	0.09
no	100	89.3	174	94.6	
Do you have a sexual relationship with a woman?					
yes	80	71.4	119	64.7	0.23
no	32	28.6	65	35.3	
Do you have a sexual relationship with a man?					
yes	7	6.3	9	4.9	0.62
no	105	93.7	175	95.1	
Does your partner touch your testicles?					
yes	47	42.0	70	38.0	0.50
no	65	58.0	114	62.0	
Are you a religious person?					
yes	82	73.2	116	63.0	0.07
no	30	26.8	68	37.0	

Table III. The factors which determine an interest in self-examination of testicles among young men

Do you perform self-examination of the testicles?					
	yes		no		
	N	%	N	%	p
Total	86	29.1	210	70.9	
Faculties					
– life sciences	16	27	43	73	<0.001
– humanities	12	15	66	85	
– mathematics	11	18	49	82	
– medicine – Polish language faculty	23	47	26	53	
– medicine – English language faculty	18	36	32	64	

Has a member of your family or a friend ever suffered from testicular cancer?					
yes	11	12,8	11	5.2	0.02
no	75	87.2	199	94.8	
Do you have a sexual relationship with a woman?					
yes	61	70.9	138	65.7	0.39
no	25	29.1	72	34.3	
Do you have a sexual relationship with a man?					
yes	8	9.3	8	3.8	0.06
no	78	90.7	202	96.2	
Does your partner touch your testicles?					
yes	44	51.2	73	34.8	0.009
no	42	48.8	137	65.2	
Are you a religious person?					
yes	56	65.1	142	67.6	0.68
no	30	34.9	68	32.4	
Do you know about the technique of self-examination of the testicles and do you know how to carry out such an examination?					
yes	69	80.2	24	11.4	<0.001
no	17	19.8	186	88.6	

Medicine. These students of Medicine looked for information concerning testicular cancer twice as often as students of other faculties (63 and 31% respectively; $p < 0.001$). They pointed to the Internet as the main source of information, mentioning doctors quite rarely as a source (7%) – the same with medical journals and educational materials (9%). University classes were a source of knowledge for 40% of students of Medicine and for 3% of students from other faculties (tab. IV).

Discussion

Knowledge concerning testicular cancer among adolescents and young men is insufficient: for example young men from Northern Ireland were unable to define the age when testicular cancer occurs; additionally, they did not know the risk factors or the main symptoms of the disease. The respondents considered obesity and excessive alcohol consumption to be the main risk factors [5]. Similar responses were provided by surveyed students of the University of Warmia and Mazury in Olsztyn.

Undescended testes, even if they dropped to the scrotum during childhood, as well as the presence of testicular cancer in a father or a brother are risk factors in the development of testicular cancer [6], yet only 5% of the surveyed subjects regarded cryptorchidism as a risk factor, with only 10% of students pointing to genetic factors. Fewer than 25% of respondents were able to point to the age when testicular cancer occurs most frequently, whilst this rate was lowered down to 13% once medical students were excluded from the group. This rate was similar to the study performed by Khadra et al. (26%) [7].

So far the usefulness of the screening tests for early detection of testicular cancer has not been proven [8–10]. Moreover, there appears no effect regarding self-examination of the testicles on the reduction of disease mortality [8]. The reason for the lack of such an effect may be the very good prognosis, even in more advanced stages of the disease. In spite of this, the European Association of Urology recommends periodical self-examination of the testicles [10], and the American Cancer Society recommends testicle self-examination for males with an increased risk of developing the disease [11]. However, for young men to be willing to self-examine, awareness of the risk and a knowledge of the disease's symptoms is necessary. Young men do not know about the early symptoms of testicular cancer [5, 12]. As many as 58% of respondents in the analysis performed by Ugwumba et al. [13] pointed to a pain in a testicle as a symptom of this disease. The students of the University of Warmia and Mazury provided similar answers: 57% of respondents who claimed to know the symptoms of testicular cancer, pointed to pain as the disease symptom. The fact that an increase in the size of a testicle or a testicular tumour might be a sign of testicular cancer was known to only 19% and 12% of all surveyed students respectively.

A few studies carried out in the 80s and 90s among American students showed that only 25–61% had heard something about testicular cancer and fewer than 20% examined their own testicles [14]. Similarly as in Europe, 87% of students out of more

Table IV. Sources of information concerning testicular cancer

Have you ever looked for any information concerning testicular cancer and if so, where? (more than one answer may be selected)										
faculties	life sciences		humanities		mathematics		medicine – Polish language faculty		medicine – English language faculty	
	N	%	N	%	N	%	N	%	N	%
I never look for such information	35	59.3	55	70.5	45	79.0	13	26.5	24	48.0
I look for this information	24	40.7	23	29.5	15	21.0	36	73.5	26	52.0
radio / television / press	1	4.2	4	17.4	1	6.7	1	2.8	2	7.7
internet	22	91.7	22	95.6	15	100.0	24	66.7	16	61.5
family	0	0.0	0	0.0	0	0.0	2	5.6	3	11.5
friends	0	0.0	3	13.0	1	6.7	2	5.6	3	11.5
school / university	2	8.4	0	0.0	0	0.0	15	41.7	10	38.5
family doctor / GP	0	0.0	4	17.4	3	20.0	5	13.9	1	3.8
other doctors / specialists	0	0.0	3	13.0	1	6.7	3	8.3	1	3.8
medical press / medical leaflets	4	16.8	6	26.1	1	6.7	13	36.1	3	11.5

than 7000 respondents from 20 countries never performed self-examination of the testicles [14, 15]. Some later research showed that more young men knew about testicular cancer, yet still very few of them performed self-examination [5, 16, 17]. In 1999–2001, out of 8000 students from 13 European countries, only 18.2% of them performed self-examination of the testicles [17]. The largest rate of students who self-examined their testicles was in Great Britain (36.3%) and Ireland (34.8%). In Poland, in a group of 359 surveyed students, 16.7% of them declared to perform testicular self-examinations [17]. The study carried out by Peltzer et al. covering more than 2000 students from African countries showed that testicles were examined by only 13.6% of these young men [18]. In the group of students from the University of Warmia and Mazury, 29% of the surveyed men declared that they self-examine their testicles at least once a year, but only half of them make the self-examination once a month.

A British study comprising 1000 patients of a urology outpatient clinic/urology ward, found that as many as 86% of men had never performed a self-examination of the testicles with 15% of them receiving the information about this examination from family doctors while 9% of them learning about it at schools [19]. In the study of Khadra et al. [7], only 16% of men who perform self-examination of the testicles were instructed by the family doctor or a nurse, and 56% of them gained the information from the media. More than half of the surveyed people believed that testicular self-examinations should be taught at school (60% of respondents) and by family doctors (55% of respondents) [19]. Young men themselves, however, are not inclined to take up the subject of testicular cancer with a doctor [5]. In the United States, it is recommended that family doctors provide information about testicular cancer and teach men between the age of 15–35 to self-examine their testicles [20]. It has been proven that men who have more knowledge about testicular cancer, perform self-examinations of their testicles more frequently than others [5, 10, 16]. It was also observed that those who talked with their GP about testicular cancer and were instructed how to perform self-examinations, contacted a specialist sooner and more frequently once they observed any abnormalities in their testicles [21]. Among the students of the University of Warmia and Mazury, 91% of the surveyed subjects claimed that a doctor never informed them about the risk of testicular cancer and never encouraged them to undergo self-examination.

Conclusions

Young men do not have any knowledge about the symptoms of testicular cancer, rarely perform self-examination of the testicles and are not informed by their GPs about the necessity to perform self-examinations. Therefore, knowledge about testicular cancer should be disseminated among young men (for example in school or university classes) and they should be encouraged to perform self-examinations.

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A review of combined treatment strategies for HPV(+), p16(+) oropharyngeal cancer – is de-escalated radiotherapy a convincing and promising paradigm?

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Biological and clinical interest on HPV-associated oropharyngeal cancer (OPC) is rapidly increasing. The genetic and biological characteristics of HPV and p16 expression are presented. The significantly better prognosis (overall survival, locoregional control) of HPV p16(+) OPC patients has been well documented. The leading studies and clinical trials in this field are selected and discussed in details. There is a convincing suggestion that some, low-risk HPV(+) OPC patients might be overtreated. Different approaches with varying degrees of radiotherapy dose de-intensification are critically reviewed and the current de-escalated treatment paradigms are presented and discussed.

Key words: HPV-associated OPC, treatment outcome, de-escalated therapy paradigms

Introduction

Interest in an impact of the HPV status of oropharyngeal cancer (OPC) patients on optimization of therapeutic modalities and on treatment outcome has been intensively growing over the last 20 years, mainly due to the increasing incidence of the HPV(+) OPCs. Retrospective studies and several clinical trials [1–13] have already shown that HPV(+) OPC patients have significantly better locoregional control (LRC) and overall survival (OS) after standard therapeutic strategies than HPV(–) OPCs.

Although tobacco consumption has consistently diminished for over 40–50 years resulting in the decreased incidence of head and neck cancer. In contrast, the age-adjusted incidence rates of the OPCs did not fall, and in fact is continuously and dramatically rising. According to the US Cancer Statistics, HPV(+) OPCs actually comprises most of the head and neck squamous cell cancer patients [14]. Nowadays, the HPV(+) OPCs are recognized as a distant disease with a different molecular profile, radiological and clinical characteristics, and response to therapy [1, 8, 12, 14–17]. It is suggested that HPV status should be considered as a "diagnostic" marker to identify different diseases (not only in the head and neck region) rather than a "prognostic" factor within a "homogeneous" disease [14].

The ICON-S Study [18] showed that in the 7th TNM edition N classification was inadequate regarding prognosis, since there was a minimal separation in the OS among N1, N2a and N2b subsets. The ICON-S consequently proposed to reclassify them into a single N1 category, while bilateral or contralateral neck nodes should be termed as N2. In 2017, this new N classification has been adopted in the 8th TNM edition for the HPV(+) OPCs, and from that time they are recognized as a distinct and new disease [18, 19], whereas T4 or N3M0 diseases are no longer classified as stage IV [20]. Also the WHO introduced "HPV(+) OPCs" as a new disease (19).

The question whether the HPV(+) status of the OPCs might be considered as a prognostic or even a predictive marker, to optimize the treatment strategy for OPCs still remains open.

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HPV OPCs biological and clinical characteristics

The HPV carcinogenesis occurs at the basal cell layer of the oropharyngeal mucosa. It may facilitate the migration of tumour cell foci to underlying lymphatics. This may, at least partially, explain early clinical neck lymph nodes involvement, even in early stages of primary tumours [7, 8, 18].

Among over 130 different identified types of papillomaviruses, with a high risk of the oncogenic HPV p16 is associated with oropharyngeal cancer. The HPV genome consists of a non-coding long-control region, six early genes, two of which (E6 and E7) encode viral capsid proteins and facilitate viral DNA replication. The E6 oncoprotein disrupts normal apoptosis by binding and inactivating tumour suppressor p53, to promote its degradation. The E7 oncoprotein binds and degradates the RB protein. The expression of the E6 and E7 results in the inhibition of p53 – mediated apoptosis (allows the virus to replicate) and is confined to the basal layer, where the stem cells reside and cause abrogation of the cell cycle checkpoint [7, 8, 20–24].

Ang et al. [1] and Shi et al. [25] observed a strong correlation between HPV status and expression of the p16 (established as a biomarker for the function of the HPV E7 oncoprotein), suggesting that p16-expression status is likely a good surrogate for tumour HPV(+) status. This suggestion has been supported by other authors [24–28]. According to Rietbergen et al. [7, 8] epidemiologic analyses revealed the most frequent profile of HPV(+) OPC patients. They are generally younger by about 10 years, more often male, and likely have a history of tobacco and/or alcohol consumption, and have a higher number of sexual partners. The HPV(+) OPCs tend to be poorly differentiated, and mostly occur in the early tumour stage with a relatively more advanced nodal disease. It also seems that this tumour type might have a relatively low level of cancer stem cells.

Superior prognosis (locoregional control – LRC, overall survival – OS) for HPV(+) OPCs, as compared with that for the HPV(–) OPCs has been convincingly well documented in many retrospective, single arm studies and clinical trials. Higher LRC and OS among HPV p16(+) OPC patients may likely reflect higher intrinsic radio-chemosensitivity. Although response rates of the HPV p16+ OPCs to induction chemotherapy are higher than HPV p16(–) tumours [11], single agent cisplatin did not show a different impact on the elimination of occult distant metastases. Ang et al. [1, 17] and O'Sullivan et al. [2, 4] clearly documented the HPV status with respect to tobacco smoking as a major independent prognostic factor for the OPC patients, probably because these factors have an impact on the molecular profile of the cancer, and as a consequence, also on the response to therapy. Although HPV p16(+) OPCs differ from the HPV p16(–) tumours with respect to patterns of loss of heterozygosity, chromosomal abnormalities and gene-expression profiles [8, 14, 20, 22–24, 26, 29], and inversely correlate with poor prognostic markers (e.g. p13 mutations or EGFR expression), Ang [17] and Fahry [11] suggest that no specific mechanism has been found to explain directly the higher rates of response to radiation therapy and chemotherapy among patients with HPV(+) OPCs.

RT and CH-RT efficacy for HPV(+) *vs.* HPV(–) OPCs

Numerous clinical studies, including phase II–III trials, have clearly documented much higher overall survival (OC), progression free survival (PFS) and specific cause survival (SCS) of the HPV(+) OPC patients than those with HPV(–). Moreover, strong agreement HPV status with p16 expression in the OPCs was noted. Analyses performed by Ang and Sturgia [17] and Rietbergen et al. [7, 8], showed a dramatic increase in the discrimination power when OPC patients are assigned to one of the three classes (fig. 1). For

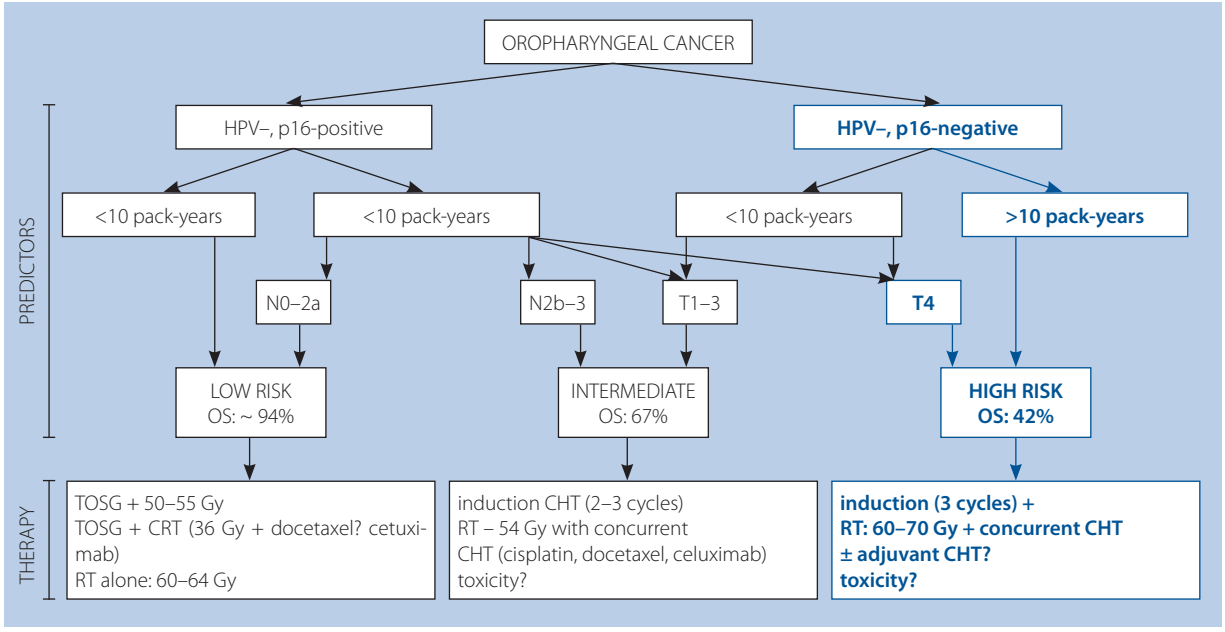

Figure 1. Overall survival of three risk subgroups of the HPV(+) OPC patients. TOSG – transoral surgery; CRT – chemoradiation; CHT – chemotherapy; OS – overall survival

class I patients, with HPV(–) and p16(–), 5-year OS ranged from 35–55%, and 59–69% for class II with HPV(–) p16(+), and 88–94% for class III with HPV(+) p16(+). According to Ang et al. dose rates of OS for the OPC patients with HPV(–) p16(+) dose to those with HPV(+) p16(+) may lead to misclassification of HPV(+) tumours as HPV(–) lesions if the OPCs status would be based on the p16 expression only. Therefore, it seems that tumours status should be expressed by an estimation of both, HPV and p16 markers.

Hong et al. [26] analyzed the impact of a combination of EGFR, HPV and p16 estimates on treatment outcome of about 270 OPC patients after radical treatment. After adjustment for age, year of diagnosis, gender, grade, T and N category and primary site within OPCs, the authors noted that the OPC patients with HPV(–)/EGFR(+) had a 13-fold higher risk of local failure and about a 4-fold higher risk of death than those with HPV(+)/EGFR(–) status. This suggests that the impact of EGFR

Table I. Review of selected studies on treatment outcomes of OPC patients depending on HPV status and treatment strategies

Study	No. cases Stage	Treatment schedules	HPV status	Outcome end-points (follow-up years)				Author(s)
				OS (%)	CSS (%)	LRC (%)	DM (%)	
RTOG 0129 (USA)	**720** OPC + LRX III–IV	72 Gy/42 fx *vs.* 70 Gy/35 fx	**HPV(+)** **HPV(–)** **risk:** low intermed high	82.4 57.1 p < 0.0001 93.5 67.0 p < 0.0001 46.2		86 65 p < 0.001	10 13 p = 0.23	Ang et al. [1, 17] (3 yrs.)
DAHANCA-6, 7 (Denmark)	**331** OPC + LRX I–IV	66–68 Gy/33–34 fx ± nimorazole (Nm)	**HPV** p16+ Nm+ Nm– **HPV** p16– Nm+ Nm–		70 63 p = 0.8 58 40 (p < 0.0001) 42 28 p = 0.02	61 35 (p < 0.001)		Lassen et al. [3] (5 yrs.)
PMH Canada (2011–2013)	**449** OPC, I–IV	60 Gy/25 fx – 70 Gy/35 fx ± cisplatin (concurr.)	**HPV(+)** RT alone CRT (cispl) **HPV(–)**	81 70 89 44	88 80 93 p < 0.001 58	93 90 93 p < 0.001 76	11 12 7 15 n.s.	O'Sullivan et al. [2, 4] (3 yrs.)
PMH Canada (2019)	**289** OPC, T1-2N1-2b	70 Gy/35 fx + cisplatin – weekly cetuximab – infrequent	**HPV(+)** r EN– r ENE+	92 68 p < 0.02		97 93 p = 0.33	5 22 p < 0.001	Billfalk-Kelly et al. [12] (2 yrs.)
UCLA (phase III) (USA)	**45** OPC, III–IV	induct. CHT (2 cycles paclitaxel + carboplatin) + 54 Gy/27 fx	**HPV(+)**			95	2	Chen et al. [5] (2 yrs.)
ECOG 1308 (phase II – USA)	**90** OPC, T1-3N0-2b	induct. CHT paclitaxel, cispl, cetuximab + 54Gy/27fx	**HPV(+)** <10 pck. tabac. >10 pck. tabac.	96 95 p = 0.04 71		78		Marur et al. [6] (3 yrs.)
Vrije Univ. Amsterdam (Denmark)	**723** OPC, II–IV	surgery + RT, RT alone CHT (various schedules)	**HPV(+)** **HPV(–)**	82.2 51.8 p < 0.0001				Rietbergen et al. [7] (3 yrs.)
TROG 02.02. (Australia)	**185** OPC + LRX II–IV	70 Gy/35 fx + Cispl 70 Gy/35 fx + tirapazamine	**HPV, p16(+)** **HPV, p16(–)**	91 74 p < 0.0001				Rischin et al. [9] (2 yrs.)
TAX 324 (USA)	**264** OPC + LRX III–IV	induct. CHT (3 cycles) docetaxol, cispl, 5-Fu + 70–75 Gy/7.5 wks.	**HPV(+)** **HPV(–)**	80 31 p < 0.0001			5 11	Posner et al. [10] (5 yrs.)
ECOG 2399 (USA)	**111** OPC + LRX II–IV	induct. CHT (2cycles) carboplatin, paclitaxel CRT – 70 Gy/7 wks. + paclitaxel	**HPV(+)** **HPV(–)**	95 62 p = 0.005				Fakhry et al. [11] (3 yrs.)

OPC – oropharyngeal cancer; LRX – laryngeal cancer; OS – overall survival; CSS – cause specific survival; LRC – locoregional control; DM – distant metastases; CHT – chemotherapy; CRT – concurrent radio-chemotherapy;, Surg – surgery; Nm – nimorazol, r ENE – radiologic extracapsular nodal extension; pck. tabac – pack-years tobacco

expression on treatment outcome might be limited to HPV(–) OPC patients, because EGFR expression was substantially greater in HPV(–) than in HPV(+) OPCs. Multimarker analyses showed that high HPV and low EGFR estimates better predict OS and CSS (cause specific survival) similar to high p16 and low EGFR. Ang et al. [1] suggest that relationships between HPV, p16 and EGFR estimates have a multifunctional character.

Tobacco smoking was found as an independent prognostic factor for OS and CSS. In the group of OPC patients the median pack-years of tobacco smoking were 12.2 for HPV(+) patients, compared with 36.5 for HPV(–) patients. Results of various studies strongly suggest that tobacco smoking likely induces additional molecular alternations in HPV-associated OPCs, that alter their biologic behavior and response to therapy.

Numerous studies, including clinical trials, on the relationship between the prognostic value of HPV and p16 status and the treatment outcome of the OPC patients are clinically heterogeneous, since they include a wide variation of T and N status and different, often combined treatment strategies. Among them, some studies with a high citation index are arbitrarily selected and presented in table I. All of these studies (fig. 2) show significantly ($p < 0.005 - p < 0.0001$) higher OS (80–95%) and LRC (61 > 90%) for HPV(+) OPCs than for HPV(–) series (31–74% and 35–75%, respectively). Some of the selected studies need detailed comments.

RTOG 0129 Trial [1, 17] and Vrije study [7]

The RTOG 0129 Trial was primarily designed to compare the efficacy of high-dose cisplatin used concurrently with either accelerated RT (72 Gy in 42 fx) or standard fractionation (70 Gy in 35 fx). Altogether, 721 H&N cancer patients with stage T2-4N0–N3 were recruited to this trial. Among the study group of 323 OPC patients (44.8%), HPV and p16 status were estimated retrospectively using stored tumour samples. Overall survival (OS) and locoregional control (LRC) end-points were evaluated. The results have shown HPV status to be the major determinant of the OS and LRC (about 20% higher for HPV(+) subset of patients than for HPV(–) ones, followed by the number of pack-years of tobacco (<10 *vs.* >10) and the nodal status (N0-2a *vs.* N2b-3) for HPV(+) tumours and tumour stage (T2–3 *vs.* T4) for HPV(–) ones. Superior prognosis for HPV(+) than HPV(–) OPCs likely reflects the higher radiosensitivity and radioresponsiveness of HPV(+) OPCs after RT combined with single agent cisplatin, but cisplatin did not differentially affect the risk of DM (10% *vs.* 13%).

The results of this study allowed the classification of OPC patients into 3 categories (fig. 1) regarding the risk of death: a low risk cohort with average 3-year OS of 93% (85 > 95%), an intermediate risk with average 3-year OS of 71% (65–75%) and a high risk cohort with average 3-year OS of about 46% (35–50%) (fig. 2). Very similar results and conclusions have been reported by Rietbergen et al. [7], who analyzed the Dutch study of HPV status in 723 OPC patients [fig. 3].

Comparing the prognostic power of the p16 vs. HPV expression in the OPCs, Ang et al. [17] noted that p16(+) correlates with a 2.2-fold higher OS than p16(–) whereas HPV(+) predicts a 1.6-fold higher OS than HPV(–). The most important observation was that OS for HPV(–) p16(+) cases was similar to the survival curve for OPC patients with both HPV(+) and p16(+). It may suggest that the prognostic value of HPV and p16 expressions should be cautiously interpreted if they are analyzed separately.

DAHANCA-6,7 Trials [3]

DAHANCA-6,7 Trials were performed (331 OPCs and LRX in stage I–IV) to test the efficacy of the hypoxic cell radiosensitizer nimorazole or placebo combined with conventionally

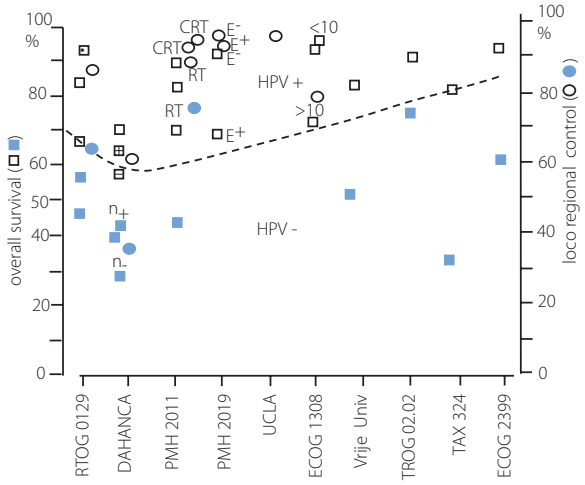

Figure 2. Scattergram of the OS and LRC reported in the various studies or clinical trials depending on the HPV status: HPV(+) – □ – low risk; ⊟ – intermediate risk; ⊞ – high risk; ⊡ – no risk estimated; HPV(–); ■, ● E (+, –) – nodal extracapsular extension; RT – radiotherapy alone; CRT – chemoradiation; <, > – pack-years tobacco; N (+, –) – nimorazole

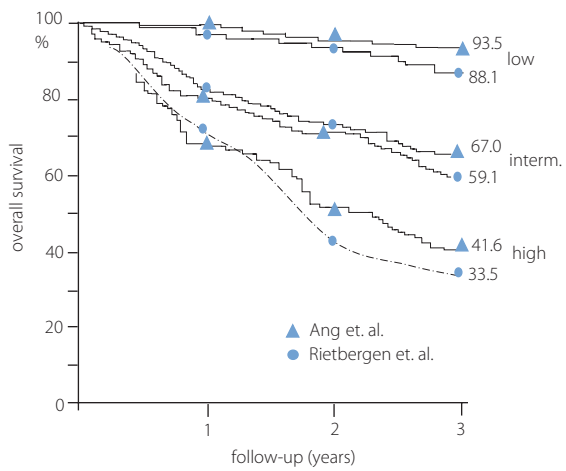

Figure 3. Algorithm of three risk subsets of the OPCs depending on HPV, p16, tobacco smoking and the respective therapy modalitied (modified from Ang et al. 1,17 and Rietbergen et al. 7).

fractionated 66-68 Gy in 33–34 fractions. The use of nimorazole significantly (p = 0.01) improved locoregional control by 14% compared to the placebo group (48% *vs.* 35%). The results of this study confirmed previous conclusions that HPV(+) p16(+) OPC patients had a significantly (p < 0.0001) superior outcome (7.5-year OS of 70% and 61% of LRC) compared with HPV(–) p16(–) patients (40% and 35% respectively). The use of nimorazole during RT significantly improved LRC compared with the placebo subgroup for p16(–) but not in the p16(+) subset. The authors suggest that the use of nimorazole can be beneficial, as long as tumours harbour hypoxic stem cells. Therefore, it might be that p16(+) tumours probably do not contain hypoxic stem cells, which would render them less resistant to RT than hypoxic tumours. Moreover, Overgaard et al. [27] have estimated plasma osteopontin level as a marker of hypoxia associated with a poor outcome after RT. They found significantly (p < 0.0001) higher concentration of osteopontin in the HPV(–) p16(–) tumours compared with about a 3-fold lower concentration in HPV(+) p16(+) tumours (41% *vs.* 16%). This findings likely support the hypothesis that HPV(+) p16(+) OPCs are less hypoxic than HPV(–) p16(–) ones, or at least, the HPV(+) OPC cells under hypoxia are approximately similarly radiosensitive as HPV(–) cells under normoxia, and it seems that hypoxic radioresistance is likely not clinically relevant in the HPV(+) p16(+) tumours.

TROG 02.02. trial

In this trial Rischin et al. [9] analyzed a prognostic power HPV p16 expression in 185 OPC patients in stage III–IV. They received RT of 70 Gy in 7 weeks with concurrent cisplatin with or without tirapazamine. The 3-year OS was significantly (p = 0.004) 17% higher in HPV(+) p16(+) group than in HPV(–) p16(–) (91% *vs.* 74%). The OS rates with/without tirapazamine were 94% *vs.* 80%, but not significant (p = 0.09), however there was a trend for improved locoregional control with tirapazamine regimen in the HPV p16(–) patients.

PMH 2011–2013 study

In this retrospective study 449 consecutive OPC patients in stage I–IV treated with RT alone were included. Four different RT regimes (70 Gy in 35 fx in 7 or 6 wks., 60 Gy in 25 fx in 5 wks. and 64 Gy in 40 fx in 4 wks.) were used. The 3-year OS in the HPV(+) subset was about 2-fold higher than in the HPV(–) subset (81% *vs.* 44%, p < 0.001). Similarly, the 3-year LRC was significantly (p < 0.001) higher for HPV(+) (93%) than that for HPV(–) (76%). The HPV(+) patients were younger, and had less tobacco (<10 pack-years), and lower alcohol consumption, and less T4 or N0 disease. Since 121 OPC HPV(+) patients with positive neck lymph nodes received concurrent chemoradiation (CRT), generally, CRT (chemoradiation) cohort had better OS than RT alone (89% *vs.*70%, p = 0.005) but similar toxicity. However, within the subset of HPV(+) patients with stage IV and minimal smokers (<10 pack-years) 3-year OS and LRC for RT alone and CRT (86% *vs.* 88% and 95% *vs.* 92%, p = 0.45–0.52) were similar but the late toxicity rate was insignificantly higher after CRT than RT alone (16% *vs.* 6%, p = 0.08). A lower OS rate in the RT-alone subset should not be entirely surprising and likely may be explained by an imbalance of several prognostic factors between the RT-alone and the CRT.

Despite very good LRC in HPV(+) patients, the DM rate did not differ much than from that for HPV(–) patients, but was slightly reduced by CRT. Although the RT-alone schedule for HPV(+), stage IV and minimal smoking patients in this study resulted in quite high OS and LCR, it consisted largely of altered, accelerated fractionation regimes. The authors suggest that the use of conventional RT-alone might be questioned and remains rather uncertain. Nonetheless, conventional or moderately accelerated RT-alone could be a reasonable option for low-risk, early stage HPV(+) patients with a minimal smoking.

TAX – 324 trial

This trial was dedicated to previously untreated OPC patients in stage III–IV and it explored the efficacy of pretty aggressive combined therapy which consisted of 3 cycles induction CHT (docetaxol, cisplatin and 5-fluorouracil) followed by RT of 70–74 Gy in 7–7.5 weeks plus concurrent weekly carboplatin with a median 5-year follow-up. The OS rate for patients with HPV(+) was about 2.5-fold higher than for those with HPV(–) (80% *vs.* 31%, p = 0.0001), but the rates of DM were not significantly different. The effects of regimes with or without taxans in patients with HPV(+) or HPV(–) did not reveal any statistical difference.

Many clinical studies, including those presently discussed, have shown unequivocally that HPV, and the p16 status of the OPCs should be considered as a major prognostic factor. However, because of the heterogeneity of other biological and clinical factors, the HPV and p16 predictors should be followed by tobacco smoking (>, < 10 pack-years), also by nodal status (N0–2a *vs.* N2b–3), and by tumour stage T2–3 for HPV(+) and T4 for HPV(–) factors.

Are HPV(+) OPCs proper candidates to dose de-escalated RT or they might be a case of "one bridge too far"?

The favourable locoregional control and overall survival of the HPV(+) OPC patients compared with the HPV(–) ones have been documented by many single-arm studies and clinical trials, however distant metastases rates are more or less the same for both [1, 2, 4, 7, 10] and seem to be the major cause of death in HPV(+) patients. On the other hand, such satisfied outcome of the HPV(+) OPC patients lead to the question of whether standard RT-doses might expose HPV(+) patients to overtreatment and to unnecessary toxic side-effects.

It seems that de-escalated treatment strategies should be proceeded with caution (23), because although the HPV status alone has occurred as an independent good prognosticator,

there is still a subset of biologically aggressive HPV(+) oropharyngeal tumours. One of the most interesting de-escalated single-arm studies was performed by Chen et al. [5]. The aim of this UCLA study (tab. I) was to investigate whether CRT with a reduced RT dose would maintain high OS while improving tolerance of the HPV(+) OPC patients. A small group of 45 HPV(+) OPCs in stage III–IV were treated with two induction cycles of paclitaxel and carboplatin. These with a complete or partial response (CR-PR), received RT after 2 weeks, with the dose reduced to 54 Gy in 27 fractions to the primary tumour, and 43 Gy to the uninvolved nodal areas. For patients with less than PR, 60 Gy in 30 fx was delivered. Acute and late toxicity was mild and grade 3 occurred in about 3–7%. At least 2-year LRC was 95%. This study shows that for the HPV(+) OPCs, stage III–IV patients RT doses could be successfully reduced by 10–15% compared with the standard doses.

A similar RT-regimen with a total dose reduced to 54 Gy in 27 fx was used by Marur et al. [6] in the ECOG 1308 phase III trial (tab. I), which consisted of 80 OPCs in stage T1–3N0–2b. The RT was preceded by 3 cycles of induction CHT (IC) with cisplatin, paclitaxel and cetuximab. The RT dose was reduced when CR or PR occurred after IC. Patients with less than PR received 69.3 Gy in 33 fx. The two-year OS was 96%, but it decreases to 71% ($p = 0.04$) in the subgroup of patients smoking more than 10 pack-years. The small sample size demands careful interpretation of these results. Nevertheless, the authors suggest that low-risk HPV(+) T1–2N0–2b OPC patients seem to be proper candidates to de-escalated RT, but not in the case of the HPV(+)/HPV(–) T3–4N2c–3 cases. This suggestion is strongly supported by O'Sullivan et al. [2, 20], Ang et al. [17] and others authors [5, 6, 14, 29, 30]. However, the relatively long overall treatment time of all therapeutic modalities (including 9 weeks of the IC) used in the ECOG 1308 trial, even with RT time reduced by 1–1.5 week, likely suggests that the net de-escalation might be close to "zero".

Chera et al. [30] carried-out a phase II NCT 0153 0997 trial of de-escalated chemoradiation for favourable-risk 45 HPV(+) p16(+) OPC patients in stage T0–T3N0–2b. Therapy consisted of 60 Gy IMRT, instead of 70 Gy and a concurrent weekly low-dose of cisplatin. The two-years OC was 98% and LRC of 87%, with evidence of decreased toxicity compared with standard therapies. The authors suggest to explore three other major approaches of dose de-escalation in HPV(+) OPCs. The first substitutes EGFR inhibitor (cetuximab) by cisplatin with the assumption of the decreased toxicity. A second approach uses transoral surgery, which is less invasive and toxic than conventional techniques, applied for early, low-risk T1–2N0–2b HPV(+) OPCs, with an IMRT dose-reduced to about 40 Gy, in case of negative margins. Finally, the third approach is limited to radiation alone, omitting chemotherapy, for HPV(+) OPC patients with stage T1-2N0-1, especially for those with <10-pack-years smoking history. Moreover Chera et al. [29] and Hong et al. [26] suggest that efficacy of cetuximab in HPV-associated OPCs might be questioned because EGFR expression in HPV(+) OPCs is lower than in HPV(–) ones, and it might be less effective than cytotoxic IC combined with RT.

Billfalk-Kelly et al. [12] have analyzed in a retrospective PMH 2019 study the impact of a radiological extracapsular nodal extension (ENE) on treatment outcome in the group of 289 T1–2N1 HPV(+) OPCs patients, based on the assumption that HPV(+) OPCs have a tendency for early nodal involvement, even in early T0–T2 tumours. The results showed significantly lower two-year OS of the r ENE(+) HPV(+) patients than for those with r ENE(–) (68% *vs.* 92%, $p < 0.02$), but there was no substantial difference in the LRC (tab. I). This study also shows that the r ENE(+) represents a subset with a significantly higher risk of distant metastases (22% *vs.* 5%, $p < 0.001$) in a population that should have an excellent prognosis. Surprisingly, in a recent study [12] of 238 stage I HPV(+) OPC patients, the authors did not find the r ENE to be a prognostic factor, but nodal status was not determined by a radiologist and the interrater reliability was not evaluated. The poor prognosis of the r ENE(+) status has been evaluated in any of RT dose-reduced studies.

An interesting small pilot study within MSKCC prospective trial IREB 04–070 [31] was focused on an assessment of pre-treatment hypoxia in the subset of 33 HPV(+) OPC patients in stage III and IVB using 18F-MISO (fluoromisonidazole) PET to select patients as candidates to de-escalated RT. 10 OPC patients (30%) had normoxic lymph nodes, and they received a total dose de-escalated by 10 Gy (from 70 Gy to 60 Gy) to the involved neck area, whereas the dose to primary tumours was 70 Gy. Twenty-six OPCs (81%) patients were hypoxic at the primary site. The 2-year OS and LRC was 100%. Overgaard [7, 27] has suggested that HPV(+) p16(+) OPC tumours probably do not contain hypoxic stem cells. Results of the pilot study of Lee [31] do not support Overgaard's suggestion, at least regarding primary tumours. In fact, the Lee' study shows that although HPV status is a valuable prognosticator, when it is used as a single factor, but it seems insufficient to guide de-escalation decision because there is still a subset of biologically aggressive HPV(+) OPCs that can recur after chemoradiation. Moreover, Sorensen et al. [32] noted that HPV(+) cells under hypoxia have approximately similar radiosensitivity as HPV(–) cells under normoxia. So, attempts at nonselective reduction either chemotherapy or radiotherapy for HPV(+) tumours should proceed carefully with caution and the use of 18F-MISO PET estimates could be an additional and helpful indicator together with other clinical factors, to identify patients who really could be candidates for de-escalation treatment modalities.

Recently, Ma et al. [33] from the Mayo Clinic (USA) made a few steps forward regarding dose de-escalated RT for HPV(+) p16(+) OPC patients. After margin-negative surgery, 80 OPC patients with ≤ 10-pack-years tobacco smoking were included into the MC1273 single arm phase II trial. Cohort A (low risk) received 30 Gy with 20 fractions of 1.5 Gy given twice-a-day over 2 weeks along with 15 mg/m^2 docetaxel on-

ce-a-week. In fact, the biological dose was even lower being 22.5 izoGy2.0 if given in 2.0 Gy fraction. Cohort B (patients with node' extracapsular extension – ECE(+)) received the same dose fractionation plus a simultaneous integrated boost to the nodal area with ECE of 36 Gy in 1.8 Gy twice-a-day fractions (biological dose = 32.4 izoGy 2.0). Overall 2-year OS for both cohorts was 98.7% and a 2-year LRC of 96.2% (100% in cohort A and 93% in cohort B). Grade 2 and 3 toxicity was generally low at 0% and 6–7% respectively. Furthermore, this study had a 33% reduction in RT costs and a 21% reduction in total treatment costs compared with standard chemoradiation. This study, like all phase II trials, requires confirmation by a phase III trials before broad applicability. Nevertheless, this aggressive de-escalation regimen (more than half of a biological standard dose of 60 Gy in 30 fractions, and shortened OTT to 2 weeks could be considered as promising and highly effective for carefully selected homogeneous subset HPV(+) p16(+) low risk OPC patients.

Summary

The HPV(+) OPCs are widely recognized as a distinct head and neck cancers. Nodal disease appears more extensive for HPV(+) OPCs at the diagnosis. The p16 can be considered a surrogate for the HPV status and the use of estimates for both HPV and p16 seems obvious. The HPV(+) p16(+) OPCs respond better to current standard therapies, including RT alone, surgery with or without adjuvant treatment, or combined chemoradiation. Consequently HPV(+) p16(+) OPC patients have a much better prognosis than those with a HPV(–) p16(–) status. The results of selected studies to the present analysis and discussion are shown in figure 2. Some of the studies suggest that smoking and some molecular deregulations, (e.g. P53 mutation and high EGFR expression) can increase the resistance of HPV(+) OPCs to therapy. Numerous available data allow to stratify OPC patients into three distinct low-, intermediate- and high-risk classes, as it has been proposed by Ang and Sturgis [17]. Their algorithm is modified and presented in figure 3 and might be a useful guide for daily clinical practice.

The general belief that low-risk HPV(+) OPCs with 3-year OS of more than 90% could be overtreated by standard therapeutic modalities has led to the concept of de-escalated treatment strategies for HPV(+) p16(+) OPCs. However actual knowledge in this field arouses some caveats and uncertainties since many studies include a relatively small number of patients, and follow-up is often too short. It seems that de-escalated strategies should be focused mainly on the low-risk HPV(+) p16(+) category of patients and consider transoral resection with or without adjuvant RT/CRT, dose-reduction in RT combined with induction chemotherapy in the group of good responders as well as reduction of RT dose to regional lymph nodes with pretreatment normoxia. For some patients with intermediate-risk and all of those with high-risk there is no room for any de-escalated treatment strategies and immunotherapy is recommended for T4N3 HPV(–) (or even HPV(+)) patients. Subsequently, large clinical trials need to be checked and actual promising observations validated, however, it seems that even well designed phase II studies might be good enough to modify treatment strategies for HPV(+) p16(+) oropharyngeal cancers. In conclusion, numerous studies the results of which are published so far convincingly show that dose de-escalation in combined treatment strategies for carefully selected HPV(+) p16(+) OPC patients offer a safe, promising and effective way across the "bridge".

Conflict of interest: none declared

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Review article

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Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) in axillary lymph nodes – a case report and review of 29 other cases from world literature

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Introduction. Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is a new disease established by the WHO in 2016. BIA-ALCL is one of the most severe adverse effects of breast augmentation or breast reconstruction with the use of silicone implants.

Material and methods. In our report we present a case of a 46-year-old patient diagnosed with BIA-ALCL in the General and Oncological Surgery Clinic of the Pomeranian Medical University in Szczecin. This is one of the first described cases of this disease in Poland. Especially interesting is the fact that the lymphoma developed two years after the removal of the implants and the pathology occurred in the axillary lymph nodes. In order to compare the published case of BIA-ALCL we reviewed 29 cases from literature.

Results. We described the most clinically relevant factors. The age range of females analysed with diagnosed BIA-ALCL is between 27 to 87 years. The time from implant insertion to the appearance of the first symptoms varies. The use of textured implants seems to be one of the most important risk factors of novel lymphoma.

Conclusions. The patients with breast implants should be informed about the risk of BIA-ALCL and related symptoms. The number of articles about BIA-ALCL is minimal, therefore knowledge about the disease remains limited. There is a need to broaden knowledge about the pathological process, clinical manifestations, risk factors and medical tests crucial to achieve an accurate diagnosis.

Key words: breast implant, lymphoma, lymphadenopathy, PET-CT, Poland

Introduction

In 2016 the World Health Organization (WHO) established a new disease entity entitled Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALC) [1]. The first case of a 41-year-old woman after bilateral breast augmentation and associated lymphoma was published in 1997 [2]. Until November 2018, only 656 cases had been registered [3]. According to E. Berlin et. al., frequency is estimated at 1 per 30 000 females with breast implants [4]. This recent, uncommon type of non Hodgkin's lymphoma originates from T-cell lineage and is characterised by the presence of peculiar antigen CD30 expression and the absence of Anaplastic Lymphoma Kinase (ALK) expression. The histopathological image presents specific large cells, called "hallmark cells" due to hoof-shaped nuclei [5]. In most patients BIA-ALCL manifests itself with effusion, associated breast oedema and related

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discomfort. Additionally, enlarged axillary lymph nodes are frequently observed [6].

As BIA-ALCL is a new disease established by the WHO recently, little is known about its possible pathogenesis. Several theories have been developed and many centres perform research to understand this process correctly. Knowledge about this rare complication is crucial, as many women nowadays undergo breast reconstruction or augmentation. Most theories share the view that pathogenesis is connected to a chronic inflammatory condition developing in the breast. It might be initiated as a result of capsule scarring and the involvement of the surrounding tissue. Furthermore, the type of implant capsule seems to have a significant impact on the risk. The majority of women suffering from BIA-ALCL had textured implants instead of smooth ones. This could lead to increased bacterial growth which may also contribute to intensified leukocyte activation [7]. Chronic antigen stimulation can be an incentive for the T-lymphocytes to transform into breast implant associated-ALCL. In the lymphoma, T helper cell types have been detected [5]. It has also been found that patients with BIA-ALCL have mutations of JAK1 and STAT3 genes. One of the theories suggests that it might have an influence on inflammatory-associated malignancies [8]. Currently, there is no information about surgical techniques that may increase the risks of the lymphoma developing. Moreover, researchers are attempting to find specific genetic factors that play a part in this process.

Material and methods

In this article, we present a 46-year-old woman diagnosed with BIA-ALCL, 11 years after bilateral, aesthetic breast augmentation and two years after the removal of implants. We report one of the very few cases ever to be diagnosed in Poland. Furthermore, we reviewed 29 cases of the aforementioned disease from world literature.

Case report

A 46-year-old female was admitted to the General and Oncological Surgery Clinic in 2019. The patient had undergone aesthetic, bilateral breast augmentation in 2008. Nine years later, both implants were removed due to a suspicion of a rupture in the left implant. During this procedure, material from the implant pocket was collected for cytological examination. The procedure did not reveal the presence of malignant cells.

At the time of admission the patient complained of an axillary mass associated with periodically recurring inflammation and swelling in this area. Furthermore, dry skin and hair loss as well as fever and sweating was also reported. During the physical examination, three enlarged, left axillary lymph nodes were detected. Both breasts and the right axilla were without lesions. An ultrasound examination confirmed three enlarged lymph nodes measuring over 5 cm, which were subjected to a core needle biopsy. A histopathological examination revealed stromal connective tissue with numerous inflammatory cells, areas of necrosis and several solid foci of neoplastic large cells with cytological features of malignancy and CD30 immunohistochemical expression. Histological features together with the available immunohistochemical stainings suggested a non-Hodgkin's lymphoma, but the tissue sample was too small to evaluate the exact type of lymphoma. For this reason, a surgical biopsy was performed. During this procedure five axillary lymph nodes were collected. The dimensions of the largest node were 7,5 cm x 5 cm x 3 cm. The histopathological examination revealed that the neoplasm was composed of aggregates of pleomorphic large cells with features of malignancy, including irregularly shaped nuclei (fig. 1A). Aside from tumour cells, numerous T-cell lymphocytes, plasma cells, and necrotic fields with eosinophils were seen (fig. 1B). The cells were strongly positive for the CD30 antigen (fig. 1C) Additionally CD3, CD4, CD5, CD43, CD99, MUM1 expression was also confirmed. ALK expression was negative (fig. 1D) and the proliferation index was approximately 70%. The fact of the previous breast augmentation procedure in correlation with the obtained test results allowed a diagnosis of BIA-ALCL.

The patient underwent PET-CT, which did not show any areas of increased 18F-FDG activity. Adjuvant treatment was limited to chemotherapy. Follow-up tests, performed after 3, 6 and 12 months, did not reveal any signs of a recurrence in the process.

Review of 29 case reports in world literature

In order to compare our analysed case of BIA-ALCL, we reviewed 29 other cases from world literature. Therefore, we describe the most clinically relevant factors in table I.

Discussion

The age range of the females in question with diagnosed BIA-ALCL was between 27 and 87 years. As much as 60% of affected patients at the time of diagnosis were between 47 and 66 years old, whereas the average age of the analysed patients is approximately 53 years. The frequency of the disease in three age categories is featured in figure 2. The patient who reported to the General and Oncological Surgery Clinic was 46 years old. According to the presented data, risk at this age tends to increase.

The time from implant insertion to the appearance of the first symptoms of BIA-ALCL varies. In our study group, the range was from 0 to 22 years. In 65% of patients, symptoms occurred between 0 to 10 years from the day of implant placement. Figure 3 shows the correlation between the time of implant placement and the manifestation of symptoms . The presented patient developed symptoms 11 years after breast augmentation.

12 out of 30 reviewed cases reported the appearance of BIA-ALCL in patients with textured implants. Unfortunately,

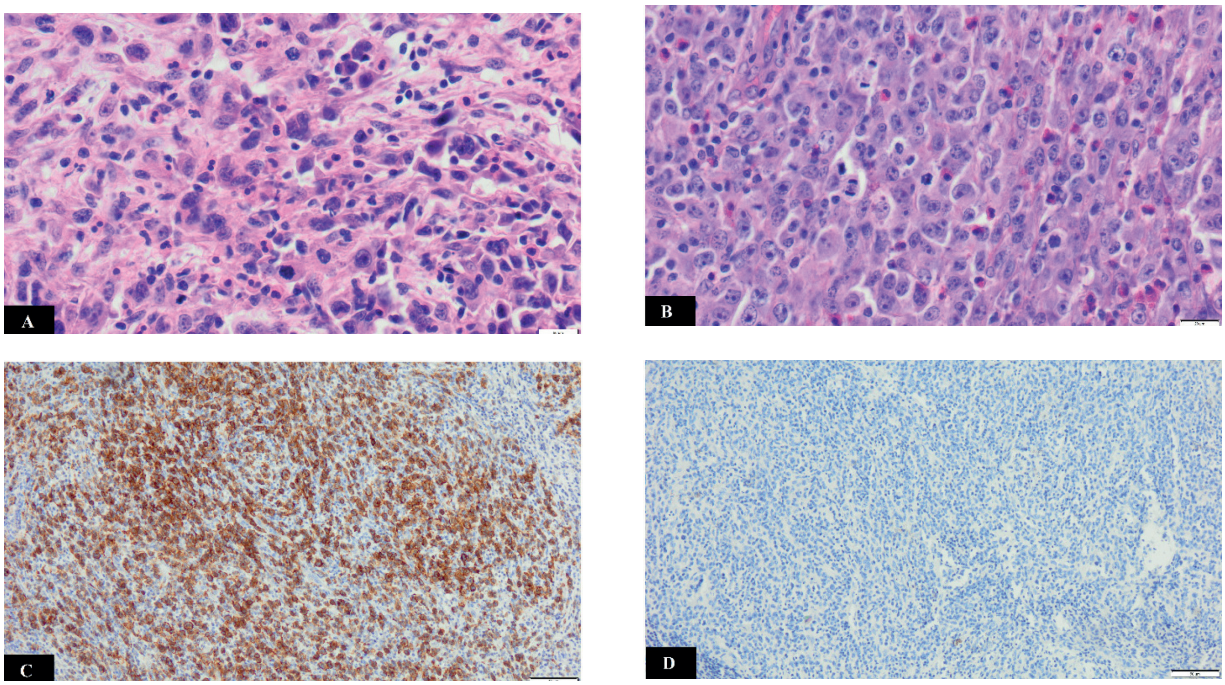

Figure 1. A – anaplastic large cells with characteristic irregular nuclei and numerous mitosis visible (H/E, 40X); **B** – the structure of the tumour with multiple mitosis and eosinophilic infiltration of cell clusters (H/E, 40X); **C** – CD30+ on IHC (20X); **D** – ALK negative on IHC (20X)

Table I. The most clinically relevant factors of reviewed cases

Author	Age	Time from implant placement to symptom manifestations	Textured implants	Swelling of the breast or axillary area	Lymphadenopathy	Breast cancer burden
Taylor/2011[9]	58	3 years	+	+	–	–
Taylor/2011[9]	37	4 years	+	+	–	–
Taylor/2011[9]	54	5 years	+	–	–	–
Boer/2017[10]	56	20 years	+	+	–	–
Crevecoueur/2019 [11]	58	7 years	+	+	–	–
Crevecoueur/2019 [11]	47	–	+	+	–	–
Carty/2011[12]	57	22 years	+	–	–	–
Alderuccio/2018[13]	57	9 years	not reported	+	+	+
Berlin/2017[4]	58	2 years	not reported	+	+	–
Hwang/2015[14]	48	8 years	+	+	–	–
Pastorello/2018[15]	56	7 years	not reported	+	+	+
Richardson/2017 [16]	55	10 years	not reported	+	–	+
Olack/2007[17]	56	8 years	not reported	+	–	+
Roden/2008[18]	45	7 years	not reported	–	–	+
Roden/2008[18]	59	3 years	not reported	–	–	+
Roden/2008[18]	34	3 years	not reported	+	–	–
Roden/2008[18]	44	–	not reported	–	–	–
Adlard/2019[19]	53	14 years	+	+	+	–
Ezekwudo/2017[20]	65	–	+	+	–	–

Fricke/2019[21]	56	7 years	+	+	+	+
Gardani/ 2019[22]	75	–	not reported	+	+	+
Patzelt / 2017[23]	27	7 years	+	–	–	–
Gaudet/ 2009[24]	87	10 years	not reported	+	–	+
Gaudet/ 2009[24]	50	<1 year	not reported	–	–	+
Keech/1997 [2]	41	4 years	not reported	+	–	–
Sahoo/2003[25]	33	9 years	not reported	+	–	–
Alobeid/2009[26]	68	16 years	not reported	–	+	+
Bishaara/2009[27]	66	7 years	not reported	–	–	+
Wong/ 2008[28]	40	19 years	not reported	+	–	–
Dymek et al. 2020	46	11 years	not reported	+	+	–

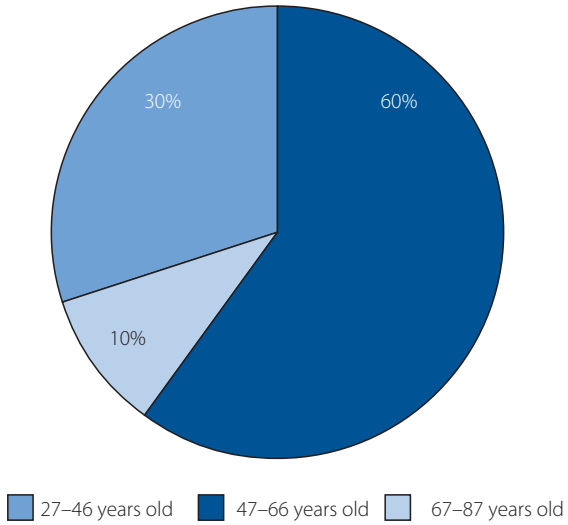

Figure 2. Age range of patients with BIA-ALCL

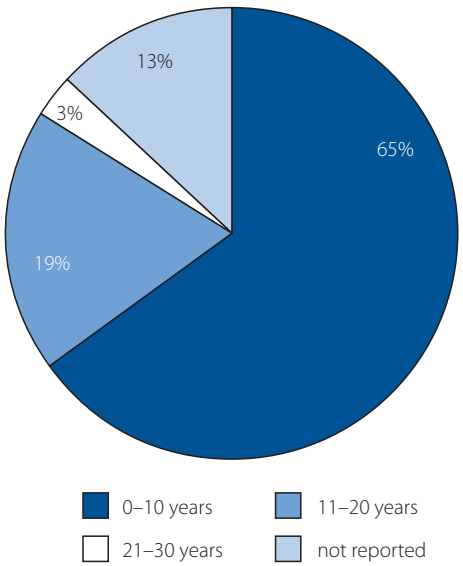

Figure 3. Time from implant placement to symptom manifestation

including in our case, the type of implant was not specified in 18 of the cases. This may be due to the fact that females decide to undergo breast augmentation surgery because of aesthetic reasons and those surgeries are performed mainly in private clinics, therefore, the medical documentation can be difficult to access. The use of textured breast implants seems to be the most crucial and clinically important risk factor of BIA-ALC [23]. The research results of a clinical trial by Broody et al. showed that up to 171 of 173 BIA-ALCL cases were related to the textured structure of the breast implant [29]. It is crucial to broaden knowledge amongst patients about the possible complications arising from textured implants.

The reported 46-year-old female described a swelling of the axillary area due to developing lymphadenopathy. Only 26.7% of patients were diagnosed with lymphadenopathy in the studied case reports. In the literature, the coexistence of lymphadenopathy in the course of BIA-ALCL is estimated at 15% [30]. Lymph node involvement might suggest a more aggressive course of BIA-ALCL compared to cases localised to the breast [31]. In our patient, special attention is drawn to the fact that lymphoma developed two years after the removal of implants and the pathology occurred in the axillary lymph nodes.

Another common manifestation is enlargement of the breast or axillary area, which was identified in 70% of reviewed patients.

In the analysed group, 40% of patients were diagnosed with breast cancer formerly. Our patient had no previous oncological history. The summary of the clinical features of patients with BIA-ALC is presented in figure 4.

Considering the immunophenotype of all 30 patients, it is clear that there are some significant antigens related to BIA-ALCL. In 90% of cases, expression of the CD30+ antigen was identified. CD3 and CD4 expression was found in 50% of reviewed patients.

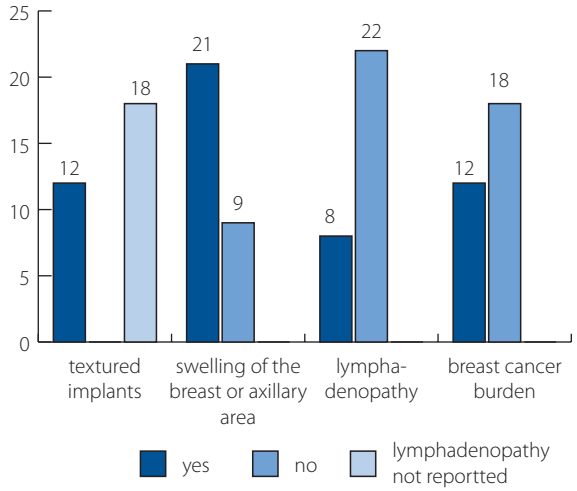

Figure 4. Summary of the clinical features of patients with BIA-ALCL

Patients with diagnosed BIA-ALCL are tested for expression of the ALK protein by the tumour cells [32]. Approximately 97% of the reviewed cases did not express ALK. None of the cases was ALK positive and in one case ALK status was not reported. The IHC profile of our patient: CD30+ as well as CD3+ CD4+ and lack of ALK expression, corresponds with the immunohistochemical features from other case reports.

A crucial treatment for BIA-ALCL is surgical capsulectomy. An important factor during this procedure is to excise the whole capsule, including the adjacent tissue. There is no need to perform a mastectomy or to remove the surrounding lymph nodes, unless there are lymph nodes metastases [33]. To prevent oversight the metastasis, 18F-FDG PET-CT should be performed, preoperatively as well as postoperatively [34].

Currently, there are no strict guidelines for adjuvant treatment. Consequently, these treatment methods should be applied individually to the patients needs. Chemotherapy or radiotherapy are usually iniciated as adjuvant treatment [33].

Conclusions

Breast implants have rare but significant side effects. One of them is BIA-ALCL. The number of articles about BIA-ALCL is very much limited. The small number of published cases also make it difficult to find direct guidelines about managing this condition. That said, even though the frequency of described lymphoma is exceedingly uncommon, information on the risks and possible symptoms of BIA-ALCL should be presented to those patients interested in breast augmentation or breast reconstruction with the use of implants. Patients should be more aware of alarming symptoms, so they can then report to the hospital early before the progression of the disease.

In the case of symptoms like those presented in our patient, including the rupture of the implant or lymphadenopathy, BIA-ALCL should always be included in differential diagnosis. Furthermore, it is recommended that a 18F-FDG PET-CT examination should be performed, since this may reveal the possible spread of BIA-ALCL, which might otherwise be overlooked. Further research and analysis of BIA-ALCL cases will enable more successful future treatment.

Abbreviations

BIA-ALCL – Breast Implant Associated Anaplastic Large Cell Lymphoma
WHO – World Health Organization
ALK – anaplastic lymphoma kinase
JAK 1 – janus kinase 1
STAT 3 – signal transducer and activator of transcription 3
PET-CT – positron emission tomography – computed tomography
18F-FDG – 18F-fluorodeoxyglucose
IHC – immunohistochemistry

Conflict of interest: none declared

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New WHO classification of breast tumours – as published in 2019

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At the end of 2019, a new classification of breast malignancies was published by the World Health Organization (WHO). Popular name of the classification is the "blue book" and it derives from the colour of its cover. New classification was made available after 7 years from the previous one. In 2019 the WHO introduced new disease entities: mucinous cystadenocarcinoma and tall cell carcinoma of reverse polarity. The most recent classification also contains classification of the microscopic evaluation of ductal carcinoma in situ (DCIS) and of the evaluation of the parameters necessary to define the tumour grade of breast cancer as well as predictive or prognostic parameters. All of above mentioned changes are presented and commented on in the article.

Key words: **breast cancer, WHO classification, mucinous cystadenocarcinoma, tall cell carcinoma of reverse polarity**

Introduction

At the end of 2019, a new classification of breast cancers was published by the World Health Organization (WHO). The previous classification, binding until then, had been published in 2012. Therefore, the new, fifth edition of this classification, whose popular name, the "blue book", derives from the colour of its cover, comes after 7 years and introduces noteworthy changes. These changes are not as revolutionary as those introduced in the fourth edition (2012), yet studies which concern such an important issue, as breast cancer definitely is, are worth reporting on an ongoing basis.

General WHO characteristics of cancers

In all current WHO classifications, each cancer is described in the same manner, including, among others:

- diagnostic criteria,
- typical microscopic characteristics,
- accompanying molecular lesions.

The objective of this description of specific cancers in the WHO classification is to provide coherent international diagnostic standards.

In the era of digitalisation and in the presence of the pandemic which reduces both interpersonal contacts and the custom of sharing books, it seems especially worthwhile to purchase an annual subscription – an option which has been introduced by the WHO this year, and which gives access to the most recent classifications in digital form: (https://tumourclassification.iarc.who.int/welcome/).

The subscription price (currently 100 EUR annually) does not seem very high, especially given the price of a paper version of one book. Currently, the purchase of the subscription allows access to nine books (their most recent editions), which discuss the tumours of the gastrointestinal (GI) tract, breasts, endocrine system, eyeballs, skin, head and neck, central nervous system, soft tissues and bones, haematopoietic and lymphatic tissues (beta version).

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Currently, online access to these publications does not have to be recommended to anyone: the benefits are clear. Digitalisation has allowed progress in "digital pathology" and image analysis systems. Thanks to this, pathologists worldwide have access to microscopic images with much better resolution than those published in traditional, paper books.

The first conclusion that arises from a comparison of the book and the current, digital version of the breast cancer classification is that the latter has a clearer chapter layout. A reduced number of chapters in the 2019 edition results from the fact that all epithelial breast tumours are discussed in one large chapter. Additionally, pathological lesions developing within the breast are discussed in a more logical way – beginning with completely benign lesions, through pre-cancerous lesions and ending with non-malignant and malignant tumours. Each disease entity is described in the same, regularly repeating manner, so the reader can easily find all the necessary information.

What is also worth noting is the attempt to unify various classifications. And thus, the tumours which occur in many organ systems (such as neuroendocrine, haematological and mesenchymal tumours) are described in separate chapters of the book(s). Moreover, the criteria for the evaluation and diagnosis of these tumours proposed by the WHO are the same, regardless of the tumour location.

Apart from these general modifications to the method of establishing diagnostic criteria and other information concerning specific morphological units within the breast and also presenting them to the reader, **the recent edition of the WHO classification contains a lot of new data, even including new disease entities**.

New entities, introduced in the current WHO classification of breast cancers

In 2019 – in the currently binding classification of breast cancers – the WHO introduced new disease entities:

- mucinous cystadenocarcinoma, and
- tall cell carcinoma of reverse polarity.

Mucinous cystadenocarcinoma is a rare form of breast cancer, whose microscopic picture resembles pancreatic or ovarian cancers – the dominating forms are cystic spaces with papillary structures. For a clinician, one important note is that this is a triple negative tumour – in its cells, no expression of oestrogen, progesterone or HER2 protein is found. This property allows this rare form of cancer to be differentiated from the classical mucinous cancer which is characterised by the expression of these hormone receptors.

Tall-cell carcinoma of reverse polarity is a cancer whose cytological properties resemble the papillary carcinomas which develop in the thyroid gland. This type of cancer grows as a solid tumour, creating papillary structures within its architecture. It is included in the parotid type tumours and is also, with regards to its molecular properties, a triple negative tumour (usually no hormone receptors and no HER2 expression are found in the cancer cells).

Selected modifications of the current WHO classification of breast cancer

The most recent classification also contains significant (especially for pathologists) classifications of the microscopic evaluation of ductal carcinoma *in situ* (DCIS) and of the evaluation of the parameters necessary to define the tumour grade of breast cancer as well as predictive or prognostic parameters.

In comparison with the previous edition of the classification of the breast cancers, **the manner of evaluation of tumour grade in the case of ductal breast carcinoma *in situ* (DCIS) has been modified**. Previously, when evaluating this parameter, a pathologist took into consideration both the architecture of the epithelial lesions and the degree of the nuclear atypia. Now, it has been agreed that, for larger compliance of the diagnoses made by various doctors, it is necessary to take into consideration only the morphology of the cells and their nuclei, because the architecture of the lesions vary between specific grades and is not as homogenous as the morphology of the cancer cells. The structures created by cancer cells within the lumens of the ducts may be considered, yet is not necessary for determining the DCIS grade. The distinction between low, medium and high grade remains unchanged.

The next parameter which must be mentioned in the context of the recent classification is the **evaluation of tumour-infiltrating lymphocytes** (TILs). The authors of the classification decided not to include data concerning TILs in the obligatory panel of the parameters under evaluation, but they clearly point out that the micro-environment of the tumour plays a very important role and that an evaluation of the intensity of the host response to the presence of the infiltrating carcinoma – i.e. the amount of the infiltration of lymphatic cells within the cancer tissue – is a recognised prognostic factor for the response to neo-adjuvant treatment in triple negative breast cancers and in HER-positive cancers. At the same time, it is emphasised that this parameter should be an element of clinical studies (taking into consideration existing international guidelines for its evaluation) and, within the progress of the system of digital evaluation of microscopic images, allowing for the standardisation of the entire procedure, this should become a routinely evaluated parameter the value of which should be presented in the case of infiltrating breast cancers.

One significant issue here is also the diagnosis of medullary type cancers. The classification from 2012 listed three types of such cancers of the breast gland. In the current edition, the authors have decided to give up this distinction and specify only one cancer type: no special type (NST) with characteristic morphological properties. This is **invasive carcinoma NST with basal-like and medullary pattern**. The reasons for this decision were as follows:

- the limited repeatability of diagnoses of the previous types of the cancer out of many pathologists,
- the overlapping features of the described cancers with cancers with a molecularly confirmed profile of basal carcinoma and the cancers connected with a *BRCA1* gene mutation.

For clinical reasons, it is now believed that the cancers discussed belong rather to a spectrum of various breast cancers in whose architecture numerous TILs are found, but they do not make up a separate disease entity.

In spite of the extensive debate which has been going on for many years among pathologists dealing with the diseases of the breast, the authors of the classification discussed here, have maintained, in its newest edition, the nomenclature of the lobular breast cancers. Therefore, the term lobular carcinoma *in situ* (LCIS), can still be used, although it is emphasized that both the classical form of LCIS, and atypical lobular hyperplasia (ALH) are merely risk factors and they are non-obligatory precursors of infiltrating cancer. In spite of the lack of adequate data, the authors of the classification, only recommend the resection of the breast lesions in which the pathologist has described a hyperplasia of the types florid LCIS or pleomorphic LCIS. This is meant to reflect the biological diversity of the latter neoplasias and their more aggressive character.

In the above, very brief and obviously unobjective summary of the changes in the recent WHO classification, I have tried to discuss those issues which are significant from a clinical point of view and reflect the rapidly changing medical reality, now strongly dominated by new technologies. In the era of interdisciplinary oncology, the nomenclature must be unambiguous and clear for other members of the oncological multidisciplinary team.

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Oral mucositis (OM) – a common problem for oncologists and dentists

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Oral mucositis (OM) caused by ionizing radiation is a significant therapeutic problem concerning almost all patients with head and neck cancers undergoing irradiation, however, an effective treatment method is still missing. Therapeutic actions concentrate mostly on prophylaxis, including the maintenance of the correct hygiene of the oral cavity. In 2014 the International Society of Oral Oncology (ISOO) together with the (Multinational Association of Supportive Care in Cancer (MASCC) worked out the guidelines for the treatment of patients with z OM induced by radiotherapy and chemotherapy. In 2019 these guidelines were updated.

Research is ongoing to find medication which could be applicable for the prevention and treatment of OM. The problem is grave as it might complicate the progress of oncological treatment, deteriorate the patient's quality of life or even affect the prognosis.

This paper describes the pathogenesis of oral mucositis, the current trends in treatment and discusses the role of a dentistry doctors in the care of the patient with symptoms of this condition. The article also refers to the role of a multidisciplinary team – the OM prophylaxis – as part of the preparation of an oncological patient for irradiation.

Key words: oral mucositis, prophylaxis, oral hygiene, radiotherapy, chemotherapy, head and neck cancers

Introduction

Unaffected oral mucosa makes up the best protection against pathogens and other external factors. In the majority of patients, the lesions of the oral mucosa – irrespective of their origin – cause significant discomfort, as they are usually accompanied by pain and difficulties in chewing and swallowing. In recent years, on account of the growing number of patients receiving the anti-cancer treatment and due to their prolonged duration of life, the number of patients contacting dentists due to various complains about the condition of oral mucosa caused by complications arising from oncological treatment has increased.

Malignant cancers are one of the main causes of death in Poland and worldwide. According to the National Cancer Register, the incidence of malignant tumours in Poland, in the last 30 years has doubled, whilst the number of deaths within the last 50 years has increased 2.4-fold. [1]. Cancers located in the area of the head and neck account for between 5.5% and 6.2% of all malignant cancers in Poland. Other European countries and the United States have noted similar prevalence rates [2]. The basic methods of treatment in the case of this type of cancer comprise surgery and radiotherapy – often combined with systemic treatment. However, the use of irradiation is connected with the risk of development of oral mucositis (OM), which might be exacerbated in patients undergoing chemotherapy together with radiotherapy. OM is induced by ionising irradiation and is regarded as one of post-radiation acute reactions. It concerns almost all patients undergoing chemotherapy in the area of the head and neck [4, 5, 7–10]. Such a reaction was described for the first time

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in 1980 in patients with head and neck cancers undergoing radiotherapy [5, 6]. In 2007 the World Health Organization (WHO) considered oral mucositis as a separate disease unit [3, 4].

Patomechanism

OM is caused by mechanisms which directly and indirectly affect the cells of the oral epithelium, including their division and maturation [5]. The direct impact of irradiation is connected with apoptosis induction [5, 11]. Indirect mechanisms consist in the release of proinflammatory mediators with simultaneous reduction of the release of anti-inflammatory mediators in the cells of the oral epithelium [5]. Sonis worked out the five-stage model of OM development induced by radio- and chemotherapy [3]. In the first stage, called the **initiation stage**, direct DNA damage occurs and reactive oxygen species (ROS) are released. [3, 12, 13]. The second stage is called **signalling**: in this stage transcription factors, such as NF-kB, are activated. As a result of complex biological processes, the number of proinflammatory cytokines – such as TNF-α, IL-1-β, IL-6 – increases [3, 5, 14], whereas, at the same time, the number of anti-inflammatory cytokines, such as IL-10 and TGF-β decreases [3, 14]. As a result of the expression of more than 200 various genes, the molecules responsible for epithelial damage and the activation of other molecular pathways are produced [3]. It must be emphasised that the NF-kB protein complex plays a main role in the development of radiotherapy induced OM. OM may develop directly under the influence of chemotherapy or radiotherapy, and indirectly – by ROS [3, 6, 12]. The effect of the activation of this pathway may be programmed cell death by means of apoptosis [3]. The third stage of OM development is **amplification**, i.e. m signal magnification. At this point the inflammatory cascade is activated. The clinical manifestation is comprised of oedema and erythema caused by the activation of proinflammatory cytokines [3]. The fourth phase – **ulceration** – is regarded as the most significant with respect to its clinical picture [3]. The rapid development of biological processes leads to the apoptosis of the epithelial cells. Deep, clinically overt ulceration develops and this might easily be colonised by pathogens. Bacteria cause mucositis, whilst the products of the lysis of the cellular walls penetrate to the submucosal membrane, increasing the proinflammatory effect. After the penetration of living bacteria into the blood vessels in the submucosal layer of the mucosal membrane, inflammation might develop into a systemic infection (sepsis). The risk of sepsis, originating in the oral cavity is especially present in patients with additional risk factors, such as granulocytopenia induced by anti-cancer treatment [6, 12]. The fifth phase of the OM evolution patomechanism is **healing** [12]. The majority of cases of oral mucositis, thanks to biological reparatory pathways, are spontaneously healed [3].

Risk factors and location of the lesions

There are risk factors which predispose the development of OM: their analysis facilitates taking preventive steps and the definition of therapeutic goals [3]. The OM risk factors comprise:

- poor hygiene status of the oral cavity,
- the presence of defects caused by dental caries,
- lesions of the oral mucosa,
- tobacco smoking,
- poor nutritional status,
- systemic comorbidities (e.g. neutropenia),
- folic acid and B12 vitamin deficit,
- oral cavity dryness,
- some medication (e.g. cytotoxic drugs with muco-toxic action),
- age (the risk is higher before 20 and after 50 years of age),
- sex (OM is more frequent in women),
- genetic factors (np. *MTHFR C677T* nucleotide polymorphism in patients treated with methotrexate) [5, 9, 10].

Lesions connected with OM are located mainly in the movable, non-keratinising mucosa. They affect mostly the buccal mucosa, the inside surface of the lips, the lateral and ventral side of the tongue, the fundus of the oral cavity, soft palate and pharynx mucosa [3, 7, 15, 16].

The course of the disease

The one of the main symptom of OM is a burning sensation in the oral cavity. Ulceration is deeper than in the case of *aphthous stomatitis* and makes a gateway for bacterial infection (Gram+ and Gram–) infections. Opportunistic infections (OIs) may hinder diagnosis and treatment [3, 11, 15]. Within the course of oral mucositis, the probability of infections increases – not only of bacterial origin, but also mycotic or viral [11, 17]. The infections are also stimulated by decreased saliva production caused by the anti-cancer treatment (damage of salivary glands) and neutropenia [3, 5, 9, 18].

In patients suffering from head and neck cancers, the lesions induced by OM may vary with regards to their intensity, depending, among others on the irradiation dose and its possible combination with chemotherapy [9, 11].

Oral mucositis may lead not only to difficulties in food consumption, but also in everyday life [19]. The immunity of these patients is compromised, and thus the risk of developing other diseases, also in the oral region, is greater [15]. Loss of body weight or emaciation of the whole organism as well as resulting outcomes such as sepsis and death are likely [12]. The total duration of treatment and hospital stay are longer, more medication is required, and the patient needs interventions in hospital more frequently [5]. Also the economic outcomes of OM are significant for the healthcare system [5, 10]. OM symptoms also impair the patient's quality of life and may lead to depression and social isolation resulting from problems with food intake and speech [5]. Moreover the quality of life is decreased and swallowing problems can occur. In such

situations it is necessary to modify the anti-cancer treatment or even completely discontinue it, which can certainly lead to rather adverse outcomes [5, 9, 10].

Diagnosis

There are many classifications applied for the evaluation of the intensity of OM [3]. The majority of centres base their evaluation on the five-grade scale worked by the WHO [15] (tab. I).

In order to make a quick diagnosis of OM, it is necessary to make a frequent and detailed physical examination and take a detailed history of the patients undergoing radiotherapy. The time of symptom occurrence and the intensity of OM must be monitored during therapy [11].

Prevention and treatment

So far, no effective method of OM treatment has been introduced [22], that is why a key role is played by prophylaxis [9]. The preventive actions concentrate in the improvement and maintenance of the correct oral cavity hygiene and symptomatic treatment [22]. Laser therapy and cryo-therapy play an important role. In patients undergoing chemotherapy, Bockel et al. used laser therapy 2–3 times per week with a low power laser (630–660 nm) and obtained good therapeutic effects [13]. Daugėlaitė et al., in 2019 published a metanalysis of research papers concerning OM treatment published in 2007–2017 [22]. The authors described the substances used for prevention and treatment of OM, comprising, among others: a balm with *Lactobacillus Brevis* or royal jelly [22]. Other substances helpful in the treatment of OM were chamomile [23], calendula [11], aloe, curcumin [24], honey [14, 24, 25, 26], as well as vitamins C and E [13, 22, 26, 27].

Chamomile *(Matricaria recutita)* has the ability of inhibiting cyclooxygenase, 5-lipoxygenase and prostaglandins, and thus has anti-inflammatory and anti-microbic properties. It alleviates burning sensation and pain [9] and also has an anti-oxidating action, thus decreasing the amount of IL-1b and TNF-α [23].

Aloe *(Aloe vera)* has antipruritic, moisturising, anti-inflammatory and astringent properties. It is also a source of minerals, amino-acids, vitamins and fatty acids; moreover it is an immunostimulant with anti-cancer activity properties[9, 24].

Vitamin E has strong antioxidant action [26].

Table I. OM intensity scale according to WHO [10, 20, 21]

OM intensity stage	Symptoms
0	no lesions
1	pain, erythema
2	erythema, erosions – yet the patient is able to eat solid food
3	ulceration – liquid diet is required
4	the patient is unable to consume fluids – parenteral nutrition

Honey has an antibacterial and anti-inflammatory action [30], and, according to some experimental research, inhibits the initiation of NF-kB [14, 26].

Despite the extensive research which provides very positive evaluations of the above substances, available literature lacks any clear recommendations concerning their use in OM prevention and treatment in patients with head and neck cancers undergoing chemotherapy or radiotherapy. Prospective trials conducted on large groups of patients are necessary.

In 2014, the International Society of Oral Oncology (ISOO) and the Multinational Association of Supportive Care in Cancer (MASCC) published guidelines for treating patients with OM. The authors emphasise the role of oral hygiene in the prevention of the disease. They pay special attention to teeth brushing and rinsing the oral cavity [6, 8, 16].

In June 2019, the guidelines of MASCC/ISOO were updated and this revised version confirmed the previous guidelines concerning the basic rules of oral hygiene in OM prevention. The benefits from patients education were emphasised [28]. The study group MASCC/ISOO based this update on 9 source articles, 8 of which concern OM prophylaxis and treatment. The review concerned the principles of oral cavity care, the role of anti-inflammatory agents, natural substances, vitamins, dietary supplements, photo-biomodulation, and oral hygiene (tab. II). However, many binding guidelines have remained unchanged. The need for further research was stressed which might affect the next update of the guidelines [28–32].

What draws attention in the MASCC/ISOO guidelines from 2019 is an important change concerning the use of zinc and glutamine administered systemically [16, 31]. It is stressed that **zinc** is necessary for the correct functioning of the immune system and antibody production, as it has the ability to remove superoxide free radicals [9]. **Benzydamine**, in turn is a non-steroid anti-inflammatory drug – its efficacy has been proven in patients after irradiation treatment [22].

No recommendations concerning the administration of zinc, supersaturated *calcium phosphate rinse* (SCPR), an elemental diet and vitamin E [31] in the prevention of OM in patients with head and neck cancers undergoing RT and/or RT-CT were made. However, there was a suggestion of oral administration of glutamine in patients undergoing radiotherapy in order to prevent the development of OM. It must be remembered, however, that patients suffering from MS who are treated with hematopoietic stem cell transplantation (HSCT), should be administered glutamine with caution. In patients who received glutamine systemically, some treatment failures have occurred [31].

As a result of the lack of adequate number of trials, MASCC/ISOO did not publish any guidelines concerning the use of anti-inflammatory drugs, such as celexibe, misoprostol or rebamipide, for the prevention of OM in patients with head and neck cancers. In the OM prophylaxis, experts recommend rinsing the oral cavity with benzydamine in patients receiving

Table II. Interventions connected with radiotherapy in patients with head and neck cancer, published by MASCC/ISOO – guidelines update from 2019 [28–32]

Intervention	Guideline
Photo-biomodulation – laser and other light therapies, intraoral low-power laser therapy	• OM prevention in patients with head and neck cancers: – radiotherapy: change of the guidelines from suggestions to recommendations; – patients in chemotherapy: novelty – use recommendation • OM treatment: no guidelines
Glutamine – oral	• OM prevention in patients with head and neck cancer: – radiotherapy: no guidelines – radio-chemotherapy – use suggestion
Elemental diet	• no guidelines
Zinc	• OM prevention in patients with head and neck cancer: – radio- or radio-chemotherapy: change – currently no guidelines
Supplements: vitamin E, selenium, folic acid, calcitriol	• no guidelines
Rinsing oral cavity with benzydamine	• OM prevention in patients with head and neck cancer: – radiotherapy, dose up to 50 Gy: confirmation of the previous guidelines – rinsing oral cavity with benzydamine – radio-chemotherapy: use suggestion • OM treatment: – radiotherapy: no guidelines – radio-chemotherapy: no guidelines

radiotherapy, as an independent treatment, up to a dose of 50 Gy [32]. It is also advisable to rinse the oral cavity with saline and calcium bicarbonate as this facilitates the maintenance of the correct oral hygiene for patients [28]. That said, similarly to the previous guidelines, chlorhexidine is not recommended as a mouth wash [28].

The MSCC/ISOO guidelines from 2014 concerning the prevention of oral mucositis in patients undergoing high-dose chemotherapy and whole body irradiation, before an autologous transplant of stem cells in the treatment of haematological cancers, recommend the use of palifermin [6, 8, 16]. **Palifermin** is a recombined human keratinocyte growth factor (KGF1), which affects the growth and differentiation of epithelial cells, playing also a role in inhibiting the process of apoptosis [5]. In spite of the promising results of the trials concerning the efficacy of this medication in OM prevention [22, 33, 34], there are also published reports about the adverse effects of this drug on cancers of the head and neck area treated with combined chemotherapy [35].

As a result of radiotherapy, reactive oxygen species (ROS) are produced which damage the cells of the mucous membrane. For the treatment of this condition, there were attempts to use the anti-oxidation enzyme: **superoxide dismutase** (SOD). A derivative of SOD, based on manganese, was produced and named **GC4419** – this substance has the ability to dissociate superoxide anions [5]. Barbor et al. described the beneficial the effect of this substance [36], including the results of the studies carried out by Anderson et al. are promising. In patients undergoing combined chemotherapy, after an intravenous administration of SOD, the intensification and duration of OM was decreased [37].

It must be remembered that it is prophylaxis that plays the key role in patients undergoing radiotherapy. That is why a patient qualified for irradiation of the head and neck area requires a thorough dental assessment and detailed instructions concerning oral hygiene. Correct oral care makes up a significant element of cancer patient treatment. Oral cavity hygenisation in order to remove potential inflammatory foci, requires the folowing procedures:

- completed treatment of cavities resulting from caries,
- correction of sharp filling edges,
- extraction of teeth not qualified for further treatment, and
- treatment of other inflammations within the oral cavity

It is necessary to control, and, if necessary, correct dentures and also to inform patients about nutritional requirements during radiotherapy. Sour, hot and overly hard products are not recommended. A large amount of fluid intake is recommended. The priority is to prevent any inflammatory condition within the oral mucosa as during anti-cancer treatment it is subject to irradiation. During oncological treatment the patient should be under the regular supervision of their dentist, so that a quick intervention in the case of inflammatory lesions within the oral cavity is possible [11].

Tables III and IV present detailed recommendations concerning prophylaxis and treatment in patients with symptoms of OM after radiotherapy, based on the selected, leading clinical recommendations [38].

For many years OM has been in the interest of dental associations. In 2015 the recommendation of the Polish Group of Specialists in Prophylaxis and Treatment of Complications within the Oral Cavity was published. The prophylactic and treatment procedures connected with irradiation were discussed in detail in this publication. These recommendations, in a brief from are presented in table V [39].

In 2009 Pytko-Polończyk proposed an algorithm of dental care in patients undergoing radio- and chemotherapy [40].

Table III. The comparison of the methods of oral mucositis (OM) prevention [38]

Before the commencement of anti-cancer treatment • dental treatment • prospective tooth extractions – 10–14 days before the planned radiotherapy
During radiotherapy and after its completion (for ≥2 weeks) • washing teeth with a toothpaste and soft toothbrush (regularly exchanged) ≥3 times per day • using dental floss • frequent drinking of small amounts of water and/or rinsing oral cavity with 0.9% saline, sodium bicarbonate or liquid containing benzydamine (Hascosept, Tantum verde) – 4–6 times per day • not using the solutions of chlorhexidine and alcohol
Absolutely forbidden • tobacco smoking • alcohol consumption • hot spices • tough food
It is recommended to use ice cubes (only when there oral mucosa is not damaged)

Table IV. The treatment of the patients with OM symptoms [38]

Symptom	Recommendations
Oral cavity dryness	• sugar-free chewing gum, sugar-free sweets • rinsing oral cavity with 0.9% NaCl solution or sodium bicarbonate • artificial saliva
Mild to moderate pain	• local agents – benzocaine or benzydamine (used a few times per day onto the affected oral mucosa)
Strong pain	• analgesic treatment according to the WHO recommendations or rinsing with 0.2% morphine solution or 0.5% doxepin oral solution.
Suspected infection	• a swab followed by empirical treatment with a broad- spectrum antibiotic (aminoglycoside or 3rd generation cephalosporin)
Suspected oral candidiasis	• anti-fungal treatment
Inability of oral consumption	• parenteral nutrition to be considered
Irrespectively of symptoms	• zinc supplementation to be considered

Table V. Recommendation of the Polish Group of Specialists in Prophylaxis and Treatment of Complications within the Oral Cavity [39]

Prophylaxis before treatment	• oral hygiene (brushing teeth 3 times per day with a very soft toothbrush, rinsing oral cavity with 0.9% NaCl solution or with baking soda solution – 1 teaspoonful per 100 ml of boiled water, flossing) • temporary removal of orthodontic appliance • limitation of use of movable dentures • dietary recommendations • evaluation of the patient's nutrition status and, if necessary, gastrostomy tube feeding
Preparation to head and neck irradiation	• evaluation of the condition of oral cavity, orthopantomogram • hygenisation of oral cavity • conservative treatment, periodontology treatment with post-extraction wound dressing • evaluation of prosthetic restorations • removal of permanent dentures
Patients in radiotherapy or chemotherapy – prophylaxis	• proper oral hygiene • brushing teeth with a soft toothbrush • dental flosses • cleaning of movable prosthetic restorations, at night – storing dentures in dry conditions • oral cavity rinsing with 0.9% NaCl solution or baking soda solution – 5 times/day • oral cavity rinsing with benzydamine 4 times/day • oral cavity rinsing with – Caphosol solution 4–6 times/day • oral cavity rinsing with – complex preparations – Alpha Med, laryngology mix • secretion diluting agents • fluoridation • dietary consultation
Patients in radiotherapy or chemotherapy – treatment	• fungal infection – fluconazole 200–400 mg/day, nystatin – 5 times/day • bacterial infection – antibiotic therapy according to the antibiogram or empirical • Caphosol – rinsing oral cavity – 6–10 times/day • benzydamine – 4 times/day

	• viral infection – acyclovir *p.o.*, *i.v.* to be considered • analgesic treatment – medication and dose to be selected according to the WHO recommendations • saliva substitutes • high-protein and high-energy diet • laser therapy
Patients after healing of acute post-irradiation reaction	• saliva substitutes • dental consultation – evaluation of the oral cavity condition, hygiene instruction, soft toothbrushes, toothpaste with increased fluoride contents, brushing teeth after each meal, defects filling, fluoridation • surgical intervention 6 months after the end of treatment with antibiotic cover • dental check-up every 3 months

Knowledge of the general principles of dental management in such patients should be, at least in general, known to oncology specialists, as this is an element of multispecialist patient care in cases of malignant cancers.

In **the first period**, before the commencement of anti-cancer treatments, a decontamination of the oral cavity should be performed. This process should be completed at least one week before the start of oncological treatment. This process comprises professional hygienisation procedures connected with detailed instructions for the patient, the removal of foci of inflammation and caries, filling the cavities and elimination of all traumatising factors. In **the second period**, during the anti-cancer treatment, a proper collaboration between the dentist and the oncology specialist is necessary. The procedures comprise the use of agents treating local lesions in the mucosa, including the first symptoms of OM and also the use of medication to alleviate xerostomia. The drugs which alleviate such lesions comprise a protein-free dialysate of calf blood (Solcoseryl paste; Meda), vitamin A + D3 in a fluid form, dental washes containing herbal mix, allantoin, D-panthenol, linseed (e.g. Alfa-med Atos, Alfa-implant Atos), a solution of calcium-phosphate ions (Caphosol [7, 40], Fomucal [41]). Also fluids containing benzydamine have a beneficial effect (Hascosept, Tantum verde) [38]. Often in patients after oncological treatment, it is necessary to introduce antibacterial and/or anti-mycotic treatments. It is recommended to have a low-carbohydrate diet, rich in vegetables and fruit, kephir and milk. The use of vitamin B is also helpful. The **third period** of dental care begins after the completion of oncological therapy, and is comprised of the continuation of the collaboration between the dentist and the patient, motivating them to maintain correct oral hygiene, the elimination of radiotherapy side-effects, such as: xerostomia, candidosis, bacterial infections. The patient should visit their dentist every one to three months and, then every three to six months [7, 40].

Conclusions

Dentists play an important role in the prophylaxis of OM, especially in the multispecialist treatment of patients with cancers of the head and neck region who have developed symptoms of oral mucositis. That is why it is justifiable that oncological centres should create specialist teams, consisting of an oncologist, a dentist and a nurse. The members of these teams could provide multidisciplinary care to patients with head and neck cancers with regards to the prevention of OM and the treatment of this complication within the oral cavity.

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Commentary

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Commentary: *Oral mucositis (OM) – a common problem of oncologists and dentists*

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Oral mucositis (OM) is a clinically significant problem affecting more than 90% of patients with cancers of the head and neck area, undergoing radiotherapy where the oral cavity is located within the clinical target volume (CTV). The clinical effect of OM is the result of the existence of the following factors:

- generating symptoms (pain, taste disorders, difficulties in swallowing), leading to disorders of the water and electrolyte metabolism and, finally, malnutrition,
- significant deterioration in quality of life, and
- limitation of radiotherapy tolerance which might lessen treatment effects [1–3].

The patomechanism of the development of radiotherapy-induced OM is well studied and described. This is a multi-stage process, comprising:

- damage (as a result of the ionising irradiation) and the death of cells within the basal layer and generation of free radicals,
- development of an inflammatory reaction which stimulates the cells' death,
- the production of proinflammatory cytokines stimulating the development of ulceration, leading to secondary infection,
- final stage (healing), with the proliferation and differentiation of epithelial cells [4, 5].

This process was described in detail in the paper: *Oral mucositis (OM) – a common problem of oncologists and dentists.*

There are also many factors affecting the risk of OM development during radiotherapy [1, 3, 6–12] – three groups of factors can be distinguished here:

1. **Treatment induced**, comprising: the size of the radiotherapy dose and the fractionating pattern, as well as the use of chemotherapy; these factors not only affect the intensification of OM, but also the moment of its development (positive correlation between the dose and intensity of OM; in the case of the administration of accelerated fractionation (AF) of a dose, the symptoms of OM develop earlier and they are more intensive, whilst the application of combined treatment – chemo-radiotherapy, especially with weekly administration of cisplatin – leads to an effect

Table I. The comparison of the scales RTOG/EORTC and CTCAE, to complete the publication in which the WHO scale was discussed by the authors of the paper Oral Mucositis (OM) – a Common Problem for Oncologists and Dentists

Intensity	RTOG/EORTC [13]	CTCAE [14]
G1	low intensity of erythema and pain (does not require treatment)	no symptoms or mild symptoms
G2	focal serous mucositis, moderate pain (require the use of analgesic agents)	moderate pain, retained ability of oral food intake, necessity to modify diet
G3	diffuse inflammation with fibrin production, significant pain (require the administration of narcotic analgesics)	severe pain, impaired food intake
G4	ulceration, bleeding, necrosis	life threatening condition, requiring urgent intervention
G5		death

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which is cumulative with regards both to the intensity and duration of OM);

2. **Cancer-induced**, which comprise, first of all, the location and size of the primary tumour, determining the clinical target volume and the size of the irradiated mucosal membrane of the oral cavity and salivary glands;
3. **Characteristic of the patient,** which do not only determine the risk of development, but also the intensity and duration of OM. These comprise: patient age, a history of tobacco and alcohol consumption, the presence of metal dentures, co-existing periodontal conditions, low body mass index (BMI), limited degree of physical fitness, decreased leucocyte count, advanced cancer stage, a history of oral cavity diseases, comorbidities and gene polymorphism (*XRCC1*, *NBN*), determining the cytokine phenotype facilitating the development of OM.

There are various scales used in clinical practice for the evaluation of the intensity of lesions within the oral mucosa (RTOG/EOTC, WHO, CTCAE) [1, 13, 14] (tab I).

OM is a problem which decreases the efficacy of radiotherapy (as it involves the necessity of intervals in therapy), deteriorates the patients' quality of life (OM symptoms and clinical outcomes), therefore the selection of effective treatment methods is necessary. Correct prophylaxis and treatment (i.e. symptomatic interventions and targeted methods) reduce OM intensity and thus will allow for the improvement of the efficacy of the local treatment and of patient survival. The significance of this grave clinical problem, as the development OM definitely is, justifies thoroughly working out the guidelines concerning its prophylaxis and treatment.

In 2019 an attempt was made to update the guidelines of MASCC/ISOO on the basis of the existing publications [16]. The results of this update and the recommendations of the Polish Group of Specialists in Prophylaxis and Treatment of Complications within the Oral Cavity published in 2015, and comprising the prophylaxis and treatment to be applied in patients undergoing radiotherapy, were discussed in detail in the paper: *Oral Mucositis (OM) – a Common Problem of Oncologists and Dentists*.

The MASCC/ISOO guidelines (update from 2019) confirm the significance of basic rules of oral hygiene in OM prophylaxis and the benefits resulting from adequate patient education [16].

The clinical significance of OM as well as the data coming from current publications point to the importance of oral hygiene in OM prophylaxis and treatment, and delineate the role of dentists in multi-disciplinary therapeutic proceedings in patients with head and neck cancers. The role of the dentist in OM prophylaxis and treatment cannot be overestimated. The algorithm of dental care of oncological patients, worked out in 2009 [17], confirms the necessity of interdisciplinary collaboration between oncologists and dentists.

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COVID-19

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The launch of a COVID-19 diagnostic laboratory in an oncology hospital – a review of guidelines and the laboratory team's own experiences

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The first case of the coronavirus SARS-CoV-2 infection was confirmed in December 2019 in Wuhan, China, from whence the virus spread across the world within several weeks. Due to the alarming level of infections, the World Health Organisation (WHO) announced a SARS-CoV-2 pandemic on 12 March. This dynamic and unprecedented epidemiological situation created an urgent need to carry out SARS-CoV-2 tests in individuals meeting the criteria defined for COVID-19 suspect cases. According to the current WHO recommendations, active SARS-CoV-2 infection diagnostics is based on molecular method using a real-time reverse transcription – polymerase chain reaction (real-time RT-PCR). Highly specific and sensitive, this method makes it possible to detect even a small amount of RNA particles of the virus in the tested sample. Undoubtedly, the launch of new COVID laboratories and the implementation of adequate procedures increases the effectiveness of activities aimed at directly combatting the SARS-CoV-2 pandemic. The population of oncological patients is particularly exposed to the risk of complications and death resulting from the SARS-CoV-2 infection; therefore it is essential to ensure them the possibility of quick testing for COVID-19. This article presents the authors' own experiences as well as technical and formal issues related to the launching of a SARS-CoV-2 laboratory.

Key words: COVID-19, SARS-CoV-2, diagnostics, real-time RT-PCR

The SARS-CoV-2 pandemic, whose first case was confirmed in Poland in March 2020, forced many medical laboratories to address the need to launch departments focused on SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection diagnostics. According to the World Health Organisation recommendations, molecular tests using a real-time reverse transcription polymerase chain reaction (RT-PCR) which detect the virus genetic material in a sample collected from a patient are performed [1, 2].

The material for SARS-CoV-2 tests includes samples collected from the upper respiratory tract (nasopharyngeal swabs or tracheal and mucosal swabs) and the lower respiratory tract (trans-tracheal aspirates, broncho-alveolar lavage or non-induced sputum) [3–6].

Molecular tests are essential to detect an infection with SARS-CoV-2. At present, the number of confirmed cases in Poland exceeds 93 thousand (as of 1 October 2020), which is the result of work of over 197 laboratories. This means that in a short time many laboratories had to modify or expand the profile of their activity and adjust rooms, equipment and procedures to SARS-CoV-2 molecular diagnostics using the real-time RT-PCR method. This paper presents the experiences

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of the team involved in the launch of the COVID laboratory in Wroclaw Comprehensive Cancer Centre, Poland, which routinely used real-time PCR, PCR, Sanger sequencing and next generation sequencing methods (NGS) to detect somatic and germline mutations in oncological patients prior to the pandemic.

Cancer has been the second most common death cause in Poland. They are responsible for the death of almost 100 thousand patients per year and about 300 per day. According to the recommendations of the Polish Oncological Society (Polskie Towarzystwo Onkologiczne – PTO) and the Polish Society of Clinical Oncology (Polskie Towarzystwo Onkologii Klinicznej – PTOK), all healthcare units providing oncological treatment should implement stringent safety procedures and continue to provide healthcare services to patients during the SARS-CoV-2 pandemic [7, 8]. It is generally known that elderly persons and individuals with reduced immunity are at the highest risk of the severe form of COVID-19 and death [9]. On the basis of the Polish National Cancer Registry data, there are about one million cancer patients in Poland at present and over 60% of them are over 65 years of age, which means that the risk of complications as a result of the SARS-CoV-2 infection is severe for this population [10]. Pursuant to the current recommendations of the Chief Sanitary Inspectorate (Główny Inspektor Sanitarny – GIS) and the Health Ministry, each patient suspected of having COVID-19 should undergo tests for SARS-CoV-2 before his or her admission to an oncology centre [9]. Currently, in order to continue to provide treatment to patients at oncology centres, it is essential to ensure stringent protection systems for patients and personnel, among others by launching laboratories offering SARS-CoV-2 molecular diagnostics.

Sample collection and qualification

SARS-CoV-2 test samples are collected in a separate room which is located in an epidemic airlock within the hospital. The swab collection point is divided into 3 zones:

- the patient zone (collecting swabs),
- the working zone (sample description and packing),
- the staff changing zone (including a place where the staff members may change their clothing, a storeroom with personal protection equipment (PPE), additional materials necessary for swabs, waste disposal, etc.).

All items in the storeroom are divided into smaller packages and packed into airtight containers, which facilitates disinfection. At the beginning of the pandemic, swabs were collected in two shifts: the morning shift (8–10 AM) and the afternoon shift (1–3 PM). The morning shift was designed for the patients of the Wroclaw Comprehensive Cancer Centre in Wroclaw and the afternoon shift was for the staff working at the centre. With the stable epidemic situation at present, swabs are only collected in the morning. The staff and patients of the hospital are separated, which is also the case for symptomatic individuals. The last persons in the queue are those qualified for next test in order to confirm the virus eradication. The time between swabs (about 5 minutes) is used for surface disinfection as well as sample description and packing. Following the guidelines of the Chief Sanitary Inspector, samples are packed into three packages and stored in a fridge (located at the collection point) [5]. Swabs may also be collected at any department where employees have received the relevant training. The work schedule for the collection point staff is prepared one month ahead. Occasionally, a staff member may be sent using a hospital's means of transport to a person who is not able to come to the collection point. Each person collecting samples is equipped with PPE pursuant to the WHO guidelines (which applies both to the collection point, the ward and swabs collected outside the hospital area). The qualification of individuals for swabs is coordinated by the Hospital Infection Control Department, which verifies indications for swabs and their timing. The list of patients for admission is prepared after their qualification at outpatient clinics and the confirmation of the patient's introductory negative epidemiological history (obtained over the phone) by the secretariat of each ward.

Laboratory rooms and equipment

A COVID laboratory requires isolated rooms of biosafety level 2 (BSL – 2). Ideally, it should be located in a separate building or part of the building, but because of the sudden outbreak of the pandemic and the need to launch such laboratories quickly, this was impossible in most cases. The COVID lab should have at least 2 rooms: one for the isolation of nucleic acids, divided by an airlock, and the other one for real-time RT-PCR. Sample unpacking and virus RNA isolation should be carried out in a laminar flow cabinet of minimum biosafety level 2. Lab employees must be wearing safety clothing in the laboratory described here it includes Tyvek 500 Labo Cat. III uniforms, FFP2 or FFP3 masks and face shields, talc-free gloves, caps and shoe covers).

Each entry into and leaving of COVID laboratory rooms must be in strict compliance with very detailed safety rules. This is why SARS-CoV-2 RNA isolation is performed by one team successively for all swabs registered in a given diagnostic cycle. In this way, it is possible to reduce the need for frequent changes of protective clothing and moving between the zones separated for the purpose of diagnostics. In the early period of the pandemic, i.e. from March to May 2020, the laboratory team was divided into two smaller teams that performed tests every second day, which increased the staff's safety as these groups had no personal contact with each other. After restrictions were relaxed in June 2020, the lab went back to its standard operation. Apart from the BSL-2 laminar flow cabinet (BIO130 Alpina model), the COVID lab is equipped with the Maxwell RSC48 (Promega) device for automatic isolation of genetic material from 48 samples at the same time. Alternatively, the

genetic material can be isolated manually, but using automation, it was possible to reduce the time needed to obtain results and achieve high quality RNA. The Maxwell Blood DNA kit (Promega) and the Maxwell RSC Viral RNA kit (Promega), designed for the lab equipment, are used interchangeably to isolate RNA, depending on their availability on the market. Both have been validated by the producer as kits for the isolation of the SARS-CoV-2 genetic material and ensure the high efficiency and high quality of RNA.

According to the latest report on the results of an external quality assessment of molecular tests for SARS-CoV-2 prepared by two international organisations, the European Molecular Genetics Quality Network (EMQN) and Quality Control for Molecular Diagnostic (QCMD), the proportion of correct results obtained with the application of the Promega Maxwell RSC Viral kit is 95.5% (n = 176, p = 0.644) [11]. RNA isolation is performed according to the producer's protocol with one modification: each swab moistened with physiological saline, which is placed in a separate dry tube after material collection, is transferred to a sterile Eppendorf tube and broken off from the stick by holding the lid. Next, 300 µL of phosphate-buffered saline (PBS) is added to the tube. This step is omitted for samples collected to physiological saline. After brief mixing in a vortex, 300 µL of a buffer for lysis and 30 µL of proteinase is added. The sample is mixed in a vortex for 15 seconds and incubated for 15 minutes in the temperature of 56°C. The subsequent steps are carried out following the producer's manual. The laboratory described here decided to apply this method of collection and isolation (as compared with the isolation from physiological saline in which entire swabs are usually immersed) because it considerably facilitated the transfer of the biological material from the long tube in which the swab was placed to the Eppendorf tube and reduced the risk for the transfer of the solution potentially containing the virus onto gloves or working surfaces. According to the recommendations of the Health Minister of 21 April 2020, it is permitted to use substitutes of the equipment and/or reagents in the test method verification process without the need to carry out a full method validation if the substitute, according to the laboratory, enables the correct test performance [12]. The concentration and quality of the isolate obtained is evaluated using a NanoPhotometer N60 (Implen). Samples with low concentration, the concentration of 10 ng/µl or below or samples of poor quality are reported for another swab collection. This is especially important when there is no internal control of the housekeeping gene in the diagnostic tests used. Synthetic bacteriophage RNA added to reagents as an internal control does not make it possible to check whether the required RNA level has been achieved in the tested sample after isolation.

Apart from the basic research equipment and standard small devices (microcentrifuges, pipettes, stands, etc.) used in molecular laboratories, which must be part of the equipment in both rooms (the equipment cannot be transferred between rooms), UV flow lamps and direct UV lamps are useful for air and surface sterilisation. The advantage of UV flow lamps is that they can be turned on during the diagnosticians' work.

Swabs

The selection of swabs for sample collection from the nasopharynx in the second quarter of this year was limited due to great demand across the world. Sterile swabs must be made of artificial materials (polyester or viscose). After the selection of the type of swabs, each laboratory should check the quality of the samples collected and adjust the manner of collection to its own procedures. Due to the fact that the laboratory described here was in operation as early as in March 2020, the method of nasopharynx sample collection from healthy individuals was tested at the beginning. The total RNA from the swab, including human RNA, is isolated, so the evaluation of its concentration in the isolate made it possible to determine whether the swabs (Equimed) used were adequate. A smear was collected on a dry swab moistened just before collection with a few drops of physiological saline. Pouring 2 ml of physiological saline solution to the probe with a swab resulted in the reduced efficiency of nucleic acid isolation and impeded its first step, i.e. the separation of the swab from the stick. There were also difficulties with the transfer of the solution from the long tube containing the swab to the Eppendorf tube. The quality of the sample collected is also important. The swab should not contain blood or other contaminants (as they may contain inhibitors of the PCR reaction). Swabs were transported following the WHO guidelines and the rules specified in the document published on the website of the National Chamber of Laboratory Diagnosticians (https://kidl.org.pl/get-file/2671). Because of the limited selection of tests available on the market in the early period of the pandemic, the laboratory described here used the two-gene test Vitassay qPCR SARS CoV-2 (Vitassay) CE-IVD (genes of SARS-CoV-2: *ORF1ab* [FAM signal] and *N* gene [ROX signal] as well as an RNA internal control [HEX signal]). But this did not solve the need for the quality control of the isolated genetic material (the same results were achieved for samples without nucleic acids and for the so-called zero controls). At present, because of better parameters, the three-target test GeneFirst-Novel Coronavirus (COVID-19) Nucleic Acid Test Kit, CE-IVD (GeneFirst), is used (genes of SARS-CoV-2: *ORF1ab* [FAM signal] and *N* gene [ROX signal] as well as the human gene: *GAPDH* [CY5 signal]). The reaction was performed with the application of the CFX96™ Real-Time PCR Detection System (Bio-Rad). The detection limit for the test is 10–100 copies of the virus RNA per one reaction. The reaction is performed according to the producer's protocol for the tested samples as well as a positive control (containing synthesised sequences of the nucleic acid to detect genes ORF1ab and N of the SARS-CoV-2 virus, as well as human *GAPDH*) and a negative control (non-template control – NTC). An undeniable advantage of this kit is the detection of the GAPDH human gene, which is

the evidence for the RNA presence in the tested sample and significantly reduces the risk of a false negative result. Moreover, as has already been mentioned, the nucleic acid concentration is determined for each sample before the reaction. At the same time, along with positive and negative controls added to the kit, there is an isolation control for each series of samples (zero control), an isolation from a clean swab moistened only with sterile physiological saline. In this way, it is possible to evaluate the purity of isolation – a positive result confirms contamination and the need to repeat the entire series of tests. The quality of the isolated material depends largely on the manner of swab collection. Because the virus RNA and the patient's RNA are isolated together, there is no certainty that the sample contains SARS-CoV-2 nucleic acid despite the evaluation of the RNA concentration. This might be the reason why false negative results are obtained.

The analysis of the data obtained from real-time RT-PCR is carried out using the Bio-Rad CFX Maestro software (Bio-Rad) following the producer's manual. According to - the manual, a sample is positive when fluorescence curves for both tested viral genes have the correct shape and cross the threshold. The presence of SARS-CoV-2 is confirmed in the sample when the signal is amplified with Ct ≤ 39 in FAM and ROX channels. A sample is negative when the signal is amplified with Ct > 39.0 or without Ct in FAM and ROX channels. If one of the two tested genes produces a positive result in a FAM or ROX channel, the sample may be positive and the patient needs to be tested again. It is crucial to follow the test producer's guidelines, which enables a reduction of the risk of false positive results. Samples with a positive signal but below the threshold for which an infection onset (low viremia) may be suspected are always reported for another test in the laboratory described here. In – more than half of such cases (8/14, 57%) analysed in March–April 2020, an infection was confirmed after a few days (positive result).

It should be emphasised that the guidelines of the National Institute of Public Health – National Institute of Hygiene (Narodowy Instytut Zdrowia – Państwowy Zakład Higieny NIZP-PZH) indicate that a negative test result is not tantamount to the absence of an infection and each test result should be interpreted with reference to clinical data.

Laboratory personnel

The laboratory employs diagnosticians with extensive experience in molecular biology and two members of its staff have previously worked on molecular diagnostics of viruses. The experience of these two staff members was employed when the rooms and the layout of the equipment in the rooms for SARS-CoV-2 diagnostics were prepared and the laboratory's own decontamination procedures based on WHO recommendations were developed. Because of the need to report results to various institutions, numerous administrative employees are also involved in the work of the COVID laboratory.

Laboratory decontamination

Because of large numbers of SARS-CoV-2 samples at one time and place, the virus genome size of about 30 kb and high viremia of some patients, there is a high risk of sample contamination and false positive results regardless of the application of all possible safety measures. Each laboratory should develop and implement procedures reducing such a risk, i.e. detailed rules for the work within the BSL-2 laminar flow cabinet, handling positive control samples, handling samples from patients and decontamination of all equipment and surfaces on a regular basis.

Apart from thorough disinfection every day, it is necessary to carry out a systematic general decontamination of rooms, including surfaces and the entire equipment, on a set date. The frequency of decontamination should increase with the number of samples handled. Apart from 70% ethanol, the WHO guidelines recommend the following substances to be used for this purpose: 0.1% sodium hypochlorite (the so-called ace or bleach), hydrogen peroxide, quaternary ammonium compounds and phenolic compounds (following the producer's recommendations). Good results can also be achieved when solutions for the disintegration of nucleic acids (e.g. PDS-250 Biosan) are applied directly on surfaces in the laminar flow cabinet and on small equipment on a regular basis.

External quality control

A laboratory that performs tests for SARS-CoV-2 must be registered with the Health Ministry and undergo an external quality test offered by the NIZP-PZH in Warsaw (which is free of charge). The test involves submitting 15 of the lab's own samples (swabs or the liquid in which swabs were placed) together with the required documentation and information about the method applied. At present, international quality control programmes are also available for the purpose of SARS-CoV-2 diagnostics. Participation in such a programme significantly increases the credibility of results obtained in a laboratory. Such international organisations as EMQN and QCMD have introduced a pilot programme for the external control of the quality of diagnostic tests for SARS-CoV-2. Study results, which were published in a paper by Matheeussen et. al., present a review of the assessment carried out in 365 laboratories from 36 countries [11]. The laboratory described here has implemented a quality control system and keeps a record of pre-analytical errors. Each deviation is reported to the contracting unit and the Epidemiology Department of the Wroclaw Comprehensive Cancer Centre. If a pre-analytical or laboratory error is confirmed or results are ambiguous, the need to collect another swab is reported.

Reporting of results

An important part of the COVID laboratory's work is to report the results. Below, there is a list of web portals and institutions that require everyday reports.

- Health Ministry – reports through the portal https://wsse.mz.gov.pl (WSSE once daily (tests) at 8:00 AM and WSSE twice daily (queues) at 8:00 AM and 8:00 PM) including the number of tests available at the laboratory, the number of tests ordered individually, the number of tests performed on patients in the past 24 hours, the number of positive results in new patients in the past 24 hours, the number of tests which may be performed at the same time, the number of samples under examination, the number of samples waiting for examination and the number of samples in isolation.
- Provincial Sanitary and Epidemiological Station (Wojewódzka Stacja Sanitarno-Epidemiologiczna – WSSE) – reports on new positive cases (three times daily at 7:00 AM, 1:00 PM and 7:00 PM).

Additionally, depending on whether the result obtained was negative or positive, the COVID laboratory must provide information about:

- a positive result together with the patient's data to:
  - the contracting unit,
  - the dedicated COVID-19 hospital with competence over the patient's place of residence (result scan and ZLB.1 form),
  - the District Sanitary Inspector with competence over the tested person's place of residence (result scan and ZLB.1 form),
  - the Provincial Sanitary and Epidemiological Station (Powiatowa Stacja Sanitarno-Epidemiologiczna – PSSE) (ZLB.1 form).
- a negative result together with the patient's data to:
  - the contracting unit
  - the District Sanitary Inspector with competence over the tested person's place of residence (scan of the laboratory result report).

The COVID laboratory is also obliged to submit weekly reports on the number of molecular tests performed to the Provincial Sanitary Inspectorate (Wojewódzki Inspektorat Sanitarny).

If tests are reimbursed by the National Health Fund, the laboratory has to enter data and results into the EWP3 system (https://ewp3.mz.gov.pl).

Moreover, the laboratory described here must prepare everyday reports on all the results obtained in a day and on the numbers/amount of the personal protection equipment in stock for the hospital unit.

Conclusion

From March until the end of September 2020 over 5,700 tests were performed at the COVID Laboratory of the Wroclaw Comprehensive Cancer Centre to meet the hospital's needs (tests of employees and patients, including those hospitalised during the pandemic and patients before admission), which made it possible to ensure the hospital's operation in the pandemic peak as well as after some of the restrictions were lifted and has currently become a standard part of its activity. This article describes the most important aspects related to the launch and operation of a COVID laboratory at an oncology hospital. The authors hope that their experiences will facilitate the planning and implementation of SARS-CoV-2 diagnostics for new units. As there were no prior attempts of diagnosing this infection in Poland and any experiences in this area go back to mid-March 2020, the authors of this paper are open to any constructive critical remarks.

Conflict of interest: none declared

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Other frailty assessment instruments

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At present there is strong evidence demonstrating that not chronological age, but the presence of frailty before surgery is associated with a significant increase in postoperative morbidity, mortality, along with increased risk of delirium, disability, increased length of hospital stay and resource use. Therefore, preoperative frailty evaluations should become obligatory prior to high-risk surgery of older patients suffering from cancer. Currently, the golden standard is the full Geriatric Assessment. However, it requires time and, first of all, experience. Various simple frailty screening tools have been developed,, however, currently there is no single ideal one. Therefore, there is a constant search for the "holy grail" of preoperative geriatric evaluations. The Tilburg Frailty Indicator, the Edmonton Frail Scale, the Cardiovascular Health Study index, the Clinical Frailty Scale, the Study of Osteoporotic Fractures index and Frailty Index are examples of evaluation tools that have some features of screening scores and the full Geriatric Assessment. In the present article they were characterised briefly to familiarize the reader with the advantages and disadvantages of each.

Key words: frailty screening, Tilburg Frailty Indicator, Edmonton Frail Scale, Study of Osteoporotic Fractures Index, Frailty Index

As was mentioned in the previous article, the routine format of current preoperative requirements do not provide the information needed for optimal, tailored treatment of older patients with cancer. Therefore, the Geriatric Assessment (GA) was introduced allowing for a preoperative assessment of the patient's condition, the identification of previously unknown health problems, diagnosis of frailty, and assessment of the likelihood of complications and outcome [1]. However, the GA requires experience, it is time-consuming (although the additional 40 minutes required during the preoperative assessment seems to be a low price to pay for the possibility to decrease perioperative morbidity) and not necessary for all patients [2, 3]. Therefore, various screening tools for frailty have been developed: the Vulnerable Elderly Survey 13 [4], Triage Risk Screening Tool [5], Geriatric 8 [6], Groningen Frailty Index [7], abbreviated Comprehensive Geriatric Assessment [8], Rockwood [9], Balducci [10]. Details of their features were presented in the previous article in the Nowotwory Journal of Oncology – Oncogeriatric (part 8). Frailty screening tools can be very beneficial as they can identify patients at risk of frailty and check for adverse outcomes, particularly in situations where there is a lack of experience in the full GA, in acute admitted patients and with low-/moderate-risk surgery [11]. However, only the full GA currently allows for appropriate and full preoperative evaluation and treatment optimisation.

There are also other evaluation instruments that can be used to determine the frailty status of older patients. Some researchers place them between the screening scores and the full GA. This is not entirely true since these instruments have some of the features of both screening scores and the GA. This article aims to systematise current knowledge on the most commonly used instruments. Following the geriatric approach, the tools were divided into: objective (based on direct measurements), subjective (based on medical interviews) and mixed – table I.

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Table I. Other instruments for frailty assessment used in older cancer patients

Subjective tools	Objective tools	Mixed tools
Tilburg Frailty Indicator CSHA Clinical Frailty Scale	gait speed (as a single measure)	Fried Frailty Phenotype criteria Edmonton Frail Scale Study of Osteoporotic Fractures Index Frailty Index

Subjective tools

The Tilburg Frailty Indicator (TFI) is a tool proposed by Gobbens et al. [12]. Its concept is based on the definition of frailty being a complex, multidimensional, transitional state of increased vulnerability and loss of adaptive capacity/resistant to external stressors (in one or more domains of human functioning: physical, psychological, social, etc.), resulting in an increased risk of adverse outcomes [13].

The TFI consists of two different parts. The first one addresses sociodemographic characteristics |(sex, age, marital status, education level, monthly income and country of origin) and what the potential determinants of frailty can be. The second part evaluates the components of frailty in the form of 15 self reported questions divided into three categories: physical, psychological and social. The physical domain (0–8 points) comprises eight questions related to physical functioning, unexplained weight loss, difficulty in walking, balance, hearing and vision problems, strength in hands, and physical tiredness. The psychological domain (0–4 points) consists of four items related to cognition, depressive symptoms, anxiety, and coping. In turn, the social domain (0–3 points) comprises three questions related to living alone, social relations and social support. The total score may range from 0 to 15; the higher the score, the more severe the frailty. The frailty state is diagnosed when the total score is even or more than five [12]. The tool is simple (it takes less than 15 minutes to complete), does not require face-to-face contact [14], and it was also validated in Polish [15]. A consensus group on frailty in the year 2013 agreed that the TFI is a well-validated model of the frailty concept [16].

The Clinical Frailty Scale (CFS) [17] was introduced in the second clinical examination of the Canadian Study of Health and Aging as a way to summarise the overall level of fitness/frailty of an older adult after being evaluated by an experienced clinician. It is not a questionnaire, but a way to summarise information regarding the health status of an older person. Assessing physicians assign a score from 1 to 7 based on their own clinical judgment. The scale ranges from very fit to severely frail: 1 = very fit, 2 = well, 3 = well with treated comorbidities, 4 = apparently vulnerable, 5 = mildly frail (some dependence on others for instrumental activities of daily living), 6 = moderately frail (help needed with instrumental and non-instrumental activities of daily living), 7 = severely frail (total dependence on others for activities of daily living, or terminally ill).

In 2020, the CFS was further revised (version 2.0) with minor clarifying edits to the level descriptions and their corresponding labels. Most notably, CFS level 2 changed from "well" to "fit", level 4 from "vulnerable" to "living with very mild frailty", and levels 5–8 were restated as "living with..." mild, moderate, severe, and very severe frailty, respectively [18].

The chart also consists of information on scoring frailty in people with dementia. The degree of frailty generally corresponds to the degree of dementia. In mild dementia patients forget the details of a recent event, although still remembering the event itself, repeating the same question/story and there is usually some degree of social withdrawal. In moderate dementia short-term memory is very impaired, however, personal care is still performed without any support. In severe and very severe dementia, daily activities cannot be performed without help.

Objective tools

Gait Speed (as a single measure) [19], the time it takes for patients to walk over 4 meters. Gait sped <0.8 m/s is the cut off point for increased risk of adverse health outcomes. Gait speed <0.2 m/s is the cut off point for extreme frailty. A slow gait speed was an independent predictor of post-operative morbidity in older patients undergoing various abdominal operations due to cancer [20, 21].

Mixed tools

Fried Frailty Phenotype criteria developed by Fried et al. [13] is one of the most widely used frailty assessment tools. It uses five relatively easily measured criteria: unintentional weight loss (4.5 kg in the last 12 months), reporting poor energy (using the Depression Scale of the Center for Epidemiologic Studies, weakness (grip strength stratified according to sex and body mass index quartiles), slowness (based on the time taken to walk 4.6 m = 15 feet), adjusted for sex and height), low physical activity level (based on the short version of the Minnesota Leisure Time Activity Questionnaire). The score ranges from 0 to 5. Patients are recognised as being frail if they have three or more criteria, pre-frail in the case of one or two criteria and non-frail if none of the criteria are present, respectively. The study in a population of over 10 000 older patients has shown that frailty diagnosed on the basis of the above criteria was associated with an unfavourable prognosis; increased risk of death, hospitalisation, disability and falls during the 3- and 7-year follow-up. The risk was correspondingly lower with one or two of the CHS criteria. Despite the wide application of this method, it has significant limitations affecting the possibility of routine use. It includes criteria that require additional measure-

ments such as grip strength (using a hand-held dynamometer) and is of little use for immobile patients, as well as for people with significant severity of cognitive disorders.

The role in older oncologic surgical patients is still a matter of debate. In our analysis, comparing eight different frailty tools in older cancer patients undergoing high-risk abdominal surgeries, the Fried Frailty Criteria had only moderate accuracy predicting frailty, 30-day morbidity and mortality [11].

The Edmonton Frail Scale (EFS), developed by Rolfson et al. is a performance-based multidimensional frailty assessment tool that is simple (can be completed within 5 min) and easy to use by medical personnel without special geriatric training. It is an 11-question questionnaire which analyses nine domains of frailty (cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence, functional performance), with the maximum score of 17 representing the highest level of frailty. Based on the EFS scores, patients can be classified into five categories, ranging from "fit" (0–3), "vulnerable" (4–5), "mildly frail" (6–7), "moderately frail" (8–9) and "severely frail" (≥10) [22]. The EFS correlates very well with geriatricians' clinical impressions [22, 23], captures appropriately every area of frailty, with a high degree of correlation between the EFS scores and Geriatric Assessment as well as other frailty scales [23]. It has also been shown to be able to predict postoperative outcomes when used as a screening tool in the Caucasian and Asian population. In studies by He Y., Dasgupta M., increasing EFS scores were, independent of the age, associated with increased length of hospital stay, postoperative complications, in various abdominal operations [24, 25]. Moreover, The European Society of Anaesthesiology recommends the use of the EFS in preoperative evaluation of older patients [26].

The Frailty Index (FI) [27] and its modifications are based on the concept that frailty is a consequence of interrelated physical, psychological and social factors. As deficits accumulate, people become increasingly vulnerable to adverse outcomes. The FI, which is a continuous measure ranging from 0 to a theoretical maximum of 1.0, is calculated as the number of deficits the patient has, divided by the number of deficits considered. The original version of the FI, developed by Rockwood K. et al. includes 70 items, possible deficits, clinical signs and symptoms. They range from physical disease to psychological and cognitive problems to limitations in the ability to manage daily activities. Other modifications of the FI with a lower number of items have also been developed, including even an 11 variables list [28]. However, there are studies showing that risk evaluation is significant when at least 50 items are considered. The FI is also strongly correlated with the risk of postoperative morbidity and mortality in a wide range of oncologic procedures and is now recognised as a risk stratification tool [29, 30]. The FI, particularly the original version, takes a lot of time and includes functional dependence as a deficit, which may cause confusion between disability and frailty).

The Osteoporotic Fractures index (SOF index) is a short 3-item instrument, an adaptation of Frieds' frailty phenotype score, and is designed to measure pre-frailty and frailty status. As defined by the SOF index, frailty was identified by the presence of two or more of the following three components: weight loss of ≥5% during the preceding year (regardless of any intention to lose weight), an inability to rise from a chair five times without using arms, and an answer of "no" to the question "Do you feel full of energy?". Patients with no impairments were considered to be robust, and those with one disability were considered to be in a pre-frailty status [31]. The SOF index, among others, was used with success to evaluate gastric cancer patients preoperatively [32].

Conclusion

Not chronological age but rather frailty is recognised as one of the strongest preoperative predictors of postoperative complications in one of the most recently published meta-analysis [33]. Having a clear understanding of postoperative recovery trajectories is essential for conducting appropriate discussions about treatment plans with patients and family [34]. McIsaac et al. have observed that almost all older patients are willing to participate in a frailty assessment before going for major surgery [35]. Therefore, preoperative frailty evaluations should become obligatory prior to high-risk surgery of older patients suffering from cancer.

The value of the Geriatric Assessment, the current gold standard for frailty, was shown in many studies. However, its applicability in a busy preoperative clinic setting without experience is difficult. As a result, there is a constant search for the holy grail of preoperative assessments. A recently published systematic review and meta-analysis of 70 studies, presenting the accuracy and feasibility of clinically applied frailty instruments before surgery, concluded that specific frailty scales might be better predictors for some adverse outcomes when compared to others. The Clinical Frailty Score was strongly associated with mortality (a 4.9-fold increase in the odds) and discharge to nursing facility (a 6.3-fold increase in the odds). In turn, the Edmonton Frailty Score was a better predictor of complications (a 2.9-fold increase in the odds) and the frailty phenotype was most strongly associated with postoperative delirium (a 3.8-fold increase in the odds) [36]. At present, we do not have a conclusive answer as to which scale should be used preoperatively, apart from the full Geriatric Assessment. Clinicians should consider factors such as accuracy and feasibility when choosing a frailty instrument. The usefulness of most of them is significantly limited due to the quality of their psychometric properties. According to the COSMIN criteria, only the Frailty Index based on the Geriatric Assessment and the Tilburg Frailty Indicator were characterised by significant fair to excellent quality [37] and these are the scales that I recommend to evaluate older cancer patients before high-risk abdominal surgery. The preferred tool of choice is the Geriatric

Assessment, but in cases where there is a lack of experience, Frailty Index is more suited.

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Case report

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Histiocytic lymphadenopathy secondary to metallosis following endoprosthetic replacement in osteosarcoma patient – a potential diagnostic pitfall

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We present the case of a 43-year old patient with inguinal lymphadenopathy 22 years after distal femoral resection for osteosarcoma with cemented distal femoral replacement reconstruction. Seven years after initial distal femoral resection patient underwent metal on metal hip resurfacing arthroplasty on the affected side. Twenty years after distal femoral replacement and 13 years after metal on metal hip resurfacing procedure, the patient underwent left inguinal lymphadenectomy for an enlarged mass of inguinal lymph nodes on suspicion for a sarcoma recurrence. On microscopic examination, excised lymph nodes were massively infiltrated with macrophages and multinucleated giant cells with focal asteroid bodies. An examination in polarized light revealed numerous metal particles; immunohistochemical stainings confirmed reactive character of changes, and florid metal-related sinus histiocytosis was finally diagnosed. Microscopic assessment of lymph nodes in the course of malignancy is a standard procedure; we present a rare case of non-neoplastic lymph node enlargement due to the late onset of metallosis, which might be a diagnostic challenge.

Key words: metallosis, osteosarcoma, lymphadenopathy, endoprosthesis, metal on metal

Introduction

Lymphadenopathy in patients who underwent osteosarcoma treatment firstly suggests metastatic spread, however other potential causes must also be considered as lymph nodes are parts of an immune system which functions include filtration of various antigens from the extracellular fluid. Lymph nodes consist of macrophages, lymphocytes, and antigen-presenting cells, depending on the immunological status, age, and localization [1]. Essential differential diagnosis of enlarged lymph nodes leads to classification into one of a category: infectious (fungal, viral, protozoal, bacterial), inflammatory (drug, foreign body), neoplastic (primary neoplasm, metastasis), trauma, autoimmune, idiopathic (e.g., sarcoidosis). Often hematoxylin and eosin staining can target differential diagnostics; usually, additional immunohistochemical and/or histochemical evaluation is necessary. The critical point to the exclusion of sarcoma metastasis or primary lymph node malignancy (lymphoma) is morphology. In the histopathological assessment of osteosarcoma, no specific antibodies are routinely used, and in the absence of data from the medical history or a non-specific microscopic appearance, a broad immunohistochemical panel is used to narrow down the diagnosis. In the presence of foreign particles, it is suggested to perform the microscopic evaluation in polarized

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light; some metal particles, including steel alloys, may exhibit birefringence with pale green luminescence [2, 3].

In our paper, we present a case of histiocytic lymphadenopathy secondary to metallosis following limb-sparing surgery for osteosarcoma and metal on metal hip resurfacing on the affected size. The differential diagnosis with a discussion of overlapping morphological images are revised.

Material and methods

Clinical history

A 43-year-old Caucasian male was admitted to the hospital due to enlarging left inguinal mass. In 1998 patient underwent limb-sparing resection and reconstruction of the distal femur for a classical high-grade osteosarcoma (fig. 1: A, B). The patient was initially fitted with a cemented distal femoral replacement in 1998, followed by metal on metal hip resurfacing in 2005 for hip arthritis (fig.1: C, D). The patient had a soft tissue relapse of osteosarcoma in 2002 that was treated with a second-line chemotherapy and radical excision. Due to previous oncological history, the enlarged inguinal mass was suspected to be a metastatic relapse of osteosarcoma. Ultrasound examination showed enlarged lymph nodes – the largest measuring 28 mm in diameter. Radiologist described lymph nodes as suspicious for a neoplastic process. Fine needle biopsy of the lymph node showed only elements of a peripheral blood smear. There were no significant changes in laboratory tests. Lymph nodes were surgically removed and examined histopathologically.

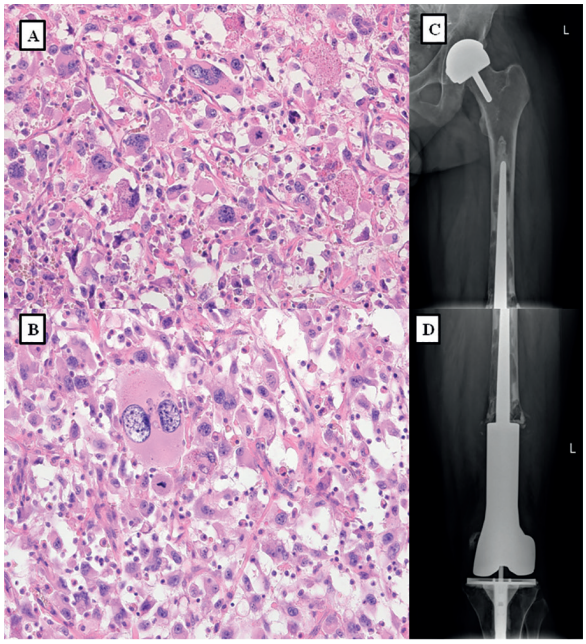

Figure 1. A, B – microscopic presentation of primary bone osteosarcoma, highly apoptotic with scattered "giant" neoplastic cells (A – HE, 200x; B – HE, 400x); **C, D** – X-ray showing cemented distal femoral replacement and metal on metal hip resurfacing in 2013 and in 2018 when the progression of a stem loosening and cortical thinning is clearly visible

Histopathology

The resected lymph nodes were fixated with 4% formalin and paraffin-embedded; the five µm-thick sections were made for hematoxylin and eosin staining (HE), Grocott-Gomori's methenamine silver (GMS), Periodic acid–Schiff (PAS), acid--fast stain (AFB), and immunostained with S100 (RTU, DAKO--Agilent, CD23 (RTU, DAK-23, DAKO-Agilent), CD20 (RTU, L26, DAKO-Agilent), Ki-67 (RTU, MIB-1, DAKO-Agilent), CD68 (RTU, KP1, DAKO-Agilent), CD163 (RTU, MRQ-26, Cell Marque), CD1a (RTU, 010, DAKO-Agilent), CD3 (1:50, F7.2.38, DAKO-Agilent).

Results

Histopathological and immunohistochemical findings and visualization in polarized light

Microscopically, a reactive lymph node with massive histiocytic and macrophage infiltration. There were many giant multinucleated cells, some with asteroid bodies. Macrophages showed a lot of "dust" particles that were bright green in the polarized light. The histochemical stains (PAS, GMS, AFB) did not indicate any microorganisms; CD3 showed normal mantle distribution of small T-cells, CD20 pointed germinal center B-cells, CD23 revealed a typical structure of dendritic cells in the germinal center, there were few Langerhans cells CD1a-positive. Macrophage infiltration was CD68KP1 and CD163-positive. Ki-67 was high in germinal centers; it was low, below 5% elsewhere. Finally, the diagnosis of florid metal-related sinus histiocytosis was made. The histopathological, immunohistochemical, and polarized light images are presented in figure 2.

Discussion

Bone malignant neoplasms are relatively rare and consist of only 0.2% of incidents of malignancies in Poland [4]. There are twice as frequent in men as in women. The most common bone sarcoma is osteosarcoma, with 60–100 new incidents per year. Osteosarcoma has a bimodal age distribution, having the first peak during adolescence and the second peak in older adulthood [5]. Osteosarcoma develops most often at the metaphysis of lower extremity long bones (~75% of cases). Histologically osteosarcoma demonstrates malignant spindle cells with pleomorphic nuclei, scattered mitotic figures, and varying levels of anaplasia. Conventional osteosarcomas are classified into osteoblastic, chondroblastic, or fibroblastic types, depending on which matrix-producing cells dominate [6–8].

Before the development of chemotherapy, osteosarcoma was a fatal disease with severe outcomes. Patients with locally advanced tumors used to develop metastases in the lungs and bone marrow quickly and died a few months after [9]. Less common histological subtypes like osteoblastoma-like and chondroblastoma-like osteosarcoma more common metastasize than its' conventional counterparts [10]. Metastases of osteosarcoma in lymph nodes are rare entities; most reports estimate that it occurs in about 1–4% of patients with

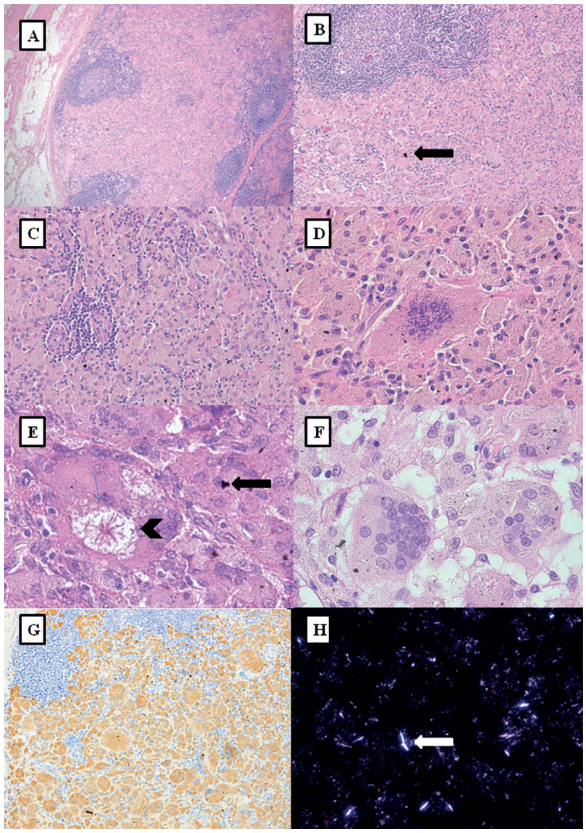

Figure 2. Metal-related sinus histiocytosis. **A**, **B**, **C** – lymph node with massive histiocytic and macrophage infiltration, with sparse typical germinal centers preserved (A – HE, 20x, B – 100x, C – 200x); **D**, **E**, **F** – giant multinucleated Langhans cells, some with asteroid bodies (arrowhead) and macrophages with black metal "dust" (arrow) which were released from endoprosthesis (D – HE, 400x, E – HE, 1000x, F – HE, 600x); **G** – CD63 diffuse positive reaction among macrophages (CD163, 200x); **H** – macrophages are presenting with the "dust" bright particles in the polarized light (HE, polarized light, 400x)

osteosarcoma [11, 12]. We found no literature describing any connection between the histological type of osteosarcoma and lymph node metastases rate. Adjuvant chemotherapy and surgery procedures highly improve outcomes [10, 13]. Development of modern endoprosthetic reconstruction techniques and the introduction of modular tumor endoprostheses heavily reduced the number of amputations in osteosarcoma patients [9, 14, 15].

Endoprostheses of joints can wear in time, producing debris particles in surrounding tissues [16–18]. The generation of wear debris from any part of the prosthesis is unavoidable. Implant loosening secondary to osteolysis is the most common mode of failure of arthroplasty [19]. Local and regional lymphadenopathy that is caused by wear particles released from a joint-replacement prosthesis is increasingly becoming recognized as a possible complication of arthroplasty [20]. Accumulation of such particles causes an inflammatory response, including macrophagic activation with the formation of giant cells and fibrosis. Soft tissue infiltration by metal debris shed by the prosthesis or lymphatic uptake of metal debris following its wear is called metallosis [17, 21].

Local lymphadenopathy in patients with endoprosthetic reconstruction needs differential diagnosis of join infection, implant-associated allergic reaction, or hypersensitivity related to implant itself. In some cases, those particles from prosthesis are drained through lymph vessels to regional lymph nodes [3, 22]. Accumulation of histiocytes with the debris is responsible for the enlarging of lymph nodes – some histocytes fuse in multinucleated giant cells [20]. Metallic particles are usually seen as very small (0,5–5 μm) dark brown or black bodies. Other components of a prosthesis (usually polyethylene, polymethylmethacrylate) are bright and not seen in HE staining in a light microscope, but are bright in polarized light [23].

It has to be emphasized that only some of the patients after joint replacement surgery develop lymphadenopathy [3]. Different studies describe that the metallosis rate depends on materials and operated joint and happened in about 5–23% of patients [17, 21]. It seems that there is no explanation for this phenomenon. In animal models, 1% of radioactive label particles injected intra-articular sites migrated to regional lymph nodes after 24. In a similar experiment, radioactive label particles were injected into femur bone marrow. In that case, particles moved to the lung via the blood vessels within 15 seconds, and no migration to the lymph node was detected [20].

Histologically, asteroid body is characteristic but not specific microscopical finding. Although it is commonly associating with sarcoidosis [24] and may occur in different pathological diagnoses. e.g. foreign body reaction in silicon transplant leaking [25, 26], other foreign body reaction [27], fungal infection [28], rarely in some neoplasm [29]. As in our case, palpably asteroid body mechanism of creation is similar for that in foreign body reactions [30, 31].

Besides local symptoms, the presence of metal and ethylene particles in a human body may also cause generalizes symptoms like cardiomyopathy, neuropathy, psychological status changes, skin rash, visual impairment [17]. It is essential to recognize this state and introduce treatment before generalized symptoms occurred. Treatment includes surgical revision of prosthesis, removal of damaged parts, and changed tissues and bone grafting [17, 21].

Conclusion

Enlarged lymph nodes in tumor surgery patients may be suggestive of a recurrence of the malignancy; however, both neoplastic and non-neoplastic conditions must also be considered. We presented a case of a lymph node foreign body reaction in the form of florid histiocytosis in osteosarcoma patient after long-term follow up of both limb-sparing surgery with massive endoprosthetic reconstruction and metal on metal hip resurfacing. It is important to know that both implants are prone to massive wear debris, especially after long term follow up, resulting in catastrophic failures [32, 33]. Histiocytic lymphadenopathy secondary to metallosis in patients who underwent joint replacement surgery is usually indicative

of increased endoprosthetic wear that requires immediate attention, usually followed by revision surgery. It is paramount to compare both clinical and radiological presentation for a complete image.

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The need for individual testing of applications aimed at early detection of skin cancer

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The increasing use of smartphones and technological advances has given rise to a range of applications for medical and healthcare purposes. The field of oncology is no exception, with applications being made available for, amongst others, education, treatment information, prevention and early detection [1]. A large proportion of the applications claiming to provide the opportunity for early detection are active within the field of skin cancer.

Several types of apps are available in the area of skin cancer. Some apps provide general information about melanoma, others provide information about prevention and a number of apps provide an estimate of the risk whether a certain lesion is malignant based on a picture taken [2]. A systematic review conducted in 2018 showed that the accuracy of the latter type of app was not sufficient at that time [3]. The evidence was also rather limited in quality and quantity. This was confirmed by a very recent systematic review [4] which showed that apps currently are unable to identify all skin cancers. In this case, the studies were also of limited methodological quality and had relatively small sample sizes. In another review [5], the sensitivity ranged from 7% to 87%. Another problem that was often mentioned, is the high rate of unusable images taken [2, 3, 5].

Due to the variation in accuracy between apps, it is important that every app intended for medical use is individually tested for accuracy. This could be set as a requirement for regulatory approval. Currently this is not always the case when applying for a CE-mark. An example of an application that is aiming to become part of medical care is SkinVision (SkinVision, Amsterdam) In the Benelux, it seems that this app has gone the furthest in the direction of regulatory approval. It is included in the Belgian mHealth validation pyramid and has received a CE-mark as a class I medical device. It is additionally cooperating with a Dutch health insurer. However, the app has also attracted criticism from the Dutch association of dermatologists.

In general, several types of skin cancer applications can provide useful information for users. However, it seems that more research is needed to allow for applications that provide enough sensitivity and specificity for routine medical use and self-screening. Each application that is used for such purposes should be independently assessed using an adequate study design before by being utilised. By making these results public, they can be assessed by the different stakeholders.

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World Tobacco Quitting Day 2020 – the united voice of Polish experts on tobacco prevention and control

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On November 19th, 2020 we will celebrate annual World Tobacco Quitting Day. On this occasion, we would like call to action for a stronger and united tobacco prevention activities in Poland.

Despite many successes in tobacco prevention and control, use of tobacco products in Poland is still a great public health challenge. Whereas the prevalence of traditional cigarettes smoking is declining, new tobacco products are more and more popular – particularly among young people. It has been estimated that about 28% of boys and 18.6% of girls aged 13–15 years in Poland use e-cigarettes. Moreover, in the same age group 15.6% of boys and 14.9% of girls smoke traditional cigarettes [1]. Considering adult population, e-cigarettes are less popular – about 4% of men and about 1% of women use this particular tobacco product [2]. However, the use of traditional cigarettes is much higher – 26% and 17% of Polish men and women, respectively, are regular smokers [3].

Being aware of overwhelming influence of SARS-CoV-2 pandemic on health care systems, we cannot ignore impact

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of other pandemic, which lasts for decades and is evolving just in front of our eyes. Only between 2011 and 2014, e-cigarettes use among young Poles has increased from 6% to 29.9% [4]. Compared to other EU-countries, Poland has one of the highest rates of e-cigarettes use among teenagers [1]. Moreover, Poland is among a few European Union (EU) countries with a very high level (17.5% to <20%) of tobacco attributable Disability-Adjusted Life Years (DALYs) [5]. For comparison, Romania and Czech Republic are in the group of countries with DALY between 15% to <17.5%, Germany and Spain 12.5% to <15%, and France and Italy 10% to <12.5%.

Considering these data, we appeal to all involved parties – researchers, health professionals, and stakeholder and policymakers to advocate for a stronger and more tailored anti tobacco law, health education and stable long lasting financing of such actions. We believe that we need to stand together to stop, or at least to slow down tobacco epidemic in Poland.

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Advances in the management of gastrointestinal stromal tumors (GISTs)

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Gastrointestinal stromal tumors are rare neoplasms developing from cells of Cajal in the gastrointestinal tract. The mainstay of such tumors treatment is surgery, whenever possible. The therapeutic management of inoperable and metastatic disease is based on tyrosine kinase inhibitors and imatinib is the main drug recommended for first line treatment. The introduction of imatinib and other inhibitors improved survival outcomes for this disease, but due to primary and secondary resistance there is still the urgent need for new medications. This paper presents the progress in the systemic therapy of GISTs based on the latest scientific data. The newly developed agents (ripretinib, avapritinib) meet the need to treat patients after the failure of previously available therapies and those with *PDGFRA* mutation D842V associated with resistance to imatinib.

Key words: gastrointestinal stromal tumor, GIST, tyrosine kinase inhibitor, imatinib, regorafenib, sunitinib, sorafenib, avapritinib, repritinib, BLU-285, DCC-2618

Introduction

Gastrointestinal stromal tumors (GIST) develop from interstitial cells of Cajal in the gastrointestinal tract or their precursors. GISTs are rare neoplasms but are also the most common mesenchymal tumors of the gastrointestinal tract. The incidence of GIST in most published studies is reported at 10–15 new cases/100,000 per year and it is reported as having increased during the last decades [1]. GISTs are most often located in the stomach (50–70%) and in the small bowel (30% in the jejunum or ileum, 5% in the duodenum) but less frequently they can be found in other parts of the gastrointestinal tract and also in the omentum, mesentery, peritoneum and pancreas [2, 3]. The median age at diagnosis is about 60–65 years [1, 3, 4]. Small GISTs usually remain asymptomatic but patients with larger tumors may have different symptoms depending on the location of the tumor. Suspicion of possible GIST is usually based on imaging or endoscopic tests and should be confirmed with a pathology test including immunohistchemistry staining and molecular testing. GIST management should be implemented, especially in unresectable and metastatic cases, based on the decision of the multidisciplinary team who are experienced in soft tissue sarcomas.

Diagnostics and molecular abnormalities

Suspicion of GIST is usually done based on imaging and endoscopic studies but this requires confirmation with pathology results. A biopsy is an important step in this diagnosis. There are 2 typical histological patterns of GIST: a spindle cell (60–70% of cases) or epithelioid (30–40% of cases) character, or a combination of both in variable proportions [5]. GISTs stain positive for KIT (CD117) and DOG1. Almost all except about 5% of GISTs are immunohistochemically positive for CD117. These minority of cases refer mostly to GISTs with the *PDGFRA* mutation. DOG1 expression is almost exclusively characteristic for GIST and is independent of the KIT status. Immunohistochemistry is important to differentiate GISTs from other mesenchymal

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tumors. The differential diagnosis most often includes IHC staining with the following antibodies: CD34, SMA, h-caldesmon, desmin, general cytokeratin or CK18, S100, HMB-45, and melan A. Three of the most important prognostic factors in GIST are: location (gastric GISTs have a better prognosis than the small bowel or rectal GISTs), size and mitotic activity. It is important to note that tumor rupture is an additional adverse prognostic factor. Risk assessment based on the mitotic count, tumor size and tumor location is important for therapeutic decisions as well choosing the follow-up procedures after radical treatment. High-risk patients generally reccure within 1–3 years after the end of adjuvant therapy and low-risk patients may reccure later, but this is much less likely. This should be taken into consideration during follow-up procedures [6]. Mutational status is not included in any risk classification but has an important prognostic value and predictive significance for targeted therapies. GISTs with the *PDGFR D842V* mutation are associated with imatinib resistance and *KIT/PDGFRA* wild type GISTs may have a special clinical presentation and course [6]. Mutations of the *KIT* gene are present in 80–85% of GIST cases. The most common mutation in sporadic GIST (approximately 60%) and the best response to imatinib is the mutation in exon 11 of the *KIT* gene. This mutation is also observed in the familial GIST. Mutation in exon 9 *KIT* is more common in GISTs originating from the small intestine and the colon; this mutation is related to a worse response to imatinib. Patients with a mutation in exon 9 of the *KIT* gene may benefit from a higher dose of imatinib i.e. 800 mg daily and from a sunitinib. Mutations in exon 13 and 17 *KIT* are very rarely present, those aberrations are described in the familial GIST and in such cases a response to imatinib was observed. *PDGFRA* gene mutations are present in 5–8% of GISTs. In the case of mutations in exon 12 and exon 14 of the *PDGFRA* gene, a clinical response to imatinib was observed. Most mutations in exon 18 of the *PDGFRA* gene are present in cases of tumors located in the stomach or the omentum; the *D842V* mutation is resistant to imatinib and sunitinib, while other types of *PDGFRA* mutations are sensitive to them. Wild-type GISTs, i.e. GISTs with no *KIT* or *PDGRA* mutations, constitute 12-15% of cases and are characterized by a poor response to imatinib and a better response to sunitinib. Such cases often include pediatric GISTs (as SDH-deficient), typically GISTs related to NF1 or Carney's triad [3].

The system most often used for GIST staging is the American Joint Committee on Cancer (AJCC) TNM (TNM tumor/node/metastasis) classification system with the latest update from 2018.

Treatment

The treatment of GIST should be implemented, especially in unresectable cases, based on the experience of the GIST management multidisciplinary team and their decision. The therapeutic approach may include endoscopic resection (in the case of small asymptomatic lesions), surgery and medical therapy, and in some cases radiotherapy, chemotherapy, hepatic artery embolization, chemoembolisation of the hepatic artery branches, radiofrequency ablation and supportive care.

Surgical treatment, if possible, remains the mainstay of GIST management. The main goal of surgery is an R0 resection (negative margins). The surgical approach depends on the tumor's location and size, its adherence or invasion into adjacent structures and the patient's general condition and comorbidities. In the case of smaller lesions, the laparoscopic approach can be considered but this needs to follow all rules for oncological surgery. It can be considered especially for GISTs located in the stomach. This procedure is clearly discouraged in patients with large tumors, because of the risk of tumor rupture, which is associated with a very high risk of relapse. Usually GISTs do not metastasize to the lymph nodes and consequently routine local lymph node dissection is not required unless suspected on imaging. Due to the high recurrence potential in each case of GIST, the possible use of adjuvant imatinib should be assessed based on the recurrence risk assessment. In case of R1 resection, it is recommended to assess the possibility to do secondary surgery (re-excision). It should be considered if there is a possibility to determine the location of the primary tumor and if the procedure is not related with serious consequences for the functioning of the gastrointestinal tract. In some cases resection R1 can be acceptable, for example, in cases when the resection R0 is associated with major functional sequalae and there is no response for preoperative systemic therapy, especially for low-risk lesions [4, 6].

Imatinib can be recommended in a preoperative setting until the maximum response is obtained, which usually takes 6–12 months from the beginning of treatment. During preoperative therapy the response has to be strictly assessed with imaging tests so as not to miss disease resistance and progression. The main indications for preoperative imatinib therapy are: a locally advanced tumor not eligible for a non-mutilating surgery like abdominoperineal excision, pelvic exenteration, negative margins (R0 resection) achievement can be problematic or the risk of perforation is high; preoperative treatment can allow for saving surgery like gastric wedge resection instead of gastrectomy, local excision instead of pancreatoduodenectomy [7]. Imatinib should be continued in an adjuvant setting for a total treatment duration of three years. The decision about implementation of adjuvant imatinib should be done based on a risk assessment. Based on the scale of Miettinen and Lasota (2006), which defines the risk assessment of GIST aggressiveness (frequency of metastases or cancer-related death) depending on the location, size, and mitotic activity, there are 6 prognostic groups defined. Adjuvant imatinib for 3 years should be used for patients with a high risk of relapse. 3-years therapy prolonged relapse-free survival (RFS) and overall survival (OS) in comparison to the

one-year treatment. The RFS was 65.6% *vs.* 47.9% for 36-month and 12-month imatinib therapy, respectively, and the five-year OS was 92% *vs.* 81.7%, respectively (NCT00116935) [8]. In 2020 the updated data after a 10-year follow-up of this trial were presented and in the intent-to-treat cohorts for the 36-month group; the 5-year and 10-year OS rates were 92.0% and 79.0%, and in the 12-month group, 85.5% and 65.3%, respectively (HR 0.55, 95% CI 0.37–0.83; p = 0.004). It was concluded that about 50% of deaths can be avoided during the first decade of follow-up after surgery with the 3-year imatinib treatment as compared to the 1-year treatment [9]. Polish real-life data confirmed the efficacy of 3-year adjuvant therapy with imatinib in patients with high-risk molecular profiled GIST. The authors found overrepresentation of exon 9 *KIT* mutants and ruptured tumors in a group of patients with disease relapses [10]. In addition to risk assessment, it is required to perform molecular tests to determine the status of the GIST mutation to avoid treatment of patients with low sensitivity or resistance to imatinib [11, 12].

Imatinib is the standard of care in the first line of unresectable/metastatic disease. The introduction of imatinib to the treatment of GIST was a crucial point in the management of this disease. Median overall survival in patients with advanced/metastatic disease before imatinib was about 12–15 months. In cases of inoperable or metastatic disease, the treatment of choice is the use of imatinib, the tyrosine kinase inhibitor (TKI), in the standard dose of 400 mg per day, orally. The efficacy of imatinib in first line treatment of unresectable or metastatic GISTs was demonstrated in prospective clinical trials [13, 14]. Based on the long-term follow-up of patients treated in prospective clinical trials, the median PFS was about 2–3 years and the median OS was about 5 years. The clinical benefit in prospective clinical trials was mostly due to partial responses (40%) and disease stabilization (36%); complete responses were rarely observed (5–7%). This efficacy has been confirmed in retrospective real-world studies [15, 16].

Primary and early resistance to imatinib during the first 6 months of therapy is observed in about 10–15% of patients with GIST. In responders the acquired resistance may appear along with the duration of treatment. Approximately 40–50% of patients show signs of disease progression in 2–3 years of treatment with imatinib. Most often the acquired resistance results from a new mutation or additional mutations in the *KIT* or *PDGFRA* genes, leading to a conformation change of the receptor and the inability to bind to imatinib.

In case of progression, it is recommended to increase the dose of imatinib to 800 mg daily, and in the case of lack of efficacy, to use sunitinib which is approved for second line treatment at an initial dose of 50 mg daily based on phase III study results (NCT00075218). The use of other TKIs, with different targets in the pathway can help overcome resistance to imatinib. They can also be used in the case of imatinib intolerance. Sunitinib is a multikinase inhibitor that targets PDGFR, KIT, VEGFR (vascular endothelial growth factor) and CSF-1R (colony stimulating factor 1 receptor). In a randomized phase III trial sunitinib was administered 50 mg orally once daily for 4 weeks, followed by a 2-week period off. In this study the median PFS was 27 weeks in sunitinib group in comparison to 6 weeks in the placebo group [17–19]. In case of further progression or sunitinib intolerance, regorafenib and sorafenib are subsequent therapeutic options, although sorafenib is not approved for GIST treatment [20, 21]. Regorafenib, another multikinase inhibitor targeting KIT, PDGFR, VEGFR, FGFR (fibroblast growth factor receptor) and RET, was registered in third-line treatment based on a phase III study named GRID (NCT01271712). In this study, regorafenib was dosed 160 mg daily every 3 out of 4 weeks. The patients treated with regorafenib achieved median PFS of 4.8 months compared to 0.9 months in the placebo group [22].

Taking into consideration the limited options of systemic therapy, re-challenge with previously tolerated and effective TKI for palliation of symptoms in case of PD, can be considered. The results of the randomized study published in 2013 indicate that rechallenge with imatinib can significantly improve PFS and DCR (the disease control rate) in patients with GIST after failure with at least imatinib and sunitinib, although the survival benefit was minimal [23].

Patients who progressed despite prior therapy or recurred should be considered for participation in clinical trials, if available [24]. There are currently ongoing clinical trials with tyrosine kinase inhibitors of KIT and/or *PDGFRA* (sunitinib, regorafenib, crenolanib, ripretinib, avapritinib, cabozantinib, axitinib), immunotherapy (nivolumab and iplimumab, avelumab, pembrolizumab), tyrosine kinase inhibitors of MEK (binimetinib), mTOR inhibitor (temsirolimus) and other molecules [25]. Researchers from the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland, lead the clinical trial on the combination of axitinib with avelumab (AXAGIST) in imatinib and sunitinib refractory GIST (NCT04258956).

In patients with a preliminary inoperable disease, the resectability should be regularly assessed during treatment with imatinib and surgery should be done if at all possible. Similarly, in patients with oligometastatic disease, who experience response and subsequent stabilization of the lesions in two subsequent imaging tests done within 4–6 months, resection may be considered with the assumption of continuation of systemic therapy after surgery. This approach can improve progression-free survival and overall survival [26–28]. Surgical treatment is not appropriate for patients with multifocal progression during systemic therapy with imatinib or sunitinib.

Recently approved systemic therapies

Recently, two new medications – avapritinib (BLU-285) and ripretinib (DCC-2618) – have been assessed in clinical trials in patients with GIST and included in GIST treatment in clinical

practice. The new medications meet the need to treat patients after the failure of previously available therapies and those with a *PDGFRA* mutation D842V associated with resistance to imatinib.

Avapritinib is approved in Europe in monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the platelet-derived growth factor receptor alpha (*PDGFRA*) *D842V* mutation [29]. In the US, the drug is approved for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including the *PDGFRA D842V* mutations [30].

Avapritinib is a Type 1 kinase inhibitor which demonstrated in vitro activity on the *PDGFRA D842V* and *KIT D816V* mutants associated with resistance to imatinib, sunitinib and regorafenib. The drug demonstrated greater potency against clinically relevant *KIT* exon 11 and *KIT* exon 17 mutants than against the *KIT* wild-type [29, 31]. Avapritinib's safety, tolerability and anti-tumor activity were assessed in patients with advanced GIST in the NAVIGATOR study (NCT02508532) [32]. This was an open-label, phase I study, which consisted of dose-escalation and dose-expansion parts. The study was done over 17 sites in 9 countries. Patients with unresectable GISTs were enrolled into the dose-escalation part of the study (n = 46, among them 20 patients with a *PDGFRA D842V*-mutant GIST). The dose-expansion part of the study included patients with an unresectable *PDGFRA D842V*-mutant GISTs (n = 36) regardless of previous treatment and patients with GISTs with other mutations whose disease either progressed on imatinib alone or on imatinib along with at least one other TKI. Adult patients (at least 18 years old), with an ECOG (Eastern Cooperative Oncology Group) PS 0–2 (performance status), and with adequate organ function were eligible. Avapritinib was administered orally, once daily in the dose-escalation part, starting with a dose of 30 mg, in 28-day cycles. Treatment was continued until unacceptable toxicity, noncompliance, withdrawal of consent, physician decision, disease progression, death, or the closure of the study. Primary endpoints were MTD (maximum tolerated dose), the dose recommended for part 2, safety, and overall response in the dose-expansion part. Safety was assessed in all patients from the dose-escalation part and all patients with the *PDGFRA D842V*-mutant GIST from the dose-expansion part. The secondary endpoints were pharmacokinetics, the clinical benefit rate, the duration of the response, and PFS per mRECIST 1.1. The pre-specified exploratory endpoint was OS (overall survival). The activity was assessed in all patients with *PDGFRA D842V*-mutant GIST who received avapritinib and who had at least one target lesion and at least one post-baseline disease assessment by central radiology. The efficacy was assessed based on mRECIST 1.1. (modified Response Evaluation Criteria in Solid Tumors, version 1.1). Response assessment was done using CT or MRI at screening, on day 1 of cycle 3, every 2 cycles up to cycle 13, and then every 3 months until disease progression or discontinuation. Safety was assessed from the first dose of the study drug until 30 days after the last dose. The AEs were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03).

The safety population included 82 patients, and the D842V population 56 patients. The median age was 62 years, 60% were men and 76% were white, in the safety population. 98% of patients had metastatic disease and 87% of patients were previously treated with at least one TKI. The median follow-up of patients in the safety population was 19.1 months. In the dose-expansion part of the study, the MTD 400 mg from the dose-escalation part was used. The higher incidence of grade 3 cognitive adverse events (AEs) was observed during the early expansion part of the study and further dose reductions with the 400 mg starting dose after multiple cycles of treatment. The dose was subsequently reduced to 300 mg and eventually recommended for the second part of the study. Most treatment-related adverse events (TRAEs) were grade G1–G2. At the 400 mg dose, the most commonly reported TRAEs G1–G2 were nausea (in 71% of patients), periorbital edema (47%), fatigue (47%) and vomiting (47%). At the 300 mg dose, the most common TRAEs G1-G2 were nausea (in 69% of patients), diarrhea (41%), fatigue (38%) and decreased appetite (38%). TRAEs G3–G4 regardless of the dose, occurred in 57% of patients and the most commonly reported was anemia (in 17% of patients). Drug-related serious AEs of any grade were reported in 26% of patients. The most commonly observed were anemia (4% of patients), pleural effusion (4%), vertigo (2%) and diarrhea (2%). No treatment-related deaths were reported. There were 2 categories of AEs of special interest (AESI) determined: cognitive effects and intracranial bleeding. The first category, cognitive effects (any cause), occurred in 40% of patients and included memory impairment (30%), cognitive disorder (10%), confusional state (9%), and encephalopathy (2%). Cognitive effects were mostly G1 (23%) and resulted in treatment discontinuation in 2% of patients. Intracranial bleeding occurred in 2 patients (2%) and both AEs were G3, reported as possibly related to the study drug. 84% of patients required at least one dose reduction or treatment interruption. In the safety population, 54% of patients discontinued treatment, mostly due to disease progression (32%) and AEs (18%). 11 deaths were reported but there were no treatment-related deaths. In the D842V population 34% of patients discontinued treatment, mostly due to disease progression (7%) and AEs (21%).

The efficacy results for patients with *PDGFRA D842V*-mutation GISTs treated with the approved dose of avapritinib are summarized in table I.

In the patients with *PDGFRA D842V*-mutation GISTs treated at any dose level, confirmed overall responses (according to mRECIST v. 1.1, central review) were reported in 88% of patients (complete response, CR, in 9%; partial response, PR, in 79%; and disease stabilization, SD, in 13%). PFS at 3 months

Table I. The best confirmed response by central assessment per mRECIST v. 1.1 in patients with *PDGFRA* D842V-mutant GISTs in the group treated with avapritinib with a registered dose of 300 mg per day (n = 28) [32]

complete response	1 (4%)
partial response	25 (89%)
stable disease	2 (7%)
disease progression	0 (0%)
overall response	26 (93%; 95% CI 77–99)
clinical benefit	28 (100%; 95% CI 88–100)

was 100% (95% CI 100–100), at 6 months 94% (88–100), and at 12 months 81% (69–93). The estimated OS at 6 months was 100% (95% CI 100–100), at 12 months 91% (83–100), and at 24 months 81% (67–94).

The updated long-term data with the median follow-up of 26 months from the phase I study NAVIGATOR were presented in 2020 during the annual ESMO (European Society for Medical Oncology Conference) [33]. The ORR among 38 patients with *PDGFRA D842V*-mutant GIST treated with avapritinib at a dose 300/400 mg was 95% (CR in 13%, PR in 82%). The median duration of response was 22 months, median PFS was 24 months and median OS was not reached. The PFS and OS rates at 36 months were 34% and 71%, respectively. 21% of patients discontinued treatment due to treatment related AEs. No treatment-related deaths were reported. The most common AEs in 10% of patients with *PDGFRA D842V*-mutant GIST treated at a dose of 300/400 mg were nausea, anemia, diarrhea, fatigue, memory impairment, periorbital edema, decreased appetite, increased lacrimation, abdominal pain, vomiting, peripheral edema, hypokalemia and increased bilirubin.

The results of another study, with the acronym VOYAGER, phase III, open-label, randomized study in patients with locally advanced unresectable or metastatic GIST of avapritinib versus regorafenib in patients previously treated with imatinib and 1 or 2 other TKIs (NCT03465722) were announced by the study sponsor in April, 2020 [34, 35]. In this study the patients were randomized in 1:1 ratio to treatment with avapritinib at a dose of 300 mg daily (n = 240) or regorafenib at a dose of 160 mg per day for 3 weeks out of every 4 weeks (n = 236). The primary endpoint was PFS determined by central radiological assessment per mRECIST v. 1.1. The reported median PFS for the avapritinib group was 4.2 months in comparison to 5.6 months in the regorafenib group. The difference between the arms was not statistically significant. The overall response rate (ORR) was 17% with avapritinib versus 7% for the regorafenib group. The secondary end point of the study included ORR (overall response rate), OS and quality of life.

Ripretinib is approved in the US by the FDA for the treatment of adult patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib [36]. The drug has not yet been authorized in Europe.

Ripretinib is a switch-control multikinase inhibitor that broadly inhibits *KIT* and *PDGFRA* kinases, including activity for wild-type *KIT* and *PDGFRA* mutations and multiple primary and secondary mutations associated with drug-resistant GISTs. Ripretinib demonstrates a dual mechanism of action and specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in an inactive state. In this way the molecule prevents downstream signalling and cell proliferation. In vitro ripretinib inhibited PDGFRB (platelet derived growth factor receptor β), TIE-2 (angiopoietin-1 receptor), VEGFR2 (vascular endothelial growth factor receptor 2), and BRAF (serine and threonine-protein kinase B-raf), among others [36–38]. A first-in-human phase I study (NCT02571036) in patients with GISTs and other advanced solid tumors determined the recommended phase II dose of ripretinib as 150 mg, once daily. This phase I study included expansion cohorts to assess the clinical benefit in 2 and 3 line treatment in patients with GIST. 150 patients with GIST were enrolled into the study and received the ripretinib dose of at least 100 mg daily. Among them 141 had *KIT* mutations, 8 had *PDGFRA* mutations and 1 patient had SDH-deficient GIST. 114 GIST patients were treated at the dose of 150 mg daily. The patients were previously treated with other TKIs, 19 patients with previous 1 line, 27 with 2 lines and 68 patients with at least 3 lines. The ORR among patients treated with the dose of 150 mg was 14%, the median PF was 24 weeks and for the patients treated in 2. or 3. line, the ORR was 22% and median PFS was 36 weeks. G3–G4 AEs reported by patients treated at the dose of 150 mg daily were asymptomatic lipase increases, anemia, blood bilirubin increased, hypertension, diarrhea, abdominal pain, back pain, hyperkalemia, hyponatremia, hypophosphatemia [39].

Ripretinib was then assessed in the INVICTUS study (NCT03353753) (tab. II). It was a double-blind, randomized, placebo-controlled phase III study in patients with previously treated, advanced GISTs. This study was done in 29 sites in 12 countries. Adult patients (at least 18 years old) with advanced GISTs with progression on at least imatinib, sunitinib and regorafenib or documented intolerance to any of these medications despite dose modifications with an ECOG PS 0–2 as well as adequate organ and bone marrow function were eligible for the study. The patients were randomly assigned in a ratio 2:1 to receive either oral ripretinib 150 mg or placebo, once daily for 28-day cycles. The patients were treated until disease progression, unacceptable toxicity, or consent withdrawal. The patients assigned to the placebo arm were allowed to cross over to ripretinib 150 mg at the time of progression. Randomization stratification was done according to the number of previous therapies and ECOG PS. The efficacy was assessed using mRECIST v. 1.1. Tumor assessments were done using CT scans at screening, then every cycle (for 4 weeks) up to cycle 4. After cycle 4 assessments were continued every other cycle. In patients who crossed over from placebo to the ripretinib arm, tumor assessments were done every other cycle and at

Table II. The summary of efficacy results based on the INVICTUS study [36]

	Ripretinib (n = 85)	Placebo (n = 44)	p value	HR (95% CI)
PFS[a] (median, 95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)	< 0.0001	0.15 (0.09, 0.25)
ORR[a] (%) (95% CI)	9 (4.2, 18)	0 (0, 8)		0.0504
OS (median, 95% CI)	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)		0.36 (0.21, 0.62)

PFS – progression free survival; OS – overall survival; ORR – objective response rate; HR – hazard ratio; CI – confidence interval; [a] – assessed by BICR (blinded independent central review)

the end of treatment. During the double-blind period, tumor assessments were done on the basis of BICR (blinded independent central review). Safety was assessed continuously from the signing of the informed consent until 30 days after the last dose of the study treatment. AEs were graded according to NCI-CTCAE v. 4.03. The primary endpoint was PFS, assessed by BICR. The key secondary efficacy endpoint was ORR and other secondary endpoints included OS, time to progression, time to best response, PFS by investigator assessment, QOL (quality of life), safety, disease control rate at 12 weeks and pharmacokinetic/pharmacodynamic analyses. The primary analysis was done in the intention-to-treat population (ITT). ITT was defined as all patients who signed informed consent and were randomized. Safety was assessed in patients who received at least one dose of the study drug. 154 patients were assessed for eligibility. 129 patients were randomly assigned to either the ripretinib group (n = 85) or the placebo group (n = 44). The median follow-up in the ripretinib group was 6.3 months and in the placebo arm it was 1.6 months. The relative dose intensity in the double-blind period was 100% in the ripretinib arm and 97% in the placebo arm. 15 patients did not cross over from the placebo group to the ripretinib group. Median PFS by BICR was 6.3 months (95% CI 4.6–6.9) in ripretinib group versus 1.0 month (0.9–1.7) in the placebo group (HR 0.15, 95% CI 0.09–0.25; p < 0.0001). Median PFS based on investigator assessment was 4.7 months (95% CI 4.2–8.2) in the ripretinib group and 1.0 months (0.9–1.4) in the placebo group (HR 0.19, 95% CI 0.12–0.32). PFS at 6 months was estimated to be 51% for the ripretinib arm and 3.2% for the placebo arm. The median time to progression was 6.4 months (95% CI 4.6–8.4) in the ripretinib group and 1.0 month (0.9–1.7) in the placebo group. Median OS was 15.1 months (95% CI 12.3–15.1) in the ripretinib group and 6.6 months (4.1–11.6) in the placebo group (HR 0.36, 95% CI 0.21–0.62). At 6 months, estimated OS at 6 months was 84.3% for the ripretinib arm and 55.9% for the placebo arm; 12 months estimated OS was 65.4% for the ripretinib arm and 25.9% for the placebo arm.

The most common TRAEs (reported in ≥20% of patients in the ripretinib group) in patients receiving ripretinib were alopecia, fatigue, nausea, myalgia, palmar–plantar erythrodysesthesia and diarrhea. Palmar–plantar erythrodysesthesia was reported in patients treated with ripretinib only and all events were G1 (in 13% of patients) and G2 (8%). The most commonly reported G3–G4 TRAEs in the ripretinib group were lipase increase (in 5% of patients), hypertension (4%), fatigue (2%), and hypophosphataemia (2%). The most commonly reported G3–G4 TRAEs in the placebo group were anaemia (7%), diarrhea (2%), fatigue (2%), dehydration (2%), hyperkalaemia (2%), decreased appetite (2%), acute kidney injury (2%), and pulmonary edema (2%). Treatment-related serious AEs were reported in 8 (9%) of the 85 patients treated with ripretinib and 3 (7%) of the 43 patients receiving placebo. Treatment-related treatment-emergent AEs leading to a dose reduction were reported in 6% of patients in the group who received ripretinib and in 2% of the patients receiving placebo. Treatment-related treatment-emergent adverse events leading to study treatment discontinuation were reported respectively in 5% and 2% of patients. 1 treatment-related death was reported in the placebo and 1 in the ripretinib group.

Role and physical functioning assessed by EORTC-QLQ--C30 as well overall health assessed by EQ-VAS were stable from the beginning to cycle 2 day 1 in the ripretinib group in comparison to decreases observed in the placebo group indicating a clinically relevant difference between ripretinib and the placebo [38].

Conclusions

GISTs are rare diseases and treatment should be based on multidisciplinary team decisions. This approach is especially important for unresectable tumors. The diagnosis must be based on imaging and endoscopic tests, and should be confirmed with pathology tests including IHC and molecular tests from the tissue from the biopsy. The main goal of GIST management is surgery with R0 resection. In some cases there is the need to administer preoperative therapy with imatinib with a careful follow-up during treatment with regards to the possibility of undergoing surgery. In high risk GISTs, perioperative imatinib therapy should be continued up to 3 years in total. In the case of a primarily operative GIST, risk assessment should be done and for high risk patients 3 years imatinib therapy should be implemented. For unresectable locally advanced or metastatic disease, systemic treatment with TKI should be started. The therapeutic options are limited and include imatinib, an increased dose of imatinib, sunitinib, regorafenib and sorafenib. For patients with mutations associated with resistance to imatinib, therapeutic options remain limited.

Recently 2 new medicines – avapritinib and ripretinib – have been assessed in clinical trials in patients with GIST and

implemented in clinical practice in GIST management. The new medications represent significant progress in patients after the failure of previously available therapies and those with a *PDGFRA* mutation D842V associated with resistance to imatinib.

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Current advances in radiotherapy for soft tissue sarcomas

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Radiotherapy (RT) is a part of the routine treatment of locally advanced or high-grade soft-tissue sarcomas (STS). However, RT has changed significantly over the last 20 years. Modern RT techniques have extended its potential application in STS treatment. That includes advances in contouring, fractionation regimens, RT techniques and combined treatment. This article summarizes the available data, current strategies and future research directions in RT for STS.

Key words: sarcoma, radiotherapy, intensity-modulated radiotherapy, image-guided radiotherapy, brachytherapy

Introduction

Perioperative radiotherapy (RT) combined with wide local excision enables over 90% of local control in patients with localized soft tissue sarcomas (STS) of extremities or the trunk wall. According to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines, RT is recommended as a part of the routine treatment of locally advanced or high-grade STS, depending on clinicopathological factors such as tumor size, grade and its resectability [1, 2]. NCCN recommends perioperative RT in selected patients with stage I and in all stage II, III extremity, superficial trunk, or head/neck STS. Likewise, ESMO recommends perioperative RT with wide excision in high-grade (G2–3), deep, large (>5 cm) STS. The role of RT in other clinical situations, such as superficial STS, high-grade <5 cm STS or low-grade >5 cm deep STS remains unclear; thus, the use of RT should be discussed at a multidisciplinary tumor board (MTB), given the risk of local recurrence, pathological diagnosis and potential toxicity. The issue of the treatment sequence is extensively discussed in literature. Currently, both neoadjuvant and adjuvant RT may be considered in localized STS, taking into account the risk of postoperative wound complications (tab. I) [3]. However, RT in STS has significantly changed over the last 20 years in many more aspects.

Moreover, contemporary RT may play an important role in the management of patients with metastatic STS. Modern RT techniques, such as stereotactic body RT (SBRT), allows the delivery of a high dose to target volume with minimal involvement of surrounding healthy tissues. The use of motion-management techniques enable the irradiation of moving tumors, for example, lung metastases that are the most frequent metastatic site of STS.

This article summarizes the available data, current strategies and future research directions in RT for STS. That includes advances in contouring, fractionation regimens, RT techniques, and combined treatment. The scope of the article does not cover selected STS subtypes with separate guidelines, namely Ewing sarcoma, rhabdomyosarcoma, gastrointestinal stromal tumors and dermatofibrosarcoma protuberans.

External beam radiotherapy

Contouring

Together with the evolution of RT techniques, RT planning in STS evolved from simple two-dimensions to complicated, volumetric shapes. Two-dimensional RT in STS required only the determination of field borders. Currently, a radiation oncologist delineates tumor volumes, elective margins and

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Table I. Comparison of neoadjuvant and adjuvant radiotherapy in soft tissue sarcomas

Issue	Adjuvant radiotherapy	Neoadjuvant radiotherapy
delineation	complicated (no GTV, fusion with preoperative imaging, postoperative changes)	easy (visible GTV)
target volume	larger (tumor bed, scars, drainage, operative route, and margins)	smaller (GTV + margin)
healthy tissues	move to the tumor bed	pushed away by the tumor
dose	higher (60–66 Gy EQD2)	lower (45–50.4 Gy EQD2)
treatment time	longer	shorter
hypofractionation	no/not known	possible
pathological assessment	unhindered	hindered
tumor response	none	possible
resection margins	no influence	could improve
tumor seeding during resection	no influence	possible reduction
risk of early toxicity[1]	lower	higher
risk of late toxicity[1]	higher	lower
combination with chemotherapy	possible	possible

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[1]In conventionally fractionated radiotherapy. EQD2 – equivalent total dose in 2-Gy fractions; GTV – gross tumor volume

the volumes of organs at risk. The contouring process varies depending on the treatment sequence. However, the main rule remains the same – the elective margin should follow the most probable path of local spread – namely areas of least resistance. In neoadjuvant RT, gross tumor volume (GTV) should be delineated on T1 contrast-enhanced magnetic resonance imaging (MRI) fusion with planning CT. The clinical target volume (CTV) should cover GTV, tumor-associated edema in T2 MRI and the elective margin of healthy tissues. In deeply-seated STS, it is recommended to add 1.5–2.0 cm to GTV radially and 4 cm longitudinally, stopping at anatomical barriers (for example bones, major vessels, fascias) [4]. In superficially-spreading STS, it is suggested to extend GTV by at least 4 cm in each direction, except the deep margin that should end at the nearest non-involved anatomical border. The delineation of organs at risk depends on the irradiated site, including large joints, skin, subcutaneous tissue and contralateral extremity. Due to the large volumes of primary tumors and extensive margins, the protection of organs at risk is challenging. However, the evidence from two clinical trials does not support a reduction of target volumes. In a phase III Randomised Trial of Volume of Post-operative Radiotherapy Given to Adult Patients With eXtremity Soft Tissue Sarcoma (VORTEX, NCT00423618), patients with STS were randomly assigned into postoperative RT with conventional and postoperative RT with reduced margins (2 cm in each direction) [5]. The small number of events did not allow conclusions to be drawn regarding local relapse-free survival. Moreover, the authors found no difference between arms in limb function at 2 years. Thus, reduced margins cannot be recommended as a standard of care. Another phase II Radiation Therapy Oncology Group (RTOG) 0630 non-randomized single-arm clinical trial indicated that modern image-guided RT with simultaneous margin reduction enabled a low rate of late toxicity with good local control [6]. However, it was a single-arm clinical trial and it was not possible to conclude which factors (image-guided RT or margin reduction or both) contributed to the aforementioned results. Thus, conventional extensive margins remain a standard of STS contouring.

Fractionation regimen

The recommended perioperative RT fractionation regimens for STS delivers 2.0 Gy per day, 5 times weekly, up to 50 Gy in preoperative radiotherapy and 60–66 Gy in postoperative radiotherapy [7]. In hypofractionated regimens, the total dose is divided into fewer fractions with an increased fraction dose. Hypofractionated RT in STS has a radiobiological rationale. The alpha/beta ratio of STS seems to be lower than 10 Gy [8]. Thus, a higher dose per fraction should result in better tumor control. Furthermore, hypofractionated RT may allow for a reduction of the delivered total dose without compromising tumor control. This may lead to healthy tissues being spared close to the target volume. Moreover, it can be combined with chemotherapy or targeted therapy [9]. Hypofractionated RT for STS was investigated in many prospective phase I or phase II clinical trials and prospective registries (tab. II); however there is no evidence from phase III trials to support its use in routine clinical practice [9–15]. Nevertheless, it may be used individually in selected patients upon the decision of the MTB.

Table II. Preoperative hypofractionated radiotherapy regimens in soft tissue sarcomas in major published studies

First author	Evidence	Number of patients	Dominant preoperative regimen	Surgery after RT	R0 %	@years local control	Reported late toxicity	@years estimated survival
Temple 1997 [52]	prospective register	42	doxorubicin 30 Gy/10 fr.	delayed (4–6 weeks)	ND	@5y 97%	ND	@5y OS 79%
Ryan 2008 [53]	retrospective cohort	25	EI 28 Gy/8 fr.	delayed (4–5 weeks)	88	@2y 88%	ND	@2y DRFS 78% OS 84%
MacDermed 2009 [54]	retrospective cohort	34 included 6 patients with DM	ifosfamide 28 Gy/8 fr.	delayed (4–8 weeks)	100	@5y 89%	fibrosis 14% edema 17%	@5y (no DM) DRFS 53% OS 45%
Meyer 2013 [55]	phase I single arm CT	16 included 2 patients with DM	sorafenib EI 28 Gy/8 fr.	delayed	94	@2y 100%	ND	@2y PFS 86%
Kosela 2014 [11]	prospective register	272 61 CHT + RT 211 RT	CHT*& 25 Gy/5 fr.	immediate (3–7 days)	79	@3y 81%	15% all 23% CHT+RT 12% RT	@5y OS 60%
Pennington 2018 [56]	retrospective cohort	116	CHT* 28 Gy/8 fr.	delayed (2–3 weeks)	93	@3y 89% @6y 83%	4%	@3y DRFS 75% OS 82% @6y DRFS 65% OS 67%
Spalek 2019 [14]	phase II single arm CT	30 marginally resectable or unresectable	1x AI 25 Gy/5 fr. 2x AI	delayed (6–8 weeks)	73	@1y 97%	ND	@1y DRFS 74%
Parsai 2020 [57]	retrospective cohort	16 3 CHT+RT 13 RT	CHT* 30 Gy /5 fr.	immediate (0–7 days)	63	@1y 100%	ND	ND
Kalbasi 2020 [10]	phase II single arm CT	50	30 Gy/5 fr.	delayed (2–6 weeks)	82	@2y 94%	G1: fibrosis 24% JS 11% edema 4% G2: fibrosis 11% JS 11% edema 4%	@2y DRFS 79%
Kosela 2020 [12]	phase II single arm CT	29 MLPS only	25 Gy /5 fr.	delayed (6–8 weeks)	93	@1y 100%	ND	@1y DRFS 86%

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AI – doxorubicin, ifosfamide; EI – epirubicin, ifosfamide; CHT – chemotherapy; CT – clinical trial; DM – distant metastases; DRFS – distant recurrence-free survival; JS – joint stiffness; MLPS – myxoid liposarcomas; ND – no data; OS – overall survival; PFS – progression-free survival; RT – radiotherapy; STS – soft tissue sarcomas; * – various regimens were used; & – only part of a group received chemotherapy

Techniques

At the beginning of the 2000s, the vast majority of STS patients were irradiated with 2D and 3D-conformal RT that was reflected in the most important STS clinical trials [16–18]. Radiation oncologists who are experienced in STS slowly adapted modern highly-conformal RT techniques. This was caused by the risk of delivery of small doses to high volumes of healthy tissues, including the whole extremity circumference

Theoretically, that may translate into a high occurrence of significant late toxicities. However, the results of two clinical trials do not confirm this hypothesis. In the RTOG-0630 trial, the authors found a significant reduction of late toxicities in patients with extremity STS who had been treated with preoperative image-guided highly conformal RT with reduced margins when compared with the results of the CAN-NCIC--SR2 trial with 3D-conformal RT [6, 17]. In another phase II clinical trial, O'Sullivan et al. investigated the use of intensity-modulated RT (IMRT) in reducing wound complications after preoperative RT for lower extremity STS [19]. IMRT was used to protect healthy tissues (skin flaps for wound closure, bone, or other uninvolved soft tissues). The incidence of wound complications in the investigated group irradiated with IMRT was lower (30.5%) than in the aforementioned CAN-NCIC-SR2 trial (43%). However, this difference was not statistically significant. Additionally, preoperative RT significantly decreased the need for tissue transfer. Due to the high probability of tumor volume size changes during preoperative RT, an image-guided approach is recommended [20]. An

interesting option for reducing the risk of errors could be the introduction of adaptive RT [21].

Other RT techniques

Stereotactic body radiotherapy

Modern diagnostic tools and the growing number of available options for effective systemic treatment introduced the terms oligometastatic and oligoprogressive disease in STS patients. For many years, surgery remained the only curative modality in the case of isolated countable metastases, mostly to the lungs. Existing data suggest an improvement in overall survival after the resection of a limited number of metastases in STS patients. The development of dynamic RT techniques with motion-management enabled precise treatment of small volumes with high-dose radiation accompanied by concomitant sparing of the surrounding healthy tissues. Thus, SBRT could be offered to patients who are not suitable candidates or refuse surgery. This kind of treatment may provide high local control with short overall treatment time and a good toxicity profile. A Swedish group analyzed the outcomes of 46 patients with 136 distant STS metastases treated with SBRT between 1994 and 2005 using a 3D-conformal multifield RT and a stereotactic body-frame. The majority of treated lesions were lung metastases. The authors described an excellent overall response rate that reached almost 90% with acceptable treatment tolerance; only two serious non-lethal adverse events were observed. In a recently designed prospective phase III international randomized clinical trial (Stereotactic Body Radiotherapy in Patients With Rare Oligometastatic Cancers, OligoRARE, NCT04498767), the authors aim to investigate the effect of adding SBRT to the standard of care treatment on overall survival in patients with rare oligometastatic cancers, including STS. SBRT will be given to all metastatic sites as an additional modality to the current standard of care. Patients will be randomly allocated to one of two arms: standard of care or standard of care with SBRT to all metastatic lesions. Full results will be available within 10 years.

Particle therapy

Particle therapy (PT), such as proton and carbon ion therapy, has several potential advantages compared to conventional photon based therapy, which, due to the Bragg curve, can provide better dose distribution. Based on these unique features, PT may allow escalation of the dose to the tumor while reducing the dose to the surrounding organs at risk. Moreover, charged particles, such as carbon ions, deposit the radiation dose in a way that causes complex DNA damage at multiple sites which is challenging for a single DNA damage response pathway to repair; this makes their usage in RT potentially effective in the management of radio- and chemo-resistant tumors like STS. The dose of PT is measured in Gray-equivalents, calculated as a carbon physical dose in Gy, multiplied by relative biological effectiveness (RBE). It is assumed that the RBE of protons is 1.1, whereas in carbon ions RBE equals 2.5-3. PT was used to irradiate sarcomas of the base of the skull and spine. It could be also considered in selected patients with extremity STS [22]. The vast majority of data concerning PT in STS, describes its efficacy in rhabdomyosarcomas and Ewing sarcomas [23]. One study was conducted to assess the effectiveness and safety of PT for unresectable or incomplete resected bone sarcomas and STS of the pelvis [24]. 91 patients, mostly with a primary tumor (90%) were treated with proton and carbon ion therapy. Results showed 83% of them with 3-year overall survival, 72% with 3-year progression-free survival, and 92% with 3-year local control. All patients completed therapy; however, acute grade ≥3 toxicities were observed in 22 patients (24%). Late grade ≥3 toxicities were observed in 23 patients (25%). Another study of 128 patients with unresectable localized axial STS, treated with carbon ion therapy, showed 65% 5-year local control and 49% 5-year overall survival [25]. Yang et al used carbon ion RT to treat patients with locally recurrent or radiation-induced second primary STS of the head and neck [26]. Among the 19 patients, 1-year local control and 1-year overall survival reached 75% and 87%, respectively. A Japanese group conducted a phase I/II trial that aimed to determine the effectiveness of carbon ion therapy for localized primary sarcomas of the extremities [27]. Nine patients had primary diseases and eight had recurrent diseases. In 65% of patients, a radiological response was observed. The 5-year overall survival and 5-year local control was 56% and 76%, respectively. Local recurrences were observed in four patients, three died due to systemic diseases and one was salvaged by repeated carbon ion RT. The aforementioned results indicate the good local efficacy and tolerance of PT in STS. However, further research on that topic is required to establish clear indications for PT in STS.

Brachytherapy

The effectiveness of interstitial brachytherapy in STS has been confirmed in several studies. Brachytherapy in STS is usually applied intraoperatively or postoperatively. Either sole brachytherapy or as a boost after external beam RT were investigated [28–31]. In selected clinical situations, brachytherapy may be superior to external beam RT due to the reduction of treatment time, higher dose intensity and better sparing of surrounding healthy tissues. However, brachytherapy and external beam RT were not directly compared in any prospective study. Moreover, the majority of available data describe the use of low dose rate brachytherapy whereas data regarding high dose rate brachytherapy are limited [32–35]. The American Brachytherapy Society summarized the available evidence on brachytherapy in STS and published a consensus statement regarding indications, techniques, implantation, fractionation regimens and special considerations [36]. Importantly, it is suggested that brachytherapy as monotherapy can be consi-

dered in low-risk STS or in situations of re-irradiation whereas a brachytherapy boost may be applied in high-risk STS or in cases of larger target volumes.

Hyperthermia

Hyperthermia is a cancer treatment in which a heated volume is exposed to temperatures between 41–43°C. It works through the application of electromagnetic energy for a defined period of time. Heat can be delivered using an electromagnetic field, ultrasound or perfusion method. Hyperthermia in oncology comprises three subgroups: whole body hyperthermia, regional hyperthermia and local hyperthermia. It is widely used in combination with RT or chemotherapy in various cancers, including STS. The effectiveness of hyperthermia combined with chemotherapy in locally advanced STS was confirmed in a phase III randomized clinical trial [37, 38]. However, there is no such data on the combination of hyperthermia with radiotherapy in STS. Currently, the Polish Sarcoma Group conducts a prospective phase II clinical trial with neoadjuvant hyperthermia with radiotherapy (3.25 Gy to 32.5 Gy, SINDIR, NCT03989596) in patients with locally advanced STS. Moreover, a combination of RT with hyperthermia may be offered to patients with radiation-induced or in-field recurrent STS. De Jong et al. retrospectively assessed a cohort of patients who received RT with hyperthermia as a treatment for STS which grew in previously irradiated volumes within the thoracic region [39]. Two hypofractionated regimens with hyperthermia twice a week were used (3 Gy to 36 Gy; or 4 Gy to 32 Gy). Thirteen patients underwent treatment with curative intent. The remaining three patients received RT with hyperthermia postoperatively. In seven patients the complete response was observed, whereas partial response was found in two patients. Despite the previous irradiation, both early and late toxicities were acceptable. The authors described only one severe late toxicity, namely arm ischemia that required limb amputation, occurring several years after treatment. Nevertheless, no prospective evidence on RT with hyperthermia in this clinical situation exists. Recently, the Polish Sarcoma Group started a phase II clinical trial with hyperthermia combined with hypofractionated RT in radiation-induced or in-field recurrent STS (HOT, NCT04398095).

Tailored radiotherapy

STS are very heterogeneous and present a wide spectrum of radiosensitivity. Some STS subtypes are considered to be especially radiosensitive compared with other STS. In a prospective phase II single arm clinical trial conducted by the Polish Sarcoma Group, patients with locally advanced myxoid liposarcomas received one-week RT (25 Gy in five fractions) followed by a 6–8 weeks gap before surgery [12]. 29 patients were enrolled on the trial. The investigated method did not increase the wound complication rate (37.9%) compared to other STS trials, whereas in all analyzed surgical specimens a significant response to RT was observed. An interesting approach could be the implementation of radiogenomics models in predicting response to the radiation of selected STS. A research group from the H. Lee Moffitt Cancer Center and Research Institute (Tampa, Florida, USA) and the Netherlands Cancer Institute (Amsterdam, the Netherlands) developed and validated a robust multigene expression model of intrinsic tumor radiosensitivity [40]. To predict the response to treatment, scientists created a model of radiosensitivity as a function of gene expression and other factors in a form of a rank-based linear regression algorithm to establish the radiosensitivity index (RSI). This model was used in further research to calculate the RSI of 113 resected STS samples [41]. The study investigated a predictive value of RSI for locoregional control with preoperative RT in STS. The whole group was divided into two cohorts based on RSI, radiosensitive and radioresistant STS. The four-year locoregional control was better in the radiosensitive STS cohort than in the cohort of the radioresistant tumor (95% *vs.* 79.3%, $p = 0.021$). The genomic-adjusted RT may be an important direction for further research in STS radiation oncology.

Nanoparticles

Using agents to radiosensitize tumor cells has been tested for many years. A multicenter, randomized, II/III phase clinical trial aimed at investigating the efficacy of hafnium oxide nanoparticles (NBTXR3) as a local radiosensitizer added to neoadjuvant RT. Patients with locally advanced resectable STS of extremities or the trunk wall, requiring preoperative RT, were enrolled. The control group received preoperative RT (2 Gy to 50 Gy) alone, whereas the study group received a single intratumoral administration of NBTXR3 before preoperative RT. The primary endpoint was the proportion of patients with a complete pathological response. Analysis of 176 patients – 87 in the study group and 89 in the control group – showed a statistically significant difference in the pathological complete response between the study group (14 patients) and the control group (7 patients) ($p = 0.044$). R0 resection was achieved more frequently in the NBTXR3 group compared to the RT alone group ($p = 0.042$). Serious adverse events occurred in 39% of patients in the NBTXR3 group and 30% of patients in the RT alone group. In both groups, the postoperative wound complication was according to Common Terminology Criteria for Adverse Events v 4.0. The most common grade ≥3 adverse event related to NBTXR3 injection was pain (4%) and hypotension (7%). The administration of NBTXR3 does not increase RT-related toxicities. The most common grade ≥3 adverse event related to RT was skin injuries in both groups: 6% in the NBTXR3 group and 4% in the RT alone group. An NBTXR3 injection before neoadjuvant RT may be a promising radioenhancer that improves the effectiveness of locally advanced STS treatment with no increase in RT-related toxicities. However, there are no long-term results, therefore the late toxicity profile and efficacy of nanoparticles with RT in STS are still unknown.

Spatially-fractionated radiotherapy

In some STS, the utilization of RT is greatly limited by the bulky size and tolerance of surrounding healthy tissue. Advances in RT has led to the development of special techniques of treating bulky tumors. One of them is spatially fractionated radiation therapy applied through sieve-like collimators, namely GRID therapy [42]. A modern adaptation of GRID, 3D-lattice RT, uses highly conformal RT techniques to emulate grid-like patterns within the tumor volume [43]. The aforementioned techniques showed promising results in the treatment of large abdominal gynecological tumors [44, 45]. In the analysis performed at the University of Kentucky (Lexington, Kentucky, USA), 37 patients with locally advanced STS were treated with single fraction 3D-lattice RT (12–20 Gy) before standard conventionally-fractionated RT (1.8–2 Gy to 50–60 Gy) or moderately hypofractionated RT (2.25–3 Gy to 30–40 Gy) [46]. The average tumor size was 14x14 cm. Among those patients who underwent surgery (15/37), a complete pathological response was observed in seven patients (47%), whereas a partial response was seen in eight patients (53%). Among those 15 patients, two experienced grade 3 skin toxicity and three presented delayed wound healing. The median survival of patients who underwent surgery was 18.6 months with a low local failure rate (20%) and high occurrence of distant metastases (74%). Among patients without surgery, two presented a complete clinical response, ten had a partial response, five showed stable disease and five were not evaluable. In another study with spatially-fractionated RT, 14 patients with bulky STS received a single dose of 18 Gy followed by conventionally fractionated RT (2 Gy to 50 Gy) with concomitant ifosfamide-based chemotherapy [47]. They were subsequently referred to surgery. Twenty patients completed the whole protocol; treatment was prematurely stopped for one patient due to grade 3 skin toxicity. One patient underwent a foot amputation, the others underwent limb-sparing surgery. In 12/13 patients, negative margins were achieved. Two patients experienced delayed wound healing. Interestingly, in 9/14 patients >90% tumor necrosis in surgical specimens was present. No local recurrences were observed. To summarize, spatially-fractionated RT may be a valuable treatment option of locally advanced STS; however, prospective trials are awaited.

Retroperitoneal soft tissue sarcomas

Particular attention should be paid to retroperitoneal STS. Perioperative RT is a part of routine treatment in extremity or trunk wall STS, whereas its role in retroperitoneal STS remains uncertain. The main limitations are large target volumes and their localization within the abdominal cavity, close to at risk radiosensitive organs. In recently published results from a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal STS (STRASS, EORTC 62092), the addition of preoperative RT to surgery did not improve the abdominal relapse-free survival [48]. Moreover, a large retrospective study performed by the Trans-Atlantic Retroperitoneal Sarcoma Working Group, showed multivariate analysis indicated no benefit in local control of perioperative RT in retroperitoneal STS [49]. In turn, another study presented prolonged local recurrence-free survival in patients with retroperitoneal STS who received preoperative RT [50]. Additionally, the Surveillance, Epidemiology, and End Results analysis showed a benefit to overall survival by adding adjuvant RT after resection of high-grade retroperitoneal STS [51]. To sum up, the current evidence does not support the routine use of perioperative RT in patients with retroperitoneal STS; however, it could be used in selected patients depending on the decision of the MTB. The role of RT in the management of residual or recurrent retroperitoneal STS is unknown. Contemporary RT techniques, such as MR-based RT or particle therapy, may open up new possibilities for this group of patients.

Summary

Multiple innovations in RT have been introduced over the last 20 years. The vast majority of them are used to improve the results of multidisciplinary treatment of STS. This includes advances in external beam RT as well as more widespread use of existing experimental methods and the introduction of new approaches. Further evaluation of new strategies is warranted, but a part of them could be currently used in selected STS patients depending on the decision of the MTB.

Conflict of interest: none declared

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Immunotherapy in sarcoma

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The introduction of immunotherapy with checkpoint inhibitors into clinical practice has radically changed the treatment and prognosis of patients with cancer. This treatment is also extensively studied in patients diagnosed with advanced sarcomas, where the number of effective therapies is limited. The following review presents the latest reports on the use of immunotherapy in the treatment of patients with sarcomas.

Key words: sarcoma, soft tissue, bone, immunotherapy, anti-PD-1

Sarcomas are rare malignant tumors comprising about 1% of all adult cancers. Sarcomas can be found both in the soft tissues (STS) and bones (BS). Moreover, they affect all age groups, with a median age for STS patients of about 50-year-old, but much younger for bone tumors such as osteosarcoma or Ewing sarcoma. The cornerstone of therapy of locally advanced sarcomas is surgery, in most cases used with adjuvant radiotherapy and chemotherapy. However, metastatic recurrence is often found and concerns even 50% of sarcoma cases, depending on the subtype and initial tumor stage. As there are more than 60 subtypes of sarcoma, with different prognosis, risk of recurrence and sensitivity to systemic therapy, heterogeneity within this group of tumors and its rarity make it extremely difficult to develop a successful clinical trial for this group of patients. Furthermore, research undertaken over recent years has proven this thesis with several negative phase three trials for new therapies in sarcomas [1, 2].

Immunotherapy is based on the idea that a patient's immune system can be stimulated or enhanced so as to attack malignant tumors. As an anecdote, it is worth recalling that one of the first successful examples of the use of immunotherapy in cancers was described more than 100 years ago in sarcoma patients. They were treated by Dr. William B. Coley, who injected streptococcal organisms into patients with inoperable cancer, with some success; this consequently resulted in him being given the title of the "Father of Immunotherapy" [3]. From that time, much has changed, and in recent years we have witnessed a real revolution in the use of immunotherapy to treat malignant tumors. We owe this breakthrough mainly to the introduction into clinical practice of drugs from the checkpoint inhibitors group, which have shown improved rates of patient survival with melanoma, lung cancer, or kidney cancer, among others.

Knowledge about the immune profile of sarcomas is still limited. Several important studies on this topic have already been published, although their results can sometimes be confusing because of the heterogeneity of this group of tumors [4]. This review will present some of the latest immunotherapy achievements in sarcoma, focusing on trails with checkpoint inhibitors in less selected groups of patients and in specific subtypes, where it seems that this type of therapy is most successful.

Immune checkpoints in sarcomas

One of the first studies analyzed the clinical impact of intra-tumoral infiltration of PD1-positive lymphocytes and PD-L1 expression in tumor cells in 105 cases of STS. Intra-tumoral infiltration of PD1-positive lymphocytes and PD-L1 expression was seen in 65% and 58% of STS, respectively. Both PD1-positivity and PD-L1 expression were significantly associated

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with advanced clinicopathological parameters such as higher clinical stage, distant metastasis, higher histological grade, a low differentiation of tumor and tumor necrosis. Moreover, both PD1-positivity and PD-L1 positivity were independent prognostic indicators of overall survival (OS) and event-free survival (EFS) of STS by multivariate analysis. The combined pattern of PD1- and PD-L1-positivity was also an independent prognostic indicator for OS and EFS by multivariate analysis. The patents with a PD1+/PD-L1+ pattern had the shortest survival time [5]. A study from the Memorial Sloan Kettering Cancer Center evaluated PD-L1 expression by immunohistochemistry in 50 sarcoma specimens and quantified tumor-infiltrating lymphocytes (TIL). Immunohistochemical staining for CD3, CD4 (helper T cells), CD8 (cytotoxic T cells), foxp3 (regulatory T cells), and PD-1 and PD-L1 expression, and multiplex immunohistochemistry for CD3/PD-1, CD3/CD8, and CD3/CD4/foxp3 were performed. Lymphocyte infiltration was observed in 98% of cases, and macrophage infiltration in 90%. "Low-density" TILs was defined as below 5% and "high-density" as above 5%; they noted that 27 patients (54%), mainly those with leiomyosarcoma (LMS, 3 of 4), synovial sarcoma (4 of 5), and chondrosarcoma (1 of 1), had low-density TILs; another 22 patients (44%), mainly those with gastrointestinal stromal tumors (9 of 14), had high-density TILs. Tumor, lymphocyte, and macrophage PD-L1 expression was 12%, 30% and 58%, respectively, with the highest frequency of PD-L1 positivity seen in gastrointestinal stromal tumors (4 of 14). There was no association between clinical features, overall survival, and PD-L1 expression in tumor or immune infiltrates [6].

In tumor tissues collected by biopsy or surgical resection, 56 osteosarcoma patients (17%) showed PD-L1 expression. PD-L1 expression was not associated with poor prognosis. PD-L1 immunoexpression was significantly associated with the infiltration of CD3+ T cells, CD4+ T cells, and CD8+ T cells [7]. In Ewing's sarcoma, CD8+ TILs were detected in 15% of samples from 370 patients, but this finding was not correlated with the histological subtypes, location of the tumor, or PD-1 and PD-L1 expression, and it did not impact progression-free survival or overall survival. PD-1 was expressed in 26% of tumors. Histological subtypes were not correlated with PD-L1 or PD-1 positivity. Metastatic tumors had higher expression of PD-L1 ($p < 0.0001$). Lesions with elevated proliferation index (Ki-67) were associated with higher PD-L1 expression ($p = 0.049$). In terms of prognosis, no significant association was found between PD-L1 expression and progression-free survival (PFS) or overall survival (OS). However lack of PD-1 expression in tumor cells was correlated with both poor PFS ($p = 0.02$) and poor OS ($p = 0.004$) [8]. In chondrosarcoma, PD-L1 expression was absent in conventional (n = 119), mesenchymal (n = 19) and clear cell (n = 20) chondrosarcomas. 41% (9 of the 22) of dedifferentiated chondrosarcomas displayed PD-L1 positivity. TILs were detectable and correlated with PD-L1 expression, being highly expressed in dedifferentiated chondrosarcomas. PD-L1 expression was also correlated with positive HLA class I expression, but not with a patient's survival [9].

Overall, it seems that the expression and clinical associations were found to be subtype dependent. A study of 208 sarcoma patients, programmed cell death-1 (PD-1), programmed death ligand-1 (PD-L1) and CD8 were assessed in tumors. Primary untreated osteosarcoma (n = 46), Ewing sarcoma (n = 32), alveolar rhabdomyosarcoma (n = 20), embryonal rhabdomyosarcoma (n = 77), synovial sarcoma (n = 22) and desmoplastic small round cell tumors (DSRCT) (n = 11) were examined immunohistochemically. PD-L1 expression was predominantly detected in alveolar and embryonal rhabdomyosarcomas (15% and 16%, respectively). In the alveolar subtype, PD-L1 expression was associated with better OS, EFS and metastases-free survival. PD-1 expression on lymphocytes was predominantly seen in synovial sarcomas (18%). High levels of CD8+ lymphocytes were predominantly detected in osteosarcomas (35%) and associated with worse event-free survival in synovial sarcomas. Ewing sarcoma and DSRCTs showed PD-1 on tumor cells instead of on tumor-infiltrating lymphocytes [10].

Using transcriptomic analysis of the microenvironment cell population, measuring the expression of eight immune and two stromal cell populations, sarcomas were classified into five different sarcoma immune classes (SIC). Each SIC exhibited a different profile, from A (immune desert-cold tumors), which showed the lowest expression of gene signatures of immune cells and vasculature expression, to E (immune and tertiary lymphoid structures) with the highest expression of genes related to immune cells. In the middle, C (vascularized) was characterized by a high expression of endothelial related genes. SIC B and D have expressed mixed profiles between A and C or C and E. This grouping of sarcomas into these five classes based on different profile expressions of tumor microenvironment also had a prognostic impact. So, SIC A patients showed poorer overall survival than SIC D ($p = 0.048$) or SIC E ($p = 0.025$). Furthermore, this genomic immune signature had a predictive role in a prospective series treated with pembrolizumab. The overall response rate (ORR) was 50%, 25%, 22%, 0% and 0% for SIC E, D, C, B and A respectively. Patients harboring SIC E had significantly higher ORR with pembrolizumab ($p = 0.026$). Patients grouped as SIC E only represented 17.8% of cases. A more detailed analysis revealed a significant correlation of survival with B-cell lineage signature, whereas CD8+ signature did not significantly correlate with survival [11, 12].

Clinical trials

A large study of immunotherapy in sarcomas was published in 2017 (SARC028 Trial) [13]. In this two-cohort, single-arm, open-label, phase 2 study, 86 patients were enrolled with soft-tissue sarcoma or bone sarcoma. Patients with soft-tissue sarcoma had to be aged 18 years or older to enroll; patients with bone sarcoma could enroll if they were aged 12 years or older.

Patients had histological evidence of metastatic or surgically unresectable locally advanced sarcoma, and had received up to three previous systemic anticancer therapy lines, with at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST). Included subtypes were leiomyosarcoma, poorly differentiated or dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma and dedifferentiated or mesenchymal chondrosarcoma. All patients were treated with 200 mg of intravenous pembrolizumab every three weeks. The primary endpoint was the investigator-assessed objective response. One-third of the patients previously received three lines of systemic therapy. The median follow-up was 17.8 months (IQR 12.3–19.3).

Seven (18%) out of the 40 patients with STS had an objective response, including four (40%) of the ten patients with undifferentiated pleomorphic sarcoma, two (20%) of the ten patients with liposarcoma, and one (10%) of the ten patients with synovial sarcoma. One (10%) patient with undifferentiated pleomorphic sarcoma – a woman aged 50 years with primarily pulmonary lesions whose response lasted for longer than 13 months – achieved a confirmed complete response. Responses in patients with soft-tissue sarcoma were generally durable, with a median duration of 33 weeks (IQR 23–49). No patients with leiomyosarcoma (n=10) had an objective response. In the bone sarcoma group, a confirmed partial response was observed in one (5%) of the 22 patients with osteosarcoma and one (20%) of the five patients with chondrosarcoma. No patient with Ewing's sarcoma had an objective response. 37 (93%) of the 40 evaluable patients with soft-tissue sarcoma had a progression event (i.e., progressed or died), and median progression-free survival (PFS) was 18 weeks (95% CI 8–21).

The 12-week PFS was 55% (95% CI 40–70), which was significantly higher than the threshold of 40% expected from an active regimen in patients with soft-tissue sarcoma ($p = 0.039$). The median PFS was 30 weeks (95% CI 8–68) for patients with undifferentiated pleomorphic sarcoma (seven [70%] of whom had a progression event), and 12-week PFS was 70% (42–98). In ten patients with liposarcoma (all of whom had a progression event), the median PFS was 25 weeks (95% CI 8–42), and the 12-week PFS was 60% (30–90). The median OS for patients with soft-tissue sarcoma was 49 weeks (95% CI 34–73); 25 patients died because of disease progression. The median OS for patients with undifferentiated pleomorphic sarcoma had not been reached at the time of this analysis; four patients had died. 38 (95%) of the 40 patients with bone sarcoma had a progression event; data for one (3%) patient has been censored. The median PFS was eight weeks (95% CI 7–9). 25 (63%) patients with bone sarcoma died because of disease progression; the median OS was 52 weeks (95% CI 40–72). The median OS was not reached in patients with chondrosarcoma. The median duration of response was 43 weeks.

The most frequent grade 3 or worse adverse events were anemia (six [14%]), a decreased lymphocyte count (five [12%]), prolonged activated partial thromboplastin time (four [10%]), and decreased platelet count (three [7%]) in the bone sarcoma group; anemia, decreased lymphocyte count and prolonged activated partial thromboplastin time was evident in the soft--tissue sarcoma group (three [7%] each). Nine (11%) patients (five [12%] in the bone sarcoma group and four [10%] in the soft-tissue sarcoma group) had treatment-emergent serious adverse events (SAEs), five of whom had immune-related SAEs, including two with adrenal insufficiency, two with pneumonitis and one with nephritis.

As the results of the treatment seemed to be best in the group of patients with undifferentiated pleomorphic sarcoma (UPS) and liposarcoma (LPS), the investigators decided to have an expansion cohort in these subtypes. The results were presented at the American Society of Clinical Oncology conference in 2019. 30 patients were additionally enrolled in each of the 2 expansion cohorts for a total of 40 UPS and 40 LPS patients. The primary endpoint was the investigator-assessed response by RECIST v1.1. Secondary endpoints were safety, PFS, the 12-week PFS rate and OS. An ORR of 25% was considered clinically meaningful, and <10% was considered to lack efficacy. The use of pembrolizumab was considered a success if 8 or more of the 40 enrolled patients had a partial response (PR) to therapy or better (1-sided $\alpha = 0.042$, 82% power). The ORR in the UPS cohort was 23% (9/40), with an additional 5/30 PRs observed in the expansion cohort In the LPS cohort, the ORR was 10% (4/39 evaluable patients), with an additional 2/30 PR observed (total 4 PR). The median PFS for the UPS group was 3 months (95% CI 2–5) and 2 months (95% CI 2–4) for the LPS group. The 12-week PFS rate was 50% in UPS (95% CI 35–65) and 44% in LPS (95% CI 28–60). The UPS group had a median OS of 12 months (95% CI 7–34) and 13 months (95% CI 8–NR) for the LPS group [14].

Results of the translational research from the study were recently published. Pretreatment (available for 78 patients) and 8-week on-treatment (from 68 patients) tumor biopsies were stained for PD-L1 and multiplex immunofluorescence panels. The density of positive cells was quantified to determine associations with the anti-PD-1 response. It turned out that patients that responded to pembrolizumab were more likely to have higher densities of activated T cells (CD8 + CD3 + PD-1+) and an increased percentage of tumor-associated macrophages expressing PD-L1 pre-treatment compared with non-responders. Pre-treatment tumors from responders also exhibited higher densities of effector memory cytotoxic T cells and regulatory T cells than non-responders. Moreover, a higher density of cytotoxic tumor-infiltrating T cells at baseline correlated with better PFS [15].

Additionally, the immunotherapy combination was studied in sarcomas. An open-label, unblinded, non-comparative multi-center randomized phase II study enrolled 96 sarcoma

patients [16]. Patients received either nivolumab 3 mg/kg every two weeks or nivolumab 3mg/kg and ipilimumab 1mg/kg every three weeks for four doses followed by nivolumab (3 mg/kg) every two weeks thereafter. Patients with a central pathology confirmation of sarcoma were included. They had to be at least 18 years old to enroll and have evidence of metastatic or unresectable disease and good performance status. Patients had to have received at least one previous systemic therapy line. The primary endpoint was the confirmed objective response rate (ORR). Secondary endpoints included safety, the duration of the response, clinical benefit rate, PFS and OS.

Patients were heavily pre-treated, with 61% of patients receiving at least three prior chemotherapy lines. The most common enrolled sarcoma types across both arms included: bone nine (10.6%), LMS 29 (34.1%), LPS five (5.9%), spindle cell sarcoma 11 (12.9%), UPS 11 (12.9%) and other 10 (11.7%).

Among the 38 patients that received nivolumab monotherapy, the confirmed ORR was 5% [92% CI 1–15%]. Responses occurred in the following histological subtypes: alveolar soft part sarcoma (ASPS), non-uterine LMS and sarcoma NOS. For the 38 patients that received combination therapy, the confirmed ORR was 16%, (92% CI 7–29%). Responses occurred in UPS, LMS, myxofibrosarcoma and angiosarcoma. The median PFS was 1.7 months [n = 42, 95% CI 1.4–4.3 months) for monotherapy. The median OS was 10.7 months (n = 42, 95% CI 5.5–15.4). The 12-month OS rates were 40,4% (n = 12, 95% CI 27.2–59.9%). For combination arm, the median PFS was 4.1 months [n = 41, 95% CI 2.6–4.7) and the median OS was 14.3 months (n = 41, 95% CI 9.6–not estimable). The 12-month OS rate for combination therapy was 54.6% (n = 41, 95% CI 41–72,7%). In the monotherapy arm, the most common grade 3 or worse adverse events included anemia (four – 10%), decreased lymphocyte count (three – 7% each) and dehydration, increased lipase, pain, pleural effusion, respiratory failure, secondary benign neoplasm and urinary tract obstruction (two – 5% each.) In the combination arm, the most common grade 3 or worse adverse events included: anemia (seven – 17%), hypotension (four – 10%), pain, and urinary tract infection (three – 7%). Treatment-related serious adverse events on the monotherapy arm occurred in eight patients and included anemia, anorexia, dehydration, decreased platelet count, diarrhea, fever, increased creatinine, and pleural effusion (one – 2% each). On the combination arm, treatment-related serious adverse events occurred in 11 patients. Three patients – 7% patients had adrenal insufficiency, two patients – 5% had increased alanine aminotransferase, two patients– 5% with hyponatremia, one patient– 2% each experienced anemia, increased aspartate aminotransferase, fatigue, pain and pruritus.

In an attempt to improve the modest results of immunotherapy alone in the treatment of advanced sarcomas, efforts have also been made to combine this treatment with other drugs commonly used in this indication.

Anthracycline-based therapy is a standard first-line treatment for most patients with advanced and metastatic sarcomas. Although multiple trials have attempted to show improved outcomes in patients with soft-tissue sarcoma over doxorubicin monotherapy, each has fallen short of demonstrating improved outcomes. A nonrandomized clinical trial used a 2-stage phase 2 design and was performed to assess the efficacy and safety of doxorubicin and pembrolizumab in patients with advanced anthracycline-naive sarcoma [17]. Patients were adults with good performance status and end-organ function. Patients with all sarcoma subtypes were allowed to enroll with the exception of those with osteosarcoma, Ewing sarcoma, and alveolar and embryonal rhabdomyosarcoma. Two dose levels of doxorubicin (45 and 75 mg/m^2) were tested for safety combined with pembrolizumab. The patients' initial cycle was pembrolizumab (200 mg administered intravenously) alone. Cycles were 21 days. Starting with cycle 2, doxorubicin was given before pembrolizumab, on the same day, every 3 weeks, for up to 6 cycles. After cycle 7, pembrolizumab treatment continued for up to 2 years. The primary endpoint was ORR. Secondary endpoints were PFS and OS. Correlative studies included immunohistochemistry, gene expression and serum cytokines.

A total of 37 patients (22 men, 15 women) were treated. The median patient age was 58,4 (ranging from 25–80) years. The most common histologic subtype was leiomyosarcoma (11 patients). Doxorubicin plus pembrolizumab was well-tolerated without significant unexpected toxic effects. The ORR was 19%, and 59% of patients had stable disease. Two of the three patients with UPS and two of the four patients with dedifferentiated liposarcoma had durable response to therapy. Three patients with chondrosarcoma had tumor regression, including one conventional chondrosarcoma with a 26% decrease in size. Median PFS was 8.1 (95% CI 7.6–10.8) months. The PFS rates at 12 and 24 weeks were 81% (95% CI 64–90%) and 73% (95% CI 56–84%), respectively. At 12 months, the PFS was 27% (95% CI 14–42%). The median OS was 27.6 (95% CI 18.7–not reached) months at the time of this analysis. Immunohistochemistry was evaluable for 29 patients; 66% had PD-L1 expression scores of 0, reflecting a low level of PD-L1 expression. Expression of PD-L1 was not associated with PFS or OS. Tumor-infiltrating lymphocytes were present in 21% of evaluable tumors and associated with inferior PFS (log-rank p = 0.03). This was confirmed in a multivariate Cox regression analysis adjusted for age, sex and the number of prior therapies (p = 0.04). No dose-limiting toxic effects were observed. The most common toxic effects were nausea (n = 32) and fatigue (n = 21). No grade 5 toxic effects were seen; the only attributable grade 4 toxic effects were neutropenia (n = 6), leukopenia (n = 1) and febrile neutropenia (n = 1), all of which resolved. Two patients had grade 3 reductions in ejection fraction attributable to doxorubicin. Notable pembrolizumab-related toxic effects included grade 3 adrenal insufficiency (n = 1) and hypothyroidism (n = 7).

This result is impressive for patients with advanced sarcoma, but of course, this result must be confirmed in a phase III trial.

Another attempt is supported by evidence that tumor angiogenesis promotes immunosuppression. A phase Ib/II trial tested the double inhibition of angiogenesis (sunitinib) and PD-1/PD-L1 axis (nivolumab). This single-arm, phase Ib/II trial enrolled adult patients with selected subtypes of sarcoma[18]. Phase Ib established two dose levels: level 0 with sunitinib 37.5 mg daily from day 1, plus nivolumab 3 mg/kg intravenously on day 15, and then every 2 weeks; and level – 1 with sunitinib 37.5 mg for the first 14 days (induction) and then 25 mg per day plus nivolumab on the same schedule. The primary endpoint was to determine the recommended dose for phase II (phase I) and the 6-month progression-free survival rate, according to RECIST in Solid Tumors 1.1 (phase II). 68 patients were enrolled and treated with the experimental compounds: 16 in phase Ib and 52 in the STS cohort of phase II. The recommended dose of sunitinib for phase II was 37.5 mg as induction and then 25 mg combined with nivolumab. The 6-month PFS, according to central and local assessments, was 48% (95% CI 41–55) and 51% (95% CI 44–58), respectively. The median PFS for central and local assessments was 5,6 months (3.0–8.1) and 6 months (3.1–9), respectively. Remarkably, the proportion of patients alive at 12 and 18 months was 75% (95% CI 68–81) and 67% (95% CI 59–74), respectively, and the median OS was 24 months (95%CI NA).

The central radiological assessment according to RECIST reported 1 complete response in 46 evaluable patients (2%), 5 partial responses (11%), 33 stabilizations (72%) and 7 progressions (15%). A complete response was observed in one patient with angiosarcoma and partial response in patients diagnosed with ASPS (n = 2), angiosarcoma (n = 1), extraskeletal myxoid chondrosarcoma (n = 1) and synovial sarcoma (n = 1). Central assessment, according to Choi criteria, showed 25 patients with partial response (63%), 10 with stable disease (25%), and 5 with progressive disease (12%). According to RECIST, the response assessment showed a significant prognostic difference for PFS and OS; by contrast, the Choi assessment only had prognostic relevance for PFS. Adding the 12 evaluable STS cases of phase I to the 46 evaluable patients with STS in phase II, the RECIST Overall Response Rate (ORR) was 21% (12 out of 58). The 18-month OS proportion was 100%, 75%, and 44% for those with a response, stable disease, and progressive disease, according to RECIST, respectively (p = 0.01).

The most frequent treatment-related toxicities per subject in phase II were fatigue in 33 of the 52 patients (63,5%) and increased aspartate aminotransferase (AST) in 25 out of 52 patients (48%). The most common reported grade 3 or 4 side effects were transaminitis in 9 out of 52 patients (17.3%) and neutropenia in 6 out of 52 patients (11.5%).

Alveolar soft part sarcoma (ASPS) is an exceedingly rare STS subtype inherently resistant to cytotoxic chemotherapy. It usually affects adolescents and young adults and presents early with widespread metastases that are ultimately fatal. The conserved translocation of the *ASPSCR1-TFE3* fusion gene in ASPS leads to aberrant transcription of downstream target genes, including HIF-1α, which upregulates proangiogenic factors, including VEGF. Tyrosine-kinase inhibitors are the most active treatment to date for patients with ASPS, although most patients ultimately develop resistance and die due to the disease [19, 20]. This subtype is interesting because, compared to other sarcomas, it is characterized by its exceptional sensitivity to immunotherapy treatment. There are many case reports of patients diagnosed with advanced ASPS who have been successfully treated with checkpoint inhibitors, including the case of a patient treated in the clinic where the author works [21, 22]. The phase II trial with atezolizumab monotherapy, a monoclonal antibody directed against a ligand of a PD-L1, proved to be a success in this setting. The results were presented during the Connective Tissue Oncology Society Annual Conference in 2018. 22 patients with advanced, metastatic ASPS were enrolled in the trials; most of them had previously undergone other therapies. According to RECIST criteria, a partial response was confirmed in 9 patients, disease stabilization in 9 patients and disease progression in 1 patient. In the 3 other patients treated, it was too early to make any evaluations [23]. The summary of studies in ASPS with immunotherapy is shown in table I.

A single-arm, phase 2 study was conducted on the safety and efficacy of the antiangiogenic drug axitinib (VEGF inhibitor) plus pembrolizumab in patients with advanced sarcomas, including alveolar soft-part sarcoma [24]. Patients were eligible if they were aged 16 years or older and had histologically confirmed advanced or metastatic sarcomas, including alveolar soft-part sarcoma (ASPS – who constituted 36% of the whole group of 33 patients); an ECOG performance status of 0–1; and disease progression after previous treatment with at least one line of systemic therapy (unless no standard treatment existed or the patient declined therapy). The first five patients were enrolled in a lead-in cohort and were given axitinib 5 mg orally, twice daily, and pembrolizumab 200 mg intravenously for 30 min on day 8 and every 3 weeks for cycles of 6 weeks for up to 2 years. After that, patients received escalating doses of axitinib (2–10 mg) plus a flat dose of pembrolizumab according to the schedule above. The 3-month PFS for all patients was 65.6% (95% CI 46.6–79.3), and the median PFS was 4.7 months (95% CI 3–9.4). The 6-month PFS was 46.9% (95% CI 29.2–62.8) and the 12-month PFS was 27.5% (13.4–43.6). The median overall survival for all 33 patients was 18.7 months (95% CI 12–not reached) with a 1-year overall survival of 72% (95% CI 53–84.4). Of the 32 patients evaluable for objective response, none achieved a complete response. Eight (25%, 95% CI 12.1–43.8) achieved a partial response at any point during treatment, and nine (28%) achieved stable disease, so the proportion of patients who achieved a clinical benefit was 53 % (n = 17; 95% CI 35–70.5). The median duration of response was 29 weeks (IQR 21.8–76.5), and the median time to achieve partial

Table I. The summary of clinical trials with immunotherapy in ASPS

Therapy	Patient number	Response rate (95% CI)	Median progression-free survival (PFS); months, 95% CI	Reference
OSCAR, nivolumab (ASPS only)	14	7.1% (0.2–33.9)	6.0 (3.7–9.3)	Kawai et al., CTOS 2020
Hindi i wsp. Anti-PD-1/anti-PD-L1 + antiangiogenic drugs (retrospective data)	21	47.6% (not reported)	10.9 (9.9–11.9)	Hindi et al., CTOS 2020
durvalumab/tremelimumab (ASPS cohort)	10	50% (not reported)	34.23 (1.84–not reached)	Somaiah et al., ASCO 2019
atezolizumab (anti-PD-L1)	31	32% (not reported)	not reported	Coyne et al., CTOS 2019
axitinib/pembrolizumab (ASPS kohort)	11	54.5% (24.6–81.9)	12.4 (2.7–22.3)	Wilky et al., Lancet Oncol 2019
geptanolimab (GB226, anti-PD-1)	37	37.8% (22.5–55.2)	6.9 (5.0–not reached)	Shi et al., Clin Cancer Res 2020
toripalimab (anti-PD1), ASPS kohort	12	25.0% (not reported)	11.1 (not reported)	Yang et al., Eur J Cancer 2020

response was 19,4 weeks (IQR 12.8–31.4). Most responses occurred in patients with ASPS, with six of the eleven evaluable patients with ASPS achieving a partial response (54.5%, 95% CI 24.6–81.9), and two (18%) of the eleven achieving stable disease, so the proportion of patients who achieved a clinical benefit was 72.7% (n = 8; 95% CI 32.3–92.7). The median time to partial response in patients with ASPS was 25.1 weeks (IQR 12.7–34.3). In addition, partial responses were observed in two patients, one with conventional type epithelioid sarcoma and one with soft tissue leiomyosarcoma, and minor responses (a decrease in the size of the target lesion of less than 30%) in three patients, one with soft tissue leiomyosarcoma, one with synovial sarcoma and one with high-grade undifferentiated pleomorphic sarcoma.

The toxicity profile of axitinib plus pembrolizumab therapy was consistent with the drugs' previous clinical trials as monotherapy. Treatment-related toxicity occurred in only two (40%) of the five patients in the safety lead-in cohort, and no application of the early stopping rule was needed throughout the study. Treatment-related grade 3 or 4 adverse events occurred in 13 (39%) of the 33 patients, and grade 3 or 4 autoimmune, toxic effects in five (15%) patients. The most common treatment-related adverse events of any grade included fatigue (26–79%), oral mucositis (23–70%), hypothyroidism or hyperthyroidism (21–64%), nausea or vomiting (22–67%), nasopharyngeal congestion (18–55%), and diarrhoea (19–58%). Serious treatment-related adverse events occurred in seven (21%) of the 33 patients, including autoimmune colitis, transaminitis, pneumothorax, hemoptysis, seizures and hypertriglyceridemia.

Conclusion

The rarity and heterogeneity within sarcoma groups have contributed to the slow development of effective new therapies; outcomes for patients with advanced stages of the disease remain poor. The progress of immunotherapy, mainly with the development of checkpoint inhibitors, has been spectacular and revolutionized everyday oncology practice over the last few years. Naturally, this approach is also being studied in sarcomas, with some success, as has been shown in this review. It is worth emphasizing that immunotherapy in sarcomas is also studied in other aspects, such as vaccines or adoptive cell therapy. This approach makes particular sense in some of the STS subtypes, although so far, evidence of their effectiveness is limited [12]. That said, the author does not doubt that in the coming years there will be optimistic news on breakthrough therapies for patients with advanced sarcomas, as has happened, for example, with melanoma. The development of immunotherapy will also undoubtedly, in this case, contribute to this.

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