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Average glandular doses reported by mammography units: how reliable are they?

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Introduction. Average glandular dose (AGD) values displayed by mammography units are often used to compare doses with diagnostic reference levels, with acceptable and achievable dose levels given with in the European guidelines on breast cancer screening, or between mammography units. The aim of the work was to check the reliability of displayed AGD values by comparing them with independently calculated values.

Material and methods. The comparison was performed for five mammography units, for 20 groups of patients (50 patients each), examined in various periods between the years 2015 and 2020. AGD values were calculated independently for the same patients using the results of measurements.

Results. Observed differences between displayed and calculated doses affected their comparison with acceptable and achievable dose levels.

Conclusions. The displayed AGD values should be used with caution. If reliable information on AGD values is needed, they should be independently calculated using the results of measurements.

Key words: mammography, average glandular dose, DICOM

Introduction

Breast cancer is one of the most common cancers. Mammography is widely used in breast cancer screening and diagnosis [1, 2]. Since mammography uses ionizing radiation, the radiation dose is of radiation dose is an important issue. This is true especially in breast cancer screening, in which examinations are performed largely on asymptomatic women [3, 4]. Diagnostic reference levels (DRLs) should be established and used in all countries belonging to the European Union, and information relating to patient exposure should be included in the report of the medical radiological procedure [5]. In Poland, an internal clinical audit should be carried out every year in each diagnostic radiology facility. During the audit, data on patient exposure should be compared with diagnostic reference levels. The data should be included in the internal clinical audit report, which is submitted to the procedures and audits' committee, and a copy sent to the National Centre for Radiation Protection in Health Care [6].

Radiation dose is expressed in mammography usually as the average glandular dose (AGD) [3, 4, 7]. Acceptable and achievable dose levels in breast cancer screening, as stipulated in the European guidelines on breast cancer screening, are also expressed as average glandular doses [8, 9]. AGD is also used in dose monitoring and optimization [10, 11]. In modern mammography, the average glandular dose is automatically calculated for each exposure and displayed to the operator, as well as stored within a header of a DICOM file. The information may be gathered by dose management systems, allowing

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further analysis [10]. Average glandular doses are calculated by multiplication of air kerma by conversion factors. The conversion factors depend on beam quality, the thickness of the compressed breast, and tissue composition (share of adipose and glandular tissue), and they are based on Monte Carlo calculations. Several different methodologies of AGD calculation are used in various areas of the world [12]. European guidelines on breast cancer screening [8, 9] and the International Atomic Energy Agency (IAEA) recommendations [13] endorse the methodology described by Dance et al. [14, 15].

The aim of the work was to check the reliability of AGD values displayed by mammography units by comparing them with values calculated independently with the Dance method, based on the measurements.

Material and methods

A dose comparison was performed for five full-field digital mammography units of three different manufacturers used in our institute (tab. I). For each unit, data was gathered for several groups of 50 patients (200 exposures), examined in various periods between the years 2015 and 2020 (a total of 20 groups of patients), either for screening or diagnosis. The data included exposure parameters (anode, filter, tube voltage, tube loading), displayed AGD values, compressed breast thickness, and image size (18 x 24 cm^2 or 24 x 30 cm^2). Depending on the period, the data were either noted manually or taken from the headers of DICOM files (e.g. AGD is stored in the DICOM header in the "organ dose" tag, coded [0040,0316]).

Table I. Mammography units used in the comparison

Code	Mammography unit type	Year of installation
A	Siemens Mammomat Inspiration	2010
B	Siemens Mammomat Inspiration	2011
C	Siemens Mammomat Inspiration	2011
D	GE Pristina	2018
E	Hologic Selenia	2007

Several measurements were made in each period, providing the data necessary for an independent calculation of AGD. Air kerma and half-value layer values were measured for all clinically used beam qualities with the Piranha Black 657 meter (RTI Electronics AB, Sweden). Additionally, tests of thickness indicator accuracy were performed according to international guidelines [8, 9, 13], and separately for small and large compression plates. Several 18 × 24 cm slabs of polymethylmethacrylate (PMMA) were used for the test, with thickness ranging from 2 cm to 7 cm. The results of the test were then used to correct data on breast thickness.

Individual average glandular doses were calculated independently for patients, using Dance's method [8, 9, 14–16] and an in-house Excel spreadsheet. Actual exposure parameters, corrected breast thickness data, and the results of tube output measurements were used to calculate incident air kerma. Information on beam quality (anode/filter/HVL) and corrected breast thickness were used to obtain conversion factors. Since the conversion factors are given only for discrete thickness and HVL values, linear interpolation was used.

For each group of patients, displayed and calculated doses were cross-compared, and compared with achievable and acceptable dose levels as outlined in the European guidelines on breast cancer screening [8, 9], including an update published on the website of the European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services (EUREF) in 2017 [16]. The number of cases, where the displayed and calculated doses do not exceed the acceptable and achievable dose levels, was calculated as a percentage of all evaluated cases. Displayed AGD values were compared against dose levels calculated for the displayed breast thickness, while calculated AGD values were compared against dose levels calculated for corrected breast thickness. Since the acceptable and achievable dose levels are given only for discrete thickness values, they were interpolated with a second-degree polynomial.

Table II. Summary of results of dose comparison

Group	Unit	Year/month	Mean AGD [mGy]			% of doses ≤ acceptable level		% of doses ≤ achievable level	
			Calculated values	Displayed values	Mean difference	Calculated values	Displayed values	Calculated values	Displayed values
#1	A	2016/01	1.43	1.39	-0.04	99%	99%	94%	92%
#2	A	2019/03	1.18	1.16	-0.02	100%	100%	100%	100%
#3	B	2015/06	1.30	1.38	0.08	97%	95%	91%	82%
#4	B	2016/07	1.37	1.51	0.13	100%	100%	100%	84%
#5	B	2018/11	1.18	1.17	0.00	100%	100%	97%	97%
#6	B	2019/06	1.05	1.12	0.06	100%	100%	100%	100%
#7	B	2020/07	1.03	1.12	0.09	100%	100%	99%	98%
#8	C	2015/06	1.29	1.32	0.03	98%	97%	95%	92%
#9	C	2016/07	1.31	1.31	0.00	99%	100%	99%	97%
#10	C	2018/11	1.05	1.20	0.14	100%	100%	100%	100%
#11	C	2019/09	1.14	1.27	0.13	100%	100%	100%	97%

Group	Unit	Year/month	Mean AGD [mGy]			% of doses ≤ acceptable level		% of doses ≤ achievable level	
			Calculated values	Displayed values	Mean difference	Calculated values	Displayed values	Calculated values	Displayed values
#12	C	2020/07	1.23	1.37	0.14	100%	100%	100%	98%
#13	D	2018/11	1.72	1.55	–0.17	97%	100%	69%	96%
#14	D	2019/09	1.55	1.39	–0.17	100%	100%	92%	100%
#15	D	2020/07	1.52	1.30	–0.22	99%	100%	93%	100%
#16	E	2015/05	1.96	2.09	0.13	49%	86%	3%	33%
#17	E	2016/07	1.80	2.21	0.41	58%	58%	26%	17%
#18	E	2016/10	1.80	2.05	0.25	67%	73%	36%	46%
#19	E	2018/08	2.13	2.04	-0.09	68%	79%	31%	59%
#20	E	2019/03	2.07	2.10	0.03	66%	81%	34%	48%

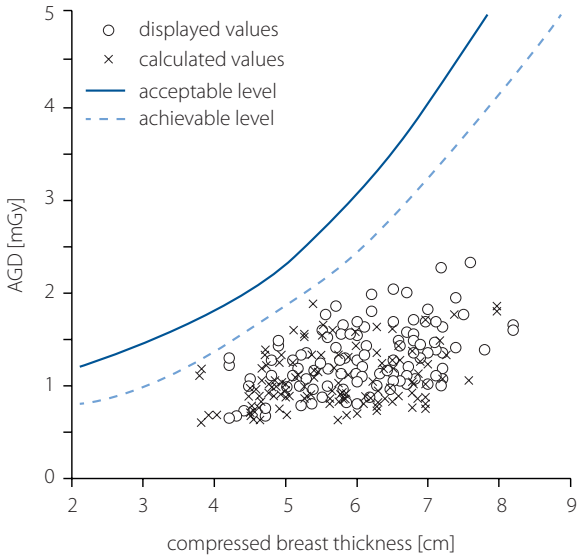

Figure 1. Comparison of displayed and calculated AGD values with acceptable and achievable dose levels for group #10 (Siemens Mammomat Inspiration unit)

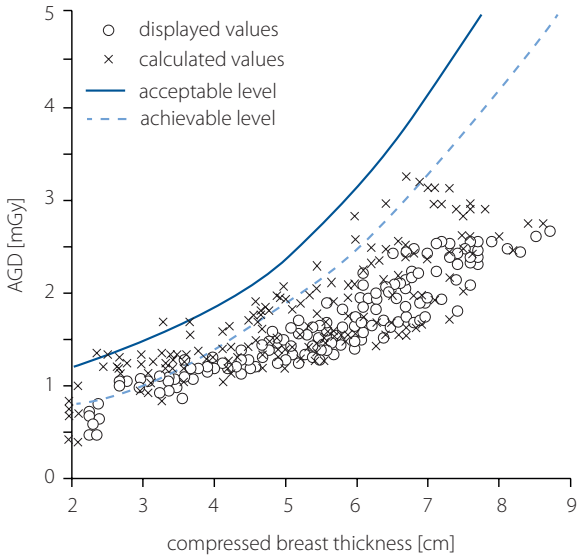

Figure 2. Comparison of displayed and calculated AGD values with acceptable and achievable dose levels for group #13 (GE Senographe Pristina unit)

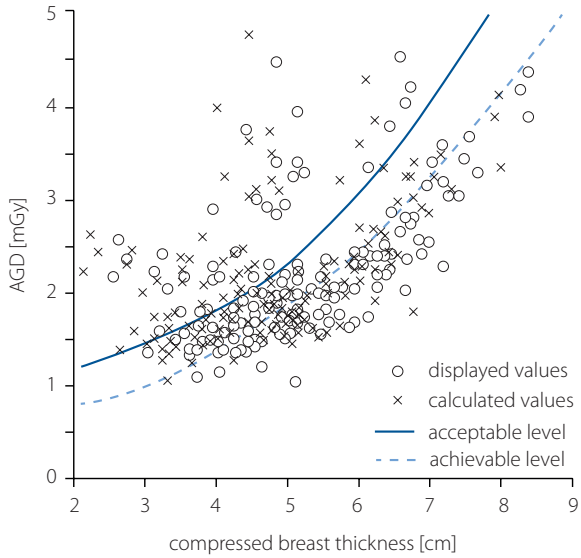

Figure 3. Comparison of displayed and calculated AGD values with acceptable and achievable dose levels for group #20 (Hologic Selenia unit)

Results

The summary of the results is presented in table II. The maximum difference between the displayed and calculated doses in a group of 50 patients was equal to 0.41 mGy (22% of the average dose calculated for that group). Figures 1–3 present a comparison of displayed and calculated doses with achievable and acceptable dose levels for three patient groups examined on three different units. The same scaling was applied on all figures to allow comparisons between them. For data presented in figure 1, the average difference between displayed and calculated doses is relatively large, as it equals 14% of the calculated doses. Despite the differences, all doses (both displayed and calculated) are lower than acceptable and achievable dose levels. For data presented in figure 2, the average dose difference expressed as a percentage of the calculated dose is smaller (9%), but the difference influences the result of the dose assessment. For the displayed values,

achievable dose levels are not exceeded in 96% of cases, but for the calculated values, it is only 69%. For the data presented in figure 3, the average difference of doses is close to zero (1%), but the relatively large inaccuracy of the thickness indicator changes the result of dose evaluation, as the same doses are compared with a lower dose limit (calculated for the corrected breast thickness).

Figure 4 presents a comparison of doses for two groups of patients examined on two different mammography units, separately for the displayed and calculated doses. For the displayed doses, the average and median are lower for the GE unit. The opposite is observed for the calculated doses. Figure 5 presents a comparison of displayed and calculated doses for one patient group, separately for two filtrations (Mo and Rh). The calculated values are mostly within ±5% of the displayed values for one anode/filter combination (Mo/Mo), while for the other one (Mo/Rh), the calculated values are on average 14% lower than the displayed values.

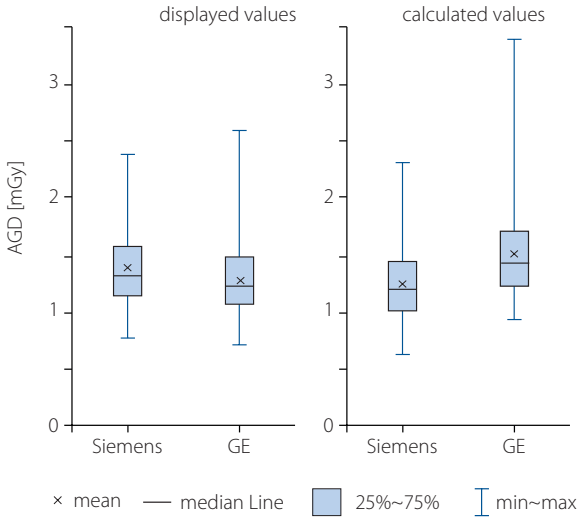

Figure 4. Comparison of displayed and calculated AGD values for two patient groups examined on different units (Siemens Mammomat Inspiration #12 and GE Senographe Pristina #15)

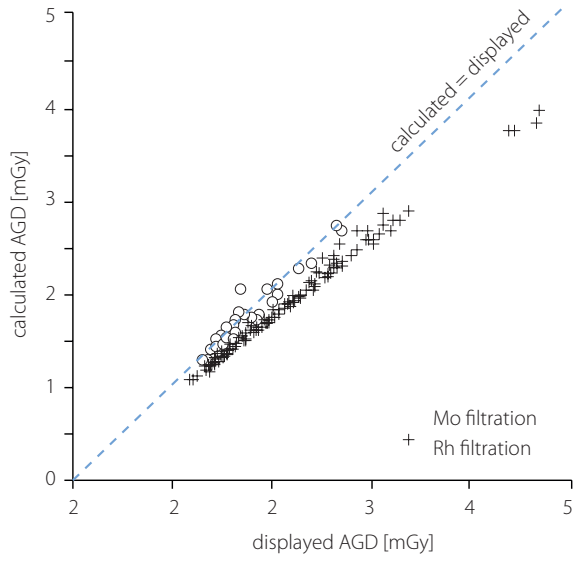

Figure 5. Comparison of displayed and calculated doses for one patient group (#16, Hologic Selenia unit), separately for two filtrations (Mo and Rh)

Discussion

Even a relatively large difference between the calculated and displayed dose values may not influence the comparison of doses with dose limits if the doses are low (fig. 1). On the other hand, a small difference may strongly affect the results of the evaluation if doses are close to the limits (fig. 2). The correction of breast thickness has a twofold effect on dose calculations [17]. Firstly, it has an impact on the calculated distance between the focal spot and beam entrance, thus affecting incident air kerma. Secondly, it has an impact on the conversion factors, which are dependent of breast thickness. Finally, it also has an impact on the effect of dose evaluation, as the dose limits are dependent on thickness (fig. 3). In the European Guidelines, the acceptable difference in thickness indication is ±5 mm [8, 9], while in the IAEA guidelines it is as much as ±8 mm [13]. Different vendors may use different methods for thickness indicator calibration; thus differences of a few mm can be expected. The discrepancies may be different for different beam qualities (fig. 5), and the comparison of displayed AGD values between different units may be misleading (fig. 4).

The differences between displayed and calculated values result from various factors. Aside from the inaccuracy of the thickness indicator, displayed values are determined using tube output data and HVL values stored in the software of mammography units. Since air kerma and half-value layer values may change over time, in this research they were measured independently in each assessed period. Such measurements are repeated in our institute every year and after each major service maintenance (e.g. tube replacement, detector replacement, detector calibration performed by service) to keep the calculated values reliable.

Calculated values also have limited accuracy. Measurement uncertainty of calculated AGD values may be as large as 14–20% [18, 19]. However, all the measurements and calculations presented in the current work were at least performed with the same methods and equipment. Testing thickness indicator accuracy with rectangular PMMA may not be equivalent to the clinical situation, but it was performed in the same way for all units. The same radiation detector, the same formulas, and conversion coefficients were used in all calculations. That said, methods used by different vendors to determine displayed AGD values are not described in detail. Additionally, while to our knowledge Dance's method was used by all vendors in our study, several other methods exist [12]. Another breast dosimetry method is under development by one group, which is simultaneously an American Association of Physicists in Medicine task group (AAPM TG282) and a working group of

the European Federation of Organisations for Medical Physics (EFOMP). Ultimately, this may result in the standardization of methods, but during the transitional period there will be even more methods in use.

In the case of screening examinations, patient groups consist of asymptomatic women. Breasts have typical structure, and the dose generally raises with breast thickness (e.g. fig. 1). In diagnostic examinations, lesions of various types may be presented in the breast [20]. Patient groups are less uniform, which may explain the presence of outliers in dose distribution (fig. 3). Relatively small groups of patients which were used in the work were enough to compare displayed and calculated doses and to prove that the effects of such comparison will be different for different mammography units. The presented results may not fully represent the distribution of doses for all women examined with a given mammography unit. Larger datasets maybe needed for evaluation of patient doses, for dose optimization, or to establish reference dose levels. In general, AGD values could be independently calculated for each exposure, based on the measured HVL and air kerma values, and using corrections of thickness readings. This would make it possible to include reliable information on patient exposure in the report of the medical radiological procedure.

Other researchers reported similarly: for a given method, differences between the displayed and calculated dose for a standard breast may reach 18% [12]. The situation may be similar in other X-ray imaging modalities. Documents published by the European Commission allow for relatively high uncertainty for DAP/KAP (dose/kerma-area product) meters, which provide patient exposure information in radiography and fluoroscopy (acceptability limit is ±25% for radiography, ±35% for fluoroscopy) [21]. It is also known that the energy response of a DAP/KAP meter may vary by 20% between the different beam qualities (different kVp and filtration settings) [22]. In computed tomography, it is expected that there will be agreement between measured and displayed computed tomography dose index (CTDI) within ±20% [21]. Discrepancies higher than 20% are occasionally observed, especially for low kV values [23]. Besides, the definition of CTDI has changed over time, and different CT models may use different definitions [24]. Recently, the size-specific dose estimate (SSDE) is gaining popularity in CT. While it is not yet routinely reported by CT scanners, it may be calculated by dose management systems. However, various methods may be used for it, which leads to different results [25]. The differences may affect comparisons of dose quantities with DRLs and between units in a similar way as in mammography.

Conclusions

The observed differences between displayed and calculated doses can affect the results of comparison of doses with acceptable and achievable dose levels, DRLs, or comparisons between different units in various ways, depending on dose levels and the type of mammography unit. If reliable information on average glandular dose is needed, e.g. for quality audit purposes, the values should be independently calculated using current results of measurements. The displayed values should be used with caution, and the uncertainty of displayed doses and compressed breast thickness should be taken into account.

Conflict of interest: none declared

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Strategies and results of oncofertility counseling in young breast cancer patients

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Introduction. Breast cancer (BC) is the most common female neoplasm in Poland and worldwide, yet up to 7% of all cases is diagnosed < 40 years of age. The increased BC morbidity rate in this age group as well as hope for late maternity need special attention.

Material and methods. The data concerning the number of children and further procreation needs in women (n = 68), aged 18–40, diagnosed and treated for early breast cancer at the Greater Poland Cancer Center in 2018–2019, were taken from patients' histories by an oncologist before (neo-)adjuvant systemic therapy.

Results. Out of the 68 females surveyed, aged 18–40 (median age 36), 14 (21%) were childless at the moment of diagnosis. After being informed about the therapy, prognosis, side effects and oncofertility, 12 patients (18%) decided to have a consultation with a specialist in reproductive medicine; 5 of them (7%) already had children. In 2 women (3%), hormonal stimulation in combination with tamoxifen was used; then, oocytes were collected and cryopreserved. In 19 (28%), gonadotropine analogues were added to (neo-)adjuvant chemotherapy. In 17 patients (25%) pathogenic mutations in *BRCA1/2* genes were found.

Conclusions. Oncofertility counseling in young BC patients should be one of the fundamental elements of complex patient care.

Key words: oncofertility, breast cancer, BRCA1/2 mutation, young women

Introduction

Breast cancer is the most frequently diagnosed cancer among women in Poland and in the world, but it rarely occurs in young women. Patients under 40 years of age constitute about 7% of all cases. The prognosis for young women is worse than that of older women mainly due to the more frequent occurrence of unfavorable phenotypes of breast cancer and the presence of numerous genetic disorders in the tumor tissue, which is the reason for the more aggressive course of the disease [1]. In addition, at

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the time of diagnosis, young women are more often diagnosed with more advanced disease than older women. The therapy of breast cancer, apart from surgery, often requires complementary treatment: chemotherapy, hormone therapy or radiotherapy. Systemic treatment is more likely to temporarily or irreversibly impair fertility than other cancers, which may be due in part to the duration of breast cancer therapy (up to 10 years) [2].

Diagnosis of breast cancer may have devastating effects on a woman and her loved ones, and affects every sphere of their lives. In the case of young women, it often occurs during the period of starting a family and planning offspring. The prospect of having to undergo cancer treatment and the desire to have children should not be mutually exclusive, and any woman in her reproductive years who expresses a desire to have children should have a consultation with a reproductive medicine specialist before starting treatment, preferably immediately after breast cancer diagnosis. If the consultation is delayed, the chances of fertility preservation after treatment are reduced [2].

The oncologist's role is to present the patient with a treatment plan, and to inform her about the possible effects of therapy, including the potential impact on ovarian dysfunction. The stress associated with a cancer diagnosis causes woman to postpone procreation plans, and instead focus on the cancer therapy. For most patients with early breast cancer, postponing therapy by 3–4 weeks does not affect prognosis. During this time, patients can take care of fertility preservation and enjoy motherhood after treatment. A significant proportion of young breast cancer patients are diagnosed with a mutation in their genes that increases the risk of breast and ovarian cancer (*BRCA1/2*), and the only treatment to reduce the risk of developing subsequent cancers is surgery: bilateral mastectomy and ovariectomy [3]. Carrying pathogenic mutations in *BRCA1/2* genes by the patient can impact decisions to have offspring after breast cancer therapy and before ovarian removal.

Objective

The aim of this paper was to assess the interest of young patients with early breast cancer in fertility preservation techniques, treated in the Chemotherapy Outpatient Clinic of the Greater Poland Cancer Center, Poznan, Poland, in consultation with a reproductive medicine specialist. An additional aim was to draw physicians' attention to the problem of infertility accompanying cancer therapy.

Material and methods

It was a retrospective study. Patients with early breast cancer aged 18–40 years who were treated in the Chemotherapy Outpatient Clinic of the Greater Poland Cancer Center at Poznan, Poland during 2018–2019 and informed about the possibility of fertility preservation techniques were covered with the study. Medical data were obtained from medical history regarding age, offspring, desire to have children in the future, consultation with a reproductive medicine specialist, and fertility preservation techniques used, as well as carrying pathogenic mutations in genes that increase breast cancer risk. Fertility preservation techniques included ovarian stimulation, oocyte collection and freezing, as well as the inclusion of gonadotropin-releasing hormone analoges during systemic treatment.

Statistic

The IBM SPSS Statistics 26 program was used for the analysis. The significance level was adopted as 0.05. The Shapiro-Wilk test was used to test the normality of data distribution. The nonparametric Mann-Whitney U test was used to compare the data distributions (due to the lack of normal data distribution). The chi-square test and z-test were used to investigate correlations.

Ethics

An oncologist and gynecologist's analysis of patient records does not require the opinion of a bioethical committee.

Results

66 patients with early breast cancer who underwent treatment in the Chemotherapy Outpatient Clinic of the Greater Poland Cancer Center at Poznan, Poland during 2018–2019 were included in the analysis. The median age of patients was 36 years (26–40 years). All patients were informed by the treating physician about the potential effects of systemic treatment and the possibility of fertility preservation techniques prior to systemic treatment. Those who received consultation with a reproductive medicine specialist were characterized by their younger age (33.5 *vs.* 36.5 years).

At the time of treatment planning for early breast cancer, 14 patients (20.6%) had no children. After discussion with the oncologist about prognosis, treatment plan, and the possibility of complications, including infertility, 12 patients (17.6%) decided to have a consultation with a reproductive medicine specialist; among those without children (n = 14 patients), half (n = 7 patients, 50%) had a consultation with a specialist, whereas among those with at least one child, less than 10% (n= 5 of a group of n = 54 patients; 9.3%) decided to have such a consultation. 19 patients (27.9%) were treated with gonadotropin-releasing hormone (GnRH) analoges, while 2 patients (2.9%) underwent hormonal stimulation combined with tamoxifen, followed by oocyte collection and freezing (tab. I).

Table I. Applied fertility preservation techniques

Fertility preservation techniques	No. of patients (%)
oocyte freezing	n = 2 (2.9)
use of GnRH	n = 19 (27.9)

Table II. Test results found in medical history

Type of test	No. of patients
test for founder mutations in *BRCA1* gene (c.5266dupC, c.4035delA, c.181T>G, c. 3700_3704delGTAAA, c.68_69delAG)	n = 7 (10.3%)
test extended to include further mutations in *BRCA1/2* + *CHEK2* + *PALB* genes (749delT(c.675delT), 185delAG (c.68_69delAG), 5370>T (c.5251>T), 3819del5 (c.3700_3704delGTAAA), 3875del4 (c.3756_3759delGTCT), 8138del5 (c.7910_7914delCCTTT), 886delGT (c.658_659deGT), 6174delT (c.5946delT), 5467insT (c.5239_5240insT), 4075delGT (c.3847_3848delGT) CHEK2 gene (c.1100delC, del5395, c.444+1G>A, p.I157T) PALB gene (c.172_175delTTGT, c.509_510delGA)	n = 32 (47.1%)
next generation sequencing (NGS) of *BRCA1/2* genes or multigene test	n = 15 (22.1%)

The majority of patients had genetic counseling (54–79.4%). 6 patients (10.3%) had a test for founder mutations in *BRCA1* gene, 32 patients (47.1%) had an extended test for further mutations in *BRCA1/2* genes as well as in *CHEK2* and *PALB* genes, 15 patients (22.1%) had performed Next Generation Sequencing (NGS) of *BRCA1/2* genes or a multigene test, and 16 patients (23.5%) had no genetic test results found in their medical history (tab. II). In 17 patients (25%), pathogenic mutations were found in *BRCA1/2* genes.

No significant age differences were observed between *BRCA1/2* gene mutation carriers and patients without the identified mutation (average 34.24 *vs.* 35.87; median 34 *vs.* 36). Patients who were carriers of mutations in *BRCA1/2* genes were less likely (n = 12; 70.6%) to consult a reproductive medicine specialist than patients without known mutations (n = 46; 86.8%), but no statistical significance was found. None of the *BRCA1/2* mutation carriers opted for oocyte freezing.

Among the women with *BRCA1/2* mutation, the GnRH analogues were used in 10 individuals (58.8%), whereas among those without B*RCA1/2* mutation, the GnRH analogues were included in 8 individuals (19%) which was statistically significant (tab. III).

Discussion

Breast cancer in young women is rare, but the prognosis is poorer than in older women regardless of biological subtype. This includes a higher stage of the disease at the time of referral to the physician due to the glandular structure of the breast and associated diagnostic difficulties. More aggressive biological subtypes (triple-negative carcinoma, without expression of hormone receptors and without overexpression of the HER2 receptor or amplification of its gene, HER2-positive carcinoma showing overexpression of the HER2 receptor or amplification of its gene) and other molecular background are more common in young women than in older breast cancer patients [4]. Young women are even over ten times more likely to be diagnosed with pathogenic mutations in genes that increase the risk of breast and ovarian cancer (*BRCA1/2*) than older women (2.5% *vs.* 25%) [5]. In the European Union, the average age at which the first child is born is 29.3 years, which means that often the diagnosis of breast cancer occurs among women who have not yet completed childbearing and are still planning offspring [6].

The principal treatment for breast cancer is surgery, but complementary treatments (chemotherapy, immunotherapy, hormone therapy, or radiotherapy) are also often used. Systemic treatment can significantly impair a woman's reproductive function, leading to temporary or irreversible infertility. The impairment of ovarian function depends on the patient's age, type of chemotherapy used, and the dose of drugs given. The commonly used perioperative chemotherapy involves anthracyclines and taxanes (4 x doxorubicin + cyclophosphamide, 12 x paclitaxel), and cytostatic drugs with an intermediate risk of causing permanent infertility in women. Infertility is always related with menopause induced changes like sexual distress. Chemotherapy-induced menopause symptoms can be more pronounced. Physiological menopause is a process, which lasts for many months, while iatrogenic menopause affects young patients experiencing a sudden decrease in estrogen level within a short time [7].

The authors of a paper published in July 2020 in the journal JAMA emphasize that despite ASCO recommendations, less than half of patients (44%) with cancer of reproductive age – women aged 18 to 40, men aged 18 to 50 – were informed about the possibility of fertility disorders caused by cancer treatment and the possibility of consultation with a reproductive medicine specialist. This was more often the case for young, female patients, especially those suffering from breast cancer or hematological malignancies. Patients treated

Table III. Characteristics of patients according to genetic load

Pathogenic mutation in *BRCA1/2* genes	No. of patients (%)	Average age (years)	Median age (years)	Oocyte freezing	Use of GnRH(%) analogues
current mutation	n = 17 (25)	n = 34.24	n = 34	n = 0	n = 10 (58.8)
no mutation	n = 35 (51.5)	n = 35.87	n = 36	n = 2 (5.7)	n = 8 (19%)
no medical history	n = 16 (23.5)				

in academic centers or in places where fertility preservation procedures were reimbursed were better informed [8].

Also, according to the guidelines of Polish scientific societies, every patient with breast cancer of reproductive age should be informed about the possible complications of systemic treatment, including fertility disorders, which is confirmed by the results of our study [9]. The vast majority of patients qualified for the study, almost 80%, had children. Twelve had a consultation with a reproductive medicine specialist, and 5 of them had already become mothers. Despite the patients' interest in fertility, only 2 patients decided to undergo oocyte freezing after oncological treatment and consultations with reproductive medicine specialists; this may be a result of the lack of reimbursement of fertility preservation procedures in Poland and in many countries and regions of the world.

The issue of informing patients about the problem of fertility and taking preventive measures is still unresolved. However, an evaluation of this problem was not the aim of this paper, and all patients were informed about the possibility of fertility disorders related to oncological treatment.

Young patients are found to carry pathogenic mutations in *BRCA1/2* genes far more often than older patients. *BRCA1/2* mutations increase the lifetime risk of breast cancer from 45% to 85% and ovarian cancer from 10% to 60%. Effective measures to reduce the risk of breast and ovarian cancer in mutation carriers include a bilateral mastectomy and bilateral oophorectomy, which reduces the risk of cancer by 80–90%. Mutation carriers who qualified for our study, and were aware of their situation, often took advantage of consultations with a reproductive medicine specialist and agreed to start GnRH analogues during systemic treatment. The prospect of needing cancer-reducing surgery in the future may be a factor prompting patients to implement fertility preservation procedures.

Ovarian stimulation, oocyte collection, oocyte freezing or fertilization and embryo freezing require postponement of the main oncological treatment by 3–4 weeks. The effectiveness of presented methods reaches 30% and is similar to the effectiveness of in vitro fertilization in infertile couples without cancer history. In clinical practice, gonadotropin-releasing hormone analoges are also used during perioperative chemotherapy, the role of which is to inhibit ovarian function and thus reduce their susceptibility to cytostatic damage. However, the effectiveness of this method is limited [10].

The experience of our center highlights the importance of this problem and presents the decisions of patients who were offered the consultation of a reproductive medicine specialist and fertility preservation techniques. The awareness of fertility preservation by patients often results in reduced anxiety during therapy and improves cooperation between the patient and the oncologist.

Conclusions

Consultation with a reproductive medicine specialist should be a primary element of care for patients in their reproductive years who have been diagnosed with early breast cancer. The presence of pathogenic mutations in genes that increase the risk of breast and ovarian cancer (BRCA1/2) is an important factor in the decision to have offspring after treatment and before surgery with bilateral mastectomy and oophorectomy.

Advantages and disadvantages of the study

The study involved a homogeneous group of breast cancer patients. All patients were informed about the possible complications of cancer treatment, including impaired fertility. Decisions made by patients may differ from their actual beliefs and wishes due to the lack of reimbursement of fertility preservation procedures in Poland. The financial aspect may be the biggest factor for breast cancer patients to take action.

Conflict of interest: none declared

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What new dose distribution statistics may be included in the optimization of dose distribution in radiotherapy for post-mastectomy patients

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Introduction. The main aim of this study was to evaluate the doses delivered to heart substructures and calculate normal tissue complication probability (NTCP) for the intensity modulation radiotherpy (IMRT) irradiated group of left-sided post-mastectomy patients.

Material and methods. In this retrospective study for 30 randomly chosen breast cancer patients, the mean dose, V_2, V_4, V_{10}, V_{20} and D2% in the heart substructures were evaluated.

Results. The mean heart dose was 12.3 Gy, the mean left anterior descending artery (LAD) dose was 28.5 Gy. The average value of long-term cardiac mortality was 0.17%, pericarditis 0.0%, left ventricle perfusion defects 24.5% and LAD toxicity 0.2%. In the literature, for the IMRT technique for left-sided mastectomy patients, the mean heart dose ranged from 8.7–14.0 Gy and the V_{20} 10.5–14%. Additional studies are needed to describe the cardiac toxicity.

Conclusions. It is necessary to contour cardiac substructures for reliable assessment of the dose distribution, although the mean heart dose is simplification for modern radiotherapy techniques.

Key words: heart, breast cancer, post-mastectomy, IMRT, NTCP

Introduction

Many large randomized trials have demonstrated that post-mastectomy irradiation is beneficial, at least for patients with high-risk disease [1, 2]. However, for women irradiated on the left side, the dose delivered to the heart increases the risk of ischemic heart disease [3]. Taylor and co-workers have shown, there are many factors that affect doses deposited in the heart. The most important being the individual anatomy of a patient and the irradiation technique [4]. For older techniques, such as the tangential pair technique, the dose distribution in the heart and its substructures may be well estimated with the maximum heart distance (MHD) [4].

According to Darby, the cumulative relative risk of a major coronary event increases linearly by approximately 7% for each increase of 1 Gy of the mean heart dose in the tangential field technique [3]. The cumulative risk of death from ischemic heart disease is higher in radiotherapy patients compared to non-radiotherapy patients [3]. Uwe Schneider suggested [5] that in the intensity modulation techniques (IMRT) or volumetric modulated arc therapy (VMAT) techniques, with large volumes of the heart receiving low doses the risk of major coronary events might not be linear as proposed by Darby [3].

Despite these enormous changes in technology and irradiation methods, optimization of dose distributions in the

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heart is still based on the same assumptions. The dose to the heart is most often evaluated with the mean dose to the organ at risk. The heart is a complicated organ composed of muscular tissue, blood vessels, valves, nerve tissue fibres. The risk of damage to various heart structures by dosage may require a different quantitative description. Therefore, the statistics like the mean heart dose might not be the best predictor of all types of complications. An exact description of the interplay between radiotherapy and chemotherapy in heart damage is required. This is especially true in breast cancer patients, where systematic treatment is associated with heart toxicity [6, 7]. For post-mastectomy patients, there is a limited literature base describing doses received by individual heart structures in dynamic radiotherapy techniques [8]. Most of the available articles analyse the technique of two tangential fields in a group of breast conserving therapy patients (BCT).

The main aim of this study was to evaluate the doses delivered to substructures of the heart for the IMRT irradiated group of left-sided post-mastectomy patients. The doses to heart substructures were described in terms of dosed distribution and the model based on normal tissue complication probability (NTCP).

Material and methods

Patients

In this retrospective study for 30 randomly chosen breast cancer patients, we analysed the doses delivered to the heart and its substructures. All of these patients, of a median age of 53 years (32–88), were after a left-sided mastectomy. From the group of 30 patients, 29 patients underwent a modified radical mastectomy (MRM) with axillary fossa extraction, 1 patient had a simple mastectomy with a sentinel lymph node biopsy. Chemotherapy was applied throughout the group of 30 patients, 13 patients received pre-surgical chemotherapy. Radiotherapy was applied after surgery and chemotherapy. Pathological tumour nodus metastases (pTNM) staging was made according to the VII edition of the International Union Against Cancer (UICC) [9].

CT scan and contouring

Patients were placed supine in the treatment position, with their arms raised above their head, immobilized with OncoPoRT board. Computed tomography (CT) scans for treatment planning were acquired during free breathing, with 1.5 mm slice thickness, using a Siemens CT scanner. Scans were acquired from the hyoid bone to the end of the thoracic vertebrae, with 10 mm tissue-equivalent bolus placed on the thoracic wall. Next, the target volumes and organs at risk were delineated on the CT scans. For planning, the clinical target volume (CTV) included chest wall (CTV_{chest}) and axillary, infra and supraclavicular nodal areas (CTV_{nodes}) being delineated. Planning target volume (PTV) was created by adding a 6 mm isotropic margin to CTV. Organs at risk included the heart, lungs, coronary arteries, defined as 6 mm margins of the heart anterior wall and the spinal canal.

For the purpose of a retrospective analysis of the doses absorbed to the heart, additional heart substructures were segmented based on Mary Feng Cardiac Atlas Heart [10]. The contoured heart substructures were: the pericardium defined as 2 mm sac, created as margin from internal and external of the heart surface, ascending aorta, aortic arch, descending aorta, superior vena cava (SVC), inferior vena cava (IVC), pulmonary artery, coronary arteries: left coronary artery (LCA), left anterior descending coronary artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA), left atrium, right atrium, left ventricle, right ventricle (fig. 1). Contoured structures were approved by a radiation oncologist.

Treatment planning and dose evaluation

For each patient, the IMRT treatment plan was prepared in Eclipse version 15 (Varian) treatment planning system. The total dose was 45 Gy, delivered in 2.25 Gy fraction doses. Dose distribution was calculated with the Analytical Anisotropic Algorithm (AAA) version 15. From five to seven 6 MV coplanar photon fields were used arranged in a fan pattern. The dose was prescribed to the CTV ($CTV_{wall} + CTV_{nodes}$) mean dose. During plan preparation, the following dose-volume constraints were used: for the PTV D98% > 95%, D2% < 107%, for the heart the mean dose <16 Gy and $V_{20} < 14\%$, for the lungs the mean dose <12 Gy, $V_{20} < 14\%$ and $V_{30} < 9\%$.

Treatment plans were retrospectively analysed. In each heart substructure the mean dose, V_2, V_4, V_{10}, V_{20} and D2% were evaluated.

Calculation of the NTCP

To calculate the NTCP, the Lyman Kutcher Burman (LKB) model was used (equations 1–3) [11].

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{\frac{x^2}{2}} dx \quad (1)$$

$$t = \frac{D_{eff} - TD_{50}}{mTD_{50}} \quad (2)$$

$$D_{eff} = (\Sigma_i V_i D_i^{1/n})^n \quad (3)$$

where: D_{eff} is the dose that, if given uniformly to the entire volume, will lead to the same NTCP as the non-uniform dose distribution, TD_{50} is the uniform dose delivered to the entire organ that results in a 50% complication risk, m is a measure of the slope of the sigmoid curve, n is the volume effect parameter, and V_i is the fractional organ volume receiving a dose D_i.

End-point model parameters were taken from the literature. Long term cardiac mortality (TD_{50} = 52.3 Gy, n = 1, m = 0.28, α/β = 3 Gy) [10], pericarditis (TD_{50} = 50.6 Gy, n = 0.64, m = 0.13, α/β = 2.5 Gy) [11], left ventricle perfusions defect (TD_{50} = 29 Gy, n = 0.16 m = 0.41 α/β = 2.5 Gy) [12], LAD toxicity (TD_{50} = 48 Gy, n = 0.35, m = 0.10, α/β = 2.5 Gy) [13].

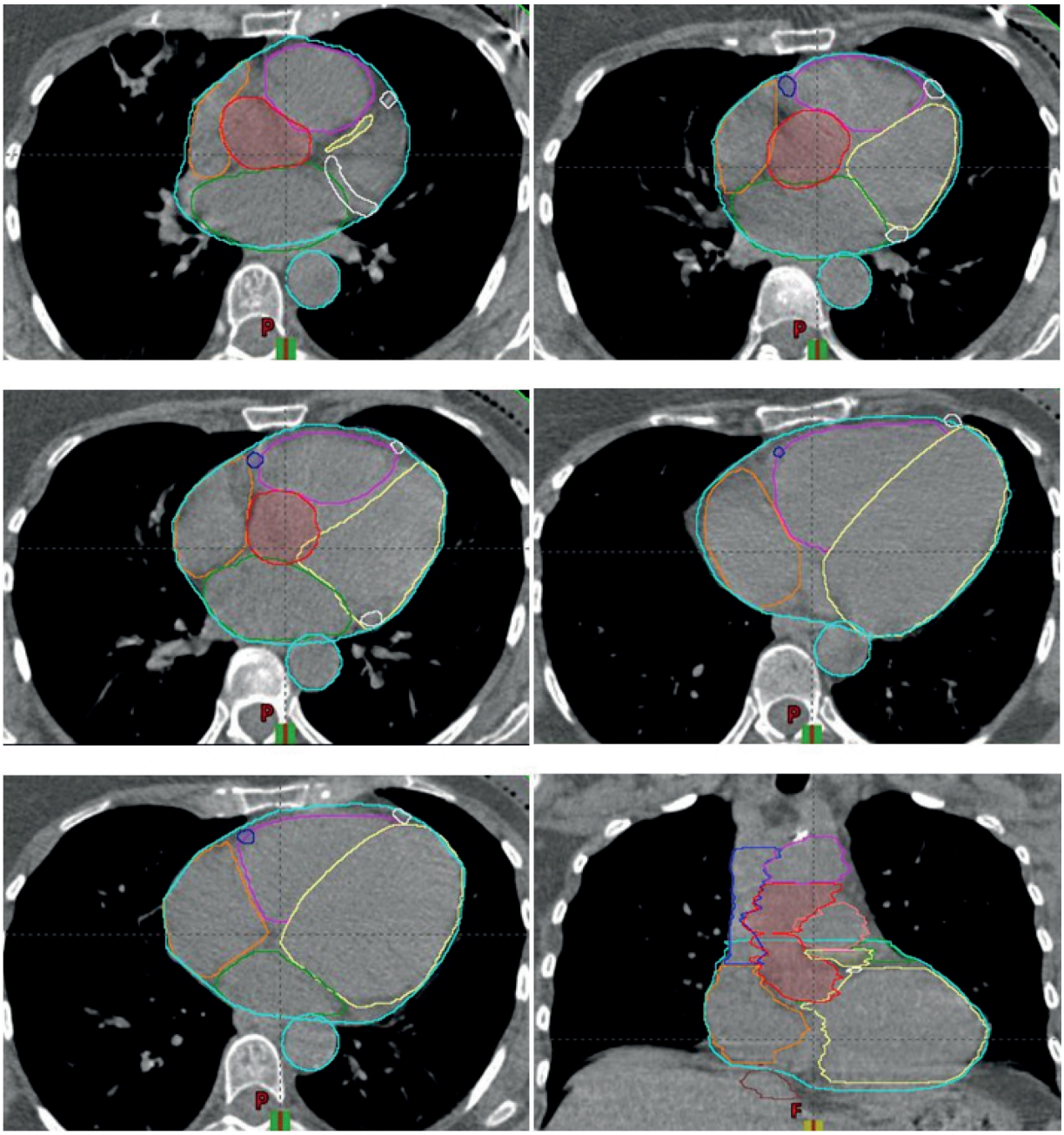

Figure 1. CT scan with heart substructures: cyan heart, red ascending aorta, magenta aortic arch, cyan descending aorta, blue superior vena cava, brown inferior vena cava, pink pulmonary artery, orange left atrium, green right atrium, yellow left ventricle, purple right ventricle, yellow LCA, white LAD, white LCX, blue RCA

Statistical Analysis

Data was described by the average value (AVG) and standard deviation (SD) of all analysed statistics obtained for the 30 patients – AVG (SD). For the relationship between dose distribution statistics and NTCP, dose fitted curves were done.

Results

Dose distribution in heart structures

Heart dose distribution parameters are summarised in table I. The average value of the mean heart dose was 12.3 Gy (1.1 Gy). The lowest average value of the mean dose was in IVC 5.5 Gy (1.4 Gy), the highest value of the mean dose was in LAD 28.5 Gy (5.0 Gy). The average value of V_{20} Gy in the heart was 11.5% (5.3%). The lowest average value of V_{20} Gy was in the descending aorta 0% (0%), IVC 0% (0%), SVC 0% (0%) and LCX 0% (0%). The highest average value of V_{20} Gy was in the LAD 73.3% (21.0%). The average value of the V_{10} in the heart was 59.9% (8.7%), the lowest average V_{10} value was in the vena cava inferior 0.2% (1.2%), the highest in the LAD 99.3% (3.4%). The average values of V_2–V_4 were high in all heart structures, 100% (0.2%) and 98.1%. The lowest value of V_2 and V_4 was in the descending aorta 87.1% (9.4%) and 72.6% (17.5%).

Table I. Average values and SD of dose distribution statistics in the group of 30 patients

	V_2 [%]	V_4 [%]	V_{10} [%]	V_{20} [%]	D m. [Gy]	D2% [Gy]
heart	100 (0.2)	98.1 (2.7)	52.9 (8.7)	11.5 (3.3)	12.3 (1.1)	33.8 (3.6)
pericardium	99.7 (1.1)	95.8 (5.3)	54.0 (7.6)	23.7 (6.1)	14.7 (1.7)	39.7 (3.3)
right ventricle	99.9 (0.3)	99.8 (1.3)	82.2 (13.3)	20.1 (9.5)	15.7 (2.3)	31.4 (5.5)
left ventricle	100 (0.1)	99.4 (1.6)	68.5 (17.5)	12.9 (5.6)	13.7 (1.7)	33.1 (5.1)
right atrium	99.9 (0.3)	96.2 (7.8)	19.9 (19.1)	0.1 (0.3)	7.9 (1.7)	13.8 (3.1)
left atrium	100 (0.0)	93.9 (11.7)	14.1 (15.3)	0.1 (0.1)	7.4 (1.6)	12.7 (2.6)
ascending aorta	100 (0.0)	99.9 (0.3)	49.5 (29.2)	3.7 (8.0)	10.8 (2.6)	17.8 (5.5)
aortic arch	100 (0.0)	100 (0.1)	70.5 (27.3)	11.0 (20.3)	13.4 (4.3)	21.1 (7.7)
descending aorta	87.1 (9.4)	72.6 (17.5)	5.3 (6.2)	0.0 (0.0)	5.5 (1.4)	10.7 (2.9)
SCV	100 (0.0)	98.5 (5.6)	16.8 (25.8)	0.0 (0.0)	8.0 (2.2)	10.7 (2.9)
IVC	100 (0.0)	85.8 (18.5)	0.2 (1.2)	0.0 (0.0)	5.7 (1.3)	7.3 (1.3)
pulmonary artery	100 (0.0)	99.4 (2.2)	65.9 (19.1)	12.1 (12.0)	13.1 (3.0)	25.6 (5.9)
LCA	100 (0.0)	100 (0.0)	65.9 (35.2)	0.6 (2.0)	11.7 (2.4)	14.8 (3.5)
LAD	100 (0.0)	100 (0.0)	99.3 (3.4)	73.3 (21.0)	28.5 (5.0)	40.3 (4.1)
LCX	100 (0.0)	98.4 (6.1)	45.3 (35.8)	0.0 (0.0)	9.7 (2.4)	12.5 (2.8)
RCA	100 (0.0)	100.0 (0.0)	73.8 (35.9)	6.3 (17.1)	12.9 (3.6)	15.8 (4.9)

VX – volume receiving X Gy and more; D m. – mean dose; D2% – near-maximum dose

NTCP values

Long term cardiac mortality

The average value of the long-term cardiac mortality for 30 patients was 0.17% (0.04%). Graphs present the NTCP-dose relationship for which the value of $R^2 > 0.5$. For the relationship between long-term cardiac mortality and the mean heart dose, the second degree polynomial was fitted ($R^2 = 0.96$), for V_{20} ($R^2 = 0.76$) and for V_{10} ($R^2 = 0.70$) a linear fit was used (fig. 2–4).

Pericarditis

In the group of 30 patients, the average value of the calculated NTCP for pericarditis was 0.0% (0.0%).

Left ventricle perfusions defect

The average value of left ventricle perfusion defects in 30 patients was 24.5% (8.0%). The graphs present the NTCP-dose relationship for which the value of $R^2 > 0.5$. For the relationship between left ventricle perfusion defects and D2%, the second-degree polynomial was fitted (R^2=0.97), for V20 ($R^2 = 0.68$) a linear fit was applied (fig. 5–6).

LAD toxicity

The average value of LAD toxicity in 30 patients was 0.2% (0.4%). The graphs presents the NTCP-dose relationship for which the value of $R^2 > 0.5$. For the relationship between LAD toxicity and the mean LAD dose (fig. 7), a two-parameter exponential function was fitted ($R^2 = 0.95$).

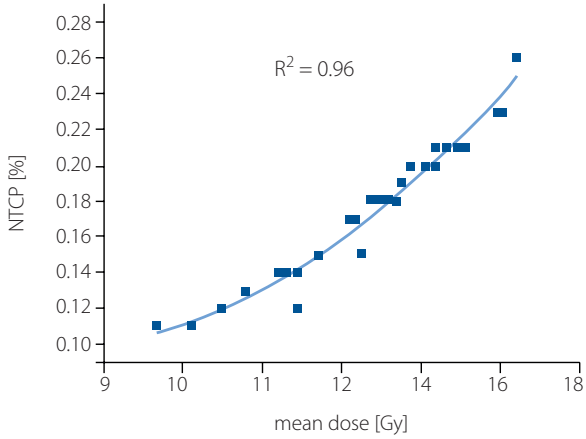

Figure 2. Relationship between the mean heart dose and long term cardiac mortality

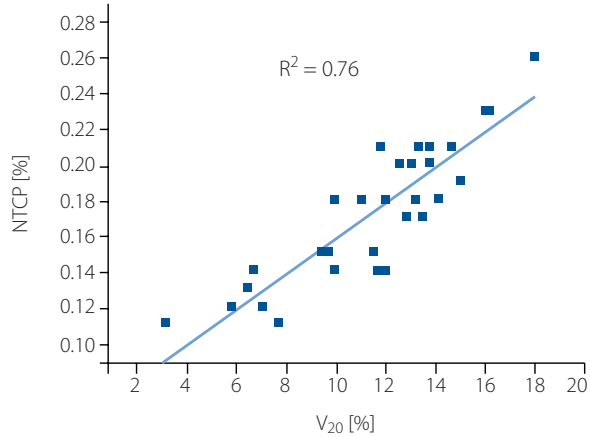

Figure 3. Relationship between heart V_{20} and long term cardiac mortality

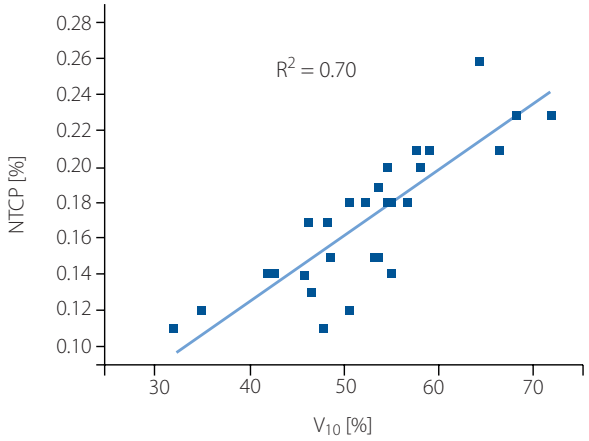

Figure 4. Relationship between heart V_{10} and long term cardiac mortality

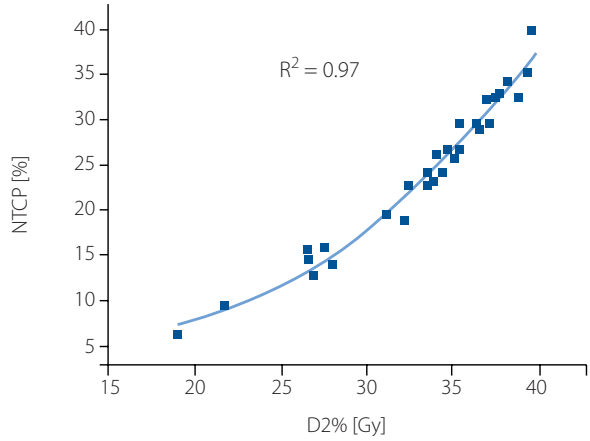

Figure 5. Relationship between D2% left ventricle dose and left ventricle perfusion defects

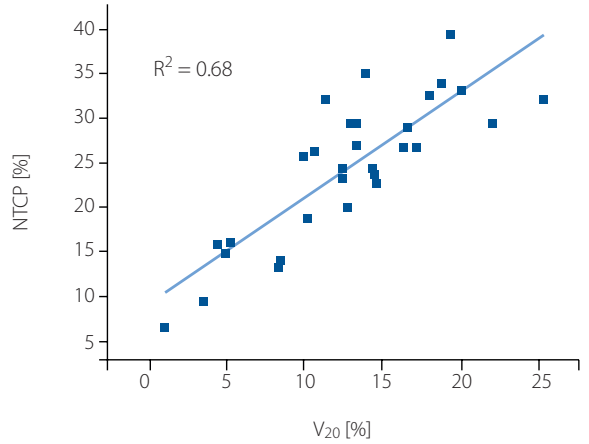

Figure 6. Relationship between V_{20} left ventricle dose and left ventricle perfusion defects

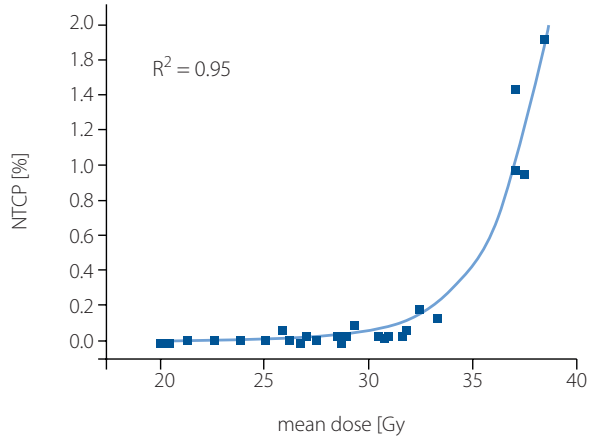

Figure 7. Relationship between mean LAD dose and LAD toxicity

Discussion

Dose distribution in heart structures

In our group of patients, the average value of the mean heart doses was 12.3 Gy (1.1 Gy) and the average volume V_{20} was 11.5% (3.3%). In the literature, for the IMRT technique for left-sided mastectomy patients, the mean heart dose ranged from 8.7 Gy to 14.0 Gy [12, 13] and the V_{20} value from 10.5% (5.2%) to 14% (6%)[12, 14, 15]. A large dispersion of the V_{10} also occurs in literature, a V_{10} ranged from 17.8% (7.1%) to 55.7% (29.6%) [12, 13, 15, 16].

Due to the proximity of the heart to PTV, the mean dose received by the left ventricle was 13.7 Gy (1.7 Gy) and 15.7 Gy (2.3 Gy) for the right ventricle. The D2% were 33.1 Gy (5.1 Gy) for the left ventricle and 31.4 Gy (5.5 Gy) for the right ventricle. In Li Zhang's article, a similar analysis was carried out for the IMRT technique and the mean left ventricle dose and the maximum left ventricle dose came to 12.7 Gy and 48.7 Gy, respectively, whereas the right ventricle mean dose was 14.7 Gy [8].

Among coronary arteries, the highest average values of mean dose of 28 Gy (5 Gy), was obtained for LAD. In Li Zang's article describing the IMRT technique for post-mastectomy patients, a high mean dose value of 37.7 Gy for LAD was obtained [8]. The high dose values received by LAD were also reported by other authors. In J. Caudrelier's article about the IMRT technique in BCT patients, a higher median dose and maximum doses for LAD of 10.8 Gy (7.8 Gy) and 26.7 Gy (15.7 Gy) and RCA of 12.4 Gy (5.7 Gy) and 27.0 Gy (12.4 Gy) were reported [17]. In our group of patients, the RCA average values of the mean dose were 12.9 Gy (3.6 Gy), and D2% – 15.8 Gy (4.9 Gy). In the LCA, average values of the mean dose were 11.7 Gy (2.4 Gy) and D2 – 14.8 Gy (3.5 Gy). The lowest values of the mean dose – 9.7 Gy (2.4 Gy), and D2% – 12.5 Gy (2.8 Gy) were obtained by the LCX similar to J. Caudrelier's article where the median dose was 4.5 Gy (1.7 Gy) and a maximum dose was 8.8 Gy (3.2 Gy) for LCX [17].

In the case of the IMRT technique, many therapeutic beams are used to achieve a conformal dose distribution. This results in an increased amount of scattered radiation which leads to an increase in the volume of tissues exposed to low doses. The dose range of 2–4 Gy covers from 100% to 72.6% of the volume of the heart structures.

NTCP values in IMRT

NTCP models take the form of empirical models based on dose distribution statistics from the treatment planning system and data from prospective and retrospective clinical trials. The values of the parameters used in radiobiological models are obtained by fitting curves to clinical data. The calculated NTCP value is always susceptible to the limitations of the used model and results from the uncertainty parameters used for modelling. The complicated structure of the heart causes that the probability of injuries of different heart structures is unlikely to be well described with a single parameter of dose distribution eg. mean dose [3].

Long term cardiac mortality

Darby estimated [3] the linear increase in the risk of major coronary events with a rising mean heart dose. This result was obtained for breast cancer patients irradiated with two tangential fields. In this technique, a small volume of the heart receives a high dose but the mean dose in the heart is smaller than in IMRT. Uwe Schneider suggested [5], that in IMRT, VMAT techniques there were large volumes of the heart receiving low doses the risk of major coronary events might not be linear as proposed by Darby [3]. The NTCP calculated by Schneider with Darby's data showed that the risk has a sigmoidal nature; it can be considered negligible if the mean heart dose does not exceed 15 Gy.

The probability of heart damage related with the mean heart dose analysed in this paper for IMRT for left-sided mastectomy patients showed similarity with Schneider's results. For a mean heart dose of 12 Gy, the LKB model based the probability of long term cardiac mortality at only 0.17%. A limitation of this approach is to use the same mean heart dose parameter to calculate NTCP for IMRT and the tangential field technique, due to different dose distributions in the heart.

Pericarditis

Pericarditis is the first clinical symptom for which dose-volume effect was found. In patients undergoing mediastinal radiotherapy, estimated pericarditis was about 6% if more than 50% of the external heart contour was in the radiation therapy field [18]. The probability of pericarditis was reduced from 20% to 7% by using left ventricle shielding and reduced to about 2.5% by shielding the left ventricle after 30 Gy [19]. Martel considered a mean dose of 27.1 Gy and a maximum dose of 47 Gy as predictors of pericarditis [20]. Wei and co-authors considered the volume of pericardium receiving a dose of 30 Gy and more (V_{30}) as statistics associated with the occurrence of complications [21]. The probability of pericarditis estimated by Wei was about 13%, if the $V_{30} < 46\%$ or a mean dose <26 Gy. If the mean dose exceeds 26 Gy and the V_{30} exceeds 46%, the probability increases to about 73% [21].

In the analysed group of 30 patients irradiated with IMRT, for a mean pericardial dose of 14.8 Gy and V_{20} of 23.7%, the LKB model based the probability of pericarditis at 0%.

Left ventricle perfusion defects

The clinical manifestation of subclinical perfusion defects is not well understood and the perfusion changes themselves can be reversible [22]. Based on single-photon emission computed tomography (SPECT) perfusion scans, Marks et al. demonstrated perfusion defects, limited to the part of the myocarcium which had received a dose higher than 15 Gy [22]. In the five-year follow-up, a reduction of the left ventricular wall contractility was demonstrated. The NTCP of left ventricular perfusion defects, estimated by Das et al. by LKB and relative seriality (RS) models, shows that this complication can be classified as for a serial organ [23]. Marks et al. analysed the left ventricular perfusion defects in a group of 73 breast cancer patients irradiated by the tangential fields technique [22]. The probability of damage was estimated to be below 20% if less than 5% of the left ventricle volume was in the therapeutic field. The probability of perfusion defects increases if more than 5% of the left ventricle volume is in the therapeutic field. Literature reports indicate a proportional increase in risk with an increase in the left ventricular volume and an increase in the mean left ventricle dose when the tangential field technique is used [24].

The average value of the LKB model based the probability of left ventricular perfusion in the group of 30 IMRT patients at 24.5% (8.0%) with a serial-like nature of the complication. An increase in the D2% in the left ventricle results in increasing NTCP .

LAD toxicity

Literature indicates the high sensitivity of coronary arteries to exposure from ionizing radiation. This is particularly important for the LAD, as an artery associated with the development of myocardial infarction in breast cancer patient radiotherapy [25]. The studies showed a higher percentage of LAD stenosis in patients undergoing left-sided radiotherapy for breast cancer, due to the presence of LAD in the therapeutic field and the large doses received by this artery [26–29]. The relationship between the occurrence of radiation damage and the coronary arteries indicated that the coronary arteries should be treated as a separate organ at risk, and tolerance doses may differ from the doses of tolerance for the remaining structures of the heart [30]. Some authors claim that high point doses in the coronary arteries can lead to an increased risk of myocardial infarction within 10 years from the application of radiotherapy [24].

The average LKB model based probability of LAD toxicity was 0.2% (0.4%). For the mean LAD dose and NTCP pseudo-threshold relationship was shown ($R^2 = 0.95$). Below 30 Gy of the mean LAD dose, the probability seems to be negligible. Pseudo-threshold may by caused by small group of patients, so can greatly impact the fit. Due to the small amount of data available and the difficulty in precise contouring, modelling LAD damage is challenging. Additional studies are needed to describe the LAD threshold doses and dose-volume relationships.

Conclusions

The collected data show that the assessment of the quality of the treatment plan for patients after a left-sided mastectomy performed only with the mean heart dose can be a significant simplification for modern radiotherapy techniques. It seems necessary to draw individual heart substructures for reliable assessment of the dose distribution and NTCP calculation.

Conflict of interest: none declared

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Use of complementary and alternative medicine among Polish cancer patients

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Introduction. The aim of this prospective study was to estimate the perception and popularity of complementary and alternative medicine (CAM) subtypes and the reasons for usage among adult Polish cancer patients.

Material and methods. The validated questionnaire was conducted among 310 patients. 24.1% of the patients used CAM during their oncological treatment. Risk factors for CAM usage were: female gender, university degree and radical treatment. The most common reasons for CAM usage were: boosting the immune system (46.1%), improving well-being/ counteracting the ill effects of cancer and its treatment (40.8%). The average level of satisfaction with CAM was high (≥3/5 on a Likert scale). Nearly half of the patients (46.6%) admitted not informing their doctors about their CAM usage.

Conclusions. The growing popularity and heterogeneity of CAM methods make it an important issue for patient–doctor relations in Poland and other Central European countries. The results of this study indicate what topics should be covered while introducing patient education programs.

Key words: cancer, complementary and alternative medicine, CAM, questionnaire, patients

Introduction

Over the last few decades, the treatment of cancer has improved considerably. However, patients are constantly turning to methods that are not part of routine procedures. Complementary and alternative medicine (CAM) is a huge group of practices varying from alternative medical systems through mind-body interventions, biologically-based therapies, manipulation and body-based methods to energy "therapies". According to the National Center for Complementary and Alternative Medicine, it is "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine" [1] (tab. I).

Results obtained in numerous countries show that the range of CAM usage by cancer patients varies between 14.8% and 73.1% [2, 3]. These data were obtained before the COVID-19 era and may be even higher now as during this period access to standard diagnostic and treatment procedures was limited, although results from Germany show similar statistics to those from pre-COVID-19 times [3]. There is also a shortage of current information about the application of CAM in Poland

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Table I. The definition of the term "complementary and alternative medicine" [1, 2]

Complementary and alternative medicine				
"the use of unproven interventions by individuals in conjunction with, or in place of, traditional or conventional means of treatment of various diseases or disease-related symptoms"				
Complementary therapies		**Alternative therapies**		
"refers to using a non-mainstream approach together with conventional medicine"		"refers to using a non-mainstream approach in place of conventional medicine"		
manipulation and body-based methods	movement therapies	mind-body interventions	biologically based therapies	alternative medical systems
• massage	• yoga	• meditation	• herbs/herbal remedies	• traditional Chinese medicine
• relaxation techniques	• pilates	• prayer	• dietary supplements	• ayurveda
• chiropractic		• supportive groups	• vitamins	
			• special diets	

and Central or Eastern Europe. It is important to estimate the popularity and perception of CAM among cancer patients in order to increase the awareness among physicians.

The aim of this study was to estimate the general perception of Polish cancer patients regarding CAM, its popularity, its types, and the reasons for its application. This research was also conducted to check if the profile of patients using CAM in Poland is similar to other countries and if there is any correlation between medical or sociodemographic factors and the popularity of CAM.

To the best of our knowledge, our study has been the first concerning the usage of CAM in Central or Eastern Europe among the cancer patient population.

Material and methods

Ethical approval

The study was approved by Jagiellonian University Ethics Committee (Decision No. KBET/3/B/2012). The study was performed in accordance with the ethical standards laid down in the 1964 Helsinki Declaration and its later amendments. All patients gave their written, informed consent to participate in the study. No conflict of interest was declared.

Building a tool

The questionnaire development process is describes in table II [4, 5]. We followed the European Organization for Research and Treatment of Cancer Quality of Life Group guidelines for questionnaire development with some changes concerning: single country cultural consistency and creating the initial questionnaire in Polish instead of English [4]. Data for the validation process were gathered between January 2012 and January 2013.

Study group

Inclusion and exclusion criteria

Patients' inclusion criteria were: adult age (>18 years) and primary diagnosis confirmed by histopathological examination. There was no restriction as to the type of neoplastic disease or treatment type or intention. The exclusion criteria were: lack of informed consent to complete the questionnaire or refusal regarding accessing medical records.

Data gathering

The validated survey was conducted as a personal interview among patients between February 2013 and January 2016, with both men and women, at the Department of Clinical Oncology, University Hospital in Krakow. The inpatients of the Oncological Ward and outpatients from the Ambulatory Chemotherapy Clinic were recruited. Interviewers assured them about confidentiality before the interview started. In order to avoid concealment of information by the patients in the presence of their physicians, the interviewers were not involved in patients' treatment. Patients were instructed on how to complete the questionnaire and were allowed to ask questions whenever any uncertainties arose. After completing questions about the sociodemographic data, the patients were asked if they had used CAM. All patients were asked a question about their perception of what CAM is and if it is approved by conventional medicine. If patients admitted using CAM, they were asked follow up questions. The whole procedure lasted 10–25 minutes, depending on whether the patient used CAM or not.

Data gathered from the questionnaires were supplemented by patients' clinical records. Information acquired from patients' histories included questions about:

- type/intention of treatment (radical *vs.* palliative),
- current treatment (chemotherapy *vs.* radiotherapy *vs.* radiochemotherapy *vs.* hormonal therapy),
- history of previous oncological treatment (yes/ what type of treatment *vs.* no),
- date of diagnosis.

Table III shows the sociodemographic and medical data for 310 patients who completed the questionnaire.

Statistical analysis

Statistical analysis was performed with the use of Statistica 10.0 PL (Statsoft). Elements of descriptive statistics

Table II. Actions taken to compile the questionnaire [4, 5]

Phases	Action	Description
Phase 1. Generation of issues	searching databases	• Medline (1993–January 2012), Scopus and Up-To-Date databases were screened for all studies published in English concerning the use of CAM among adult oncological patients in Europe • the following keywords were used according to Boolean logic rules: *complementary and alternative medicine, alternative medicine, alternative therapies, CAM, cancer, complementary therapies, Poland, neoplasm, oncology, patients, survey, questionnaire* • the search strategy was developed specifically for each database • the information was obtained initially from abstracts and then further complete papers
	interviewing the patients	• the interviews with patients (n = 20; age range 18 to 72 years; 10 females and 10 males) were performed • the patients were asked to describe their experience concerning CAM and were permitted to provide information freely • the procedure was stopped when no new issue arose
	• discussing among health-care professionalsA list of 33 issues was generated and discussed among the authors of this study and a group of six other health-care professionals (two nurses, two medical students and two oncologists) • all assessed the relevance of each issue on the Likert scale (1 – not relevant at all, 5 – very relevant) and chose 15 issues for further consideration • the issue was selected if it achieved a mean score of 3.5 on the Likert scale and at least one-third of respondents prioritized the issue • finally, one overlapping issue was deleted	
Phase 2. Building a provisional questionnaire	generating a list of questions	• the chosen issues were used to build the items for the questionnaire • the provisional version consisted of 21 questions: eight about sociodemographic data and 13 about CAM compiled by the research team
	• review by an expert • review by an independent expert was performed	
Phase 3. Testing the provisional questionnaire	assessment by health-care professionals	the provisional questionnaire was assessed by a group of five doctors, one nurse, one psychologist and five medical students
	testing on a group of patients	the provisional questionnaire was tested by 30 patients at the Oncology Clinic (age range 41 to 70 years; 18 females and 12 males)
		• health-care professionals and patients found the questions easy to understand and acceptable • confusing, upsetting or intrusive questions and issues were corrected (according to suggestions) after discussion between co-authors. E.g. question about earnings was deleted to avoid sensitive issues not directly pertaining to the study's aim
Phase 4. Questionnaire field-testing	field-testing on a group of patients	• the final questionnaire developed for this study consisted of 19 items • questions were mostly closed-ended with an open answer category after a list of possible answers • questions were divided into three parts: sociodemographic data (six questions), usage and perception of the CAM term (two questions), and questions about CAM usage – only for patients who admitted usage of CAM (11 questions) • the main issues and most commonly used methods of CAM were specified. The number of respondents used for field-testing was 96 (age range 31 to 88 years; 55 females and 41 males) • results for test-retest reliability with an assessment 2 weeks after the baseline by using interclass correlations showed a correlation from 0.8 to 0.92, which is considered excellent • in terms of construct validity, Cronbach's alpha coefficient for the final questionnaire was 0.77. This value was considered acceptable
	final review of the questionnaire	• the questionnaire was accepted by the research team

were applied (mean, standard deviation, percentage distribution). The Student's t-test was used when comparing quantitative variables and the Mann–Whitney U test was applied in the absence of normal distribution of factors. The results of the univariate logistic regression were presented as odds ratios (OR) and 95% confidence intervals (95% CI). P-values of less than 0.05 were considered to indicate statistical significance.

Results

Over 24.1% of all patients used CAM during their oncological treatment. The mean age was 58.1 years (+/– 11.7 SD). CAM users were more often women (OR = 1.84; 95% CI: 1.07–3.13; p = 0.025) and had a university education (OR = 2.05; 95% CI: 1.18–3.57; p = 0.0107. Between CAM users and non-users, there were no differences as regards duration of the oncological treatment, the place of residence, marital status or age (p > 0.05). Patients during radical treatment tended to use more CAM than palliative patients (OR = 1.81; 95% CI: 1.07–3.07; p = 0.0277). Patients with breast cancer used CAM more often than patients with other types of malignancies (OR = 2.67; 95% CI: 1.38–5.16; p = 0.0036).

Polish society is homogeneous – all patients from this study were Polish citizens and Caucasian. Regardless of whether they were CAM users or non-users, all patients were asked a question about their definition of CAM. Table IV shows what their comprehension of the CAM term was. The higher the education level of patients (secondary and university education) the better their knowledge of CAM (p < 0.0001). The term "Other" in table IV means patients' own comments related to

Table III. Sociodemographic and medical information about respondents

		All participants		CAM users		Non-users	
		No.	%	No.	% of all participants	No.	% of all participants
sex	women	161	51.9	48	15.5	113	36.5
	men	149	48.1	28	9.0	121	39.0
age (years)		58.1		56.2		58.7	
marital status	single	23	7.4	7	30.4	16	69.6
	married	240	77.4	56	23.3	184	76.7
	widowed	34	11.0	11	32.4	23	67.6
	divorced	12	3.9	2	16.7	10	83.3
place of living	rural area	117	37.7	31	26.5	86	73.5
	town/city of <20 000 inhabitants	25	8.1	6	24.0	19	76.0
	town/city of 20 000–150 000 inhabitants	35	11.3	10	28.6	25	71.4
	town/city of >150 000 inhabitants	133	42.9	29	21.8	104	78.2
education	elementary	29	9.4	7	2.3	22	7.1
	vocational	84	27.1	13	4.2	71	22.9
	secondary	113	36.5	26	8.4	87	28.1
	university	84	27.1	30	9.7	54	17.4
intention of treatment	radical	110	35.5	35	11.3	75	24.2
	palliative	200	64.5	41	13.2	159	51.3
type of current treatment	chemotherapy	253	81.6	58	18.7	195	62.9
	chemoradiotherapy	40	12.9	13	4.2	27	8.7
	radiotherapy	3	1.0	2	0.6	1	0.3
	hormonal therapy	13	4.2	3	1.0	10	3.2
type of treatment used in the past (more than one is possible)	chemotherapy	147	47.4	40	12.9	107	34.5
	radiotherapy	82	26.5	21	6.8	61	19.7
	surgery	237	76.5	64	20.6	173	55.8
	other	16	5.2	6	1.9	10	3.2
	no previous treatment	22	7.1	2	0.6	20	6.5
place of treatment	inpatient ward	227	73.2	54	17.4	173	55.8
	outpatient clinic	83	26.8	22	7.1	61	19.8
type of cancer	colorectal cancer	59	19.0	23	30.3	78	33.3
	stomach cancer	59	19.0	10	13.2	49	20.9
	breast cancer	45	14.5	19	25.0	26	11.1
	lung cancer	17	5.5	1	1.3	16	6.8
	head and neck cancer	13	4.2	4	5.3	9	3.8
	pancreatic cancer	9	2.9	1	1.3	8	3.4
	ovarian cancer	9	2.9	3	3.9	6	2.6
	testicular cancer	7	2.3	2	2.6	5	2.1
	others	51	16.5	20	6.5	53	17.1

Table IV. Patients' perception of the CAM term

		All participants		CAM users		Non-users	
		No.	%	No.	%	No.	%
What, in your opinion, does the term "complementary and alternative medicine" mean?	they are methods that are moderately approved by conventional medicine (CM)	58	18.7	20	6.5	38	12.3
	they are salutary methods unapproved by CM	39	12.6	11	0.0	28	0.1
	they are methods that could be used instead of the CM	4	1.3	2	0.0	2	0.0
	they are methods that could be used alongside CM	109	35.2	39	0.1	70	0.2
	I do not have any opinion	101	32.6	14	0.0	87	0.3
	other	70	22.6	10	0.0	60	0.2

decisions about the usage of CAM, like: "My family and friends encouraged me to use it, and I trust them; I think that CAM is safe for my health; I wanted to try everything possible; I do not trust CAM or I think CAM is a mind therapy, not body therapy".

Table V presents the prevalence of using particular CAM methods. Most patients had more trust in conventional medicine (CM) (67.1%), but there was also a group of CAM users (17.1%) who trusted both CAM and CM the same way. Only 2.6% (2 responders) trusted CAM more. The most commonly mentioned reason for using CAM was boosting the immune system (46.1%). Other popular arguments were: improving well-being/ counteracting the ill effects of cancer and its treatment (40.8%); improving the prognosis (38.2%) and increasing the chance of recovery (28.9%). The most common source of information about CAM was family and friends (57.9%), over 34.2% of CAM users employed some CAM methods before their oncological treatment. The amount of money spent each month on CAM was lower than 50 PLN (around 13 USD) for

Table V. Prevalence of CAM usage

Method		CAM users	
		No.	%
manipulation and body-based methods	massage	3	3.9
	relaxation techniques	2	2.6
movement therapies	yoga	3	3.9
mind-body interventions	prayer	24	31.6
	psychotherapy/ support groups	6	7.9
biologically based therapies	dietary supplements	31	40.8
	herbal medicine	20	26.3
	special diet/modification of diet	17	22.4
	apitherapy	8	10.5
	amygdalin	4	5.3
	capsaicin	4	5.3
	aromatherapy	1	1.3
alternative medical systems	quackery/ bioenergotherapy	7	9.2
	homeopathy	5	6.6
	acupuncture	0	0
	Ashkar method	0	0
	folk/traditional medicine	0	0
other methods not listed above		20	26.3

27.6% of respondents: 50–100 PLN for 25.0%. About 17.1% of CAM users spent 100–200 PLN monthly, 6.6% – 200–500 PLN and 7.9% more than 500 PLN. The most popular treatments mentioned by respondents were:

- alkylglycerol (Ecomer, containing shark liver oil) (6.7% of CAM users),
- specially prepared juices from vegetables or fruit (6.7%),
- vitamin B_{17} – amygdalin (5.3%),
- shark cartilage (5.3%),
- noni juices (*Morinda citrifolia*) (5.3%),
- extract from shiitake mushroom (*Lentinula edodes*) (4%),
- extract from *Polyporus betulinus nigricans* (4%),
- elements from *Betula pendula* (2.7%),
- Graviola Immune (2.7%),
- ayurweda (1.3%) and pilates (1.3%).

Discussion

CAM usage – the profile of users and potential reasons for CAM usage

Numerous researchers prove that CAM usage among cancer patients is higher than in the general population, but similar to patients with chronic diseases. Indeed, a recently published study regarding Polish patients with epilepsy showed similar percentages of CAM users in comparison to our population [6].

In this research, the profile of CAM users is the same as in many other research studies – patients with cancer using CAM tended to be female with higher education levels and were suffering from breast cancer. Better educated patients are probably more aware of their health status and show more interest in the process of their illness and treatment. CAM usage is connected with higher educational levels; in Israel, however, dietary supplement usage is more popular among people who are less formally educated. CAM can be seen as an active way to manage the disease, with some data suggesting that the intention of patients using CAM was to have a positive influence on their disease [7–10]. In this study, better educated patients seemed to have more ideas and reflections about CAM and they were probably more involved in the treatment of their disease. 4.5% of CAM users, in comparison to almost one third of non-users, did not have their own opinion about what CAM was. In Poland, the use of CAM was mainly affected by the influence of family and friends, while in the United Kingdom (UK), the Internet played a main role [11].

Alternative methods were nearly fifteen times more popular among Polish patients than complementary ones, while in other studies this disparity is smaller – alternative methods are only three times more popular [12]. An explanation for this might be the different motivations for choosing CAM. In this research, the most popular reason for using CAM was "boosting the immune system" and diet supplements seem to be the most suitable and accessible way of achieving this. Huebner et al. (Germany) indicated the importance of "the reduction of side effects" and a "desire to become active" as equally important, while Molassiotis et al. and other European researchers reported "increasing the body's ability to fight cancer" as the most popular reason; complementary methods may more effectively fulfill these demands [13, 14]. Other reasons for the use of CAM by Polish patients were generally similar to those from other studies.

In Poland, patients during radical treatment tended to use CAM nearly twice as often as during palliative treatment, while other papers suggested that palliative patients, who have a poorer quality of life, are usually expected to use CAM more often. According to Eliott et al., palliative patients might be more depressive and hopeless and some of them might fail to continue to use CAM due to different practical and financial difficulties [15, 16]. Complementary methods like relaxation or psychotherapy might be especially favorable for palliative patients. However, in Poland there is little general awareness about these methods. During palliative oncological treatment, the spiritual needs of patients and the various problems associated with the end of life should not be omitted or unnoticed. Unfortunately, in Poland the palliative treatment financed by the National Health Fund (NFZ) does not satisfy these demands. Moreover, overall psychological care in oncological and palliative departments is insufficient [17].

CAM methods used

Poland is a mainly Catholic country: 91.4% of the total population (2018, http://stat.gov.pl/) belong to the Latin Church of the Roman Catholic Church. 24% of our participants claimed that they were praying for a cure. In this research, prayer was the second most common CAM among cancer patients, which is similar or less frequent to the outcomes from North Africa or Asia, while in Western Europe other methods were usually more popular [9, 18–20].

The profile of the method used in Poland is halfway between the profile from Western Europe or the USA and Asia. In Poland, like in Western countries and the USA, the most popular methods were mainly various diet supplements (tab. V) [8, 9]. Diet supplements – regardless of their effectiveness – are the simplest methods that can be applied. They do not usually require major changes in lifestyle or involve much time, attention or effort.

In Poland, methods like mind and body and relaxation techniques or acupuncture are still not very popular. In other European countries, relaxation is used by up to 32.4%, acupuncture up to 13% and spiritual methods up to 20.0%, while in our research it is only 7.8% for manipulation and body-based methods (also including relaxation), 3.9% for movement therapies and 0% for acupuncture (tab. V).

A systematic review from the USA names exercises, acupuncture and meditation, yoga, massage and music therapy among the most frequently mentioned on comprehensive cancer center websites. They are offered to cancer patients as commonly as dietary supplements and even more commonly than herbs [21–22]. According to Scott et al., in the UK, where

the average income is higher than in Poland, the most popular methods among cancer patients are relaxation, meditation and medicinal teas [12]. In Polish society these interventions are probably still regarded as "exclusive" and accessible only to younger people in bigger cities with higher incomes. In this study, participants were not asked about their income to avoid tactlessness, nevertheless the mean value of a salary in Poland in the first half of 2019 was 4951 PLN (1293 USD) (http://stat.gov.pl). More expensive methods (like acupuncture or massage) are unaffordable for many patients in Poland.

Moreover, in Poland and other countries from the Eastern Block (the former communist states of Central and Eastern Europe), common access to some methods, techniques and innovations was restricted for many years. 30 years ago this isolation ended, and the difficult and still ongoing reform of the health care sector began. It may still take many more years to overcome the challenges faced [23]. The mean age of this study population was 58.1 years which might suggest that many of the respondents might not be very familiar with the benefits of complementary therapies due to their age. Maybe the proportion of CAM types used will change over the coming decades. The last important factor is the fact that people living in smaller Polish cities or rural areas have limited access to some practices requiring professional staff (like yoga, pilates or support groups).

Safety and patient–doctor communication issues

7.9% of our respondents claimed that using CAM delayed presenting oneself to a physician or oncologist with disturbing symptoms. This percentage is much lower than for the Asian population. A recently published retrospective study regarding a huge population (almost 2 000 000) of cancer patients concluded that CAM usage was associated with refusal of standard treatment options and a higher risk of death. Earlier, Han et al. proved that CAM used as primary treatment for breast cancer increased the risk of progression, recurrence and death, however a study by Neuhouser et al. did not confirm this. Nevertheless, the risk of drug interactions when some of CAM methods are applied, in addition to standard oncological treatment, or even higher a risk of infections in some cases cannot be neglected [20, 24–27].

In our study, almost half the patients (46.57%) admitted not informing their doctors about CAM usage and this matches the results of the review by Davis et al. regarding the number of patients who do not disclose CAM usage (20–70%) [28]. Our patients point to their doctor's lack of inquiry as to the main reason for nondisclosure, and this was also demonstrated by other studies. It seems that patients lack the proper conversations about supportive methods for their oncological treatment. Other studies reported similar results about patients' fear of being judged by clinicians when sharing such information and their desire to be actively involved in their treatment [29–30].

Limitations of the study

The study has certain limitations, one of the biggest being the inequality of the groups – there were almost twice as many palliative patients involved than radical and more inward patients than outward. The survey did not investigate the usage of vitamin C infusions and this method was explored together with other methods as "dietary supplements". Regarding the growing popularity of vitamin C infusions, this topic should be covered separately [10, 31]. An important influence on the proportion of women and men using CAM in our study was women with breast cancer – they accounted for 14.5% of all patients, but as many as 25.0% of all CAM users. Moreover, the response rate was not measured and the patients who did not give their consent to complete the questionnaire were not asked about their reason for refusal. The questionnaire needs a cross-cultural adaptation and a proper English translation in order to be used in other studies.

Conclusions

The study showed the differences between the USA, Western European and post-communist countries in terms of CAM usage in cancer patients. The profile of a Central European CAM user is also different from their Asian equivalent. Looking at the updated data from other regions, it can be assumed that Poland will also experience a shift in prevalence or types of CAM being commonly used.

The growing popularity and heterogeneity of CAM methods make it an important issue for patient–doctor relations in Poland and other Central European countries. Oncologists and general practitioners in our region should start talking about CAM with their cancer patients. The results of this study indicate what topics should be covered while introducing patient education programs in Poland.

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The surgical treatment of rectal cancer in Poland. The findings of a multi-center observational study by the Polish Society of Surgical Oncology (PSSO-01)

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Introduction. PSSO-01, a Polish prospective multi-center project on rectal cancer, started in 2016 with participation on a voluntary basis. This study evaluates the early outcome of the surgical treatment of rectal cancer in Poland according to hospital volume.

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Material and methods. The dataset derives from 17 clinical centers registered in the PSSO-01 study. From 2016 to 2020, the data of 1,607 patients were collected. Taking into account the number of patients enrolled in the study, the centers were divided into three categories: high volume, medium volume, and low volume. Nominal variables were compared between different categories of centers using the chi-square test. The STROBE guidelines were used to guarantee the reporting of this observational study.
Results. More patients with metastatic disease were operated on in the low volume centers ($p = 0.020$). Neoadjuvant treatment was used in 35%, 52%, and 66% of patients operated on in low, medium, and high volume centers respectively ($p < 0.001$). Laparoscopic resection in medium volume centers was performed more often than in other centers ($p < 0.001$). The total rate of postoperative complications related to high, medium, and low centers was 22%, 26%, 18% ($p = 0.044$). One year following surgery, a stoma was present in 63% of patients. A defunctioning stoma following anterior resection was reversed in only 55% of patients. Anastomotic leakage was the main reason for a non-reversal diverting stoma.
Conclusions. The representation of low volume centers in the PSSO-01 study was understated. However, the outcomes may show the actual situation of surgical treatment of rectal cancer in high and medium volume centers in Poland.

Key words: rectal cancer, surgery, volume center, stoma

Introduction

Every year, about 6,000 new cases of rectal cancer are recorded in Poland. Most of them require surgical treatment. Unfortunately, we neither have a nationwide registry that allows us to determine the stage of the disease at the time of diagnosis, nor the ability to use prospective monitoring of the surgical outcomes with a nationwide scope.

In 2016, the Polish Society of Surgical Oncology (PSSO) began collecting data on the surgical treatment of rectal cancer as part of a multi-center observational study (PSSO-01). One of the objectives of this project was to evaluate the early results of surgical treatment and to determine the proportion of patients who had a permanent intestinal stoma in long-term follow-up (up to 12 months after surgery). The purpose of this study was to provide basic data on the current surgical treatment of rectal cancer in Poland.

Material and methods

Study centers

The participation of the institutions in the research project PSSO-01 was voluntary. The main criterion for the qualification of the centers was the possibility of monitoring postoperative complications within a minimum of 30 days after surgery and long-term outcomes up to 12 months after surgery. At the beginning of the study (April 2016), there were 7 registered centers. Others joined during the study. 17 out of 24 registered centers were active in the study. The activity of the centers during the study period is shown in figure 1. The recruitment process for the study has been described in detail and published previously [1]. Taking into account the number of patients enrolled in the study from each institution, the centers were divided into three categories: high volume (>50 operations per year), medium volume (25–50 operations per year), and low volume (<25 operations per year). Due to the COVID-19 pandemic and the temporary interruption of the normal work of the hospitals, the volume was calculated according to the following formula: (number of patients recruited until 31st March 2020 ÷ the time of the center's activity [in months] to the date of 31st March 2021) × 12.

Population of the study

The project of the study received the approval of the Bioethical Committee. During the study period, all patients with primary

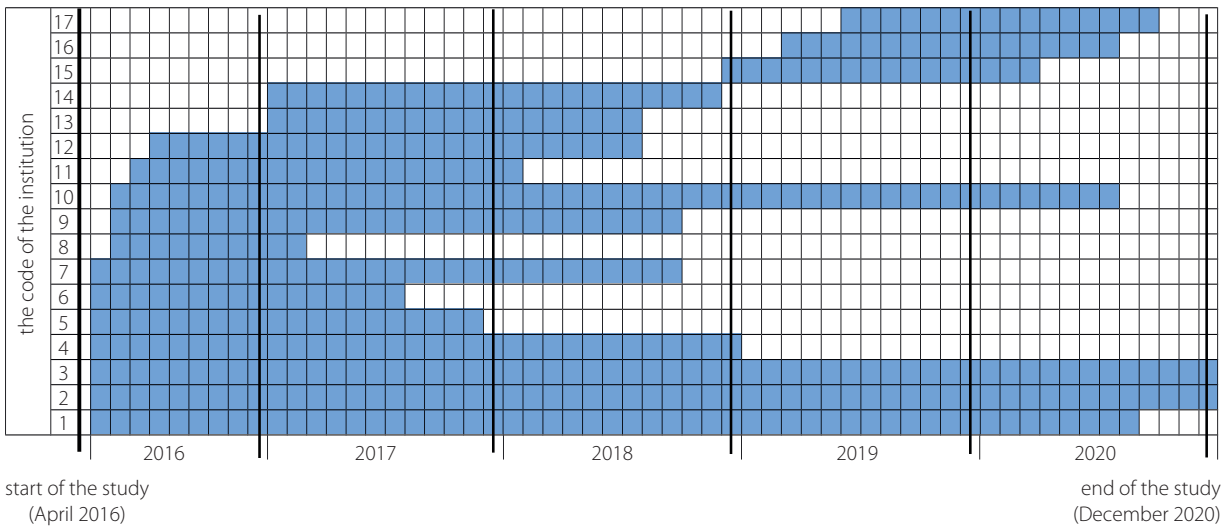

Figure 1. Activity of the centers in the study period

rectal cancer (coded as C20, International Classification of Disease-10) operated on at the research centers were registered. The following data were prospectively collected:

- gender – distant metastases,
- concomitant diseases,
- preoperative treatment,
- technique and type of surgery, postoperative complications according to the Dindo-Clavien classification.

Because the main purpose of the PSSO-01 study focused on anastomotic leakage, wider data were collected only in the group of patients after anterior resection.

Follow-up

The data of the presence of a stoma after anterior resection was prospectively collected within 12 months from the date of surgery. If a stoma at the evaluation points specified above was still present, the reasons for this has been described. The information on bowel restoration following Hartmann's procedure was retrospectively collected.

Statistical analysis

Missing data were not defaulted to negative, and denominators reflect only actual reported cases. Summary statistics were expressed by percentages for categorial variables. Nominal variables were compared between the three groups of patients operated on at different volume centers using the chi-square test. For all tests, the statistical significance was accepted at $\alpha = 0.05$. All tests were two sided. The data were analyzed with SPSS version 19 for Windows (SPSS, Chicago, Illinois, USA).

Results

From April 2016 to December 2020, 1,607 patients undergoing surgical treatment for rectal cancer were registered. The characteristics of the patients are shown in table I. More than half of the patients (53%; [95% confidence interval (CI): 49–57]) had concomitant diseases, the most common of which was hypertension 45% (95% CI: 43–47). Diabetes occurred in 15% (95% CI: 13–17) and ischemic heart disease in 14% (95% CI: 12–16). The rate of patients with cancer spread (distant metastases) at the time of the rectal cancer diagnosis was 13% [95% CI: 8–18]. Preoperative treatment of any kind was used in 920 (57%) patients. During the operation, a stoma (permanent or temporary) was created in 890 (56%) patients. Taking into account the patients' characteristics and their treatment, many statistically significant differences were found between the centers of different volumes – table II.

More patients with advanced cancer (metastatic disease) were operated on in the low volume centers than in high volume centers: 18% *vs.* 11% respectively (p = 0.020; relative risk (RR): 1.61 [95% CI: 1.10–2.35]). There was also a difference in the proportion of patients with concomitant disorders (such as ischemic heart disease, hypertension, and diabetes) who were treated in different centers: high volume centers 48% *vs.* medium volume centers 57% (p = 0.005; RR 1.18 [95% CI: 1.06–1.30] *vs.* low volume centers 60% (p = 0,006; RR 1.24 [95% CI: 1.08–1.42]). Preoperative radiotherapy or chemo-radiotherapy was used in only 35% of patients operated on in low volume centers. This was less than in medium volume centers (p < 0.001; RR 1.52 [95% CI: 1.23–1.87]) and in high volume centers (p < 0.001; RR 1.90 [95% CI: 1.55–2.32]). There were also differences in neoadjuvant treatment between high volume centers and medium volume centers: 66% and 52% respectively (p < 0.001; RR 1.25 [95% CI: 1.14–1.37]).

Table I. Characteristic of the study group

	Patients n (%)
volume of the study center:	
• high (>50 operations per year)	853 (53)
• medium (25–50 operations per year)	563 (35)
• low (<25 operations per year)	191 (12)
gender:	
• male	981 (61)
• female	626 (39)
metastatic disease:	
• yes	197 (13)
• not specified	59
concomitant disorders:	
• yes	846 (53)
preoperative RTH or CRT:	
• yes	920 (57)
• no	687 (43)
mode of surgery:	
• urgent	49 (3)
• elective	1540 (97)
• no data	18
abdominal approach:	
• open	1325 (85)
• laparoscopic	233 (15)
• no data or not applicable (*)	49
type of operation:	
• ASR/APR	341 (21)
• RA	530 (33)
• LAR	322 (20)
• HRTM	200 (13)
• PRCOL	5 (0.3)
• LExc	28 (2)
• STOM	130 (8)
• LPT	7 (0.4)
• other	28 (2)
• no data	16

RTH – preoperative radiotherapy; CRT – preoperative chemo-radiotherapy; ASR – abdomino-sacralis resection; APR – abdomino-perineal resection; RA – anterior resection; LAR – low anterior resection (anastomosis ≤5 cm from the anal verge); HRTM – Hartmann's procedure; PRCOL – proctocolectomy; LExc – local excision; STOM – colostomy; LPT – laparotomy; (*) – resection without laparotomy (for example: local excision)

Surgical treatment

Emergency operations were performed more frequently in low volume centers than in medium and high volume centers (p < 0.001; RR 3.04 [95% CI: 1.67–5.53]). The rate of laparoscopic resection in medium volume centers was higher than in high volume centers (22% *vs.* 13%: p < 0.001; RR 1.70 [95% CI: 1.34–2.16)]

Table II. The surgical treatment and volume of the center

Factor	Volume of the center			p value
	High n = 853	Medium n = 563	Low n = 191	
gender:				0.354
• male	534 (63%)	331 (59%)	116 (61%)	
• female	319 (37%)	232 (41%)	75 (39%)	
concomitant disorders:				0.001
• yes	412 (48%)	320 (57%)	114 (60%)	
clinical stage (TNM):				0.047
• IV (metastatic disease)	94 (11%)	73 (13%)	30 (18%)	
• I–III	739 (89%)	477 (87%)	135 (82%)	
• not specified	20	13	26	
preoperative RTH or CRT:				<0.001
• yes	559 (66%)	295 (52%)	66 (35%)	
urgency of surgery:				0.001
• urgent	22 (3%)	13 (2%)	14 (8%)	
• elective	829 (97%)	540 (98%)	171 (92%)	
• no data	2	10	6	
surgical abdominal approach:				<0.001
• open (classic approach)	725 (87%)	424 (78%)	176 (96%)	
• laparoscopic	107 (13%)	119 (22%)	7 (4%)	
• no data or not applicable (*)	21	20	8	
surgical procedure:				0.102
• ASR/APR	190 (22%)	116 (21%)	35 (19%)	
• RA	265 (31%)	195 (35%)	70 (38%)	
• LAR	171 (20%)	126 (23%)	25 (13%)	
• HRTM	108 (13%)	61(11%)	31 (17%)	
• PRCOL	3 (0.4%)	1 (0.2%)	1 (0.5%)	
• LExc	16 (2%)	9 (2%)	3 (2%)	
• STOM	76 (9%)	40 (7%)	14 (8%)	
• LPT	4 (0.5%)	2 (0.4%)	1 (0.5%)	
• other	18 (2%)	4 (0.7%)	6 (3%)	
• no data	2	9	5	
defunctioning stoma: (**)				<0.001
• yes	138 (31%)	71 (22%)	5 (5%)	
• no data	0	1	1	

RTH – preoperative radiotherapy; CRT – preoperative chemo-radiotherapy; ASR – abdomino-sacralis resection; APR – abdomino-perineal resection; RA – anterior resection; LAR – low anterior resection (anastomosis ≤5 cm from the anal verge); HRTM – Hartmann's procedure; PRCOL – proctocolectomy; LExc – local excision; STOM – colostomy; LPT – laparotomy; (*) – resection without laparotomy (for example: local excision); (**) – percentage is related to the performed anastomoses

and low volume centers (22% *vs.* 4%: p < 0.001; RR 5.53 [95% CI: 2.72–12.05)]. There were no statistically significant differences between centers of different volume, taking into account the type of performed operations (p = 0.102). However, analysis of individual types of operations has shown that fewer low anterior resections in low volume centers were performed than in high and medium volume centers (13% *vs.* 21%: p = 0.018; RR 1.57 [95% CI: 1.08–2.30]). Diverting stoma in resection with primary anastomosis was performed most often in high volume centers, and the least in low centers (p < 0.001) – table II.

The early outcomes of surgical treatment

Most palliative resections were performed in low volume centers (19%), and it was a statistically significant difference in proportion to medium volume centers (p = 0.018; RR 1.61 [95% CI: 1.11–2.32]) – table III. There were no differences in palliative resections between high and medium volume centers (p = 0.075; RR 1,28 [95% CI: 0,97–1,68]). Postoperative complications was recorded in 359 (23%) patients. Most of them occurred in medium volume centers (26%). The difference in proportion to high and low volume centers were 26% *vs.* 22% (p = 0.056; RR 1.21 [95% CI: 1.00–1.47]) and 26% *vs.* 18% (p = 0.034; RR 1.42 [95% CI: 1.02–1.98]) respectively. Taking into account only serious postoperative complications (grade 3–5 according to the Dindo-Clavien Classification), the difference between medium and high volume centers was not significant (p = 0.110), but ≥3 grade complications were higher in medium volume centers in relation to low volume centers (p = 0.016; RR 1.55 [95% CI: 1.13–2.12]). The rate of anastomotic leakage was similar in centers with different volume (8%, 10%, and 7%). Postoperative mortality was less than 1%. At the end of postoperative hospitalization, 707 (45%) patients had a permanent end-colostomy.

Persistent stoma in long term observation

The full follow-up covered 1,243 patients. Patients who had been lost from the follow-up (death or an observation pe-

Table III. The early outcomes of surgical treatment

Factor	Total n = 1607	Volume of the center			p value
		High n = 853	Medium n = 563	Low n = 191	
type of resection:					0.035
• palliative	235 (15%)	132 (16%)	67 (12%)	36 (19%)	
• radical	1354 (85%)	719 (84%)	486 (88%)	149 (81%)	
• no data	18	2	10	6	
postoperative complications:					0.044
• yes	359 (23%)	182 (22%)	143 (26%)	34 (18%)	
• no data	28	7	15	6	
the grade of complications [1]					0.632
• 1	72 (5%)	23 (3%)	44 (8%)	5 (3%)	
• 2	110 (7%)	65 (8%)	38 (7%)	7 (4%)	
• 3	129 (8%)	70 (8%)	42 (8%)	17 (9%)	
• 4	29 (2%)	13 (2%)	13 (2%)	3 (2%)	
• 5	14 (1%)	8 (1%)	4 (1%)	2 (1%)	
• no data	33	10	17	6	
anastomotic leakage (*)					0.607
• yes	75 (9%)	36 (8%)	32 (10%)	7 (7%)	
• no data	4	0	3	1	
end-colostomy present at the end of hospitalization: [2]					0.318
• yes	707 (45%)	390 (47%)	234 (43%)	83 (46%)	
• no data	46	19	15	12	

(*) – percentage is related to the performed anastomoses; [1] – according to the Dindo-Clavien Classification; [2] – any surgical procedures with permanent stoma performed. Disconnection of the anastomosis due to anastomotic leakage after anterior resection and end-colostomy performed – included

riod less than 12 months) were excluded from the analysis of long-term outcomes. One year after the operation, a stoma was present in 777 (63%) patients. In 533 (43%) patients, it was connected with the primary type of surgery: abdomino-sacral resection / abdomino-perineal resection (ASR/APR; n = 341), proctocolectomy (PRCOL; n = 5), palliative Hartmann's procedure (HRTM; n = 31), only colostomy (STOM; n = 133). In addition, in this group there were patients in whom primary anastomosis was a disconnection due to leakage, and a definitive end-colostomy was created (n = 23). In the remaining 244 patients, a stoma was still present because no reversal of defunctioning stoma or no bowel restorative surgery after the radical Hartmann's procedure was performed. The overall rate of bowel restorative surgery following the radical Hartmann's procedure was only 2.4%. The defunctioning stoma following anterior resection (RA) or low anterior resection (LAR) was reversed in only 92 (55.4%) patients – figure 2. The reasons for delay in defunctioning stoma reversal is shown in table IV.

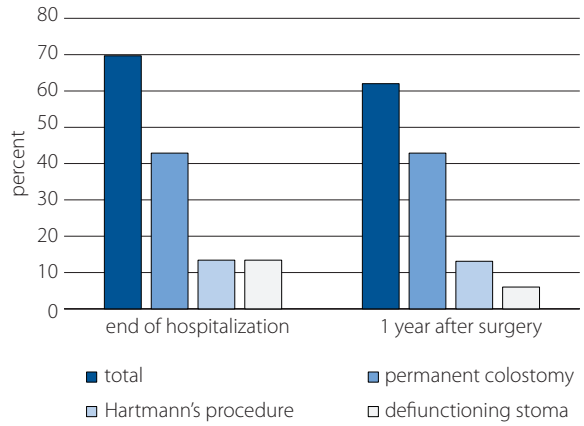

Figure 2. Persistent stoma in 1-year follow-up; analysis of 1243 patients (patients with incomplete data – excluded)

Discussion

Interim analysis of the secondary purpose of the PSSO-01 study was published previously [1]. This paper reports the final outcomes based on the data of the 1607 patients enrolled in this study. Despite the large number of subjects enrolled on this trial, it should be kept in mind that the PSSO-01 project was not a registry of rectal cancer, and the results of this analysis should be treated with caution. Furthermore, the data collected during the study do not allow for detailed analysis of the reasons for the individual results of the observations. The purpose of the study was not to assess the quality of rectal cancer surgical treatment, but to present the current situation.

Metastatic disease at the time of rectal cancer diagnosis (stage IV according to UICC) was found in 13% of the patients. Although some audit projects show similar data [2, 3], it must be assumed that this percentage is understated and does not reflect the actual situation. European population-based studies show that there are 22–26% of such cases [4] – table V. The actual proportion of patients in the advanced stages of the disease in Poland can reach 36–46% [5]. The low percentage presented in the PSSO-01 study may be due to the small representation of low volume centers, where the majority of patients with advanced stages of the disease are operated on.

Table IV. The reasons for delay in defunctioning stoma reversal (up to 12 months)

	No. of patients and percentage
anastomotic leakage	17 (23.0)
cancer disease progression	9 (13.4)
stricture of anastomosis	2 (2.7)
disagreement to restorative operations	5 (6.8)
ileus of the bowel	2 (2.7)
other (*)	39 (52.7)

(*) – adjuvant or palliative chemotherapy, the COVID-19 pandemic and other institutional burdens

In addition, some patients with multi-metastatic disease can not be treated surgically.

Numerous European audit projects present important information on the effect of center volume on the outcomes of rectal cancer surgery. A population-based study provided in the Netherlands showed improved survival in cT4 rectal cancer patients treated in high volume centers, compared with low volume hospitals, but, after correction for neoadjuvant treatment, this difference was not statistically significant [6–8]. The criteria for dividing centers into high, medium, and small were similar to those in our study. In the Netherland's study, the overall rate of neoadjuvant radiotherapy or chemo-radiotherapy treatment was very high, and there were small differences between low, medium, and high volume centers: 89%, 88%, and 90% respectively. Compared to this data, the information collected in the PSSO-01 study show much lower rate of patients treated preoperatively in different volume hospitals (66%, 52%, and 35%). The reason for these differences are due to the fact that the PSSO-01 study patients with a tumor in the upper part of the rectum were enrolled. However, compared to data from Denmark, England, Norway, and Sweden, the overall rate of patients receiving radiotherapy is similar [4].

A laparoscopic resection of rectal cancer was performed less frequently than in other European countries. Schnitzbauer et al. has shown that the use of laparoscopy in Germany increased constantly from 12.3% to 48.1% between 2007 and 2016 [9]. In the initial period of the PSSO 01 study (2016), the percentage of laparoscopic operations was only 9%, but it increased somewhat to 15% after 4 years. Although this is still a small rate, the upward trend is clearly visible and can be expected to reach the same level as other European countries in the coming years. Currently, the most laparoscopic resections are performed in medium volume centers (22%), and the least in low volume centers (4%). Other than that, data from the Dutch centers show that the most laparoscopic operations are performed in high volume centers (59.8%), but low volume centers perform 45.7% [7].

The total rate of restorative rectal resection (anterior resection or low anterior resection) was 53% (51–58% depending on the center's volume). For Hartmann's procedure (HRTM), this was 13% (11–17%), and abdomino-sacral resection / abdomino-perineal resection (ASR/APR) 21% (19–22%). The differences between different volume centers were not statistically significant. The exception was for low anterior resection (LAR), which was performed less frequently in low volume centers than in high and medium volume centers. Data from Belgian

Table V. Rectal cancer surgery in Europe

	Denmark	England	Norway	Sweden	Netherlands	Belgium	Germany	Poland
sours: [refferences]	population--based study [4]	population--based study [4]	population--based study [4]	population--based study [4]	DSCA [1] [2]	PROCARE [2] BCR [3] IMA [4] [3]	population--based study [9]	observational study [PSSO-01]
years of data collected	2010–2012	2010–2012	2010–2012	2010–2012	2009–2011	2006–2008	2007–2016	2016–2020
No. of patients	4391	27599	3111	5797	7099	6353	23001	1607
gender:								
• male	61%	64%	59%	59%	62%	60%	63% (^)	61%
• female	39%	36%	41%	41%	38%	40%	37% (^)	39%
disease stage at diagnosis:								
• stage I–III	75%	78%	74%	76%	92%	88%	80%	87%
• stage IV	25%	22%	26%	24%	8%	12%	20%	13%
• unknown stage (*)	13%	16%	13% (*)	8%	4%	41%	ND	4%
received radiotherapy	27%	41%	43%	51%	83%	50%	40% (^)	57%
laparoscopic approach	ND	ND	ND	ND	38%	ND	28%	15%
received resectional surgery	68%	60%	66%	71%	95%	81%	ND	89%

(*) – percentage is related to the whole study group; (^) – percentage is related to only UICC stage I–III, R0 resection and planned operation; ND – no data; [1] – The Dutch Surgical Colorectal Audit; [2] – Belgian multidisciplinary project on cancer of the rectum; [3] – Belgian Cancer Registry; [4] – InterMutualistic Agency database

databases show a 59% rate of sphincter saving operations, 3% of HRTM and 17% of ASR [3]. A population-based study from the Netherlands (based on the Dutch Surgical Colorectal Audit – DSCA) presents statistically significant differences between different volume centers by taking into account the type of surgery: more sphincter saving procedures (LAR and HRTM account together) and low ASR in high volume centers [6]. The DSCA audit showed that the total ASR percentage was 30.5% [2], which is higher than in the PSSO-01 study. However, all this data is difficult to compare because the type of resection, such as ASR/APR or LAR, is mainly determined by the location of the tumor. For the Belgian and the Netherland's registry, patients with a tumor located in the lower and middle third of the rectum were enrolled. In our study, we included patients with primary adenocarcinoma of the rectum between 0 and 15 cm above the anal verge.

In our study, the overall rate of postoperative complications was higher in medium volume centers compared to high and low volume centers. Jonker et al [7] reported similar observations, although the overall complication rate was higher than in our study. The low rate of defunctioning stoma in LAR (5–31% depending on the volume of the center) reported in our study is surprising because the data from the Netherlands show a significantly higher percentage of anastomosis with a defunctioning stoma (65.5–80.3% depending on the hospital volume) [7]. Despite this, the rate of anastomotic leakage in PSSO-01 was similar to the population-based data of the DSCA [10]. These outcomes confirm the observations that a high tendency towards defunctioning stoma construction did not result in lower overall anastomotic leakage and the ability to select patients for stoma construction plays the most important role in the choice of optimal surgical strategy [10].

The long-term outcomes of the present study showed a high rate (63%) of persistent stoma over the 1 year follow-up. After excluding the surgical procedures connected with permanent end-colostomy, we conclude that most of curative HRTM is a definitive surgical procedure and almost half of the defunctioning stomas are not closed following 12 months. The reasons for leaving the protective stoma allow us to assume that most of them will remain permanently. Data from DSCA has shown 54.2% end-colostomy procedures (included ASR) [2]. It is higher than in our study (43%). European multi-center studies present data that most diverting stoma is reversed within 12 months, but that one in four defunctioning stomas is not reversed 3 years after surgery [11–13]. Anastomotic leakage is one of the most important risk factors for not reversing stomas. A Swedish retrospective multi-center study [14] including 1442 patients undergoing anterior resection observed that the overall rate of permanent stoma among patients with anastomotic leakage was 65%. The rate of definitive stoma at a level of >60% following 12 months in our study seems to be high. However, other studies showed similar results. In a retrospective study conducted in Sweden, the permanent stoma rate was 63.2% when emergency and palliative procedures were included, and 54.9% when only elective curative cases were considered. The authors concluded that stoma rates taken at face value may not provide an accurate picture of a particular colorectal unit's quality of care [15].

Conclusions

We are presenting the results obtained in the prospective multi-center study PSSO-01, which focused on the surgical treatment of rectal cancer. We compared our outcomes with European population-based studies. Finally, the question should be asked: are these results representative of the population of rectal cancer patients undergoing surgery in Poland? Although the study had a prospective nature, it has several important limitations. Firstly, there was the administrative burden associated with data collection. There was no monitoring of the quality of recorded data at each of the centers by an independent study office. The accurate measurement of quality of care is complex and requires the collection of multiple data points from different phases of the care process. Therefore, the dataset is limited, but still entails valid information. Secondly, PSSO-01 has a limitation regarding the possibility of selection bias since the participation of the centers in the study was voluntary. Nevertheless, different volume centers were represented in this study. Unfortunately, in comparison to data from European population-based studies, the proportion of high, medium, and low centers in PSSO-01 underrepresented low volume centers. However, the results reported by the high and medium volume centers may correspond to the actual situation.

Conflict of interest: none declared

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Resection margins do not influence survival in vulvar cancer: treatment results in patients with a long-term follow-up

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Introduction. The main purpose of the study was to assess margin resection as a prognostic factor of vulvar cancer in patients with a long term follow-up.

Materials and methods. The study included 84 vulvar cancer patients who underwent radical treatment: surgery (n = 84), radiotherapy (n = 16), chemoradiotherapy (n = 5). Clinicopathological factors regarding survival and recurrence were analyzed. The median follow-up was 74 months.

Results. Resection margins were not related to progression-free survival (PFS) (p = 0.93) and overall survival (OS) (p = 0.84). On the multivariate analysis, a maximum tumor size >25 mm (p = 0.026) and inguinal lymph node involvement (p = 0.028) were factors increasing the risk of death. The risk of recurrence was related to tumor dimension >25 mm (p = 0.011), but not to inguinal node metastasis (p = 0.086).

Discussion. Inadequate surgical margin would be salvaged by adjuvant treatment.

Conclusions. A maximum tumor dimension >25 mm and metastases in the inguinal lymph nodes are independent prognostic factors for the survival of patients with vulvar cancer.

Key words: vulva, cancer, prognosis, recurrence

Introduction

Inguinal lymph node involvement is unquestionably a prognostic factor in vulvar cancer. It is believed that resection margins are also of great importance in the management of vulvar cancer. Subsequently, the main goal of surgical treatment is to achieve a wide margin (according to NCCN: 1–2 cm, ESGO – 8 mm) [1, 2]. Recently, some studies question the importance of a wide excision and show no correlation between margin width and recurrence [3, 4].

Follow-up is recommended in all patients for 4–5 years after treatment [1, 2]; conducting longer observations is difficult due to the advanced age of patients at diagnosis, limitations of healthcare, rare incidence and the dispersal of patients.

The main purpose of the study was to assess margin resections as a prognostic factor of vulvar cancer in long term follow-up. An additional aim was to identify clinicopathological and treatment related-factors (other than margin) influencing survival and affecting treatment failures in vulvar cancer patients in long term follow-up scenarios.

Material and methods

The retrospective analysis included 84 patients with vulvar cancer treated at Maria Sklodowska-Curie National Research

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Institute of Oncology between 2001 and 2007. Women with contraindications to surgical treatment due to advanced disease and severe comorbidities were not included. The stage of the disease was evaluated according to the 1994 FIGO classification, which was valid at the time. For this study, staging was reclassified to the 2009 FIGO. All patients were diagnosed with vulvar squamous cell carcinoma and underwent a radical vulvectomy with inguinal lymphadenectomy. 31 patients required adjuvant treatment according to the following criteria:

- resection margin ≤1 mm or positive,
- metastasis to ≥1 inguinal lymph node.

Ten patients did not undergo adjuvant therapy due to comorbidities and poor general condition (n = 3), lack of consent to radiotherapy (n = 2), abnormal wound healing (n = 2), skipping appointments (n = 1), the patient's death (n = 1), unknown reasons (n = 1). 21 patients were treated with radiotherapy (RT, n = 16) and radiochemotherapy (RCT, n = 5).

Adjuvant external beam radiation therapy (EBRT) with linear accelerator and energy of 4–15 MeV was applied to the vulva (n = 6), vulva and groins (n = 5), groins (n = 5) and pelvic region (n = 5). A total dose of 4800–6000 cGy was administered in 24–31 fractions. In 5 patients, concomitant cisplatin intravenously was administered intravenously with a dose of 40 mg/m^2, once a week. The duration of RT and RCT was 31–43 and 38–48 days, respectively. Adjuvant treatment started within 6 weeks of surgery.

Follow-up: gynecological examination, transvaginal and inguinal ultrasonography were conducted every 3–4 months for 2 years, then every 6 months for the next 3 years. A chest X-ray was carried out once a year. Computed tomography or magnetic resonance were performed in patients with suspicion of relapse. After 5 years, patients continued follow-up once a year in our outpatient clinic or outpatient clinic near their place of residence. Information was obtained by telephone for those patients who carried out a gynecological follow-up outside our center, Data on death were collected from the National Cancer Registry.

Recurrence: a biopsy of the suspicious lesion was performed to obtain a histopathological confirmation; the date of the positive biopsy was considered as the moment of relapse. Locoregional recurrence was defined as relapse in the vulva and/or groins. Distant metastases were not observed in the study group. Treatment of relapse disease was presented in table I.

Age, tumor grade, staging, maximum tumor dimension, depth of stromal invasion, status of inguinal lymph nodes, and the number of metastatic lymph nodes were considered as clinicopathological factors, while margin, number of resected lymph node and lymph node ratio were treatment-related factors.

Methods of statistical analysis

Efficacy of treatment was measured by the probability of survival – overall survival (OS), progression-free survival (PFS) and cumulative incidence function (CIF) of local relapses. Survival curves were calculated using the Kaplan-Meier method. Overall survival was estimated from the date of treatment initiation to death or the last information provided when the patient was alive. Progression-free survival was measured from the date of treatment initiation to its first failure: local relapse, distant metastases or death from other causes; in the absence of treatment failure, PFS was estimated to the last clinical observation. To evaluate the influence of selected factors such as age, grading, staging, tumor size, lymph node metastases, depth of invasion, margins, total number of lymph nodes removed, and the number of metastatic lymph nodes on OS and PFS, the Cox proportional hazard model was used. The influence of these factors on the risk of recurrence was analyzed using a multivariate model for competitive risks. The modeling process used a step-by-step elimination of variables by adopting standard thresholds: off (>0.1) and on (<0.05). The analysis was carried out using the IBM SPSS Statistics 23.0 statistical package and the Bob Gray package [6].

Ethics approval

All procedures were conducted according to the Declaration of Helsinki for Medical Research involving Human Subjects. Institutional ethics committee approval was not required – the research is an ex-post analysis of clinical experience. The clinical decisions concerning the treatment were not influenced by the purpose of this paper.

Table I. Treatment of recurrence of vulvar cancer depending on location

Treatment	Location of relapse		
	vulva (n = 23)	groin (n = 12)	vulva and groin (n = 2)
surgery	10	3	0
radiotherapy	3	3	0
chemotherapy	5	0	0
radiochemotherapy	2	1	0
brachyterapy	3	0	0
palliative	2	5	2

Table II. Clinicopathological characteristics of study group

Factor		n (%)
age (years)	<62	26 (31%)
	62–73	30 (35.7%)
	≥74	28 (33.3%)
lymphadenectomy	unilateral	10 (11.9%)
	bilateral	74 (88.1%)
median resected lymph nodes		11 (3–28)
FIGO 1994/2009	IA	1 (1.2%) / 1 (1.2%)
	IB	11 (13.1%) / 46 (54.8%)
	II	35 (41.7%) / 12 (14.3%)
	III	31 (36.9%) / 21 (25%)
	IV	6 (7.14%) / 4 (4.7%)
grading	1	29 (34.5%)
	2	37 (44%)
	3	12 (14.3%)
	unknown	6 (7.14%)
maximum tumor diameter (mm)	≤25	31 (36.9%)
	26–44	22 (26.2%)
	≥45	30 (35.7%)
	unknown	1 (1.2%)
multifocal lesion	no	79 (94%)
	yes	5 (6%)
depth of invasion (mm)	≤5	28 (33.33%)
	>5	40 (47.62%)
	unknown	16 (19.05%)
margin (mm)	positive	5 (5.95%)
	≤1	15 (17.86%)
	>1–5	30 (35.71%)
	>5	30 (35.71%)
	negative (not measured)	4 (4.76%)

Results

The clinicopathological characteristics of the study group (n = 84) was shown in table II. Patients' average age was 66 years (18–94). The median tumor size was 35 mm (5–90 mm). Microinvasion (depth of stromal invasion <1 mm) was found in 1 patient (1.2%). Median number of resected lymph nodes per groin was 6 (1–15). In 26 (30.95%) patients, metastases to the inguinal lymph nodes were found; 13 (17.86%) patients had involved >1 inguinal lymph node (2 metastatic LNs in 4 patients, 3 metastatic LNs in 3 patients, 5 metastatic LN in 3 patients, 8 metastatic LNs in 2 patients and 9 metastatic LNs in 1 patient).

Survival

The median overall survival (OS) and progression free survival (PFS) was 87 (95% CI: 60–114) and 60 (95% CI: 37–84) months, respectively. The overall 5- and 10-year survival rates were 62% (95% CI: 51–73%) and 39% (95%CI: 28–50%), while 5- and 10-year PFS were 51% (95% CI: 40–62%) and 32% (95% CI: 22–42%), respectively.

On the multivariate analysis, the resection margin was not related to PFS (HR = 1.033; 95% CI: 0.51–2.11; p = 0.93) and OS (HR = 0.84; 95%CI: 0.41–1.73; p = 0.84).

On the multivariate analysis, factors influencing survival were: maximum tumor size and inguinal lymph node status (fig. 1, tab. III). Other clinicopathological and treatment- related factors did not have a significant effect on survival.

Maximum tumor size was the only factor influencing PFS on multivariate analysis; nor inguinal lymph node involvement or other analyzed factors were not relevant to PFS (fig. 2, tab. III).

Failure patterns

The majority of relapses occurred within 2 years from the end of treatment and were localized on the vulva and groins. Cumulative incidence function (CIF) curves according to the site of relapse as competing risk had similar patterns for 2 years (fig. 3). At 15 years, CIF by site of relapse and non-cancer death as competing risk were: vulva 28% (95% CI: 18–38%), groin 17% (95% CI: 8.7–25%) and non-cancer death 27% (95% CI: 18–37%). Late recurrences (>5 years after the end of the treatment) affected the vulva.

Occurrence of locoregional relapse (vulva and/or groins) was significantly dependent on the maximum tumor size (p = 0.019). In the final model, the HR was 2.37 (95% CI: 1.15–4.89) for tumors >25 mm *vs.* ≤25 mm. The CIF curves are presented in figure 4. Other clinicopathological and treatment-related factors (including resection margin) did not have an influence on the risk of relapse.

Survival after recurrence

Groin recurrence influenced OS significantly (p < 0.007). The median survival after relapse in patients with groin recurrence vs vulva recurrence was 6.1 (95% CI: 2.7–9.5) *vs.* 16 (95% CI: 8.7–23.5) months, respectively.

Discussion

The principles of surgical treatment of vulvar cancer are inguinal lymph node assessment and wide margin excision. It was showed that margins ≥5 mm or ≥8 mm were significantly associated with risk of recurrence and survival [5–7]. In our study, the margin did not influence survival and recurrence. However, some patients with a close resection margin received adjuvant radiotherapy, which could affect the results. Similar results to ours were obtained in other studies [8–10]. Arvas et al. showed that a margin ≤2 mm may increase the risk of recurrence, but was not an independent predictive factor for PFS and OS [11]. Woelber et al. showed a similar rate of local recurrence in patients with a margin <8 mm *vs.* ≥8 mm (12.6% *vs.* 10.2% respectively) [12]. German recommendations accept a margin of 3 mm as sufficient [13]. Several authors claim that a positive margin is the only risk factor for recurrence; a complete resection with no lower limit (besides positive margin) should be recommended [14–16].

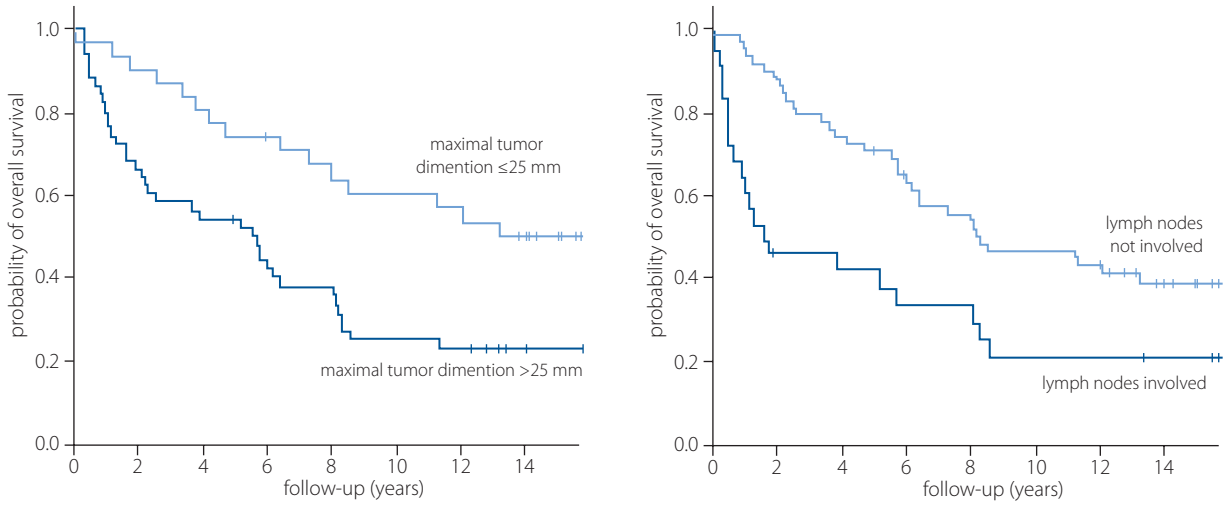

Figure 1. Overall survival by tumor dimension (p = 0.026) and status of inguinal lymph nodes (p = 0.028)

Table III. Multivariate analysis of clinicopathological factors affecting overall survival

Endpoint	Factor		HR	95% CI	p
overall survival	maximum tumor dimension	≤25 mm	1		
		>25 mm	2.038	1.091–3.808	0.026
	groin lymph nodes metastasis	no	1		
		yes	1.903	1.074–3.372	0.028
progression free survival	maximum tumor dimension	≤25 mm	1		
		>25 mm	2.208	1.203–4.055	0.011
	groin lymph node metastasis	no	1		
		yes	1.625	0.933–2.830	0.086

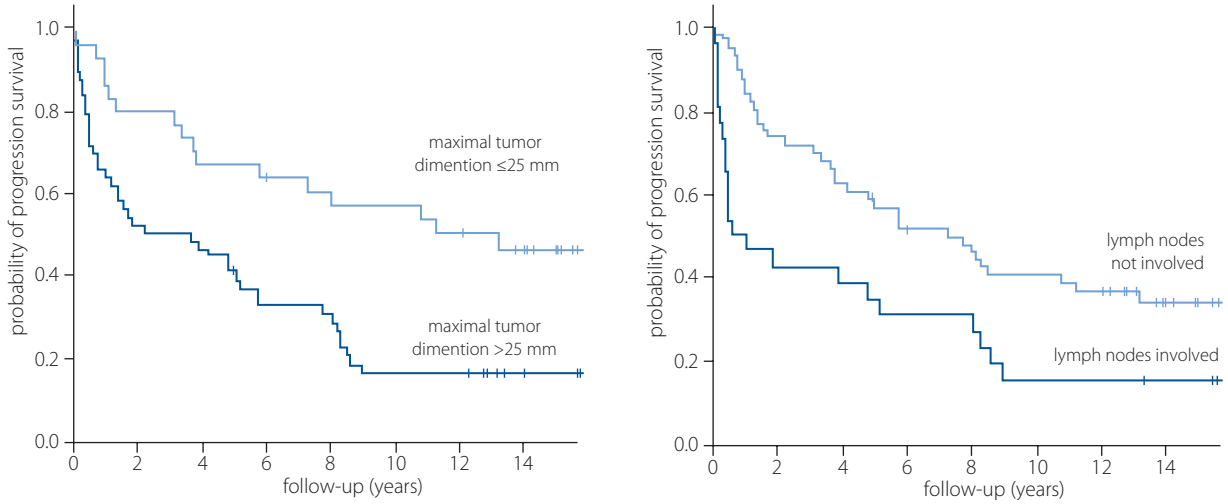

Figure 2. Progression free survival by maximum tumor size (p = 0.011) and status of inguinal lymph nodes (p = 0.086)

Long-term observation showed that a tumor size >25 mm and metastases to regional lymph nodes increased the risk of death in patients with vulvar cancer. Inguinal lymph node involvement has been directly related to shorter survival, while maximum tumor size negatively influenced survival by increasing the risk of recurrence. The results of other authors also indicate that the tumor size and the involvement of regional lymph nodes influence survival. Minar et al. showed that a tumor dimension >40 mm and metastases in inguinal lymph nodes are significantly associated with a risk of recurrence [17].

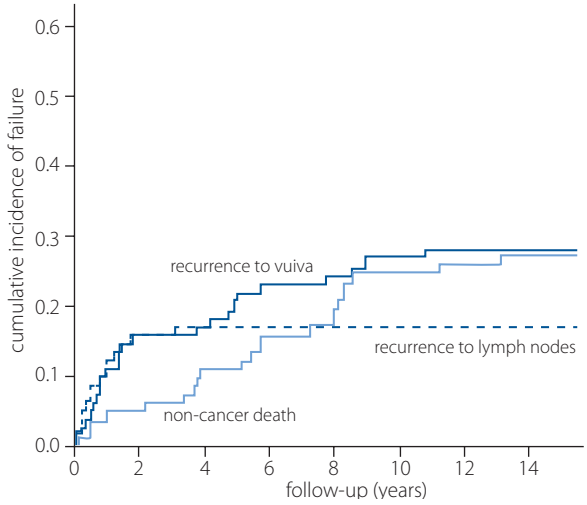

Figure 3. Cumulative incidence function (CIF) curves by site of recurrence and non-cancer death as competing risk

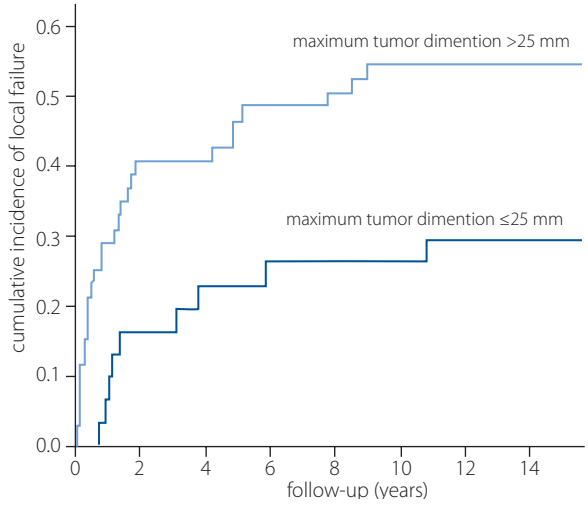

Figure 4. Cumulative incidence function (CIF) of locoregional relapse depending on the size of the tumor

Hay et al. found that tumors >4 cm increased disease-specific mortality 4-fold , but were not related to relapse [18]. Imoto et al., on multivariate analysis, showed that inguinal lymph node involvement influenced PFS, but not OS [5].

The extracapsular spread of lymph nodes was found to be an independent prognostic factor for recurrence (HR 13.54; 95% CI: 2.87–64.07; p = 0.01) and overall survival (HR 10.63; 95% CI: 1.65–68.57; p = 0.01) [19]. An increasing number of metastatic lymph nodes was associated with a risk of recurrence and death [20, 21]. In our study, there was no relationship between the number of metastatic lymph nodes and survival, probably due to the insufficient number of patients.

Our results, showing that tumor grade did not influence recurrence risk and survival, were consistent with other studies [8, 19, 21–24]. Although Nicoletto et al. on univariate analysis showed that grading was associated with PFS and OS (5-year survival 52% for grade 1; 24% for grade 2 *vs.* 0% for grade 3, p = 0.0021); these findings were not confirmed on multivariate analysis [25]. Mahner et al. and Polterauer et al. demonstrated that tumor grade is predictive for PFS, but not for OS [21, 26]. Multivariable analysis by Sznurkowski et al. revealed that grading was an independent prognostic factor [27].

The depth of stromal infiltration is crucial to confirm microinvasion (≤1 mm; FIGO IA). In these cases, verification of inguinal lymph nodes may be omitted due to the minimal risk of metastases. The depth of infiltration in invasive disease does not influence therapeutic decisions and its impact on survival is doubtful. We did not find a relationship between the depth of invasion and the risk of relapse in the primary site, PFS and OS length. Similar results were obtained by other authors [19, 21, 23, 27, 28]. Contrary to this, Nicoletto et al. demonstrated that stromal invasion >9 mm was an important prognostic factor for PFS (HR = 3.1; 95% CI: 1.3–7.7) (25). While in the VULCAN study, stromal invasion >5 mm appeared to significantly impact overall survival [29].

The results of our study indicate the need for long-term observation of vulvar cancer patients. Relapses of the disease can occur years after the end of the treatment (fig. 4). In our study group, all cases of late recurrence were located in the vulva. Many patients after the standard 5-year follow-up continue healthcare beside oncology unit/outpatient clinic. General practitioners or obstetricians/gynecologists as well as patients should be informed about the possibility of late relapse and its most frequent location.

The site of locoregional relapse influenced survival. Groin recurrence was associated with a much poorer prognosis than vulvar relapse. Moreover, almost all cases of inguinal relapse occurred within 2 years after the end of treatment (fig. 4). Similar observations were presented by Cormio et al., who showed that the median survival after groin recurrence was 9 months and the median time from primary surgery to groin relapse was 7 months [30].

Conclusions

The conclusions of the study are:

- a tumor size >25 mm and inguinal lymph node involvement are independent prognostic factors for survival in vulvar cancer patients,
- groin recurrence is associated with an unfavorable prognosis,
- vulvar cancer relapses may occur many years after treatment; at the time it is located on the vulva,
- an inadequate surgical margin would be salvaged by RT or RCT.

Conflict of interest: none declared

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Individually personalized radiotherapy *vs.* evidence (trials) based standards – paradigms and dilemmas

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This paper opens up to discussion whether some questions, points of view, and doubts counterbalance the belief and dogmas that randomized clinical trials (mainly in radiotherapy) should be considered as the only source of guidelines to design novel therapeutic standards in radiotherapy. A number of the physics, radiotherapy, clinical radiobiology and genetic and molecular tumor's characteristics suggest that radiotherapy protocols based on the "evidence based trials" seem to be antonymous to individually personalized therapy. The major goal of this paper is to consider and discuss whether individually personalized radiotherapy is already attainable and reliable or still remains the exception.

Key words: physical *vs.* biological doses, randomized trials, personalized radiotherapy, *caveat emptor*

Introduction

During the previous century, the use of ionizing radiation to treat malignant tumors has led to various assessments of the effectiveness of radiotherapy (RT): optimistic or rather critical? Fulfilled the aims and expectations? mainly successes or some disappointments? There is no single and simple unequivocal and convincing answer, but it raises some important doubts and uncertainties. Subsequently, such a situation presents a forum for discussion.

Physics!... physics?

The role of radiotherapy as an effective method of treatment for malignant tumors is unquestioned. Technological and methodological progress in this field since its beginning is highly impressive (fig. 1). Orthovoltage machines and cobalt "units" have been replaced by sophisticated linear accelerators emitting photon and/or electron beams with a wide range of energy. Neutron, proton, and recently, boron therapy are all being used. Instead of simple planning of the two-dimensional isodose distributions of the depth doses, the computerized 3D planning systems, e.g. 3, 4D-CRT, IMRT, IART, Vmat, respiratory gating and volumetric dose-volume-histograms (DVH) are being widely used in daily practice. The general "belief" in the system's individualized reliability and precision is increasingly common. Is it certainly unquestioned? Are the doses absorbed in the defined target volumes the same as those which were planned and reported in the treatment charts? Not necessarily! This has been clearly documented by the dosimetry *in vivo*. A relatively high rate of inconsistency has been noted between the absorbed and planned dose in the tumor's target. This fact is not a mere suggestion but proof that dosimetry *in vivo* should be an inherent attribute of quality control in radiotherapy (RT), but it is still uncommon.

Spatial dose distribution is rarely verified during fractionated RT, although tumor regression during RT results in changes in its topography and the surrounding normal tissues.

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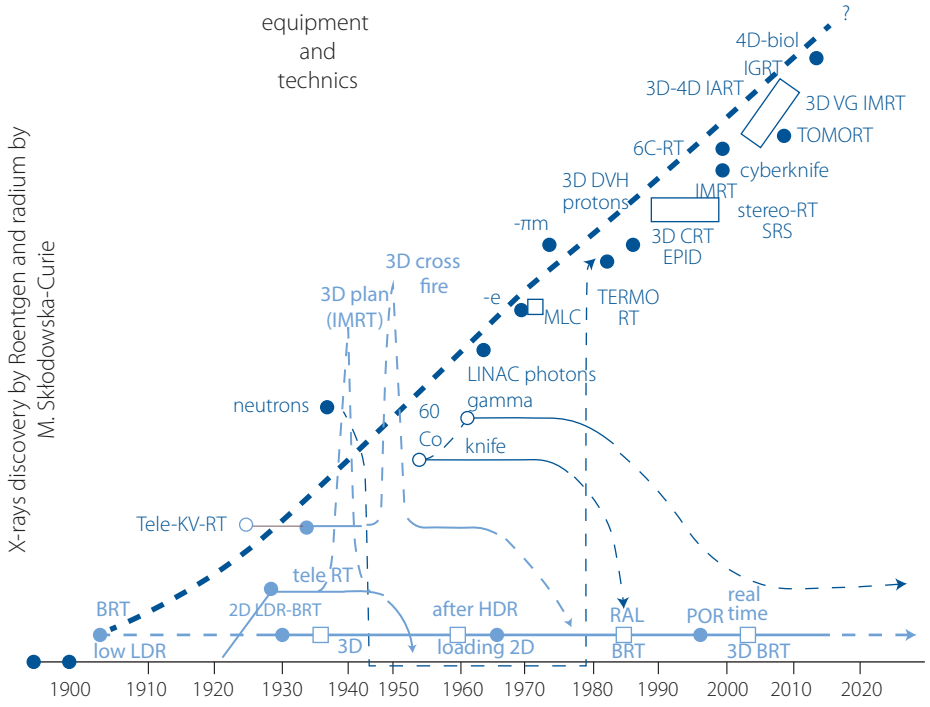

Figure 1. A key-points in the progress in radiotherapy equipment and techniques during 1900–2020

As a consequence, no one can be sure that the high dose gradient beyond the tumor's boundary remains unchanged during fractionated radiotherapy, and in fact, it does not (may be except bone or maxillary tumors). Tumor regression during RT usually changes the topography of both the tumor and the surrounding normal tissue. As a result, normal tissues are shifted into the region of the higher dose than that which had been preliminarily planned, and it likely may lead to an increased risk of late complications.

Radiotherapy 3D is called "conformal", which means that instead of geometrically regular radiation beams, individually shaped beams are adjusted to an irregular tumor's margins. This allows a heterogeneous dose distribution to be achieved; high within the tumor volume and with a large gradient in the surrounding normal tissue. The other side of this coin is that the risk of dose heterogeneity within the gross tumor volume (GTV) is often ignored. According to the International Commission on Radiation Units and Measurements (ICRU) recommendations, dose TD_{95} (95% isodose) is usually accepted as the GTV reference dose. Meanwhile, Fowler [1, 2] definitely pointed out that for 3D-RT dose D_{100} should only be used to cover homogeneously the whole GTV volume. An underdose ($TD < D_{100}$), delivered even to a small part of the tumor volume (the so-called "cold spot") almost always ruins preliminarly predicted local tumor control probability (TCP) – usually pretty high for early T and N0M0 tumors [3, 4]. Withers, Peters and Thames [5, 6] convincingly pointed out that in contrary to treatment planning and to tumor control expectations, the delivery of an extra dose (boost) in such cases can be ineffective, because it does not prevent the repair of the biological effects in the previous underdosed part of the tumor GTV.

In daily practice, the following two terms of "optimization" of RT planning are usually used by radiation oncologists – "dose escalation" (DE) and "dose intensity" (DI). The term "optimization" means that the planned dose fractionation and the technique of irradiation offer the highest effectiveness as possible (the highest probability of local tumor control [LTC]). Is this also true when only a single RT plan is evaluated? In fact, "optimization" is the choice of the best DVH among a few [3–4] RT plans, but such a procedure happens rarely.

The term dose escalation is often abused and improperly interpreted. This term belongs to physics, and it exclusively means an increase in the total dose, e.g. from 60 Gy to 70 Gy or to 80 Gy, and nothing else. However, it is generally assumed that dose escalation also leads to higher effectiveness of RT, which is not true. In conventional radiotherapy, an increase in the total dose (TD) is inseparably accompanied by an extension of the overall treatment time (OTT). Delivery of 60 Gy needs on average OTT of 42 days, 70 Gy – 49 days, 80 Gy – 56 days, but the treatment efficacy does not change a lot.

Meanwhile dose intensity is more clinically important, which is the number of Gy delivered per day (or per hour). For total doses mentioned earlier, the value of the DI is the same, and it equals 1.43 Gy/day. Therefore, it should not be surprising that their efficacy is also similar. For the majority of epithelial cancers (e.g. in the head and neck region), the respective part of the dose-tumor response curve flattens (effect plateau) when increasing the DE, resulting in no gain

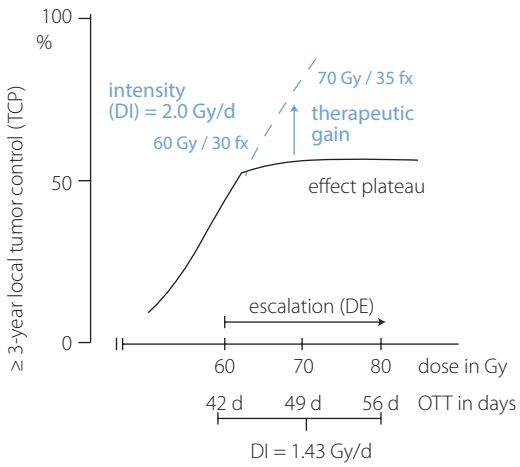

Figure 2. Radiotherapy effectiveness (tumor cure probability – TCP) depending on dose escalation (DE) compared with dose intensity (DI) [DE = TD + ΔD + ΔOTT; DI = TD/OTT]; TD – total dose; ΔD – dose increment; ΔOTT – overall treatment time extension

in the LTC (fig. 2). What can be expected is a higher risk of late complications (which does not depend on the OTT), as a result of the accumulation of the higher TD in normal tissue. On the contrary, the increase of the DI, e.g. from 1.43 Gy/day to 2.0 Gy/day or even 3.0 Gy/day (as a result of shortening the OTT) results in higher biological intensity (higher efficacy) of the delivered total dose in a shorter OTT. Therefore, it seems that DI should be considered as a more clinically useful radiobiological parameter than a physical one (DE).

Is radiobiology meaningful for radiotherapy – yes or not necessarily?

Has radiobiology had any impact on clinical radiotherapy or it is only a theoretical field of research? Empirical clinical experience gathered throughout decades has proven that radiobiology is the essential and unquestioned basis for radiotherapy. The skeptics consider radiobiology as an experimental science and research because it uses cell line colonies, or transplanted animal tumors, and it does not necessarily concern clinical radiotherapy. On the contrary, advocates try to argue that radiobiology has always been the basis for clinical RT, and all radiobiological mechanisms always somehow occur during fractionated RT, but they are not clearly manifested; they are hidden in the shadow of much more complex and heterogeneous mechanisms of radiation response of human tumors than those which appear in genetically and morphologically homogenous experimental cell lines or animal tumors.

All processes discovered and defined by experimental radiobiology always have clinical implications. The scope of this article will not permit us to discuss all of them in detail, and therefore we will concentrate only on two of them which have had a pronounced and undeniable impact on progress in clinical radiotherapy.

The first one is the "time factor". For a long time (over the course of the first 70 years of radiotherapy) there was a general belief that the natural growth of the majority of human tumors was generally slow, with volume doubling time taking about 50–60 days. During 6–7 week fractionated irradiation, tumors are unable to double their volume, and therefore the time factor had been considered as much less important, and usually ignored.

A few retrospective clinical studies [7, 9, 11] in the 1980s (not clinical trials) convincingly proved the key-role of treatment time as a major determinant of RT efficacy. It was clearly documented that with the extension of the OTT tumor cells which survived consecutive dose fractions begin to repopulate faster and faster; at the end of the sixth week of irradiation cell kill effect of more than a half of 2.0 Gy of the daily fraction is counterbalanced by altered repopulation of the survived cancer cells. Therefore, after a 2.5-day weekend (from Friday afternoon till Monday morning) 10 Gy of the previous weekly dose reduces the effective dose to only 7 Gy. Due to accelerated repopulation of cancer cells, the OTT extension by 1 day decreases the LTC probability by about 1.5–1.6% [1, 9]. It became obvious that during the RT, the natural tumor doubling time of 50–60 days rapidly decreases to only 4–5 days. The time factor is no longer being ignored but is recognized as a crucial factor to initiate clinical studies on various novel altered fractionation regimes with the shorter OTT.

The radiobiological "time phenomenon" concerns not only RT but also surgery and chemotherapy. If surgery is microscopically non-radical, then the doubling time of cancer cell microlesions beyond surgical margins accelerates to about 10–11 days, similarly as to what happens during the time intervals between subsequent chemotherapy cycles. The general belief that cancer treatment should begin directly after diagnosis, without any unnecessary delay has been commonly accepted as the most important prognosticator. However, on the contrary, Withers [11] decidedly argued that therapy can be delayed and can start even 60 days after diagnosis; the crucial point is that once therapy has begun, it should be completed in the shortest overall time period as possible. This conclusion should be considered as a key-paradigm of radiotherapy and combined treatment modalities as well.

The unquestioned importance of the time factor has led to many studies on various fractionation regimes with a shorter OTT than conventional. Finally, it has resulted in the revival of hypofractionated radiotherapy with high single (10–12 Gy) or a few large fraction doses (e.g. 5 x 9 Gy), called "stereotactic hypofractionated radiotherapy or radiosurgery (SHRS)". For these regimes, the DI increases from conventional 1.43 Gy/day to 9 Gy/day or even 12–20 Gy/day. This also allows for a shortening of the patient's hospitalization from weeks to days.

The second important contribution radiobiology has made to radiotherapy is to dispute TNM system credibility in radio-

therapy. The proper choice of dose and fractionation based on a given T or N quasi-quantitative ranks might be uncertain. There is no doubt that the sole aim of irradiation is to kill all cancer cells, which should lead to the irreversible elimination of two major attributes of malignant cells: immortality and repopulation.

Experimental tumor cell cultures *in vitro* or transplanted animal tumors endlessly guarantee these two attributes, due to colony forming and the ability to produce subsequent generations of descendants, but it (at least immortality) does not concern human tumors. They stay alive and grow by exploiting the host (patient) as a supplier of nutrients and oxygen which the tumor needs to survive. These processes last as long as the tumor sponges on the host, but it ultimately leads to host death, which automatically causes the tumor's death also. Tumor cell repopulation can be reduced by radiation and/or chemotherapy. The more aggressive therapy is the lower and lower chance for tumor cells to produce descendants until zero, which results in definitive tumor death, whereas the patient will survive and will be cured. To achieve such a goal, dose-time fractionation should be tailored to the initial number of tumor clonogenic cells. Assuming that D_{10} equals 7 Gy (D_{10} is the dose which reduces cell survival by one decade [e.g. from 10^{10} to 10^{9}]), then a tumor with 10^{10} clonogens needs 11 x 7 Gy (77 Gy) to reduce tumor cell survival to on average 10^{-1} (0.1 cell/tumor), which corresponds with the LTC of 90% (TCP = $e^{-0.1}$ = 0.9). The initial number of tumor cells can be easily estimated based on initial tumor volume (e.g. GTV), which can be simply counted from serial CT scans. Therefore, it seems logical that tumor (or neck node) volumetric staging is a proper criterion for tailoring the most effective fractionated radiotherapy, instead of the TNM rank system "what's that got to do with anything".

The initial number of tumor clonogens varies even within a given T category. For example, the initial number of tumor clonogens in the smallest and largest tumors within the T2N0M 0 category differs by at least one decade ($10^{9.5}$ *vs.* $10^{10.5}$). Therefore, it is logical that the largest tumor should receive a total dose higher by at least 7 Gy than the smallest one. Meanwhile, in daily practice using "evidence based" protocols, the planned total dose is usually the same for different tumor volumes within the same T category. While for the smallest tumors, 90% TCP can be predicted ($e^{-0.1}$), whereas for the largest, within the same T category, the TCP would decrease to 37% (e^{-1}). If the total dose is tailored based on the T category, it should not be surprising that an average overall TCP would not be higher than 60–70%, or even less. Therefore, the overall TCP will depend on the advantage of smaller or larger tumors in the study group (fig. 3).

The situation becomes even more complex when the study group includes patients with various T stage (from T2 to T4). As long as the RT protocols are designed based on the TNM rank system, therapeutic gain (TCP improvement) will remain

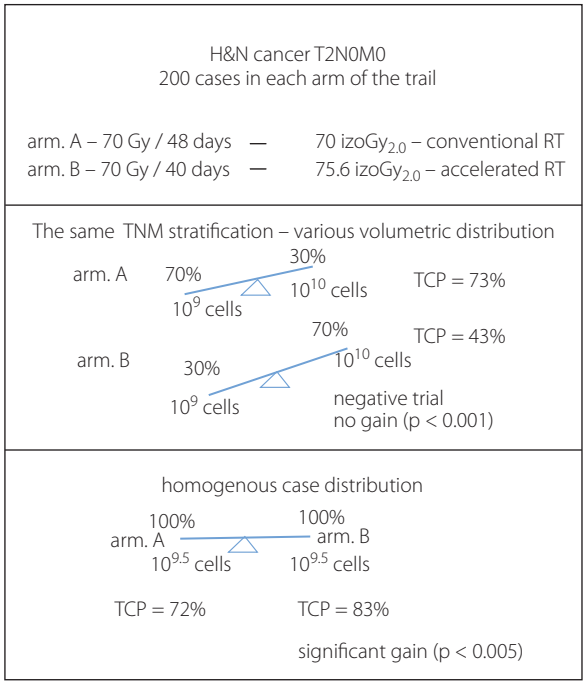

Figure 3. Theoretical example of a trial showing the effectiveness of the arm B > A (evidence based?) occurs untrue and proper statistical analysis shows lack of evidence

expectable but not necessarily achievable. It is difficult to understand why such an inaccurate system is still persistently used in practice, against all logic and the available genetic, molecular and imaging diagnostics. Unfortunately, in such situations, the more and more often used term "individually personalized radiotherapy" remains unjustified.

Evidence-based radiotherapy: belief or proven facts?

This is often forced out (belief rather than conviction) that the results of randomized clinical trials should be considered as the one and only reliable source of facts, which should be the basis to design novel, modified therapeutic protocols, recommended as obligatory standards.

It is often suggested that the novel "evidence based" strategies should replace empirical clinical experience and retrospective studies. Some authors believe that the results of evidence based studies should be taken for granted, if the statistical significance is below 0.05.

Bentzen [4, 17] and Glatstein [18] have convincingly questioned the logic and reliability of the "result-significance-certainty-belief" relationships and their impact on the results of the trials accepted as "evidence based". Meta-analyzes of numerous studies on altered radiotherapy and radiochemotherapy carried out for head and neck cancers [10, 12, 14] revealed an average overall therapeutic gain of only 6%. Should this be proof and evidence in favor of altered radiotherapy? If yes, immediately the next question arises: which schedule should then be recommended? At which tumor stage and localiza-

tion? The reliability and strength of such far from unequivocal clinical evidence seems uncertain and doubtful.

Why meta-analyzes included only 19 among the 50 trials still remains unexplained; in each arm of these trials there were a wide range of various tumor localizations and TNM stages recruited. Such huge clinical heterogeneity becomes even larger, when the TNM ranks are replaced by tumor volumetric staging. Moreover, it is surprising that the local control rates noted for the tested arm in some trials were almost the same as those for the control arm in other trials. Where is the proof of evidence in these trials, if their expected advantage and reliability generates so many uncertainties and doubts. The head and neck trials are not the only example [19].

Glatstein [18] firmly warned against so-called "tyranny of mediana", which is often used as a measure of treatment efficacy. The author pointed out that the 5-year actuarial results (e.g. survival or local tumor control), match in fact no more than 2.5 years of the real time of the follow-up for all patients (crude data). The statistics of the actuarial results can by itself be often misleading. The results of cases with even a short follow-up (even a few days) are not withdrawn but are censored. Therefore, only the initial part of the e.g. disease-free survival, should be considered as the most reliable. The shorter follow-up the lower the credibility of a middle or final part of the censored survival curves. This also concerns the median values of survival or curability estimated from those parts of the survival or local control curve. If, for example, the 5-year median value of disease-free survival after the tested therapy B would be significantly higher by 25% than that representing conventional therapy A (fig. 4), it would likely be recognized as evidence based proof that therapy B is significantly more effective than therapy A.

However, Bentzen [17] mentioned that high significance it is not necessarily unquestionable proof. Instead of the median value at the fifth year, careful analysis of a whole course of curve A reveals early incidence of failures (recurrences) during the first 12 months of the follow-up (fig. 4). It may likely suggest that tumor cell microlesions beyond the target volume had already existed but passed over the diagnosis (too small to be detected), and they were out of the irradiated volume. Therefore they should not be accounted for in the analysis, because they have not had any impact on the results of treatment A. If they are ignored then the remaining part of curve A will shift closer to curve B, showing in fact no difference in the efficacy of both therapies. Therefore, the practical value of such (false) preliminarily established evidence is zero.

The majority of cancer patients are treated beyond any trials [18], so, why evidence based results of carefully selected and randomized trials should be referred to a large number of patients who were not recruited to the trials. Bentzen [17] has warned that "the lack of significance does not necessarily mean the lack of evidence". Glatstein [18] has pointed out that careful and critical interpretation of the retrospective

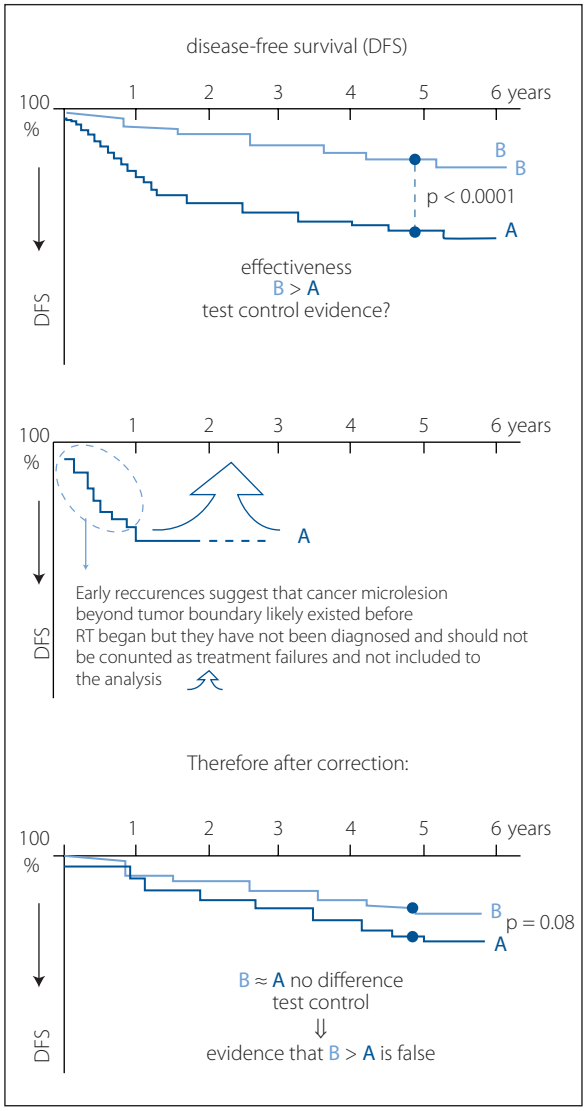

Figure 4. "TNM tyranny" in clinical trials – randomization and stratification without 2 (3) arms based on the TNM system but not on volumetric staging do not assure biological homogeneity and identical (or at least similar) tumor cell numbers and other molecular and clinical predictors. It shows that the results of such a trial may differ

results should not be ignored, and sometimes, empirical clinical experience and common sense are more important than acceptance of the trial's evidence without criticism (*caveat emptor*).

Belief that randomized trials are the only source of evidence to modify therapeutic modalities might be questioned because the methodical rules of the trials create the illusory conviction that two or three arms of the trial are biologically and clinically homogeneous. Theoretically, the trial could be considered as a source of reliable and unquestioned evidence based proof, if it includes cases with the same (or within a very narrow range) volumetric stage (not TNM) of primary tumor (GTV) and total nodal volume (TNM) of the regional nodes in each of the trial arms. Apart from that, the prognostic molecular profiles should also be the same, or at least similar for

all patients recruited to the trial. The accomplishment of the homogeneity of all biological and clinical factors in all arms of the trial is practically unattainable, but if it could be theoretically possible, patients recruitment will last many years. Such an idealized model is still unavailable.

The trials on altered fractionated radiotherapy for head and neck cancer enrolled patients with different tumor localizations and stages (T2N0–T3N3). The GTV volumes ranged from 0.4 cm^3 to more than 170 cm^3. Thus, homogeneity, even within these two parameters was none, and the average therapeutic gain of 6%, estimated in the meta-analyzes, does not seems reliable, but instead misleading. For example, the 5-year DFS gain of 5% in the CHART trial, after a 10-year follow-up decreased to 0%. This is one of the critical arguments against trials as carriers of the "only" evidence based guidance for radiotherapy practice. Evidence and proof of what?

Despite the fact that randomized trial results have been published in prestigious journals, their reliability and recommendations as "evidence based proof", unfortunately remains uncertain, and therefore they should be very carefully interpreted (*caveat emptor*).

Individually personalized radiotherapy or "evidence based" standard protocols?

Genetic or molecular profiles of malignant human tumors have been intensively gathered during the last 10–15 years. This has inclined radiation oncologists to utilized them in clinical practice to improve treatment efficacy (to increase LTC). Growing knowledge on individualized tumors' geno- and fenotypes – even within the same tumor type, stage and localization – leads to the expectation that the tailoring of individually personalized therapy will be able to replace conventional "stiffed" standard protocols. It looks like a belief that we are getting closer and closer to finding where the goalposts are, whereas the goalposts are always continuously moving. Therefore, an accomplishment of the skyline remains the illusion only.

It is already well substantiated that cancer cells have developed various molecular receptors on their surface and respective molecular inhibitors have already been produced. Cancer cells are however, "smart" enough and they develop a signaling network which transfer information from the cellular membrane receptors to the nucleus in order to survive. When one receptor is blocked by the respective inhibitor (e.g. EGFR), another signal pathway is automatically activated. Clinical studies have shown that the inactivation of a single cancer cell receptor is often not enough to cause cell death, and clinical expectations can be only partially effective.

A new concept has suggested using a few molecular inhibitors (monoclonal antibodies) instead of only one. In 2006, two inhibitors – EGFR (cetuximab) and VEGFR (PTK 787/ZK) – were used in the MD Cancer Institute in Houston to improve radiotherapy for glioblastoma multiforme. Unfortunately, no therapeutic gain occurred, but on the contrary, unacceptable high incidence of serious late complications often led to patients' death. Although glioblastoma cells are able to compensate for the block of the two signaling pathways by activation of other ways, it has been shown that the patient's tolerance is limited and it does not accept the use of more than one molecular inhibitor.

Supporters of "evidence based" therapy will likely be outraged that their beliefs on the trial's evidence is being undermined and they will use the argument that, after all, the 3D-IMRT, respiratory gating or stereotactic RT are in fact nothing more than individualized therapy. It is not easy to challenge such a point of view, except that the "individualization" of the 3D physical dose distribution within the irradiated volume often disappears when physical doses are converted into biological doses and individual tumor biology is accounted for. A tumor's molecular profile as a prerequisite for so-called individualized therapy is not very often used. For example, although higher radiosensitivity of HPV+ p16+ oropharyngeal cancer has been quite well documented, but the suggested dose-de-escalation in such cancer patients is rather supposed. If someone decides to de-escalate the dose, it should be at least restricted to low risk T1–2N0–1 patients. A similar situation concerns breast cancer patients. Although molecular and hormonal profiles are used to modify the standards of combined therapy, radiotherapy is unvaryingly tailored to the TNM stage of the disease, what undoubtedly is antonymous to the personalized therapy?

In many studies on the geno- and fenotype heterogeneity of various human malignant tumors, more and more attention is being focused on the reserve pool and the role of cancer stem cells (CSC). Their relative higher radioresistance and lower lethal effect have already been recognized [21, 22]. If the only one CSC would survive radiotherapy, it will become the source of permanent tumor regrowth, with the ability to produce genetically mutated metastatic cells. Therefore, the quantitation of the size and localization of the CSC-lesions within the tumor volume might likely be a key-predictor to optimize mono- or combined therapy. Although the identification of CSCs using monoclonal antibodies can be partly realized (at least for some tumors, e.g. glioblastoma, breast cancer), quantitation of the CSC population and its localization within the tumor is not yet possible. The genetic plasticity of the CSC makes this situation even more complex by the presence and role of hypoxic, apoptotic and angiogenetic cancer cells. Seemingly, the static tumor geno- and fenotype image established during diagnostics is unstable, but it is likely changing more or less during therapy. At the beginning of therapy, a tumor cell, e.g. type A, during subsequent mitotic cell cycles, genetically evolves into the cell genetically type B, C, etc., whereas the dose and fractionation planning is tailored for the initial profile of the cells A. Therefore, if radiotherapy is initially individualized based on the biological tumor eye-view, it should be repeated and corrected during

treatment, depending on the geno-fenotypic changes, but this would be highly expensive and time-consuming.

A malignant tumor is a family of cells with various functions and with multifaceted interactions which have revolted against physiological homeostatic mechanisms. Its individualism is binary (yes–no) but morphologically, molecularly and functionally unstable. Such a complex of characteristics and interactions cannot be quantified yet, even by very sophisticated computerized systems. This seems unlikely to quantitate some regulations among enormous number of variable abnormalities. If it would be possible, then and only then, could attributes of individually personalized therapy be fulfilled. Currently this term remains unlegitimately abused. Although perspectives may look promising, they can be paraphrased by the words of the British song "It's a long, long way to Tipperary". There are still many questions, controversies and uncertainties which still wait to be answered. The major message of this likely controversial article is that scientific and research progress in radiotherapy must be admired, widely recognized and continued, but the results and conclusions of many studies do not always settle an advantage of ones over the others. They should be considered with caution and criticism. We must keep in mind that common sense, logic and our own professional experience are often the most important.

Conflict of interest: none declared

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De-escalation of the systemic therapy in advanced colorectal cancer – justified clinical practice from the point of view of efficiency and safety

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Colorectal cancer is one of the most frequent malignant tumours in Poland, making up the third cause of cancer deaths both in women and in men with regards to the frequency of occurrence. The therapy of patients with high-stage colorectal cancer is palliative and should be conducted in a continual manner until the disease progression or unacceptable toxicity of treatment. By definition, palliative care aims at prolongation of the period to the exacerbation of the disease and of the overall survival with simultaneous guarantee of appropriate quality of life to the patients. A long-term use of a multidrug chemotherapy is often connected with the presence of clinically significant toxicity, therefore, de-escalation of systemic treatment is currently the subject of numerous analyses. The studies evaluating the effect of maintenance therapy on patient survival, prove that this kind of treatment makes up a valuable option in the case of patients in whom a good clinical effect is maintained with a concurrent reduction of toxicity of treatment. Especially in the context of the ongoing SARS-CoV-2 pandemic, monotherapy or less aggressive therapy should be discussed with patients.

Key words: advanced colorectal cancer, de-escalation therapy, cetuximab, panitumumab, bevacizumab

Introduction

Colorectal cancer is one of the most frequent tumours in Poland, making up the third cause of cancer deaths in women (7.6%) and in men (8%) with regards to the frequency of occurrence [1]. Thanks to the inclusion of new biological drugs to the classical chemotherapy in patients with metastatic colorectal cancer (mCRC) a significant improvement of the median overall survival (currently 24 months, whilst – after metastasectomy – up to 57 months) [2–5].

However, a large problem which still remains here, is the toxicity of treatment and its effect on the quality of life (QoL). Because the accessibility of chemotherapy infusions in Poland is relatively limited, a condition necessary for the safe therapy is therefore a few days' hospital stay, which is inconvenient for the patients and poses a great burden for the healthcare.

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Additionally, the SARS-CoV-2 pandemic contributed to the search for new solutions aimed at the limitation the contacts with the healthcare system staff to the necessary minimum. That is why, the de-escalation of the treatment of patients with mCRC – the therapy which, by definition, is long and is carried out until the disease progression or unacceptable toxicity – is the subject of debates and analyses.

This paper describes some selected aspects of the embryonal development of the large intestine, as they form the theoretical basis for the diversity of the observed treatment effects. Moreover, the authors present an overview of the research concerning the maintenance therapy and the binding Polish and European recommendations in this area (taking into consideration the recommendations concerning the treatment during the SARS-CoV-2 pandemic).

Embryological and anatomic foundations

Large intestine develops from endoderm. In the 4th week of embryonal life, the head-gut is closed with the oropharyngeal membrane, whilst its caudal part – with the cloacal membrane. As a result of the embryonic folding, the archenteron is divided into three parts: foregut, midgut and hindgut. The organs of the gastro-intestinal system, which are vascularised by the celiac artery, (oesophagus, stomach, duodenum, liver, pancreas, bile ducts) develop from foregut. The small and large intestine, as well as the caecum up till ⅔ length of the transverse colon, are developed from midgut (vascularised by the upper mesenteric artery and innervated by the parasympathetic vagal nerve). The remaining part of the large intestine (from ⅓ of the left transverse colon to the anal canal) develop from hindgut and are vascularised by the inferior mesenteric artery and innervated anatomically by the pelvic plexus (parasympathetic fibres are innervated from the intermediomedial nucleus of the spinal cord on the level of S2–S4) [6, 7].

These embryological differences translate into a diverse characteristics of the cancer developing on the right and on the left side of the large intestine. Right-sided tumours are characterised with slightly poorer prognosis; more frequently they affect women, elderly people or patients with HNPCC. These tumours also have a larger number of mutations in *BRAF, KRAS, PTEN, BRCA1* genes and are more sensitive to immunotherapy. The tumours located on the left side of the intestine, in turn, more frequently affect male patients, younger persons, people with familial adenomatous polyposis and with *APC, TP53, NRAS* mutations [8, 9].

The retrospective analyses of the clinical studies with the use of monoclonal antibodies manifested a different treatment effect depending on the tumour location. The CRYSTAL study revealed that the inclusion of cetuximab into the treatment is not beneficial with respect to progression-free survival (PFS) and overall survival (OS). In the case of left-sided location of the tumour, in turn, the addition of cetuximab to the therapy had a beneficial effect on the prolongation of PFS and OS. In the FIRE-3 study, in the patients with right-sided location, no increase of treatment efficiency was observed after adding cetuximab or bevacizumab to the FOLFIRI (5-fluorouracil + calcium folinate + irinotecan) chemotherapy scheme. However, in the case of the tumours located on the left side, the patients treated with cetuximab lived significantly longer (yet there were no differences with regards to PFS) [10].

Maintenance treatment / chemotherapy de-escalation

The treatment of patients with mCRC has a palliative character and usually does not provide for a possibility of permanent cure. Palliative therapy should prolong PFS and OS, allowing for an appropriate quality of life in the patients. Long-term use of multidrug therapy is often connected with the existence of significant toxicity and deteriorates the quality of life. The concept of the de-escalation of systemic treatment of mCRC was coined many years ago, even before the era of biological drugs. In 2006, the OPTIMOX1 study [11] proved that such way of treatment allowed to reduce toxicity, preserving the treatment efficacy at the same time. In order to reduce neurotoxicity caused by oxaliplatin, the stop-and-go strategy was used. The patients received the FOLFOX treatment regimen (oxaliplatin, 5-fluorouracil, calcium folinate). Group A received treatment continually till the disease progression, whilst group B received 6 cycles of full therapy and then only fluoropyrimidine with calcium folinate was administered in this group (12 cycles; de-escalation), and then the full FOLFOX regimen was resumed (next 6 cycles). In the group with the multidrug chemotherapy (FOLFOX) used in a continual way, PFS was slightly longer, whilst OS was not significantly affected (tab. I). Toxicity grade 3 or 4, as defined by of the National Cancer Institute Common Toxicity Criteria (NCICTC), was observed in 54.4% patients from group A and in 48.7% patients in group B. Moreover, in group A sensory neuropathy grade 3 was diagnosed in 17.9% patients, whilst in group B – in 13.3% ($p = 0.12$). This means that such treatment strategy allowed for the reduction of oxaliplatin neurotoxicity with concurrent maintenance of the therapy efficiency .

The OPTIMOX2 study [12] proved that temporary complete discontinuation of chemotherapy had an adverse effect on the treatment efficacy and that is why it should not be used. The results of treatment in two groups of patients were compared. In one group, after the administration of 6 cycles of the FOLFOX chemotherapy, the treatment was completely discontinued, and then – after the progression of the disease – the therapy was resumed according to the same regimen. In the second group of patients, the treatment was used in a continual way, yet after 6 cycles, de-escalation was used, restricting the number of the administered drugs to two (fluorouracil with calcium folinate), whilst the return to full, multidrug FOLFOX regimen was made only after the disease progression (analogically as in the B arm in the OPTIMOX1 study). The main endpoint of

Table I. A comparison of the most significant clinical studies with maintenance treatment with monoclonal antibodies

Study	Intervention	ITT	mPFS (months)	HR PFS (95% CI)	mOS (months)	HR OS (95% CI)
OPTIMOX1 [11]	FOLFOX4 continual treatment *vs.* 6 FOLFOX7 cycles ⟶ 12 5FUL/LV cycles ⟶ FOLFOX7	311 *vs.* 309	9 *vs.* 8,7	1.06 (0.89–1.2)	19.3 *vs.* 21.2	0.93 (0.72–1.11)
OPTIMOX2 [12]	6 FOLFOX7 ⟶ 5FU/LV cycles *vs.* 6 FOLFOX7 cycles ⟶ follow-up	98 *vs.* 104	8.6 *vs.* 6.6	0.61 no data	23.8 *vs.* 19.5	0.88
PRODIGE-9 [21]	12 FOLFIRI cycles + bevacizumab ⟶ bevacizumab *vs.* 12 FOLFIRI cycles + bevacizumab ⟶ follow-up	247 *vs.* 247	9.2 *vs.* 8.9	0.91 (0.76–1.09)	21.7 *vs.* 22	1.07 (0.88–1.29)
CAIRO3 [22]	6 CAPOX cycles + bevacizumab ⟶ capecitabine + bevacizumab *vs.* 6 CAPOX cycles ⟶ follow-up after PD (PFS1) CAPOX + bevacizumab until PD (PFS2)	279 *vs.* 279	11.7 *vs.* 8.5	0.67 (0.56–0.81)	25.9 *vs.* 22.4	0.89 (0.73–1.07)
VELVET [24]	1–6 i FOLFOX7 cycles + aflibercept ⟶ 5FU/LV/capecitabine + aflibercept	48	9.3 (8.3–12.5)	–	22.2 (18.2–24.7)	–
SAPPHIRE [25]	6 FOLFOX6 cycles + panitumumab ⟶ FOLFOX6 + panitumumab, continual treatment *vs.* 6 FOLFOX6 cycles + panitumumab ⟶ 5FU/LV + panitumumab	56 *vs.* 57	9.1 *vs.* 9.3	0.93 (0.60–1.43)	not reached	1.41 (0.69–2.88)*
VALENTINO [26]	8 FOLFOX4 cycles + panitumumab ⟶ 5FU/LV + panitumumab *vs.* 8 FOLFOX4 cycles + panitumumab ⟶ panitumumab	117 *vs.* 112	12 *vs.* 9.9	1.51 (1.11–2.07)	–	1.13 (0.71–1.81)
MACRO-2 [27]	FOLFOX6 + cetuximab ⟶ cetuximab *vs.* FOLFOX6 + cetuximab, continual treatment	129 *vs.* 64	9 *vs.* 10	1.19 (0.80–1.79)	23 *vs.* 27	1.24 (0.85–1.79)
COIN-B [28]	FOLFOX + cetuximab 12 weeks ⟶ Interval till PD *vs.* FOLFOX + cetuximab 12 weeks ⟶ cetuximab	64 *vs.* 66	3.1 *vs.* 5.8	–	16 *vs.* 17.5	–
MACBETH [29]	FOLFOXIRI + cetuximab ⟶ cetuximab *vs.* FOLFOXIRI + cetuximab ⟶ bewacizumab	59 *vs.* 57	13.3 *vs.* 10.8	0.73 (0.46–1.17)	37.5 *vs.* 37	0.98 (0.52–1.87)
Jiang et al. [30]	9–12 FOLFIRI cycles + cetuximab ⟶ follow-up *vs.* 9–12 FOLFIRI cycles + cetuximab ⟶ irinotecan + cetuximab (M1) *vs.* 9–12 FOLFIRI cycles + cetuximab ⟶ 6–12 irinotecan cycles + cetuximab ⟶ cetuximab (M2)	28 *vs.* 44 *vs.* 25	6.1 (M1) *vs.* 8.7 (M2)	–	–	–
NORDIC-7.5 [32]	8 FLOX cycles + cetuximab ⟶ cetuximab	152	8.0	–	23.2	–
Chan et al. [31]	2–12 FOLFOX / FOLFIRI cycles + cetuximab ⟶ cetuximab	15	6.8	–	17.0	–

CI – confidence interval; HR – hazard ratio; ITT – intention-to-treat; mOS – median overall survival; mPFS – median progression-free survival; FOLFOX: 5-fluorouracil + calcium folinate + oxaliplatin; 5FU/LV – 5-fluorouracil + calcium folinate; FOLFIRI – 5-fluorouracil + calcium folinate + irinotecan; CAPOX – capecitabine + oxaliplatin; FOLFOXIRI – 5-fluorouracil + oxaliplatin + oxaliplatin; Nordic FLOX – 5-fluorouracil (bolus) + calcium folinate + oxaliplatin; * – estimated value

the study was the duration of disease control (DDC). Median DDC was 13.1 months in the patients treated in a continual way and 9.2 months in the patients in whom the therapy was temporarily suspended (p = 0.46). Median PFS and median OS were longer in the group treated in a continual way (tab. I), whereas elective complete discontinuation of chemotherapy had a negative effect on the efficiency of treatment.

The results of metanalysis carried out by Berry et al. [13] clearly show that de-escalation does not deteriorate the treatment results only when the maintenance chemotherapy is continued and not when the systemic treatment is completely discontinued.

Biological therapy of high stage colorectal cancer

The first biological agent which was added to the ILF regimen (irinotecan, fluorouracil, calcium foliate) and which confirmed its efficacy in the third phase study was bevacizumab [14]. This drug is an IgG subclass humanised antibody, specific for vascular endothelial growth factor (VEGF). It manifests an antiangiogenic effect by means of inactivating all the VEGF isoforms and improves the penetration of cytostatic drugs into the tumour by means of decreasing the pressure inside it [15]proliferative processes. Numerous regulators of angiogenesis have been identified and characterized over the last decades. Among these, vascular endothelial growth factor (VEGF. In the group of patients in whom bevacizumab was added to their chemotherapy, OS was about 5 months longer in comparison to the group of patients treated with chemotherapy alone (20.3 *vs.* 15.6 months). Another antiangiogenic drug introduced to therapy was aflibercept. It binds with VEGFA and VEGFB, blocking their ability of connecting to the receptor. In the second line of treatment, in combination with the FOLFIRI chemotherapy, aflibercept contributed to the prolongation of the median PFS by about 2 months, whilst to the median OS – by 1 month [16].

A significant progress in the systemic treatment of mCRC was made together with the introduction of the antibodies directed against epidermal growth factor receptor (EGFR): panitumumab and cetuximab. Panitumumab is an IgG2 subclass human antibody, whilst cetuximab is a chimeric monoclonal antibody. These drugs manifest affinity to EGFR and prevent EGFR from binding ligands, by inhibiting the pathway of the EGFR/RAS/RAF/MEK signal transduction to the cell nucleus [17, 18]. The presence of mutation in the *KRAS* or *BRAF* gene results in permanent activation of this pathway, irrespectively of the EGFR activation. Mutations in the *KRAS* gene occur in about 30–40% colorectal cancer patients [19]. In these people, the drugs against EGFR are ineffective. The PRIME study [3] proved that adding the therapy directed against EGFR to the FOLFOX chemotherapy in the patients without mutation in *RAS* genes allowed to prolong their survival to more than 2 years (26 *vs.* 20.2 months in the group treated with chemotherapy alone). The study performed by Van Cutsem et al. [20] confirmed that the FOLFIRI chemotherapy combined with cetuximab used in the first line of treatment is more efficacious in comparison with chemotherapy alone.

Maintenance therapy with bevacizumab

In the third phase study, PRODIGE-9 [21]phase III, randomized controlled trial, we compared the tumor control duration (TCD in patients untreated earlier for mCRC, induction chemotherapy with FOLFIRI regimen was used in combination with bevacizumab, and then the patients with response to the treatment were assigned to the arm with maintenance therapy with bevacizumab (5 mg/kg every 2 weeks) or to the group with follow-up alone. At the moment of progression, the patients received 8 cycles of FOLFIRI + bevacizumab, and then they continued maintenance treatment or follow-up in accordance with earlier randomisation. Such a sequence of treatment was continued till the moment of disease progression during chemotherapy. The primary endpoint in this study was DDC. Median DDC was in both arms of the study was 15 months, and no significant differences between PFS and OS were found (tab. I).

The CAIRO3 study [22] phase 3, randomised controlled trial, we recruited patients in 64 hospitals in the Netherlands. We included patients older than 18 years with previously untreated metastatic colorectal cancer, with stable disease or better after induction treatment with six 3-weekly cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B evaluated the efficiency of maintenance therapy with capecitabine with bevacizumab (*vs.* follow-up) after the administration of 6 CAPOX chemotherapy cycles (capecitabine, oxaliplatin). At the moment of disease progression (PFS1), the patients received CAPOX treatment again, combined with z bevacizumab until the next progression (PFS2 – primary endpoint). In the arm which used only the maintenance therapy, the PFS2 prolongation was observed with good treatment tolerance (tab. I). Solely the hand-foot syndrome (HFS) was more frequent in the group using the maintenance therapy. This allowed the authors of the study to conclude that the maintenance therapy with capecitabine with bevacizumab is effective and does not have a negative effect on the patients' quality of life.

The metanalysis performed by Ma et al. [23] confirmed that in maintenance therapy bevacizumab is effective in combination with chemotherapy.

Maintenance therapy with aflibercept

The data concerning maintenance therapy with aflibercept is very limited. In one arm, second phase VELVET prospective study [24], the patients, previously untreated for mCRC received FOLFOX with aflibercept (1–6 cycles), and then maintenance therapy with fluoropyrimidine with aflibercept (4 mg/kg every 2 weeks) until the disease progression or the occurrence of toxicity. At the moment of progression, therapy with oxaliplatin was resumed. The primary endpoint was PFS

after 6 months. After this period, 67.4% patients (n = 33) did not experience the disease progression, whilst median PFS was 9.3 months (95% CI: 8.3–12.5), also 23% patients developed G3/G4 arterial hypertension.

Maintenance therapy with panitumumab

In order to evaluate the efficacy and possibilities of de-escalation of chemotherapy in combination with panitumumab, the second phase study – SAPPHIRE [25] was conducted. Initially, all the patients received 6 cycles of chemotherapy with FOLFOX regimen in combination with panitumumab, and then, in one group (arm A) the full treatment regimen was continued, whilst in the other group (arm B), the therapy was de-escalated (to fluorouracil with calcium folinate in combination with panitumumab). Maintenance therapy was connected with a similar efficiency after 6 treatment cycles in comparison with the full FOLFOX regimen with panitumumab (PFS 9.1 *vs.* 9.3 months). Temporary suspension of oxaliplatin treatment allowed for the decrease of the frequency of clinically significant neurotoxicity (≥G2; in arm A and arm B: 57.4% *vs.* 9.3% respectively).

In the second-phase study, VALENTINO [26], the efficacy of the use panitumumab in monotherapy as maintenance treatment was evaluated. Initially all the patients received 8 cycles of the FOLFOX chemotherapy in combination with panitumumab. In the next stage, the therapy was de-escalated. One group of patients received fluorouracil with calcium folinate in combination with panitumumab, whilst the other – panitumumab in monotherapy. The rate of 10-month survival and median PFS treated with panitumumab fluorouracil and calcium folinate were significantly higher in comparison with panitumumab in monotherapy (with slight increase of toxicity).

The results of the above studies justify the use of maintenance therapy with the use of panitumumab in combination with fluorouracil and calcium folinate – also as an efficient form of treatment de-escalation.

Maintenance therapy with cetuximab

The MACRO-2 study evaluated the efficiency and safety of the treatment according to the FOLFOX regimen with the use of cetuximab followed by cetuximab in monotherapy every week (arm A) in comparison with the continual treatment with FOLFOX chemotherapy in combination with cetuximab (arm B). The patients, on average, received 1–8 cycles of induction treatment. After 9 months of follow-up, the non-inferiority of the compared regimens was evaluated with respect to the time to progression ($p < 0.1$) and no differences were observed in median PFS, median OS and in objective response rate (ORR) – tab. I. Serious adverse events (SAEs) were reported in 20% patients (n = 25) in arm A and in 25% (n = 17) in arm B [27]. The results of the study confirmed the same value of the continual treatment in comparison with maintenance therapy.

In the COIN-B study, the patients who had already received FOLFOX chemotherapy with cetuximab for 12 weeks were randomly divided into a group in which the treatment was completely suspended and the group in which maintenance therapy with cetuximab was continued (1 x week). At the moment of progression, the treatment with FOLFOX regimen with cetuximab or with FOLFOX chemotherapy only was reintroduced for 12 weeks and then it was discontinued again (or cetuximab alone was used). The primary endpoint of the study was failure-free survival (FFS). Median FFS was 12.2 months (95% CI: 8.8–15.6) in the group with discontinued treatment in comparison with 14.3 months (95% CI: 10.7–20.4) in the group with continual treatment. Median OS and median PFS in the intention-to-treat (ITT) group are presented in table I. Some adverse effects were similar in both groups. According to the authors of the study, maintenance therapy with cetuximab guaranteed a better treatment effect than interrupted treatment, in spite of the lack of statistical significance [28].

Cremolini at al. [29] in turn, conducted a retrospective second phase study with randomisation (MACBETH) which evaluated the effect of maintenance treatment with cetuximab (arm A) or bevacizumab (arm B) after an induction chemotherapy (up to 8 cycles) with FOLFOXIRI regimen (fluorouracil, calcium folinate, oxaliplatin, irinotecan) + cetuximab. The study did not reach the predicted endpoint which was the improvement of the 10-month period to the disease progression from 50% to >70%. Median OS and median PFS were comparable in both arms of the study (tab. I). Also the adverse effects were comparable, with the exception for the skin toxicity, which was more frequently observed in arm A (20% *vs.* 3%, $p = 0.03$). Although the endpoint was not reached, the authors concluded that an intensive induction treatment followed by maintenance therapy with a biological drug was effective.

In a retrospective analysis carried out by Jiang et al. [30], the patients received the FOLFIRI chemotherapy + cetuximab and were either assigned to the control group or continued maintenance treatment with cetuximab with irinotecan (M1 – the first group with maintenance therapy). After 6–12 cycles of maintenance therapy, the patients with treatment response (n = 21) were assigned to the second group (M2) with maintenance therapy with cetuximab in monotherapy continued till the disease progression, death or unacceptable toxicity. The primary endpoint was the failure-free survival (FFS) period which was 12.7 months (95% CI: 6–19.4) in M1 group in comparison with 3 months (95% CI: 2.6–3.4) in the control group. Median PFS is presented in table I. The authors of the study observed that maintenance therapy with cetuximab prolongs FFS and is well tolerated by the patients.

The results of one arm studies with maintenance therapy with cetuximab are summarised in table [31, 32]. The subject literature describes a few clinical cases which confirm the efficiency of monotherapy with cetuximab following a previous induction chemotherapy [33, 34].

Polish and foreign recommendations

The national diagnostic and therapeutic guidelines concerning the treatment of the patients with colorectal cancer, published in 2020, emphasise that treatment de-escalation may be considered, although its value has not been confirmed by prospective randomised studies. In particular, this strategy must be taken into consideration in the case of toxicity (oxaliplatin-induced polyneuropathy). Monotherapy with biological agents may shorten the time to disease progression, so it should not be applied as a standard treatment after a few cycles of chemotherapy, but only when there are grounds for it (permanent control of the disease confirmed in imaging diagnostics, accompanied by increasing side effects of cytostatic drugs or the patient's exhaustion with the intensity of treatment) [35].

According to the recommendations of the European Society for Medical Oncology (ESMO,) in the patients with mCRC treatment should not be discontinued. Active maintenance therapy with fluoropyrimidine and a biological agent should remain a standard. The limited data concerning the treatment with anti-EGFR antibodies in monotherapy do not permit for definite conclusions here. Each decision about the de-escalation of treatment should be discussed with the patient [36, 37].

Maintenance therapy during the SARS-CoV-2 pandemic

General recommendations concerning the patients treated palliatively in the period of COVID-19 pandemic stipulate that the treatment should be continued. However, in order to guarantee the patient safety, it is advised to modify the treatment regimens (e.g. the use of oral or metronomic therapies or de-escalation).

The published standpoint of the experts of the Polish Society of Clinical Oncology concerning the treatment of patients with palliative therapy during the SARS-CoV-2 pandemic, provides for the possibility of discontinuance of chemotherapy in the persons in whose case:

- a good disease control is maintained,
- the intervals between treatment have been maximally prolonged, or
- intravenous infusions have been given up and replaced with the oral treatment with capecitabin.

In the patients treated within the drug programmes of the Ministry of Health, the experts recommend the use of chemotherapy with a biological agent in 4-week intervals. However, the experts emphasise that monotherapy with an anti-EGRF or anti-VEGF agent is less effective than its combination with cytostatic drugs.

Moreover, all the patients with a period of G3 neutropenia during the therapy, should, according to the CTCAE, receive prophylactic treatment with granulocyte colony-stimulating factor (G-CSF). This recommendation applies also to the patients receiving chemotherapy connected with the risk of developing neutropenic fever (10–20%) [38, 39]. In patients with mCRC this risk varies between 3 and 14% for the chemotherapy with FOLFIRI regimen and 0–8% for the FOLFOX regimen respectively [40].

The recommendations of the ESMO experts are consistent with the recommendations of the national experts. They propose prophylactic use of G-CSF in the treatment schemes connected with the risk of developing neutropenic fever and maintenance therapy with capecitabine instead of long-hour fluorouracil infusions. Moreover, the treatment should be conducted on an outpatient basis [41, 42].

Conclusions

The studies which evaluate the effect of maintenance treatment on the effectiveness of therapy measured with OS and PFS show that this strategy works in the mCRC patients who have a persistent good clinical effect with concurrent reduction of clinically significant adverse effects. This allows for a good quality of life in the patients, accompanied with treatment efficacy. It must be stressed, however, that a complete interruption in the therapy (and, in case of progression, its resumption) worsens the results and is not justified. The treatment should be carried out till the moment of disease progression or unacceptable toxicity. However, the study results quoted here, allow to recommend the de-escalation of the therapy and maintaining the anti-EGFR/anti-VEGF treatment with fluoropyrimidine. In selected patients with unacceptable marrow toxicity, monotherapy with a targeted anti-EGFR agent could be applied. Antiangiogenic agents should be used in connection with fluoropyrimidine. The currently binding drug programme provides for the possibility of interrupting chemotherapy (in the case of persistent response to the first-line treatment confirmed in two consecutive imaging examinations) and the use of biological agent alone (in the case of bevacizumab, monotherapy is possible only in the second line of treatment) or the continuation of chemotherapy with fluoropyrimidine in combination with a biological drug, on condition of a systematic evaluation of the treatment response. In the case of disease progression, the patients may receive the treatment which they have had so far (provided that they still meet the qualification criteria) [43]. On account of the ongoing pandemic, de-escalation is justified in the light of the Polish and international recommendations. Each time, however, such treatment should be considered individually with an active participation of the patient in the decision making process.

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Pictures in oncology

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Late melanoma metastasis to the urinary bladder mimicking bladder primary tumor

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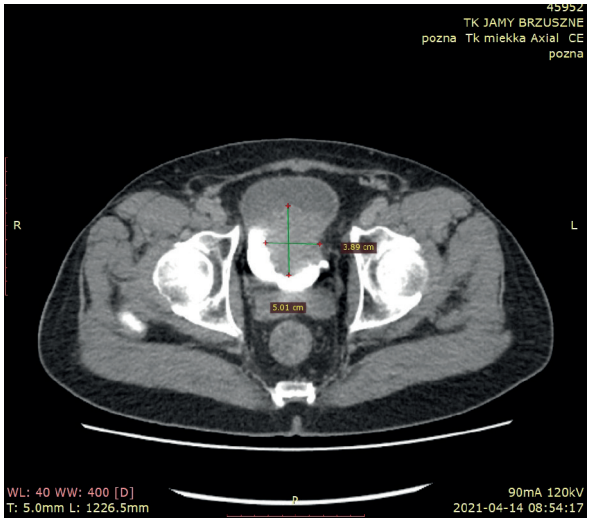

Figure 1. A CT scan of an extensively infiltrating 5 cm mass in the urinary bladder

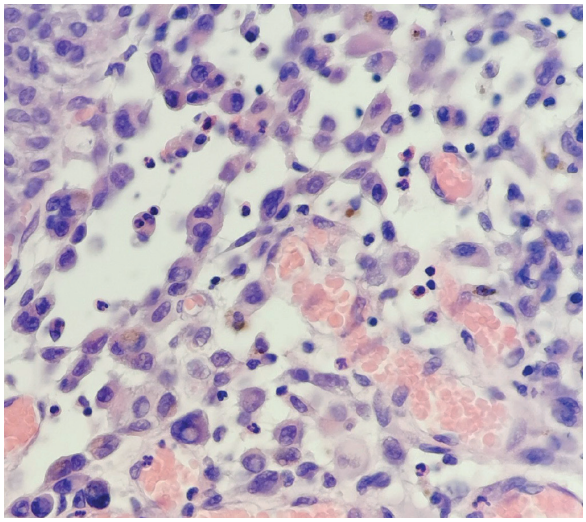

Figure 2. Microsopic image of melanoma submucosal infiltration in urinary bladder wall (HE 20x, courtesy of Dariusz Pabis MD)

A 60-year-old patient was diagnosed by CT with an extensively infiltrating 5 cm mass in the urinary bladder, in search of primary focus due to multiple brain metastases.

No known risk factors for urinary bladder carcinoma were present, however, in 2011 the patient underwent treatment for melanoma (Breslow 1.9 mm mitotic index 5/mm^2, SNB positive 2/3, completion axillary lymph node dissection 0/18, no adjuvant treatment).

The patient was referred for a transurethral bladder resection. On the left bladder wall a large mass was seen, partially ulcerated, with concomitant minor similar changes on the posterior wall and fundus. On histology a metastatic melanoma was diagnosed, with positive BRAF status. The patient was referred to brain irradiation for an unresectable brain foci and immunotherapy [1]. The urinary bladder is rare location for secondary seeds (up to 2–3% of all bladder malignancies), and melanoma is extremely seldom among them (5% of all bladder secondary malignancies) [2]. An upfront correct diagnosis is difficult from a clinical perspective (melanoma is a "great mimicker" of other diseases, like a primary bladder tumor in this case). Detailed history taking (including remote in-time medical details) and understating melanoma's ability to produce late-onset systematic recurrence might improve diagnostic specificity.

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Reviewers just don't care anymore

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Fraud in medical publications is a constantly growing concern. Throughout the world the majority of teaching hospitals and university departments of medicine require their physicians to constantly publish new, preferably meaningful publications. It is generally preferred that those publications be of high impact, as measured by journals' impact factors. However, publications in lower profile journals are also welcome since both parties gain something: academics want to prove their importance and create opportunities for academic promotion and institutions need to show their publication activity. Nevertheless, as medical professionals become more and more overwhelmed with clinical and administrative duties, it is becoming difficult simply to find time for real academic work. Unfortunately, one of the solutions to this problem is academic fraud in all its variants. And as the number of papers and journals grows exponentially, so does the number of fraudulent publications.

Medical publication fraud can be of a relatively innocent nature, such as "salami slicing" (multiple publications of small fragments of a what could easily be a single larger publication) and self-plagiarism (using parts of one's own work in another publication) both of which, while ethically questionable, do not necessarily mean plagiarism as defined by copyright law [1].

Much more serious from a legal and ethical point of view are cases of direct plagiarism (copying the work of other authors and attributing authorship to another individual) and using falsified or completely made-up data. In the vast majority of such serious academic sins the fraud is not evident at first glance. The paper as received by the editor seems genuine. All parts are written more or less coherently, the research method is described, there are results and there is a conclusion. It is then up to the reviewers to find whether the paper is a genuine academic work or a fraud. As far as plagiarism is concerned, it is easy to commit but also quite easy to detect. A simple copy-and-paste manoeuvre still used by some "authors" can be detected by simply running parts of the text in the search engine Google. More advanced plagiarism can be detected by specialist software used by the majority of universities and editors throughout the world [2]. Once plagiarism is detected, it is up to the scientific and academic community to proceed with legal action against the culprit. This, however, even in cases of evident and blatant plagiarism, can prove difficult, especially when the parties involved have an established academic rank [3].

The letter by Teixeira da Silva is an alarming sign of the decline in the quality of data that is accepted for publication [4]. As stated above, fraud in a medical publication is not always evident. However, it doesn't take a highly educated editor-in-chief of a medical journal to know that a biological female does not have a prostate gland and thus the incidence of prostate cancer in women is 0%. This is a fact you need to know to pass your first year of medical college. And yet a publication stating a prostate cancer incidence rate of 52% in the group of female patients analysed got accepted and published in a journal with quite a decent impact factor of 3.0 [5]. Not surprisingly, the paper was later retracted, but still the main questions remain: how was it possible that it passed the review process? Why didn't the editor realise what kind of "science" would make it to the pages of his journal? Do we as

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scientists and institutions really need those publication points so badly? Has corporate greed made its way into academic publishing? The latter question makes a lot of sense when it comes to open access journals – which is the case in the papers described by Teixeira. All of these questions (or to be more specific – the answers to these questions) should really sadden the academic community and the general public. If medical science is infected with fraud than inevitably the art of medicine will slowly decline. And this will affect all of us.

A recent analysis of publications on perioperative care proved that this is happening already. Over the last 30 years 375 papers (sic!) in the area of anaesthesia and critical care alone have been retracted because of their fraudulent nature [6]. Given that medical professionals read the latest papers in order to remain at the forefront of clinical practice, but don't necessarily read the notice of retraction, this can have a negative impact on the quality of care they provide.

I would really like to finish this editorial with a conclusion that gives us hope that the quality of science will be better in the future. Unfortunately, it is not an easy task to find premises for such a conclusion on the basis of the facts discussed above and one's daily observations. Reviewers are supposed to be guardians of quality in medical publications. But how is one to write a quality review when you don't have time for your own work and don't get any recognition for it? Once again, the answer is frequently a simple one: copy and paste. When a senior reviewer is committing self-plagiarism using the ctrl-c/ctrl-v technique while reviewing a doctoral dissertation at one of the best technical universities in Poland [3] we know we are in trouble. The same happens when we don't use the instruments we have because we don't want to. It is all too common to hear laudations of the great academic achievements of a person who over a quarter of a century has only published a load of case reports. Or read an evaluation of someone's scientific achievements that says he is a "promising scientist in the world's premiere league", who at the same time has a Hirsch index rating of just 2. Can't those reviewers use PubMed? Don't they understand what HI means? Don't they know that their professional and evidence-based review is the foundation of achieving or maintaining quality in science? I'm sure they do. For some reason they decide not to care. Well, we can sense where this attitude will lead us: soon we will be seriously analysing the prostate cancer risk of people without a prostate.

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Prostate cancer in women – a rare medical event or a new disease of peer-reviewed science publications?

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Reliability of research and publications are the pillars of modern science. Unfortunately, its ethos is more often built not on the quality of research results but on the number of publications and citations, which are the essential criteria for evaluating scientific achievements. The citation rate of published articles also influences the rankings and prestige of scientific journals, indexed based on the Journal Impact Factor (JIF). JIF and the reviewing process should effectively ensure the quality and originality of publications. Unfortunately, sometimes they do not guarantee it.

The obligation to comply with publication and citation requirements increases the temptation to build scientific output with the help of legally and ethically questionable solutions, among which plagiarism has been making a "career" for many years. However, the list of manifestations of unreliability in research and publications and scientific fraud is getting longer. It is especially influenced by easy access to resources available via electronic open access databases and the growing demand for scientific publications in high-scoring journals.

Teixeira da Silva's article *Paper mill-derived cancer research: the improbability of prostate cancer in women, and ovarian and breast cancer in men* published in a recent issue of *Nowotwory. Journal of Oncology* exposes the dark side of the institutionalized mechanism of custom-made fictitious research results (so-called paper-mills) and the imperfection of the system of reviewing medical texts. The author describes a glaring example of a publication from a journal indexed in Web of Science and PubMed (the European Review for Medical and Pharmacological Sciences, IPF 3.024 in 2019), which presented, among other things, high statistics of prostate cancer in women. Moreover, this is not an exception [1]. Da Silva calls this phenomenon as an urgent-to-treat "academic cancer", and this diagnosis – unfortunately – is highly accurate.

In contrast to other forms of abuse committed by researchers (e.g. plagiarism, theft of research results, multiplication of scientific output), the publicized phenomenon has a new dimension. The problem also concerns reviewers and indexed medical journals.

From the legal point of view, it isn't clear how to assess the incompatibility of such an action with the binding regulations. However, one can determine fraud without specialized medical knowledge, which consists of disseminating fictitious results contrary to basic anatomical knowledge. He will also recognize the severe misconduct of reviewers who allowed the publication of compromising texts. However, how to classify and punish this type of pathology is not easy to answer.

The least problematic is to judge the behavior of authors who publish fabricated or falsified research results. According to the current Code of Ethics of Research Workers, such scientific activity is unequivocally a gross violation of the basic principles of doing science [2]. Ordering data, using universal publication templates with data from a specific research area, and lacking published results verification violate the basic ethical principles underlying science's integrity and credibility. Such activity does not meet the requirement of publishing the results of one's research and the researcher's responsibility

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for the social consequences of the formulated conclusions. On the other hand, one cannot speak of a violation of copyright or personal rights. The results themselves (especially those generated automatically) are not subject to protection. An infringement can be considered only in attributing someone else's authorship and not in the case of misrepresentation of one's authorship [3]. However, an author aware of personal and social responsibility, who decides to put his name to an unreliable study, should expect public evaluation and scientific ostracism [4]. Activities of the scientific community (e.g., *Retraction Watch* or *PubPeer* platforms), which identify and stigmatize scientific dishonesty, can be effective way of combating it.

Unfortunately, it is more difficult to find formal grounds to question the legality of entities that offer custom-made, paid templates with results, figures or images. As long as they do not reproduce protected content from other publications, they do not infringe the law. This is not an optimistic conclusion, especially as tools that use artificial intelligence to help create fictional scientific results are increasingly available.

The publication of texts such as the title 'prostate cancer in women' is also a problem that undermines the credibility of medical journals, which, after all, enjoy particular prestige and trust compared to other scientific journals. This includes both the new online pseudo-scientific journals, which use lowered publication standards and gaps in accepting submitted texts for review and publication. The substantive review of a scientific article should certainly not be bogus, as peer review measures a journal's quality. Publishers should be held accountable for quality, but they cannot always effectively adjudicate scientific ethics and integrity violations. Instead, in case of doubts about the integrity of submitted or published work, they can initiate appropriate procedures, e.g. following the guidelines of the International Committee for Medical Journal Editors (ICMJE). Recommended by guidelines the Committee on Publication Ethics (COPE) [5] provides instructions for dealing with suspected fabricated data contained in an article submitted for publication or reported manipulation of figures and images [6].

To increase the efficiency of verifying submitted papers and detecting fraud, journal editors can use specialized IT tools (e.g., the tested *CrossCheck*), employ data integrity analysts [7], and emphasize an effective reviewing system. Undoubtedly, so-called blind reviews cannot be truly blind in the sense that an article qualifies as a publication by blindly approval. It is not the task of reviewers to check whether an article contains accurate information and reliable results [8]. However, the positively reviewed content must not raise obvious suspicions regarding basic medical knowledge and scientific principles. In this sense, the allegations of unreliable review (or rather, lack of it) should be signaled in evident cases – such as those exposed by da Silva.

Although the problem of pathology in the scientific community is not new, da Silva's article is a serious signal that the medical publication ecosystem should be sealed, even if fictitious scientific texts represent a negligible percentage of all publications. When growing public health threats and increasing marginalization of science, a loss of trust in published research can have serious scientific and social consequences.

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Pregnancy-associated breast cancer as a screening and diagnostic challenge

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Pregnancy-associated cancer (diagnosed during pregnancy or up to a year after), also known as gestational cancer, is a rare situation with an estimated incidence of 1 case in every 1000 pregnancies and accounting for approximately 0.1% of all malignant tumors.

The most common type of pregnancy-associated cancer is breast cancer, which comprises 50% of all cancers during pregnancy. There is also cervical cancer, malignant melanoma, lymphomas (Hodgkin's and non-Hodgkin's) and leukemias, ovarian cancer, and colorectal cancer diagnosed [1]. These histological types of malignancies are also among the most frequent cancer sites in non-pregnant women at younger ages.

It is estimated that 1 in 3,000 to 10,000 pregnant women will develop breast cancer. The number of women diagnosed with cancer while pregnant is expected to increase because more women are delaying childbirth into their thirties; the risk of developing most cancers increases with age. The age of pregnant women with breast cancer ranges from 32 to 38 years (median 34 years). The risk of breast cancer varies throughout a woman's life. In patients with a genetic predisposition, it is higher in the reproductive period; *BRCA1* mutations are associated with a 3.8% annual risk between the ages of 25 and 40 [2, 3]. There is a lack of solid literature-based evidence pertaining to high-risk cancer screening in pregnant and lactating women, although this issue becomes increasingly clinically relevant because women are delaying childbearing [3]. The authors of the literature review indicate that the opinions of experts dominate among the reports on this issue, which explains the lack of standardized guidelines for high-risk breast cancer screening in this population [3]. Physical breast examination screenings during pregnancy and breastfeeding is strongly recommended, while mammography (MMG), magnetic resonance imaging (MRI) and ultrasound imaging (USG) is not considered appropriate for screening in this population [3].

Diagnosing and treating pregnant women is particularly difficult because it affects both the pregnant woman and the fetus. No randomized, controlled trials for this issue are available and most of the data guiding diagnosis and treatment come from case reports, small case series, or retrospective cohort analysis [10].

Pregnancy-associated breast cancer (PABC) is usually diagnosed at a more advanced stage than in the non-pregnant population. A growing mass in the breast can be treated as a physiological response of glandular tissue to hormonal changes related to pregnancy like increased glandularity and density of the breast tissue. Diagnostics in pregnant women is delayed by 2–7 months after the first symptoms appear. Delay in the diagnosis of PABC remains an important concern regarding the impact on prognosis because it affects the increase in the number of patients with metastases to the regional lymph nodes [4]. Most patients present with a lump detected through breast self-examination [5]. A gynecologist should perform a physical examination of the breast on every

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pregnant woman. A new palpable mass that does not resolve within 2 weeks should be investigated further, although it is reported that approximately 80% of such breast biopsies are benign [6, 7, 10]. The risk of development of a milk-fistula after such a biopsy is low.

USG is the preferred imaging modality because it does not carry a risk for fetal radiation exposure. It is very useful in distinguishing cystic and solid tumors, and sensitive (93–100% sensitivity) methods in pregnant and lactating women and for detecting axillary metastases [8]. Ultrasound examination should include both breasts (not only suspected) and regional lymph nodes [4]. In approximately 90% of women, USG imaging confirms clinical suspicion of breast cancer.

MMG with abdominal shielding can be performed with minimal risk to the fetus (radiation exposure is estimated ad 0.4 cGy) [9]. But reported sensitivity of MMG for detecting breast cancers in a pregnant breast is low, with ranges from 63% to 78% [10]. Due to increased water content in the pregnant breast and loss of contrasting fat, the interpretation of mammography is difficult [10]. Therefore, this imaging method is not recommended during pregnancy [10].

There are no obvious contraindications to the use of MRI even in the first trimester of pregnancy, but MRI of both the breasts and other regions of the body in pregnant women is not routinely recommended and there is currently no consensus on this matter. In special cases (e.g., suspected central nervous system metastases) it can be ordered. The experience with MRI from the second trimester of pregnancy, including the administration of gadolinium, indicates the risk of toxic effects on the fetus because gadolinium can cross the placenta [11]. Nevertheless, the use of gadolinium-based and iodinated contrast agents during pregnancy and lactation has not been well studied in human subjects [12].

All staging investigations that are likely to cause any risk to the fetus should be undertaken only if the benefits outweigh the risks [13]. A chest radiography (X-ray) with adequate shielding is considered safe in pregnant women and should be performed when necessary [4]. Positron emission computed tomography (PET-CT), computed tomography (CT), and pelvic radiography involves more radiation than MRI, and hence are not the preferred imaging modalities [13]. Bone scans, although rarely used, result in only 0.00194 Gy of radiation exposure to the fetus [13].

Considering the young age of patients with breast cancer during pregnancy, proper genetic counseling should be offered [14].

In any case where breast cancer is suspected, a histopathological diagnosis should be performed. A USG guided core-needle biopsy is recommended and in the case of suspicious lymph nodes, a fine needle biopsy should be performed. The histopathological examination confirms diagnosis and assesses the prognostic and predictive factors: expression of estrogen receptors (ER) and progesterone receptors (PgR), expression of the human epidermal growth factor receptor 2 (HER2), Ki-67. It is important to inform the pathologist that the biopsy is being performed on a pregnant woman [4].

Doctors should be mindful of the possibility of breast cancer in pregnant women, present oncological vigilance, and, in the case of abnormalities, conduct immediate diagnostics. There are reports highlighting the importance of proper breast oncology surveillance during pregnancy [15]. The management of pregnant women with diagnosed breast cancer requires an experienced and multidisciplinary medical team working closely with each other. The team must assess the benefits of the ongoing oncological treatment and the risks associated with the therapy for the fetus. The prognosis of pregnant women with proper treatment is comparable to that of women with the disease at the same stage of disease, but not pregnant. This fact should be clearly stated to the patient during the first consultation. Delivery should be performed on time and iatrogenic prematurity should be avoided [16].

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RECIST criteria and clinical practice

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The objective of response evaluation criteria in solid tumours is to assess the reaction of cancer lesions to the applied treatment. Categorisation of the response to oncological treatment was proposed for the first time by the WHO in 1981 [1], however, over the subsequent two decades, no detailed or generally accepted guidelines were actually established. It was only in the mid-1990s that work on the standardisation of treatment response criteria began, and, in 2000, the first version of RECIST criteria was published [2]. The criteria were soon accepted by international regulatory agencies, such as the FDA or EMA. In 2009 the criteria were updated, making up RECIST 1.1 [3]; this version, with only some modifications connected with the introduction of immunotherapy [4], has defined the standards of objective evaluation of treatment response in oncology until today. In 2014 *Nowotwory. Journal of Oncology* published a paper introducing the RECIST 1.1 evaluation criteria to Polish readers [5].

The core issue that all oncologists must remember is the fact that RECIST criteria cannot assess whether patients will objectively benefit from treatment; instead it can verify if there was an objective reduction of the cancer stage in the cases of these patients. Thus, RECIST criteria, though very useful for the evaluation and comparison of new medication and treatment strategies with the standard ones, should not be the only decision criterion in oncological practice. What is more, in some cases such a means of treatment could turn out to be adverse for patients.

One can imagine a situation in which a patient with a massive and symptomatic cancer dissemination into the visceral organs, receives systemic treatment which allows for a clear imagining and clinical response within all the metastatic lesions. However, after a few months of disease control in the visceral organs, two new metastases appear in the bone system. In accordance with RECIST criteria, this means disease progression. Does it mean, though, that in a patient with a very good and permanent clinical response (symptom resolution, improvement of organ efficiency), effective systemic treatment must be discontinued because of two new asymptomatic lesions appearing? The answer is – no. Systemic treatment must be maintained as it comprehensively controls the disease whilst the introduction of local treatment must be taken into consideration, e.g. stereotactic radiotherapy which can get rid of asymptomatic progression in the bones. Such situations are quite frequent in clinical practice. This confirms only that the possibility of response evaluation according to RECIST criteria does not exempt oncologists from thinking and treating the patient's wellbeing, and not the size or number of cancer lesions, as the priority.

Drug programmes which we have at our disposal were created on the basis of clinical trial protocols so as to maximise the probability of reaching therapeutic effect compliant with the results of registration studies for a specific therapy. This is why many patients who do not meet the strictly defined inclusion criteria may not have access to new treatment methods. At the same time, following the study protocols is necessary for the reimbursement of extremely costly specific therapies. Qualification and treatment within the drug programmes requires

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a good knowledge and interpretation of these provisions. This is to ensure that the chances of inclusion into the programmes of the patients who meet the detailed requirements of the payer can be increased.

The Polish Society of Clinical Oncology, in collaboration with marketing authorisation holders, carried out a number of courses and online conferences concerning drug programmes, regularly answering questions from doctors about the methods of interpretation of specific provisions in the regulations. The objective is to increase the chances of oncological patients in Poland getting access to the most novel strategies of systemic treatment which may potentially improve their prognoses. Thanks to this process, doubts concerning qualifications to the drug programmes without the changes measurable according to RECIST 1.1 criteria were finally resolved. At the same time, it was explained that the lesions which can be assessed are all the lesions (both target and non-target) visible in the imaging diagnostics which can be monitored both with regards to their size and also their number and morphology.

To sum up, it must be emphasised that RECIST criteria are of key importance first of all in clinical studies and, in some respect, also in the monitoring of patients treated within the drug programmes. In clinical practice in turn, they make up an additional source of information about the activity of various oncological therapies. They should not, however, exempt oncologists from clinical diligence and from ensuring the patient's wellbeing is the central point of the decision-making process. Such an attitude is necessary for obtaining the best possible effect of the systemic oncological treatment applied – irrespective of whether it is carried out within the drug programmes or the therapy available in the catalogue.

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Pancreatoduodenectomy due to cancer in the older population

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By 2030, 70% of all pancreatic cancer will be diagnosed in the older population. However, pancreas operations are a complex surgical procedure with a high rate of morbidity and mortality. Therefore, the benefits of surgical resection in older patients are controversial and decisions about treatment for this group must be well balanced. Chronological age alone should not be a contraindication for multimodal radical treatment in older patients. Fit patients, according to the comprehensive geriatric assessment (SGA), should be qualified for the same treatment as younger patients to benefit the same outcomes. However, they should be operated on in high-volume hospitals by experienced surgeons. Prefrail patients should undergo prehabilitation, during neoadjuvant treatment also, and then reevaluated. Frail patients should be discussed in an oncogeriatric meeting. We still do not have evidence-based data to design a tailored approach for them so as to balanced good oncologic outcomes and the appropriate postoperative quality of life.

Key words: older patients, pancreatic cancer, pancreatoduodenectomy, elderly

Pancreatic ductal adenocarcinoma (PC) is common in the older population, with incidence increasing with age, reaching the highest peak after 60 years of age. It is estimated that by 2030, approximately 70% of PC will be diagnosed in this group [1]. It also has one of the worst prognoses of all malignancies. At present, 5-year relative survival is 8% [2] and improvements seen for most cancers over the last 20 years, is unfortunately not the case for PC and progress remains very slow. Surgical resection is the only curative treatment option; it is possible in only 15–20% of patients. Even among those who undergo surgery, 5-year survival is just 20–25% due to local or metastatic relapse during the first two years after resection. Thus, PC has the potential to become the second leading cause of cancer-related death before 2030 [3].

Resection of the pancreas (pancreaticoduodenectomy, partial or total pancreatectomy) is a complex surgical procedure with a high rate of morbidity and mortality. Compared with younger patients, many older patients may not be good candidates for surgery, and they are less likely to receive other treatments. Therefore, the benefits of surgical resection for PC in older patients remain controversial and the decision about this treatment in older patients must be well balanced. Moreover, the most important problem in the treatment of older patients with PC is the underrepresentation of this population in clinical trials. This results in treatment decisions taken for older patients that are extrapolated from studies performed on younger patients. Although the situation is improving constantly, most of the studies still use chronological age, the Karnofsky scale or the Eastern Cooperative Oncology Group/ World Health Organization scale and not biological age [4].

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Clinical and pathological characteristics of PC in older patients

Very little data is available regarding PC in the older population. Kamisawa et al. compared the pathologic features of it in older and younger patients and found no differences in location, stage, grade and local spread, although older patients seem to develop fewer hematogenous metastases. Older patients may present more diploid tumours or more p53 mutations, which are associated with a poorer prognosis [5].

Preoperative assessment and treatment decisions

As was mentioned in our previous publications, the population of older patients is very heterogeneous in terms of co-morbidity, physical reserve, cognitive function and social support. Chronological age alone is a poor predictor of cancer treatment outcomes and toxicities [6]. Current routine pre--operative assessment cannot adequately identify patients at risk. Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with morbidity and early mortality. Therefore, the Comprehensive Geriatric Assessment (CGA) was introduced to help determine the primary status of the older patient, to diagnose frailty syndrome and to identify how to optimise the patient's condition before the start of treatment [7–10].

Frailty syndrome (a surrogate of biological age), is defined as a multisystem reduction in reserve capacity leading to shorter life expectancy, higher risk of complications after surgery/chemotherapy, higher risk of hospital readmission and institutionalisation. Considering their limited remaining lifetime and their postoperative quality of life, the CGA is as valuable as the need to cure or remove their cancers. Therefore, the International Society of Geriatric Oncology (SIOG) and The European Society for Medical Oncology (ESMO) recommends the use of the CGA to determine the biological age before the beginning of treatment. Rostoft et al. analysed the literature regarding the role of the CGA in predicting the outcome in hepatobiliary and pancreatic surgery among older patients with cancer; they concluded that although scarcely investigated, frailty and elements from the CGA are significantly associated with negative short- and long-term treatment outcomes in older patients with HBP [11].

In general, based on the CGA, we can differentiate three groups of older patients:

1. **Fit:** patients without any deficits in the CGA domains. In this group, standard oncologic treatment can be offered and postoperative outcomes are comparable to younger patients.
2. **Pre-frail:** patients with one or two deficits in the CGA domains. In these patients prehabilitation should be recommended to improved resilience to surgical stress by, at least, augmenting functional capacity and nutritional status before surgery.
3. **Frail patients:** patients with three or more impaired domains in the CGA. A tailored approach should be discussed in a geriatric multidisciplinary team meeting [9].

It is also possible to determine the severity of the frailty using the cumulative deficit model for the CGA [10]. Such assessments may guide treatment decisions through evaluations of the balance of benefits and risk-factors associated with performing or omitting specific oncologic interventions.

To operate or to not operate?

There have been only a few studies that compare the prognosis of patients with resectable pancreatic cancer between the surgery and no surgery group. He et al. showed that the first group had a significantly higher 5-year OS rate (25.0 *vs.* 2.3%; $p < 0.0001$) and a higher median survival time (24.3 *vs.* 5.8 months) [12]. Similarly, in the study by Park HM et al., surgical resection resulted in better prognosis than the non--surgical approach. Only for patients with a high Charlson comorbidity index was this approach not beneficial [13]. In turn, Marmor et al. reported that for the overall cohort, the median survival rate was significantly longer for patients treated with pancreatectomy as compared with chemotherapy (15 months *vs.* 10 months). However, for patients 80 years of age and older, the absolute survival benefit was only 3 months (13 months *vs.* 10 months). Similarly, for patients who underwent pancreatectomy and had positive lymph nodes, the median survival benefit was only 3 months compared to chemotherapy (13 months *vs.* 10 months) [14]. None of the studies investigated any elements of the CGA.

To conclude, fit and pre-frail patients based on the CGA, should be operated on (the latter group after prehabilitation) with no regard for the chronological age. We do not have good data to draw a conclusion about what would be most beneficial for frail patients in the long-term follow-up. In severe frailty, the best support treatment seems the best option.

It surgery safe for older patients?

The most up-dated systematic review and metanalysis on pancreatoduodenectomy in older patients was performed by Ten E. et al. in 2019. The study included 12 retrospective studies with 4860 patients. There were 919 patients in the older group and 3941 patients in the younger group. The authors concluded that pancreatic surgery had become a safe procedure for older patients in high-volume hospitals when operated on by an experienced surgeon [15].

The general postoperative mortality rate decreased from 30% in the 1980s to 1% at the present time. However, the complication rate remains high at 40–70%. A similar situation is reported in older patients, it does not matter what kind of age cut-off was used to define "elderly". In comparison to the younger population, some authors report higher postoperative morbidity and mortality, a higher requirement for an intensive care unit stay, increased length of hospital

stay and higher rates of hospital readmission after pancreatectomy [16–20]. There are also studies reporting lack of significant differences between these groups. The reason for the significant differences was the volume of the hospital; <50 *vs.* >50 pancreatoduodenectomies per year. Across high volume centres, there was no significant difference in the rate of overall and major complications between patients ≥80 years old and <80 years. Higher volume centres also had significantly lower in-hospital mortality and failure to rescue rates (in some centres even 0%!) when compared to lower volume centres. Thus, the increased mortality in older patients was attributed to worse preoperative selection and higher failure to rescue rates in patients in the older group. The three most common causes of failure to rescue were: postoperative pneumonia, cardiovascular accidents and postoperative bleeding [21]. Therefore, early recognition and timely management of complications are crucial as regards decreasing mortality in older patients.

Specific surgical complications, such as postoperative pancreatic fistula, delayed gastric emptying, postpancreatectomy hemorrhaging and intraabdominal abscess were comparable between the older and younger group [22]. Barabas et al. concluded their study with an observation that older patients who can successfully complete the course of neoadjuvant therapy and tolerate its associated morbidity probably had adequate physiological reserve to withstand the surgery [23].

When it comes to the overall survival of older patients after pancreatic resection, it was shorter than younger patients. Finlayson observed the 5-year survival of patients following surgery for PC and demonstrated a decrease from 16.4% in patients aged 65–69 years to 15.6% in patients aged 70–79 years and 11.3% in patients aged 80 years or older. However, this difference did not achieve statistical significance. Moreover, patients with more than two comorbidities had a 5-year-survival rate of 10% compared with 14% in patients with fewer than two comorbidities; the difference was insignificant [24]. This was mainly because older patients did not receive standard treatment for pancreatic cancer. Older patients were less likely to receive a pancreatectomy with concomitant venous resection, achieve negative margins after surgical resection and receive adjuvant chemotherapy treatment. Moreover, older patients might have been excluded, or might have refused standard "aggressive" therapies, which in turn may have affected their long-term survival outcomes [25].

The limitations of the systematic review were retrospective design of the studies, patients with unresectable tumors or those who declined or have been declined surgical treatment leading to potential selection and information bias. Furthermore, the statistical power of this study was not high.

To conclude, pancreatic resection due to cancer can be performed safely in older patients with acceptable risk in high-volume centres where operations were performed by experienced surgeons. Chronological age alone should not be the only determinant for the selection of patients for surgical treatment. In fit and pre-frail patients, aggressive surgery is recommended to achieve clear surgical margins. However, these data have to be confirmed in large prospective studies with the consideration of non-operative treatment, particularly, when biological age is taken into consideration.

Minimal invasive surgery in pancreatic cancer

In 2021, Zhu et al. performed a systematic review and metanalysis of seven retrospective studies involving 2727 patients. Three of them compared a minimal invasive pancreaticoduodenectomy (MIP) and an open pancreaticoduodenectomy (OPD) in older patients, two compared MIP between older and young patients and two included both outcomes. Compared to those with OPD, older patients who underwent minimal invasive surgery had a lower 90-day mortality (OR 0.56; 95% CI: 0.32–0.97; $p = 0.04$) and less delayed gastric emptying (OR 0.54; 95% CI: 0.33–0.88; $p = 0.01$). On the other hand, no significant difference was observed in terms of 30-day mortality, major morbidity, postoperative pancreatic fistula (grade B/C), postoperative hemorrhaging, reoperations, 30-day readmissions and operative time. There was no significant difference in operative time between MIP and OPD after the learning curve in case of early cancer stage [26]. However, we have to be aware that most of the studies included in the metanalysis had significant selection bias regarding who was a candidate for minimal invasive surgery; excluding those patients with larger tumours, vascular involvement and prior surgery. Most of the studies were underpowered. Long-term outcomes, such as overall survival and disease-free survival, were not systematically reported [27, 28].

To conclude, this meta-analysis demonstrates that MIPD is a safe and feasible procedure for select older patients if performed by experienced surgeons from high-volume pancreatic surgery centres. Older patients can benefit from the advantages of minimal invasive surgery in the case of uneventful postoperative course [29].

Quality of life after PD

All studies showed a deterioration in patient-reported outcomes and functions after a pancreatoduodenectomy. They were at their worst level after 6 weeks after the resection. Most of the symptoms abated after 3 months and function after 6 months when adjuvant chemotherapy was not introduced. Quality of life has been shown to recover 12 months from potentially curative surgery [30]. In turn, body weight, triceps skin-fold thickness and serum albumin levels recovered in the following 3–6 months [31, 32]. In 33–55% of all studied patients with PC, depression was observed; this was significantly higher than in patients with other malignancies [33]. Diouf et al. identified fatigue, appetite loss and functioning as the most important aspects of quality of life in predicting prognosis [34].

In the long-term evaluation, the quality of life of patients who had remained recurrence-free following surgery for PC, was generally good within 24 months of follow-up. Between 24% and 69% of patients may develop fat-soluble vitamin and mineral deficiencies, dumping syndrome, diabetes mellitus and delayed gastric emptying [35].

Adjuvant / neoadjuvant treatment

There is still an under representation of older patients in clinical trials evaluating the role of perioperative treatment. Therefore, it is impossible to draw evidence-based conclusions on the optimal treatment model, not to mention the treatment of frail patients [36]. Adjuvant therapy includes systemic chemotherapy to reduce the risk of distant metastases (80% of cases) and chemoradiotherapy to reduce the risk of locoregional failure (20% of cases). European guidelines favour chemotherapy alone and do not recommend the use of chemoradiotherapy outside of a clinical trial setting. In the United States, guidelines recommend chemoradiotherapy as a suitable alternative to adjuvant chemotherapy alone [37].

Based on mainly retrospective studies, it can be concluded that despite the repeatedly demonstrated benefits of adjuvant treatment (increasing 5-year overall survival by up to 25%, independently of age), multimodal therapy seems to be underutilised in the older population [38]. Parmar et al. showed that only 11% of over 10 thousand studied patients older than 65 years with PC received surgery and chemotherapy. Taking into consideration the whole population, less than half of patients undergoing resection received chemotherapy [39]. In the older group, this could be due to longer postoperative recovery and the subjective perception of the limited life expectancy of patients with PC, considering mainly the chronological age, the ASA or ECOG/WHO scale. However, available data shows that older patients may benefit from chemotherapy in both adjuvant and advanced disease settings. Despite the discordant results, gemcitabine-based treatment and dose-adapted fluorouracil combination regimens seem to be effective and well tolerated in this subset of patients [40]. Not receiving chemotherapy was an independent prognostic factor for poor OS in the older population (HR: 1.89; CI: 1.27–2.78; p = 0.002). Patients at the age of ≥70 years of age who received adjuvant treatment had a survival benefit of the same magnitude as younger patients (21.8 *vs.* 22.5 months) [41].

Neoadjuvant therapies have been introduced with the aim of downstaging the tumour in order to improve microscopic resection rates. Older patients, with borderline or resectable pancreatic cancer in which the initiation of adjuvant chemotherapy is frequently delayed due to surgical complications, comorbidities and general health status could particularly benefit from this approach. Preoperative therapies also provide a time window allowing not only a clear view of the "ugly" biology of the cancer but also a chance to carry out the multimodal prehabilitation of pre- and frail patients. Barabas et al. observed that older patients who can successfully complete a course of neoadjuvant therapy and tolerate its associated morbidity probably had adequate physiological reserve to withstand surgery. In turn, Miura et al. reported the outcomes associated with neoadjuvant therapy (chemotherapy or chemoradiotherapy) in older patients with resectable or borderline resectable pancreatic cancer. The authors showed that the 75+ group compared with the younger group had more hospitalisations during the therapy (50 *vs.* 28%) and were also less likely to complete the therapy (72.4 *vs.* 89.5%). However, among the patients who completed the therapy, there were no significant differences in complication rates or median overall survival between the two groups. In turn, Marmor et al. showed that, compared with chemotherapy, surgical resection is associated with a very small survival advantage in older patients (aged ≥80 years with lymph node metastasis) [42].

In conclusion, the neoadjuvant approach seems to be an attractive treatment option in older patients with borderline resectable pancreatic cancer and for patients who are not candidates for surgery, allowing also for prerehabilitation and reevaluation possibilities. The role of adjuvant therapy has been demonstrated to be beneficial, however, older patients are often not included due to longer postoperative recovery and subjective evaluation of the patient's health status or life expectancy. We urgently need well-designed

Table I. Therapeutic options for pancreatic cancer depending on the cancer stage, including options for frail older patients

Stage factors	Fit patients	Frail patients
resectable pancreatic cancer	surgery ⟶ adjuvant chemotherapy	• prehabilitation + reevaluation ⟶ surgery • neoadjuvant chemotherapy (in the meantime +/– prehabilitation) ⟶ surgery • best supportive care in severe frailty
border-line resectability	preoperative chemotherapy + reevaluation ⟶ surgery ⟶ postoperative chemotherapy	• neoadjuvant chemotherapy (in the meantime +/– prehabilitation) ⟶ surgery • palliative treatment • best supportive care in severe frailty
not-resectable metastatic	palliative treatment clinical trials	• best supportive care

prospective studies evaluating their role in the treatment of the older population with PC. However, the basis for the selection of patients must be biological and not chronological age [43–45].

Palliative treatment

There are only few studies dedicated to older patients. In the prospective PRODIGE clinical trial, age was an adverse prognostic factor in metastatic PC [46]. In other studies, the use of systemic therapy was proven to have a survival benefit in selected old and very old patients [47]. Considering the results of published studies, Higuera et al. proposed the following treatment for older patients with metastatic PC [48]:

1. Patients <75 years old:
- ECOG 0–1: FOLFIRINOX or gemcitabine-nab-paclitaxel schedule,
- ECOG 2: nab-paclitaxel-gemcitabine,
- ECOG 2 or more: best supportive care.
2. Patients >75 years old:
- ECOG 0–2: gemcitabine-nab-paclitaxel schedule,
- ECOG >2: best supportive care.

Best supportive care

At the time of diagnosis, the majority of patients had a locally advanced PC or metastatic disease characterised by a high symptom burden. The most common complications observed in patients with PC are: cachexia (80%; due to complex pathophysiological processes), pain (75%; due to pancreatic and celiac plexus infiltration), biliary obstruction (70%; in case of head location), duodenal obstruction (20%), and thromboembolic events.

Cachexia is characterised by the loss of skeletal muscle mass that cannot be fully reversed via conventional nutritional support and leads to progressive functional impairments. This state is therefore particularly dangerous for older patients, very often influencing the decision regarding further treatment. Weight stabilisation in patients with PDAC has been associated with improved OS and quality of life [49].

Older patients usually underreport pain. Thus, it remains not poorly treated, leading to a decrease in the quality of life, depression and a deterioration of performance status [50]. Biliary obstruction can be treated successfully with an endoscopically placed stent. However, in the case of a plastic stent, older age was found to be an unfavourable prognostic factor for stent patency [51]. In the case of duodenal obstruction, stent placement or palliative surgery will resolve the symptoms [52].

Conclusions

Chronological age alone should not be a contraindication for multimodal radical treatment in older patients. The frailty (a surrogate of biological age) evaluation should be the basis for a discussion on treatment planning. At present, it is one of the most reliable factors in older patients.

Therefore, before treatment begins, the following questions should be discussed:

- Is the currently planned treatment strategy correct? Are there any alternative treatment options?
- What is the result of the Comprehensive Geriatric Assessment? Can frailty syndrome be diagnosed in the patient?
- What are the risk of complications?
- What would be the patient's lifespan without treatment?
- What are the goals, preferences and expectations of the patient? What effect might treatment have on these goals?
- Is it possible to improve the patient's state prior to the surgical procedure?

Surgical resection is the only curative treatment option for PC and pancreas surgery has become a safe procedure for older patients in high-volume hospitals when operated on by an experienced surgeon. Fit and pre-frail (after prehabilitation) patients, according to the Comprehensive Geriatric Assessment, should be qualified for the same treatment as younger patients. Frail patients should be discussed in an oncogeriatric meeting. We do not have good data to draw a conclusion regarding what would be the most beneficial for this subpopulation of older patients both in the short- and long-term follow-up. In the case of severe frailty, best supportive treatment can be the best option.

The goal of the modifications should be a reduction in surgical stress, since in older patients, the pathological outcome and postoperative complications are the most important predictors of survival. Therefore, preoperative CGA in older patients is not the end of geriatric intervention, but merely the beginning.

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Significance of genetic and radiological examinations in diagnosis and therapy of brain glioma in adult patients

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Molecular and imaging studies are applied along with histopathology in diagnosis and differential diagnosis of brain gliomas and they enable personalised clinical management. With knowledge of the patient's clinical condition, a decision whether to observe the patient or proceed to immediate surgical treatment is made based on imaging results. On the other hand, knowledge of molecular predictive markers allows optimisation of chemotherapeutic decisions, e.g., introduction of personalised therapy (application of such drugs as temozolomide, bevacizumab, vemurafenib, dabrafenib and trametinib).

Key words: brain gliomas, personalised medicine, molecular diagnostics, imaging diagnostics, MRI, perfusion MRI, MR spectroscopy, diffusion tensor MRI, fMRI, temozolomide, bevacizumab

Gliomas are among the most common brain tumours (they account for approximately 60% of all tumours in this region), and their clinical course is highly malignant (the average survival time of treated patients is 14–15 months, and for untreated patients 2–4 months). About 3–5 / 100,000 of these neoplasms are diagnosed each year, with a slight predominance of men. Gliomas can develop at any age, but the peak incidence occurs in the fifth and sixth decades of life. Diagnostics is based on the clinical symptoms of the disease, results of imaging studies and histopathological diagnosis [1].

Gliomas are classified by their location (supratentorial and infratentorial), malignancy (from more benign – grade I, to the most malignant ones – grade IV) and the origin of the glial cells [2]. Histopathologically, these tumours are classified based on the cell morphology. With the development of molecular techniques, molecular classification has been introduced, contributing to establishment of an integrated histopathological and molecular classification of brain gliomas.

Histopathological classification of brain gliomas

Histopathologically, gliomas are classified according to the origin of the glial cells into the following categories (tab. I):

- astrocyte tumours (*astrocytomas*),
- tumours of glial ependyma (*ependymomas*),
- oligodendrocyte tumours (*oligodendrogliomas*),
- mixed gliomas (arising simultaneously from different types of cells, but mostly originating from astrocytes or oligodendrocytes) [1, 3].

Currently, according to the 2016 WHO classification, typology of gliomas takes into account not only the histopathologic diagnosis (phenotype), but also molecular alterations of the tumour cells (genotype). The objective is to apply persona-

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lised therapy (individual for a given patient). In rare cases of incompatibility, the genotype of the tumour dominates its phenotype [4].

Molecular classification of brain gliomas

Gliomas are characterised by high genetic heterogeneity, which is observed both within the tumour itself and in brain tumours of the same histopathological diagnosis in different patients. The high molecular diversity of gliomas has substantiated the questioning of clonal theory of development of these tumours (from a single cell) in favour of the multicellular aetiology. Molecular heterogeneity makes both the diagnosis and treatment of gliomas difficult.

Molecular changes in gliomas, as in all neoplasms, can occur at different levels of genome organisation and functioning, that is:

- mutations in genes crucial for neoplastic transformation of gliomas,
- copy number alterations – CNA (the number of copies of genome fragments may change,
- alterations of genes expression (promoter hypermethylation).

Detailed molecular studies of gliomas have shown that among tumours classified by histopathology into the same group, there are subgroups defined by pattern of molecular alterations. This molecular variation is the cause of different clinical course and response to treatment in patients with the same form of tumour, as defined by histology. Therefore, understanding the genetic changes underlying the neoplastic transformation of cells allows for searching for a targeted treatment.

First systemic classification of glioblastoma multiforme (GB) based on molecular alterations has been published in 2008 (The Cancer Genome Atlas [TCGA] Research Network). GBM has been divided into four subtypes with defined dominant genetic changes in each of these subtypes:

- classical – amplification of chromosome 7, deletion of chromosome 10 and amplification of the *EGFR* gene – present in almost 100% of these tumours,
- mesenchymal – deletion or inactivating mutation of the *NF1* gene,
- neural – mutations in the *NEFL, GABR1, SLC12A5, SYT1* genes,
- proneural – mutations in the *IDH1* and *PDGFRA* genes.

Particular GBM subtypes are associated with specific prognosis and treatment response [5, 6]. As demonstrated by Verhak et al., comprehensive treatment with chemotherapy and radiotherapy, or with more than three cycles of chemotherapy, gave positive results in patients with classical, mesenchymal and neural glioblastoma multiforme [7].

Development of molecular testing techniques deepened the knowledge of genetic changes in brain tumour cells, leading to publication in 2016 of the WHO classification of brain gliomas based on integrated histopathologic and molecular assessment [8, 9]. In this approach, gliomas – classified histopathologically as astrocytomas, oligodendrogliomas and oligoastrocytomas are divided depending on the present genetic changes into the group of tumours with *IDH* mutation and:

- with *ATRX* and *P53* mutation (diffuse astrocytomas with *IDH* mutation),
- 1p / 19q codeletion (oligodendrogliomas with the *IDH* mutation and 1 / 19q codeletion),
- without *IDH* mutation (diffuse astrocytomas without *IDH* mutation, oligodendrogliomas without *IDH* mutation),
- undefined in other groups (not otherwise specified – NOS).

The presence of the *IDH1 / IDH2* gene mutation is of key importance in the classification of diffuse brain gliomas. Diversity of molecular alterations observed in the said types of gliomas indicates that these are molecularly separate sub-groups.

GBMs without *IDH* mutation are clinically classified as *de novo* tumours. They occur in almost 90% of patients over 55 years of age and display a more aggressive clinical course than gliomas with *IDH* mutation. They are also characterised by frequent (30–50% of cases) hypermethylation of the promoter of *MGMT* gene, which is associated with a better response to treatment with alkylating agents such as temozolomide.

GBMs with *IDH* mutation are usually tumours derived from diffuse poorly differentiated gliomas and are most often diagnosed in younger patients. The NOS group includes tumours in which the mutational status of *IDH* could not be identified. In such cases, in order to rule out the rare *IDH* mutations, sequencing of these genes is highly recommended [8].

Table I. Classification of gliomas by the type of cells they originate from and by malignancy [1, 3]

Cell type	Examples of gliomas	WHO grade
astrocytomas	pilocytic astrocytoma diffuse astrocytoma anaplastic astrocytoma glioblastoma multiforme	grade I grade II grade III grade IV
ependymomas	ependymoma subependymoma ependymoma anaplastic ependymoma	grade I grade I grade II grade III
oligodendrogliomas	oligodendroglioma anaplastic oligodendroglioma	grade II grade III
mixed gliomas	oligoastrocytoma	grade II/III

Tumours with *IDH* gene mutation are divided, depending on the molecular changes, into two subgroups:

- with codeletion of short arm of chromosome 1 (1p) / long arm of chromosome 19 (19q) and mutation of the promoter of *TERT* gene,
- with mutation of *ATRX* and *P53* genes.

With these mutations, it is possible to determine which group of glial cells (astrocytes or oligodendrocytes) is the origin of the lesion, and 1p / 19q deletion is the differentiating feature for oligodendrocytes regardless of the histopathologic image of the lesion.

In GBMs with the *IDH* mutation derived from poorly differentiated astrocytomas (identifiable by presence of *ATRX* and *TP53* mutations), hypermethylation of the *MGMT* promoter is also common. It involves better prognosis for patients treated with alkylating agents [10].

Radiological diagnosis of gliomas

The imaging method of choice in diagnosing gliomas is magnetic resonance imaging (MRI) [11, 12]. Computed tomography (CT) may be helpful in detecting calcifications, which are quite common in oligodendrogliomas and ependymomas. Moreover, as a method more easily available than MRI, CT is often used as a preliminary examination in cases of unclear neurological symptoms. Positron emission tomography (*PET*) combined with CT (PET / CT) is a complementary method that allows assessment of malignancy of gliomas by determining the degree of uptake of fluorodeoxyglucose (FDG) or other radiometabolites [13, 14]. There is hope for future developments with combination of PET and MRI (PET/MRI) in which functional advantages of PET in defining malignancy of gliomas are added to precise morphological assessment with MRI [15].

However, the currently recommended primary MRI protocol for imaging brain tumours includes the following sequences: 3D T_1-weighted imaging, T_2 / FLAIR, DWI, SWI, contrast-enhanced 3D T_1-weighted imaging performed with a MR unit with a magnetic field strength of at least 1.5 tesla [16]. In everyday clinical practice, thin-section (1 mm) 3D T_1 sequence with contrast enhancement is applied. It is used to develop a 3D plan of neurosurgery, referred to as neuronavigation [17, 18].

Objectives of MRI in diagnosing gliomas

Confirmation of a proliferative process

Gliomas are easily detected by MRI. Most of them are hypointense in T_1-weighted images, and hyperintense in T_2-weighted images and the FLAIR sequence. They are usually surrounded by a zone of finger-like vasogenic oedema and cause a mass effect of compression of the ventricular system, extracerebral fluid spaces and other intracranial structures. Upon contrast administration, malignant gliomas (HGG, WHO 3 and 4) display regular contrast enhancement, while highly differentiated gliomas (LGG, WHO 1 and 2) usually enhance minimally or do not enhance at all [19, 20].

Differentiation with non-neoplasmatic processes, such as ischaemic changes

Some non-neoplasmatic processes may mimic gliomas. For example, ischaemic changes in the subacute period may have similar signal characteristics and display partial contrast enhancement [21]. Differentiation is based on history, additional MRI sequences (restriction of diffusion in diffusion-weighted imaging in the first 7–15 days after ischaemic stroke; decreased perfusion in perfusion MRI) and the dynamics of the MRI image in follow-up studies (evolution of ischaemic infarction). Also, brain abscesses and other inflammatory processes can mimic the appearance of gliomas, especially highly differentiated ones. Patient history, microbiological tests and the MRI pattern itself are helpful in diagnosis [22, 23].

Differentiation of gliomas from other proliferative processes e.g., lymphomas, metastases

MRI appearance in non-glioma intracranial tumours may be similar to those of gliomas, but their detailed analysis often allows for proper diagnosis. For example, lymphomas, as hypercellular tumours, show diffusion restriction and at the same time have low perfusion [24]. Metastases are typically located on the interface of the white and grey matter, and have a disproportionately large zone of oedema compared to the size of the tumour itself [25]. Meningiomas and neuromas are located extraaxially and usually provide strong and uniform enhancement [26].

Grading of gliomas

Standard MRI has limited potential of assessing the grade of tumour malignancy. The main symptom in this regard is the contrast enhancement. Low-grade gliomas (highly differentiated) most often do not enhance or their enhancement is slight, while high-grade, undifferentiated gliomas generally display strong, although heterogeneous, contrast enhancement. Further, malignant gliomas frequently contain hypointense necrotic zones and are surrounded by a more extensive oedema zone than low-grade gliomas [27, 28]. Advanced MRI techniques are also useful in assessing the malignancy of the tumour.

Attempt at differentiating particular forms of gliomas

The possibilities of suggesting a specific histopathological type of cerebral glioma based on a standard MRI examination are limited. Glioblastoma multiforme usually displays a characteristic pattern of a multifocal tumour, frequently affecting both cerebral hemispheres (butterfly glioma) with irregular contrast enhancement and areas of necrosis [29]. Calcifications are a characteristic feature of oligodendrogliomas [30], while ependymomas are distinguished by a characteristic intraventricular location [31].

Importance of radiological studies in the prognosis and treatment planning of brain gliomas

Correct diagnosis of glioma, and especially determination of its malignancy grade, is of key importance in determining the therapeutic management.

In the case of benign gliomas (low-grade glioma – LGG), patient follow-up is often used to avoid postoperative complications (watch and wait approach). On the other hand, in the case of malignant gliomas (high-grade glioma – HGG), surgical intervention is indicated as soon as possible. However, in a standard MRI examination, the appearance of some HGGs may mimic LGGs and vice versa [32, 33]. Therefore, advanced magnetic resonance imaging techniques are increasingly used to determine the severity of gliomas, which is important for the decision on the type of treatment and correct qualification for surgery. These techniques provide more precise information about the tumour's aggressiveness and thus they help to distinguish LGGs from HGGs or to diagnose low-grade gliomas with a high risk of progression to HGG and to facilitate the decision on the application of the *watch and wait approach* or surgical procedure [16].

Among the advanced MRI techniques applied in diagnosis of gliomas, MR spectroscopy (magnetic resonance spectroscopy – MRS), perfusion MRI (perfusion-weighted imaging – PWI), diffusion tensor imaging (DTI) and functional MRI (fMRI) are the most commonly applied [34].

The main goals of the MRI examinations are:

- to confirm the neoplastic nature of the lesion,
- to assess the tumour's location,
- to assess the mass effect,
- to assess compression of the ventricular system and surrounding structures,
- to assess vascularity of the lesion [35, 36].

Among the basic MRI techniques, the following are of special importance: contrast-enhanced T1-weighted sequence, diffusion-weighted imaging (DWI) and magnetic susceptibility sequence (susceptibility-weighted imaging – SWI).

As the blood-brain barrier is damaged in abnormal tumour tissues, there is pathological enhancement of this area in sequences following administration of a contrast agent. The literature describes a positive correlation between presence of contrast enhancement and higher degree of malignancy of gliomas [37].

The DWI sequence is based on assessment of free movement of water molecules, and thus it enables definition of:

- cell structure of the lesion,
- oedema surrounding the lesion,
- hypoxia area inside the tumour,
- integrity of white matter tracts,
- presence of postoperative injuries [38].

In order to fully assess diffusion, DWI images should be interpreted together with the values of the apparent diffusion coefficient (ADC), which is automatically visible as an ADC map. Numerous studies have shown that a reduced ADC value is an independent biomarker that indicates a much worse prognosis in both gliomas and brain lymphomas [34].

Meanwhile, SWI sequence is highly sensitive to blood products, as well as calcifications. It allows visualisation of even very small microbleeds inside the tumour, as well as assessment of vessel structure. It has also been observed that presence of bleeding and necrosis within the lesion is more common in poorly differentiated gliomas (HGG) [38].

Among the advanced sequences, magnetic resonance perfusion imaging (PWI) is the most important. It is performed after administration of gadolinium contrast using the DSC (dynamic susceptibility contrast) or DSE (dynamic contrast enhancement) technique, or without contrast administration using the ASL technique (arterial spin labelling) [34]. With PWI, tumour angiogenesis and vessel proliferation can be defined. In malignant gliomas, vessels are tortuous and improperly formed, which results in leakage and abnormal blood flow in the brain. Perfusion studies are assessed on colour maps which display cerebral blood volume (CBV) and vascular wall permeability, expressed by the Ktrans parameter [16]. High-grade tumours show an increase in CBV as well as of Ktrans parameter. It is assumed that the rCBV value > 1.75 (determined in relation to normal white matter) may indicate pathological, neoplastic angiogenesis [16]. Increased perfusion parameters in imaging studies within the long-term follow-up of LGG patients are important for assessment of tumour progression, because approximately 50% of LGGs transform to a higher grade within 5 years. This can be detected in a PWI study [33]. Moreover, within the oedema surrounding gliomas with a lower degree of differentiation, an increased rCBV values were also observed, which indicates tumour infiltration into the surrounding tissues - this is not found in the oedema surrounding metastatic lesions. PWI enables a more precise biopsy of the tumour (which should be performed in the part of the tumour with the highest perfusion), which in turn translates into qualification for appropriate treatment [39]. The Ktrans perfusion parameter enables an additional assessment of malignancy of gliomas. With greater vascular permeability, probability of malignancy is higher [37].

Magnetic resonance spectroscopy provides information about the biochemical as well as metabolic profiles of the tissue. In the course of brain glioma development, an increase in choline (Cho) and a decrease in N-acetylaspartate (NAA) are observed. Higher values of the Cho/NAA ratio and the Cho/Cr ratio (choline / creatine) indicate the lower degree of tumour differentiation, which means a higher grade of malignancy [38]. Moreover, Castillo et al. demonstrated that in LGG tumours values of the ml/Cr ratio (myoinositol/creatine) are statistically significantly higher than in other types of brain tumours [40].

The challenge in treating gliomas is to perform surgery to remove the neoplastic lesion as accurately as possible without

excessively damaging healthy brain tissues. There are further advanced MRI sequences which are very useful in planning the procedure: DTI and fMRI.

Diffusion tensor imaging (DTI) along with diffusion *tensor* tractography (DTT) can detect disturbances of the direction and continuity of white matter nerve fibres. Therefore, this imaging study may be applied before the planned glioma resection, because it helps differentiate infiltration from displacement of the white matter nerve fibres adjacent to the tumour [41]. Changes in DTI can be quantified – most often using the fractional anisotropy (FA) parameter – a lower FA coefficient is associated with greater damage to white matter [41].

Promising results are observed with functional magnetic resonance imaging (fMRI), but this method is used rather in specialised clinical centres and in scientific research. fMRI evaluates brain activation by detecting changes in blood oxygenation levels (BOLD sequence). A reduced BOLD signal is recorded in the cerebral cortex occupied by the tumour – especially in HGG gliomas [38]. This technique allows for precise determination of the tumour's relationship to eloquent areas, such as: speech, sensory, motor and memory areas. This can be a key factor in planning of the course of the surgery.

Predictive and prognostic significance of genetic changes in gliomas

Despite huge advances in molecular diagnosis of gliomas, possibilities of personalised treatment, including targeted therapy, are still limited.

The classic therapeutic approach for patients with GBM, based on histopathological assessment of the tumour and patients clinical condition, is limited to surgical resection of the tumour (which never leads to removal of the entire tumour mass, due to infiltrative growth pattern), followed by radiation therapy and chemotherapy.

The primary drug used in these patients is temozolomide, approved in 1999 for treatment of patients with anaplastic astrocytoma [42] and subsequently in 2005 for treatment of patients with newly diagnosed brain tumours [43]. Temozolomide is an alkalising compound, i.e., its action consists in attaching an alkyl group to the DNA. As a result, multiple mutations occur, leading to cell death. This process is inhibited by the intracellular DNA repair system by cutting out abnormal bases (base excision repair – BER). The key enzyme for this mechanism is the MGMT protein (methyltransferase O6 – methylguanine, O6-alkylguanine-DNA alkyltransferase – MGMT), encoded by the *MGMT* gene. Loss of this gene's activity due to hypermethylation of its promoter (a mechanism of epigenetic regulation of gene expression) leads to impaired DNA repair and, consequently, to increased effectiveness of alkylating anticancer drugs. It was shown that patients with hypermethylation of the *MGMT* gene promoter respond better to treatment with these agents, although the effect is not as pronounced as expected [44]. To a large extent, this is due to the genetic heterogeneity of gliomas, as one of its symptoms involves high variability in the degree of hypermethylation of the *MGMT* promoter in different parts of the tumour. However, the methylation level of the *MGMT* gene promoter is currently an accepted predictor marker for application of temozolomide in patients with brain gliomas.

Another useful drug in treatment of brain gliomas is a monoclonal antibody, bevacizumab. Its effect involves blocking new vessel formation within tumour mass (anti-vascular endothelial growth factor – VEGF). Bevacizumab was approved by the FDA in 2004 as a drug used in metastatic colorectal cancer. In 2009, it was approved in treatment of various cancers, including brain gliomas [43].

Current studies are investigating new methods of targeted treatment of gliomas, for example compounds to block hyperactivity of the EGFR receptor with tyrosine kinase inhibitors (TKIs). The use of depatuxizumab mafodotin (a conjugated EGFR blocking antibody) in combination with temozolomide showed positive therapeutic effects in patients with a relapse of EGFR-positive GBM in the second phase of clinical trials. However, in the third phase of clinical trials concerning application of depatuxizumab mafodotin in combination with standard therapy in newly diagnosed FGFR-positive GBMs, this therapeutic approach has been proved ineffective [10].

Other unsuccessful clinical trials concerned application of drugs targeted at mutations within the *PI3K/mTOR* signalling pathway, which is frequently deregulated in GBMs without *IDH* mutation, frequently with *PTEN* gene deletion and *PIK3CA* or *PIK3R1* mutation. However, a weak but positive therapeutic effect was achieved in the case of buparlisib monotherapy (PI3K tyrosine kinase inhibitor; pan-PI3K TKI) in patients with a relapse of *PI3K*-active GBM. Once more, there was no clearly positive effect recorded by clinical trial on application of VEGF inhibitors and tyrosine kinase multi-inhibitors targeted at changes in genes which modulate tumour microenvironment. However, there are promising preliminary results of trials concerning pharmacotherapy for glioma patients, e.g., administration of vemurafenib (in patients with GBM and *BRAF V600E* mutation, as well as a combination of *BRAF / MEK* inhibitors), dabrafenib and trametinib, which were applied successfully in targeted therapies for other cancers.

It seems that an interesting direction can be found in research on inhibitors of fusion genes, occurring in almost 55% of GBM (e.g., *FGFR, MET, NTRK* and less frequently fusions of *EGFR, ROS1, PDGFRA* and *NTRK*), 10% of which are fusion kinases which have known inhibitors approved for clinical use in other tumours (e.g., larotrectinib and entrectinib, approved by FDA for application in patients with solid tumours and *NTRK* fusion) [10].

Molecular changes are also prognostic markers. It was found that GBMs without *IDH* genes mutations have a more aggressive clinical course than tumours with mutations in these genes. Similarly, tumours with *TERT* gene mutations, without *IDH* mutation, have a worse prognosis. Meanwhile,

oligodendrogliomas with the 1q / 19p codeletion and *IDH* gene mutations have a milder clinical course. Similarly, a milder course of the disease and thus a better prognosis can be expected if mutations in the *ATRX* gene are present in GBM cells. It is characteristic for these tumours that *ATRX* gene mutations almost never occur simultaneously with the 1q / 19p codeletion. Better survival prognosis is observed in patients whose GBM cells have hypermethylation of *MGMT* gene promoter associated with 1q / 19p codeletion [6,45].

Conclusions

Genetic and radiological studies are currently very important in diagnosis, treatment and prognosis of patients with brain gliomas. Therefore, there is an intensive effort to correlate specific imaging features of gliomas with their molecular classification.

One of those features is the finding observed in MRI, referred to as T_2-FLAIR mismatch sign, found to be highly specific for diffuse astrocytomas with *IDH* mutation and without 1p / 19q codeletion [46, 47]. On the other hand, absence of this finding is characteristic for oligodendrogliomas. Presence of the 2-HG metabolite in MRS is also characteristic for gliomas with the *IDH* mutation [48]. In MRI of gliomas with amplification of *EGFR*, diffusion restriction in DWI along with high perfusion (rCBV > 3.0) in PWI were found with statistical significantly higher frequency, and so was left temporal location [49]. MRI proved also correlation of the molecular pattern of texture, fractal features and volume of diffuse low-grade gliomas assessed by a special computer algorithm [45].

Recently, development of advanced magnetic resonance techniques has been observed, allowing for non-invasive assessment of morphology and biological features of brain tumours, and in some cases – suspicion of genetic changes, too. This translates into an increasingly precise initial tumour malignancy assessment, allowing more precise determination of the patient's prognosis and their qualification for the right method of treatment. However, radiological-molecular-genetic relationships in brain gliomas require further in-depth studies to accurately assess their clinical usefulness.

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