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Best Original Paper Award 2021

Z radością informujemy, że główną nagrodę w drugiej edycji konkursu *Best Original Paper Award* na najlepszą pracę oryginalną opublikowaną w 2021 roku w czasopiśmie *Nowotwory. Journal of Oncology* zdobyli:

Adam Dmitruk
Tomasz Olesiński
Piotr Hevelke
Łukasz Zyskowski
Andrzej Rutkowski

autorzy artykułu:

„Long-term results of randomized studies on the use of a gentamicin-collagen sponge in rectal cancer — depending on the length of time between the completion of radiotherapy and the surgery"

(NOWOTWORY J Oncol 2021; 71: 139–145)

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Original article

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Dose estimation in patients treated with radiotherapy for SARS-COVID disease based on EPID measurement

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Introduction. COVID radiotherapy requires performance of all radiotherapy (RT) procedures during one site visit due to the infectious nature of the disease. The aim of the study was to develop methods of estimating the delivered dose based on electronic portal image device (EPID) signal during treatment.

Material and methods. Electronic portal image device signal was measured as a function of the phantom dose. The dose in 14 COVID patients was estimated for two X6MV beams.

Results. The method allows to estimate dose in phantom with uncertainty of 12%. In this case, a systematic error was reported. Therefore, coefficients for clinical data were calculated and used to determine the dose in patients. The mean difference between the dose calculated and the dose measured for the 14 patients was 1%, but the uncertainty of this method was estimated as ±6%

Conclusions. The proposed method may be useful in clinical practice as *in vivo* method. However, due to high uncertainty, it should be dedicated to the detection of "big" errors.

Key words: SARS-COVID, EPID, fluence map, QA, *in vivo* dosimetry

Introduction

In December 2020, the National Research Institute of Oncology in Poland, Gliwice Branch, began the irradiation of SARS-COVID patients [1, 2]. A dose of 1 Gy was scheduled to the lung volume. This was part of a II phase study performed on 14 patients hospitalized between December 2020 and April 2021 due to severe viral pneumonia over the course of COVID-19 in the Department of Infectious Diseases and Hepatology, Medical University of Silesia, Bytom, Poland. There were 5 females and 9 men with a median age of 66 years (range 49–78). All of them required continuous oxygen supplementation. Inclusion criteria consisted of COVID-19 infection confirmed by polymerase chain reaction (PCR), age ≥18 years, Zubrod score ≤3 points, clinical and radiological (radiography [RTG] or high resolution computed tomography [HRCT]) signs of viral pneumonia, severe COVID-19 – stage 3 according to national guidelines with SpO_2 < 90% and the need for oxygen supplementation the ability for providing of concise consent. Among the exclusion criteria were acute respiratory distress syndrome (ARDS), the need for invasive or mechanical ventilation, pregnancy,

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any thorax malignancy in the last 5 years, contraindication for medical transport for low dose radiotherapy (LDRT) procedure, cognitive impairment and therapy with another experimental therapies. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland; all participants gave written informed consent. RT administered at LDRT modulates the inflammatory response. This anti-inflammatory action of LDRT includes various mechanisms including the induction of apoptosis in immune cells, decreasing levels of some proinflammatory cytokines, inhibiting leukocyte recruitment and the reducing function of macrophages (Arenas). This feature of LDRT was discovered and clinically utilized in the first half of the 20th century prior to the era of antibiotics in the treatment of a wide range of inflammatory and infectious diseases such as sinusitis, arthritis, gas gangrene, carbuncles, inner ear infections, including pneumonia (Calabrese) [22, 23]. Due to the above facts, the concept of utilizing LDRT as a suppressor of COVID-19 related pneumonia was raised.

The radiotherapy linear accelerator TrueBeam manufactured by Varian equipped with as1200 EPID was used. As the TPS treatment planning system ECLIPSE (Varian), version 16.1, was used. During the irradiation/tratment of SARS-COVID patients, it was presumed that the following assumptions should be followed:

- the duration of the procedure should be minimized,
- the number of persons in direct contact with the patient should be minimal,
- all Radiotherapy Trials Quality Assurance (RT QA) requirements must be met.

This must be done during a one-off radiotherapy session. An important part of the RT QA procedures is the full control of the delivered dose. This task is difficult to accomplish because the standard treatment "planning path" does not exist here. The patient has no stabilization and no 3DCT imaging. All procedures of "treatment planning" and QA are carried out in a treatment room. An irradiation technique should be simple. Two opposite fields with multi-leaf collimators (MLC) were selected. The irradiation time of the 1 Gy dose was calculated for a depth of half of the AP dimension. For a beam angle 0° and 180°, a dose of 0.5 Gy was planned. This procedure is also used for palliative cases. The main question of this study was: Is it possible to verify the delivered dose during a single session?

The fluence map obtained with EPID was tested to measure the dose in real time [3–5], repeated treatment [6–9], point dose measurement [10] and dose distribution [11–14]. Fluence maps were also used to verify the correct operation of the MLC [15–18] or compatibility with the planned dose distribution [19]. EPID can be used as a dose meter in *in vivo* dosimetry [20, 21]. For this purpose, cone-beam computed tomography (CBCT) and EPIDs are excellent tools. A 3D image is obtained with CBCT and an EPID is used to acquire a fluence map during a therapeutic session to estimate a dose. The aim of the study was to develop a method of measuring the dose during a therapeutic session using the EPID.

Material and methods

Irradiation is carried out by two opposite X-6MV fields. A 1 Gy dose is defined at a point at a depth of ½ of the AP dimension in the geometric center of the right field beam (right lung). The irradiation time was calculated for this depth using the Eclipse Irreg module [1, 2]. These calculations do not take into account tissue density and are based only on dose depth, beam specification and source to surface distance (SSD) dimensions. In the case, the calculated dose may be overstated as the density of the lung tissue is less than the density of water. After a therapeutic session a CBCT is acquired. It is used

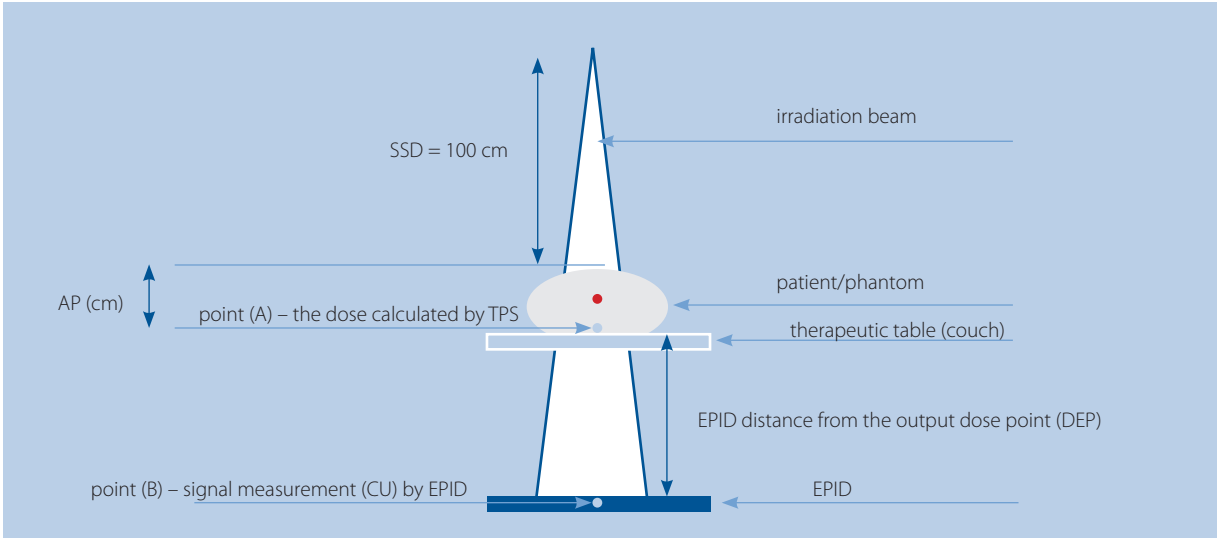

Figure 1. Patient dose estimation diagram based on EPID signal measurement. Knowing the patient's AP dimension, the distance of the output dose point from the EPID can be calculated

to calculate the 3D distribution of the dose for the previously calculated irradiation time. During irradiation a fluence map is measured by an EPID. This signal can be correlated with the dose (fig. 1).

If "A" is selected close to the exit of the beam, then the output dose takes into account the absorption of radiation. The radiation absorption through the couch can be omitted and the output dose can be correlated at "A" with the EPID signal "B". The higher the dose at "A", the greater measured signal. EPID calibration should be carried out to correlate signal (CU) and radiation dose (Gy) dependency.

The next step is to determine the dependence of the signal of dose on the distance between "A" and "B". It is assumed that the greater this distance, the smaller the measured signal if the dose at "A" is constant. Measurements were made for SSD = 90, 100 and 110 cm. The position of the EPID was set at 160 cm. The phantom is 20 cm thick, changing the SSD changes the distance between "A" and "B"; DEP – distance EPID point "A". These distances are: 50, 40 and 30 cm for SSD: 90, 100 and 110 cm. At a depth of ½ AP of the phantom, the following doses were defined: 0.5, 1.0 and 1.5 Gy, for a 10 x 10 cm beam. The dose at "A", "A1" and "A2" are due to different effective depths because the CIRS (Computerized Imaging Reference Systems, Inc., IMRT Thorax Phantom Model 002LFC) measurement phantom has a heterogeneous density (fig. 2).

The calculated doses at "A", "A1" and "A2" will take dependencies into account. In order to confirm the dose calculation model based on the EPID, a "blank test" was performed.

This method was used for 14 patients with SARS-COVID. Images (MV, kV) were taken to determine the AP dimension and define the irradiated volume by determining the MLC shape. Based on the AP dimension and the shape of fields, the irradiation time was calculated for 1 Gy using the Irreg module. The middle of the AP dimension was situated in the middle of the left lung beam. The Irreg module calculates irradiation time based on the depth for 1 g/cm^3 density for the defined dimension of the field. After irradiation, a CBCT imaging was performed to determine the density and to define treated volumes and critical organs. The shape of the irradiation fields was copied onto the acquired 3DCBCT. 3D radiation dose distribution calculations were performed using the ECLIPSE Acuros algorithm v 16.1 [1, 2]. Dose output points were selected for field 0° and 180°. Four points were obtained to compare the

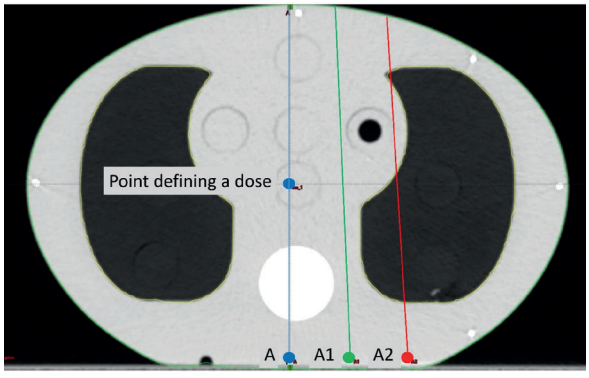

Figure 2. Phantom and points "A", "A1" and "A2" location for which the doses used for EPID calibration as a function of distance were calculated. Equivalent depths should be 21.5 cm, 19.3 cm and 12.1 cm respectively for points "A", "A1" and "A2". The difference in these depths is related to the densities through which the beam's "radius" passes

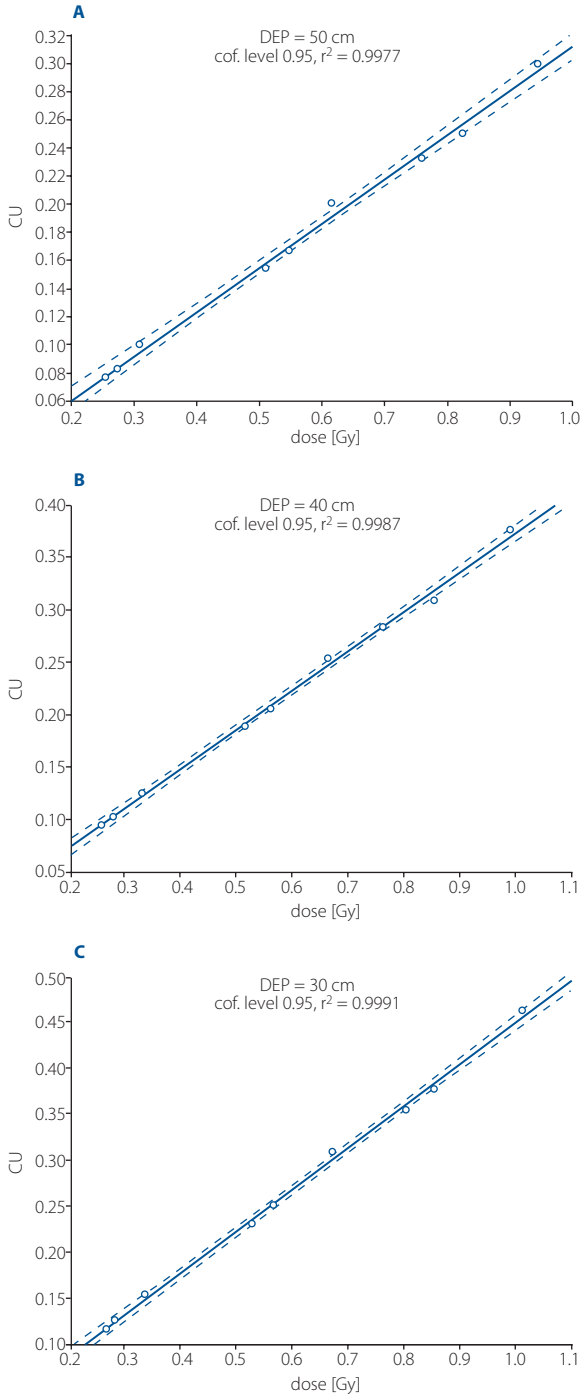

Figure 3. Relationship between the EPID signal (CU) and the output dose for different therapeutic table distances from the EPID: A 50 cm, B 40 cm and C 30 cm. The straight directional coefficient depends on the DEP, and the correlation coefficients for all DEP are above 0.99

measured and calculated doses. These points were selected in the homogeneous dose volume. These single measurement points can be subject to great uncertainty, therefore average values, from four points, were analyzed.

To assess the conformity of the calculated and measured values, non-parametric tests such as the Wilcoxon signed-rank test were used, taking a p value less than 0.05 as the level of statistical significance.

Results

The dependence of the EPID value on the value of the output dose was measured. In the dose range from 0.15 Gy to 0.9 Gy, a linear relationship ($r^2 = 0.99$) was found between the output dose (phantom) and the signal value (EPID–CU). The next stage involved measuring the EPID signal at a distance from the position of the therapeutic table for different output dose values. Figure 3 shows the results of the EPID signal dependency on different distances from the therapeutic table and different output doses.

The measurements showed a linear relationship of 0.95 confidence for a correlation coefficient above 0.99. On this basis, a directional factor "K" could be determined for the DEP dependency (EPID distance from the output dose):

$$\text{Dose [Gy]} = \text{CU} \times K(\text{DEP}) \quad [1]$$

The calculations showed the following values of the coefficient "K": 3.2106 for DEP = 50 cm, 2.6871 for DEP = 40 cm, 2.2304 for DEP = 30 cm. These dependencies describe an exponential function:

$$K(\text{DEP}) = a \times \exp(b \times \text{DEP}) \quad [2]$$

The least squared method was used to calculate coefficients "a" and "b", which were equal to: 1.2932 and 0.0182. The correlation coefficient of the match was above 0.99.

The sets of "K" coefficients obtained from the measurements were then compared:

$$K(\text{DEP}) = \text{dose [Gy] outlet} / \text{CU (measured)} \quad [3]$$

and contrasted with the "K" factor calculated from formula [2], for the calculated coefficients "a" and "b". The Wilcoxon test was used to compare the results, which did not show statistically significant differences between them ($p > 0.05$).

A blank evaluation of the output dose was performed, based on the CU measurement, to validate the developed model. The dose should have been estimated at the defined point (fig. 2). The EPID signal was read as described before. Since the dose was defined in the middle of the AP dimension of the phantom, it was necessary to introduce a relationship between the point of its definition and the point of the output dose. The % depth dose (%DD) value was used for the equivalent depth and read from the dose distribution. This approach is consistent with the actual dose estimation conditions for treated patients. The results of the comparison are presented in table I.

The mean dose differences – measured and calculated for "A", "A1" and "A2" were: 0.75% for SSD = 100 cm, 1.97% for SSD = 110 cm, and 1.22% for SSD = 90 cm. Doses were compared using the Wilcoxon test. No differences were reported between them, which would have been statistically significant ($p = 0.5165$). It can be assumed that it is possible to estimate the dose (in a phantom) based on EPID signal measurements. Table I shows that the maximum difference between the calculated and measured doses was 5.56%, and it was found that the method of estimating the dose based on EPID was subject to uncertainty of 12% (±5.56%).

The developed method was used to estimate the dose received by irradiated SARS-COVID patients. Figure 4 shows the points that were selected to estimate the dose and the geometry of the measurement.

Table I. Doses calculated by the treatment planning system and estimated based on the EPID signal measurement. Model validation conditions on the measurement phantom for geometry is similar to the patient's irradiation conditions

SSD [cm]	Measurement point	CU read from EPID	DEP [cm]	Measured output dose [Gy]	% of output dose	Measured dose [Gy]	Dose [Gy] calculated by TPS	% Diff.
100	A	0.1446	40	0.3887	53.6	0.73	0.75	–3.30%
100	A1	0.1539	40	0.4137	56.3	0.73	0.75	–2.02%
100	A2	0.1876	40	0.5043	63.7	0.79	0.75	5.56%
110	A	0.4713	30	1.0562	54.9	1.92	2	–3.76%
110	A1	0.5046	30	1.1308	58.5	1.93	2	–3.34%
110	A2	0.6136	30	1.3750	67.4	2.04	2	2.06%
90	A	0.1945	50	0.6272	52.0	1.21	1.25	–3.50%
90	A1	0.2093	50	0.6750	55.3	1.22	1.25	–2.29%
90	A2	0.2449	50	0.7898	63.8	1.24	1.25	–0.96%

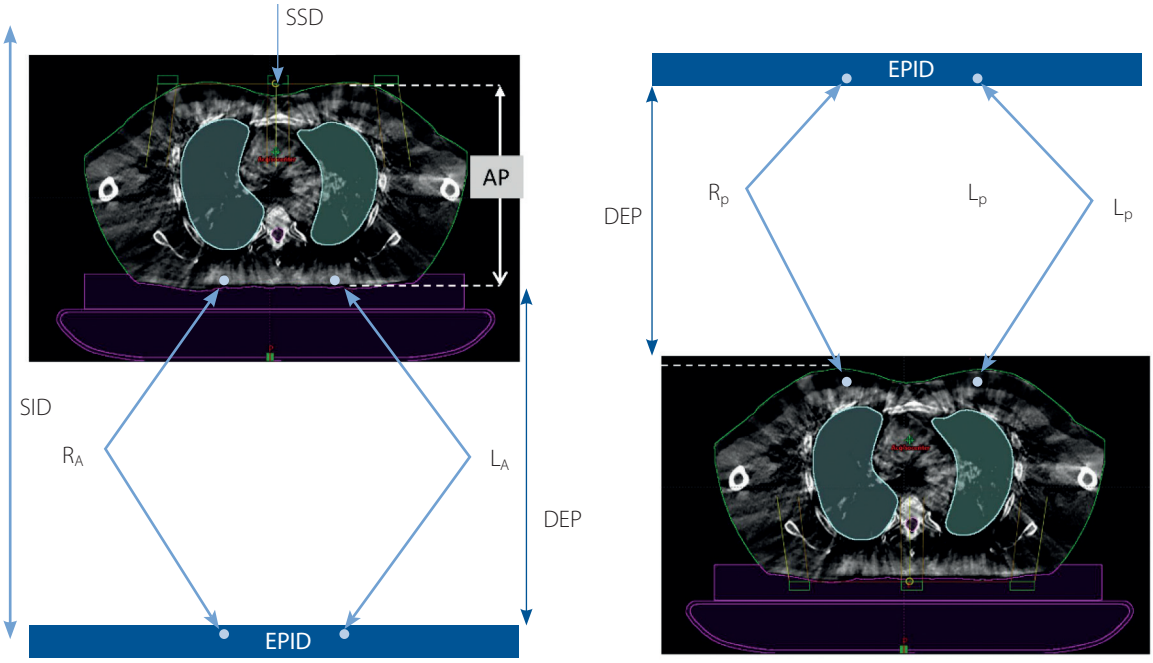

Figure 4. Geometry for measuring the CU value on the basis of which the dose is calculated. SSD = 100 cm, for each irradiation field, and SID (EPID setting) = 160 cm (or 150 cm). DEP depends on the AP dimension of the patient

Table II. The comparison of measured (EPID) and calculated (TPS) doses. %Δ is the mean difference for the four measuring points: R_A, L_A, R_P, and L_P, calculated as: 100% x ($EPID_{dose}$ –TPS_{dose})/TPS_{dose}.

Beam angle [deg]	Measurement point	Fluence [CU]	Dose measured by EPID [Gy]	Dose [Gy] calculated by TPS	Mean %Δ	AP [cm] Patient's dimension	DEP [cm]	EPID Vertical position – SID [cm]
0	R_A	0.1774	0.332193	0.3423	7.14%	29.66	20.34	150
	L_A	0.1573	0.294554	0.3376			20.34	
180	R_P	0.1623	0.303917	0.337			20.34	
	L_P	0.1544	0.289124	0.298246			20.34	

Table II shows the results of the measured EPID dose for one of the patients. The results, for all patients, indicate that all measured doses were lower than the calculated average of 12%. Only 4 out of 14 measurements were within the uncertainty level (<12%). The Wilcoxon test showed statistically significant differences ($p < 0.05$) between the set of calculated and measured doses. Shifting the result of this measurement in one direction indicates a systematic error.

The measured dose was lower than planned for all studied patients. The geometry of the dose measurement using a phantom is different than in the case of patient irradiation e.g., patient dimensions vs phantom dimension. The EPID calibration was performed for a 10 x 10 cm beam, the actual dimension of the irradiation beam was 22 x 25 cm.

The dose output was correlated with the EPID signal for the relationship received from the clinical data using the same method as the phantom. The coefficients "a" and "b" from formula 2 were recalculated and values were obtained: a = 1.4405 and b = 0.0191. Based on these coefficient values, differences between the measured and calculated dose were found to be below 6% (except for one patient). This value falls within the uncertainty of the method estimated at ±6%. The mean difference for all patients between the calculated and measured doses was less than 1% (tab. III).

The Wilcoxon's statistical tests did not show statistically significant differences between the sets of calculated and measured doses ($p = 0.8937$).

Discussion

With regard to clinical dosimetry, in order to calculate the right dose for patients a method needs to be developed. This path determines all necessary factors that are used in clinical practice. It is necessary to explain why the described method allowed for dose estimation in the phantom model based on the EPID signal and showed a systematic error in the calculated dose when used in the patient model.

Figure 5 shows the relationship between the calculated dose and the EPID signal measured under phantom and pa-

Table III. Mean values (points R_A, L_A, R_P, L_P) of the calculated and measured doses. The differences between them are much smaller than in the case of calculations based on the coefficients obtained from phantom measurements

Patient	Mean measured dose [Gy] by EPID	Mean calculated dose [Gy] by TPS	Mean %Δ
1	0.3542	0.3475	2.36%
2	0.3875	0.3700	–4.50%
3	0.3100	0.2913	–5.92%
4	0.2695	0.2560	–4.18%
5	0.2325	0.2407	4.25%
6	0.3825	0.3912	2.44%
7	0.3115	0.3082	0.13%
8	0.3288	0.3463	5.43%
9	0.3775	0.3780	0.27%
10	0.3528	0.3306	–6.00%
11	0.2032	0.2296	13.25%
12	0.3014	0.2946	–2.22%
13	0.2709	0.2825	5.15%
14	0.3514	0.3551	1.34%

tient. It can be seen that the r^2 factor has different values, which indicates a greater dispersion of measuring points in clinical conditions. This shows that in clinical practice the uncertainty of the described method is greater. Not all phenomena associated with patient irradiation were included in the phantom model.

The selection of the CU point from the fluence map is highly uncertain and coordinates do not fully match the position of the output dose. Beam divergence is not taken into account. Phantom measurements are made for a 10 x 10 cm beam field. By correcting the field size – the output factor from TPS, the difference between the 10 x 10 cm and 25 x 25 cm field amounting to 6% – the consistency between the doses would improve, reducing the mean difference from 12% to 9%. There is also a diffused radiation issue. The performed phantom measurements allow for the determination of coefficients that can be used to calculate the dose in a patient. It needs to be remembered that there is more than 12% uncertainty, and the result is only for evaluating whether a big mistake was made. Despite the differences in the measurement geometry, the developed method of correlating the CU signal with the dose for clinical data was applied. When deciding to use an EPID in estimating the dose, the described procedure seems justified. Measurements need to be done on a phantom to prepare a method. For the "first" patients, the values calculated for a phantom should be used, taking into account the uncertainty of 12%. It is an estimate of the dose the patient receives rather than its accurate measurement. As the number of patients increases, the factors used in this method can be derived from

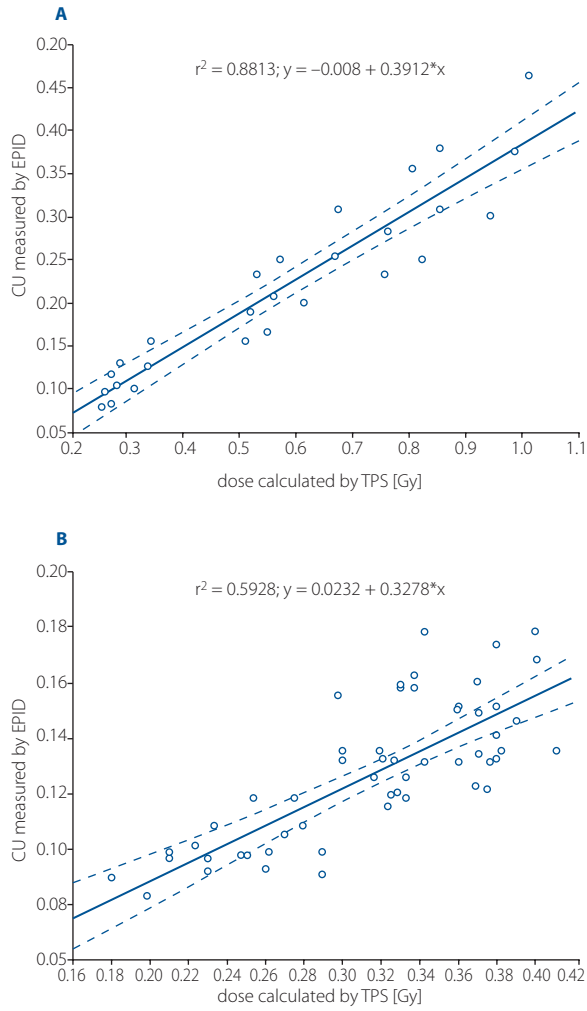

Figure 5. Relationship between the outlet dose calculated by TPS and the signal measured by the EPID for a phantom (A) and treated patients (B). It can be seen that there are differences between the directional coefficients of the two straight lines and a greater dispersion of the measurement points in clinical conditions

clinical data. This method makes it possible to estimate the dose with a measurement uncertainty of 6%.

When IMRT, VMAT were not used in RT, *in vivo* dosimetry was widely utilized [21]. The question arises: should we use the presented method? Direct contact with the patient during an irradiation session is minimized, the presence of physicists measurements does not seem to be justified. The instruments and meters used for these measurements would require sterilization due to special COVID treatment conditions. The delivery of a dose of 1 Gy should not induce negative radiation effects. The dose verification is an additional procedure. The proposed method of using an EPID does not compromise the irradiation process. This is the only method that can be used without extending the irradiation session time.

Electronic portal image device as a dose measurement system was studied [3, 10, 12]. Publications show the possibilities of EPID in dose estimation [3, 21]. Based on dynamic techniques [4, 7, 8], the comparison of fluence maps is an optimal way

of assessing the calculated dose and its real distribution. This comparison is not about one point, but the matrix of points. Measuring a matrix (a fluence map) reduces measurement uncertainty. There is no commercial solution that would estimate patient's volume dose based on a fluence map. The proposed method is burdened with uncertainty of 12%, but it is possible to use it in clinical conditions for estimating "big errors". For SARS-COVID patients, information about the received dose of radiation is useful. Further work will be carried out in the direction of using a larger number of points for reading the signal.

Conclusions

The method of dose estimation based on EPID signal measurement allows for its application in clinical practice only under certain conditions. It must be prepared in advance using phantom measurements and validated by the measurement data of real patients. Its uncertainty is within 12% and it should be treated as a method of detecting a "gross" dosimetry error.

Conflict of interest: none declared

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Sexual health in breast cancer patients in Poland

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Introduction. Breast cancer is the most common malignancy among women in Poland and in the world, with a mortality rate second only to that of lung cancer. Breasts are one of the most important symbols of femininity and sexuality. Cancer surgery, but also systemic therapy (chemotherapy and hormone therapy) cause a change in the perception of one's body. The aim of the survey proposed by us was to assess interest in sex by breast cancer patients during and after oncological treatment, as well as to identify ways to improve the quality of patients' sex lives.

Materials and methods. The proposed survey consisted of 3 parts: the first part included questions about the demographic, in the second part there were the author's questions about sexual dysfunction (12 questions), in the third part there was the Female Sexual Function Index (FSFI) form assessing the sexual functioning of women. The questionnaires were made available online from October 13, 2020 to December 20, 2020 through the social networks of patient organizations involved in breast cancer care. 287 women diagnosed with breast cancer were included in the survey.

Results. Before the disease almost all patients were sexually active and had a partner (95.5%; n = 274); at the time of filling the questionnaire only slightly more than half of the patients remained sexually active (57.1%; n = 164). About 30.7% (n = 88) stated that the disease was the main reason for not being sexually active. More than 60% of patients (60.9%; n = 137) used products to improve the comfort of sexual intercourse, mainly lubricants (39.7%; n = 114). Only about ⅓ of the patients (32.1%; n = 92) were satisfied with their sex life, 48.1% (n = 138) stated they were not satisfied with their sex life, 19.9% (n = 57) did not answer this question. The main reasons for lack of satisfaction with sex life included: decreased libido (65.9%; n = 189), vaginal dryness (55.1%; n = 158). The mean score of forms filled out by the respondents was 24.50 in FSFI form.

Conclusions. Assessment of sexual dysfunction in patients with breast cancer should be performed on a routine basis before treatment and regularly during treatment.

Key words: breast cancer, sexual health, FSFI, chemotherapy

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Introduction

Breast cancer is the most common malignancy among women in Poland and in the world, with a mortality rate second only to that of lung cancer [1]. The increasing incidence concerns patients of all age groups, resulting in younger, sexually active women struggling with cancer and the negative effects of oncological therapy. Among the most common are a significant reduction in sex hormone levels, and the following:

- mood deterioration,
- vaginal dryness,
- decreased libido or painful sexual intercourse.

Breasts are one of the most important symbols of femininity and sexuality. Cancer surgery, but also systemic therapy (chemotherapy and hormone therapy) cause a change in the perception of one's body [2–4].

It is emphasized in the literature that the negative effects of breast cancer and cancer therapy affect patients of reproductive age to a greater extent than those after menopause [5]. Breast cancer in women of reproductive age has a negative impact on many spheres of a woman's life that do not affect postmenopausal patients: premature cessation of ovarian function, a rapid decline in the level of sex hormones and the appearance of all the symptoms of menopause, cytostatic-induced infertility, disruption of the family model, interruption of the continuity of work during the greatest period of a woman's life [6–8].

The course of cancer in the young tends to be more aggressive, biological subtypes with higher malignancy are more often diagnosed, as well as cancers diagnosed at higher stages due to their unusual course and diagnostic difficulties, for example, pregnant or postpartum patients. Cancer treatment of young women is more intensive and sometimes prolonged, may last for years, and frequently occurs at the time of greatest sexual activity [9].

Sexual dysfunction is a serious complication of oncological therapy that affects the quality of patients' lives [10]. They should be diagnosed and regularly evaluated during anticancer treatment, and the patient should receive support from specialists (gynecologists, sexologists, psychologists).

Aim of study

The aim of the survey proposed by us was to assess the interest in sex by breast cancer patients during and after oncological treatment as well as to identify ways to improve the quality of patients' sex lives.

Material and methods

The proposed survey consisted of 3 parts: the first part included questions about the demographic data of respondents (10 questions – age, place of residence, education, employment, year of breast cancer diagnosis, place of treatment, type of surgical and systemic treatment, children), in the second part there were the author's questions about sexual dysfunction (12 questions), in the third part there was the Female Sexual Function Index (FSFI) form assessing the sexual functioning of women.

The questionnaires were made available online from October 13, 2020 to December 20, 2020 through the social networks of patient organizations involved in breast cancer care. The FSFI questionnaire was available in Polish.

Statistics

The analysis was performed using IBM SPSS Statistics 26. The significance level was adopted as 0.05. In the analysis, the Spearman correlation coefficient was counted for numerical, ordinal, and binary data (due to the lack of normal distribution in the data). For the remaining data, the values of statistics for the chi square test for independence of data were counted. In order to make the correlations more detailed, the z-test was used to compare the structure indexes (percentages).

Ethics

Personal data was not processed, the survey was fully anonymous and voluntary. The anonymous survey does not have to be submitted to the opinion of the institutional review board, which was confirmed by the institutional review board at the Poznan University of Medical Science in Poland.

Results

Participants

A total of 287 women diagnosed with breast cancer were included in the survey. The mean age for the entire group was 41.42 years, the median age was 41 years, 199 (72.89%) constituted women 20–45 years old, the remaining respondents (n = 74; 27.11%) were from 46–64 years old.

More than ⅓ of respondents came from cities with a population over 250 thousand (36.6%, n = 105), then from cities with population up to 50 thousand (17.8%, n = 51) and from villages (17.4%, n = 50); 15.7% (n = 45) of respondents came from cities with population between 50 thousand and 100 thousand, 12.5% (n = 36) from cities with population between 100 thousand and 250 thousand.

More than half of the respondents were employed (52.3%, n = 150), almost ⅓ were on sick leave (31.7%, n = 91), and 7.3% of the patients (n = 21) were on pension, then 5.9% of the respondents (n = 17) were unemployed and 2.8% of the patients (n = 8) were on maternity leave. The vast majority of patients declared higher education (66.0%, n = 192), more than ¼ secondary education (28.6%, n = 82) and 4.2% vocational education (n = 12).

In the majority of patients (77.7%), cancer was diagnosed in the last 4 years: for 19.9% (n = 57) in 2020, for 28.9% (n = 83) in 2019, and for 17.8% (n = 51) in 2018, and for 11.1% (n = 32) in 2017. The diagnosis of breast cancer in 2016–2014 was declared by less than 10% of patients (2016 – 7.7%, n = 22;

2015 – 4.2%, n = 12; 2014 – 3.8%, n = 11). The vast majority of patients (83.6%; n = 240) had children.

More than half of the patients (62.0%, n = 178) were treated in cancer centers, 16.7% (n = 48) in multispecialty hospitals, 14.6% (n = 42) in university hospitals – and the smallest group of patients was treated in specialty clinics – 6.6% (n = 19). 42.9% (n = 123) of patients underwent a mastectomy with reconstruction, 22.3% (n = 64) underwent breast-conserving treatment, and 34.8% (n = 100) underwent a mastectomy.

More than ¾ of patients (76.6%; n = 220) were undergoing systemic treatment (56.4% under hormone therapy, 20.2% under chemotherapy or immunotherapy); 81.2% of respondents had received systemic treatment in the past (72.1% chemotherapy, 9.1% hormone therapy).

Sexual activity

Before the disease, almost all patients were sexually active and had a partner (95.5%; n = 274), at the time of filling the questionnaire only slightly more than half of the patients remained sexually active (57.1%; n = 164), 95.5% (n = 274) had a partner.

About 30.7% (n = 88) stated that the disease was the main reason for not being sexually active, 2.1% (n = 6) did not have a partner, 0.3% (n = 1) never liked sex, 10.5% (n = 30) mentioned other reasons for not being sexually active (vaginal pain and dryness, decreased libido, fear of infection during treatment, fear and dislike of partner, dislike of their body, loss of regular partner due to disease) (tab. I).

More than 60% of patients (60.9%; n = 137) used products to improve the comfort of sexual intercourse, mainly lubricants (39.7%; n = 114), vaginal globules (19.9%; n = 57), rarely estrogen creams (1.4%; n = 4). Respondents were asked why they would like to be sexually active: 88.5% (n = 254) would like to feel pleasure from sexual activity, 43.9% (n = 126) would like to please their partner, 12.2% (n = 35) would like to have a child.

Satisfaction with sex life

Only about ⅓ of the patients (32.1%; n = 92) were satisfied with their sex life, 48.1% (n = 138) stated they were not satisfied with their sex life, 19.9% (n = 57) did not answer this question. The main reasons for lack of satisfaction with sex life included: decreased libido (65.9%; n = 189), vaginal dryness (55.1%; n = 158), lack or loss of sexual desire (43.2%; n = 124), problem with acceptance of own body (36.2%; n = 104), not feeling pleasure during intercourse (34.1%; n = 98), reluctance and lack of sexual pleasure (32.1%; n = 92), pain during intercourse (31.4%; n = 90), lower sense of attraction to sexual partner (28.6%; n = 82), orgasmic disturbance (21.6%; n = 62), sense of frustration (14.6%; n = 42), as well as partner leaving due to breast cancer, partner's reluctance to have intercourse, fear of acceptance from partner, shame of undressing due to failed reconstruction, shoulder and mastectomy site pain, recurrent infections, menopause (tab. II).

Support from medical staff

The vast majority of respondents (98.3%; n = 282) reported that they did not receive any information from medical staff about possible sexual dysfunction related to cancer or treatment, or methods to support sexual problems related to the disease (96.5%; n = 277).

The Female Sexual Functioning Index form

The Female Sexual Functioning Index (FSFI) is a self-report measure of sexual functioning that has been validated on a clinically diagnosed sample of women with female sexual arousal disorder. The present investigation extended the validation of the FSFI to include women with a breast cancer diagnosis. The form is a standardized, validated, and recognized form regarding aspects of a woman's sexual sphere.

Table II. Reasons for lack of satisfaction with sex life

Do any of the following problems apply to you?		
	frequency	percent
pain during intercourse (dyspareunia)	90	31.4%
reluctance or lack of sexual pleasure	92	32.1%
lack or loss of sexual desire	124	43.2%
lack of pleasure during intercourse	98	34.1%
orgasmic disturbances	62	21.6%
decreased libido	189	65.9%
lubrication disorder (vaginal dryness)	158	55.1%
lower sense of attraction to a sexual partner	82	28.6%
problems with acceptance of one's body	104	36.2%
depression	31	10.8%
feelings of frustration	42	14.6%
none of the above applies to me	24	8.4%
other	14	4.9%

Table I. Discontinuation of sexual activity

If NO, what is the reason that you are not currently sexually active? (if you are, please skip this question)			
	frequency	percent to total (n = 287)	percent to inactive (n = 123)
I do not have a partner	6	2.1%	4.9%
I have not been sexually active due to my disease	88	30.7%	71.5%
I have never enjoyed sex	1	0.3%	0.8%
other	30	10.5%	24.4%

The advantage of this form is the possibility to compare the obtained results with literature data. The assessment concerns 6 domains: desire, excitement, lubrication, orgasm, sexual satisfaction, and pain related to sexuality. The assessment covers the past 4 weeks. The outcome refers to sexual functioning ranging from 2 to 36 points. A value of 26 points or less indicates the presence of significantly clinical sexual dysfunction [11].

The mean score for the surveyed population was 24.5, and the lowest mean scores were obtained for questions on the desire domain (3.67), followed by the pain (4.04) and orgasm (4.09) domains.

Women after a mastectomy with reconstruction + BCT obtained significantly higher results in the overall assessment of sexual functioning than women after reconstruction only. Women after a mastectomy with reconstruction + BCT obtained significantly higher results in the lubrication domain ($p = 0.013$) and in the domain of pain related sexuality ($p = 0.008$) than in women after a mastectomy. In the case of other domains, there are no significant differences in the obtained results.

Discussion

Cancer treatment

Breast cancer is the most common malignancy among women in Poland and in the world, the increasing incidence concerns patients of all age groups. The increasing overall survival of breast cancer patients is associated with modern diagnostic methods and increasingly effective therapies. Perioperative treatment (pre- and postoperative) protects patients from cancer recurrence, but affects their quality of life.

Chemotherapy causes changes in a woman's appearance, loss of hair, eyelashes, eyebrows, change in shape and color of nails and many others. However, its effect is limited mainly to the time of treatment, while later complications of chemotherapy are much rarer (cardiotoxicity, nephrotoxicity, inhibition of ovarian function) [12]. The mentioned changes in the patient's appearance are not without influence on self-esteem, the woman's sense of beauty and aesthetics. For many women, especially the younger ones, good looks, an attractive appearance and beauty are extremely important [13, 14]. Lack of self-acceptance may lead to depression, withdrawal from partner and social relations, and further to a feeling of loneliness, rejection or social exclusion. Shame, sadness, sometimes anger or resignation, which may appear when looking in the mirror during everyday care or social interaction, also significantly affect the patient's psyche and lower self-esteem. Therefore, an important part of the therapy is also taking care of the patient's psychological comfort. The patient should feel attractive and self-confident regardless of the undesirable side effects of the treatment.

Menopause caused by chemotherapy depends on the drugs used, the time of their use and, above all, the patient's age. In very young women (about 35 years of age) it may be temporary, whereas in slightly older women it may occur even a few years earlier than natural menopause and carry all the consequences of premature cessation of ovarian function [15]. Natural menopause is a process that takes several years, occurs in a gradual manner, while idiopathic menopause occurs abruptly, almost overnight, and causes significantly increased prolapse symptoms, worsening the well-being of patients and reducing their quality of life, as well as leading to infertility, destroying women's maternity plans [16]. Among the respondents, 57.1% remained sexually active despite oncological treatment, and 12.2% of the respondents indicated the desire to have offspring as one of the most important reasons for sexual activity. Taking care to preserve the fertility of breast cancer patients prior to anticancer treatment should be a standard component of breast cancer care. The awareness of having frozen oocytes or embryos and the possibility of using them for *in vitro* fertilization after completion of cancer therapy significantly improves the quality of life of breast cancer patients and offers hope for a return to full activity [17].

The vast majority of breast cancers, approximately 80%, are hormone-dependent cancers that express estrogen and/or progesterone receptors in the nuclei of tumor cells and require long-term (5–10 years) adjuvant hormonal therapy.

Premenopausal patients may receive tamoxifen as monotherapy or a gonadoliberin analog in combination with tamoxifen or an aromatase inhibitor. Tamoxifen is a selective modulator of the estrogen receptor, stimulating its effects in the bones or endometrium and inhibiting its effects in the mammary gland. Tamoxifen monotherapy does not reduce blood estrogen levels and does not induce menopause in patients of reproductive age. Aromatase inhibitors, by inhibiting aromatization of androgens to estrogens, reduce the production of sex hormones in adipose tissue, which is the largest source of estrogens in postmenopausal women. They can be used as monotherapy in postmenopausal women or in combination with a gonadoliberin analog in premenopausal women. Studies show that extending hormone therapy to 10 years in patients with the highest risk of cancer recurrence, reduces this risk, but this is not without impact on the patients' quality of life [12].

The effects of chemotherapy are most troublesome and visible during the therapy, late complications occur with varying severity and do not affect all patients. On the other hand, the long-term use of hormone therapy causes permanent and burdensome changes in the well-being and functioning of the body, which also affects the sexual sphere of women [18]. The study was performed among conscious women, almost all patients had at least secondary education (28.6% secondary; 66.9% higher), half of them were professionally active (52.3%). The respondents were treated in highly specialized centers (oncology centers, university hospitals and multi-specialty hospitals). About $^2/_3$ of the patients (64.8%) were from cities

with a population of more than 50,000. Despite the fact that the effects of systemic treatment are long-lasting and predictable, the vast majority of patients (98.3%) were not informed by medical personnel about the possibility of a deterioration in the quality of their sex life, nor about methods of assisting sexual dysfunction (96.5%).

In a study conducted by Usher et al., 68% of patients stated that they would like to receive information about sexual dysfunction, but only 41% received it [19]. Almost half of the respondents (47.7%) who took part in our study independently sought methods to improve the comfort of sexual intercourse, which indicates the great need of women for support from medical personnel.

An open and frank conversation about the problems, disease, and thus clear communication on the part of the medical staff should constitute an important support during therapy. It should be an fundamental point, an element of properly conducted sexual rehabilitation.

The sexual dysfunction of breast cancer patients are often perceived as negative effects of systemic treatment (chemotherapy and hormone therapy), but the problem is much more complex. Surgical treatment changes the appearance of a woman with breast cancer, which affects both the perception of herself and her partner, thereby potentially affecting their mutual relationships.

An extremely important psychological aspect of the treatment process is the feeling of attractiveness to the partner, which undoubtedly has an impact on the quality of sexual life. It is strongly related to the female psyche and acceptance of her body, often changed as a result of treatment [20]. This was also shown in our study. Patients after a mastectomy with reconstruction and after breast conserving surgeries had higher scores in the FSFI than those after a mastectomy without reconstruction. Patients with breast after breast surgery had less pain related to intercourse and less vaginal dryness.

Among the respondents, 34.8% had a mastectomy, i.e. removal of the entire breast, while the remaining patients had either a breast-conserving operation (22.3%) or a mastectomy with simultaneous reconstruction (42.9%), where the woman has never had to face life without the breast, one of the most important symbols of female sexuality. In a study conducted by Collins et al., patients with T1–T3 tumors undergoing breast-conserving treatment had a better perception of their bodies than those undergoing mastectomy with reconstruction. This was not the case for patients with greater local disease severity (T4). Patients with T2 tumors perceived their bodies better after mastectomy than those after mastectomy with reconstruction.

The Female Sexual Functioning Index form

The mean score of forms filled out by the respondents was 24.50, which indicates clinically significant sexual dysfunction and correlates with the data obtained by Blouett et al. where the mean total score of the form was 25.14 [20]. These results differ from those obtained in the control population reported in the literature: in the study by Rosen et al., where 30.5 ± 5.3 was obtained; and in the study by Wiegel et al. 30.75 ± 4.8 [21]. Both the study population and Blouett's study were dominated by young breast cancer patients. In both studies, the greatest problems were found with the feeling of desire and the feeling of orgasm. Both of these domains are closely related to each other, but also have a huge psychological basis [21].

Sexual dysfunction – the main part of the survey

Young women of reproductive age participated in this study, with a mean age of 41.42. Most studies on the quality of life of patients focus on postmenopausal women, who account for over 90% of all breast cancer cases. However, the deterioration of sexual quality of life is much less expressed in this group than in patients of reproductive age, which is also confirmed by the study conducted by Bloulet et al. [20]. This study included patients under 35 years of age, about half of them declared dissatisfaction with sexual activity. Similar results were obtained by analyzing data from a questionnaire, where almost 73% were women aged 20–45 years. Before beginning therapy, 95.5% of patients had a partner and exactly the same number of women were sexually active; at the time of filling the questionnaire, only 57.1% of patients remained sexually active, still 95.5% had a partner. Almost ⅓ (30.7%) of the patients indicated cancer as the main reason for not being sexually active, another 10% mentioned decreased libido, vaginal dryness, or dislike of their own bodies, without directly linking the reason to cancer or cancer therapy.

Only 32.1% remained satisfied with their sex life. The main reasons for dissatisfaction were: decrease of libido, vaginal dryness, loss of sexual needs, lack of pleasure during sexual intercourse, problems with acceptance of own body, depression.

Among the respondents, women after a mastectomy with reconstruction obtained significantly higher results in the lubrication domain than women after a mastectomy. Women after a mastectomy with reconstruction obtained significantly higher results in the domain of pain related sexuality than women after mastectomy. In the case of the remaining domains (desire, excitement, orgasm, sexual satisfaction) there were no significant differences in the obtained results.

Summary

The study included women undergoing active systemic treatment, 56.4% on hormone therapy, 12.2% on chemotherapy. The FSFI test is a useful diagnostic tool for sexual dysfunction occurring in a woman in the past four weeks. The author's questions in the main part of the survey are an interesting source of information on sexual activity and the sex life satisfaction of patients during oncological treatment. Almost all of the women declared having a partner (95.5%), and 69.7% were satisfied

with the emotional relationship between them, thus the reasons for the discontinuation of sexual activity in as many as 38.4% of the patients should be considered as follows: decrease of libido, problems with body acclimatization and physical changes making intercourse difficult. These results do not correlate with the results of the FSFI test, where the biggest problem for patients seemed to be achieving orgasm and pain during sexual activity.

Conclusions

Breast cancer diagnosis, surgical and systemic therapy can worsen the quality of a patient's sex life. From the very beginning of the treatment, preventive measures should be implemented to reduce the impact of the therapy on the patients' sex life. Currently, there are many treatment options available to improve libido in women with breast cancer. One should remember about an individual approach for each patient. Correct communication is also extremely important, i.e. the way of talking to the patient and her partner. Medical staff should be open to discussions about the sexuality of patients treated for breast cancer and be careful and empathetic about these topics. This is why:

- Patients should be informed by medical personnel about the possibility of sexual dysfunction during breast cancer treatment.
- Patients should be informed by medical personnel about the possibility of oncofertility counselling before the therapy.
- Patients should receive appropriate support from medical staff in improving the quality of their sex lives.

Recommendations for physical sexual dysfunction:

- moisturizers (lubricants),
- anti-inflammatory agents,
- vaginally administered estrogen,
- relaxation exercises for the vaginal muscles.

Psychological and sexual support:

- psychotherapy,
- sexual rehabilitation,
- psychotherapy for the partner.

Conflict of interest: none declared

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The dose no longer plays a paramount role in radiotherapy (oncology), but time apparently does

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Overall 80 clinical data sets (head and neck, breast, lung and prostate) have been selected from the literature (about 10,000 patients) to analyze and compare the importance of the total dose (D) *vs.* overall therapy time (OTT). There was no correlation between local tumor control (LTC) and dose used as a single parameter. On the contrary, for tumors (larynx and cervix cancer) treated with a constant $TCD_{50} \pm 5\%$, any extension of the ORT resulted in a significant decrease of the LTC by about 1.5–2% per each one day extension of the ORT. Dose intensity (DI) expressed by the number of gray per unit of time (day) strongly correlated with the LTC, which significantly increases when the DI becomes larger than 7 Gy/day. The results lead to a final conclusion that suggests inverse order of the planned treatment parameters, i.e. TIME plays the primary role in treatment and the DOSE (and its fractionation) is a consequence of the primary choice.

Key words: total dose, overall therapy time, dose intensity

Introduction

Over the past years, the final diagnosis of malignant solid tumors has been continuously widened by various prognostic and predictive parameters, including histological type, stage and localization, molecular, genetic, hormonal and kinetics factors or parameters. This has resulted in an increasing variety of tumor geno- and fenotypes, even within the same histological type, stage and localization.

The choice of a proper and optimal combined therapeutic strategy for a given tumor has become more and more individualized, but it may raise some doubts and uncertainties. This situation also applies to radiotherapy.

Through the last decades, new sophisticated and precise accelerators, techniques and dose fractionation schedules have entered the market and daily radiotherapy practice. Since the early years of radiotherapy, despite all these novel biological, clinical and technological options and solutions, the total dose invariably has remained of paramount importance and is still the first parameter chosen in the radiotherapy planning.

Is the TOTAL DOSE really the leading parameter and the most important factor which determines treatment efficacy (permanent local tumor control is not always equivalent to the patient's curability)? Is it proven with no doubts or is it only a unequivocally accepted paradigm or custom? The present review tries to answer this question.

Material and methods

Among many widely recognized studies on radiotherapy for various tumor types, four important cancers have been chosen i.e. head and neck [1–6, 24], breast [7–16], lung [18–21] and

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prostate [23–24]. It is obvious that such studies include various clinical factors and a variety of combined treatment strategies. Therefore, from numerous important papers published in leading journals, data sets were selected which comply with the following criteria:

- radiotherapy was the primary or the only treatment modality,
- at least a 3-year local tumor control follow-up (in some data sets it was even 5- or 10-years, e.g. breast and prostate),
- all fractionation parameters and irradiation methods were reported in details,
- epithelial or adenocarcinomas only.

Altogether, 75 data sets (10,000 cases) were selected (tab. I), among which 15 were treated with conventional fractionation, 23 with altered, and 32 with stereotactic hypofractionated radiotherapy.

Even though the individual TNM stage was considered, the tumor data sets were arbitrarily subdivided into two groups: early and advanced. Fractionation schemes concerned conventional, altered (accelerated, hyperfractionated or hybrid) and stereotactic hypofractionated radiosurgery.

The first step of the analysis was focused on the relationship between minimum 3-year local tumor control (LTC) and a given TOTAL DOSE only. In the next, the data sets have been used to estimate TCD_{50} values (total dose producing 50% LTC). Only cases which received such TCD_{50} doses were chosen, and at least the 3-year LTC rates were related to the overall radiotherapy time (ORT).

Finally, using fractionation parameters characterizing individual data sets, dose intensity (DI) values were calculating using the following simple formula: DI = TD/ORT [1], representing the number of g rays delivered in the unit of time (Gy/day).

Once again, the 3-year LTC were related to a given Gy/day values. This part of the analysis is important because it illustrates the biological/clinical power (LTC) of the delivered irradiation independently on the number and size of dose per fraction. For example, doses of 60 Gy in 30 fractions in 42 days, 70 Gy in 35 fractions in 49 days, and 80 Gy in 40 fractions given in 56 days characterize the same DI value of 1.43 Gy/day, whereas, i.e. 20 Gy given in 10 days the DI equals 2.0 Gy/day, compared with the DI of 10 Gy/day if 20 Gy is delivered in 2 days.

Table I. Data sets characteristic

Tumour	Fraction		
	conventional	altered	stereo hypofx
head and neck	'4	3	4
breast	3	5	8
lung (NSCLC)	5	3	'2
prostate	3	2	8
overall	15	23	32

Results

Total dose

An analysis of the relationship between the total dose (Gy) and at least 3-year local tumor control (LTC) for four different cancer localizations (fig. 1A–D) did not reveal any correlation of the LTC with total doses – irrespective of the dose fractionation. However, high or even very high LTC occurred when stereotactic hypofractionated radiosurgery (SHRS) was used, although this is characterized by much lower total physical doses. It mainly concerns prostate cancer (fig. 1D) but not necessarily the lung cancer data sets (fig. 1C), because the SHRS produced low (<50%) for some cases or very high LTC for others. Subsequently, it is difficult to accept total dose as a primary and major or even meaningful single parameter determining the final efficacy of fractionated radiotherapy. It sounds logical because even within the same cancer type and localization, individual tumors are clinically and biologically highly heterogeneous, including their radiosensitivity as well. Thus, some fractionation schedules could be highly effective for one tumor type but not for others, and the choice of total dose as a primary parameter in the tailoring of radiotherapy planning for individual patients seems in decisive enough.

Overall radiotherapy or treatment (combined) time (ORT or OTT)

Reviewing the literature in the field of the dose-time-effect relationship, it is difficult to select studies which include as many homogenous groups of cancer cases as possible regarding tumor type, localization, and stage of disease treated with radiotherapy alone, which used total doses in the narrow range, but given in a relatively wide range of the overall radiotherapy time (ORT). Such a study allows for an estimation of the TCD_{50}, i.e., the dose producing 50% of at least 3-year local tumor control (LTC_{50}), and therefore the ORT remains the only variable. Among many published papers, two studies have been found which fulfilled all the criteria mentioned earlier, and therefore were selected for the present analysis. The first one, published in 1983, concerned supraglottic cancer patients, all in the stage T3–4N0 [4, 24] and a second [17] was published in 1992 regarding cervix cancer cases in stage III where radiotherapy was the only treatment and the ORT was the only variable.

The raw data from these three studies have been used to estimate the TCD_{50} values, which was 85 ± 7 Gy for cervix cancer and 61 ± 5 Gy for supraglottic cancer. Next, only cases which received these estimated TCD_{50} doses ± 5% were selected, and at least 3-year LTC_{50} values were calculated and the LTC_{50} *vs.* ORT curves were estimated (fig. 2). For constant TCD_{50} values, the LTC values significantly depended on the ORT. For cervix cancer, an extension of the ORT from 30 to 70 days results in a significant decrease of the LTC from 90% to 35%, which gives a loss of about 1% of the LTC by one day extension of the ORT. For supraglottic cancer, the decrease of the LTC with extension of the OTT was

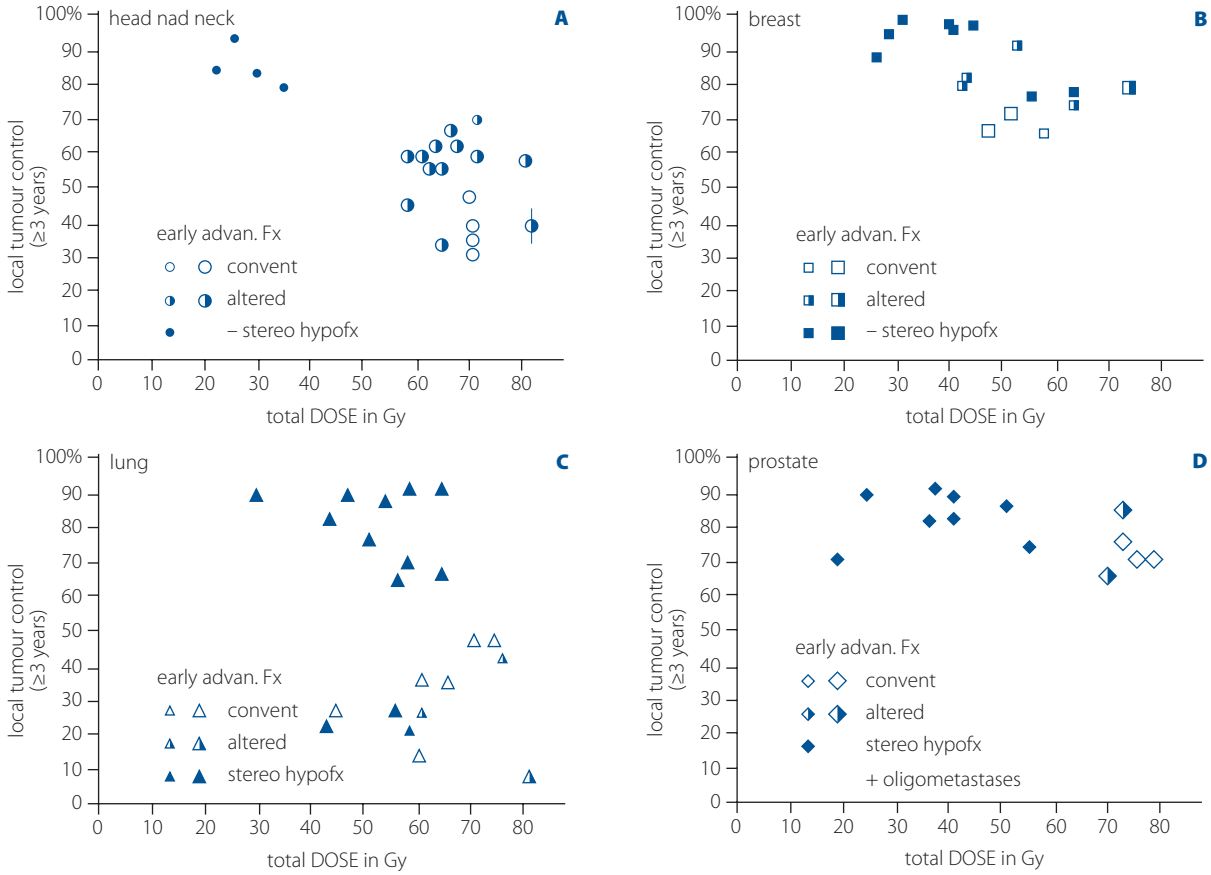

Figure 1. Local tumour control – total relationship (A–D) (A – head and neck, B – breast, C – lung, D – prostate)

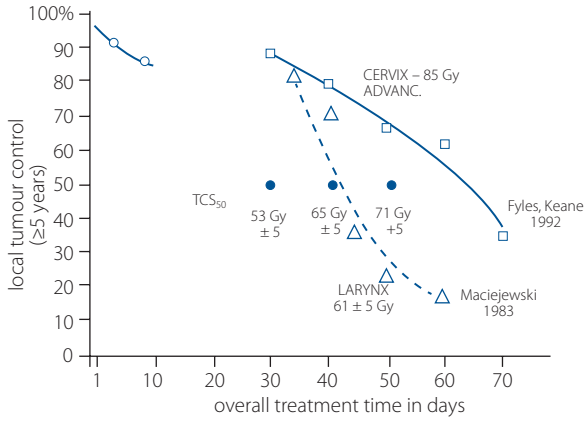

Figure 2. Local tumour control (LTC) – Dose Intensity (DI) relationship for four cancer types

even steeper, resulting in a reduction of the LTC by about 2.5% per each one extra day of the ORT.

These results convincingly suggest that time as a single parameter has a much higher prognostic and predictive power then the dose. However, it does not discredit (compromise) the importance of the prescribed total dose, but it does show that the ORT is more important – "the shorter the better".

A very short ORT which generally characterizes stereotactic hypofractionated radiotherapy (left top on fig. 2) strongly correlates with unexpectedly high probability of the LTC; it is not possible to separate the ORT or OTT (for combined treatment modalities) from the dose. They depend one on one another and the Dose-intensity factor (DI) quantatively expresses such a relationship. Figure 3 clearly shows that the LTC continuously improves with increasing the DI for all four analyzed tumor types and the LTC above 70% can be predicted if the DI gets higher than 5–6 Gy/day.

The paramount importance of TIME as a factor has a key and universal meaning, not only for radiotherapy as a sole treatment but also for combined therapy which is used more

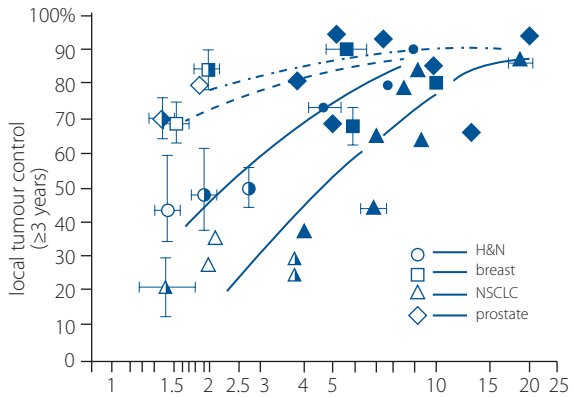

Figure 3. Local tumour control (LTC) – dose intensity (DI) relationship for four cancer types

and more frequently. In the contrary to radiotherapy time (ORT), overall therapy time (OTT) is measured from the first to the last day of combined treatment modalities. Therefore any unnecessary breaks or delays between therapeutic modalities could significantly decrease preliminarily the predicted clinical efficacy of such a strategy.

Recently, the importance of TIME has been the major focus of the published study on intraoperative radiotherapy (IORT) during conservative surgery for early advanced breast cancer patients in stage T1–2N0M0 with at least one risk factor, combined with postoperative chemotherapy and radiotherapy [17]. Two options of combined therapy were used. In the first, adjuvant chemotherapy was primarily used, followed by so-called delayed RT, whereas in the second, concurrent chemo-radiation was applied where OTT was about 4-times shorter (56 days *vs.* at least 235 days). As a consequence, overall DI for the first option was about 0.49 Gy/d compared with 2.25 Gy/d for the second one (tab. II). For the concurrent CHT-RT, the HR (hazard ratio) factor was 0.07, what means that this option, due to shortening the OTT, correlated with a decreased risk of local recurrence by 93% (1 – HR = 1 – 0.07 = 0.93), whereas in the first option, the HR for the delayed RT reached the highest value of 14.28. If the delayed time of the RT was longer than 20 days above an average of 60 days (HR = 1.02) than the risk of local recurrence increased by about 49% (HR = 1.02^{20} = 1.485 ~ 49%). Therefore the clinical efficacy of the intraoperative IORT was in fact neglected and thereafter its use occurs unnecessary. This example clearly illustrates the leading prognostic power of the time factor. It becomes even more evident for the SHRS. In that modality the ORT is significantly shortened to 1–10 days, resulting in a tremendous increase of the DI, being in the range of 6–20 Gy/day. As a consequence, much lower total doses of 1 x 20 Gy or 3 x 18 Gy produce very high LTC (85–95%) of various tumors (fig. 2A–D, fig. 3) what not necessarily always means patient's permanent cure.

Discussion

Despite and contrary to the gathered experience over the last few decades and many well documented studies, the first decision in radiotherapy planning immutably still concentrates on the choice of total dose (TD), followed by the choice of dose per fraction, overall radiotherapy time (ORT) and the optimal 3D technique of irradiation. In the case of combined therapy, the same steps are applied and not necessarily enough attention is paid to the duration of intermodality breaks.

Thus, the ORT or OTT may differ and even be prolonged whereas the total dose does not change. The clinical consequence of such a situation is that the cell kill power of the prescribed dose significantly decreases (fig. 2 and fig. 4).

In H&N cancers, any dose escalation beyond 83 Gy, even if hyperfractionated does not significantly yield any LTC improvement [1, 3, 4, 24]. For locally advanced tumors, concurrent chemo-radiation is an optimal solution and chemo-shots during continued daily irradiation can be considered as "cell-kill boosts" resulting in LTC improvement [1–5, 24]. Even though H&N cancers are not best suited to the SHRS [20, 26], for selected early advanced small tumors, mainly localized in the midface region, it is highly effective; 24 Gy in 2 fractions or 5 fractions of 3 Gy produce about 80–85% 3-year LTC. It seems that SHRS could be feasible and a reasonable and effective option for local tumor recurrences [20, 22]. This is convincing evidence that the therapeutic power of the time factor is advantageous to the effect of the dose.

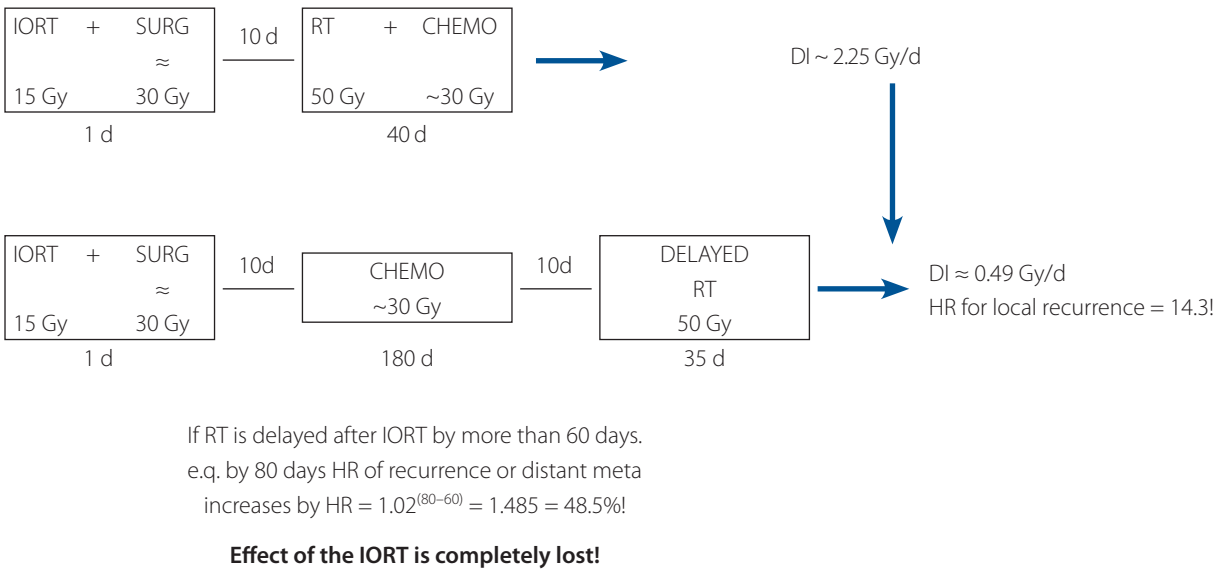

Figure 4. Two options of the IORT – conservative surgery combined adjuvant chemo- and radiotherpay for early breast cancer

For breast cancer, the use of RT is the object of extensive discussion [7–16]. In principle, the discussion is focused on early breast cancer with or without conservative surgery. The number of the individual tumor's characteristics is continuously growing. In one recent Int J Radiat Oncol Biol Phys issue, Francis et al. [16] used as an example the case of pT1cpN0(i+) cM0, multifocal, dose margins, pleomorphic calcification, high grade Ki >50, oncotype DX24, BRCA1 and BRCA2 positive breast cancer and the authors have raised the question to three independent experts – what would you do? Would you recommend post-op radiotherapy or not? There were no unanimous answer, with many ranging from – "yes, of course" to "not necessarily", suggesting that the risk of complications may outweigh the benefits. In 2021 Rodin et al. [7] have convincingly pointed out, based on the results of three independent trials [12–14], that standard fractionation for breast cancer is no longer standard. These trials have documented strong evidence to support stereotactic hypofractionation as optimal irradiation of early-stage breast cancers regardless of its characteristics. Various hypofractionated schedules, ranging from 26 Gy in 5 fractions to 54 Gy in 3 fractions produced high 80–95% 6–8-year local tumor control. The present review clearly supports these results (fig. 2 and 3) and simultaneously show the prognostic advantage of the time factor over the total dose.

Finally, De Paula et al. [8] and Mutter et al. [9] recommended a hypofractionated regimen of 38.5 Gy delivered in 10 fractions in the ORT of 12 days as a highly effective standard option for patients with early-stage breast cancer, which significantly shortens the ORT from about 5 weeks to only 1.5 week.

A similar conclusion concerns non-small-cell lung cancer [18–21]. Even in the 70ts Fletcher [24] pointed out that using conventional fractions of 1.8–2.0 Gy, a total dose of 100 Gy or higher might be required for local control of most NSC lung cancer, but such high doses would not be achievable without excessive toxicity. Stereotactic hypofractionated radiotherapy (SHRT) has been recognized and recommended mainly by Timmerman et al. [20] and Tateisi et al. [21] as the most favorable alternative, but it remains limited for early stage and small tumors (T1–2N0M0) and also as a postoperative treatment. Various fractionation schedules were tested ranging from 45 Gy in 3 fractions in 6 days to even 60 Gy in 3 fractions in 6 days which resulted in unexpectedly high 3–5 year LTC – from 75% to even more than 85% (fig. 1C and fig. 3). Such a high LTC corresponds with a DI higher than 7 Gy/day, which convincingly although indirectly suggests favorable and advantageous prognostic power of the time over the total dose.

Undoubtedly, prostate cancer has become a major candidate for the SHRT [22, 23, 26], and 46 Gy in 5 fractions or 40 Gy in 3 fractions in 6 days produces high, over 80% 5-year biochemical no evidence of disease (BNED). Therefore, such schedules seem to be serious challengers to conventional 78 Gy in 39 fractions in 55 days.

If combined therapy is planned instead of radiotherapy alone, the prognostic priority of time factors remain. This means that each treatment modality should be completed at the shortest OTT possible and concurrent chemo-radiation is much more effective than the sequential option due to the shortened OTT.

If each therapeutic modality, part of the combined treatment, complies with treatment time rigour, then intermodality intervals (breaks) have a kay-impact on the overall effectiveness of such a therapeutic strategy. Any delays longer than required or permissible significantly reduce overall DI, which leads to lower probability of local tumor control (LTC). A convincing example of such a risk is the use of the IORT during conservative surgery for early breast cancer combined with postoperative radiotherapy or chemoradiation [17]. If the RT was delayed after postop. chemotherapy, than a one day extension of the interval between the IORT used at the beginning of the treatment and postoperative adjuvant RT delayed above 60 days resulted in an increase of local recurrence risk by 2% per each day of the intertreatment interval. A consequence of the delayed IORT--RT interval to 80 days instead of 60 days was that the risk of local recurrence increased by 42.5%. This may strongly suggest that in fact the use of the IORT was ineffective, and likely unnecessary because the efficacy of the IORT dose was reduced almost to zero. This study strongly suggests that the OTT of the combined treatment modality becomes a paramount prognostic factor; even if each modality is planned as highly effective, any protraction of its duration over the planned limit, and any unnecessary lengthened intermodality breaks are likely to ruin the preliminary expected clinical efficacy.

Conclusions

Despite the custom of planning the dose as the first prognostic parameter, the time of radiotherapy or whole therapy plays a paramount role. Therefore the OTT (ORT) should be primarily chosen as the first parameter and the planned modality (radiotherapy) should be tailored thereafter one after another, in such a way that their duration and any intermodality breaks are as short as possible. This leads to an inverse order of the treatment parameters planning, that means the time to be the first one and followed by the dose and its fractionation.

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How to manage radiation-induced dermatitis?

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Radiotherapy is one of the treatment methods available for cancer patients. More than half of all cancer patients treated with radiotherapy will experience radiodermatitis during their treatment. There are two commonly used scales to evaluate clinical manifestations: Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) scale. According to them, the severity of radiation dermatitis ranges from mild erythema to moist desquamation and ulceration. Prevention methods for radiation dermatitis include proper skin hygiene, the use of topical corticosteroids, other non-corticosteroid agents and systemic drugs. Treatment of radiation dermatitis is guided by the severity of skin damage. In grade 1 it can be limited to moisturising the irritated skin field but in more severe reactions (grade 2–4) the use of dressing is essential. There is still a need to investigate new products, techniques or novel approaches to minimize, prevent or treat radiation dermatitis in patients undergoing radiotherapy.

Key words: radiation dermatitis, radiodermatitis, acute skin toxicity, radiotherapy

Introduction

More than half of all patients treated for cancer will receive some form of radiation therapy (RT). Irradiation affects not only the cancer cells but also normal tissues, often resulting in significant side effects during and after the completion of therapy [1–5]. Radiodermatitis is a side effect of radiation therapy. Radiation reactions apply to any tissue that is in the irradiated volume due to the topography. The tissues that are always in the volume to be treated include the skin. Skin complications arise after both irradiation and systemic treatment, i.e. chemotherapy or treatment directed at molecular disorders.

Radiotermatitis occurs only in irradiated volume. [1]. Radiodermatitis can occur as an early side effect during the actual treatment period or some months after the radiotherapy is completed. Skin changes can be experienced by 72–95% of patients undergoing radiotherapy and radiation dermatitis (RD) is the most common adverse reaction in the sites of radiation [2, 6, 7]. The severity of early skin radiation reactions depends on both the irradiation technique, the treatment regimens, i.e. a combination of systemic treatment, the fractional dose as well as the total dose, and also to a large extent, the individual predispositions of the patient. Late changes in the skin and subcutaneous tissue are most often manifested in the form of fibrosis, atrophy of the subcutaneous tissue and telangiectasia.

At present, due to the use of modern radiation techniques, fibrosis and telangiectasia are very rarely seen. All these clinical symptoms of radiation dermatitis are associated with discomfort, burning of the skin and also very often with pain. The described symptoms have a negative impact on the patient's

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quality of life. Radiodermatitis ranges from mild to severe and may be acute or chronic [8–10]. This review will discuss the risk factors, pathophysiology, clinical manifestations, prevention and treatment of radiation dermatitis.

Risk factors

The factors that may influence the response of the patient's skin to RT have been grouped into two categories: host factors that depend on the patient's biological characteristics and treatment-related factors. These factors may place the patient at increased risk of dermatitis and should be considered at the baseline skin assessment. The risk factors of developing radiodermatitis are summarised in table I. Patient-related factors:

- age,
- sun exposure,
- smoking,
- nutritional status, body mass index (BMI) >25,
- inflammatory skin disease – atopic eczema with sensitive skin,
- autoimmune diseases – sclerodermia, lupus erythematosus, rheumatoid arthritis.

Different body areas have different sensitivity to radiation. The most sensitive skin regions of the body are the anterior of the neck, face, extremities, chest and abdomen [11]. Skin folds are also susceptible to develop severe radiodermatitis due to a phenomenon called the "bolus effect". These areas are more likely to receive a higher dose of radiation and more prone to bacterial contamination and secondary infection [12]. Elderly, obese (BMI ≥25) patients and smokers are more prone to radiodermatitis [13–15]. Ex-smokers are also at higher risk of severe skin reactions, probably because of vessel changes [13]. In patients who have undergone breast reconstruction after surgical procedures, the skin is thought to be more susceptible to burns. This is due to the sensory and thermoregulatory changes that develop after surgery [16]. There are a few congenital diseases which can adversely influence the severity of radiodermatitis. Patients with pre-existing conditions, for example systemic lupus erythematosus [17] or ataxia telangiectasia [18], may experience increased frequency of severe forms of radiodermatitis.

Table I. Risk factors for radiodermatitis development

Category	Risk factor
intrinsic	advanced age [7, 87]
	BMI ≥25 [13, 14, 88]
	chronic sun exposure [14]
	comorbidities (e.g. SLE) [17]
	female sex [7, 88]
	location (skin folds) [12]
	poor nutritional status [87]
	previous breast reconstruction/implants [16]
	radiosensitive disorders (ataxia telangiectasia) [18]
	smoking [13, 87, 89].
extrinsic	concurrent chemotherapy [13, 22]
	dose rate [90, 91]
	dosing schedule [90, 91]
	EGFR inhibitors [21]
	radiosensitizers (e.g. paclitaxel, docetaxel) [22]
	radiation quality [20, 92, 93]
	total radiation dose [90]

Treatment-related factors

Treatment-related factors such as dose per fraction, total dose and radiotherapy techniques are very important and can influence the severity of skin reaction. The surface area exposed and the radiotherapy techniques used have an impact on developing radiodermatitis. Treatment delivered with a higher dose per fraction >2 Gy or a higher total dose means the skin area in question is at risk of developing sever radiodermatitis [19]. The use of bolus or lower energy beams has an impact on the skin's reaction. The total doses of radiation required to induce skin injury are summarised in table II.

New techniques such as intensity modulated radiotherapy (IMRT) can reduce the dose for skin and healthy tissue which is associated with a decrease in the severity of radiodermatitis compared with 3D conformal conventional radiation therapy [20]. Radiotherapy combined with chemotherapy or immunotherapy as well as anticancer therapies with EGFR inhibitors can be a factor as regards increased severity of radiodermatitis [21]. Some chemotherapeutic agents (for examples paclitaxel and docetaxel) can be a radiosensitizer. Combining treatment with radiotherapy: concomitant chemoradiotherapy, especially for head and neck cancers or gynaecological cancers, can lead to more sever skin reaction. Patients with advanced head and neck cancer who are referred for induction chemotherapy with

Table II. Dose-dependent acute skin changes with localized radiation dose [10, 11, 32]

Skin reaction	Radiation dose (Gy)	Onset
early transient erythema [32]	2	<24 hours
permanent epilation [11]	7	3 weeks
definite erythema [10]	12–20	2–3 weeks
hyperpigmenation [32]	≥20	2–4 weeks
dry desquamation [10]	20–25	3–4 weeks
moist desquamation [10, 32]	30–40/45–60	≥4 weeks
ulceration [10]	>40	≥6 weeks
dermal atrophy/necrosis [10]	>45	months
complete hair loss [32]	>55	2 months

5-fluorouracil followed by chemoradiotherapy can develop more severe radiodermatitis [22]. Some systemic treatment can sensitize skin cells for irradiation. It can be given before, simultaneous or after irradiation. The mechanism of these drugs is very similar to irradiation. It is a reason of more severe side effects. Radiation dermatitis which occurs in patients receiving cetuximab concomitantly with radiotherapy for locally advanced head and neck cancer have different pathophysiological and clinical characteristics. Bernier et al. proposed a new classification of radiodermatitis that takes into account the side effects of cetuximab on the skin of the entire body and the irradiated area.

Pathophysiology

Modern radiotherapy techniques is delivered mostly from accelerators which generate photons. The newest conformal radiotherapy treatment, especially of the head and neck regions or for children, uses protons beams [23]. Radiation therapy using high energy radiation kills cancer cells via free radicals. Free radicals are damaging deoxyribonucleic acid (DNA) and the cells are killed through the mechanism of of apoptosis. This way is called a direct mechanism. In 1906 Bergonie and Tricondeau [24] stated that any cells which are actively dividing are more radiosensitive than mature, non-dividing cells. This occurs not only in cancer cells, but also in healthy tissues. It is the reason why basal keratinocytes and hair follicle stem cells are the primary target for radiation, but also the activity of melanocytes is affected by radiation energy [25]. Radiation activates various cellular signalling pathways leading to activation and expression of many cytokines, vascular injury and activation in coagulation cascade [26]. Increased levels of IL-1 and TNF-α stimulate the production of metalloproteinases causing degradation of dermal matrix components and a disruption of the epidermal basal cell layer [27–30]. A vascular response occurs with extra-capillary cell injury and capillary dilation [31, 32]. Irradiation via free radicals changes the mitotic activity in the germinal cells of the epidermis [11, 33]. Free radical production is a very important mechanism for cancer treatment. It leads to cancer cell death and side effects not only for skin, but also for oral and gastrointestinal mucosa [11]. Free radicals also activate a cascade of pro inflammatory cytokines and cytokine TGF-β in the irradiated cells. It leads to death of the epidermal basal cell in indirect way.

Clinical manifestations

The first early skin changes occur within 1–4 weeks from the beginning of radiotherapy and persist during the treatment period [32]. The first clinical manifestations of radiodermatitis occur in the form of erythema (I grade according to the EORTC/RTOG scale), then dry exfoliation (II grade according to the EORTC/RTOG scale) appears; the next phase is wet exfoliation (III grade according to the EORTC/RTOG scale). Sometimes there are severe skin lesions in the form of ulcers (IV grade according to the EORTC/RTOG scale). The phase of wet exfoliation and ulceration (severity of reaction III and IV) is often accompanied by bacterial and fungal infection (tab. III) [35]. All these clinical symptoms of radiation dermatitis are associated with discomfort, burning of the skin and very often also with pain. The described symptoms have a negative impact on the patient's quality of life. Late changes in the skin and subcutaneous tissue are most often manifested in the form of fibrosis, atrophy of the subcutaneous tissue and telangiectasia. At present, due to the use of modern radiation techniques, fibrosis and telangiectasia are very rarely see. According to CTCAE version 4.0 [34], the severity of radiodermatitis can be graded on a scale of 0–5, and in RTOG 0–4.(tab. III, tab. IV). In both scales, grade 0 means no changes. In grade 1 changes occurs as an erythema (fig. 1). Erythema starts as a result of capillary dilatation and oedema in the dermis. Both these mechanism due to increased vascularity and obstruction [31, 36]. Erythema is dose dependent and can be asymptomatic. The erythema manifestation depends on a balance between pro-inflammatory and anti-inflammatory processes. [27]. Other skin changes that may be seen in grade 1 include: epilation and dyspigmentation [8]. Grade

Table III. Classification of radiodermatitis

	0	1	2	3	4	5
CTCAE [34]	none	faint erythema or dry desquamation	moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	death
RTOG [35]	none	erythema; dry desquamation; epilation	bright erythema; moist desquamation; edema	confluent moist desquamation; pitting edema	ulceration, hemorrhage, necrosis	

Table IV. Radiodermatitis score NCJ clasification

Radiation dermatitis NCI Common Terminology Criteria for Adverse Events (version 4.03)				
grade 1 (mild)	grade 2 (moderate)	grade 3 (severe)	grade 4 (life–threatening)	grade 5
faint erythema or dry desquamation	moderate to risk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	death

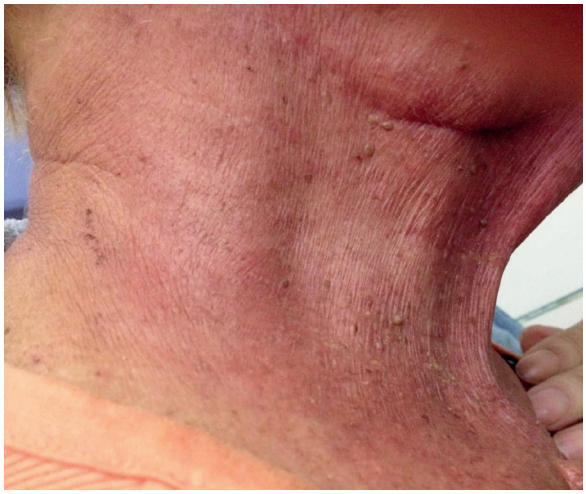

Figure 1. Faint erythema and dry desquamation (grade 1 RD)

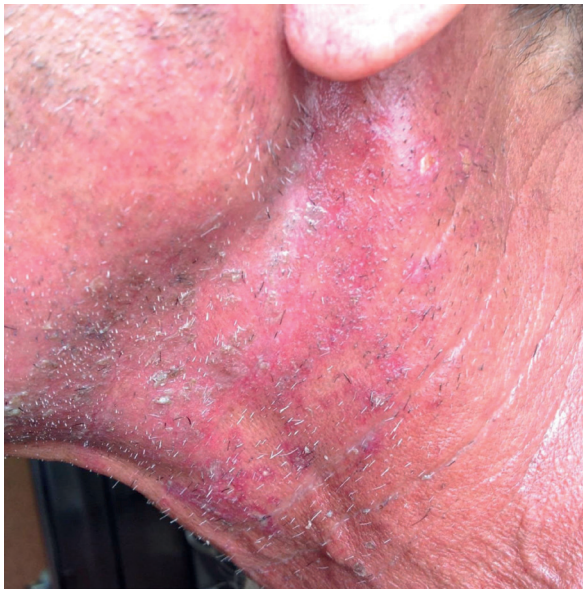

Figure 2. Grade 2 RD with moderate erythema and desquamation

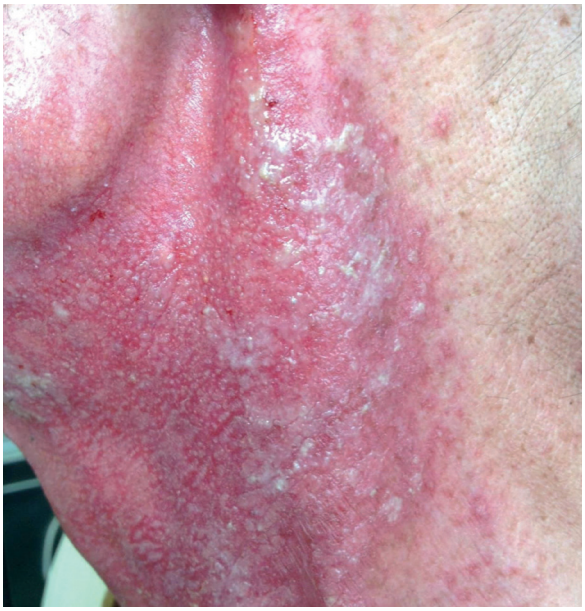

Figure 3. Grade 3 RD with moist desquamation and persistent erythema

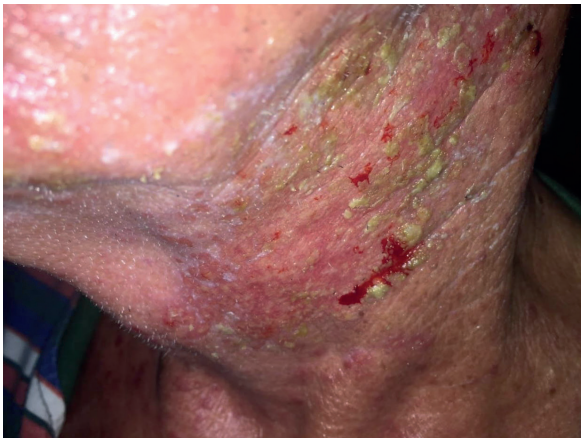

Figure 4. Moderate erythema with moist desquamation, spontaneous bleeding and bacterial infection (grade 4 RD)

2 appears very often in the forth or fifth week of treatment [33] as a dry desquamation. Dry desquamation can occur as a pruritus, an increase in melanin pigmentation or scaling – grade 2 (fig. 2) [33]. When the total dose of irradiation becomes higher than 50 Gy, the moist desquamation phase occurs. It happens mostly in the fifth week of treatment. [25]. Grade 3 changes consist of confluent moist desquamation (fig. 3), pitting and oedema may also be present. Grade 4 dermatitis is characterized by ulcers, haemorrhage, and skin necrosis (fig. 4). In most cases, the radiodermatitis is mild to moderate but about 20–25% of patients experience severe reactions [37, 38]. In the absence of infection, radiodermatitis is self-limiting and will resolve in 2–3 weeks with complete healing within 1 to 3 months [39, 40]. The reepithelization of

the denuded skin usually begins within 10 days [33]. Seldom acute radiation skin changes become consequential-late changes. These can lead to chronic wounds and skin necrosis [8]. Patients who underwent radiation therapy have skin hypersensitivity to UVA and UVB radiation. It lingers in varying degrees of severity over the rest of the patient's life.

The management of radiodermatitis

A lot of research has been carried out due to the serious problem of skin changes occurring after irradiation, as well as after systemic treatment. Thanks to this we can now assess the effectiveness of various methods of prevention and treatment of skin reactions [41–44]. Despite great commitment and the emergence of new publications every year, the unambiguous best practices for the so-called "golden standard" have still not been agreed upon. There are some products in the world with proven anti-inflammatory effectiveness in the prevention and treatment phase. In practice, each cancer centre has its own methods of preventing and treating skin radiodermatitis.

General skin care recommendation

1. Everyday cleansing is recommended. The use of a delicate washing gel, with a unique composition and a pH close to 5, delays the appearance of symptoms associated with radiation reactions. It helps to remove epidermal cell fragments formed in the course of radiation therapy, which subsequently has a positive effect on maintaining the natural protective barrier of the skin. It is recommended at the onset of radiotherapy and after its completion. The way irradiated skin is cleaned is very important. It should be done by hand with warm water. The skin should afterwards be dried with a paper towel. Hydration of the skin. Apply an emulsion or emollient cream with a delicate consistency and unique composition including ceramides that can moisturise the skin with hyaluronic acid; due to its strong hygroscopic properties this produces a moisturising effect due to water retention in the stratum corneum. The cream should be applied two to three times per day after radiotherapy and one hour before irradiation. Natural, soft clothes are recommended, synthetic clothes should be avoided.
2. For shaving, an electric razor should be used.
3. All products which contain alcohol should be avoided e.g. *eau de toilette*, perfume.

Protection and treatment

Management of skin care for patients during radiotherapy remains controversial. Recommendations of the so-called "golden standard" for preventing and treating radiodermatitis have not been fully agreed upon. We can find recommendations which are implemented for different countries or even institutions. A study published in the United Kingdom showed that different advice is given to patients by radiotherapy departments. There is no consensus on how to manage radiodermatitis [41]. It remains a problem for all patients who receive radiotherapy throughout the world. Prevention is management of skin which is irradiated to postpone or prolonged a time when radiodermatitis in III EORTC/RTOG grade occurs. Many radiotherapy departments advise cleaning irradiated skin. Roy et al. [45] and Campbell et al. [46] showed that washing irradiated skin during the course of irradiation for breast cancer is not associated with increased skin toxicity and should not be discouraged. In fact, cleaning reduces bacterial load and the risk of secondary infection [8]. Also Wesbury et al. [47] advises to maintain normal hair washing during cranial radiotherapy. The use of delicate washing gels, with a unique composition and with a pH close to 5, delays the appearance of symptoms associated with radiation reactions. It helps to remove epidermal cell fragments formed over the course of the radiation therapy; this has a positive effect on maintaining the natural protective barrier of the skin. It is recommended from the first days of radiotherapy and after its completion. The use of antiperspirants or deodorants remains controversial despite the results of a few trials [48–50] showing no evidence as regards increasing skin reaction. To prevent severe, acute and late skin toxicity that optimises the treatment plan, the use of intensity-modulated radiotherapy (IMRT) has the potential to reduce the severity of skin reaction. Intensity-modulated radiotherapy techniques are a highly conformal therapy that modulates the intensity of the radiotherapy delivered at a high dose of irradiation to the tumour target with significant sparing of the surrounding healthy skin [42, 43]. Some authors suggest that irradiated skin should not be exposed to sun light for many months or even years [44]. The use of sun block with very high SPF 50 protection is recommended for patients.

Topical corticosteroids

There are few products in the world with proven anti-inflammatory effectiveness in the prevention and treatment phase. Topical corticosteroids are known for their anti-inflammatory effectiveness in the way they inhibit the pro inflammatory cytokines IL-6 cascade which is stimulated by free radicals [8]. They play a huge role in prevention and treatment of radiodermatitis with variable results. The results of a study (n = 176) conducted by Miller et al. [51] showed that patients receiving daily 0.1% of mometasone furoate (MF) during radiotherapy notice less acute skin toxicity than the patients receiving placebo. They reported less itching, irritation, burning and discomfort. Another study published by Hindley et al. [52] in a double-blind study demonstrated that 0.1% of mometasone furoate not only reduces radiodermatitis when applied during and after radiotherapy, but it also has a beneficial effect on quality of life. Boström et al. [53] showed that a combination of 0.1% mometasone furoate with emollient cream treatment significantly decreased acute radiodermatitis. The outcome of another trial [54] for just 20 patients showed statistically significantly better

results at preventing radiodermatitis in patients receiving prednisolone with neomycin compared to patients in the control group. Meghrajani et al. [55] in the publication showed benefits of preventive use of 1% hydrocortisone in women with breast cancer (n = 50). Omidvari et al. [56] and Schmuth et al. [57] reported that prophylactic use of topical corticosteroids (betamethasone 0.1% and 0.1% metylprednisolone respectively) during irradiation in patients treated for breast cancer delays the occurrence of acute radiodermatitis.

Other topical agents

There are some products in the world with proven anti-inflammatory effectiveness in the prevention and treatment phase. Turmeric oil – a mixture of turmerones which together with other fats form the protective barrier on the surface of the skin by sealing the outer skin layer, has an antioxidant effect, preventing microbial contamination. The basic mechanism of turmeric oil is associated with its chemopreventive and antimutagenic activity.

Palatty et al. [58] published the outcome of a random study in 50 patients treated for head and neck cancer during 7 weeks. All patients underwent 7 week irradiation. The experimental group receiving turmeric oil based cream from the first day of treatment. The control group received mineral baby oil for irradiated skin. The study showed a statistically significant decrease in the severity of radiodermatitis in the experimental group compared to the baby oil group. Liguori et al. [59] conducted a study on 134 patients undergoing irradiation. Patients were randomized into two groups. The experimental group received 0.2% hyaluronic acid cream. The control group received a placebo. The hyaluronic cream or placebo were applied to the skin twice daily at the start of radiation. The outcome of this study showed a statistically significant improvement in delaying severe skin reaction in the experimental group. The duration of intensity of radiodermatitis was statistically shorter in the group using the hyaluronic cream [59]. It is likely that hyaluronic acid, due to its strong hygroscopic properties, provides a moisturising effect as a result of water retention in the stratum corneum.

Another randomized trial [60] on breast cancer patients, showed a statistically significant higher rate of radiodermatitis grade ≥2 in the group using the hyaluronic gel comparing to the group of patients receiving petrolatum-based cream. This negative outcome is probably the effect of the gel formula of the hyaluronic product. The products used for protection should have an emollient formula. In 2016 Ben-David et al. [61] in his II phase, prospective, double-blind randomized trial showed that patients treated with melatonin-containing emulsion experienced significantly reduced radiodermatitis compared to patients receiving a placebo. Emulsions containing trolamine are sometimes used in clinical practice, because trolamine is believed to have radioprotective properties as a result of macrophage cell stimulation and removing necrotic tissue, promoting fibroblast proliferation, reducing vascular alterations, restoring CD34 expression, promoting epithelial cell proliferation and decreasing IL-1 expression and collagen secretion [8]. However, the radioprotective properties were not yet confirmed in the clinical studies [62–64].

D-panthenol is a substance that is a natural component of the skin, and necessary for its normal functioning. It has a toning effect, strongly moisturises, makes the skin soft and elastic, soothes irritations, supports the regeneration of any damaged to the epidermis and prevents peeling of the skin. In a study [65] on 86 laryngeal and breast cancer patients undergoing radiotherapy, a dexpanthenol cream (Bepanthen – Roche) was applied on irradiated skin. The study did not show any clinically important benefits of using Bepanthen cream for skin reactions [65]. Silver sulfadiazine cream was investigated by Hemati et al. [66] in 102 women receiving RT for breast cancer. Silver sulfadiazine cream reduced the severity of radiation-induced skin injury compared with general skin care alone.

A new double-blind, placebo-controlled study [67] on 47 patients showed the effectiveness of boron-based gel in reduction of radiodermatitis. An interesting preclinical test with vasoconstrictors was performed on rats by Fahl [68]. All tested adrenergic vasoconstrictors (epinephrine, norepinephrine, or phenylephrine) applied before irradiation gave 80–100% prevention from increased risk of radiation dermatitis. Further preclinical and clinical studies assessing their effectiveness and safety are needed. Evidence from a limited number of trials does not support the use of aloe vera [69, 70], sucralfate [13, 71], calendula [72], tocopherol [73]. From the first day of irradiation, the skin loses its natural protective layer. The natural biological barrier is also disturbed, which in turn exposes the skin to bacteria, fungi and viruses causing inflammation and dehydration. Very promising in the prevention and management of radiodermatitis is STRATA-XRT – a silicone based film which forms a gel dressing. This product was under investigation in 197 patients treated with irradiation for head and neck cancer. It was a single blind randomised controlled study comparing the use of silicone film and 10% glycerine cream as a comparator. The outcome of this study showed that STRATA HRT is effective for preventing, delaying and reducing the severity of radiation-induced dermatitis. Another very interesting product is ectoine, which seems to be a natural skin protectant. Ectoine functions as a superior moisturiser with long term efficacy. Some other agents appear promising (e.i. pentoxiphilline [74], sylimarin [75]) but more long-term studies assessing their effect on irritated skin are essential.

Treatment

After the second or third week of radiotherapy, when erythema occurs, a smooth emollient should be used [25]. Some authors suggest the use of non-scented, hydrophilic, lanolin-free cream [9, 76–78]. It is better to use some forms of creams or ointments than lotions for dry desquamation [8]. The emulsion should

include: shea butter. The basic mechanism of shea butter action is similar to all vegetable oils.It creates a protective barrier on the surface of the skin (occlusive layer, the so-called film), which directly reduces water loss through the skin. In addition, it reduces the destabilization of the homeostasis of the stratum corneum, and thus the remaining layers of the skin. Additionally, emulsion which contains glycerin, moisturises and improves the condition of the skin, collecting water and binding it to the epidermis.

The management of more severe skin reactions with moist confluent desquamation (grade 3) requires more intensive treatment to prevent secondary bacterial and fungal infection [37, 39]. The use of micro-silver (micronized silver) helps to protect burned, exfoliated skin against bacterial and fungal infections to which it is exposed. A microsilver is remaining on the surface and accumulating mainly in its micro cavities. Micro-silver is added to cosmetics in order to maintain its proper functioning; secondary microbial contamination (both during storage and use, as well as after application to irradiated skin) may increase the risk of adverse effects related to the excessive growth of microorganisms on the surface of irradiated skin. Micro-silver can be use as a dressing. Dressings may protect irradiated skin from bacterial contamination or absorb fluids from oozing weeping wounds. The use of dressings in the treatment of moist desquamation is based upon the observation that a moist environment promotes the rate of re-epithelization and increases the speed of wound healing [80]. Other benefits include simplifying wound care and pain control [8, 33]. Hydrogel (with or without moisturising cream) and hydrocolloid dressings have been used in the manage-

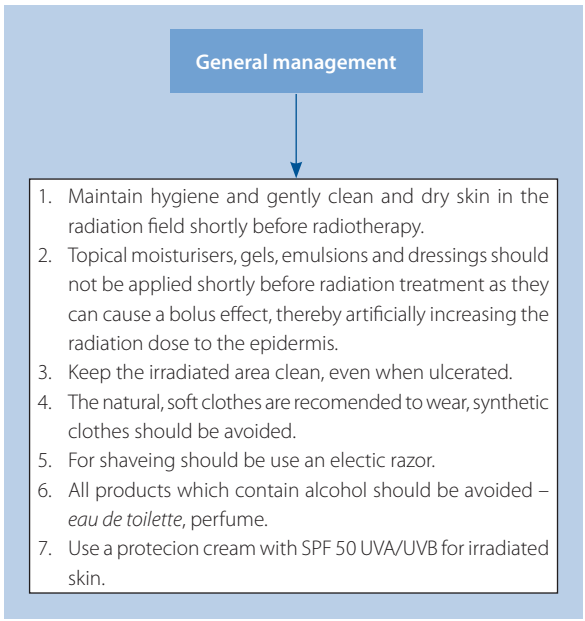

Figure 5. General management approaches

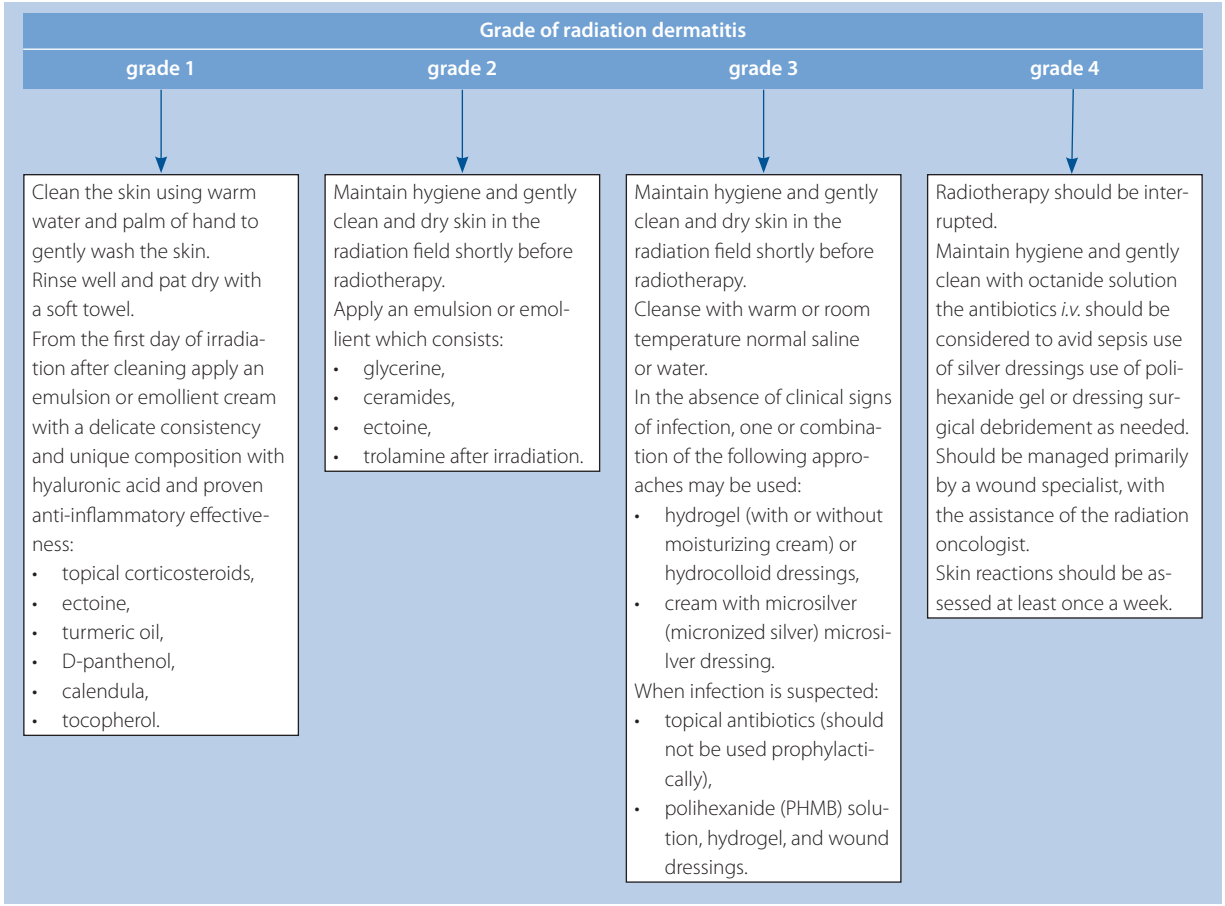

Figure 6. How to manage radiation dermatitis – algorithm

ment of moist desquamation in order to promote a moist environment for reepithelization [8, 33]. Dressings should be changed 1 to 3 times daily or less often, depending on the dressing type and drainage needed [33]. Diggelmann et al. [81] investigated the clinical efficacy of Mepilex Lite dressings in reducing radiation-induced erythema in 24 women with breast cancer. Those dressings significantly reduced the severity of radiation-induced erythema compared with the standard aqueous cream [81]. The results of the study conducted by Vuong et al. [12] suggest that silver leaf nylon dressing is effective in reducing radiodermatitis because of its antibacterial properties. Polihexanide (PHMB) is available as a solution, a hydrogel and in wound dressings [83]. It is well tolerated [84], anti-septically effective against MRSA and VRE (vancomycin-resistant *Enterococcus*) [85–86], can be used for wound irrigation and is suitable as an antiseptic for critically colonized and infected wounds and moist desquamation. The worst skin side effects are radiodermatitis which occurs as a skin necrosis and ulceration. Thanks to new radiotherapy techniques this complication is very rare. When it occurs, radiotherapy should be interrupted [37]. Possible treatment methods include use of silver dressings and surgical debridement sometimes with full-thickness skin grafts [87, 88]. The use of polihexanide PHMB dressing and gel is very promising in the treatment of grade 4 radiodermatitis. The use of Polihexanide gel or dressing is recommended as a therapeutic option for acute wounds, chronic ulcers and second-degree burns due to its analgesic effect and treatment of wound infections, including promoting wound healing [89]. Therefore, PHMB may be considered the first choice agent for infected chronic wounds and burn wounds (gel, dressing). Off-label use of low-intensity heliumlaser (HPLT) has shown to be effective in some patients with chronic ulcerations after RT [90]. There are case reports of patients with IV radiodermatitis in which mesenchymal stem cells injected into and around the wound after the excision of necrotic skin promoted wound healing [91].

Conclusions

Radiodermatitis is a very common side effect of anticancer treatment. This is a huge problem not only for oncologists and dermatologists, but also for GPs. Despite the great commitment and the emergence of new publications every year, a set of unambiguous best practices for the so-called "golden standard" have still not been agreed upon. There are few products in the world with proven anti-inflammatory effectiveness in the prevention and treatment phase. In practice, each cancer centre has its own methods of preventing and treating skin radiodermatitis. There is a need to process recommendations for the management of radiodermatitis.

We can propose an algorithm – "How to manage radiation induce dermatitis" (fig. 5, fig. 6).

Conflict of interest: none declared

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Selected platinum complexes in standard and modern anti-cancer therapies

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The constantly observed increase in the number of cancer cases inspires research aimed at searching for new compounds with anti-cancer potential. In recent years, much research has focused on platinum complexes, especially their anti-cancer properties. Platinum derivatives are characterized by high cytotoxic activity against many types of cancer cells. However, among the numerous developed complexes, only cisplatin, carboplatin and oxaliplatin have found wide application in chemotherapeutic treatment. Nedaplatin, lobaplatin and heptaplatin have also gained recognition, and have been implemented in oncological therapy in Japan, China and Korea. Some of the platinum complexes are still at the stage of pre-clinical and clinical trials. The aim of the research conducted today is to search for platinum compounds that show high pharmacological effectiveness, with clearly limited side effects. In future therapeutic strategies, the possibility of using platinum complexes in conjunction with other chemotherapeutic compounds is being considered, which may contribute to increasing the efficacy of anti-cancer therapy.

Key words: cisplatin, platinum complexes, anticancer drugs, chemotherapy

Introduction

According to the National Cancer Registry, cancer diseases, along with cardiovascular diseases, are the most common cause of death in Poland [1, 2]. Literature data show that the number of patients with neoplastic diseases may systematically increase, and cancer may become the main cause of premature deaths, for both women and men [3]. The most frequent cases of cancer are lung, ovarian, cervical, prostate, testicular, stomach and colon cancers. In addition to many currently used methods of treating oncological diseases, it is important to implement appropriate preventive measures in everyday life, which would significantly slow down the processes of carcinogenesis.

The etiology of neoplastic diseases is complex and multifaceted, conditioned by both external (environmental) and internal factors [4]. It has been shown that some behavioral and psychosocial factors (including stress and depression) as well as genetic predispositions may contribute to the development and progression of neoplastic diseases [5–7]. An improper diet, low physical activity and chronic stress are more and more often mentioned as some of the basic indicators influencing the development of the carcinogenesis process [5–7, 8, 9].

Despite the wide range of preventive tests implemented, the development of diagnostic techniques and the constantly growing public awareness, it has still not been possible to find appropriate therapeutic methods that would effectively combat all types of cancer. In recent years, special attention has been paid to the side effects of treatment, resulting from the high toxicity of the cytostatics used [10, 11]. It was also

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noticed that the problem of cancer cells resistance to the drugs used is becoming more and more frequent [12, 13]. Numerous metal compounds, including platinum and its derivatives, play an important role in the treatment of neoplastic diseases. Currently, some platinum complexes are used effectively in the chemotherapy of malignant neoplasms. However, there are still some platinum derivatives whose anti-tumor activity is not yet sufficiently known and described.

The aim of this study is to explain the most important mechanisms of action of the selected platinum compounds, their potential therapeutic properties, and to determine the role of new platinum complexes that would be characterized by low toxicity over a broad spectrum of anti-tumor activity.

Platinum complexes in anti-cancer therapy

Due to the multidirectional scope of action of platinum, platinum drugs are now quite widely used in the treatment of cancer. One of them is the platinum compound (II) called cisplatin. It was introduced to clinical practice at the earliest, in the literature it is described as a first-generation platinum drug. The confirmation of the anti-cancer effect of cisplatin has resulted in the search for other platinum complexes, effective in anti-cancer therapy, but with limited side effects [14]. In recent years, a number of *in vitro* and *in vivo* studies have been conducted to determine the potential anti-tumor properties of cisplatin analogues. Of these, only carboplatin and oxaliplatin are used in oncological therapy, and a number of others (picoplatin, phenanthriplatin, satraplatin, adamplatin, oxoplatin, ethacraplatin, lipoplatin, BBR3464) are still at the experimental or clinical trial stage (tab. I). The mechanisms underlying the anti-tumor activity of the new platinum (II) and (IV) complexes are still insufficiently elucidated. It is known, however, that platinum compounds are characterized by quite diverse therapeutic effects, which may result from a different chemical structure, geometric isomerism and the degree of oxidation of platinum [15].

Cisplatin – a first-generation platinum drug

Cisplatin was first synthesized by Alfred Werner in 1845, and its chemical structure was described in 1893. In 1965, Barnett Rosenberg showed that platinum complexes generated during electrolysis significantly weaken the multiplication of *Escherichia coli* bacteria [14, 16]. This discovery became the basis for further research aimed at determining the inhibitory effect of cisplatin on the proliferation of cancer cells. It was then revealed that the compound can effectively inhibit cell division of murine sarcoma and L1210 leukemia [16]. In clinical practice, cisplatin was first used in 1971, while 7 years later this compound was approved by the Food and Drug Administration (FDA) and became an available drug with an anti-cancer effect [17–19]. Currently, cisplatin is used with great effectiveness in the treatment of breast, ovarian, cervical, prostate, testicular, esophagus, stomach, head and neck cancer, multiple myeloma, melanoma, non-Hodgkin's lymphoma and cell lung cancer [17, 18, 20].

The drug can be used both as monotherapy and in combination therapy with radiotherapy, taxoids (paclitaxel and docetaxel), doxorubicin, 5-fluorouracil, leucovorin and gemcitabine. The combined effects of cisplatin and other compounds in the treatment of various types of cancer are still undergoing numerous experimental and clinical evaluations [21–23]. Cisplatin has been shown to be highly effective in the treatment of neoplastic diseases, but at the same time it has been found to be highly toxic to normal cells. Side effects are multi-organ, include cardiotoxicity, ototoxicity, myelosuppressive and immunosuppressive activity [17, 24–26]. Moreover, cisplatin is a highly nephrotoxic drug leading to the development of acute renal failure, which may significantly impede dosing of the drug and limit its use [17, 27, 28].

Cisplatin is a cytostatic, belonging to the group of drugs with an alkylating effect [13]. It has pro-apoptotic [20, 29–31] and antiproliferative [20, 32, 33] properties, which allows it to be used in the treatment of many types of malignant neoplasms. However, it is important to remember about the factors influencing the effectiveness of cisplatin treatment, such as: the diverse biological response of cancer cells, various sensitivity and resistance to the drug. Neoplastic cell resistance to cisplatin may lead to disease recurrences, sometimes shortly after chemotherapy has been completed.

The mechanisms underlying platinum resistance are complex and are currently not fully understood. This process is multifactorial in nature. In general, several signals are activated simultaneously, which weaken the effectiveness of the therapy [33]. This is a key problem in overcoming the resistance of cancer cells to cisplatin. Therefore, it is extremely important to conduct research that will allow an explanation of the interaction between the factors, responsible for both the sensitivity and resistance, of cancer cells to the action of platinum complexes.

Cisplatin analogues currently used in cancer chemotherapy

The available literature shows that cisplatin is a long-used anticancer drug showing high toxicity and numerous dose-dependent side effects [17, 32–36]. In addition, acquired resistance to this drug has been found [33–35]. These data inspired the search for new compounds with cisplatin-like properties but with high therapeutic efficacy and limited adverse effects on normal cells. The platinum derivatives, carboplatin and oxaliplatin, turned out to be drugs with a broad spectrum of antitumor activity, with low toxicity and reduced acquired resistance. In addition to carboplatin and oxaliplatin, which have been approved and introduced in medicine, the platinum complexes such as nedaplatin, lobaplatin and heptaplatin are also gaining recognition. To date, only a few Asian countries have obtained consent to use these compounds in oncological therapy (tab. I).

Table I. Selected platinum complexes in contemporary and future therapeutic strategies [18, 36, 37, 71, 77, 96]. Current status as of July 2021

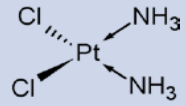
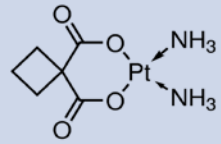
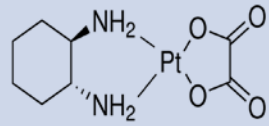
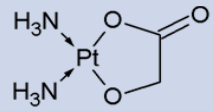
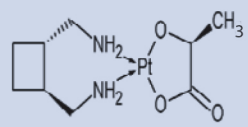
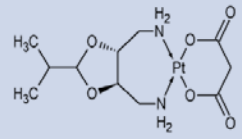
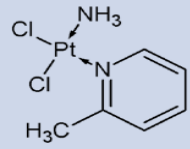
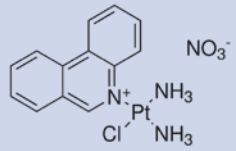
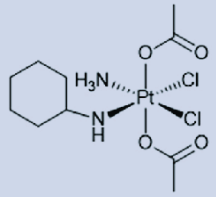
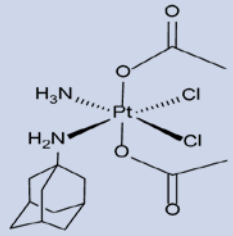
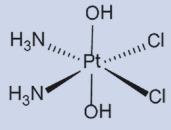
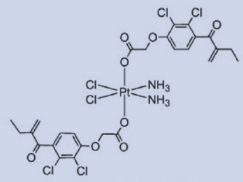
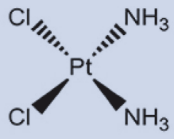
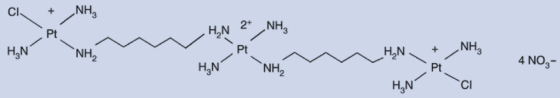
Platinum complex		Molecular formula	Structure	Clinical or experimental status
PLATINUM COMPLEXES (II)	cisplatin platinol	cis-dichlorodiammine platinum $Pt(NH_3)_2Cl_2$		The drug was approved by the FDA. It has been used in medicine since 1978.
	carboplatin paraplatin	cis-diammine(1.1-cyclobutanedicarboxylato) platinum $[C_4H_6(CO_2)_2]Pt(NH_3)_2$		The drug was approved by the FDA. It has been used in medicine since 1989.
	oxaliplatin eloxatin	(trans-R,R-cyclohexane-1.2-diammine) oxalatoplatinum [SP-4-2-(1R-trans)]-(1.2-cyclohexanediamine-N,N')[ethanedioata(2--)-O,O']platinum (DACH)$PtCl_2$ $C_8H_{14}N_2O_4Pt$		The drug was approved by the FDA. It has been used in Europe since 1999 and in the USA since 2002.
	nedaplatin aqupla	cis-diammine(glycolato)platinum $C_2H_8N_2O_3Pt$		The drug has been used in Japan since 1995. It is still the subject of numerous clinical trials.
	lobaplatin D-19466	1,2-diammino-1-methyl-cyclobutane-platinum-lactate $C_9H_{18}N_2O_3Pt$		The drug has been used in China since 2004. It is still the subject of numerous clinical trials..
	heptaplatin SKI-2053R sunpla	cis-malonato[(4R,5R)-4.5-bis(aminomethyl)-2-isopropyl-1.3-dioxolane]platinum $C_{11}H_{22}N_2O_6Pt$		The drug has been used in Korea since 2005..
	picoplatin AMD473 JM473 ZD0473	cis-diammine-dichloro (2-methylpyridine)platinum $C_6H_{10}Cl_2N_2Pt$		The compound is in clinical trials.
	phenanthriplatin	(SP-4-3)-diamminechlorido(phenanthridine) platinum nitrate, cis-Pt(NH3)2(phenanthridine)Cl]NO_3 cis-[Pt(NH3)2Cl(phenanthridine)]$^+$ $C_{13}H_{15}ClN_4O_3Pt$		The compound is at the stage of experimental research..
PLATINUM COMPLEXES (IV)	satraplatin JM216	bis-acetato-amminedichloro (cyclohexylamine) platinum $C_{10}H_{22}Cl_2N_2O_4Pt$		The compound is in clinical trials.
	adamplatin LA-12	trans-[$PtCl_2(CH_3COO)_2(NH_3)$ (1-adamantylamine)] $C_{14}H_{26}Cl_2N_2O_4Pt$		The compound is at the stage of experimental research.
	oxoplatin	cis-diammine-dichlorido-trans-dihydroxy-platinum $Cl_2H_8N_2O_2Pt$ $Pt(NH_3)_2Cl_2(OH)_2$		The compound is at the stage of experimental research.

Table I. cont. Selected platinum complexes in contemporary and future therapeutic strategies [18, 36, 37, 71, 77, 96]. Current status as of July 2021

Platinum complex		Molecular formuła	Structure	Clinical or experimental status
	ethacraplatin	cis,cis,trans-diamminodichloridobis (ethacrynato)platinum		The compound is at the stage of experimental research.
PLATINUM COMPLEX PACKED IN LIPOSOMES	lipoplatin liposomal cisplatin	encapsulated cis-diammine-dichloroplatinum(II)		The compound is in clinical trials.
TRI-NUCLEAR PLATINUM COMPLEX	BBR3464 triplatin tetranitrate	((trans-PtCl(NH$_3$)$_2$)$_2$-(trans-Pt(NH$_3$)$_2$ (NH$_2$(CH$_2$)$_6$NH$_2$)$_2$)NO$_3$)$_4$ $C_{12}H_{50}Cl_2N_{14}O_{12}Pt_3$		The compound is in clinical trials.

Carboplatin

Carboplatin is a second generation platinum compound with a structure similar to cisplatin. In the structure of carboplatin, instead of chlorine atoms, there is a 1.1-cyclobutyl dicarboxylic anion [36–38]. After penetrating the cell membrane, this compound is hydrolyzed to active forms, this process is much slower than the hydrolysis of cisplatin, therefore carboplatin may be better tolerated by patients. Through covalent bonds with N7 purine atoms, it forms adducts with DNA analogous to cisplatin, so that the mechanism of its biological activity is similar to that of cisplatin [25, 39]. The binding of carboplatin to the DNA of neoplastic cells leads to changes in the nucleic acid structure and inhibition of the replication process. This results in the induction of apoptosis and determines the cytotoxic properties of the compound [40]. The kinetics of carboplatin binding to DNA, however, is much slower than that of cisplatin. The slow hydrolysis of carboplatin shows, depending on the type of cancer, reduced effectiveness of the therapeutic effect compared to the effect of cisplatin [18, 41]. Literature data show that in order to obtain a cytotoxic effect similar to cisplatin, it is necessary to use up to 10 times higher doses of carboplatin [42]. Currently, carboplatin is used in the treatment of ovarian cancer of epithelial origin and non-small-cell lung cancer, and it is also administered in multi-drug therapy in the case of insufficient tolerance of the organism to cisplatin treatment [43]. The use of carboplatin in combination with taxoids and vincristine has also been suggested in the treatment of malignant tumors of the testicle, head and neck, cervical and breast cancer, and malignant glioma [39, 44–46]. Despite the lower pharmacological efficacy of carboplatin, a positive aspect of its use is its reduced systemic toxicity, especially its nephrotoxicity. On the other hand, an adverse effect demonstrated with carboplatin therapy is bone marrow dysfunction [47].

Oxaliplatin

Oxaliplatin is a platinum drug of the 3rd generation, the structure of which incorporates, in place of the amine ligands, a 1.2-diaminocyclohexane (DACH) group, which determines the cytotoxic activity of this complex [48]. This drug inhibits DNA repair processes, leading to inhibition of the cell cycle and increasing the sensitivity of cancer cells to signals from the apoptotic pathway [49]. Oxaliplatin exhibits a biological effect similar to first and second generation platinum drugs, consisting in the formation of specific adducts with DNA, interfering with replication and transcription of the deoxyribonucleic acid double helix [50]. As a result of oxaliplatin biotransformation, a secondary metabolite other than for cisplatin and carboplatin (trans-diaminacyclohexane-dihydroxy-platinum [II]) is formed, which may result in a different pharmacokinetic profile of the drug and various toxic effects [43, 48]. Oxaliplatin has been shown to have a relatively low activity in monotherapy, so it is most often administered in combination with other chemotherapeutic compounds (e.g., fluorouracil, irinotecan, leucovorin, ifosfamide, etoposide and gemcitabine) [48, 51]. Currently, this drug is used mainly in the multi-drug therapy of testicular, stomach and pancreatic cancer, breast cancer, non-Hodgkin's lymphoma and neoplasms showing resistance to cisplatin and carboplatin [37]. High efficacy in the treatment of advanced and platinum-resistant cancers of the colon has been demonstrated after combining oxaliplatin with 5-fluorouracil and leucovorin [52]. Currently, oxaliplatin is successfully used in the treatment of gastric cancer, however, clinical trials are still being conducted to evaluate the effectiveness of oxaliplatin therapy in combination, among others with S-1 (a prodrug of 5-fluorouracil) [53, 54]. Oxaliplatin, like other platinum drugs, can also cause side effects. Chelation of extracellular Ca^{2+} ion may disrupt the function of sodium channels and induce acute or chronic peripheral neuropathy [42, 51].

Nedaplatin

Nedaplatin is a cisplatin analogue, a second-generation drug developed in 1983 in Japan. Like cisplatin and carboplatin, its chemical structure has two amine ligands and additionally a glycolic acid dianion [55]. Nedaplatin undergoes hydrolysis, which leads to the formation of a pharmacologically active secondary metabolite (cis-diaminadihydroxyplatin [II]), analogous to cisplatin and carboplatin, capable of forming coordination bonds with DNA bases [43]. This compound is characterized by a reduced nephrotoxic effect and therapeutic effectiveness similar to carboplatin [55]. Nedaplatin has a beneficial effect on squamous cells in lung cancer, head and neck cancers. This drug can be used in patients with recurrent changes of cervical and ovarian cancer after treatment with cisplatin [56]. Nedaplatin can also be used in patients with hypersensitivity reactions to carboplatin therapy [57]. In clinical trials, nedaplatin has been shown to be highly effective pharmacologically in combination with radiotherapy, paclitaxel and irinotecan [58–60]. In combination therapy, its high effectiveness has also been found in the treatment of malignant urological tumors [61].

Lobaplatin

In turn, lobaplatin is a third generation platinum drug. In China, this drug has been approved for the treatment of advanced breast cancer, small-cell lung cancer and chronic myeloid leukemia [62, 63]. According to the literature, lobaplatin is also effective in the treatment of malignant neoplasms of the ovary, cervix, large intestine and stomach [64, 65]. It has been observed that in the treatment of gastric cancer, the antitumor effect of lobaplatin may enhance its combined effect with paclitaxel [62]. It is possible that paclitaxel enhances the effect of lobaplatin and reduces drug resistance by inhibiting the PI3K/Akt pathway also in lung cancer cells [66]. Increased sensitivity of cancer cells to radiation and to the pro-apoptotic activity of lobaplatin was revealed in its cumulative action with radiotherapy [67]. The preliminary results of *in vitro* and *in vivo* studies show that lobaplatin may have antitumor efficacy higher than carboplatin, with limited nephro-, neuro- and ototoxicity [68]. Nevertheless, a side effect limiting the use of the drug is the found thrombocytopenia [69].

Heptaplatin

Heptaplatin is a 3rd generation platinum complex with a slight undesirable nephrotoxic effect. It was assumed that the mechanism of its therapeutic action was similar to that of cisplatin and oxaliplatin [70]. In Korea, this drug has been approved for the treatment of advanced stomach tumors [71]. A wide spectrum of anti-tumor activity of heptaplatin was observed in phase I and II clinical trials against gastric, head and neck cancer cells, also in combination therapy with 5-fluorouracil and leucovorin [72–74]. Heptaplatin has also been shown to be effective in the treatment of L1210 cisplatin-resistant leukemia cells [72]. Presumably, the activity of the drug may be partly related to the decreased expression of metallothioneins as a result of heptaplatin action [72].

However, the exact mechanisms of the biological actions of heptaplatin have not yet been fully elucidated.

Therapeutic strategies for new platinum complexes

Since the treatment of neoplastic diseases with classic platinum drugs, apart from their high efficiency, is burdened with many side effects, the search for new platinum complexes, analogous to cisplatin but with low toxicity, is still being sought. Promising platinum compounds at the stage of clinical trials include, among others: picoplatin and phenanthriplatin.

Picoplatin

A new generation of platinum (II) compounds with significant anti-cancer potential is picoplatin. The mechanism of action of picoplatin is similar to that of cisplatin. It consists in creating specific bonds with DNA, although the resulting adducts show greater selectivity of action [37]. The 2-methylpyridine group present in the chemical structure of the compound slows down its intracellular hydrolysis and binding to DNA, which may possibly affect the profile of pharmacological activity and reduced toxicity of the complex [75]. Picoplatin has been shown to be highly effective in treating ovarian and lung cancer that are resistant to cisplatin and carboplatin treatment [76]. This compound was subjected to phase II and III clinical trials, in which the antitumor activity of picoplatin in the treatment of small-cell lung cancer was assessed. In contrast, phase I clinical trials focused on the efficacy of picoplatin in monotherapy in non-haematological malignancies and in combination with 5-fluorouracil and leucovorin in the treatment of colorectal cancer. Phase I studies also focused on the combination of picoplatin and docetaxel in the treatment of hormone refractory prostate cancer and the cumulative effect with liposomal doxorubicin in the treatment of lymphoma and small intestine cancer [77].

Phenanthriplatin

A monofunctional platinum (II) complex, implemented to overcome the mechanisms of cancer cell resistance, is phenanthriplatin, which contains a phenanthridine ligand in its structure. This complex, by means of covalent bonds, with high efficiency, forms adducts with DNA, a result of which means it strongly inhibits the transcription process [19]. Presumably, the DNA-binding profile of phenanthriplatin is different from that of cisplatin, which influences its different biological activity [78]. Although the mechanism of action of phenanthriplatin has not been fully established, it has been observed that this compound may act on cancer cells with greater efficiency than cisplatin and oxaliplatin [79]. The interaction of the complex with organic cation transporters (OCT) contributes to the strong effect of phenanthriplatin on tumor cells, which may

suggest that OCT overexpressing tumor cells (e.g. colon cancer) are particularly sensitive to the therapeutic effect of this compound [80]. Moreover, the increased cytotoxic activity of the complex may result from increased cellular uptake [79]. Phenanthriplatin-induced cell death may also result from impaired ribosome biogenesis and increased activation of the L11 ribosomal protein, which, by inhibiting Mdm2 binding to p53, triggers an apoptotic signal [81]. Phenanthriplatin inhibits the mechanisms related to the development of cellular resistance, therefore it may be effective in cancer cells resistant to cisplatin therapy [79, 80]. The beneficial effect of phenanthriplatin has been demonstrated, among others, by on small-cell lung cancer lines [78, 82, 83]. However, in preliminary analyses of clinical trials, significant adverse effects caused by phenanthriplatin were observed, therefore the assessment of its cytotoxic properties is still based on ongoing experimental studies.

Platinum (IV) complexes in anti-cancer therapy

In order to change the biological and chemical properties and improve the pharmacokinetic effects of platinum drugs, the degree of platinum oxidation was modified. In addition to platinum (II) compounds, platinum (IV) compounds have been synthesized. The literature data show that changing the geometry of the molecule from polar to octahedral results in the production of compounds with specific pharmacological properties [15]. Platinum (IV) derivatives are defined as prodrugs which, when reduced to Pt (II) forms, are only activated inside the cell [84]. Platinum (IV) compounds are characterized by increased kinetic activity, lipophilicity and stability, relatively low toxicity and increased activity against drug-resistant cells [85]. The advantage of platinum (IV) complexes is the possibility of their oral use, which can significantly facilitate the form of therapy and improve the quality of life of patients [85].

Satraplatin

Satraplatin is an example of a platinum (IV) complex. It is an analog of carboplatin containing two acetyl groups in its chemical structure, this largely contributes to the increased lipophilicity of the compound and its bioavailability [43]. Increased intracellular biotransformation of satraplatin leads to the formation of the active metabolite (JM118, $PtCl_2$ [NH_3] [cha]) [37, 61]. The spectrum of anti-cancer activity of this drug includes platinum-resistant cancer cells of the cervix, prostate, ovary and lungs [61]. The clinical trials performed included the I, II and III phase of the assessment of the antitumor effect in the treatment of prostate cancer, both as monotherapy and in combination with prednisone. In turn, the effect of co-administration of satraplatin with erlotinib and paclitaxel was assessed in relation to breast and lung cancer. Phase I studies also assessed the efficacy of satraplatin in combination with docetaxel and paclitaxel in the treatment of advanced solid tumors. Detailed studies are currently underway to determine the effect of satraplatin in the treatment of patients with high-risk prostate cancer [77].

Adamplatin

An analog of satraplatin with an equally high lipophilicity is adamplatin (IV). This compound is characterized by a broad spectrum of activity, through increased accumulation inside cells, strong inhibition of DNA polymerization and impaired repair of DNA structure damage [15]. Increased cellular uptake of the complex also influences the anti-cancer effect of adamplatin [86]. In addition, sulfur-containing compounds may play a less important role in the mechanisms of cell resistance to adamplatin than to cisplatin. Significant cytotoxic activity of adamplatin was found in in vitro studies against colon cancer cells, leukemia and ovaries, as well as cell lines resistant to cisplatin therapy [84]. Currently, adamplatin has not been implemented in clinical trials.

Oxoplatin

Another platinum (IV) compound with potential anti-cancer properties is oxoplatin. This complex was first synthesized in 1927 by Chugaev and Khlopin [85]. Oxoplatin is activated inside the cell in the presence of ascorbic acid and hydrogen chloride, therefore, oral administration of the compound can significantly accelerate and enhance its biological activity [87]. The increased distribution of this complex in the blood helps to quickly reach the target site of action. The *in vitro* studies conducted so far show that oxoplatin has a prolonged therapeutic effect and higher pharmacokinetic activity than cisplatin. It has also been found that it inhibits the growth of neoplastic tumors more than cisplatin and may weaken the process of distant metastases [85]. The cytotoxic properties of oxoplatin have been observed in vitro in neoplastic cells of the pancreas, colon, prostate and stomach [85, 88]. However, the mechanism of action of this compound has, as yet, not been fully determined.

Ethacraplatin

So far, the spectrum of the biological and pharmacotherapeutic effects of ethacraplatin (IV) on cancer cells is unexplained. Ethacraplatin is a cisplatin molecule linked to two ethacrynic acid ligands and has the ability to inhibit the activity of glutathione transferase (GST) [89]. This mechanism of action accelerates the formation of adducts with DNA, promotes damage, reduces cellular resistance and thus enhances the pro-apoptotic properties of the complex. However, ethacraplatin is characterized by antitumor activity with a relatively short duration of action [90]. Therefore, work is currently underway to develop encapsulated ethacraplatin, which will increase the amount of the preparation directly in neoplastic tissues, which may contribute to the improvement of therapeutic efficacy in platinum-resistant cells [89].

Liposomal platinum complexes

In order to reduce the nephrotoxicity of platinum complexes and increase their antitumor activity, drug carriers have been

designed, e.g. liposomes. To date, two liposomal CDDP compounds have been developed: SPI-077 and lipoplatin [61, 91].

The SPI-077 preparation was characterized by an extended half-life and a fairly good tolerance of the organism, but it showed a relatively low therapeutic activity observed in phase I and II clinical trials. The insufficient therapeutic effect of SPI--077 was most likely due to the limited release of cisplatin from liposomes inside the tumors [92].

Lipoplatin

Clinical trials are currently underway to assess the therapeutic properties of lipoplatin. Lipoplatin nanoparticles with a diameter of 110 nm, covered with a polymer coating, consist of a lipid envelope and a central core composed of a cisplatin molecule. The lipid layer consists of: cholesterol, phosphatidylcholine, soybeans, dipalmitoylphosphatidylglycerol and methoxypolyethyleneglycol conjugated with disteroylphosphatidylethanolamine [91, 93, 94]. The lipid layer of nanoparticles facilitates their transport to cancer cells by endocytosis [95]. The mechanism of action of lipoplatin is based on the increased accumulation of cisplatin molecules in the tissues of primary tumors and metastatic sites. On the other hand, the accumulation of the drug in neighbouring healthy cells was many times lower [92, 95]. This is because the drug can penetrate the blood vessel endothelium directly within the neoplastic lesions [93]. By releasing the cisplatin molecule, lipoplatin activates the mitochondrial apoptotic pathway [95]. The liposomal form of cisplatin reduces systemic toxicity and enhances the anti-cancer effect by targeting the drug directly into the tumor [94]. To date, phase I and II clinical trials have been conducted to assess the anti-tumor effect of liposomal cisplatin as monotherapy in the treatment of osteosarcoma and phase III of the treatment of pancreatic cancer in combination with fluorouracil and gemcitabine. The phase I clinical trials also concerned the efficacy of lipoplatin in patients with pleural malignancies after verteporfin therapy. The research evaluating the effects of liposomal cisplatin in the treatment of advanced and refractory solid tumors (phase I) and breast, prostate and skin cancer (phase II) are still ongoing [77].

Multi-core platinum complexes

New therapeutic possibilities are also created by platinum multi-core complexes, which have been developed to increase the platinum-to-DNA binding capacity. Among them, one can distinguish two- and three-core complexes containing at least two platinum atoms in their structure [96]. The BBR3464 gained the greatest recognition among multi-core complexes.

BBR3464

In the chemical structure of the compound, based on the structure of cisplatin, there are two monofunctional groups [trans-$PtCl(NH_3)_2$]platinum, linked by platinum tetra-amine (trans-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2)^{2+}$ [97]. The unique structure of BBR3464 ensures increased cellular uptake and enhanced DNA binding resulting from the appropriate electrostatic interaction and the formation of hydrogen bonds [97, 98]. BBR3464 adducts formed from DNA differ significantly from those created as a result of fusion with cisplatin, which may provide a higher therapeutic activity of the complex [98]. This compound is characterized by a prolonged pharmacological effect, which results in the inhibition of the growth of neoplastic tumors even after the end of therapy. This may indicate that the mechanism of action of BBR3464 on cell cycle disorders is different from that of cisplatin [97, 99]. *In vitro* and *in vivo* studies have demonstrated the high efficacy of BBR3464 in cisplatin sensitive and resistant tumors, as well as in cells with a mutation of the p53 oncosuppressive gene [99]. Proapoptotic properties of BBR3464 have been observed against ovarian cancer cells and malignant melanoma [97, 100]. In preclinical studies, the cytotoxic activity of BBR3464 was noted at concentrations several times lower than in cisplatin [75]. However, in a clinical evaluation, the antitumor activity of the complex was diversified, depending on the type of neoplastic cells. BBR3464's inadequate efficacy in some cancers, including gastric cancer may result from the increased metabolic degradation of the compound, which leads to the development of a more appropriate pharmacokinetic profile [97]. To date, BBR3464 has undergone phase II clinical trials to determine its cytotoxic effect against adenocarcinoma of the pancreas and small-cell lung cancer [77].

Conclusions

The discovery and approval of cisplatin for the treatment of cancer at the turn of the 20th century was of great importance for modern oncological medicine. Currently, cisplatin is one of the basic cytostatics used in the treatment of neoplastic diseases, both as monotherapy and in multi-drug therapy in combination with other anticancer compounds. Understanding the broad spectrum of anti-cancer activity of cisplatin has contributed to the search for new platinum complexes showing high therapeutic efficacy, with limited side effects, and the possibility of overcoming platinum resistance. The unique properties of the new platinum complexes may contribute to their wider use in anti-cancer therapy in the future.

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Guidelines and recommendations

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Recommendations of the Polish Sarcoma Group on diagnostic-therapeutic procedures and control in patients with type 1 neurofibromatosis (NF1) and the associated malignant neoplasm of peripheral nerve sheaths

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Type 1 neurofibromatosis (NF1 syndrome in von Recklinghausen's disease) is inherited as an autosomal dominant disease, caused by mutations in the NF1 gene encoding the neurofibromin protein. NF1 patients are at an increased risk of the development of a malignant neoplasm and their life span is shorter by 20 years than that of the general population. National Institute of Health (NIH) criteria make a diagnosis possible from about 4 years of age. Examination of children and adults should encompass a physical and a subjective component, but also next-generation sequencing (NGS) genetic analysis, histopathological

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examination of skin lesions, neurological, ophthalmological and radiological examination. If a malignant peripheral nerve sheath tumor (MNPST) is diagnosed in a patient with NF1, the therapeutic procedure should not differ from the general principles of treating soft tissue sarcomas. Patients from the high risk group should be monitored at least once a year, the remaining patients once every 2–3 years by a specialized medical team, and every year by their primary physicians, internal medicine specialists and dermatologists. Patients should have access to genetic counselling.

Key words: neurofibromatosis 1, diagnosis, sarcomas

Aim

The guidelines contain recommendations concerning the diagnosis, treatment and control of type 1 neurofibromatosis (NF1) and of malignant peripheral nerve sheath tumor (MPNST) associated with NF1. Their aim is to help all persons who can affect decisions made in patient care, including physicians, nurses and pharmacists.

The recommendations contained in the guidelines concern the vast majority of patients in a defined clinical situation. At the same time – taking into consideration particular populations and the individual clinical situation of the patients – the document presents a number of diagnostic-therapeutic options, which allow the clinicians to select the best method of proceeding for each patient. The guidelines present interventions which may be chosen on the basis of efficacy and safety in comparison with other medical technologies and are financed in the Polish medical healthcare system. Moreover, they contain an analysis of the efficacy of alternative treatment options (including non-refunded ones). The guidelines and recommendations – on the basis of the best available evidence – have been elaborated by a multidisciplinary expert group.

Methods

The group which prepared the guidelines

The group elaborating the guidelines was made up of the panel chairman and of experts representing all specializations involved in diagnosis and treatment of soft tissue sarcomas in children and adults.

The chairman of the panel on neurofibromatosis guidelines ensured supervision of the activities related to preparation of the text and the inclusion and participation of relevant clinical experts. He moreover supervised the process of joint decision taking and ensured that each member of the panel having a significant conflict of interest would be excluded from taking part in discussions concerning the area of the conflict.

Members of the panel (tab. I) represented their specializations in all reviews and meetings. In order to ensure a multidisciplinary representation, the panel for neurofibromatosis guidelines was made up of representatives of all basic medical specializations, that is clinical oncology, pediatric oncology and hematology, radiotherapy, oncological surgery, molecular diagnostics, radiology, pathomorphology, nuclear medicine and physical therapy.

Table I. Members of the panel elaborating the recommendation including their specializations and the scope of their work

Author	Specialization	Scope of work
Piotr Rutkowski	general and oncological surgery	guideline scope, literature search, guideline approval, evaluation of the quality and strength of the recommendations, approval of final version
Anna Raciborska	• hematology and pediatric oncology • pediatrics	approval of recommendations concerning pediatric patients, participation in preparation of chapters concerning pediatric patients, analysis of the literature concerning pediatric patients, correction of the manuscript
Anna Szumera-Ciećkiewicz	pathology	preparation of text concerning histopathological diagnosis, analysis of the literature concerning histopathological diagnosis, preparation of histopathological photographs, correction of the manuscript
Paweł Sobczuk	clinical oncology	preparation of text on MPNST treatment, editing the reference list
Mateusz Spałek	radiation oncology	preparation of text on MPNST treatment
Hanna Koseła-Paterczyk	clinical oncology	preparation of an outline of the guidelines during consensus meetings
Iwona Ługowska	clinical oncology	preparation of an outline of the guidelines during consensus meetings
Katarzyna Bilska	• medical rehabilitation • pediatrics	participation in preparation of chapters concerning the pediatric population, participation in preparation of the reference list

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Table I. cd. Members of the panel elaborating the recommendation including their specializations and the scope of their work

Author	Specialization	Scope of work
Monika Gos	laboratory medical genetics	participation in preparation of chapters concerning molecular diagnosis, participation in preparation of the reference list
Janusz Ryś	pathology	participation in preparation of the text concerning histopathological diagnosis
Ewa Chmielik	pathology	participation in preparation of the text concerning histopathological diagnosis
Andrzej Tysarowski	molecular biology	participation in preparation of the text concerning molecular diagnosis
Konrad Zaborowski	general surgery	participation in preparation of the text concerning surgical treatment
Małgorzata Oczko-Wojciechowska	pathomorphology	preparation of an outline of the guidelines during consensus meetings
Patrycja Castaneda-Wysocka	radiology	preparation of text on radiological diagnosis
Donata Makuła	radiology	preparation of an outline of the guidelines during consensus meetings
Marcin Zdzienicki	general, oncological and vascular surgery	preparation of an outline of the guidelines during consensus meetings
Marcin Ziętek	general and oncological surgery	preparation of an outline of the guidelines during consensus meetings
Piotr Fonrobert	patient association	preparation of an outline of the guidelines during consensus meetings
Kamil Dolecki	patient association	preparation of an outline of the guidelines during consensus meetings
Marek Dedecjus	nuclear medicicine	preparation of text on PET analysis
Anna M. Czarnecka	• clinical oncology • molecular biology	literature analysis, participation in elaborating the basis of the guidelines, participation in preparation of chapters concerning molecular diagnosis, pediatric patient and oncology, participation in preparation of reference list, editing and correction of the manuscript, approval of final version

Search for evidence and formulating the recommendations

In order to find significant scientific evidence, non-systematic searches were performed on clinical practice guidelines and databases of medical information. The search for clinical practice guidelines encompassed recommendations of diagnostic-therapeutic procedures in soft tissue sarcomas /type 1 neurofibromatosis published in Polish and English during the last 5 years. The quality of the found guidelines was evaluated using the AGREE II tool. A non-systematic search was also performed on medical information databases (PubMed) in order to obtain crucial literature. Papers from additional sources considered as important for the guidelines could be included in the process of literature review. In particular, a review was made of all phase II and III clinical trials available in PubMed, published in the years 1990–2021 and containing the word neurofibromatosis 1 and MPNST and current ESMO, ASCO, NCCN and PTOK recommendations

Recommendations contained in the guidelines are based on a critical evaluation of the evidence combined with clinical knowledge and consensus of a multidisciplinary expert panel. They were agreed upon by members of the panel after a review and discussion of clinical evidence and a discussion of their interpretation. Decisions concerning the inclusion of the found evidence into the created guidelines were made on the basis of an informal consensus.

Quality of the evidence and strength of the recommendations

Randomized controlled trials (RCT) are considered to be the basis of high quality clinical evidence. However, much of the available evidence is based on data from trials without randomization or on retrospective or prospective observational trials. In many clinical situations there are no significant clinical data and the procedure is based on clinical experience.

For this purpose the classification of recommendations was based both on the available clinical evidence as well as the consensus of the panel reached during an informal process. The level of the evidence depends on the following factors, which were taken into consideration during the discussion process: quality, quantity and data integrity (tab. II, III).

The participation of the chairman and the members (authors) of the panel was voluntary and they did not receive remuneration for their engagement in the process of guideline elaboration. All authors were asked to divulge information on potential conflicts of interest. Each author presented a DOI declaration even if there were no areas of conflict. Each author was responsible for ensuring that their DOI declaration was precise and truthful. Each member of the panel who had a significant conflict of interests was excluded from participation in discussions and voting concerning the area of conflict.

Table II. Quality of the evidence

Grade	Definition
I	evidence from at least one large randomized clinical trial (RCT) with a high methodological quality (low risk of a systematic error) or metaanalyses of properly planned RCT without heterogeneity
II	small RCT or large RCT with the risk of a systematic error (lower quality of the methodology) or metaanalysis of such trials, or of RCT with demonstrated heterogeneity
III	prospective cohort trials
IV	retrospective cohort trials or clinical-control trials
V	trials without control group, case descriptions, expert opinions

Source: ESMO Guidelines Committee (2020); Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores; accesss on 16.07.2021

Table III. Strength of the recommendations

Category	Definition
category 1	recommendation based on high quality evidence, with a unanimous approval or high degree of consensus from the expert panel
category 2A	recommendation based on lower quality evidence, with a unanimous approval or high degree of consensus from the expert panel
category 2B	recommendation based on lower quality evidence, in respect to which the expert panel attained a moderate level of consensus

Source: AOTMiT elaboration on the basis of The National Comprehensive Cancer Network. Development and Update of the NCCN Guidelines®, access on 16.07.2021

According to the authors, this elaboration contains the most justified principles of diagnostic-therapeutic procedures. They should, however, be interpreted in relation to the particular clinical situation. The recommendations do not always correspond to the current bases of refunding treatment in force in Poland (which is noted in the text). In the case of doubt, the current possibilities of refunding particular procedures should be ascertained.

Introduction

Type 1 neurofibromatosis (NF1 syndrome, von Recklinghausen disease) is a disease unit with the symbol OMIM 613113 in the catalogue of genetic diseases *Online Mendelian Inheritance in Man* (the so-called McKusick catalogue). NF1 is an inborn syndrome of skin and neurological diseases (facomatoses), observed regardless of the ethic group, race and sex with a frequency of 1:2500–3000 births [1, 2]. The disease is inherited in an autosomal dominant way and is caused by mutations in the *NF1* gene located on the long arm of chromosome 17 encoding the neurofibromin protein. Children of patients with an NF1 diagnosis have a 50% risk of inheriting the disease. However, one-half of NF1 cases are due to new mutations and are not familial (II) [3]. *De novo* mutations occur mainly in paternal chromosomes [4]. Patients with NF1 have an increased risk of developing malignant neoplasms and their life spans are about 10–20 years shorter than in the general population [5, 6]. The most recent analysis of the whole population of France indicated that an NF1 diagnosis has a much stronger effect on the expected life span in women than in men – 16.5 years for men and 26.1 years for women [7, 8]. Similar results have been published by Italians, who observed an average shortening of the lifespan of NF1 patients by 20 years [5]. Analysis of death certificates in the United States indicated that persons with NF1 lived for 54.4 years on the average and the median was 59 years – considerably below population norms which were respectively 70.1 and 74 years for the same period [6].

From the point of view of oncology it is important that the *NF1* gene is a tumor suppressor in cells [3]. Neurofibromin is a member of a family of proteins which activate guanosine triphosphate hydrolase (GTPases) (guanine nucleotide activating protein – GAP), which stimulate endogenous GTPase activity in the RAS (rat sarcoma virus protein*)* protein family – p21. A key role of neurofibromin is decreasing the level of activated RAS bound to GTP through stimulation of low endogenous GTPase activity of the RAS proteins themselves, thus promoting the conversion of active RAS-GTP to its inactive state RAS-GDP [9]. RAS activates a number of signal pathways which include the signal pathway of stem cell factor (SCF)/c-kit, mammalian target of rapamycin (mTOR) and mitogen-activated protein kinases (MAPK) [10].

Detecting the *NF1* mutation does not allow prediction of the intensity or complications of the disease. No direct genotype-phenotype correlations have been identified for patients with *NF1* mutations [7]. In patients with mutations of this gene, optic nerve gliomas may occur, or gliomas of the central nervous system, sarcomas of the malignant peripheral nerve sheath tumor (MPNST) type and other more rare neoplasms (among others gastrointestinal stromal tumors – GIST). In agreement with the role of the *NF1* gene as a classical tumor suppressor, in some neoplasms of NF1 patients loss of heterozygosity (LOH) or somatic mutations have been detected in the second initially normal allele of the gene [3]. The frequency of occurrence of somatic *NF1* mutations in the cells of selected neoplasms is [11, 12]:

- acute myelocytic leukemia (AML) 3.5–23.6%
- desmoplastic melanoma 45–90%
- skin melanoma 12–30%
- gliomas 14–23%
- colorectal adenocarcinoma 3.8–6.25%
- neuroblastoma 2.2–6%
- acute T-cell lymphoblastic anemia 3%
- paraganglioma / phaeochromocytoma 21–26%
- ovarian cancer 12–34.4%
- lung adenocarcinoma 7–11.8%
- breast cancer 2.5–27.7%
- squamous cell carcinoma of the lung 1.3–11%
- transitional cell carcinoma of the bladder 6–14%

Clinical diagnosis of type 1 neurofibromatosis

The general principles of NF1 diagnosis are similar in all age groups. Differences in the diagnosis criteria concern the size of the *café au lait* (CAL) spots – in small children 0.5 cm spots can already be classified as a disease symptom (in adults the minimum is 1.5 cm) [13]. Defined diagnostic criteria did not exist until 1987, when they were elaborated and presented by the National Institute of Health (NIH) in the USA during the NIH Consensus Development Conference – NIH-CC-86 with later modifications [14]. These criteria were maintained in successive guidelines for neurofibromatosis treatment [1]. NIH guidelines state that to diagnose the disease at least 2 of the symptoms mentioned below have to be present:

- at least 6 *café au lait* spots with a diameter of 0.5 cm or larger before puberty and 1.5 cm or larger after this period
- 2 or more neurofibromas or 1 plexiform neurofibroma,
- freckles on areas of the body not accessible to light (armpits, groin, area of pubic mound) – Crowe symptom,
- optic nerve glioma(s)
- 2 or more Lisch nodules (iris hamartoma),
- characteristic bone symptoms (sphenoid bone dysplasia and/or thinning of the core layer or long bone dysplasia with or without formation of pseudoarthrosis),
- 1st degree relative (parents, siblings, children) fulfilling the above criteria.

The criteria defined by NIH make it possible to diagnose the disease at about 4 years of age, whereas fully symptomatic disease generally develops up to the age of reaching sexual maturity; 97% patients with NF1 fulfill NIH criteria at the age of 8 years, and all at the age of 20 years [15]. Characteristic bone lesions generally appear within the first year, and the average age of diagnosing an optic nerve glioma varies between 3 to 6 years [7]. In clinical practice NF1 can be suspected with a high probability in babies with *café au lait* type spots who have an affected parent; in babies in whom specific bone dysplasias are diagnosed, or plexiform neurofibroma; in children up to 2 years of age in whom >6 *café au lait* spots were observed; and in children up to 3 years of age, in whom >10 such *café au lait* spots were detected [16, 17].

A pathognomic symptom for NF1 are also FASI, or focal areas of increased signal intensity in the T_2 sequence in MRI, described also in practice as UBO, or unidentified bright objects. For this reason an NF1 diagnosis may also be made in patients with many *café au lait* spots, for whom MRI of the central nervous system has been shown to have FASI. The first MRI analysis is in general performed in children aged 3 to 4 years, as for such small patients it requires general anesthesia [16, 17].

The fulfilling by the patient of the above-mentioned NIH criteria is associated with a high probability of identifying a mutation in the *NF1* gene. The mutation in the *NF1* gene is detected in 97% of fully symptomatic patients, if all available diagnostic methods, including NGS, are used together [18]. If the genetic analysis is performed in patients only fulfilling NIH criteria, mutations are detected in 78–95% depending on the used method of diagnosis and sequencing. In recent years a revision of the NIH criteria has been recommended in order to take into consideration the availability of molecular analyses in respect to pathogenic NF1 variants and also clinical characteristics (e.g. choroid abnormalities, *nevus anemicus*), which often occur in childhood, but were unknown during the NIH Consensus Conference [19, 20]. Currently NIH criteria are also considered insufficient for diagnosing babies. Over 50% of children under the age of 2 years with sporadic NF1 fulfill only one NIH criterium, which often leads to delayed diagnosis. Juvenile xanthogranuloma (JXG) and *nevus anemicus* occur in most children under the age of 2 years with NF1 and have been observed in 80% of patients not fulfilling the NIH criteria [7].

The new diagnostic consensus elaborated in 2021 [21] encompasses the following criteria:

A.

Diagnostic criteria for NF1 are fulfilled in a person whose parent has not been diagnosed with NF1 if 2 or more of the properties listed below are present:

- 6 or more *café au lait* spots with the largest diameter over 5 mm in persons before puberty and over 15 mm in persons after puberty,
- freckles in the armpit or groin area,
- 2 or more neurofibromas of any type or 1 plexiform neurofibroma,
- optic pathway glioma,
- at least two 2 Lisch iris nodules identified by a slit lamp examination or at least 2 choroid abnormalities (CA) – defined as light, heterogeneous nodules visualized by optical coherent tomography (OCT) / near infrared reflection (NIR),
- characteristic bone lesions, such as of the sphenoid bone such as anterior-lateral flexion of the tibial bone or pseudoarthrosis of long bones,
- heterozygous pathogenic variant in the *NF1* gene with the allele fraction at least 50% in an apparently normal tissue such as leukocytes.

B.

Child of a parent who fulfills diagnostic criteria defined in A should be diagnosed with NF1, if one or more criteria from A are present.

Large NF1 symptoms include:

- *café au lait* spots (occur in >99% of affected persons),
- freckles and hyperpigmentation (70%),
- peripheral fibromas (>95%),
- Lisch nodules, that is iris hamartoma nodules, not affecting vision (>90%).

Small symptoms include:

- macrocephaly (45%),
- short stature (30%).

Moreover, in patients with NF1 secondary symptoms and complications may occur, including mental retardation (30%), epilepsy (5%), plexiform neurofibromas, which may undergo malignant transformation (35%). Orthopedic complications (25%) in the form of bone dysplasias and deformations in general manifest as chest scoliosis. The stenosis of renal vessels is rare (1.5%), but may lead to the development of arterial hypertension (nephrogenic). Tumors of the central nervous system, most commonly optic nerve gliomas, occur only in several percent of the patients, but develop already in children [7]. In children, similarly as in adults, clinical manifestations vary. The first symptoms may occur at birth or may appear as the child grows (tab. IV) [1, 13].

The diagnosis is generally based on clinical characteristics observed in a physical examination and in the medical history. Differential diagnosis should include other syndromes with perturbed pigmentation, such as the McCune-Albright, segmental NF, type 2 NF and Watson syndrome or schwannomatosis [22].

To make a diagnosis, examination of children and adults should include:

- physical examination and medical history (II, 1),
- NGS analysis of the *NF1* gene or sequencing of a panel of genes/exome,
- histopathological analysis of skin/subcutaneous tissue lesions,
- neurological examination,
- ophthalmological examination,
- radiological examination (computed tomography, magnetic resonance).

In the physical examination attention should be paid to skin lesions (*café au lait* spots, freckles in groin and armpits, neurofibromas – including plexiform, other pigmentation perturbations), ophthalmological, skeletal and neurological changes and the arterial blood pressure should be measured [23]. In imaging studies characteristic changes are often detected in the central nervous system, hyperintense foci in T_2 dependent images and the FLAR sequence in deep white matter, basal nuclei and the corpus callosum. Lesions of the lambdoid suture, meningeal calcification of the cranial vault or the *moya-moya* phenomenon are rarely detected in NF1 [24].

Table IV. Age at which particular symptoms appear during the course of type and NF

Clinical symptoms	Frequency (%)	Age of symptom appearance
café au lait spots	99	from birth to 12 years
freckles in groin and armpits	85	from 3 years to puberty
lisch nodules	90–95	from 3 years
skin neurofibromas	99	from 7 years, more common during puberty
plexiform neurofibromas	in 30% visible upon clinical examination, in 50% observed in imaging studies	from birth
disfiguring facial plexiform neurofibroma	3–5	from birth to 5 years
MPNST	2–5	from 5 to 75 years
scoliosis	10	from birth
scoliosis requiring surgery	5	from birth to 18 years
Pseudoarthrosis of the tibial bone	2	from birth to 3 years
renal artery stenosis	2	whole life
phaeochromocytoma	2	over 10 years
serious impairment of cognitive functions (IQ 70)	4–8	from birth
problems with learning	30–60	from birth
epilepsy	6–7	whole life
optic nerve glioma	15 (only 5% symptomatic)	from birth to 7 years
brain glioma	2–3	whole life
dysplasia of sphenoid bone	1	inborn
cerebral aqueduct stenosis	1.5	whole life

Molecular diagnosis of type 1 neurofibromatosis

Type 1 neurofibromatosis is a genetic disease inherited in an autosomal dominant fashion. In about 95% patients fulfilling the criteria of a clinical diagnosis of NF1 elaborated by the National Institute of Health a pathogenic variant is identified in one copy of the *NF1* gene [1]. In most cases (appr. 90%) point mutations (changes in nucleotide sequence) are found in patients. The most common mutations cause a loss of function of the protein encoded by the *NF1* gene, that is:

- mutations causing a premature STOP codon (the so-called nonsense mutations),
- insertion/deletion mutations causing a change in the reading frame,
- mutations perturbing transcript splicing (the so-called splicing mutations).

In about 5–7% patients large deletions are identified which encompass single exons, a fragment of the *NF1* gene or the whole gene. In rare cases chromosomal aberrations are detected, e.g. translocations which can affect gene expression. In about 2% of patients fulfilling NIH criteria, mutations in the *SPRED1* gene are found, however, it should be stressed that the phenotype of these patients described as Legius syndrome differs from a typical form of NF1 by the absence of neurofibromas and Lisch nodules. In single patients with spinal neurofibromas mutations in the *PTPN11* gene have been detected [2].

Molecular analysis in the case of a suspicion of type 1 NF is a supplementary procedure [25]. The disease is predominantly diagnosed on the basis of clinical criteria [22]. The clinical experience of the authors and analysis of the literature indicates that molecular analysis may be useful in the following situations [1, 18]:

- clinically doubtful cases in which single clinical symptoms occur and it is not possible to make an unequivocal diagnosis on the basis of the patient's phenotype by itself,
- family members of patients with an NF1 diagnosis, in whom clinical symptoms of NF1 have not yet occurred,
- cases in which it is necessary to make a clinical differentiation between NF1 and Legius syndrome or a RASopathy, and the clinical picture is not unequivocal for any of the clinical entities.

In the remaining cases molecular analysis has a supplementary character. The result of a molecular analysis by itself is not a confirmation of an NF1 diagnosis as clinical characteristics which indicate the possibility of the disease have to be present [13, 22].

Outline of molecular diagnosis of NF1

Because of the high percentage of point mutations in patients with the *NF1* mutation and the possibility of mutations in other genes, the optimal diagnostic technique in the case of suspected type 1 NF is targeted (panel) next generation sequencing (NGS). Because of the character of the analysis it is always necessary to obtain an informed consent declaration for the genetic analysis. The analysis is performed on material from saliva or venous blood (at least 4 ml in older children and adults and 2 ml in babies) taken on EDTA (morphological test tube). For analysis by the NGS technique, genomic DNA isolated from nucleated cells of the patient (e.g. lymphocytes) is used. This technique requires a minimum of 3µg of DNA with O.D. 260:280 nm ≥1.8. The presence of the detected variants is confirmed by Sanger sequencing. If bioinformatic analysis performed for data obtained by the NGS technique indicates the presence of quantitative changes in the DNA encompassing at least one exon, this always requires confirmation by other methods, such as qPCR or MLPA (multiplex ligation-dependent probe amplification), which is described below [26, 27].

A serious challenge for clinicians and geneticists working with NF1 is the identification and characterization of *NF1* mutations in individual patients. This problem is due to many properties of the *NF1* gene itself, including its large size (~350 kbp) and complex structure (61 exons), lack of repeated localization of mutations (so-called hot spots), and thus a broad spectrum of reported mutations. The *NF1* gene encodes neurofibromin and is localized in the 17q11.2. locus and encompasses over 350 thousand base pairs. According to the NM_001042492.3 transcript, which is currently considered to be canonical, it contains 58 exons and is transcribed to an mRNA of about 12 kb, containing an 8520 nucleotide open reading frame. Neurofibromin is a multidomain protein of 2839 amino acids. Currently in the Human Gene Mutation Database Professional 2021.2 (HGMD®, access on 10.09.2021; http://www.hgmd.cf.ac.uk/ac/index.php) over 3804 different heritable mutations in *NF1* have been reported as the cause of type 1 neurofibromatosis. The spectrum of *NF1* mutations is thus well defined and encompasses missense/nonsense mutations– appr. 32.7%, splicing mutations – 15%, small deletions – 26.1%, small insertions/duplications – 10.5%, changes of the deletion/insertion type – 2.1%, extensive deletions >20 bp – 11.2%, large insertions >20 bp – 1.5%, complex rearrangements – 0.39% and 4 putative regulatory mutations. There is no evidence of any localized, reproducible mutation clusters within the *NF1* gene. Most (>80%) of constitutive *NF1* mutations are mutations causing loss of function – their presence causes almost complete absence of the transcript or loss of function of the protein [9, 28, 29].

To classify variants identified in the *NF1* gene, a system elaborated by the American College of Medical Genetics is used [30]. Identification of a pathogenic or potentially pathogenic variant in one copy of the *NF1* gene is confirmation of a clinical diagnosis of type 1 NF. However, its absence does not confirm but also does not exclude the clinical diagnosis of the disease because of the possibility of the presence of deep intron or regulatory mutations or larger deletions, which cannot be identified by targeted sequencing. In this case another range of genetic analyses should be considered [24].

If a variant which cannot unequivocally be classified as pathogenic/potentially pathogenic or benign/potentially benign is discovered in patient, that is a variant of uncertain clinical significance, the interpretation of its pathogenicity in the context of the disease should approached with care. In this case the basic analysis which should be performed is analysis of the inheritance of the variant in the family and checking if it segregates with the disease or whether it occurs in asymptomatic parents or other members of the family. It is optimal to perform functional analyses, though this is not routinely available in diagnostic laboratories in Poland [24].

The analysis of extensive deletions/duplications in the *NF1* gene should be performed by the method of multiplex ligation-dependent probe amplification (MLPA) – a technique for analysis of the change in the copy number of DNA fragments. This makes possible the identification of the deletion of individual exons of the *NF1* gene as well as determining the extent of the deletion in the case of larger chromosome changes. Routinely in NF1 diagnosis the P081/P082-NF1 kits are used. If the whole gene is deleted, the size of the deletion can be determined using the P122-NF1 area kit (MRC-Holland) [27, 31].

In cases in which a point mutation or a deletion has been excluded, the analysis must be extended to the identification of deep intron mutations which perturb splicing of the pre-mRNA of the *NF1* gene. Such mutations may cause the deletion of a fragment of the transcript or the insertion of additional sequences, resulting in general in a change of the reading frame and the absence of the normal protein. Splicing mutations in *NF1* (deep intron mutations) are mutations resulting in the formation of new splicing acceptor/donor sires and also changes in regulatory ESE, ESS, ISS, ISE sequences or the activation of cryptic sites. This may lead to inclusion of a new exon into the transcribed mRNA and the translation to an aberrant neurofibromin protein. Deep intron mutations constitute ~2% of all described mutations in the *NF1* gene. The material for analysis in this case is RNA which is reverse transcribed into cDNA, which serves for amplification of *NF1* gene fragments which can then be sequenced using the Sanger technique or next generation sequencing. If aberrant splicing is detected, point mutations are sought in the relevant part of the *NF1* gene, as their presence is the cause of splicing perturbations [24, 32].

In the literature there are also descriptions of *NF1* mutations in a mosaic system, thus only in part of the cells. In such a situation mutations may not be detected in blood or may be present in less than 50% of the cells. If a mosaic form of NF1 is suspected, additional analysis from an affected tissue or tissues should be considered [21, 33].

For the analysis of the presence of specific mutations in members of families with NF1, generally sequencing is performed by the Sanger method. Only the sequence of a fragment of the *NF1* gene is analyzed in which in the proband the presence of a pathogenic variant/ a potentially pathogenic variant /a variant of unknown clinical significance was detected [24].

The NGS technique allows the simultaneous analysis of selected genes among which – in the case of a suspicion of NF1 – the following must be included: *NF1*, *SPRED1* and *PTPN11* (fig. 1). Their analysis should include coding sequences and sequences at the intron/exon junction (at least 10 nt, longer, if pathogenic variants located at a larger distance from the exons have been described) of the analysed genes. The analyzed panel should allow the analysis of other genes associated with the pathogenesis of diseases from the group of RASopathies, including Noonan syndrome. In the course of these diseases pigmentation perturbations may occur which accompany characteristic inborn errors and dysmorphic traits which may also be observed in some NF1 patients. It is debatable whether in the panel the *MMR* genes (*MLH1*, *MSH2*, *MSH6, PMS1* and *PMS2*) should be included, whose mutations are responsible for the constitutional mismatch repair deficiency syndrome (CMMRD) – an autosomal recessive rare disease in which in addition to higher risk for various types of neoplasms *café au lait* spots are detected. The CMMRD syndrome is estimated to be responsible for the occurrence of symptoms in 0.41% of patients with NF1 symptoms, without mutations in *NF1* and *SPRED1* genes [30, 34].

However, the authors of population studies suggest that before sequencing MMR genes a screening should be performed confirming the presence of perturbations of DNA repair systems, e.g. the analysis of minisatellite sequence instability. In differential NF1 diagnosis, depending on the clinical picture of a given patient, among others the following should be considered: Legius syndrome, Watson phenotype, Noonan syndrome, McCune-Albright syndrome, Costelo syndrome, Jaffe-Campanaci syndrome or LEOPARD syndrome [35–37].

NF1 diagnosis in oncology

Plexiform neurofibromas (PNF), which are present in 30–50% of patients with NF1, in about 10–15% of cases develop into aggressive malignant peripheral nerve sheath tumors (MPNST), which are a frequent cause of deaths [38]. In these tumors somatic mutations ensure a selective dominance of cell growth and promote the development of the tumor. NGS detects hereditary or somatic *NF1* mutations in over 90% of MPNST tumors. Diagnosis of an *NF1* mutation during evaluation of MPNST requires the preparation of a paraffin block containing a section of the neoplasm or a histopathological preparation, which enables the localization of a fragment of neoplastic tissue at least 4 mm x 4 mm x 1 mm in size containing only MPNST. The pathogenicity of the mutation should be confirmed at least on the basis of one database of pathogenic mutations, e.g. PubMed ClinVar database, LOVD (Leiden Open Variation Database – http://www.LOVD.nl/NF1), NCBI dbSNP (database of Single Nucleotide Polymorphisms, ClinVar), and in the case of changes in MPNST also on the basis of The Cancer Genome Atlas (TCGA), the database of the International Cancer

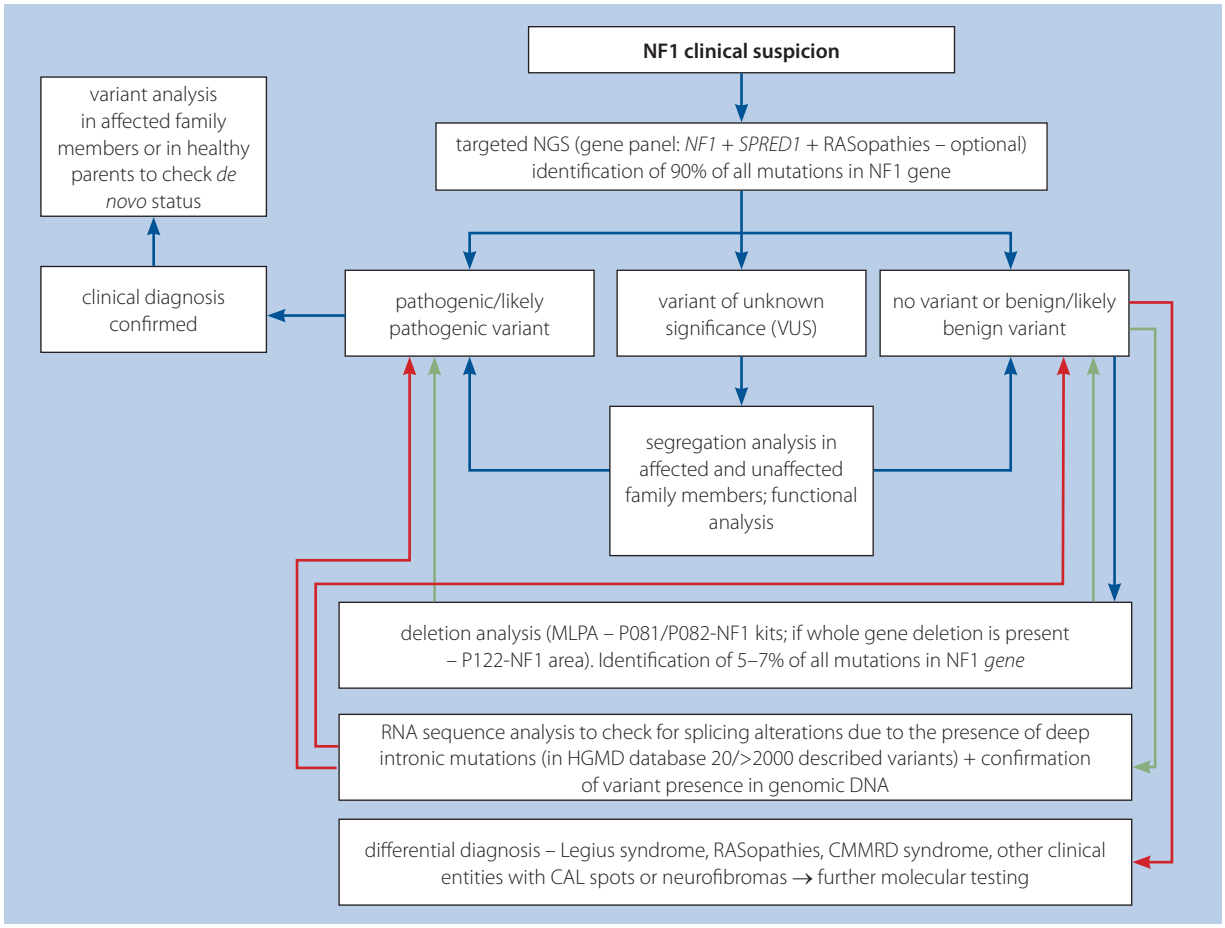

Figure 1. Proposed diagnostic procedure

Genome Consortium (ICGC) or in the Catalog of Somatic Mutations in Cancer (COSMIC – http://cancer.sanger.ac.uk/cosmic). Mutations and their putative effect at the protein level should be named according to the guidelines of the Human Genome Variation Society (https://www.hgvs.org/), and numbering of the mutations should be based on the NF1 mRNA sequence from GenBank (NM_000267.2) [31]. Analyses of somatic mutations should always be compared to germline DNA sequences as described above [1, 39].

Molecular analysis of the *NF1* gene should be performed in a medical diagnostic laboratory which specializes in medical genetic analyses, has relevant diagnostic equipment, experience in molecular techniques and appropriate certificates of quality.

Histopathological diagnosis

A key clinical manifestation of NF1 is the presence of neurofibromas, and in some patients the development of MPNST, in general from a previously present neuroma, especially of the plexiform type. Neurofibromas are benign tumors of peripheral nerve sheaths, composed of fusiform Schwann cells with hyperchromatic, wavy nuclei, often mixed with fibroblasts and collagen strands (fig. 2).

Cytological atypia in these tumors is considered to be a symptom of degeneration and as a single symptom is not troubling. Highly malignant MPNST tumors representing the other end of this histological spectrum in general show clear properties of a malignant neoplasm, including architecture typical for sarcomas, high mitotic activity and necrosis. However, diagnosis of MPNST with a low grade of malignancy is often problematic as there are no well-defined criteria. Tumors with troubling morphological properties, such as increased cell count or slightly increased mitotic activity, which do not fulfill the criteria for MPNST with a low grade of malignancy are described in the literature and diagnostic practice as atypical neurofibroma or atypical neurofibromatic neoplasm with an uncertain degree of histological malignancy [40, 41].

The usefulness of additional analyses in histopathological diagnosis (among others p16 and p53, and also Ki-67 and loss of H3K27me3) has been well described but finally is of only marginal value for differentiation.

MPNST shows loss of the *CDKN2A* gene which encodes the p16 protein leading to the loss of p16 expression. Even though most neurofibromas maintain high expression of p16, a decrease or loss may occur in atypical cases. Thus though lack of p16 staining may suggest an early stage of neoplastic

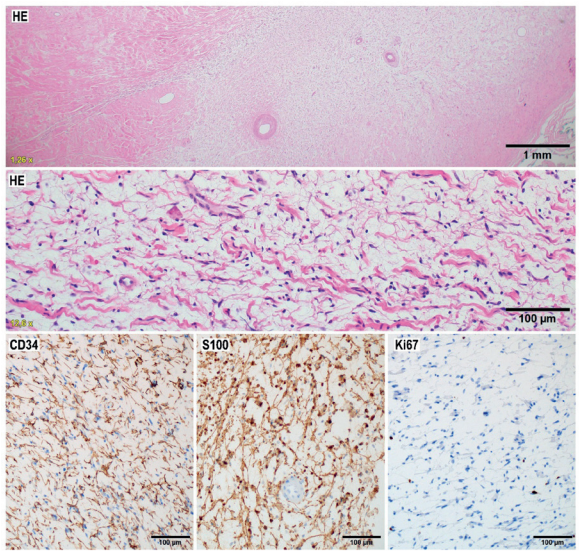

Figure 2. Classical histopathological appearance of a neurofibroma

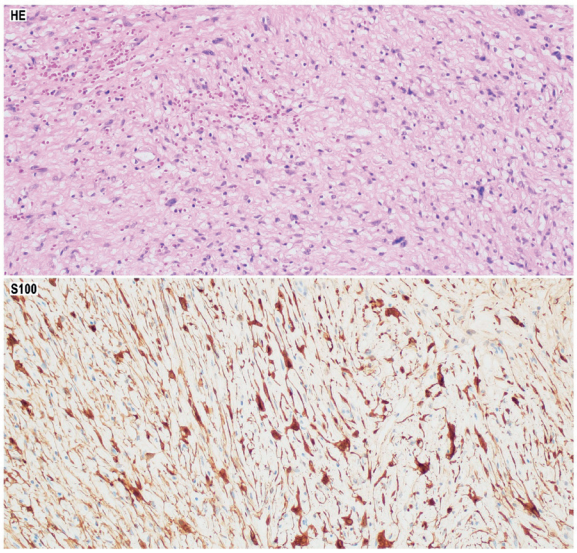

Figure 3. Neurofibroma with cytological atypia

transformation, it does not necessarily indicate malignancy. Similarly, MPNST have a tendency to show a higher p53 expression (>10% cells), but the use of this marker is limited to differentiating between atypical neurofibromas, an atypical neurofibromatic neoplasm of uncertain histological degree of malignancy and low grade MPNST as these tumors in general show a low expression of p53 (<5% cells). In the case of MPNST a higher proliferative activity can be expected (Ki-67 > 10%) in comparison to neurofibromas (Ki-67 < 5%), but there are no validated boundary values. Moreover, it has been shown that histone 3 trimethylated at the lysine 27 residue (H3K27me3) is lost in a large part of high grade MPNST, but in the tumors mentioned above this can be maintained or heterogeneous. As a consequence differentiating neurofibromas with increased cell count or slightly increased mitotic activity from low grade MPNST is based primarily on the evaluation of morphological characteristics and the pathomorphologist's experience [40–43].

In NF1 the challenge is to monitor the progression within neurofibromas, in which an inherent element is the evaluation of biopsy materials. Growing, painful lesions or the appearance of troubling properties in imaging studies (magnetic resonance and/or positron emission tomography) are indications for surgical removal or a diagnostic biopsy (optimally 4 cylinders each 2 cm long) from tumor fragments suspected of transformation on the basis of the evaluation of imaging studies [40–43].

Neurofibroma with cytological atypia or with increased cell count

Nuclear atypia occurs in some sporadic and NF1 associated neurofibromas and such neoplasms are often described as "atypical neurofibromas" (fig. 3). There are no reliable data on the frequency of occurrence – probably because there is a large variability in the use of this terminology among pathomorphologists. Initially on the basis of *CDKN2A* gene loss it was postulated that neurofibromas are lesions progressing to MPNST. However, there is no clinical evidence that cytological atypia indicates a faster malignant transformation [40].The presence of focal or even more distinct atypia in neurofibromas is not troubling when it occurs without an increase in mitotic activity in the context of classical neurofibroma architecture: randomly arranged S100- and/or SOX10-positive cells with stroma rich in collagen and a network of CD34-positive fibroblasts. This type of nuclear atypia can mean a 2–3-fold (or greater) increase in the size of the nucleus, its hyperstaining, irregular distribution of chromatin and multinuclear or "strange" forms. The state in which diffuse "strange" nuclei occur with maintained cell count without increased mitotic activity with maintained neurofibroma architecture is sometimes described as "degenerative atypia". In practice it has no clinical significance. It should be stressed that there are no scientific criteria allowing to clearly distinguish "degenerative atypia" from "true atypia" (neoplastic) which may precede a malignant transformation [40, 41].

In a cellular neurofibroma an increase in cell count is observed, which is the only troubling morphological character (without mitotic activity, cytological atypia or loss of neurofibroma architecture). The illusion of higher cell count is also noted in tumors with a massive lymphocyte-histiocytic infiltration. Similarly as in the case of with atypia alone, there are no decisive data concerning the risk of progression to MPNST. From the immunohistochemical aspect a low value of the proliferation index (Ki-67) and the small number of cells showing nuclear expression of p53 can also be considered as additional characteristics indicating the diagnosis of an atypical/cellular neurofibroma. Strong expression of the S100 (cytoplasmic and nuclear) and of SOX10 (nuclear) protein underlines the elements of Schwann cells, whereas CD34 identifies fibroblasts forming a pattern resembling a net – typical for the maintained neurofibroma architecture [40, 41].

Atypical neurofibromatic neoplasm with an uncertain degree of histological malignancy

Neurofibromatic neoplasms can be considered as showing an uncertain malignant potential when at least 2 of the characteristics mentioned below are present (tab. V) [40, 41]:

- nuclear atypia,
- increased cell count,
- variable loss of neurofibroma architecture (e.g. bundle-like growth, "herringbone", "pinwheel" and/or loss of network of CD34-positive fibroblasts),
- and/or mitotic activity outside isolated mitotic figures (>3 mitoses in 10 high power fields, <15 mitosis per 1 mm^2).

Though such tumors have sometimes been described as low grade MPNST, they were mainly associated with a low recurrence risk and essentially no risk of metastases. Qualifying these tumors as malignant could have led to excessively aggressive therapy, with the burden of an increased risk of potential undesirable side effects. Diagnosing atypical neurofibromatous neoplasms of uncertain biologic potential (ANNUBP) is also applicable to small biopsies in which worrying atypical properties are observed and the MPNST criteria are not fulfilled. In such cases the correlation of the clinical presentation with the microscopic and radiological picture is of particular importance, and in some cases it may be necessary to obtain another sample of the material for a histopathological examination [40, 41].

Currently there is no available immunohistochemical or genetic test defining the state of the malignancy in atypical neurofibromatic neoplasms. Besides a microscopic evaluation, the analysis of the variation or total loss of the expression of the S100 or/and SOX10 protein and the loss of the network of CD34-positive fibroblasts may be helpful. Neurofibromas and atypical neurofibromas in general have a low level of proliferative activity Ki-67 (2–5%). Focally higher indices of proliferation (Ki-67 at the level of 10%) may help in diag-

Table V. Criteria in histopathological diagnosis – spectrum of changes occurring in type 1 neurofibromatosis

Diagnosis	Definition	Mitotic activity		Necrosis	IHC
		mitoses/ mm^2	mitoses/ 10 HPF		
neurofibroma	benign neoplasm from Schwann cells with thin and wavy nuclei, delicate protrusions, myxoid to collagen stroma (thick bands of collagen)	absent	absent	absent	• strongly positive S100(+) and SOX10(+) staining • CD34(+) stroma of fibroblasts forming a "reticular network" • H3K27me3 • stain maintained
plexiform neurofibroma	neurofibroma growing and diffusion and replacing the nerve, often encompassing many nerve bundles	absent	absent	absent	EMA(+) w perinerve cells
neurofibroma with atypia/ ancient neurofibroma	neurofibroma exclusively with cellular atypia, often manifesting as "strange nuclei"	absent	absent	absent	as in neurofibroma
cellular neurofibroma	neurofibroma with increased cell count with maintained architectonic neurofibroma characteristics, without mitotic activity	absent	absent	absent	as in neurofibroma
atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP)	≥2 of 4 characteristics • cytological atypia • loss of neurofibroma architecture • increased cell count • mitoses – as above	<1.5	<3	absent	• S100(+/–) and SOX10(+/–) • loss of H3K27me3 expression • loss of positive stain (heterogeneous reaction more common)
MPNST, low-grade	ANNUBP characteristics and mitoses – as above	1.5–4.5	3–9	absent	• S100(+/–) positive <50% • SOX10(+/–) positive <70% • GFAP(–/+) positive 20–30% • H3K27me3# • loss of positive reaction • epitheliod MPNST: maintained strong expression of S100; SOX10; H3K27me3#; loss of expression of SMARCB1/INI1
MPNST, high-grade	ANNUBP characteristics and mitoses or/and necrosis – as above	≥5	≥10	absent	
		1.5–4.5	3–9	present	

ANNUBP – atypical neurofibromatous neoplasm of uncertain biological potential; MPNST – malignant peripheral nerve sheath tumour; HPF – high power field; IHC – immunohistochemistry; 1 mm^2 = about 5 HPF, in a field of 0.51 mm; # – staining used additionally in diagnosis, the morphological characteristics (mitoses, necrosis) are of primary importance

nosing MPNST formed in neurofibromas. Total immunohistochemical loss of the expression of p16, frequent in MPNST, with a low degree of histological malignancy can also be seen in atypical, and even in conventional neurofibromas, indicating that this is an early change in malignant progression, but it is not sufficient by itself to confirm malignancy. The p53 protein (product of the *TP53* gene) often accumulates in the nuclei of neoplastic cells because of its deregulation or mutation. There is no convincing data indicating that early malignant neurofibroma transformation can be detected on the basis of a slightly increased pattern of p53 expression. Moreover, in the case of cellular neurofibromas the staining for p53 is often positive, which constitutes another diagnostic trap [40–43].

Malignant peripheral nerve sheath tumor

MPNST in patients with NF1 in general fulfill the criteria of a high grade sarcoma with clear nuclear atypia with a mitotic index showing at least 10 mitoses per 10 large visual fields and frequently tumor necrosis. However, the rare cases without necrosis, with lower mitotic activity (3–9 mitoses per 10 large visual fields) should be classified as low grade MPNST (fig. 4) [40].

MPNST often show a sarcoma-like character of growth, with enlarged nuclei and a variable degree of nuclear pleomorphism. In MPNST a common phenomenon is the pattern of perivascular tumor growth, geographic necrosis with proliferation of glomerulous vessels, which resemble the appearance of a glioma (fig. 5). Heterologous differentiation similar to a rhabdomyosarcoma or osteo-chondrocytic occur in few cases and a phenotype similar angiosarcoma is rare [40].

Immunohistochemically most MPNST are negative or show focal expression for all staining of nerve sheaths with the exception of an epidermal MPNST subtype (strongly positive expression of S100 and/or SOX10). Other markers

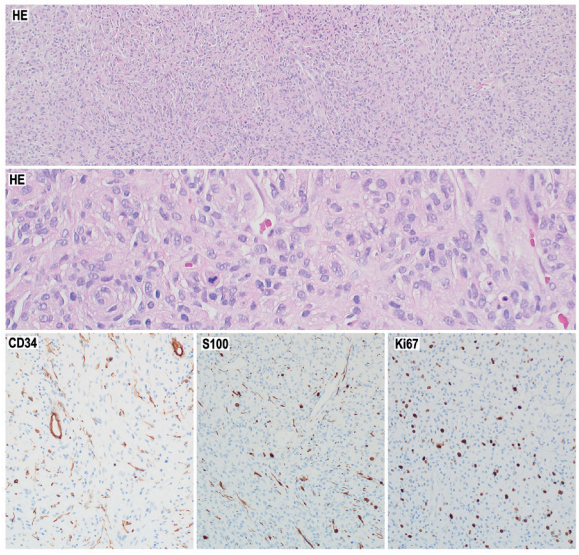

Figure 4. Low grade MPNST

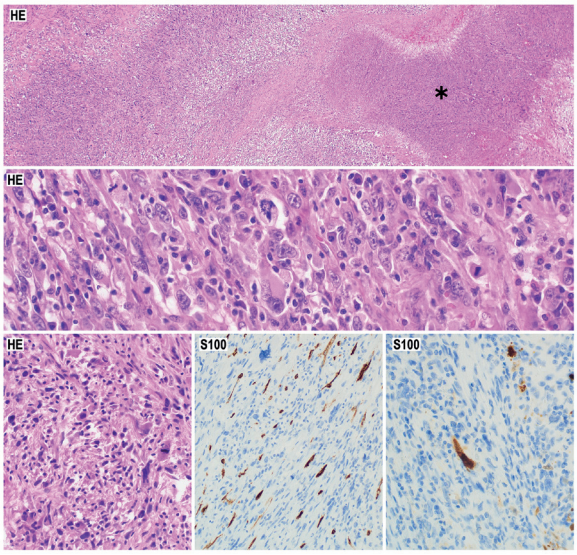

Figure 5. High grade MPNST (* – necrosis)

of Schwann cells, such as GFAP, CD57 (Leu7) and collagen IV, are characterized by a low sensitivity and/or specificity. The loss of p16 and of the CD34-positive fibroblast network are common [41]. The loss of H3K27me3 expression, due to loss of function mutations in the *EED* and *SUZ12* genes, appears to be a promising marker in MPNST diagnosis. The frequency of H3K27me3 loss varies from 30% to 90% and according to some studies is more frequent in the case of sporadic and radiotherapy associated MPNST than in MPNST developing in the course of NF1. Similarly to the evaluation of other "expression loss markers", staining of a positive internal control (mesenchymal, lymphoid or other normal cells) is necessary for a proper interpretation of the stainings. It should be kept in mind that H3K27me3 loss is not specific for MPNST and is frequently observed in in synovial sarcomas. A mosaic or heterogeneous pattern of expression (loss in some neoplastic cells) is considerably less specific and is not recommended as evidence for an MPNST diagnosis outside the typical histological and clinical context [42, 43].

In spite of considerable progress in understanding the molecular genetics of MPNST, as well as the better familiarity with the microscopic traits linked to the clinical presentation of the neoplasm, early detection of neoplastic transformation in neurofibromas associated with NF1 is still difficult, and the diagnosis of transitional lesions is still the main challenge. The introduction of the category "atypical neurofibromatous neoplasm of uncertain biological potential" is to be an introduction to the description of changes showing some microscopically troubling properties of malignant transformation, but which still do not fulfill the morphological criteria of MPNST (tab. V) [40, 41]. The introduction of more precise and objective diagnostic criteria requires the correlation of clinical, radiological, histopathological and genetic data [40, 41].

NF1 associated perturbations of various systems

The life span of persons with NF1 is on the average shorter by 10–15 years than that of the healthy population and theyhave a higher incidence of malignant neoplasms [6]. Other important clinical problems to which particular attention should be paid in caring for a patient with NF1 are:

- increased risk of vision perturbations and loss of sight (up to total blindness),
- increased probability of the occurrence of endocrinological perturbations (short stature, hypothyroidism, delayed puberty),
- increased probability of the occurrence of bone-joint, cardiovascular, neurological perturbations,
- increased probability of the occurrence of intellectual development perturbations affecting schooling readiness, limiting the choice of profession and the possibility of living independently,
- increased occurrence of perturbations of the autism spectrum and depression disorders [44, 45].

Malignant and locally aggressive neoplasms

Malignant neoplasms are the most common cause of deaths in NF1 patients, their risk of occurrence is from 2.5 to 4 times higher than the average. Malignant neoplasms which may be associated with NF1 are:

- rhabdomyosarcoma (RMS),
- neuroblastoma (NBL),
- pheochromocytoma,
- malignant peripheral nerve sheath tumor (MPNST),
- gastrointestinal stromal tumor (GIST) – in general in the form of multiple lesions located in the duodenum and the initial part of the jejunum,
- juvenile myelomonocytic leukemia (especially in patients with additional JXG type lesions),
- central nervous system tumors,
- breast cancer – women with NF1 are at an increased risk of breast cancer at a younger age and the results of treatment are much poorer than in the general population (tab. VI) [46, 47]

In persons with NF1 low grade gliomas may occur (of particular importance within the optic nerve). Because of the lack of unequivocal standards of procedure, treatment of patients in reference centers is recommended. Therapy depends on the clinical status of the patient and the maintenance of the function – e.g. of sight – strict observation is possible and if troubling symptoms occur treatment by chemotherapy with carboplatin and vincristine or monotherapy with vinblastine is initiated [48]. In patients with high grade gliomas localized treatment supplemented with temozolomide must be initiated. The average age for patients with NF1 associated gliomas is 38 years and it is lower than in the population without NF1 [49]. Another relatively common neoplasm in persons with

Table VI. Risk of occurrence of various neoplasms in children and adults with NF1

Malignant neoplasm	Risk of incidence
optic nerve glioma	15–20%
other brain tumors	>5 x increased risk
MPNST	8–13%
GIST	4–25%
breast cancer	appr. 5 × increased risk
leukemia	appr. 7 × increased risk
pheochromocytoma	0.1–5.7%
neurendocrine biliary tract neoplasms	1%
rhabdomyosarcoma	1.4–6%

MPNST – malignant peripheral nerve sheath tumor; GIST – gastrointestinal stromal tumors. Table after [46], modified

NF1 is pheochromocytoma. The frequency of occurrence is estimated as 0.1–5.7%; the median patient age is 43 years (range 14–61 years). It is multifocal in 20% of the patients and asymptomatic in 22% [50]. In care of NF1 patients attention should also be paid to symptoms associated with growing neurofibromas, which can attain considerable sizes, causing strong pain and neurological perturbations which often require a surgical intervention [51]Department of Neurology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. Plexiform neurofibromas (PN), which may be multiple, encompass many nerve plexuses and be locally aggressive and invade surrounding soft tissues are a particular problem. Their development is unpredictable, they can have periods of rapid growth, resection is in general complicated because of the occupation of surrounding structures and rich vascularity [52, 53]. They carry an increased risk of transformation into MPNST. In 2020 in the United States a MEK inhibitor – selumetinib was registered for treating pediatric patients with symptomatic and/or progressing nonresectable PN associated with NF1. In clinical trial NCT01362803, which analyzed the effect of selumetinib on noresectable plexiform neurofibromas in the course of type 1 neurofibromatosis, children aged from 3 to 18 years took part [54–56]. Registration was performed on the basis of the above one-armed trial in 50 patients with NF1 with symptomatic, nonresectable PN. The percentage of responses to selumetinib treatment was 68% with a median time of observation of a minimum of 12 months, the median of the time of response duration was not attained. In 74% patients a decrease in tumor size by at least 20% was observed. Progression-free time was on the average 3 years [57].

This treatment is not refunded in Poland but in the case of registration of the drug should be recommended for this rare pediatric patient group (III, 2A). In a phase II trial the potential of

other systemic therapies in treating advanced PN associated with NF1 has been observed: cabozantinib or mirdametinib [58, 59].

Bone-joint perturbations

A number of perturbations can develop in the bone system in patients diagnosed with NF1, such as:

- osteopenia and the associated even five-fold increased risk of bone fractures in comparison to the healthy population. This may among others be associated with the low vitamin D levels in NF1 patients [60],
- short stature, which is a consequence of endocrinological perturbations,
- scoliosis, which affects 10–26% of the patients and often requires orthopedic procedures correcting the spinal curvature already in children,
- inborn dysplasia of the tibial bone resulting in an increased risk of fractures and the formation of pseudoarthrosis,
- dysplasia of the larger wings of the sphenoid bone,
- perturbations of muscle tone [61].

Cardiovascular perturbations

Among patients with an NF1 diagnosis cardiovascular perturbations are more common than in the general population [62]. Myocardial infarction and cerebrovascular incidents occur at a younger age in NF1 patients than in the general population. This is also a common cause of death in this group. Echocardiographic data suggest that as many as 27% patients with NF1 have a cardiovascular anomaly and a constriction of the lung artery is responsible for 50% of these anomalies. Because of this, all children born with NF1 should undergo a detailed cardiological examination, and if any irregularities are observed should be under the supervision of cardiological clinics [63].

Vascular diseases associated with NF1 include among others a constriction of renal and cerebral arteries, aorta coarctation and arterial and venous malformations. Vasculopathies in general concern the arterial system and lead to a disease of cerebral vessels (e.g. constriction or dilation of vessels, aneurysms) or a constriction of the renal artery. The frequency of vasculopathy occurrence in NF1 is 0.4–6.4%. Changes in cerebral vessels occur in 2–5% and are associated with an increased risk of hemorrhagic strokes occurring both in children and in adults [64]. Renal artery stenosis often manifests as arterial hypertension, which should be regularly monitored in persons with NF1. Early detection of arterial hypertension is important because of the possibility of preventing complications, moreover, each patient with unexplained arterial hypertension should be examined for renal stenosis and pheochromocytoma [63, 65].

Dermatological lesions

In care for NF1 patients attention should also be paid to symptoms associated with growing neurofibromas, which can attain large sizes and cause very strong pain, bleeding, perturbation of functions, prurits, deformations and neurological perturbations. In such cases a surgical intervention is necessary [66]. The numer of neurofibromas was found to increase with age and in pregnancy (in 33–60% of pregnant women the numer of lesions increases) [67, 68].

In about 70% patients pruritus (mainly in the evenings) may occur which does not react to antihistamine treatment. Pruritus is generally localized in the affected areas. In such a situation treatment similar to that used in neuropathic pain (e.g. gabapentin) can be considered. *Café au lait* spots and freckles do not require treatment [69].

Neurological perturbations

Patients with NF1, in whom a new cognitive deficit occurs should be evaluated both for cerebral vascular disease and the occurrence of primary brain tumors. Patients with epileptic fits or progressive macrocephaly should be diagnosed as rapidly as possible for brain tumor development or hydrocephalus. In particular, children in whom an increase in head circumference is observed should be evaluated for hydrocephalus or CNS neoplasms. An analysis has shown that in children and adults with NF1 (n = 8579) – in comparison to a control group (n = 85 790) – headaches, Parkinson disease and sleep perturbations are more common [70].

Cognitive function perturbations

Cognitive function perturbations are typical in children with NF1 and are maintained in adults, causing poorer results in school and a lesser chance for employment. Research has shown that in comparison to the general population the IQ in adults with NF1 can be lower to a similar extent as in children with this disease. In 20 adults with NF1, who were compared to a control group, deficits in spatio-visual abilities, memory, attention and executive functions were observed [71]. A microdeletion of the NF1 gene is believed to be associated with a stronger intellectual disability [72]. Moreover, research has shown that 30–55% of adults with NF1 have depression or have other psychological problems [73]. Attention deficit hyperactive disorder (ADHD) is found relatively frequently already in the pediatric population with NF1 [74]. These persons were also found to have a significantly lower quality of life and emotional control than persons with ADHD alone or NF1 alone [75].

Proposed scheme of control examinations of children and adults

The details of control examinations depending on age are presented in table VII [76]. Imaging studies are performed with various frequencies depending on the clinical symptoms – more often in younger patients, less often in older ones – in general one a year [76]. A patient with an NF1 diagnosis should be under the care of a multi-specialist team until the end of their life [47]. Care for adult patients from a given region should be provided in coordinating centers created in particular voivodeships in the scope of the National Oncological Network.

Table VII. Details of control examinations depending on the patient's age after [76]

Age	Examination during medical visit
first month of life	• evaluation of skin lesions, of the muscle and skeletal systems, opthalmological and neurological examination • examination of parents for NF1 symptoms (if not done previously) • some specialists recommend a preliminary imaging study to detect optic nerve glioma
first years	• body weight, height and head circumference measurements • evaluation of skin lesions, of the muscle and skeletal systems, opthalmological, neurological, cardiological or other examinations (if indicated) • psychological counselling for the parents
2–5 years	• body weight, height measurement • evaluation of skin lesions • opthalmological, neurological, cardiological or other examinations (if indicated) • evaluation of hearing, psychomotor development (speech, concentration, memory, psychological problems)
5–13 years	• body weight, height measurement • evaluation of skin lesions • opthalmological, neurological, cardiological or other examinations (if indicated) • evaluation of sexual maturity • collecting information concerning school performance (difficulties with learning, hyperactivity, behavioral problems, perturbations of concentration and memory) • analysis of social adjustment • discussing the effect of puberty on the development of the disease
from 13 years	• opthalmological, neurological, orthopedic examination once a year and other examinations (if indicated) • control of arterial blood pressure • evaluation of sexual maturity • genetic and, psychological counselling, if required pain management clinic • control in objective and subjective examination and if required imaging studies to look for secondary MPNST and other neoplasms • from 30 years of age control in women for breast cancer • consider supplementation with vitamin D

It should be kept in mind that if type 1 NF is found in a child, both parents should undergo examination. If a parent is affected, all children in the family should be examined for NF1. Affected parents should be informed that for each pregnancy the risk that the child will be affected is 50%.

Control examinations in adults

In adults particular attention should be paid to selecting patients with NF1 with a "high risk" phenotype. This is the group of patients in whom there is a high probability MPNST development [79]. Risk factors are the presence of numerous lesions of the neurofibroma type associated with peripheral neuropathy and the presence of at least one internal neurofibroma. The NF1 scale allows the selection of patients who have a higher probability of developing internal changes of the NF1 type (tab. VIII) [78].

In patients with a high point count imaging studies (preferably MRI) should be performed to search for suspicious lesions. They should be monitored at least once a year. The remaining patients should be monitored by a qualified specialist group once every 2–3 years, and by basic care physicians, internists and dermatologists once a year [45]. Women with NF1 require earlier screening (from 40 years) for breast cancer [7, 9].

Genetic counseling

As NF1 is inherited in an autosomal dominant manner, genetic counseling should be provided for the patients and their families. The risk of the disease is 50% for each child of an affected parent. The couple should also be informed that the risk of having an affected child can be decreased by the use of reproductive technologies, including oocyte or sperm donation, depending on the affected parent [61].

Treatment of MPNST associated with NF1

Radiological diagnosis

Type 1 neurofibromatosis (NF1) is a syndrome which is characterized by a very broad spectrum of clinical symptoms and an increased incidence of neoplasms. The course of the disease can be different in individual patients, which is associated with the need to use diverse imaging methods depending on the region of the body affected by the disease as well as the relevant clinical symptoms [77, 78]. Imaging studies play an important auxiliary role in diagnosis and monitoring the course of the disease (e.g. evaluating the extent of the lesion before beginning treatment or observing progression after completing the treatment), however, the basic diagnostic method is still clinical evaluation, which is the basis for further procedures. Routine imaging studies in patients with NF1 are not recommended [22, 79]. Magnetic resonance should be used mainly for clinical suspicion of the presence of a tumor [80].

Neurofibromas are benign neoplasms derived from Schwann cells – in imaging studies they are visible as well delimited oval tumors. In MR analysis in T_2-dependent sequences they often present a so-called "shooting target symptom"

Table VIII. NF1 scale

NF1 scale	
independent factors associated with the occurrence of internal NF	**points**
age ≤30 years	10
presence of skin NFs	10
≥2 subcutaneous NFs	15
<6 *café au lait* spots	5
Probability of occurrence of internal neurofibromas	
NF1 points	**probability (%)**
0	5.1
5	8.3
10	13.3
15	20.7
20	30.8
25	43
30	56.1
35	68.4
40	78.7

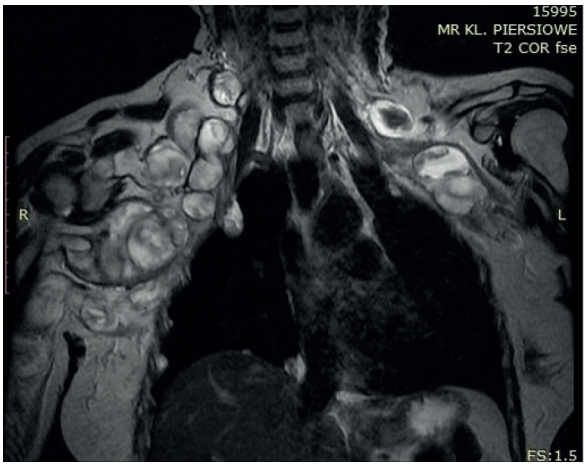

Figure 6. Type 1 neurofibromatosis. MR in a T_2W sequence showing the occurrence of multiple neurofibromas. Typical appearance of neurofibromas with visible symptom of a "shooting target"

(the center of the tumor with a low signal surrounded by a high signal border), after administration of a contrast agent they undergo non-homogeneous amplification (fig. 6). It should, however, be kept in mind that MR diagnosis is mainly indicated in the case of a clinical suspicion of a malignant neurofibroma transformation to MPNST (fig. 7). The risk of formation of MPNST in patients with NF1 (most commonly adults) is about 8–13% [81]. Among symptoms suggesting a malignant neurofibroma transformation are persistent pain, rapid growth and change of consistency of the tumor (from elastic to hard). MPNST is most commonly localized deep in soft tissues, near the nerve trunk – in T_1- and T_2-dependent sequences, with the presence of high-signaling areas in T1W images, which is helpful in differentiation from benign neurofibromas (fig. 6) [82]. MPNST show irregular, most commonly marginal contrast intensification with the possible coexistence of cystic lesions within the tumor and edema in the surrounding soft tissues. It should, however, be kept in mind that the value of imaging studies in the evaluation of the extent of plexiform neurofibroma in the absence of evidence for tumor progression is still debatable and treatment is generally based on an unequivocal determination of clinical progression. For this reason decisions about whether

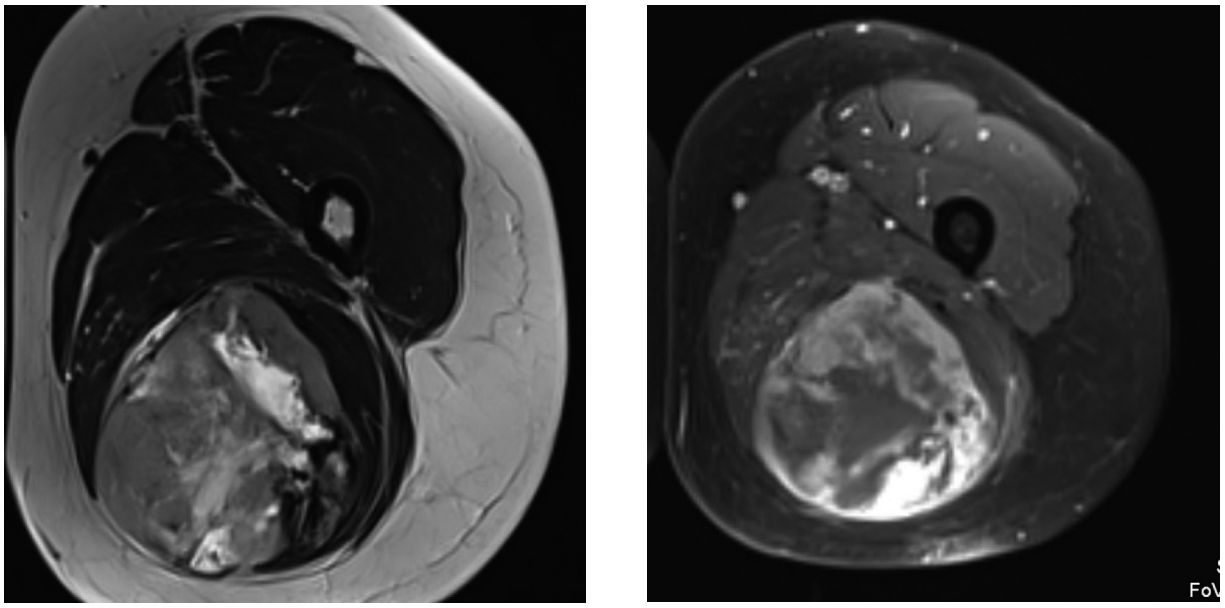

Figure 7. Malignant peripheral nerve sheath tumor (MPNST). Malignant transformation of neurofibroma in a patient with diagnosed NF1. MR in a T_2W sequence and T_1W *fatsat* with intravenous contrast agent showing a non-homogeneous tumor undergoing a pathological contrast intensification with visible areas of necrosis

and when imaging studies should be performed should best be left to physicians experienced in care for NF1 patients [22].

In patients with NF1 it is noteworthy that other soft tissue sarcomas such as rhabdomyosarcoma or other malignant neoplastic processes (e.g. acute myelocytic leukemia, phaeochromocytoma or breast cancer) are more common [83]. Renal phaeochromocytomas are rare in children with NF1. Most experts recommend screening for phaeochromocytoma if a clear increase occurs in the frequency of heart action and/or blood pressure, but do not recommend them for asymptomatic patients. In patients with NF1, phaeochromocytomas are often detected by chance in examinations performed during evaluation or monitoring of another neoplasm [84]. They appear most commonly as large, heterogeneous tumors showing areas of disintegration and cystic lesions. Typically they show a very strong contrast intensification. MR is the most sensitive imaging method in phaeochromocytoma diagnosis (sensitivity 93–98%, specificity 93%). A characteristic property is the appearance of a clearly high signal in T_2-dependent images – the so-called lightbulb sign [85].

MRI is the most popular method of visualizing the lesions within the brain. Among the most common pathologies occurring in the central nervous system is the presence of foci characteristic for NF1 with a high signal in T_2W and flair images, so-called UNO (unidentified neurofibromatosis objects) or FASI (focal abnormal signal intensity), occurring most commonly within basal ganglia, the midbrain and the cerebellum in children and teenagers (fig. 8) [86–88]. Lesions should not show an additional effect of mass nor pathological signal intensification. If this occurs transition to a glioma should be suspected [89]. UNOs most commonly undergo spontaneous regression in the second decade of life, however, some of the lesions occurring mainly the middle parts of the frontal lobes and in the thalamus, may be maintained in adults, which is probably due to a different basis for their presence a [87]. Low grade gliomas can occur in any brain localization but are often observed in the brain stem.

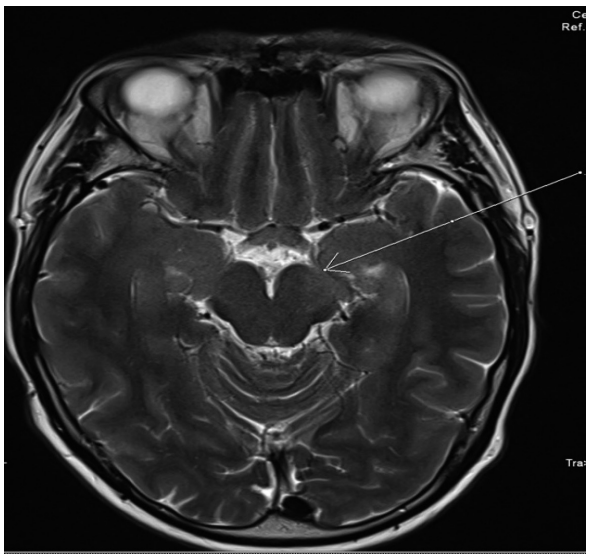

Figure 8. MR of the brain. Areas typical for NF1 with a high signal in T_2W and Flair images most commonly occurring within basal ganglia, the midbrain and the cerebellum, the so-called UNO (unidentified neurofibromatosis objects) or FASI (focal abnormal signal intensity)

The most common neoplasm of the CNS associated with NF1 is optic pathway glioma (OPG) (fig. 9) [80]. This is a low grade neoplasm (pilocytic astrocytoma WHO 1), often asymptomatic and growing slowly. However, in some cases perturbations of vision may occur and in advanced stages exophthalmos and perturbations of eyeball mobility and occupation of the hypothalamus, which may manifest as premature puberty. The risk of occurrence of an asymptomatic form of OPG is the highest in children up to the age of 7, however, routine MR examinations are not encouraged in asymptomatic children [81]. In imaging studies these tumors are characterized by an enlargement and thickening of optic nerves and the visual pathway, with possible occupation of optic nerve chiasm show an elevated signal in T_2W images, may also cause an increase in contrast (especially during treatment). Regular imaging studies of the brain are not recommended in asymptomatic children. A single initial MR of the brain remains optional [80]. During the transition into adulthood a single whole-body MR Is recommended [81].

Indications for imaging studies in patients with NF1:

- focal sensory or motor symptoms,
- epileptic episode,
- headaches (with increasing frequency and intensity),
- symptoms of increased intracranial pressure,
- TIA, stroke-like symptoms,
- visual perturbations (worsening of vision acuity or of the visual field),
- premature puberty, accelerated growth,
- growth of neurofibroma and/or appearance of pain,
- encephalopathy symptoms or worsening of cognitive functions,
- limb asymmetry,
- increase of arterial tension and/or pulse.

Musculo-skeletal perturbations associated with NF1 encompass among others macrocephaly, short stature and osteopenia, scoliosis, and also bone dysplasia. Dysplasia of long bones, dysplasia of sphenoid bone wings or scoliosis are another manifestation of NF1, though they are relatively rare (in about 10% of patients with NF1), may cause an increased incidence and complications [90, 91]. Most commonly in the diagnosis of these lesions normal X-ray images are sufficient, whereas computed tomography or magnetic resonance are used in particular cases. More frequent occurrence of a broad range of inborn cardiac problems is associated with NF1 , a higher risk of the occurrence of vascular pathologies such as stenoses and aneurysms in younger patients and atherosclerosis in older ones. The lesions most commonly concern the aorta, carotid arteries, mesenteric arteries. Stenosis of the renal artery occurring in patients with NF1 is a well-known cause of arterial hypertension. In order

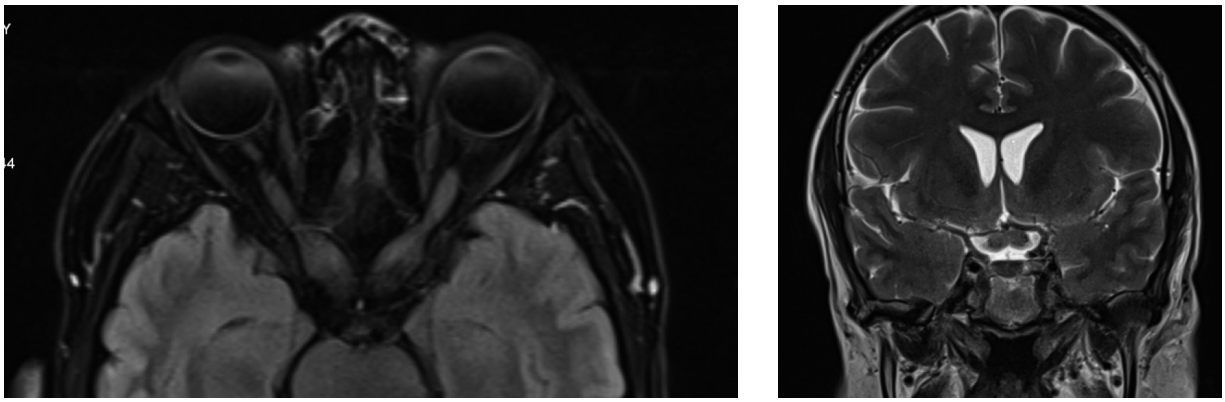

Figure 9. Glioma of optic nerve chiasm in a 27-year-old patient with NF1. MR, flair sequence in transverse section w and T_2W sequence in frontal section show clear, symmetric thickening of the optic nerves

to diagnose these lesions ultrasonographic and angiographic analyses are performed (TK, MRI or DSA) [63].

[^{18}F]-FDG PET with the use of CT or MR is being used with increasing frequency in patients with NF1 in the case of a suspicion of malignant tumor transformation, in order to determine the degree of progression and to monitor the response to treatment. This is usually [^{18}F]-FDG PET/CT. [^{18}F]-FDG PET analysis with the use of the CT or MR modality is increasingly being used in diagnosis, biopsy, determination of degree of progression and monitoring the response to treatment of patients with NF1. The use of the modality of magnetic resonance [^{18}F]-FDG PET/MR may increase the value of the imaging and decreases the exposure of the patient to ionizing radiation. Because of the rare occurrence of the disease, so far there are no prospective studies on a larger group evaluating the value of [^{18}F]-FDG PET in patients z NF1. For this differentiation of malignant from benign lesions the most commonly used is the SUV index (standard uptake value). Most studies indicate that SUV ≥ 3.5 indicates the diagnosis of a malignant lesion. The determination of the optimal SUV cutoff value is made difficult because of the differences between scanners. Using the quotient of the SUV index tissue/liver (T/L) may eliminate the difference between scanners, but the optimal value of the T/L index has not been defined. The use of repeated PET-CT with a delay increases the diagnostic value but also in parallel the costs and exposes the patient to ionizing radiation [92, 93].

Indications for a biopsy

A clinical suspicion of MPNST (rapid growth of a soft tissue tumor in a patient with NF1, especially with a subfascial localization) and in imaging studies requires determining a histopathological diagnosis before definitive treatment. For this purpose a thick needle – or in exceptional cases – an open biopsy is indicated [94, 95].

Treatment

About 30–50% of MPNST cases are associated with NF1. The risk of MPNST occurrence in patients with NF1 is 8–13% compared to 0.001% in the general population. In this group of patients MPNST is generally diagnosed at the age of 20–40 years, compared to 30–60 years in the general population. Some MPNST, in particular of the head and neck region, may be secondarily induced by prior radiotherapy because of other neoplasms, for instance optic pathway gliomas [96–98]. The risk of MPNST development increases by as much as 20-fold within plexiform neurofibromas [99].

The results of treatment and prognoses for patients with MPNST associated with NF1 are similar as for the general population. Some retrospective analyses have shown shorter survival for patients with MPNST associated with NF1 [100–102]. However, other studies did not confirm significant differences [103–105]. Because of the lack of unequivocal data concerning differences in prognosis, the procedure recommended for treating MPNST associated with NF1 is in agreement with general guidelines for MPNST treatment. Qualification of patients for treatment should be done by a multispecialist panel [106, 107].

Surgery in MPNST

In the case of an MPNST in a patient with NF1 the therapeutic procedure should not differ from the general principles of treating soft tissue sarcomas. The main aim in treatment is to provide local control of the disease. A definite cure can only be obtained by total macro- and microscopic surgical treatment (II, 1) [94, 95]. The extent of the surgery is determined by such factors as tumor localization and size, infiltration of surrounding structures (blood vessels, nerves) or the need to apply reconstructive techniques. In the case of MPNST, the nerve trunk from which it is derived must be removed, and in patients with NF1 this may be considerably overgrown [108, 109].

Perioperative treatment

The standard perioperative treatment in patients with MPNST conventionally fractionated pre- or postoperative radiotherapy (II, 2A). Its aim is to improve the local control or enabling the surgery in the case of locally advanced tumors. During qualification of patients and planning radiotherapy, current national

and international recommendations for treatment of soft tissue sarcomas should be taken into consideration. The guidelines of the American Society for Radiation Oncology (ASTRO) for the first time recommended preoperative over postoperative radiotherapy in patients without significant factors for impaired wound healing after resection [110–114]. Locally advanced MPNST, including radiation-induced MPNST should be treated, if possible, within prospective clinical trials based on combined conventionally fractionated or hypofractionated radiotherapy with systemic treatment or other methods increasing local effectiveness such as hyperthermia [115–117]. It is important to consider the higher risk of inducing secondary neoplasms after radiotherapy in the course of NF1, which is particularly important in the case of the group of young patients treated with a radical intention [118].

In selected cases of MPNST, perioperative treatment in agreement with general guidelines for treating soft tissue sarcomas should be applied [119]. Preoperative chemotherapy should be considered if there is a risk of tumor non-resectability ascertained on the basis of radiological analysis or in patients in whom rapid decrease of the tumor mass is important e.g. one pressing on surrounding nerves and causing strong pain (II, 2A). Single analyses indicate an improvement of resectability after applying preoperative chemotherapy in particular in children [120]. In agreement with the results of trial ISG-STS 1001, which indicated that chemotherapy adapted to the histological type of the sarcoma (in the case of patients with MPNST this was a combination of ifosfamide and etoposide) increases the recurrence or death risk, the use of 3 cycles based on a combination of anthracyclines and ifosfamide is preferred (II, 2A) [106, 121, 122].

Monitoring after MPNST treatment

The possibility of MPNST occurrence should in particular be kept in mind when constant pain develops in an NF1 patient, rapid increase in neurofibroma size, change from soft to hard consistency or a neurological deficit appears [123].

After MPNST treatment in a patient with NF1 the observation procedure should not differ from general principles of observation of patients after treatment of high grade soft tissue sarcomas and encompasses:

- regular physical examination,
- observation of the scar after resection of the primary focus using USG or magnetic resonance,
- observation using X-rays or/and computed tomography to look for distant metastases, in particular to the lungs [113].

Treatment of metastatic disease

Chemotherapy is the basis for treating metastatic disease. It should, however, be kept in mind that MPNST is considered to have a low sensitivity to chemotherapy and the results of treatment with cytostatics are unsatisfactory. If such a possibility exists, the participation of the patients in prospective clinical trials should be suggested. In the case of disease with a limited number of metastases, local treatment should be considered, that is surgery and/or radiotherapy (IV, 2A).

As MPNST diagnoses are rare, data concerning the effectiveness of particular chemotherapy regimens are based on metaanalyses of patients treated in clinical trials concerning various soft tissue sarcomas and also on retrospective analyses of patients treated in reference centers [106].

Analysis of 12 clinical trials run by the European Organisation for the Research and Treatment of Cancer (EORTC) indicated that using the AI combination (doxorubicin with ifosfamide) was associated with a longer, but statistically insignificant, progression-free survival (PFS) in comparison with patients treated by anthracycline as monotherapy (26.9 *vs.* 17 weeks) and the highest percentage of objective responses [124]. Monotherapy with anthracycline has PFS similar to regimens together with ifosfamide, which justifies using this treatment procedure, particularly in patients in whom the main aim of the therapy is control of metastatic disease (III, 2A). Numerous retrospective analyses also confirm the highest efficacy of regimens based on anthracyclines [102, 125–127]. If the aim of the treatment is alleviating pronounced symptoms, associated for instance with infiltration and pressure on the nerves or obtaining potential resectability of the tumor and/or the metastases, adding ifosfamide to doxorubicin seems justified. In choosing the chemotherapy regimen in clinical practice its toxicity should also be taken into consideration. The combination of doxorubicin and ifosfamide is more myelotoxic in comparison with doxorubicin in monotherapy. It should be kept in mind that during treatment with regimens based on anthracyclines, radiotherapy should be used with great care due to the risk of increased toxicity, in particular during irradiation of the chest [128].

Another regimen showing some effectiveness in patients with MPNST, which can be considered in successive lines of treatment is etoposide combined with ifosfamide (IV, 2B) [125, 129]. Besides classical chemotherapy, among targeted drugs pazopanib has shown some effectiveness in advanced MPNST (IV, 2B) [125, 130]. Clinical trials using targeted therapies and/or immunotherapy are ongoing.

Conclusions

Type 1 neurofibromatosis (NF1) is one of the most common genetic perturbations inherited in an autosomal dominant manner. Persons with NF1 generally come to a physician with characteristic pigment perturbations (*café au lait* type spots, skinfold freckles, Lisch nodules) but they are also prone to the development of many other clinical problems, including bone defects (deformation of the tibia and pseudoarthrosis, dysplasia of sphenoid bone wings), cognitive impairment, behavioral perturbations and specific difficulties in learning and benign and malignant nervous system neoplasms (neurofibromas, malignant neoplasms of peripheral nerve sheaths, optic nerve gliomas). Since the identification of the *NF1* gene

and its protein product, neurofibromin, numerous data from laboratory and clinical studies have led to a better insight into the mechanisms underlying the bases of pathogenesis and disease progression and have indicated new therapeutic targets. While the basis of care for patients with *NF1* mutations is surveillance according to guidelines appropriate for their age, recent trials encompass the identification of prognostic factors for the development of particular clinical characteristics of NF1 and the severity of the course of the disease which in the future may lead to a more personalized care for the patients.

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Synchronous cervical and ovarian cancer detected with ^{18}F-FDG PET/CT examination

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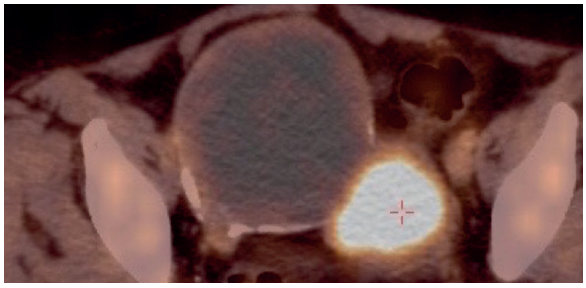

Figure 1. A litho-cystic tumor (78 x 76 x 75 mm) in the left pelvis. The upper solid part of the tumor (44 x 34 x 3 mm) shows a high accumulation of FDG with a maximum standardized uptake value (SUVmax) of 11.0 and the features of an aggressive proliferative process

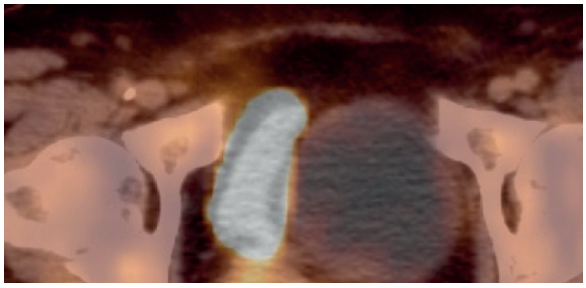

Figure 2. A hypodense area (19 mm in diameter) in the cervix with a slightly increased accumulation of FDG (SUVmax up to 2.9) and metabolic features suggesting a primary malignant lesion (transverse projection)

A 68-year-old patient was referred to the Gynecologic Oncology Outpatient Clinic with a diagnosis of bilateral ovarian tumors. The medical interview revealed that the patient had not had a gynecological examination in a long time. The ovarian tumors were evaluated with the risk of malignancy index (RMI) based on the serum CA-125 level, menopausal status, and ultrasound features. The high RMI score of 240 suggested malignant hyperplasia. Next, positron emission tomography/computed tomography with ^{18}F-fluorodeoxyglucose as a radiopharmaceutical (^{18}F-FDG PET/CT) was performed; the scan revealed a primary malignant lesion in the left ovarian tumor and cervix (fig. 1–2). Subsequent cervical diagnostics and a histopathological examination confirmed the coexistence of cervical cancer. The patient was qualified for surgery using a total hysterectomy with bilateral salpingoophorectomy and surgical staging. The evaluation of resected material confirmed left ovarian cancer (FIGO 2014 stage IA G3) and cervical cancer (FIGO 2018 stage IB1 G2). Radiotherapy was used as adjuvant treatment. Currently, the patient is under observation. The PET/CT examination is useful in assessing ovarian cancer and has shown efficacy in the diagnosis of lymph node lesions (96% accuracy) and distant metastases [1]. In the case of cervical cancer, a PET/CT scan can aid in diagnosing lesions as small as 7 mm [2].

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An extrapleural solitary fibrous tumor with low metastatic potential in a young female

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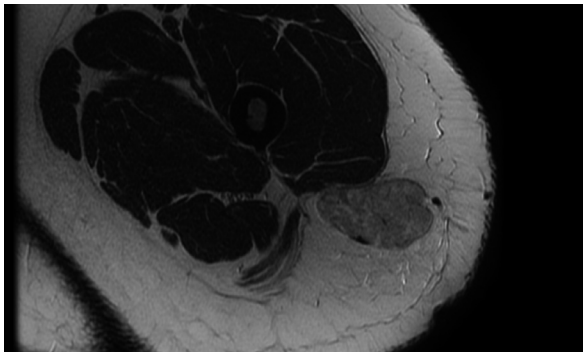

Figure 1. In the upper-posterior portion of the thigh, a well-circumscribed 5 cm tumor adjacent to the fascia can be seen

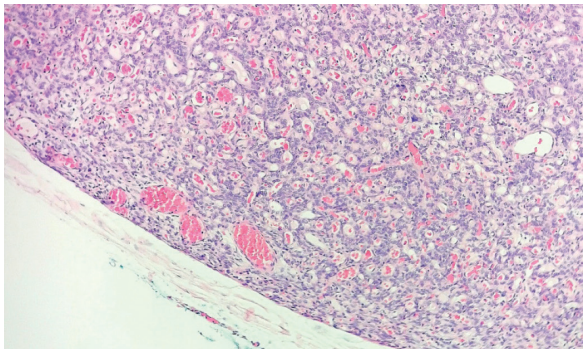

Figure 2. A microscopic image of a solitary fibrous tumor of the thigh (courtesy of Dariusz Pabis, MD)

Solitary fibrous tumors (SFT) for decades were reported only in the pleura (until the 1990s) and were considered a histomorphological entity similar to hemangiopericytoma. Currently both these neoplasms are merged together by the WHO and defined as fibroblastic neoplasms with intermediate behavior, rarely metastasizing [1].

A 25-year-old female with a 5 cm tumor on her thigh, adjacent but superficial to the fascia, with high vasculature as seen on the MRI (fig. 1), underwent a wide local excision for suspected sarcoma. Pathology reported SFT with low metastatic potential as based on the WHO risk criteria (age = 0, mitotic index = 2, tumor size = 0, necrosis = 0; altogether 2 points). Surgery was R0, with the tumor capsule intact (fig. 2). The presence of *STAT6* nuclear staining is characteristic for SFT.

Thorax (30%), meninges, (27%) and abdomen (20%) are leading locations for SFT; SFT occurs mainly >50 years (40–70). Extra-pleural locations warrant a careful pathological work-out to rule out other more frequent soft tissue tumors. A recurrence of any SFT variant is always possible, with a risk of de-differentiation [2].

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Selected syndromes of hamartomatous polyposis of the gastrointestinal tract – clinical and genetic aspects

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Hamartomatous polyp syndromes are a clinically and genetically heterogenous group of rare disorders that fall into the category of inherited predisposition to cancer. They include Peutz-Jeghers syndrome, Cowden syndrome, juvenile polyposis and mixed hereditary polyposis. Although the shared common characteristic is the presence of multiple polyps in the gastrointestinal tract, they differ by the number, age of onset and histopathological features of the polyps, clinical picture and presentation, as well as the approach to genetic testing. With the recognition of the importance of providing high quality medical care, that is equal diagnostic and therapeutic opportunities to patients with rare disorders (Uchwała nr 110 Rady Ministrów z dnia 24 sierpnia 2021 r. w sprawie przyjęcia dokumentu „Plan dla chorób rzadkich"), the authors would like to present the essential (fundamental) aspects of the above-mentioned syndromes.

Key words: hamartomatous polyps, clinical presentation, genetics

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) was originally described by J.L.A Peutz in 1921 as a co-occurrence of gastrointestinal polyposis and pigmentations in a single family. Then later, in 1949, H. Jeghers published a summary of the signs and symptoms of the disorder, based on the clinical picture of unrelated patients [1].

Peutz-Jeghers syndrome is inherited in an autosomal dominant manner, however up to 40% of mutations occur *de novo* (hence there is no family history of the disorder). PJS is caused by a heterozygous pathogenic variant in the *STK11* (serine/threonine kinase 11) gene and so far, this is the only gene that has been connected to the disorder. Most of the described mutations are point mutations that can be found on sequencing but a quarter of the pathogenic variants are so-called large gene rearrangements (duplication/deletion of exon/exons). The incidence of PJS is estimated between 1 in 8 300 and 1 in 280,000 [2].

The most characteristic and most frequent clinical manifestation is the freckling of the vermillion border and perioral region. The hyperpigmented spots may also be present on the eyelids, fingers and toes, around the nose, in the perianal and perivulval regions, as well as buccal mucosa. They develop during infancy and childhood, vary in size (from 1 to 5 mm in diameter) and have a tendency to fade with age. This sign, although very prevalent in patients with PJS, it is not a pathognomonic. It is also highly variable, from prominent to extremely subtle. It has no particular consequences to an individual's health but is quite helpful as a diagnostic feature [3].

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During the first and second decade of life, in nearly all individuals with PJS, hamartomatous polyps develop throughout the digestive tract. Most frequently they are located in the small bowel (96%), then the colon and stomach; they vary in size from 1 to 10 cm in diameter. The clinical picture is dominated by signs and symptoms of anaemia, rectal bleeding and non-specific abdominal pains. Nearly 50% of individuals with PJS experience recurrent small bowel obstruction and/or intussusception [4]. Currently, two methods of diagnosis and treatment of small intestine hamartomas are accepted: an intra-operative enteroscopy (IOE) and a double balloon enteroscopy (DBE). They allow for the resection of all polyps located in the small intestine [2]. Also, studies have demonstrated the chemopreventive efficacy of rapamycin on PJS [5, 6].

The histopathology of hamartomatous polyps in PJS is characteristic and diagnostic for the disorder. Moreover, apart from hamartomas, adenomas develop in the digestive tract of individuals with PJS and those tumours may undergo neoplastic transformation during adulthood. Colorectal cancer predominates as a malignancy seen in adults with PJS (lifetime risk of up to 39%), followed by an increased risk of pancreatic cancer (lifetime risk of 11–36%), female breast cancer (lifetime risk of 24–54%), gastric (29%), ovarian, small bowel, uterine and lung cancers [7]. Childhood malignancies associated with PJS include rare gonadal tumours: sex cord tumours with annular tubules (SCTAT) in girls and large-cell calcifying Sertoli cell tumours (LCTS) in boys [8, 9]. The criteria for PJS diagnosis are based on family history, histologically confirmed PJ polyps and characteristic mucocutaneous pigmentation [10].

Cowden syndrome

Cowden syndrome (CS), alongside Bannayan-Riley-Ruvalcaba syndrome (BRRS), belongs to an entity called PTEN hamartoma tumour syndrome (PHTS). CS was originally described by Lloyd and Dennis in 1963 and named after the reported patient, Rachel Cowden [11].

Cowden syndrome remains a clinical diagnosis and is based on consensus diagnostic criteria published (Eng C. PTEN hamartoma tumour syndrome 2001) and hence updated by the National Comprehensive Cancer Network (12). The criteria are divided into three categories: pathognomonic, major and minor. The pathognomonic criteria include mucocutaneous lesions, such as facial trichilemmomas, acral keratoses and mucosal papillomatosis, as well as adult Lhermitte-Duclos disease that is a cerebellar dysplastic gangliocytoma, a benign tumour of the cerebellum. Macrocephaly, non-medullary thyroid cancer, breast cancer and endometrial carcinoma constitute the group of four, major diagnostic criteria. Minor criteria are less specific but occur frequently, they include: thyroid lesions such as adenomas or a multinodular goitre, mild intellectual disability, lipomas, fibromas, fibrocystic disease of the breast, genitourinary tumours (especially renal cell carcinoma), uterine fibroids and hamartomatous intestinal polyps [12]. By the second decade of life, a significant majority of individuals with CS (80–90%) develop cutaneous and mucosal signs, however those are rarely a cause for medical concern [13]. A diagnosis of CS should be considered in children with macrocephaly and any of: developmental delay, dermatological features, vascular malformations or gastrointestinal hamartomatous polyps [14]. In adulthood, presentation of CS as a cancer predisposition syndrome becomes apparent. The lifetime risk of breast cancer for a female with CS is 85%, with penetrance of 50% by the age of 50. The lifetime risk for a non-medullary thyroid cancer is 35% with median age at diagnosis of 37 years; the lifetime risk for endometrial cancer is about 30% with the risk beginning in late 30s and early 40s. The above-mentioned cancers are included in the diagnosis as major criteria due to their incidence in CS, however the risk of other malignancies, such as renal carcinoma, colorectal cancer and melanoma is also increased, compared to overall population risk [11, 15, 16].

It has been reported that a pathogenic variant in the *PTEN* (phosphatase and tensin homolog deleted on chromosome 10) gene had been found in up to 85% of individuals that fulfil the clinical diagnostic criteria for CS. Those pathogenic alterations include mostly point mutations in the coding region of the *PTEN* gene and flanking intronic sequences, mutations of the promoter region in about 10% of cases and rarely duplications/deletions of large portions of the gene [17].

Although the disorder is inherited in an autosomal dominant manner, a significant proportion of the cases are simplex (with no family history, caused by *de novo* mutations). The prevalence of the disorder is estimated as 1 in 200,000 births, however this is very likely an underestimation due to the fact that a significant number of individuals remain undiagnosed. It should be underlined that the clinical expression of a mutation in the *PTEN* gene is extremely variable, even in related individuals [17].

Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) described by McColl et al. in 1964, is yet another syndrome characterised by the presence of hamartomatous polyps in the gastrointestinal tract [18]. The polyps histopathologically defined as juvenile, are characterised by hyperplasia of the mucous glands, retention cysts with oedema, obstruction of the glandular holes, profuse lamina and lack of smooth muscles [19]. Morphologically they vary in size (from a few mm to more than few cm) and shape: some are sessile, whereas others are pedunculated.

They begin to appear in the first decade of life and may be localised in the colon (98%), stomach (14%), duodenum (7%) and small intestine (7%) [20]. If sporadic, which is the most common situation, there is no increased risk of malignancy involved, however if multiple (the number varies between a few to one hundred), and with positive family history, it implies JPS through fulfilling one of the diagnostic criteria. The remaining diagnostic criteria (the Jass criteria) include: the pre-

sence of more than 5 juvenile polyps in the rectum and large intestine, or the presence of any number of juvenile polyps in the entire digestive tract. There are three clinical forms of JPS:

- juvenile polyposis of infancy that is associated with protein-losing enteropathy, additional anomalies and carries a poor prognosis,
- juvenile polyposis coli in which the polyps are limited to the colon only,
- generalized juvenile polyposis that refers to the presence of the polyps in the upper and lower digestive tract [21].

Clinically JPS presents as iron deficiency anaemia, abdominal pain, diarrhoea and/or rectal bleeding. In isolated cases, intussusception/intestinal obstruction or prolapse of a polyp were observed [22]. In more than 20% of individuals with JPS, various birth defects are detected both in the gastrointestinal tract (Meckel's diverticulum with umbilical fistula among others), and in other systems. The dysmorphic and/or extracolonic features include: pulmonary arteriovenous fistulae, ventricular septal defect, thoracic skeletal anomalies, undescended testes and hypospodias, renal agenesis and uterine defects, macrocephaly, telangiectasias, heamangiomata and lipomas [23].

In individuals with JPS, the risk of developing cancer increases, ranging from 9% to over 50%. The incidence of colorectal cancer is estimated at 17–22% by the age of 35 and 68% by the age of 60. The median age at diagnosis of colorectal cancer is 42 years. The incidence of stomach cancer is 21% in JPS patients with gastric polyps [24]. JPS is genetically heterogenous and caused by pathogenic variants in at least two genes: *SMAD4* (SMAD family member 4) and *BMPR1A* (bone morphogenetic protein receptor, type IA) are known to cause the phenotype. In both cases the inheritance pattern is autosomal dominant with about half of the cases attributed to *de novo* mutations with no family history of the disease. The frequency of JPS is estimated as 1 in 100,000 births [24].

Hereditary mixed polyposis syndrome

Hereditary mixed polyposis syndrome (HMPS) was first described in 1971 and concerned an 11-year-old girl with multiple juvenile polyps and adenomas of the colon and small intestine. In 1997, Whitelaw S.C. et al. proposed a name for this new condition that presented with atypical juvenile polyps, as well as adenomatous and hyperplastic polyps and named it hereditary mixed polyposis syndrome [25].

The clinical features of HMPS are presented in a multi-generation family, named St. Mark's family 96 (SM96). Among more than 200 members of this family, 42 showed different types of polyps, ranging from tubular adenomas, papillary adenomas and squamous adenomas, to hyperplastic polyps and atypical juvenile polyps [26]. In the histopathological examination, atypical juvenile polyps were a mosaic of hyperplastic polyps and adenomas. The mean age of diagnosis of HMPS patients in the SM96 family was 40 years [26]. Two three-generation families with a very similar course of the disease as in the SM96 family were described by Cao et al. [27]. Most frequently, the polyps were located in the large intestine. Affected family members had no extraintestinal manifestations [27]. It has also been found that individuals with HMPS show a significant predisposition to colorectal cancer development. There are no established criteria for diagnosing HMPS. It is rarely diagnosed before the age of thirty, unlike JPS, which most often affects children aged 5–15, when the number of juvenile polyps usually exceeds 50.

HMPS is inherited in an autosomal dominant manner, with some cases attributed to heterozygous duplication on chromosome 15q13-q14 that causes increased and ectopic expression of the *GREM1* (Gremlin 1) gene (HMPS 1) and in some cases is caused by heterozygous mutation in the *BMPR1A* gene [27, 28].

Conclusions

In cases of rare disorders with overlapping signs and different levels of cancer risks, genetic counselling and multi-specialist cooperation with the participation of a gastroenterologist, endocrinologist, dermatologist, neurologist, gynaecologist, oncologist and radiologist are extremely important. The goal of screening tests and imaging is prevention, early detection and treatment of the neoplasms that accompany those syndromes [29, 30].

Conflict of interest: none declared

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Complementary and alternative therapies in oncology

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Introduction

Cancer is the second leading cause of death worldwide after cardiovascular diseases, and its incidence is growing. The efficacy of cancer treatment is increasing due to a better understanding of its biology and improvements in the diagnostic and therapeutic methods involved. Active patient participation in the diagnostic and therapeutic process is encouraged to increase their well-being. However, greater patient awareness, more accessible public data, and determination often lead to seeking unproven alternative therapies. Complementary and alternative medicine (CAM), as opposed to evidence-based medicine (EBM), is not grounded on well-designed clinical studies, thus they may not be effective or can even harm patients [1]. These methods are mostly attempted to increase treatment efficacy, alleviate treatment side effects, or improve the the patient's physical and mental condition [2, 3]. However, in many instances, patients abandon the main treatment and replace it with alternative methods, which can considerably worsen their prognosis.

One of the reasons for seeking unconventional methods is the lack of time and incomprehension patients needs of medical staff. Cancer therapy requires a complete understanding of both parties and a truthful dialogue to ensure the safety and well-being of the patient. In addition, a sincere relationship with the treating physicians and their basic knowledge of alternative treatments may significantly influence a patient's decision-making process.

Increasing the use of CAM by cancer patients constitutes a challenge for health care systems [4]. Apart from social education, a crucial element of managing this problem is good communication between cancer patients and medical staff. This aim may be achieved by competence, understanding, patience, and adequate support for patients.

Health care professionals generally question the value of CAM and see no need to increase their expertise on this subject. However, a basic knowledge of CAM may facilitate discussion with patients and influence their decisions.

Discussion

Perdyan et al. analyzed 91 institutions offering alternative therapies that most often concern rheumatological, neoplastic, and chronic diseases [5]. Most institutions offered both drug therapies and therapeutic techniques. The most common were intravenous infusions of vitamin C and bioresonance therapy. According to the analysis, 40% provided anti-cancer therapies and 46% alternative methods for oncological treatment. According to the study's authors, intravenous infusions of IVCI, glutathione, and ozone dominated anti-cancer therapies. A definite minority of institutions provided specializations and doctors' names in the facility. The average consultation price was PLN 179, while anti-cancer therapies were significantly more expensive PLN 250 than non-cancer therapies – PLN 150 in the analysis.

An analysis by Perdyan et al. points out that in Poland, cancer patients often look for alternative therapies not supported by scientific evidence. The wide range of services offered by institutions dealing with alternative therapies indicates the great interest of patients. The market of pro-

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Table I. Most commonly used CAM methods by cancer patients

Most commonly used CAM methods by cancer patients					
Perdyan et al. (n = 91)			**Puskulluoglu et al. (n = 155)**		
vitamin C intravenous infusion	n = 47	52%	dietary supplements	n = 31	40.8%
bioresonance	n = 44	48%	prayer	n = 24	31.6%
vitamin intravenous infusion (other than vitamin C)	n = 42	46%	herbal medicine	n = 20	26.3%
ozone therapy – autotransfusion	n = 32	35%	special diet / modification of diet	n = 17	22.4%
intravenous infusion of alpha-lipoic acid	n = 24	26%	apitherapy	n = 8	10.5%
diet	n = 19	21%	quackery / bioenergotherapy	n = 7	9.2%
colonic irrigation	n = 19	21%	psychotherapy / support groups	n = 6	7.9%
herbal medicine	n = 13	14%	homeopathy	n = 5	6.6%
intravenous infusion of glutathione	n = 13	14%	amygdalin	n = 4	5.3%
acupuncture	n = 10	11%	capsaicin	n = 4	5.3%
massage	n = 10	11%	yoga	n = 3	3.9%

posed alternative methods has significantly developed over the last ten years, which can be deduced corroborated from the rising prices of the services offered. Polish cancer patients are willing to spend more and more on alternative methods, which significantly drives up the price of the CAM market without state regulation.

The survey conducted by Puskulluoglu et al. on a group of 310 cancer patients in Poland confirms that a significant proportion of cancer patients use alternative methods during cancer treatment [6]. The authors showed that almost a quarter (24.1%) of patients admitted using CAM during active oncological treatment. The study showed that the risk factors for CAM use include: female gender, higher education, and radical oncological treatment. Patients most often decide to use alternative methods to strengthen their immune systems (46.1%), improve well-being, and counteract the adverse effects of cancer and its treatment (40.8%). Importantly, cancer patients were satisfied with the use of alternative methods (Likert's 3.5/5). Dietary supplements (40.8%), prayer (31.6%), and herbal medicine (26.3%) are the methods that patients chose most willingly. According to the authors, almost half of the patients (46.6%) did not admit using alternative methods to their doctors (tab. I).

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Letter to the Editor

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Does the culture of science publishing need to change from the *status quo* principle of "trust me"?

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Dear *Nowotwory. Journal of Oncology* Editor,

Two recent editorials by Komorowski [1] and Ożegalska-Trybalska [2] leave readers with much to reflect on regarding the state of academic and science publishing, as well as the dynamics of the peer review process. This is because science publishing, including cancer research, is in a highly transformative – if not revolutionary – period. For authors and journals whose papers have been retracted, it is a painful period that may ultimately destroy their careers, reputations, and legends [3]. Some of that change is fueled by a desire from a segment of academia to replace the current publishing *status quo*, or the publishing oligopoly [4]. These are journals that have come to dominate fields of research, bolstered by indexing on powerful, prestigious and highly visible platforms (such as PubMed, Scopus, or Web of Science), and which have been assigned pseudo-quality metrics (the Clarivate impact factor or the Scopus CiteScore).

Collectively, these journals have operated in a vanity-based publishing culture where peer perception of academics is judged more by where they publish rather than what they publish. That *status quo* mentality, which remains the dominant "force" in academic publishing today, relies on the principle of "trust me", i.e., publishers blindly trust editors, editors blindly trust peer reviewers and authors, and authors blindly trust editors, peer reviewers, and publishers. This triangle of metrics-indexing-"trust me" subsequently breeds unhealthy competition, where academics are then "taught" to aspire to these pseudo-academic parameters, rather than focusing on core scientific values and principles. Such an unhealthy and unscholarly environment can breed a "publish or perish" culture and encourage exploitative and predatory practices, in which unscholarly forces – including predatory publishers – then try to attract intellect and money (article processing fees in the case of open access) away from *status quo* journals [5]. Ironically, actual or perceived "predatory" journals and publishers, despite being vilified, have managed to successfully capture a sector of the academic publishing market, using sometimes unscrupulous and untrustworthy means to attract work from academics that are blindly ingrained in the "trust me" culture. This includes peer reviewers and editors who are used as free labor [6], pulled between requests to serve the *status quo* and also potentially predatory publishers. This ultimately leads to the over-exploitation of peers and editors, who then become overburdened, exhausted, uninspired, strapped for time, and ultimately burnt out. As a result, attention to detail, ethics, and a whole host of basic scholarly principles are being ignored, neglected, or undetected in status quo journals during the peer review and editorial quality control. This may explain the "reviewers just don't care anymore" sentiment that Komorowski referred to [1].

A new *status quo* is trying to replace the current oligopolistic *status quo*, sometimes forcefully, especially through post-publication critique. For simplicity sake, let us refer to that new *status quo* as members of the "open science" and "replication" movements. In these movements, there is broad recognition that the current *status quo* has failed

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academia at various levels – culturally, structurally, morally, ethically and scientifically – leading to a state of "crisis", as is being evidenced in psychology [7], cancer research [8, 9], and public health and medicine [10]. A blanketed generalization cannot be made about all *status quo* journals and publishers, and many hopefully still pursue honest scientific value as their bulwark *modus operandi*. Part of post-publication peer review involves revealing errors, fraud, and lack of reproducibility, thereby revealing fraudulent paper mill-derived research, fake authors [11], and other scientific diseases that Ożegalska-Trybalska has alluded to [2].

To some extent, the tools (plagiarism detection software, Publons, etc.) and organizations (e.g., COPE, ICMJE, etc.) that were put in place to offer protection have failed the academic community [12] because they were serving the vanity-based *status quo* scientific publishing paradigm, without appreciating that the flaw actually lies with the "trust me" culture. The lack of criminalization of extreme fraud in academic publishing [13] is leading to the existence of an ethical and legal void, as Ożegalska-Trybalska [2] alludes to, while referring to paper mills: "it is more difficult to find formal grounds to question the legality of entities" (p. 315). The fact that error and retractions are part of a trend or culture of stigmatization [14] is also not helpful to reform the culture of science publishing from one of "trust me" to one of "don't trust anyone or anything; instead, build trust".

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