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Editorial

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Nowotwory. Journal of Oncology, following other leading medical journals, has recently introduced the Crossref Similarity Check – a professional, automatic anti-plagiarism system – to exclude intended plagiarism as well as to observe unintentional similarity of submitted manuscripts in order to papers published elsewhere.

Currently, the system is used routinely to screen all the manuscripts accepted for publication. Both journal editor and publisher believe that Crossref Similarity Check platform, based upon iThenticate software and developed by American company Turnitin, a subsidiary of Advance Publications company, is one of the best tools available. It was introduced by over 15 000 scientific institutions worldwide. The platform utilizes sophisticated algorithm that allows for the detection of even subtle similarities. Submitted manuscripts are checked against medical repositories, web pages, scholarly books, articles and proceedings from scientific journals.

Still, both publisher and editor are aware of the limitations of any plagiarism detection tool and realize that a high similarity score does not necessarily indicate plagiarized text. Thus, every noted similarity case is dealt with individually to determine whether there are any grounds for concern. The authors are contacted directly with specific report provided by publisher and are invited to explain and modify, if needed, their paper.

We are convinced that routine implementation of similarity detection platform will be beneficial for the *Nowotwory. Journal of Oncology*, as well to the all authors, who will gain more confidence that their work, if published, is properly protected.

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Original article

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The outcomes of limb-sparing surgery of patients with chondrosarcoma of the pelvis

Andrzej Pieńkowski[1], Andrzej Komor[2, 3], Tomasz Goryń[1], Bartłomiej Szostakowski[1], Michał Wągrodzki[4], Donata Makuła[5], Patrycja Castaneda-Wysocka[5], Wojciech Michalski[6], Aneta Borkowska[1], Piotr Rutkowski[1]

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Introduction. Chondrosarcoma (ChSa) is the second most common primary malignant bone tumour, after osteosarcoma. The aim of this study is to analyse the prognostic factors in patients operated on ChSa of the pelvic bone with limb sparing on the basis of a large retrospective group of patients. Aspects of the surgical technique are also presented, taking into account the location of the tumour within the pelvis. An attempt was also made to define the criteria for selecting patients for whom radical and limb-sparing surgery is possible.

Material and methods. We analysed 53 consecutive patients with chondrosarcoma of the pelvic and sacral bones after surgery performed at the Department of Soft Tissue/Bone Sarcoma and Melanoma in Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, between 1998 and 2020. Patients had surgery with sparing of the lower limb with the intention of cure.

Results. There were 34 patients with G1 grade, G2 – 16, and G3 – 3. The R0 resection margin was achieved in 36 cases, the R1 margin in 11, and the R2 margin in 5 cases. The 5- and 10-year overall survival rates for the entire group were 84% and 65%, respectively. The 5-year and 10-year disease-free survival (DFS) probabilities were 65% and 43%, respectively.

Conclusions. Multivariate analysis of the studied group of patients showed that the resection margin was a statistically significant factor determining prognosis (patients after R0 surgery margin have about 5 times lower death risk compared to patients after non-radical surgery with R1 or R2 margin).

Key words: chondrosarcoma, pelvic bone, resection margin, histological malignancy grade

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Introduction

Chondrosarcoma (ChSa) is the second most common primary malignant bone tumour, after osteosarcoma [1]. The majority of cases are diagnosed in patients above 50 years of age. Most frequently this cancer develops in flat bones or in limb gridles and proximal parts of long bones [2–6]. Men are more often affected.

The most frequently observed chromosomal anomalies in ChSa are: 9p21, 17p13, 13q14,10. MYC gene amplification and the amplification of the gene coding the AP-1 protein also plays an important role in the ChSa pathogenesis [5, 7].

ChSa can be divided into conventional types (approx. 85–90%) and non-conventional. Conventional (classic) ChSa is a cancer which is resistant to chemotherapy and radiotherapy. The only effective treatment methods remain surgical intervention with a radical margin [5–10]. Non-conventional forms of ChSa such as: clear-cell chondrosarcoma (1–2% of all chondrosarcoma cases), de-differentiated chondrosarcoma and mesenchymal chondrosarcoma, which make up about 10% of all chondrosarcoma cases, respond, in some degree to systemic treatment, or, possibly to radiotherapy [1, 11].

This work concerns all patients with ChSa with the exception of the mesenchymal type (on account of a different method of treatment of small-cell sarcomas). In ChSa, 3 histological grades can be distinguished (G1, G2, G3).

The majority of ChSa occurs spontaneously, yet 5% of ChSa are the outcome of the transformation of histologically mild tumours such as osteochondroma or enchondroma. That is why ChSa may be divided into primary and secondary types [1–4].

The most frequent symptom reported by patients and for which they seek medical advice for ChSa located in the pelvic bones is pain in the iliac and/or sacral area, often accompanied with the oedema of soft tissues. Apart from this – there is pain or difficulty when walking. These symptoms may persist for months or even years. Thus, they are frequently ignored by patients and even by doctors themselves. When the patient does finally get to an oncological centre, the disease is often locally advanced [12]. Sometimes a symptom may by an extensive and painless tumour or a lesion is found incidentally. Diagnosis is made on the basis of a biopsy collected from a tumour specimen. The biopsy should be preceded by imaging diagnostics (X-ray, CT and contrast enhanced MRI) [11].

The objective of this study is to analyse the prognostic factors in patients operated on for ChSa of the pelvic bone with limb sparing on the basis of a large retrospective group of patients from a reference centre for treatment of adult patients with sarcomas. Also, some aspects of the surgical technique are presented, taking into account the location of the tumour within the pelvis. An attempt was also made to define the criteria for selecting patients for whom radical and limb-sparing surgery is possible.

Material and methods

The analysis concerned 53 consecutive patients with chondrosarcoma of the pelvic and sacral bones after surgery performed at the Department of Soft Tissue/Bone Sarcoma and Melanoma in the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, treated between 1998 and 2020. These patients had lower limb sparing surgeries, the scope of which included the resection of specific fragments of pelvic bones, or sacral bone, sparing the function of the lower limb. These interventions comprised the resection of the entire iliac ala or its fragment, resections of the ischium and pubis, in one block or their fragments, resections of the hip joint with reconstruction with an endoprosthesis as well the resection of a fragment of the sacral bone, preserving the sacroiliac joint.

The prognostic value of the following factor was studied:

- age,
- sex,
- the largest dimension of the tumour (in centimetres),
- histological grade.

The histological grade was obtained on the basis of the protocols of histopathological assessment performed at the Pathomorphology Department of the Maria Sklodowska-Curie National Research Institute of Oncology. Moreover, the effect of the radicality of the intervention on the survival (R factor) was studied. The radicality of surgery was assessed on the basis of the protocols of histopathological assessment and surgery descriptions. The R0 resection meant that in the histopathological assessment the surgical margins were free from the presence of tumour cells; during the surgery, the tumour pseudo-capsule remained intact. The R1 resection described the situations in which, during the surgery no macroscopic tumour presence was found on the resected sections, the tumour pseudo-capsule remained intact, whilst in the microscopic evaluation, the resection margin was not radical. The R2 resection comprised situations in which, during the surgery, the tumour pseudo-capsule was damaged, some part of the tumour was intentionally not resected on account of the lack of technical possibilities of a macroscopically radical resection; the macroscopic assessment revealed damage of the tumour pseudo-capsule, and the margin was not radical, both macroscopically and microscopically.

In 50 patients, the classic form of ChSa was diagnosed (with a distinction into histological grades: G1, G2, G3), and in 2 patients dedifferentiated ChSa was found, whilst in 1 patient, clear cell ChSa was diagnosed. ChSa patients with the mesenchymal form of the cancer and patients with the extraosseous form of ChSa were not included in the study. In 9 patients, a secondary form of ChSa evolving from osteochondromas was diagnosed. 46 out of the 53 patients operated on for the primary tumour were solely surgically treated till the moment of disease progression or the last follow-up (and 1 patient from this group was operated on in another centre); whereas out of the remaining patients, 3 received post-operative radiotherapy, and 3 – intraoperative brachytherapy and post-operative radiotherapy. One patient received pre-operative chemotherapy (the patient in whose case de-differentiated

chondrosarcoma was diagnosed from the material harvested in a surgical biopsy, and the final post-operative diagnosis was classic chondrosarcoma G3). In none of the patients qualified to surgical treatment of the primary tumour, were remote metastases found (M0).

The factors evaluating treatment efficiency were defined as the probability of overall survival (OS) and disease-free survival (DFS). The overall survival (OS) was measured from the date of the surgery till the date of death or the last information regarding whether the patient was alive. The disease-free survival (DFS) was measured from the surgery date till the date of disease progression, the date of patient death for any causes or the date of the last follow-up.

The prognostic value of factors such as: age, sex and the largest dimension of the tumour measured in centimetres, histological grade (G), and radicality of the surgery was assessed on the basis of statistical analysis.

The univariate analysis was performed with the use of the log-rank test on the level of statistical significance of 0.1 [12].

The multivariate analysis was performed with the use of the Cox proportional hazard model [13]. In the modelling process, the stepwise selection of variables was used, adopting the standard exclusion thresholds: $p > 0.1$ and inclusion thresholds $p < 0.05$. The analysis was made with the use of the IBM SPSS Statistics 23.0 package.

Results

Patients' characteristics

The studied group of patients comprised 24 women and 29 men. Their age ranged between 17 and 71 years with the median age being 42 years. There were 34 patients with G1 grade, 16 with G2 and 3 with G3. The tumour size measured in centimetres varied between 3 and 37 cm (median 10 cm). The R0 resection margin was obtained in 36 cases, the R1 – in 11, and the R2 – in 5. The characteristics of the analysed group is presented in table I.

Table I. The characteristics of the analysed variables

Sex		
	females	24 (45.3%)
	males	29 (54.7%)
Age		
	min.–maks.	17–71
	median (IQR*)	42 (32–53)
G – histological grade		
	G1	34 (64.2%)
	G2	16 (30.2%)
	G3	3 (5.6%)
R – resection margin		
	**BD	1 (1.9%)
	R0	36 (67.9%)
	R1	11 (20.8%)
	R2	5 (9.4%)
Tumour size (cm)		
	min.–maks.	3–37
	median (IQR*)	10 (8–11)

*IQR – interquartile range, n = 53; ** – no data

Resection types of pelvic fragments with limb sparing

Aspects of surgical technique

In the analysed group of 53 patients, the following types of resections were made: the resections of the fragment of or an entire iliac ala in 25 patients, the resections of the ischium and pubis or only pubis in 17 patients and the resections of the hip joint with a reconstruction with an endoprosthesis – 6 patients; the resections of the sacral bone with sparing the sacroiliac joint or the resection of the areas of one of the sacroiliac joints – 5 patients (fig. 1).

The patient position for surgery was either a gynaecological one or lying in a contralateral side. Laying a patient on their side gives free access to the pelvis, both from inside and outside. Apart from this, it allows for control of the iliac joint and for defining the appropriate level of resection. Moreover, it allows for better peritoneum control, so that the peritoneal cavity, if possible, is not open during surgery, which prevents the implantation of the tumour into the peritoneal cavity.

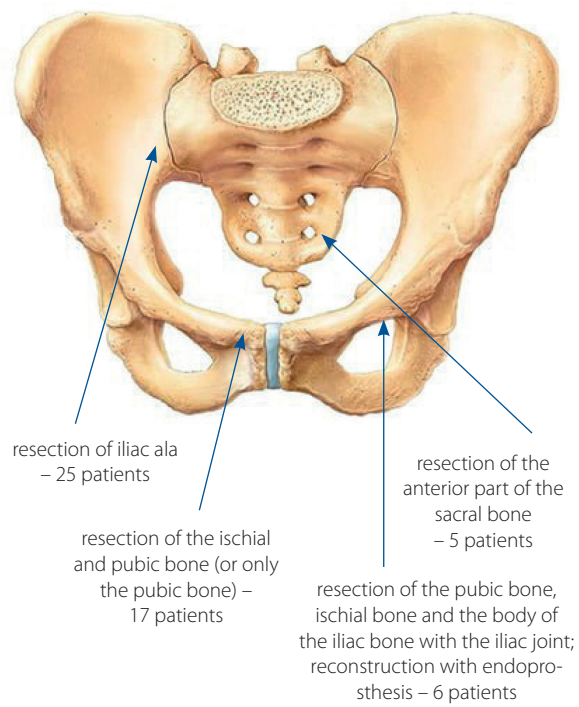


Figure 1. Resection scopes in the surgeries of pelvic bones sarcoma with limb sparing

What is more, when the patient is laid on their side, the peritoneal cavity may be moved onto the contralateral side. Patients operated on for a tumour located in the sacral bone had surgery while lying on their abdomen.

Analysis of patients' survival and the factors affecting the prognoses

As a result of the analysis, it was found that the 5- and 10-year overall survival for the entire group (with 95% confidence intervals [CI]) were respectively: 84% (72–95%) and 65% (47–83%). The follow-up scope, in months was: 0.689–356; median follow-up 90 (95% CI: 57–124). The OS curve is presented in figure 2.

The probability of disease free survival periods of 5 and 10 (with 95% CI) years were 65% (50–80%) and 43% (23–63%) respectively. The DFS curve is presented in figure 3.

In the univariate analysis which was performed, two factors with a statistically significant effect on OS and DFS ($p < 0.1$) were found: the histopathological grade (factor G) and resection radicalism (factor R). A statistically significant effect on OS was the G1 histopathological grade ($p = 0.011$) and R0 resection scope ($p = 0.007$). The same factors (G1 and R0) were found to affect the DFS: p values: 0.076 and 0.051 respectively. The results of the univariate analysis are presented in figures from 4 to 7.

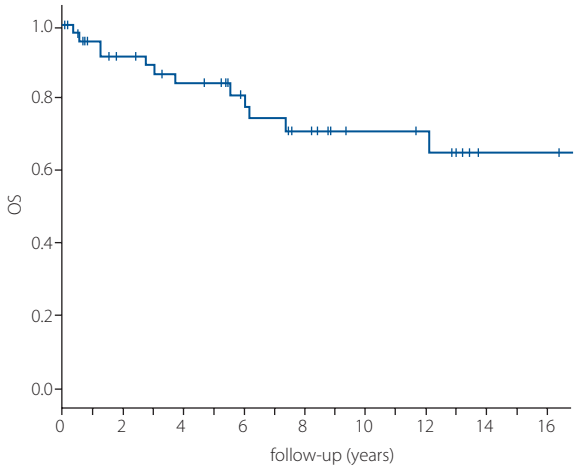


Figure 2. Overall survival (OS) for the entire group

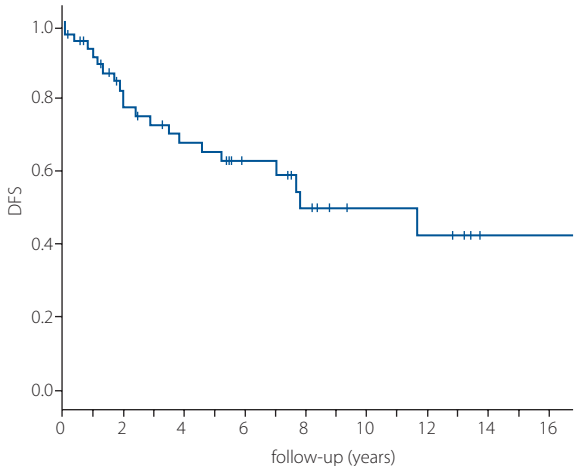


Figure 3. Disease-free survival (DFS) for the entire group

The Cox multivariate analysis allowed one to observe that only the radicality (R0 resection) of the surgery affects the overall survival and progression free survival. The relative risk of death in patients with an R0 resection makes up 0.206 of the respective risk for patients with R1 and R2 resections (i.e. patients with an R0 resection have approx. 5 times lower risk of death than patients with R1 and R2 resection). The risk of disease progression with resection R0 makes up 0.371 of the respective risk for patients with resection R1 and R2 (i.e. patients with an R0 resection have approx. 3 times lower risk of disease progression in comparison with patients with resection R1 and R2). The results of the multivariate analysis are presented in table II.

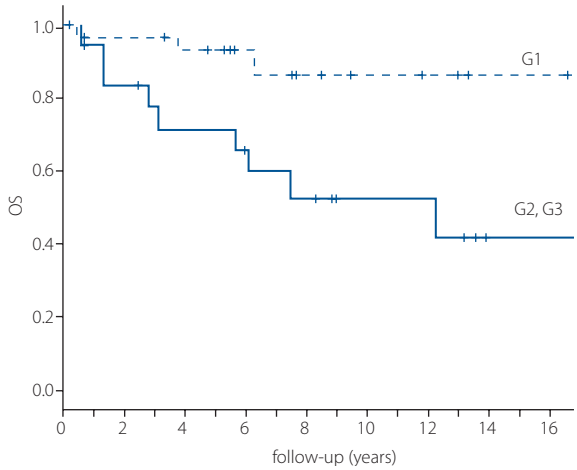


Figure 4. Overall survival (OS) depending on histological grade G. G1 – low histological grade; G2 – medium histological grade; G3 – high histological grade. Probability of 5- and 1-year survival (OS) depending on histological grade were 94.6% and 85.6% for the G1 patients, and: 71.6% and 52.3% for the G2 and G3 patients, respectively

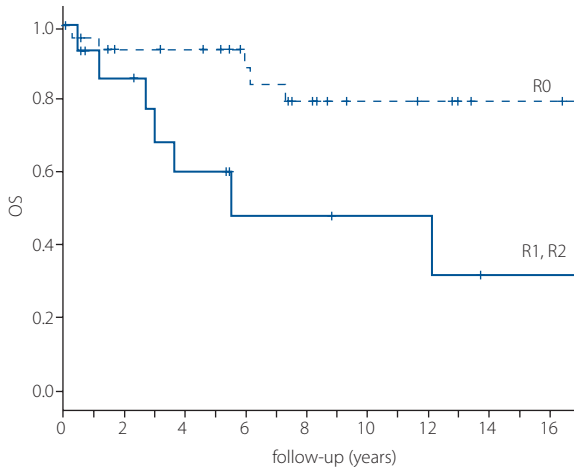


Figure 5. Overall survival (OS) depending on the radicality (R) of the surgery. R0 – radical resection, margin microscopically free from the cancer cells; R1 – microscopically non-radical resection; R2 – macroscopically non-radical resection. Probability of 5- and 10-year overall survival (OS) depending on the resection margin were: for the patients with R0 margin: 76% and 60%, whilst for the patients with R1 and R2: 40% and 20% respectively

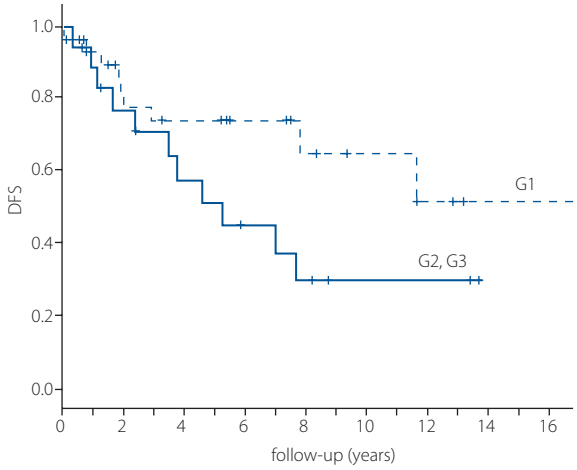


Figure 6. Disease-free survival (DFS) depending on histological grade G. G1 – low histological grade; G2 – medium histological grade; G3 – high histological grade. Probability of 5- and 1-year disease-free survival (DFS) 5 depending on histological grade were for the G1 patients: 75.7% and 65%, and for the G2 and G3 patients: 52.9% and 31.2% respectively

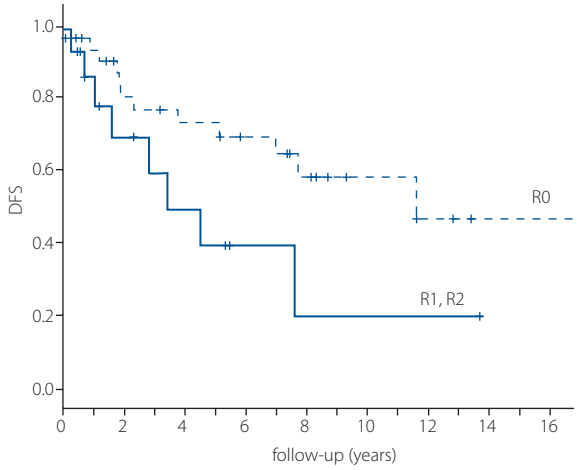


Figure 7. Disease-free survival (DFS) depending on the radicality (R) of the surgery . R0 – radical resection, margin microscopically free from the cancer cells; R1 – microscopically non-radical resection; R2 – macroscopically non-radical resection. Probability of 5- and 10-year disease-free survival (DFS) depending on the resection margin were: for the patients with R0 margin: 75.2% and 60%; whilst for the patients with R1 and R2: 20% and 40% respectively

Table II. The results of multivariate analysis – the final regression model parameters in Cox proportional hazard model

Dependent variable	Independent variable	Beta factor	Statistical error	Wald's test	p	Relative risk	95% CI – threshold:	
							upper	lower
risk of death	male sex	1.111	0.675	2.711	0.100	3.037	0.809	11.397
OS	R0	–1.578	0.604	6.825	0.009	0.206	0.063	0.674
risk of recurrence	male sex	0.783	0.478	2.685	0.101	2.189	0.858	5.588
DFS	R0	–0.992	0.475	4.355	0.037	0.371	0.146	0.941

Complications

None of the patients died within the period of 30 and 90 days from the date of surgery. In 53 operated patients, the following complications were observed:

- 1 patient was operated on for the urinary bladder fistula (15 days from the surgery),
- 1 patient was operated on for an abscess in the post-surgical wound (10 days from the surgery),
- 4 patients were operated on for post-operative wound bleeding or a haematoma (within the range between 0–26 days from the surgery),
- 1 patient was operated on for luxation of the iliac joint prothesis (3 days from surgery).

In total, complications requiring surgical interventions were found in 7 patients (13%).

Such situations as the necessity of puncture on account of lymph accumulation in the surgical wound or a poor limb function were not taken into consideration. Lymph drainage from the surgical wound and the necessity of rehabilitation are the results of surgery and are included in the post-surgical protocol.

Discussion

As a result of the statistical analysis, it was observed that the core factor affecting the overall survival (OS) and disease free survival (DFS) of patients with ChSa localised in the pelvis is the resection margin. Patients with an R0 resection have a higher probability of survival and disease free survival than those patients where a R1 or R2 resection have been performed, irrespective of tumour size or histological grade.

J. From, A. Klein, Baur-Melnyk A. et al. [14] carried out an analysis of 87 patients observing that a radical resection margin (R0) significantly affects disease free survival, whilst it does not have any effect on overall survival. It must be observed however, that the survival period was analysed in patients with various locations of ChSa (upper or lower limb, trunk and pelvis). The analysis revealed that once location is taken into consideration, the patients with ChSa located in the pelvis had the worst prognoses In the entire group, in turn, the factor which affects survival the most is the histological grade (and also the presence of metastases) [14]. In the analysed group of 53 patients with pelvic ChSa, only

the univariate analysis revealed that the histological grade affects the OS and DFS.

Another research [15] performed by X. Chen, L.J. Yu, H.M. Peng et. al presented an analysis as to whether the resection margin (R1 *vs.* R0) in patients with ChSa G1 affects overall survival or disease free survival. The multi-centre analysis showed that with the G1 grade, a non-radical margin does not affect the probability of recurrence. It must be remembered that this was a multi-centre analysis, which took into consideration mostly limb locations of ChSa, so the study group was not homogenous. It seems that in the case of the pelvic location of ChSa, irrespective of the histological grade, surgical intervention should be planned in such a way that a microscopically radical margin should be obtained.

Other authors – Y. Tsuda, S. Evans, J.D. Stevenson et al. [16] – declare that a resection margin of at least 1 mm guarantees progression free survival. Yet their study solely concerned patients with secondary ChSa which had evolved from a osteochondroma. It was also a multicentre analysis.

The analysed group of 53 patients was comprised of patients treated in one centre (with the exception of 1 patient operated on for a primary tumour outside the institute); also 1 location (pelvis) was taken into consideration; moreover about 70% of patients were operated on by surgeons as the main operators. Therefore, this can be regarded as quite a uniform patient group with respect to the conditions in which they were treated.

It must be added that in this work there was no division of margins into smaller 1 mm and at least 1 mm (the R0 margin was defined as a margin free from tumour cells – the smallest one is the tumour capsule on condition that it remained intact during the procedure).

As the analysed group of patients (53 patients after resection of the pelvic bone, and sparing the limb) is homogenous (so the effect of the same factors on patients within the process of treatment can be assessed), the conclusion that the result of the multivariate analysis shows that the best prognoses concern the patients with R0 resection is very probable.

Similar conclusions were reached by the team of C. Zoccali, J. Baldi, D. Attala et al. [5], who showed in their study that the R0 margin in surgical treatment of patients with pelvic ChSa is the most significant factor which determines the prognosis, in contrast to patients with ChSa of long bones, where the R1 margin in patients with ACT, i.e. ChSa G1 is not a significant prognostic factor. Similar conclusions were also drawn by the authors of other studies [8, 9]. Our analysis confirms these results. Examples of diagnostic images of patients operated on for chondrosarcoma of the pelvis, before and after surgery, are presented in figures from 8 to 10.

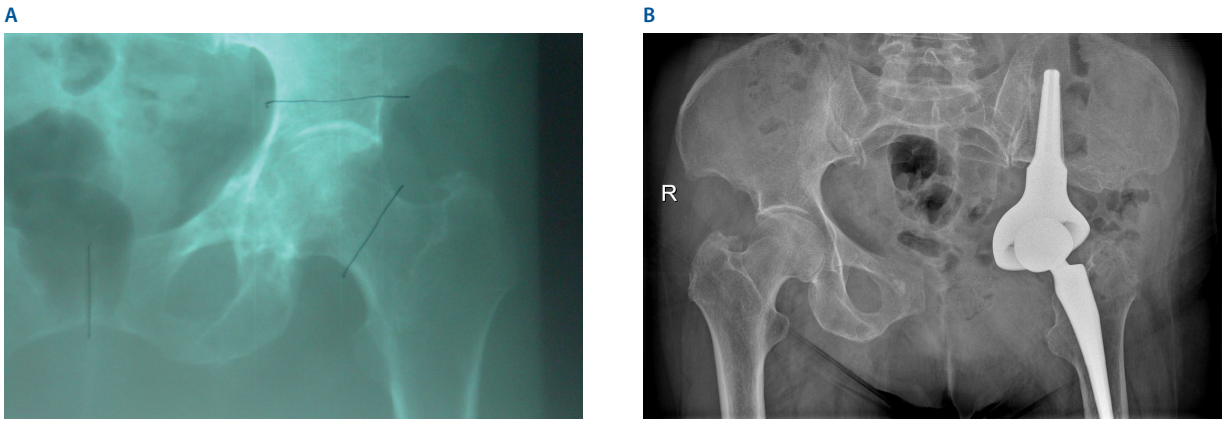


Figure 8. Female patient, aged: 69; iliac joint resection with endoprosthesis – pre-op (**A**) and post-op (**B**)

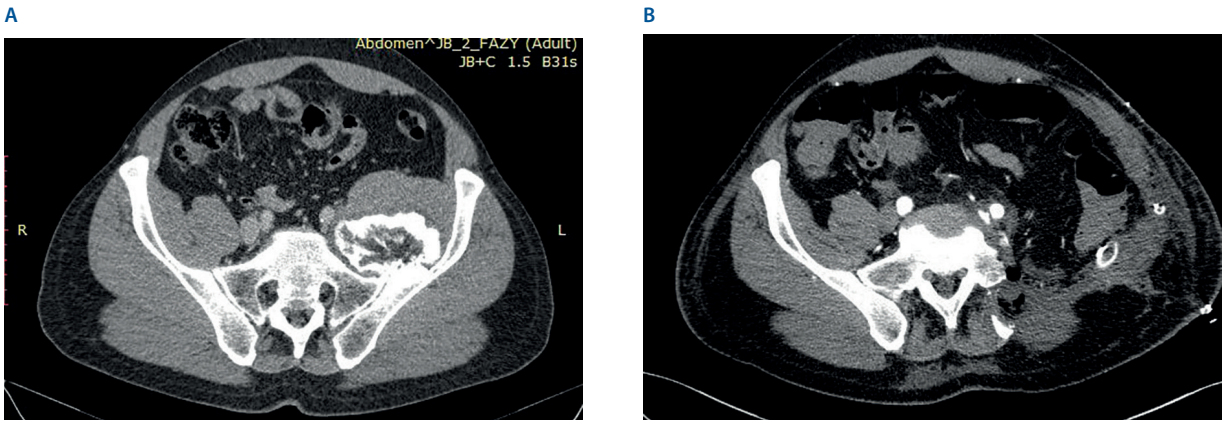
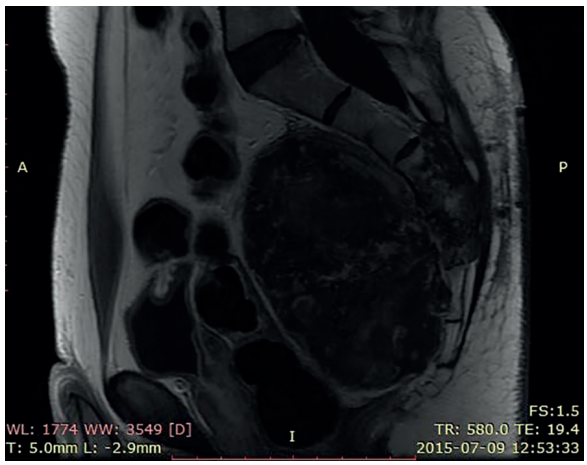


Figure 9. Male patient, aged: 41; chondrosarcoma of the iliac ala and left sacroiliac joint – CT image pre-op (**A**) and post-op (**B**)

A



B

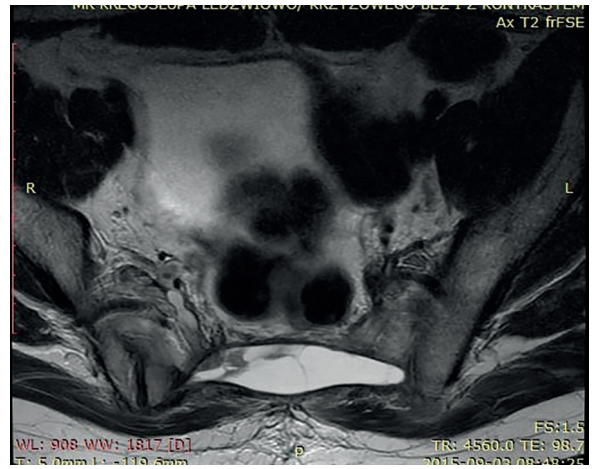


Figure 10. Male patient, aged: 39; chondrosarcoma of the sacral bone – MRI image pre-op (**A**) and post-op (**B**)

Conclusions

The univariate analysis performed the in a group of 53 patients operated for chondrosarcoma of the pelvis, with limb sparing, allowed to name the following factors affecting the overall survival (OS) and disease free survival (DFS): tumour histological grade (G) and resection margin (R). The best prognoses are associated with G1 grade and R0 resection margin.

The multivariate analysis showed that the factor which affected overall survival (OS) and disease free survival (DFS) was resection margin (R). The best prognoses are associated with R0. The success of treatment with the radical margin depends on appropriate qualification – first of all on the basis of imagining diagnostics –and surgical technique (worked out on the basis of many years' experience).

It can be concluded that the treatment success depends on the length of experience of a given centre which performs such interventions, i.e. resections of the fragments of the pelvic bone sparing the limb with an intention to achieve a radical margin (R0).

Conflict of interest: none declared

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Static-junction craniospinal irradiation: verification of daily dose and long-term treatment results

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Introduction. The study was performed to evaluate the repeatability and effectiveness of the static-junctions image guided (SJIG) method of craniospinal irradiation.
Material and methods. An analysis of 40 treatment plans was performed. All treatment plans were reviewed with regard to the distances between isocentres between in every single field of each fraction during all treatment days. Based on that data, second (actually treated) plans were created. The planned and treated parameters were compared.
Results. The study group consisted of 40 patients irradiated in the craniospinal region. Data on 902 fractions and 1635 isocentres positions was collected. 1-, 2- and 5-year overall survival was 95%, 89% and 78%, respectively. Spine metastases were observed in regions which were covered with a homogenous dose during treatment.
Conclusions. SJIG is safe and produces very good long-term outcomes. Treatment planning and delivery is simple with good reproduction of the planned dose distribution during the actual treatment.

Key words: medulloblastoma, craniospinal irradiation, image guided radiotherapy, treatment planning

Introduction

Craniospinal irradiation (CSI) is commonly used in the treatment of patients with primary central nervous system tumours which spread via cerebrospinal fluid [1, 2]. CSI is a very challenging technique due to the length and the complexity of the planning target volume (PTV) and radiosensitivity of the surrounding organs. Different approaches to this treatment technique have been developed so far, but no clear advantage of any of them is so far evident [3–18]. The analysis by SIOPE-BTG showed the benefit of modern radiotherapy techniques (intensity modulated radiotherapy – IMRT, volumetric arc therapy – VMAT or proton beam therapy – PBT), but standard (unmodulated) techniques of conformal therapy are still widely used in many treatment centres, especially in low-income countries [6–8].

In this study we evaluated the reproducibility and the effectiveness of the static-junctions image guided (SJIG) method of craniospinal irradiation (CSI) with an emphasis on actual treatment delivery implementation, long-term treatment results and patterns of progression. This method of CSI could be useful in low-income countries with a lack of more advanced treatment techniques and also in countries in which proton

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beam treatment is not available. It could also be considered a paediatric treatment technique because the impact of a low dose was associated with dynamic techniques and an integral dose is still a matter of debate.

Material and methods

Immobilization, imaging and treatment planning

A thermoplastic mask (Orfit by Stanley) was made individually for each patient. A computed tomography (CT) covering the whole spinal axis was performed with 3–5 mm slices. A fusion of the CT with a magnetic resonance of the brain was carried out for all the patients. Forty patients were treated, 35 in the supine position and 5 in the prone position.

All the plans were created in the Eclipse Advanced Treatment Planning Software from Varian Medical Systems with the pencil beam convolution (Eclipse PBC) or the analytical anisotropic algorithm (Eclipse AAA). All the retrospectively reviewed plans were created with the AA algorithm version 8.6. Each patient was irradiated with a 3D image-guided technique with static junctions between the fields (SJIG) – the field dimensions and isocenter positions were constant throughout the whole treatment.

The target volume consisted of GTV (gross tumour volume) after the subtotal resection in all cases. The clinical target volume (CTV) was defined as the intracranial content and thecal sac, including nerve roots. The PTV (planning target volume) was created by adding a 5 mm margin to the CTV. The dose was prescribed to obtain >95% of the prescribed dose in >98% of PTV.

For all the patients, a single treatment plan with static junctions between the fields was made. It consisted of 2–3 isocentres and 3–7 fields: two opposed lateral fields to treat the brain and a part of the cervical spine, and one or two adjoining posterior spinal fields to cover the rest of the spinal canal (the last one was tilted to match the beam divergence of the main spinal field). The first isocentre was located at the level of the cranial base, and treatment fields covered the brain and the upper part of the cervical spine. The second isocentre was located in the lower part of the thoracic spine (one posterior field, 180 degrees). The third was used in the case of taller patients or when the thoracic field did not acceptably cover the anterior part of the lumbosacral space. The number of spinal fields (and isocentres) depended strictly on the length of the PTV due to the limited maximum field size in the Varian system which is (with SSD of 100 cm) 40 x 40 cm at the isocentre. All the isocentres had the same vertical and lateral coordinates. Corrections in longitudinal direction during treatment were allowed only in the first isocentre position, corrections in lateral and vertical direction were allowed in all isocentres positions. The position of treatment fields between the first and the second isocentre (the first junction) was matched using the rotation of the collimator and treatment couch. The second junction (if necessary) was created using the treatment table rotation (90 degrees) and adjustment of the gantry rotation (fig. 1). This method eliminates overlapping or underdosage between the fields. All the treatment plans had dosimetric verification before the beginning of treatment.

Treatment process

All the patients were treated on standard linear accelerators with energies of 6–20 MV. Verification of the patient's position was performed with the portal view images (PVI) – the earlier years of the study or with kilovoltage imaging (kV). To assure correct treatment delivery, the couch was moved in a longitudinal axis by a constant value derived from the treatment plan, all other shifts were corrected according to the results of imaging on the treatment machine.

Review process

All the treatment plans were reviewed by the physician and the physicist with regard to the treatment couch movement (and the distance between isocentres) between every single field of each fraction during all the treatment days, based on the

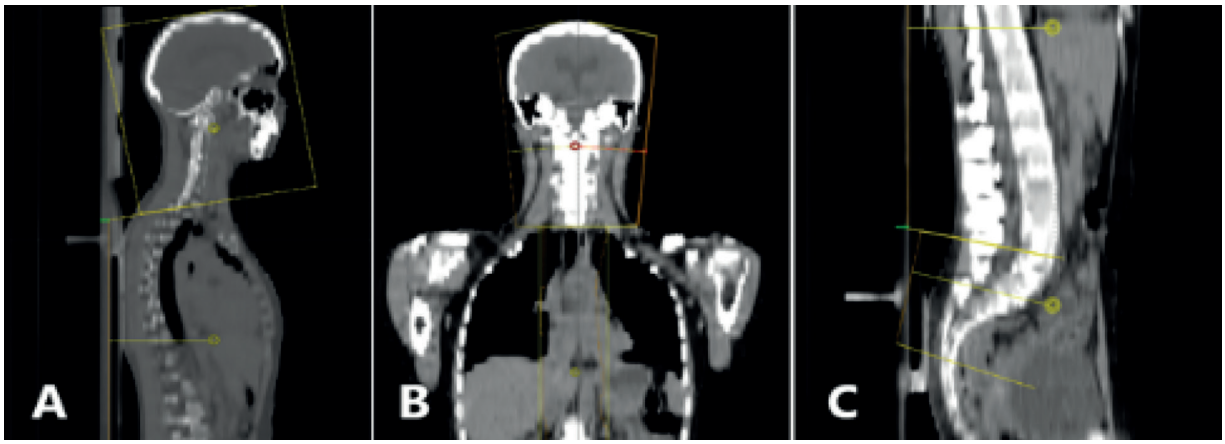

Figure 1. The effect of collimation of treatment fields between the first and the second treatment field – the first junction: **A** – lateral view; **B** – frontal view. **C** – the effect of the changing of treatment table rotation between the first and second treatment field – the second junction (lateral view)

data collected during the treatment and saved in the oncology information system (Aria). The images (kV or PV) used to verify the patient's position during the treatment were audited for all patients. Distances between the positions of the isocentres were collected and checked against the planned distances. Each shift in the direction towards the head was noted as "+ value" and each shift in the direction towards the feet was noted as a negative value compared to the planned distance. Based on that data and the differences between the planned and the treated distances between the positions of isocentres, we created second (actually treated) plans. The planned (P) and treated (T) parameters as dose delivered to particular volume of the PTV (%), minimum and maximum dose, mean and median total dose, homogeneity index – HI (RTOG) were collected and compared.

Study endpoints

Overall survival (OS) was evaluated using the Kaplan–Meier method. Progression-free survival was measured from the date of the end of treatment to the date of local or distant progression, or death. The date of death was obtained from the National Cancer Registry. Treatment plans were reviewed in patients with recurrence of the disease, in order to assess the exact location and dose delivered to the relapse site. Toxicity was evaluated based on the RTOG/EORTC criteria [19].

Results

Group characteristics

We performed a retrospective analysis of CSI treatment plans of 40 patients (27 male and 13 female) with brain tumours (22 medulloblastoma, 10 ependymoma, 5 germinoma, 2 primitive neuroectodermal tumours [PNET], 1 anaplastic oligodendroglioma) treated in our Institution between the years 2005 and 2014. The study group consisted of 14 children and 26 adults. The median age was 21 years at the time of diagnosis (range: 4–43). All the patients were treated with curative intent, including those with metastases in the spinal region, which were diagnosed in 4 patients. The mean spine volume was 129 cm^3 and the mean spine length was 57 cm.

Fractionation and doses

Patients were irradiated with a fraction dose (fd) of 1.5–1.8 Gy to the spinal regions and 1.5–2.0 Gy to the brain. All but one received a two phase treatment: in the first phase, the brain and spine were irradiated, in the second, a boost was delivered only to the residual tumour or tumour bed. The median total dose (TD) in the first phase was 36 Gy and the median boost dose was 18 Gy. The PBC algorithm was used in the case of 21 patients, AAA in 19. The mean doses delivered to the organ at risk were within the range of 0.82–6.82Gy for the lenses, 25.33–55.68 Gy for the ears, 13.36–45.26 Gy for the parotids, 3.97–31.27 Gy for the thyroid, 1.26–20.23 Gy for the heart, 1.39–9.90 Gy for the lungs, 0.35–6.18 Gy for the breasts, 2.42–8.85 Gy for the liver, 0.69–14.65 Gy for the bowel, 0.47–3.88 Gy for the kidneys and 0.14–18.9 1Gy for the bladder. Data concerning the delivery of a total number of 902 fractions and 1635 isocentre positions was collected. The planned (P) and treated (T) parameters are presented in table I.

Follow-up

During the median follow-up (FU) of 58 months, 10 patients died. One-, 2- and 5-year OS was 95%, 89% and 78%, respectively.

Table I. The dosimetric parameters obtained by comparing the original plans and reconstructed dose distribution

Parameter	% diff % in median dose (P/T)	% diff % in mean dose (P/T)	Range
$D_{70\%}$	–0.02%	–0.20%	–5.01% to +7.62%
$D_{75\%}$	–0.03%	–0.23%	–5.91% to +7.01%
$D_{80\%}$	–0.03%	–0.47%	–6.79% to +6.00%
$D_{85\%}$	–0.06%	–1.06%	–10.93% to +4.60%
$D_{90\%}$	0.00%	–1.22%	–11.93% to +3.54%
$D_{95\%}$	–0.01%	–1.84%	–16.27% to +3.49%
$D_{98\%}$	–0.06%	–2.43%	–25.36% to +3.89%
$D_{2\%}$	–0.10%	–2.55%	–27.75% to +3.21%
D_{min}	–0.13%	–3.73%	–30.02% to +4.12%
D_{max}	0.04%	2.40%	–3.03% to +26.71%
median D_{TD}	0.00%	–	–4.21% to 8.47%
mean D_{TD}	–	–0.01%	–3.67% to +9.77%
HI(P)	1.22	1.25	1.08 to 1.81
HI(T)	1.25	1.28	1.08 to 1.87
D_{max}/D_{min}(P)	1.34	1.41	1.13 to 2.10
D_{max}/D_{min}(T)	1.42	1.51	1.13 to 2.83
D_{max}/D_{min}(P/T)	0.18	0.11	–0.05% to 1.08%

% diff – (Dose planned–Dose treated)/Dose planned x 100%; Dose n – dose received by certain percentage of the volume of the PTV; range relates to all mesured plans

Tumour relapsed in 16 patients – 13 in the brain, 1 in the brain and then in the spine, and 1 in the spine only; 1 patient was diagnosed with multiple bone metastases. Eight patients with relapse died due to the progression of the disease. One-, 2- and 5-year PFS was 89%, 76% and 54%, respectively. Patients with spine relapses had plans with HI of 1.234 (P), 1.245 (T) and 1.154 (P), 1.193 (T), respectively. Spine metastases were observed inside the treatment fields, in regions which were covered with a homogenous dose during treatment. No neurologic complications caused by CSI were diagnosed. No radiologic evidence of radiation-induced necrosis was observed.

Conclusions

So far, this is the first study which evaluated CSI treatment planning techniques with regard to actual everyday treatment delivery implementation, the long-term treatment results and the pattern of progression [20–35]. The technique presented in our study is simple and can be easily implemented – even in departments with limited resources. In some countries, more sophisticated radiotherapy systems, even if potentially available, are not used due to their complexity and the time consuming planning and delivery involved [29–33]. One approach to expand the possibilities of the existing equipment is to install some kind of platform-independent expansions like the ring-based compensator IMRT system proposed by Van Schelt et al. [34]. The other is to refine the planning techniques used, as proposed in our paper to reduce workload during treatment planning and, thanks to the simple irradiation technique, also in-room time which allows for optimization of accelerator use without compromising the quality of the treatment.

Our research is not only a theoretical study dealing with the technical aspects of certain irradiation techniques. Our findings are backed both by dose distribution recalculations based on real-life, everyday position shifts, and by the clinical results of treatment. No symptoms of any spinal cord injury in our patients can be considered a strong confirmation of our theoretical assumptions; this is also supported by calculations of the dose distribution reflecting the real position of the patient.

A limitation of our study is its retrospective character, which makes it impossible to assess whether the positioning data reported in the system are indeed parameters during treatment delivery (if the data was correctly saved in the system) or e.g. the data on the isocenter position after the initial verification because not always the imaging was repeated after position correction. The data concerning dose delivered was re-checked in 6 patients, who, according to the calculations, received less than 80% of the planned doses. Half of them were planned with the PBC algorithm, half with AAA. In 3 patients "cold spots" were observed in the thoracic-lumbar junction, 2 in the cervical-thoracic junction and 1 in the lumbar part of the spine. The majority of patients were irradiated with good (>80% of the planned dose in 90% of the patients) or very good (>90% of the planned dose in 56% of the patients) accuracy. When comparing the groups: the group with less than <80% of the planned dose delivered, the group with 80–90% of the planned dose delivered and the group >90% of the planned dose delivered, we observed that patients who had the best results were those with the largest mean and median length of the spine were: in the group <80%: mean and median were 63 and 67 cm, in the group 80–90%: mean and median was 86 cm, and in the group >90%: mean and median was equal 94 cm. The necessity of sedation of children did not influence the deviations observed in table I.

When discussing the drawbacks of the study, we should also mention the histopathological diagnosis of patients with ependymoma (which is, unless disseminated, no longer an indication for craniospinal irradiation) and 1 patient with PNET (which is no longer recognized according to the new WHO classification). This fact however does not influence the conclusions of the study aimed at the technical aspects of CSI.

SJIG is safe and produces very good long-term outcomes. Treatment planning and delivery is simple and less time consuming than the junction-shift techniques, with good reproduction of the planned dose distribution during actual treatment, assuming that image guidance is available and used on a daily basis.

Conflict of interest: none declared

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Hilar cholangiocarcinoma – the long-term results of radical and palliative treatment

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Introduction. Hilar cholangiocarcinoma (HC) is a tumor that requires a multidisciplinary approach and treatment. The 3- and 5-year survival rates of HC patients treated with surgery and palliative methods were evaluated in the study.
Material and methods. The study covered 368 patients treated between 2000–2014. Of them, 137 patients were categorized for surgery (RT group), and 231 for palliative treatment (PT group). The overall 3- and 5-year survival rates were determined by the log-rank test. The Cox hazard regression model revealed the relative prognostic factors.
Results. The 3- and 5-year survival rates accounted for 38% and 21% after surgery, but 13% and 0 after palliative treatment ($p < 0.0001$). Radical tumor resection, negative lymph nodes, and early tumor T stage were the factors conducive to survival.
Conclusions. Surgery, if the radical tumor resection is possible, offers a chance for long-term survival. The effects of surgical treatment are of little consequence in the face of poor treatment outcomes of palliative patients, however.

Key words: hilar cholangiocarcinoma, Bismuth-Corlette typing, T-stage typing, hemihepatectomy, negative resection margin

Introduction

Hilar cholangiocarcinoma (HC) is a tumor of the main lobar extrahepatic bile ducts, distal to segmental bile ducts and proximal to the cystic duct [1, 2]. Radical tumor resection that also covers the extrahepatic bile ducts and the unilateral part of the liver provides a chance to cure the disease, but selection of candidates remains challenging [5].

Studies on the results of HC treatment usually show the effects of surgery or the effects of palliative treatment in the particular groups of patients [3–6]. Few studies focus on an analysis of all patients admitted and treated at a multidisciplinary department of a single institution over a long period of time [7]. This prompted the presentation of own experience in the management of HC patients undergoing radical surgery and palliative care in the multidisciplinary HPB department of Medical University of Warsaw. The 3- and 5-year cumulative overall survival rates and factors conducive to the survival of the patients were the end-points of this study.

Material and methods

The study covered a cohort of 368 patients (F 178, M 190, median age 58.3, range 23–94, SD +/–13.9 years) with Klatskin's tumors, who were transferred from public hospitals in the period of 2000–2014. Of them, 65% had already undergone bile duct stenting. Tumors were evaluated for radical surgery by using the T-stage classifications as assessed using CT, MRIch and USG imagings [8–11, 13]. The presence of adenocarcinoma

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was confirmed in each case by the pathologist based on tissue biopsies and/or tissue material removed during surgery. The TNM clinical stage (UICC) was determined in patients who underwent surgery.

Patients qualified for radical surgery

The group consisted of 137 (37.2%) patients (F 63, M 74, median age 57.3 years, (range 23–78, SD +/–12.2). 87 patients (F 37, M 50, median age 57.3 years) were already prosthetized before the transfer. The tumor was of stage Bismuth-Corlette II, IIIA, and IIIB in 6, 81 and 50 patients, respectively. Tumor clinical stage of T1 was determined for 29 patients and T2 for 108. The extended right hemihepatectomy included the right liver lobe, the inferior part of segment IV, the hilar plate, and the entire caudate lobe. The extended left hemihepatectomy included the left liver lobe, the right paramedian sector of the hilar plate, and most of the caudate lobe. Six tumors of the Bismuth II type were excised locally. Lymph nodes of the celiac axis, common hepatic artery, and all lymphatic structures in the hepatoduodenal ligament were coupled with complete resection of the extrahepatic bile duct in all of the patients. A frozen--section analysis of the margins was used to guide resection. The biliary tract continuity was restored by the anastomosis of the remaining hepatic duct to the Roux-Y jejunal loop. The postoperative course was uncomplicated in 78 patients (57%). 14 patients (10.2%) died due to postoperative complications. The result of R0, R1, and R2 tumor resection was obtained in 100 (73%), 24 (17.5%), and 13 (9.5%) of the patients, respectively. The extent of carcinoma infiltration within the removed tissues was described in details by the pathologist in every patient. The TNM clinical stage was determined as T1N0M0 in 29 patients, T2N0M0 in 58 patients, and T3N1M0 in 50 patients. Adjuvant chemotherapy was applied only to 37 patients undergoing R1/R2 tumor resection. The details are presented in table I.

Patients having tumors clearly unresectable (Palliative A)

The group consisted of 210 patients (57.3%, F 101, M 109, median age 59.9, range 26–94, SD +/–11.0 years). Of them, 66% were already prosthetized before the transfer. The tumor was of stage Bismuth-Corlette II, IIIB and IV in 5, 25, and 180 patients, respectively. Radiologic tests indicated clearly the tumor unresectability (clinical T3 stage). No distant metastases were found in any of the patients, however. Infiltration of the bile duct by cholangiocarcinoma was confirmed by the pathologist in specimens obtained by biopsy or biliary brushing during ERCP. Clinical advances of the tumor were not possible to be calculated (TxNxM0).

Patients having unresectable tumors, as found during laparotomy (Palliative B)

In 21 patients (5.7%, F 14, M 7, median age 59.2, range 48–76, SD +/–14.2 years) imaging studies indicated the possibility of radical operation. Tumor was of stage Bismuth-Corlette IIIA in 8 patients, and IIIB in 13, and the clinical stage T2 was determined by radiologic tests. The operative exploration allowed to recognize excessive tumor involvement (T3 stage) and its unresectability. The reason for withdrawing them from radical surgery was tumor involvement of the main trunk of the portal vein in 14 cases, involvement of the common hepatic artery in 4, and the tumor's extensive spread to the contralateral duct in 7 patients. Operations ended after collection of tissue specimens. All patients were treated by endoscopic stenting over the postoperative period. Postoperative complications were frequent. Pathologic diagnosis was obtained by examination of the specimens taken during the explorative operation. Perineural invasion and lymph nodes invasion of the tumor were present in all patients. No distant metastases were found. The TNM stage of T4N1M0 was determined in all patients.

Palliative care modalities

The group of palliative patients consisted of 231 patients in total (63%, F 115, M 116, median age 58.9, range 26–94, SD +/–13.6 years). Endoscopic stenting of the bile duct tree was applied to all 231 patients. Depending on individual indications, plastic stents or different types of SEMSs prosthesis were inserted to provide effective bile drainage. The procedure was effective in 199 patients (86.1% out of 231 in this group), and uncomplicated in 145 (62.7%). 13 patients (5.6 %) died due to a failure in the procedure or serious biliary complications. In the follow-up period, plastic stents were usually changed every 2–4 months. Metal SEMS prostheses were targeted for permanent decompression of the biliary tree, however, more than 50% had intermittent cholangitis along with the treatment. Early complications also included infection, bleeding, pancreatitis, and often occlusion caused by sludge in both types of stents. Dislodgment happened in 14% and in 5% of the fully and partially covered SEMS prostheses. 76 of the patients (33%) received chemotherapy by using gemcitabine and platinum-based regimens, according to the oncologist's order. The details are presented in table II.

Statistical analysis

Data were summarized with follow-up to December 31, 2019. Cumulative overall patient survival rates at 3 and 5 years were determined as percent of patients and calculated by the Kaplan–Meier method using the log-rank test with adjustment for the type of treatment. The Chi-square test was used to analyze categorical data. The Cox proportional hazard regression model was used to assess the relative prognostic factors influence on patient survival. Values of $p < 0.05$ were considered significant.

Results

14 out of 137 patients from the RT group (10.2%), and 13 out of 231 patients from the PT group (5.6%), died during treatment due to serious complications ($p > 0.71$). The median

Table I. Demographic data, tumor features, procedures used and complications in patients treated by surgery

Patients treated by surgery Number of patients: 137 (37.2%); F 63, M 74, median age 57.3 (range 23–78, SD +/–12.2) Overall results of surgery: R0 – 100 (73%), R1 – 24 (17.5%), R2 –13 (9.5%)						
Detail description of variables				**Number of patients**	**Female**	**Male**
endoscopic prosthesis procedure prior to referral			yes	87 (63%)	37	50
			no	50	26	24
Right extended hemihepatectomy for Bismuth–Corlette type IIIA						
effects of surgery	T-stage	TNM class.	No. of pts.	97	46	51
R0	T1	T1N0M0	16	73	36	37
	T2	T2N0M0	50			
		T3N1M0	7			
R1	T1	T1N0M0	none	16	6	10
		T2N0M0				
	T2	T3N1M0	16			
R2	T1	T1N0M0	none	8	4	4
		T2N0M0				
	T2	T3N1M0	8			
Left extended hemihepatectomy for Bismuth–Corlette type IIIB						
effects of surgery	T-stage	TNM class.	No. of pts.	34	12	22
R0	T1	T1N0M0	13	21	7	24
	T2	T2N0M0	5			
		T3N1M0	3			
R1	T1	T1N0M0	none	8	4	4
		T2N0M0				
	T2	T3N1M0	8			
R2	T1	T1N0M0	none	5	1	4
		T2N0M0				
	T2	T3N1M0	5			
Local tumor resection for Bismuth–Corlette type II						
effects of surgery	T-stage	TNM class.	No. of pts.	6	3	3
R0	T1	T1N0M0	6	6	3	3
Results of pathologic examination						
lymph nodes infiltration			yes	50	19	31
			no	87	44	43
liver parenchyma infiltration			yes	64	31	33
			no	73	32	42
perineural invasion			yes	33	13	20
			no	104	50	54
Postoperative course and complications (Clavien–Dindo scale)						
unomplicated				78 (57%)	40	38
grade I				12	2	10
grade II				15	9	6
grade III				5	0	5
grade IV				13	5	8
grade V (death)				14 (10.2%)	7	7
Adjuvant chemotherapy (all R1 and R2 patients)				**37 (27.7%)**	**15**	**22**

Table II. Demographic data, tumor features, procedures used and complications in patients treated by palliative methods

Patients treated by palliative methods No. of patients: 231 (63%); F 115, M 116, median age 59.9 (range 26–94, SD+/–11.6) years						
Detail description of variables				**No. of patients**	**Female**	**Male**
endoscopic prosthesis procedure prior to referral			yes	140 (66%)	77	63
			no	70	24	46
Palliative A: unequivocally not for resection						
Bismuth-Corlette staging	T-stage	presumed TNM	No. of pts.	210	101	109
Bismuth type II	T3	T4NxM0	5	210	1	4
Bismuth type III/B			25		15	10
Bismuth type IV			180		85	95
Palliative B: excessive tumor development, "unnecessary laparotomies"						
Bismuth-Corlette staging	T-stage	confirmed TNM	No. of pts	21	14	7
Bismuth type IIIA	T2	T4N1M0	8	21	3	5
Bismuth type IIIB			13		11	2
Pathologic examination of tissue samples						
lymph nodes infiltration			yes	21	14	7
liver parenchyma infiltration			not tested	not tested		
perineural invasion			yes	21	14	7
Palliative A & B: procedures used						
metal stent replacement instead of existing plastic stents				114 (49%)	27	87
new stenting procedure due to jaundice by plastic / metal stents				96	69	27
explorative laparotomy; plastic or metal stents introduced after				21	14	7
Palliative A & B: complications after procedures (Clavien–Dindo scale)						
uncomplicated				145 (69%)	80	65
grade I				24	3	21
grade II				17	10	7
grade III				25	8	17
grade IV				19	11	8
grade V (death)				13 (5.6%)	5	8
palliative A & B: adjuvant chemotherapy				76 (33%)	39	37

survival time for the 368 patients participating in the study was 15.3 months, whereas the cumulative survival rates of 3- and 5-years were 27% and 11%, respectively. The median survival time of patients treated by surgery was 19.5 months (including patients with R0, R1, R2 resections of 24, 17, and 14 months, respectively), and for patients treated by palliative methods it was 13 months ($p < 0.001$). Statistical values are shown in table III.

The effect of R0 resection

The 3- and 5-year cumulative survival rates in the 137 patients treated by surgery were 38% and 21%, whereas in the 231 patients treated with palliative methods it was 13% and 0, respectively (log-rank test – 5.01, $p < 0.0001$). On the other hand, in the 100 patients undergoing R0 resection it was 50% and 30%, but in the 37 patients undergoing R1/R2 resection it was 20.5% and 0, respectively (log-rank test – 3.15, $p < 0.002$). No significant differences in the 3- and 5-year survival rates were found between patients undergoing R1 resection (survival rates accounting for 21% and 0%) and R2 resection (survival rates accounting for 11.5% and 0), (log-rank test – 0.60, $p > 0.54$; in between patients undergoing R1/R2 resection and those treated with palliative methods (log-rank test – 0.65, $p > 0.58$); in between the palliative patients who received adjuvant chemotherapy and those who did not receive it (log-rank – 0.87, $p > 0.28$) (fig. 1).

The effect of T-stage

Patients categorized by T-stage classification were eligible for tumor resection while being in the T1 or T2 tumor stage. Resection R0 was achieved in 35 patients with T1 and 65 patients with T2 tumors, while R1 and R2 resection was achieved in 24

Table III. Analysis of patient survival based on treatment modality

Dependent variables Survival time	Value 'z' for multiple comparisons; independent variable (grouping): treatment modality Kruskal-Wallis test: H (2, N = 368) – 31.27 p < 0.0001			Dependent variable Survival time	P value for multiple comparisons; independent variable (grouping): treatment modality Kruskal-Wallis test: H (2, N = 368) – 31.27 p < 0.0001		
	R0	R1 + R2	PT		R0	R1 + R2	PT
R0			2.81	R0		0.014	0.0001
R1 + R2	2.81			R1 + R2	0.014		1.00
PT	5.56	0.85		PT	0.0001	1.00	

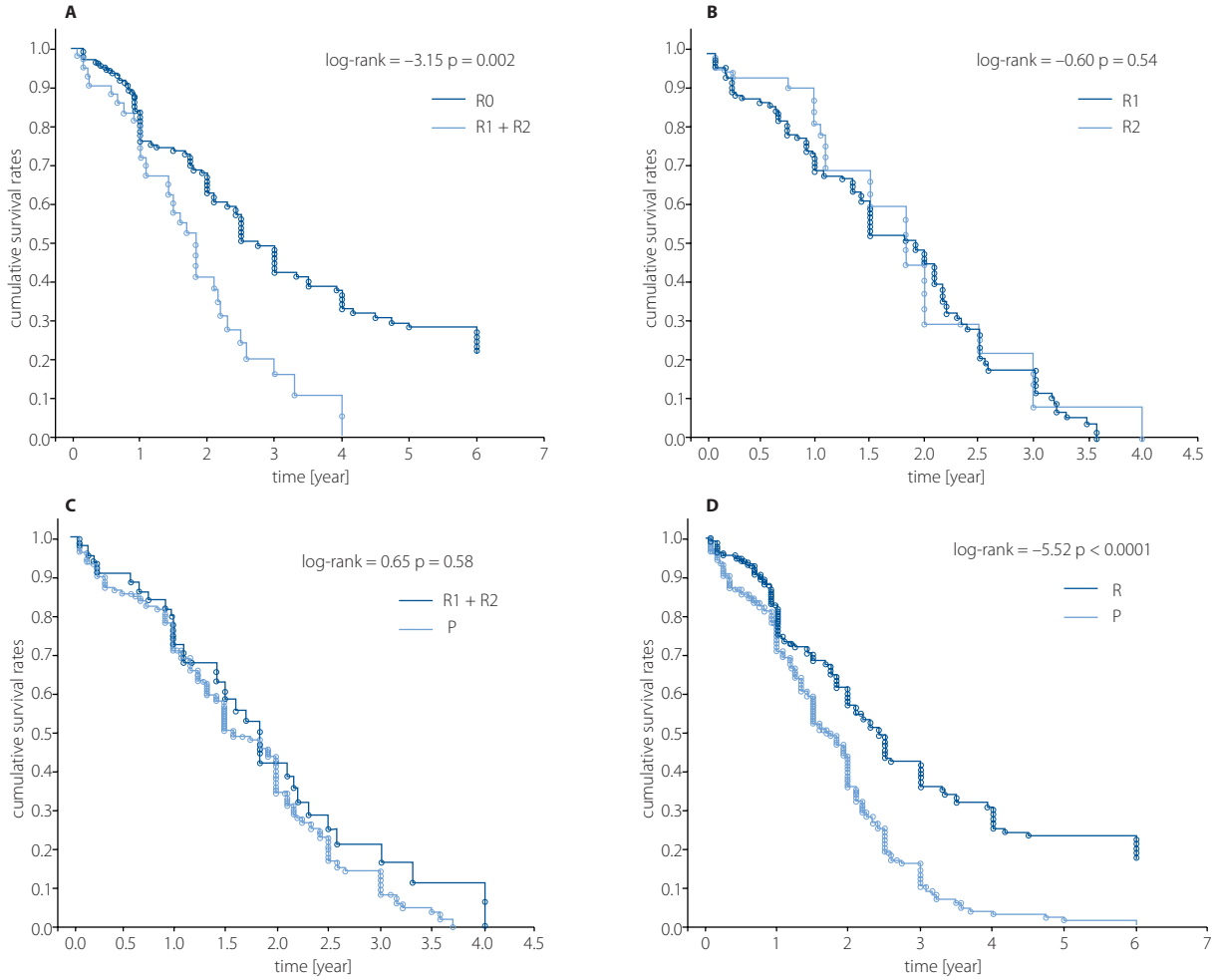

Figure 1. Kaplan–Meier survival estimate of patients with curatively intent surgeries and with patients treated with palliative methods. **A**. Survival time differed significantly between R0 and R1/R2 resection; **B**. No significant difference in survival time was found between resection R1 and R2; **C**.No significant difference in survival time was found between resection R1/R2 and palliative treatment; **D**. Survival time differed significantly between R0 resection and palliative treatment

and 13 patients, all with T2 tumors. The median survival time of patients with T1 tumors was 29.1 months and of patients with T2 tumors – 15.5 months. On the other hand, all patients with T3 tumors were suitable only for palliative treatment, with a median survival time of 13 months. The median survival of all 368 patients that were categorized by T-stage was 14.7 months. Further analysis by multiple comparisons showed that the survival time of patients with stage T1 tumors was significantly longer than those with stage T2 ($p < 0.015$), and T3 ($p < 0.002$). No significant difference was found in the survival time of patients with T2 and T3 stage tumors ($p < 1.0$), (tab. IV). The T-stage of a tumor corresponded clearly to its local growth and spread, as was confirmed by the pathologist in post--operative specimens that had been removed. Only patients determined as T1-stage possessed tumors in the early stage of development (T1N0M0), whereas in the T2 patients, tumors

Table IV. Analysis of patient survival based on T-stage classification

Dependent variables Survival time	Value 'z' for multiple comparisons; independent variable (grouping): T-staging system Kruskal-Wallis test: H (3, N = 368) – 18.33 p = 0.0004			Dependent variable Survival time	P value for multiple comparisons; independent variable (grouping): T-staging system Kruskal-Wallis test: H (3, N = 368) – 18.33 p = 0.0004		
	T1-stage	T2-stage	T3-satge		T1-stage	T2-stage	T3-stage
T1-stage		3.02	3.54	T1-stage		0.015	0.002
T2-stage	3.02		0.55	T2-stage	0.015		1.00
T3-stage	3.54	0.55		T3-stage	0.002	1.00	

Table V. Results of multivariate analysis using the Cox regression model for factors conducive to patient survival

Parameter	Chi-square	Pr > ChiSq	Hazard ratio
tumor resection R0 *vs.* R1/R2	14.79	<0.001	2.29
lymph nodes negative *vs.* involved	21.08	<0.001	2.27
tumor T1-stage *vs.* T2/T3	5.21	<0.02	1.55

were more advanced (T2N0 and T3N1). Their survival time was shorter, and unfortunately, it did not differ significantly from the survival of palliative patients treated. The results indicate the dependence of long-term outcomes from the clinical T-stage of tumor development, but also lymph node involvement in the cancer mass.

Prognostic factors

The analysis revealed that R0 tumor resection, the negative lymph nodes, and the tumor at T1-stage, are factors favorable for patients' survival ($p < 0.001$ and $0 < 0.02$). Consequently, the less advanced the tumor is, the easier it is to achieve radical resection and the better the long-term result (tab. V). The differences in the cumulative survival rates that would arise from the patients' sex, age, and postoperative complications or differences in the operative or endoscopic treatment modality were found to be statistically not significant.

Discussion

The study demonstrated that R0 tumor resection offers a chance at long-term survival, however the procedure can be applied in only circa 30% of cases. In such patients, the 3- and 5-year cumulative survival rates were 50% and 30%, respectively, with a perioperative mortality of 10.2%. Although the resection was challenging in numerous cases, the postoperative complications were not frequent, and the postoperative mortality accounted for 10.2 %, since only 14 patients died. The results corresponded to experience presented i.e. by van Gulik et al., Zhang et al., Baton, et al. and some others [19–24].

The study showed that the T-staging system served as a good indicator for postoperative prognosis. The oncologic radicalism has been achieved following the principles of liver surgery that are generally known and accepted [2, 7, 11–16, 21, 22]. A particular strength of the present study was that the diagnosis of hilum carcinoma was confirmed in all patients by positive histology or cytology. Therefore, the clinical stage of the patients could be classified according to UICC/AJCC system [7, 16, 18]. The pathologic examination of the operative specimens showed that all T1-stage patients should be classified as T1N0M0, whereas T2-stage patients as at least T2N0M0, but also as T2N1M0. This indicated a close correlation between the T-staging system, the multifactorial pTNM staging and the clinical stage of tumor development, which is obvious and confirmed by years of experience [13–17, 23–25]. Therefore, the median survival time of patients with T1 tumors was significantly longer than of patients with T2 tumors, regardless that the resection was R0 in each case ($p < 0.015$). No significant difference was found, however, in the median survival time of patients with T2 tumors undergoing palliative resection and the T3 tumors, treated with palliative methods ($p > 1.0$). In fact, all patients who underwent tumor resection, limited to the state of R1 and R2, were classified as T3N1M0 by the pathologist. The above data has suggested that patients without lymph node involvement have a better survival chance. Actually, the negative lymph nodes were found as one of the factors conductive to the survival of the patient in the multivariate analysis by using the Cox regression model in this study. The literature provides conflicting results regarding the association of lymph node status on survival, with some authors showing a clear effect [14, 22] and some showing none [7, 26]. Nonetheless, our results indicate the dependence of long-term outcomes from the clinical T-stage of tumor development, but also the lymph node involvement in the cancer mass. Consequently, the less advanced the tumor, the easier it is to achieve radical resection and the better the long-term outcome [4, 7, 13–17].

The effectiveness of the preoperative assessment has proven insufficient in over 15% of patients. In fact, they had an advanced cancer, which was confirmed during explorative

laparotomy or the surgery had to be limited to the stage R1/R2 (all T4N1M0). The problem is generally known as "unnecessary laparotomies", and is mentioned as one of the causes of poor treatment results in HC patients. However, the study by Jarnagin et al. [7], and Zhang et al. [20] reveal longer survival rates after palliative tumor resection. Also, Baton et al. [21] found that R1 hepatic resection with no other risk factors can offer better long-term survival. On the other hand, in a study by Seyama et al. [22], no difference in survival was seen between R0 resection with a margin <5 mm and R1 resection. Indeed, the 3- and 5-year cumulative survival rates were longer in R1 than R2 of patients, but, the difference was statistically irrelevant (log-rank test – 0.6, $p > 0.54$). Moreover, survival rates of patients after a palliative R1/R2 resection and patients treated with endoscopic methods were statistically also irrelevant (log-rank test – 0.65, $p > 0.58$). It was exactly one month longer than in patients treated with endoscopic palliative modalities. Stenting procedures were successful in 86.1% of unresectable patients. SEMS prostheses were generally preferred to plastic stents, however, in most advanced cases, plastic stents were considered sufficient. Complications were not numerous and hospital stay mortality concerned 5.6% of patients. Others estimate the success rate at 55% to 90% of the adequate endoscopic drainage for hilar tumors, also indicating a higher risk of cholangitis in such patients [27–29]. Surprisingly, and contrary to studies demonstrating the clear advantage of gemcitabine/cisplatin-based chemotherapy, we found no significant differences in the survival of patients who were treated this way (log-rank – 0.87, $p > 0.28$) [24–26]. The results quoted above correspond to some other reports [7, 11, 18, 19, 30].

The positive effects of surgical treatment are obscured by the vast majority of patients presented with advanced locoregional disease. This is clearly demonstrated by the poor overall survival of the whole population that is accounted in months, despite the efforts and significant achievements in the treatment of non surgical patients [1, 4, 7, 8, 15, 22, 23]. The analysis showed that 231 patients were in the T3-stage of the tumor, denoting unilateral or contralateral portal vein involvement and homolateral or contralateral hepatic atrophy, that corresponded to clinical stage T4NxM0, according to UICC/AJCC classification [7, 16, 24–26]. The main goals for the palliation of patients with advanced hilar cholangiocarcinoma are decompression of the biliary system and control of tumor growth by chemo- radiotherapy [5, 11, 27, 28]. However, adjuvant treatment (radiotherapy, chemotherapy or a combination of both procedures) for locally advanced tumors, and especially for tumors with distant metastases, seems not to influence the oncological outcome in terms of disease-free survival and overall survival [7, 14, 22, 24]. Our modest results achieved in patients with palliative methods seem to confirm this experience. This is one of the most challenging malignancies of the liver and the biliary system. The overall survival of patients suffering from hilar chiolangiocarcinoma is poor, in spite of progress in modern diagnostics and methods of treatment [7, 8, 15, 16, 18, 22]. The biological behavior of the tumor and its strategic location are the principal reasons for this state of affairs.

In Polish literature, there are no analyses of multicentre clinical studies concerning the diagnosis and treatment of the Klatskin tumor. Reports on the outcomes after radical and palliative surgical treatment are particularly lacking. Peripheral hepatico-jejunostomy is proposed by some authors as an alternative palliative surgical method of treatment in advanced cases [31, 32]. Most seem to rely on the implantation of plastic and metal stents, which in practice, was primarily used for palliation of the patients discussed in our study [33, 34]. Overall, the treatment results are poor; 5-year survival is defined as about 1% in all treated for CCA patients and up to 20%, if it is possible to treat patients by radical surgery [31–33]. The effectiveness of chemotherapy in the treatment of hilar carcinoma is low, however, it is proposed as an adjuvant or palliative in selected patients. Constant control observations, biochemical and imaging tests are recommended, depending on the clinical course [35, 36].

Polish experiences differ somewhat from the trends presented in many contemporary reports. Tumor resection is still the only potentially curative option for Klatskin tumor patients, although only a small percentage of patients are eligible for surgery. The side of the liver resection does not impact the perioperative and long term outcomes in patients undergoing curative-intent resection. A surgical strategy should be planned based on the possibility of achieving R0 resection with the confirmed negative margin of tissue by histopathologic test. The 5-year overall survival rates after radical tumor resection varied from 20% to even 40% [37, 38]. Radical operative treatment is proposed even for locally advanced tumor stages. The criteria for resectability include absence of liver metastases, absence of carcinomatosis, and absence of vascular invasion. Local tumor advancement plays a minor role in these considerations [39]. A critical assessment of the patient's preoperative imaging is necessary to determine tumor resectability. The advantage of T-stage over Bismuth-Corlette tumor classification for such purposes is stressed in many studies [40, 41]. The percentage recurrence is high. The problem is that we still lack accurate noninvasive biomarkers for the diagnosis and to estimate the prognosis while evaluating patients populations. So, definitive resection, combined with adjuvant therapy to reduce the risk of recurrence should be the standard approach for selected patients. Chemotherapy medications that are used are fluorouracil, gemcitabine, and cisplatin [39–42]. If surgery is not possible, in unresectable Klatskin tumors, the patients should be treated by radiotherapy and/or chemotherapy. Low-dose chemotherapy can make the tissue more sensitive to radiation, however, radiation therapy can be used with or without low-dose chemotherapy. Gemcitabine combined with cisplatin therapy has been recognized recently as a standard treatment for unresectable Klatskin tumors [39, 40]. In Germany, radiation

therapy for Klatskin tumor is used after partial tumor resection. It is also used as the main treatment method for advanced stages of cancer [43]. Decompression of the biliary tract plays an important role in the treatment process. Stents should be placed by percutaneous transhepatic USG or CT guided procedures instead of standard ERCP procedure to avoid possible intrahepatic infection. However, chemotherapy is not recommended as the neoadjuvant treatment since it can delay more effective therapy possibly even by months [39, 40, 42].

The results presented in the paper correspond, to a large extent, to results presented in recent professional literature. This is because the approach to the treatment has corresponded with changing and constantly modernizing treatment methods in the leading world HPB Centers. The large sample size and long study period are certainly strengths of this study, but the analysis may exhibit some bias characteristic for studies carried out over a long time period on a large sample of patients with a very specific type of disease. Thus, localization and the extent of the malignancy could be sources of bias, especially in patients with diseases in their advanced stage, since they were diagnosed and categorized mostly by evaluation and interpretation of radiologic images. The stage of classification was just presumed in some patients with advanced tumors, and this can be biased, since it was based on the results of cytology and radiologic images. Moreover, the causal-effect relationship between procedures and a patient's long-term outcome may have given rise to a small amount of bias in the interpretation of the results. However, as regarding treatment modalities, all procedures were performed by the same highly experienced specialists, according to the same operative procedures. Subsequently, any variations in performance of the procedure caused by the individual nature of a particular specialist, were too small to generate significant differences. Therefore, we believe that the study results can be generalized due to the considerable large number of patients included in the study, followed up on for a relatively long time, but with proper caution exercised due to its limitations and bias.

Conclusions

Surgery, if radical tumor resection is possible, offers some chance for long-term survival. The effects of surgical treatment are of little consequence in the face of poor treatment outcomes of palliative patients, however. Unfortunately, the majority of hilar tumors are diagnosed in their advanced loco-regional stages. This state of affairs results from the biologic behavior of the tumor and its location.

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Conflict of interest: none declared

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The scope of complementary and alternative medicine in Poland

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Introduction. Complementary and alternative medicine (CAM) is widely used by patients. The most frequent CAM users are patients with cancer, but patients with other chronic diseases also utilize these methods.
Materials and methods. Data on the use of CAM were obtained from Google searches. For each specific search term, the first three Google pages were analyzed.
Results. The analysis included 91 CAM institutions matching the inclusion criteria. The most common anticancer services were intravenous vitamin C infusion, saltwater, intravenous infusion of glutathione, colon irrigation, an anticancer diet, bio-resonance, and intravenous ozone infusions. The most common non-cancer entities treated were rheumatic diseases, chronic fatigue syndrome, arterial hypertension, allergies, borreliosis, diabetes, atherosclerosis, and depression. Anticancer therapies were more expensive than those used for non-malignant diseases (medians 250 PLN and 170 PLN, respectively; $p = 0.041$).
Conclusions. This study provides a comprehensive overview of CAM methods used in Poland. These data may facilitate social education and the development of preventive measures.

Key words: complementary medicine, alternative medicine, cancer, chronic diseases

Introduction

Complementary and alternative medicine (CAM) includes complementary medicine, which claims to reinforce standard medical treatments, and alternative medicine, which refers to methods intended to replace standard medical treatments. CAM methods are widely used all over the world [1]. The most frequent CAM users are cancer patients, but patients with other chronic diseases (e.g., type 2 diabetes, arterial hypertension, depression, obesity, chronic pain, and allergies) also practice these methods [2–6]. Despite its potential harmful effects and the lack of evidence-based benefits, the usage of CAM has significantly increased in recent years [7]. In Western countries, up to 40–90% of cancer patients admit to using CAM methods, and consistent growth has also been observed among patients with other chronic diseases [8]. Recent reports show that more than 70% of United States inhabitants have used CAM at least once in their lives [9]. In 2007, the total annual expenditure on CAM services in the United States was 34 billion USD – a 25% increase compared to 1997 [10]. In 2016, the reported yearly out-of-pocket spending on CAM services in the United States reached 58.5 billion USD [11, 12].

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Meta-analyses and systematic reviews assessing the efficacy of CAM provide conflicting results [13]. Due to their low-quality methodology, most CAM studies do not allow for meaningful conclusions [14]. CAM phase III clinical trials are less likely than non-CAM clinical trials to report disease-related outcomes, be supported by pre-trial results, and meet their endpoints [15]. Notably, the anticancer treatment mechanisms of CAM methods are often attributed to a single, specific pathophysiological effect rather than multiple regulatory pathways or influences on different effectors. CAM compounds may also have several active components whose effects may be cell-determined or epigenetically determined. Consequently, CAM methods are largely scientifically unproven. Even though some preclinical studies and preliminary clinical studies have postulated anticancer effects, the clinical relevance of these findings is highly questionable [16].

Data on types of CAM methods and their applications are scarce. The purpose of this study was to assess the scope of CAM practices offered to patients in Poland, with a particular focus on anticancer therapies.

Material and methods

In August 2020, we performed an Internet search using the Google Search web facility. The first three pages of search results were analyzed for each of the following search terms: "cancer treatment", "alternative medicine", "complementary medicine", "intravenous vitamin infusions in cancer treatment", "vitamin C in cancer treatment", "bioresonance therapy in cancer treatment", "whole-body hyperthermia in cancer treatment", "hyperthermia in cancer treatment", "saltwater in cancer treatment" and "colon irrigation in cancer treatment." Method specific search queries were selected based on their frequent use in CAM institutions found by general search terms. We only included articles that provided an institution with contact information given on its website, a list of methods used, and indications for their use.

All institutions were categorized as follows, according to the CAM methods used:

- anticancer therapies,
- supportive cancer therapies,
- anticancer and supportive cancer therapies,
- therapies for non-malignant diseases.

This subdivision into categories was performed independently by three individuals (AP, PS, and MW), and the final group assignment was based on their collective opinion. Additionally, all services were divided into those using drug substances (any substances that were ingested or injected into the body) or those using other methods. The following data were abstracted from website pages and included in the Excel database: name of the institution, city, type of institution, voivodeship, city population, contact information, website page, diseases treated, methods used, methods used for the treatment of cancer and other diseases, number of physicians employed and their medical specializations, type of service, service fees, and reference to E-published literature. Institutions without information about fees of CAM services available on the website (n = 30) were contacted by phone. For institutions that provided ranges of fees for consultations and procedures, the mean values were calculated. Institutions that set their consultation and procedure fees individually were not included in the analysis. A non-parametric (Mann-Whitney U) test for independent variables was used to compare treatment and consultation fees.

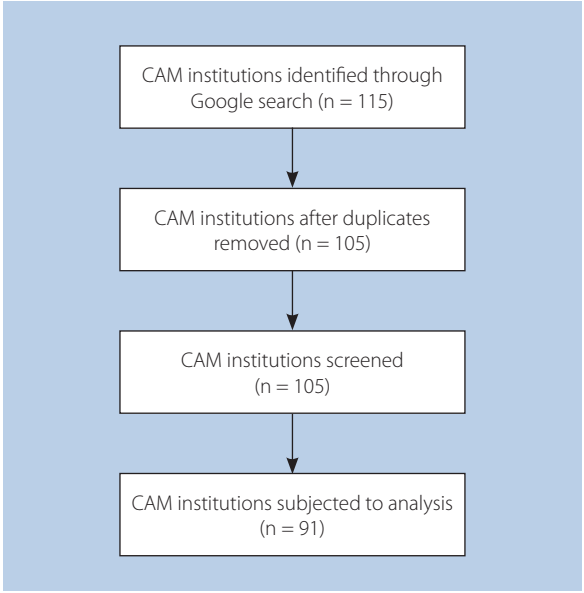

Figure 1. Flow chart of the inclusion of CAM institutions

Table I. Clinical entities treated in all CAM institutions (n = 91)

Disease	n	%
cancer	52	57%
anticancer therapy	37	41%
supportive cancer therapy	42	46%
rheumatic diseases	53	58%
chronic fatigue syndrome	51	56%
arterial hypertension	45	50%
allergies	45	49%
borreliosis	44	48%
atherosclerosis	43	47%
diabetes	43	47%
depression	42	46%
chronic infections	42	46%
migraine	40	44%
pain from various origins	39	43%
obesity	39	43%
hepatic diseases	37	41%
atopic dermatitis, psoriasis	36	40%

Table I. cont. Clinical entities treated in all CAM institutions (n = 91)

Disease	n	%
asthma	35	39%
addictions	33	36%
immunity deficiency	31	34%
acne	31	34%
ulcerative colitis, Crohn disease	31	34%
candidiasis	30	33%
heavy metals or mushroom intoxication	30	33%
neurological disorders	29	32%
oxidative stress	29	32%
parasitic diseases	26	29%
hangover	25	28%
coronary artery disease	23	25%
multiple sclerosis	22	24%
autoimmune diseases	22	24%
bedsores, burns, ulcers	22	24%
ischemic stroke	21	23%
impotence	20	22%
cardiovascular diseases	19	21%
irritable bowel syndrome	19	21%
heart diseases	18	20%
gastric and duodenal ulcers	18	20%
Alzheimer's disease	16	18%
myocardial infarction	16	18%
pneumonia, bronchitis	15	17%
thyroid diseases	14	15%
chronic inflammation of the urethra and prostate	14	15%
intermittent claudication	13	14%
gout	13	14%
Parkinson's disease	13	14%
osteoporosis	12	13%
Hashimoto's disease	12	13%
sciatica	12	13%
chronic gastritis	11	12%
eye diseases	11	12%
pancreatic function disorders	11	12%
fibromyalgia	10	11%
thromboembolism	10	11%
autism	9	10%
endocrine disorders	9	10%
kidney diseases	9	10%
digestive system diseases	9	10%
herpes	8	8.8%
anemia	8	8.8%

Disease	n	%
tinnitus	8	8.8%
varicose veins	8	8.8%
food intolerances	7	7.7%
cataract	7	7.7%
viral hepatitis	7	7.7%
paralysis	6	6.6%
heart arrhythmia	6	6.6%
hemorrhoids	6	6.6%
colon dysfunction	6	6.6%
respiratory system diseases	6	6.6%
other	5	5.5%
deafness, hearing loss	5	5.5%
infertility	5	5.5%
inflammation of women reproductive organs	5	5.5%
chickenpox	4	4.4%
sterility	4	4.4%
human immunodeficiency virus infection/ acquired immune deficiency HIV/AIDS	4	4.4%
cerebral palsy	4	4.4%
chronic diseases	4	4.4%
neuropathies	3	3.3%
bedwetting	3	3.3%
bile ducts and gall bladder inflammation	3	3.3%
posture defects	2	2.2%
heart defects	2	2.2%
endometriosis	2	2.2%
cellulite, stretch marks, scars	2	2.2%
neuritis	2	2.2%
schizophrenia	2	2.2%
viral diseases	2	2.2%
sepsis	2	2.2%
chronic obstructive pulmonary disease	2	2.2%
attention deficit hyperactivity disorder	2	2.2%
acute and chronic inflammation of reproductive organs	2	2.2%
all diseases (bioresonance therapy)	2	2.2%
stupor	1	1.1%
anorexia	1	1.1%
bulimia	1	1.1%
blindness	1	1.1%
infectious myocarditis	1	1.1%
tooth decay	1	1.1%
hair loss	1	1.1%
seasickness	1	1.1%

Table I. cont. Clinical entities treated in all CAM institutions (n = 91)

Disease	n	%
tetanus	1	1.1%
retinopathy	1	1.1%
acidosis	1	1.1%
post-infection paralysis	1	1.1%
absorption disorders	1	1.1%
Huntington's disease	1	1.1%

Disease	n	%
age-related macular degeneration	1	1.1%
hypercholesterolemia	1	1.1%
polycystic ovary syndrome	1	1.1%
Down's syndrome	1	1.1%
shingles	1	1.1%
fungal sepsis	1	1.1%

Results

The screening identified a total of 115 institutions providing CAM services, 91 of which met the study's inclusion criteria and were further analyzed (fig. 1). 91% of CAM institutions were located in cities inhabited by over 100,000 people. Of the 109 entities treated, the most common were rheumatic diseases (58%), cancer (57%), chronic fatigue syndrome (56%), arterial hypertension (50%), allergies (49%), borreliosis (48%), type 2 diabetes (47%), atherosclerosis (47%), depression (46%), and chronic infections (46%) – table I. There were 61 and 73 institutions offering drug- and non-drug-based methods, respectively. A total of 70 methods were offered (18 drug-

Table II. Practices used across all CAM institutions (n = 91)

Method	n	%
vitamin C intravenous infusion	47	52%
bioresonance	44	48%
vitamin intravenous infusion (other than vitamin C)	42	46%
ozone therapy – autotransfusion	32	35%
intravenous infusion of alpha-lipoic acid	24	26%
diet	19	21%
colon irrigation	19	21%
herbal medicine	13	14%
intravenous infusion of glutathione	13	14%
acupuncture	10	11%
massage	10	11%
ear candling	10	11%
chelation	9	10%
hyperthermia	7	7.7%
oxygen therapy	6	6.6%
medicinal leeches	6	6.6%
homeopathy	5	5.5%
iridology	5	5.5%
reflexology	5	5.5%
laser therapy	5	5.5%
energy medicine, chakra therapy	5	5.5%
quantum therapy	4	4.4%
ion detox – feet soaking in saltwater	4	4.4%
electrotherapy	4	4.4%
bubbles	3	3.3%
magnetotherapy	3	3.3%
hyperbaric chamber	3	3.3%
plasmotherapy – Rife's generator	3	3.3%
hypnosis	2	2.2%
psychotherapy	2	2.2%
reiki	2	2.2%

Method	n	%
moxibustion	2	2.2%
electromagnetic waves	2	2.2%
naturopathy	2	2.2%
matrix regenerating therapy	2	2.2%
coenzyme Q10 intravenous infusion	2	2.2%
essential oils	1	1.1%
physical therapy	1	1.1%
ganotherapy	1	1.1%
cryotherapy	1	1.1%
aromatherapy	1	1.1%
clairvoyance	1	1.1%
su jok	1	1.1%
collagen water	1	1.1%
choline intravenous infusion	1	1.1%
curcumin	1	1.1%
immunotherapy (*thymostimulinum*)	1	1.1%
dimethyl sulfoxide	1	1.1%
peptide therapy	1	1.1%
artesunate	1	1.1%
oligonucleotide therapy	1	1.1%
dowsing	1	1.1%
acupressure	1	1.1%
taping	1	1.1%
bipolar bioresonance therapy	1	1.1%
revolutionary scanning regulatory thermography	1	1.1%
viofor magnetic field therapy	1	1.1%
kangen water	1	1.1%
aloes and propolis	1	1.1%
mistletoe	1	1.1%
vibroacoustic therapy	1	1.1%
hippotherapy (horse therapy)	1	1.1%

Table II. cont. Practices used across all CAM institutions (n = 91)

Method	n	%
Zenni's electrostimulation	1	1.1%
geopathic test	1	1.1%
Bach's therapy	1	1.1%
Schumann's platform	1	1.1%
bioelectronics – beta examination	1	1.1%
fotostimulation	1	1.1%
biofeedback	1	1.1%
gemmotherapy	1	1.1%

and 52 non-drug-based), the most common of which were intravenous vitamin C infusion (IVCI; 11.5%) and bioresonance (10.7%) – table II; supplementary tables I–XI. The mean number of methods used per individual CAM institution was 4.6 (range: 1–15), and the mean number of diseases or groups of diseases treated per individual CAM institution was 18.5 (range: 1–51). 41% of institutions offered anticancer treatment; 46% offered supportive cancer treatment; 32% offered anticancer and cancer-supportive treatment; and 42% offered non-cancer treatment. Drug-based and non-drug-based methods to treat cancer were used by 73% and 78% (p = 0.52) of institutions, respectively. Anticancer therapy was used by 72% of institutions offering drug-based methods and 64% of institutions offering non-drug-based methods (p = 0.33). Oxidative stress and hangover after alcohol use were more frequently treated with drug-based methods than with non-drug-based methods (46% *vs.* 26%; p = 0.02 and 41% *vs.* 15%; p < 0.01, respectively), whereas the opposite was true for addiction (23% *vs.* 43%; p = 0.02), sciatica (3.3% *vs.* 16%; p = 0.01), allergies (38% *vs.* 59%; p = 0.01), and parasitic diseases (18% *vs.* 36%; p = 0.02) – supplementary table XII. The number of anticancer or supportive cancer therapies provided by particular institutions varied between 1 and 13, with 48% of institutions providing only 1 method (tab. III). The most common anticancer therapy was IVCI (19%), followed by intravenous infusion of glutathione and intravenous infusions of ozone (6.0% each), colon irrigation and an anticancer diet (5.3% each), and bioresonance therapy (4.6%) – table IV. Only 35% of institutions reported the names (93 total) and specialties (36 total) of their employed physicians. There were no significant differences between cancer- and non-cancer-treating institutions regarding the employment of physicians (37% *vs.* 25%, p = 0.27) or the frequency of drug-

Table III. Number of cancer services offered by CAM institutions

Number of cancer services	Number of institutions	All institutions (n = 91)	Institutions providing cancer services (n = 52)
1	25	28%	48%
2	6	6.6%	12%
3	6	6.6%	12%
4	1	1.1%	1.9%
5	6	6.6%	12%
6	3	3.3%	5.8%
7	3	3.3%	5.8%
9	1	1.1%	1.9%
13	1	1.1%	1.9%

Table IV. Services offered by CAM institutions for cancer patients

Service	n = 52	%	Median fee per procedure (PLN)*
vitamin C intravenous infusion	28	19%	225
ozone therapy – autohemotransfusion	9	6.0%	173
infusion intravenous glutathione	9	6.0%	190
colon irrigation	8	5.3%	180
diet	8	5.3%	–
bioresonance	7	4.6%	243
ozone salt intravenous infusion	7	4.6%	175
whole-body hyperthermia	6	4.0%	1450
alpha-lipoic acid intravenous infusion	6	4.0%	188
local hyperthermia	5	3.3%	550
superficial ozone therapy	5	3.3%	150
hyperbaric chamber	3	2.0%	170
vitamin B complex intravenous infusion	3	2.0%	235
bioenergotherapy	3	2.0%	–
aromatherapy	2	1.3%	–

Table IV. cont. Services offered by CAM institutions for cancer patients

Service	n = 52	%	Median fee per procedure (PLN)*
cryotherapy	2	1.3%	–
folic acid intravenous infusion	2	1.3%	–
ozone inhalation	2	1.3%	–
vitamin B_{17} intravenous infusion	2	1.3%	–
oxygen therapy	2	1.3%	430
ozone therapy – nonspecific	2	1.3%	–
microbeam radiation therapy	2	1.3%	–
coenzyme Q10 intravenous infusion	2	1.3%	75
gonotherapy	1	0.7%	–
reiki	1	0.7%	–
reflexology	1	0.7%	–
vitamin intravenous infusions	1	0.7%	–
magnesium intravenous infusion	1	0.7%	–
choline	1	0.7%	–
cobalamin intravenous infusion	1	0.7%	–
vitamin A intravenous infusion	1	0.7%	–
vitamin D intravenous infusion	1	0.7%	–
curcumin	1	0.7%	–
chelation	1	0.7%	160
peptide therapy	1	0.7%	475
artesunate	1	0.7%	–
oligonucleotide therapy	1	0.7%	–
intravenous infusion of unknown composition	1	0.7%	–
feet reflexology	1	0.7%	100
head and neck reflexology	1	0.7%	100
kangen water	1	0.7%	–
mistletoe therapy	1	0.7%	–
herbal medicine	1	0.7%	–
vibroacoustic therapy	1	0.7%	–
plasmotherapy (Rifle's generator)	1	0.7%	–
larvae therapy	1	0.7%	350
rectal ozone therapy	1	0.7%	–
bioelectronics	1	0.7%	–
Zapper's biofeedback	1	0.7%	305

*1PLN ≈ 0.22 EUR

Table V. Medical specialties of physicians working in CAM institutions

Medical specialty (n = 84)	n	%
general surgery	10	12%
internal medicine	10	12%
family medicine	6	7%
cardiology	5	6%
radiology	4	5%
oncological surgery	3	4%
gynecology	3	4%
plastic surgery	3	4%
dermatology	3	4%
orthopaedics	3	4%
neurology	3	4%
ophthalmology	2	2%
pediatrics	2	2%
oncology	2	2%
esthetic medicine	2	2%
homeopathy	2	2%
emergency medicine	2	2%
urology	2	2%
vascular surgery	1	1%
palliative medicine	1	1%
nuclear medicine	1	1%
infectious diseases	1	1%
osteopathy	1	1%
phlebology	1	1%
anesthesiology and intensive care	1	1%
hyperbaric medicine	1	1%
rheumatology	1	1%
andrology	1	1%
proctology	1	1%
Chinese medicine	1	1%
oncological radiotherapy	1	1%
environmental engineering	1	1%
geriatrics	1	1%
psychiatry	1	1%
endocrinology	1	1%

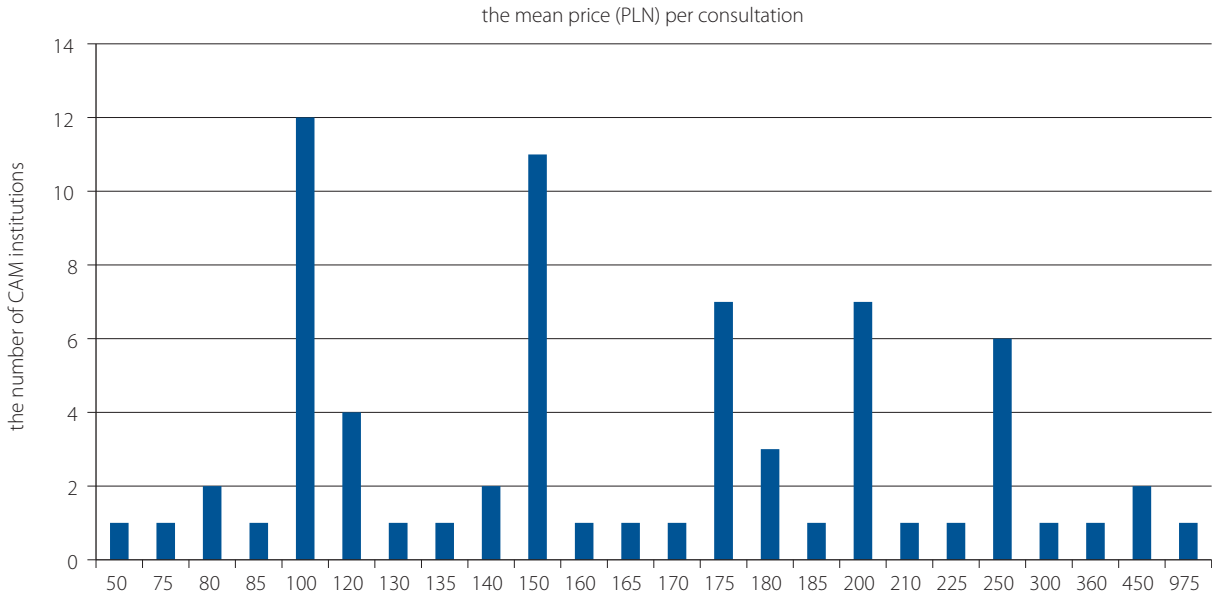

Figure 2. The mean price (PLN) per consultation in CAM institutions (n = 70)

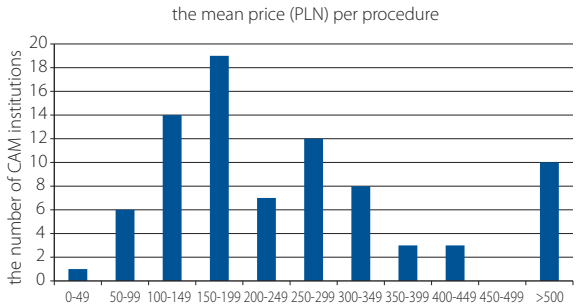

Figure 3. The mean price (PLN) per procedure in CAM institutions (n = 83)

-based and non-drug-based therapies (38% *vs.* 32%, p = 0.45). The most common physician specialties were general surgery, internal medicine, family medicine, cardiology, and radiology (tab. V). The fees for consultations and procedures were provided by 77% and 90% of institutions, respectively. The mean prices for consultations and procedures were 179.43 PLN (standard deviation 122 PLN) and 313 PLN (standard deviation 312 PLN), respectively (fig. 2 and 3). The median fees for cancer and non-cancer consultations were 150 PLN each (ranges: 50–975 PLN and 75–450 PLN, respectively; p = 0.95), whereas the median fee for anticancer therapies was higher than that for non-anticancer therapies (medians: 250 PLN and 170 PLN, respectively, p = 0.041; ranges: 90–1235 PLN and 45–1625 PLN, respectively). Only 15% of CAM institutions provided references to published articles when recommending particular services.

Discussion

To the best of our knowledge, this is the first study to investigate the scope of CAM in Poland. Our analysis demonstrated a wide variety of methods for treating cancer and other chronic diseases. Both the number of methods (18 drug-based and 52 non-drug-based) and the number of treated entities (109) identified in our study are impressive. The vast majority of CAM institutions in Poland are located in large cities, making them easily accessible. Since there is no public funding for CAM services in Poland, all institutions subjected to this analysis were private.

The legal status of CAM in Poland is unregulated, and data on its prevalence are scarce. In the Public Opinion Research Center survey in 2011, 24% of people admitted that they or a close family member had used the CAM Public Opinion Research Center 2011 [17].

The popularity of CAM among cancer patients in Poland may have several reasons. One of them is the poor general assessment of public cancer care. A study conducted in 2011 on a representative sample of 1000 Poles revealed that only 18% of responders believed that the available cancer treatment in Poland was of a standard comparable to that of other EU countries [18]. The use of CAM may also result from anxiety and a lack of emotional and psychological support during treatment. Patients often feel alone in coping with the psychological impact of a cancer diagnosis. As opposed to conventional treatment, they view CAM as an effective, safe, and holistic approach. Furthermore, many patients view conventional medicine as an aggressive and isolated treatment (cancer disease similarly to depression in Poland is often stigmatized. In result patients end up alone with the disease) and are afraid of its toxicity [19]. Hence, despite a lack of evidence, alternative methods are frequently used in line to supplement standard treatment to increase overall efficacy and alleviate side effects. Interestingly, until recently, there was a relatively high level of CAM acceptance among Polish physicians. In a survey undertaken in 2008, 42% of physicians working in oncology departments had recommended at least one CAM method to their patients [20]. However, a more recent study

showed a higher level of skepticism about the value of CAM, particularly among junior physicians [21].

The primary target of CAM is malignant diseases. A global survey of 61 studies indicated that the prevalence of CAM usage among cancer patients in the second decade of the 21st century varied from 16.5% to 93% (mean 51%) [22]. Cancer patients demonstrate an increased desire to use CAM, primarily due to their motivation to alleviate treatment--related side effects, boost immunity, and cure the disease [14, 22, 23]. In our study, 41% of CAM institutions offered anticancer treatment, 46% provided supportive cancer treatment, and 32% offered both anticancer and supportive cancer treatment. The high proportion of institutions providing cancer services in this study may bedue to Internet search criteria focused on cancer treatment. In contrast, other CAM--managed diseases were identified unintentionally and may be underreported.

The most common CAM service across all diseases (offered by more than half of institutions) was IVCI. This method was popular among cancer patients. A recent Polish study indicated that the most frequent indications for IVCI therapy were its perceived effectiveness in acting as a potent anticancer agent, enhancing the chemosensitivity of cancer cells, and reducing the intensity of chemotherapy-related toxicities [24]. The widespread use of this method may also be attributed to its ease of access, efficient marketing, as well as common belief that vitamins are generally safe and non-toxic. Other relatively common methods used by cancer patients were saltwater, intravenous infusions of glutathione, colon irrigation, diet, and bioresonance. The most frequent methods used for non-cancer chronic diseases, depending on the diagnosis, included saltwater, bioresonance, IVCI, intravenous infusions of alpha-lipoic acid, intravenous infusion of vitamins other than vitamin C, and colon irrigation.

Several demographic predictors associated with CAM usage were previously identified, (e.g., young age/female sex, higher education, higher income, and history of CAM use). However, since the incidences of cancer and other chronic diseases increase with age, older populations are also frequent CAM users [22, 23].

To the best of our knowledge, our study is the first to analyze the costs of CAM services in Poland. The money spent on CAM services often deplete patients' finances; this is especially true for the elderly. The median costs per consultation and procedure were 150 PLN (33 EUR) and 175–245 PLN (39–54 EUR), respectively, which constitute 7.7% and 16% of the national average and retirement pension in Poland, respectively [25, 26]. Notably, most CAM treatments involve repeat visits, which significantly increases the cost of the service. In 2007, the costs of nutrition-based CAM for the top five causes of cancer-related death in the US per month ranged from 4.33 USD to 263 USD (median 27 USD) [27]. CAM-related expenses for cancer patients vary significantly across the world (e.g., Europe, US, Australia, New Zealand, Turkey), from 4 EUR up to 123 EUR per month [28].

In our study, only 35% of institutions reported the names and specialties of employed doctors. This may be due to the lack of relevant scientific evidence proving the beneficial effects of their practices or fear of possible legal consequences of CAM practices. The most common medical specialties of CAM practitioners were general surgery and internal medicine. Only 15% of CAM institutions supported their services with specific references to published articles on their websites, and these articles were often of low quality or reported only preclinical data.

Our study aimed to assess the general scope of the CAM phenomenon in Poland, including the methods and diseases managed by CAM, physicians' involvement in these practices, and the related costs. We recognize that this study has several limitations. Firstly, our analysis was based on an Internet search, which is not fully representative, as some CAM providers may not advertise their services. Secondly, we used a few specific search queries which could misrepresent the prevalence of certain methods. Thirdly, our study provides only a snapshot of the CAM market in Poland. This may likely be a subject with considerable fluctuation (e.g., related to the current COVID-19 pandemic). Due to its design, our study did not address factors associated with patients' willingness to use CAM in Poland and did not attempt to perform a profound and quantitative analysis of the topic or its social, demographic, or psychological background. We also did not measure patients' preferences or their level of satisfaction related to CAM usage. Finally, we did not address the clinical value of particular CAM methods, as this was beyond the scope of our investigation.

Conclusions

Our study confirms the popularity of CAM in Poland and demonstrates the astonishing number of treated entities and the various CAM practices available to Polish patients. For the first time, we have also provided the cost of these services. These data may prompt future analyses of the medical and economic aspects of this phenomenon. Patients often conceal CAM use from their physicians. Health care professionals should discuss possible CAM use with every patient. It should be an open and nonjudgmental conversation so as to gain trust and encourage patients to share their experiences on CAM use. Patients should be counseled and redirected to evidence-based treatment options and life-style changes which are effective and will not interfere with conventional medicine. Oncologists, but also other medical specialists, should be aware of these recommendations, especially since the widespread use of CAM is prevalent among patients suffering from other chronic diseases.

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Supplementary table I. Practices used in the treatment of rheumatic diseases

Method	n	%
ozone therapy	21	21%
bioresonance	20	20%
vitamin C intravenous infusion	15	15%
systemic hyperthermia	6	6.1%
colon irrigation	5	5.1%
alpha-lipoic acid intravenous infusion	4	4.1%
hyperbaric chamber	3	3.1%
acupuncture	3	3.1%
vitamin intravenous infusion (other than vitamin C)	2	2.0%
intravenous infusion of glutathione	2	2.0%
medical leeches	2	2.0%
electromagnetic waves	2	2.0%
energy therapy	1	1.0%
diet	1	1.0%
reflexology	1	1.0%
chelation	1	1.0%
vibroacoustic therapy	1	1.0%
matrix regenerating therapy	1	1.0%
physiotherapy	1	1.0%
moxibustion	1	1.0%
massage	1	1.0%
viofor magnetic field therapy	1	1.0%
naturopathy	1	1.0%
ion detox – feet soaking in saltwater	1	1.0%
biofeedback	1	1.0%

Supplementary table II. Methods used in the treatment of chronic fatigue syndrome

Method	n	%
ozone therapy	14	23%
bioresonance	9	15%
vitamin intravenous infusion (other than vitamin C)	8	13%
intravenous infusion of glutathione	6	10%
colon irrigation	6	10%
alpha-lipoic acid intravenous infusion	3	5.0%
moxibustion	3	5.0%
systemic hyperthermia	2	3.3%
electromagnetic waves	2	3.3%
vitamin C intravenous infusion	1	1.7%
diet	1	1.7%
oxygen therapy	1	1.7%
herbal medicine	1	1.7%
biofeedback	1	1.7%
naturopathy	1	1.7%
ion detox – feet soaking in saltwater	1	1.7%

Supplementary table III. Methods used in the treatment of diabetes

Method	n	%
ozone therapy	21	24%
alpha-lipoic acid intravenous infusion	17	20%
vitamin C intravenous infusion	11	13%
bioresonance	11	13%
intravenous infusion of coenzyme Q10	5	5.8%
hyperbaric chamber	3	3.5%
chelation	3	3.5%
systemic hyperthermia	2	2.3%
vitamin intravenous infusion (other than vitamin C)	2	2.3%
oxygen therapy	2	2.3%
intravenous infusion of glutathione	1	1.2%
vibroacoustic therapy	1	1.2%
medical leeches	1	1.2%
physiotherapy	1	1.2%
fotostimulation	1	1.2%
massage	1	1.2%
viofor magnetic field therapy	1	1.2%
naturotherapy	1	1.2%
electromagnetic waves	1	1.2%

Supplementary table IV. Methods used in the treatment of allergies

Method	n	%
bioresonance	24	38%
ozone therapy	12	19%
vitamin C intravenous infusion	6	9.5%
colon irrigation	6	9.5%
vitamin intravenous infusion (other than vitamin C)	2	3.2%
matrix regenerating therapy	2	3.2%
systemic hyperthermia	1	1.6%
reflexology	1	1.6%
chelation	1	1.6%
oxygen therapy	1	1.6%
kangen water	1	1.6%
herbal medicine	1	1.6%
medical leeches	1	1.6%
biofeedback	1	1.6%
naturopathy	1	1.6%
ion detox – feet soaking in saltwater	1	1.6%
electromagnetic waves	1	1.6%

Supplementary table V. Methods used in the treatment of borreliosis

Method	n	%
bioresonance	25	29%
ozone therapy	21	25%
vitamin C intravenous infusion	11	13%
systemic hyperthermia	4	4.7%
vitamin intravenous infusion (other than vitamin C)	4	4.7%
herbal medicine	4	4.7%
diet	3	3.5%
hyperbaric chamber	3	3.5%
alpha-lipoic acid intravenous infusion	2	2.4%
intravenous infusion of glutathione	1	1.2%
homeopathy	1	1.2%
physiotherapy	1	1.2%
fotostimulation	1	1.2%
massage	1	1.2%
viofor magnetic field therapy	1	1.2%
naturopathy	1	1.2%
electromagnetic waves	1	1.2%

Supplementary table VI. Methods used in the treatment of arterial hypertension

Method	n	%
vitamin C intravenous infusion	13	19%
ozone therapy	10	15%
colon irrigation	6	8.8%
bioresonance	4	5.9%
alpha-lipoic acid intravenous infusion	4	5.9%
systemic hyperthermia	3	4.4%
vitamin intravenous infusion (other than vitamin C)	3	4.4%
hyperbaric chamber	3	4.4%
medical leeches	3	4.4%
intravenous infusion of coenzyme Q10	3	4.4%
acupuncture	3	4.4%
chelation	2	2.9%
reflexology	1	1.5%
herbal medicine	1	1.5%
vibroacoustic therapy	1	1.5%
biofeedback	1	1.5%
hypnosis	1	1.5%
physiotherapy	1	1.5%
fotostimulation	1	1.5%
massage	1	1.5%
viofor magnetic field therapy	1	1.5%
naturopathy	1	1.5%
electromagnetic waves	1	1.5%

Supplementary table VII. Methods used in the treatment of depression

Method	n	%
bioresonance	16	23%
vitamin C intravenous infusion	10	15%
vitamin intravenous infusions (other than vitamin C)	7	10%
colon irrigation	7	10%
hyperbaric chamber	4	5.8%
diet	2	2.9%
ozone therapy	2	2.9%
alpha-lipoic acid intravenous infusion	2	2.9%
matrix regenerating therapy	2	2.9%
homeopathy	2	2.9%
electromagnetic waves	2	2.9%
systemic hyperthermia	1	1.4%
energy medicine	1	1.4%
reflexology	1	1.4%
intravenous infusion of glutathione	1	1.4%
chelation	1	1.4%
oxygen therapy	1	1.4%
medical leeches	1	1.4%
acupuncture	1	1.4%
hypnosis	1	1.4%
physiotherapy	1	1.4%
moxibustion	1	1.4%
massage	1	1.4%
naturopathy	1	1.4%

Supplementary table VIII. Methods used in the treatment of chronic infections

Method	n	%
vitamin C intravenous infusion	16	21%
bioresonance	16	21%
ozone therapy	15	19%
colon irrigation	7	9.0%
alpha-lipoic acid intravenous infusion	5	6.4%
intravenous infusion of glutathione	4	5.1%
vitamin intravenous infusion (other than vitamin C)	3	3.8%
oxygen therapy	2	2.6%
systemic hyperthermia	1	1.3%
diet	1	1.3%
reflexology	1	1.3%
herbal medicine	1	1.3%
matrix regenerating therapy	1	1.3%
intravenous infusion of coenzyme Q10	1	1.3%
acupuncture	1	1.3%
naturopathy	1	1.3%
ion detox – feet soaking in saltwater	1	1.3%
electromagnetic waves	1	1.3%

Supplementary table IX. Methods used in the treatment of atherosclerosis

Method	n	%
ozone therapy	17	22%
vitamin C	13	17%
alpha-lipoic acid intravenous infusion	11	14%
chelation	8	10%
bioresonance	6	7.8%
hyperbaric chamber	3	3.9%
intravenous infusion of glutathione	3	3.9%
colon irrigation	3	3.9%
intravenous infusion of coenzyme Q10	3	3.9%
medical leeches	2	2.6%
electromagnetic waves	2	2.6%
vitamin intravenous infusions (other than vitamin C)	2	2.6%
systemic hyperthermia	1	1.3%
oxygen therapy	1	1.3%
dimethyl sulfoxide	1	1.3%
naturopathy	1	1.3%

Supplementary table X. Diseases treated by intravenous vitamin C infusion

Diseases	n	%
anticancer therapy	28	11%
chronic infections	24	9.5%
supportive cancer therapy	18	7.1%
oxidative stress	18	7.1%
arterial hypertension	15	5.9%
heart diseases	14	5.5%
rheumatic diseases	13	5.1%
chronic fatigue syndrome	10	4.0%
diabetes	9	3.6%
immunity deficiency	9	3.6%
allergies	7	2.8%
borreliosis	6	2.4%
depression	6	2.4%
candidiasis	6	2.4%
atherosclerosis	5	2.0%
parasitic diseases	5	2.0%
viral hepatitis	5	2.0%
cardiovascular diseases	5	2.0%
pain from various origins	4	1.6%
cataract	4	1.6%
heavy metals or mushroom intoxication	4	1.6%
myocardial infarction	4	1.6%
heart arrhythmia	4	1.6%
chronic diseases	4	1.6%
asthma	3	1.2%
atopic dermatitis, psoriasis	3	1.2%
hepatic diseases	2	0.8%
multiple sclerosis	2	0.8%
autoimmune diseases	2	0.8%
viral diseases	2	0.8%
Alzheimer's disease	2	0.8%
intermittent claudication	1	0.4%
migraine	1	0.4%
osteoporosis	1	0.4%
neuropathies	1	0.4%
sciatica	1	0.4%
impotence	1	0.4%
ulcerative colitis, Crohn disease	1	0.4%
thyroid diseases	1	0.4%
Parkinson's disease	1	0.4%
absorption disorders	1	0.4%

Supplementary table XI. Diseases treated by bioresonance

Diseases	n	%
allergies	25	6.9%
borreliosis	22	6.0%
addiction treatment	22	6.0%
pain from various origins	21	5.8%
chronic infections	21	5.8%
candidiasis	20	5.5%
parasitic diseases	15	4.1%
rheumatic diseases	13	3.6%
depression	12	3.3%
obesity	12	3.3%
migraine	11	3.0%
heavy metals or mushroom intoxication	11	3.0%
chronic fatigue syndrome	9	2.5%
diabetes	8	2.2%
asthma	7	1.9%
immunity deficiency	7	1.9%
ulcerative colitis, Crohn disease	7	1.9%
atopic dermatitis, psoriasis	7	1.9%
autoimmune diseases	6	1.6%
neurological disorders	6	1.6%
arterial hypertension	5	1.4%
hormonal diseases	5	1.4%
hepatic diseases	4	1.1%
sciatica	4	1.1%
multiple sclerosis	4	1.1%
gastric and duodenal ulcers	4	1.1%
anticancer therapy	4	1.1%
chronic diseases	4	1.1%
atherosclerosis	3	0.8%

Supplementary table XI. cont. Diseases treated by bioresonance Services offered by CAM institutions for cancer patients

Diseases	n	%
osteoporosis	3	0.8%
ischemic stroke	3	0.8%
chronic inflammation of the urethra and prostate	3	0.8%
thyroid diseases	3	0.8%
cardiovascular diseases	3	0.8%
other (everything)	3	0.8%
supportive cancer therapy	3	0.8%
intermittent claudication	2	0.5%
acne	2	0.5%
irritable bowel syndrome	2	0.5%
infertility	2	0.5%
heart diseases	2	0.5%
eye diseases	2	0.5%
pancreatic function disorders	2	0.5%
bedsores, burns, ulcers	2	0.5%
viral hepatitis	2	0.5%
digestive system diseases	2	0.5%
viral diseases	2	0.5%
chronic obstructive pulmonary disease	2	0.5%

Diseases	n	%
attention deficit hyperactivity disorder	2	0.5%
coronary artery disease	1	0.3%
neuropathies	1	0.3%
chronic gastritis	1	0.3%
herpetic lesions	1	0.3%
anemia	1	0.3%
pneumonia, bronchitis	1	0.3%
autism	1	0.3%
chickenpox, shingles	1	0.3%
myocardial infarction	1	0.3%
thromboembolism	1	0.3%
kidney diseases	1	0.3%
Parkinson's disease	1	0.3%
absorption disorders	1	0.3%
inflammation of the reproductive organs	1	0.3%
hemorrhoids	1	0.3%
infertility	1	0.3%
respiratory system diseases	1	0.3%
bile ducts and gall bladder inflammation	1	0.3%

Supplementary table XII. Frequency of drug-based and non-drug based methods in the treatment of non-cancer diseases

		Drug-based (n = 61)		Non-drug based (n = 73)		z-test	
	n	n	%	n	%	statistic	p
rheumatic diseases	53	37	61%	47	64%	0.444	0.6599
chronic fatigue syndrome	51	39	64%	42	58%	0.755	0.4533
arterial hypertension	45	33	54%	38	52%	0.236	0.8103
allergies	45	23	38%	43	59%	2.444	0.0147
borreliosis	44	28	46%	43	59%	1.502	0.1336
diabetes	43	35	57%	35	48%	1.089	0.2757
atherosclerosis	43	35	57%	37	51%	0.774	0.4413
depression	42	29	48%	37	51%	0.363	0.7188
chronic infections	42	27	44%	36	49%	0.584	0.5619
migraine	40	25	41%	37	51%	1.122	0.2627
obesity	39	24	39%	34	47%	0.841	0.4009
pain from various origins	39	23	38%	37	51%	1.505	0.1336
hepatic diseases	37	28	46%	30	41%	0.559	0.5755
atopic dermatitis, psoriasis	36	25	41%	33	45%	0.491	0.6214
asthma	35	24	39%	30	41%	0.206	0.8337
addiction	33	14	23%	31	43%	2.382	0.0173
acne	31	25	41%	26	36%	0.637	0.5222
immunity deficiency	31	17	28%	28	38%	1.28	0.2005
ulcerative colitis, Crohn disease	31	22	36%	28	38%	0.273	0.7872
candidiasis	30	15	25%	29	40%	1.858	0.0629
heavy metals or mushroom intoxication	30	21	34%	25	34%	0.022	0.984

Supplementary table XII. cont. Frequency of drug-based and non-drug based methods in the treatment of non-cancer diseases

		Drug-based (n = 61)		Non-drug based (n = 73)		z-test	
	n	n	%	n	%	statistic	p
oxidative stress	29	28	46%	19	26%	2.401	0.0164
neurological disorders	29	18	30%	29	40%	1.234	0.2187
parasitic diseases	26	11	18%	26	36%	2.267	0.0232
hangover	25	25	41%	11	15%	3.37	0.0008
coronary artery disease	23	19	31%	19	26%	0.655	0.5157
multiple sclerosis	22	18	30%	20	27%	0.27	0.7872
autoimmune diseases	22	17	28%	19	26%	0.24	0.8103
bedsores, burns, ulcers	22	15	25%	20	27%	0.368	0.7114
ischemic stroke	21	18	30%	19	26%	0.449	0.6527
impotence	20	16	26%	16	22%	0.583	0.5619
irritable bowel syndrome	19	8	13%	17	23%	1.505	0.131
cardiovascular diseases	19	13	21%	17	23%	0.273	0.7872
heart diseases	18	15	25%	14	19%	0.758	0.4473
gastric and duodenal ulcers	18	10	16%	17	23%	0.991	0.3222
Alzheimer's disease	16	15	25%	13	18%	0.962	0.3371
myocardial infarction	16	15	25%	12	16%	1.172	0.242
pneumonia, bronchitis	15	10	16%	15	21%	0.615	0.5419
chronic inflammation of the urethra and prostate	14	8	13%	14	19%	0.944	0.3472
thyroid diseases	14	9	15%	12	16%	0.267	0.7872
intermittent claudication	13	8	13%	10	14%	0.099	0.9203
gout	13	11	18%	13	18%	0.034	0.9761
Parkinson's disease	13	12	20%	12	16%	0.486	0.6241
osteoporosis	12	12	20%	9	12%	1.165	0.246
Hashimoto's disease	12	10	16%	11	15%	0.21	0.8337
sciatica	12	2	3.3%	12	16%	2.48	0.0131
chronic gastritis	11	6	9.8%	11	15%	0.906	0.3628
eye diseases	11	4	6.6%	11	15%	1.556	0.1188
pancreatic function disorders	11	8	13%	10	14%	0.099	0.9203
fibromyalgia	10	9	15%	9	12%	0.41	0.6818
thromboembolism	10	7	12%	9	12%	0.152	0.8808
autism	9	7	12%	8	11%	0.094	0.9283
endocrine disorders	9	3	4.9%	8	11%	1.269	0.2041
kidney diseases	9	6	9.8%	8	11%	0.212	0.8337
digestive system diseases	9	5	8.2%	9	12%	0.779	0.4354
herpes	8	5	8.2%	8	11%	0.538	0.5892
anemia	8	6	9.8%	7	9.6%	1.427	0.1527
varicose veins	8	5	8.2%	8	11%	0.538	0.5892
food intolerances	7	5	8.2%	7	9.6%	0.281	0.7795
cataract	7	7	12%	6	8.2%	0.634	0.5287
tinnitus	7	7	12%	6	8.2%	0.634	0.5287
viral hepatitis	7	5	8.2%	7	9.6%	0.281	0.7795
paralysis	6	1	1.6%	6	8.2%	1.705	0.0891

Supplementary table XII. cont. Frequency of drug-based and non-drug based methods in the treatment of non-cancer diseases

		Drug-based (n = 61)		Non-drug based (n = 73)		z-test	
	n	n	%	n	%	statistic	p
heart arrhythmia	6	5	8.2%	4	5.5%	0.626	0.5287
hemorrhoids	6	3	4.9%	6	8.2%	0.76	0.4473
colon dysfunction	6	1	1.6%	6	8.2%	1.705	0.0891
respiratory system diseases	6	4	6.6%	6	8.2%	0.365	0.7188
deafness, hearing loss	5	5	8.2%	5	6.0%	0.296	0.7642
inflammation of female reproductive organs	5	3	4.90%	5	6.8%	0.47	0.6384
infertility	5	2	3.3%	5	6.8%	0.925	0.3524
sterility	4	2	3.3%	3	4.1%	0.253	0.8026
chickenpox	4	2	3.3%	4	5.5%	0.613	0.5419
human immunodeficiency virus infection/ AIDS	4	3	4.9%	3	4.1%	0.225	0.8181
cerebral palsy	4	4	6.6%	4	5.5%	0.262	0.7949
chronic diseases	4	2	3.3%	3	4.1%	0.253	0.8026
neuropathies	3	2	3.3%	3	4.1%	0.253	0.8026
bedwetting	3	0	0.0%	3	4.1%	1.601	0.1096
bile ducts and gall bladder inflammation	3	2	3.3%	3	4.1%	0.253	0.8026
posture defects	2	1	1.6%	2	2.7%	0.429	0.6672
heart defects	2	1	1.6%	2	2.7%	0.429	0.6672
endometriosis	2	1	1.6%	2	2.7%	0.429	0.6672
cellulite, stretch marks, scars	2	2	3.3%	1	1.4%	0.744	0.4593
acute and chronic inflammation of reproductive organs	2	2	3.3%	2	2.7%	0.183	0.8572
neuritis	2	2	3.3%	1	1.4%	0.744	0.4593
schizophrenia	2	2	3.3%	1	1.4%	0.744	0.4593
viral diseases	2	2	3.3%	2	2.7%	0.183	0.8572
sepsis	2	1	1.6%	2	2.7%	0.429	0.6672
all diseases (bioresonance therapy)	2	1	1.6%	2	2.7%	0.429	0.6672
chronic obstructive pulmonary disease	2	1	1.6%	2	2.7%	0.429	0.6672
attention deficit hyperactivity disorder	2	0	0.0%	2	2.7%		
stupor	1	1	1.6%	0	0.0%	1.098	0.2713
anorexia	1	0	0.0%	1	1.4%	0.744	0.4593
bulimia	1	0	0.0%	1	1.4%	0.744	0.4593
blindness	1	0	0.0%	1	1.4%	0.744	0.4593
fungal sepsis	1	1	1.6%	1	1.4%	0.128	0.8966
infectious myocarditis	1	1	1.6%	1	1.4%	0.128	0.8966
tooth decay	1	1	1.6%	1	1.4%	0.128	0.8966
hair loss	1	1	1.6%	1	1.4%	0.128	0.8966
shingles	1	1	1.6%	0	0.0%	1.098	0.2713
seasickness	1	1	1.6%	0	0.0%	1.098	0.2713
tetanus	1	1	1.6%	0	0.0%	1.098	0.2713
retinopathy	1	1	1.6%	1	1.4%	0.128	0.8966
acidosis	1	1	1.6%	1	1.4%	0.128	0.8966
post-infection paralysis	1	1	1.6%	0	0.0%	1.098	0.2713

Supplementary table XII. cont. Frequency of drug-based and non-drug based methods in the treatment of non-cancer diseases

		Drug-based (n = 61)		Non-drug based (n = 73)		z-test	
	n	n	%	n	%	statistic	p
absorption disorders	1	1	1.6%	1	1.4%	0.128	0.8966
Huntington's disease	1	1	1.6%	1	1.4%	0.128	0.8966
age-related macular degeneration	1	1	1.6%	1	1.4%	0.128	0.8966
hypercholesterolemia	1	1	1.6%	1	1.4%	0.128	0.8966
polycystic ovary syndrome	1	1	1.6%	1	1.4%	0.128	0.8966
Down's syndrome	1	0	0.0%	1	1.4%	0.744	0.4593

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Review article

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The risk of reconstruction failure following a mastectomy, breast reconstruction and radiotherapy depending on the reconstruction technique

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Improvements in the recently observed breast reconstruction surgery techniques have changed the clinical practice in patients with breast cancer. Nowadays, every patient diagnosed with breast cancer clinical stage I, II and III, except for inflammatory breast cancer, should have the opportunity to undergo breast reconstruction. Radiation therapy increases the risk of complications following reconstruction. The aim of this paper is to review the current literature in an attempt to select the safest and most convenient reconstruction technique in patients requiring radiation therapy. Immediate autologous breast reconstruction seems to be the best option, but everyday clinical practice seems to contradict the conclusions from these data. The choice of the reconstruction type depends not only on the rate of complications but on the surgeon's skills, the patient's preference and the hospital's equipment.

Key words: breast cancer, breast reconstruction, implant reconstruction, pre-pectoral reconstruction, subcutaneous implant reconstruction

Introduction

Some years ago, candidates for immediate reconstruction following a subcutaneous mastectomy were patients with breast cancer in its early stages, in cases where it was probable that adjuvant radiotherapy would not be necessary. This applied to situations when breast conserving therapy was not possible (numerous suspicious micro-calcifications, multifocal cancer, extensive pre-invasive cancer). Patients with more advanced stages of the disease underwent delayed reconstructions, usually at least 1 year after the completion of radiation [1]. Recent years have brought significant changes in the approach to post-mastectomy breast reconstruction.

Firstly, according to the guidelines proposed by academic societies and expert panels of leading conferences, every woman after a mastectomy, should be given the possibility of undergoing breast reconstruction, whilst immediate reconstruction, made at the same time as oncological intervention, can be performed in patients with breast cancer at clinical stage I, II and III, except for the cases of inflammatory breast cancer [2–4]. This means that the majority of patients after mastectomy and immediate reconstruction may require further adjuvant irradiation.

Secondly, together with significant progress in reconstruction surgeries consisting of the introduction of synthetic meshes and acellular skin matrices of animal origin, a significant increase in the rate of immediate reconstructions can be currently observed – especially with regards to those implanted subcutaneously (prepectoral breast reconstruction),

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while there is a decrease in the number of reconstructions with the use of the patient's native tissues [5–12]. Nowadays, in some European centres (Switzerland, Germany), the rate of prepectoral breast reconstructions varies between 65% and 80% and more (Sweden, Austria) [5]. This new approach toward patients who require radiotherapy and also short follow-up periods after reconstruction, following new techniques with irradiation, presents a large challenge for radiotherapists and encourages doctors to systematize knowledge in this field and to work out an optimum strategy of action.

The objective of the work is to present a literature overview concerning the types and frequency of complications after various types of breast reconstruction and radiotherapy.

Basic definitions concerning breast reconstruction

Breast reconstructions may be divided with respect to the type of material used and also with regards to the time of surgery as compared to basic oncological surgery (Fig. 1 and 2). With regards to the material used, the reconstructions can be divided into autologous types, made from the patient's own tissues and alloplastic (implant–based) – made from synthetic materials. Autologous reconstructions employ musculocutaneous pedicled or free flaps, which require microvascular anastomoses. The most frequently used flaps comprise DIEP (deep inferior epigastric artery perforator free flap), TRAM (transverse rectus abdominis musculocutaneous pedicled flap), LD (latissimus dorsi musculocutaneous pedicled flap) and SGAP (gluteal musculocutaneous free flap) [13–18]. Autologous reconstructions comprise also autologous fat grafting.

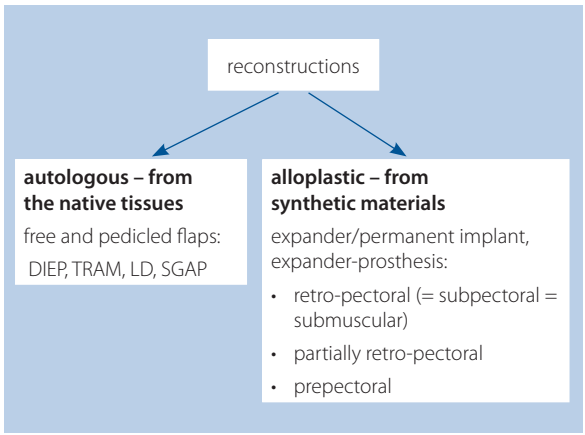

Figure 1. Types of breast reconstructions depending on the type of material used

Alloplastic reconstructions consist of the implantation of a prosthesis (implant). This can be a permanent implant (permanent prosthesis), an expander or an expander-prosthesis. An expander is used for expanding tissues before the final implanting of a breast prosthesis, so it requires exchange into a permanent implant after a previous filling the bed and expanding the skin and major pectoral muscle. A permanent implant may be located underneath both the pectoral and serratus anterior muscles (subpectoral, postpectoral and submuscular reconstruction), underneath the pectoral and on the surface of the serratus anterior muscle (partly postpectoral and submuscular reconstruction) or underneath the skin, onto the surface of the pectoral muscle (prepectoral reconstruction). In the majority of cases of partly subpectoral reconstruction and in all cases of prepectoral reconstruction, the implant is covered with a synthetic mesh (SM) or with an acellular dermal matrix (ADM) of animal origin.

As for as the time interval between oncological surgery (various types of mastectomies) and breast reconstruction, the intervention types can be divided into immediate and delayed. Immediate reconstruction is performed at the same time as oncological intervention. If the permanent implant is placed at once (prosthesis, expander-prosthesis), such a reconstruction is called an immediate one-stage breast reconstruction. If an expander is placed in the first stage following the mastectomy, and then, once the expander extends after a few weeks, it is exchanged into a permanent prosthesis or an autologous reconstruction is performed, such a procedure is named a delayed immediate breast reconstruction or immediate two-stage breast reconstruction.

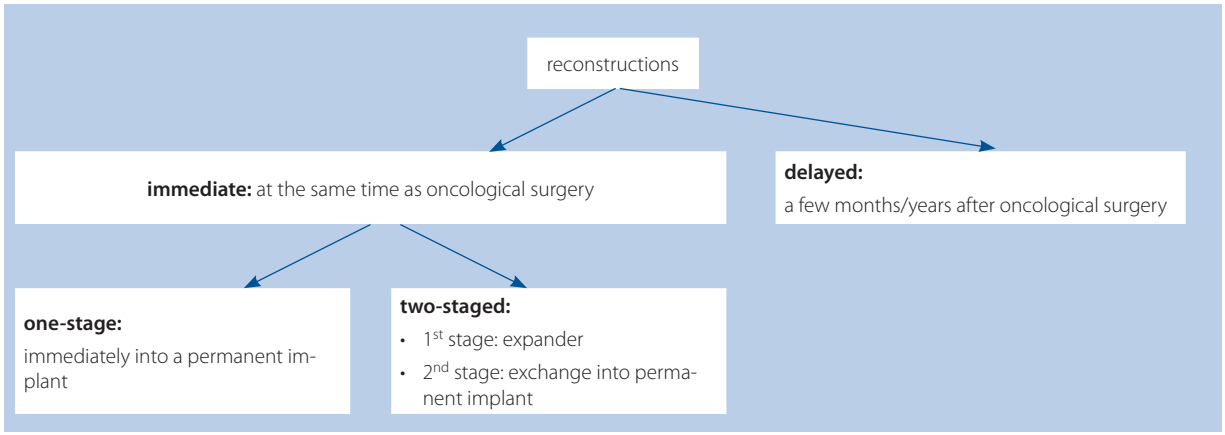

Figure 2. Types of breast reconstructions with regards to the time interval between the oncological surgery and the reconstruction

Delayed breast reconstruction is performed a few months or even years after the initial oncological surgery. The optimum time interval between the end of radiotherapy and the date of delayed reconstruction is not known [19], yet it seems that it should be at least 12 months after radiation therapy [1].

The type and rate of complications following reconstruction and radiotherapy

Breast reconstruction with or without radiotherapy, may be followed by complications such as hematoma, seroma, infection, rippling, fat necrosis, skin necrosis, expander displacement, expander exposure or rupture, fibrosis around the prosthesis or the expander, implant loss, fibrosis or loss of the musculocutaneous flap. In the literature on the subject, presentation of the risk of complications following breast reconstruction with/without radiotherapy is divided into general risk of complications and the risk of serious complications. The overall complications comprise at least one complication [20]. A serious complication is defined as a complication which requires hospitalisation and/or surgery. The most serious complication i.e. reconstruction failure, is implant loss or necrosis and the loss of the musculocutaneous flap [20].

Radiotherapy increases the risk of complications [1, 13, 14, 20–33]. The subject literature reports that the reconstruction failure rate after radiotherapy is 6–62.6% [30]. The first study concerned radiotherapy following immediate reconstruction with an implant, with a 10-year follow-up period. It reported the risk of complications in general to be 52.5% after radiotherapy and 10% without radiotherapy, whilst capsule fibrosis was observed in 32.5% after irradiation *vs.* 0% without irradiation [34]. The analyses published in the following years confirm that radiotherapy increased the risk of complications to 55% [17–25] and the risk of implant loss to 4.8%–37% [20, 22–24, 35–38].

Below, we present the types of complications following specific types of reconstruction with radiotherapy, together with the degree of risk.

Alloplastic (implant-based) breast reconstruction with radiation therapy

The meta-analysis presented by Pu et al. [39] which examined 15 studies contained a calculation of the complication rate following immediate one stage reconstruction with an implant, with and without radiotherapy (4245 and 1069 patients respectively). It was shown that radiotherapy increased the risk of complications in general more than threefold (odds ratio [OR] = 3.45), the risk of implant loss – more than twofold (OR = 2.6) and the risk of capsule fibrosis around the implant more than fivefold (OR = 5.3). Moreover, radiotherapy decreased patient satisfaction with the procedure by a factor of four in comparison with patients who were not irradiated (OR = 0.28) [39]. The meta-analysis presented by Hong et al. [40] referred to a group of 6757 patients, and 13 out of the 19 presented studies concerned an immediate, two-stage reconstruction (expander –> radiotherapy –> exchange into a permanent implant). The meta-analysis showed that radiotherapy increased the risk of complications in general more than twofold (OR = 2.52), the implant loss – more than twofold (OR = 2.57), whilst the risk of capsule fibrosis around the implant – was almost sixfold (OR = 5.99), which was connected with a decrease in patient satisfaction (OR = 0.29) and a poorer aesthetic effect (OR = 0.25) [40]. The meta-analysis presented by Ricci et al. [23] compared the complications following immediate reconstruction with radiotherapy with an expander and immediate reconstruction with radiotherapy with a permanent implant. The analysis of the histories of 2348 patients from 20 studies showed a high complication risk in both groups. In the group of patients after reconstruction and radiotherapy with an expander, more cases of implant loss were observed (20% after radiotherapy with expander *vs.* 13.4% after radiotherapy with a permanent implant; relative risk [RR] = 2.33), whilst in the group after reconstruction and radiotherapy with a permanent implant, more cases of the fibrosis of the capsule around the implant were seen (49.4% after radiotherapy with a permanent implant *vs.* 24% after radiotherapy with expander) [23].

Comparison of alloplastic prepectoral breast reconstructions with alloplastic subpectoral breast reconstructions with and without radiotherapy

According to some publications, in patients without radiotherapy, immediate prepectoral reconstruction is comparable to subpectoral with regards to the rate of complications in general, the implant loss, the necrosis of the nipple/skin, poor wound healing and infections [6, 41]. In the meta-analysis of Li et al. [41], the risk of implant loss after prepectoral and subpectoral reconstructions without radiotherapy was 4.2% and 4.5% respectively. In the meta-analysis of Abbate et al. [42], about 80% of 4040 patients were not irradiated. It was found that there were statistically significant differences concerning the rate of skin necrosis (3.3% *vs.* 5.9%, $p < 0.01$) and fibrosis of the skin around the implant (4.2% *vs.* 7.6%, $p < 0.01$) which worked to the advantage of prepectoral reconstruction. Apart from this, the rate of complications in the group of prepectoral and subpectoral surgeries was comparable. It must be observed that the complication rate following reconstructions in both groups without radiotherapy was lower than 10%.

Radiotherapy increased the complication rate, whilst the risk varied depending on the type of reconstruction [11, 43–45]. In a prospective study evaluating the risk of complications in patients after prepectoral reconstruction, with and without radiotherapy, it was found that the patient group after radiotherapy had a seven-fold higher risk of complication in general (OR = 7.11) and five-fold higher risk of implant loss (OR = 5.09) in comparison with patients who were not irradiated [45]. The work of Sinnot et al. [10] contained an analysis of the complication rate following prepectoral and subpec-

toral reconstructions with and without radiotherapy. A higher complication rate was found in the group after radiotherapy. In a group of 274 patients after prepectoral reconstruction and radiotherapy, in 16% of the cases fibroses around the implant were observed, whilst in the group of 100 patents after a subpectoral reconstruction and radiotherapy, this rate was 52% [10]. In the study of Thuman et al. [11], the risk of implant loss following prepectoral reconstruction and radiotherapy was 4.5%, whereas following a subpectoral reconstruction and radiotherapy, it was 14.9%.

The results illustrate that in patients after an immediate alloplastic reconstruction with radiotherapy, irrespective of the reconstruction type (prepectoral *vs.* subpectoral), the risk of complications is high, yet it seems that prepectoral reconstruction is safer [8, 10, 11]. In order to confirm the higher level of safety in prepectoral reconstruction with radiotherapy over subpectoral reconstruction with radiotherapy, it is necessary to have a longer follow-up period in patients after prepectoral reconstructions; in the majority of publications the median follow-up period is about 2 years.

Comparison of alloplastic breast reconstructions and radiotherapy with autologous breast reconstructions and radiotherapy

Breast reconstruction with prostheses followed by radiotherapy give more complications than autologous reconstruction with radiotherapy [1, 13, 44–56]. The meta-analysis conducted by Barry [47] compared various types of breast reconstruction (immediate and delayed, with implants and autologous) with and without radiotherapy on the basis of 11 studies and 1105 patients. In patients after immediate reconstruction with a prosthesis/expander without radiotherapy, the rate of complications in general was 21% and in patients after radiotherapy – 52%. In irradiated patients, immediate autologous reconstruction was five times safer than alloplastic reconstruction (OR = 0.21). Immediate autologous reconstruction with radiotherapy and delayed autologous reconstruction following radiotherapy were comparable with respect to complications (OR = 0.87) [47].

The objective of the meta-analysis made by O'Donell et al. [48], made on the basis of 16 studies and 2322 reconstructions, was to see what the optimum type of breast reconstruction was for women who had to be irradiated, especially, with respect to the most serious complications. Six groups of patients were analysed: those after immediate autologous breast reconstruction with radiotherapy, those after delayed immediate breast reconstruction with radiation therapy to an expander, those after delayed immediate breast reconstruction with radiation therapy to the permanent implant, those after delayed immediate reconstruction with radiation therapy to an expander and final autologous breast reconstruction and also those after 2 types of delayed reconstructions following radiotherapy: delayed autologous and delayed alloplastic breast reconstruction. The best procedure, which prevented or at least decreased the risk of reconstruction failure in irradiated patients, was an immediate autologous reconstruction. This method was better than all the reconstructions with implants. Among alloplastic reconstructions in turn, the most beneficial was the procedure of radiotherapy applied onto the permanent implant: in these cases the rate of complications in general was three times lower (OR = 0.35), yet also there were twice as many fibroses around the implant (OR = 2.58). The worst results were observed in patients who had radiotherapy during the primary oncological treatment and then underwent delayed reconstruction with an implant. The conclusions of the paper contain a note in which the authors observed that immediate reconstruction with the patient's native tissues, in patients who are scheduled for irradiation afterwards, was the best choice from the point of view of complications, however, the choice of the reconstruction method depends on the patient herself, the surgeon and the technical possibilities of the institution. If a patient who requires radiotherapy does not consent to reconstruction with her native tissues, and opts solely for a reconstruction with an implant, she should be proposed an immediate and non-delayed reconstruction [48].

The study of Jagsi et al. [53] compared the rate of complications after 2 years of follow-up in 2247 patients after an immediate reconstruction with an implant with and without radiotherapy and after an immediate autologous reconstruction with and without radiotherapy. The study showed that at least 1 complication, serious complication and the loss of the expander was significantly higher in patients undergoing radiotherapy in comparison to those not irradiated, irrespective of the reconstruction technique. At the same time, it was shown that in the group of irradiated patients, the rate of failures was significantly higher after implant-based reconstruction than in the group with an autologous reconstruction. The risk of implant loss in patients after implant-based reconstruction was 18.7% and after autologous reconstruction – 1% [53]. Similarly, in other articles, a high rate of implant loss was shown (18.7–37%) following immediate implant-based reconstructions and radiotherapy as well as a low rate of the loss of musculocutaneous flap (0–4.4%) after immediate autologous reconstructions and radiotherapy [51, 52, 54–56].

A study performed by Chetta et al. [52], analysed 4781 irradiated patients, and the rate of reconstructions with implants in comparison to the autologous reconstructions made in 2009–2012 was 80%. The risk of implant/flap loss after immediate alloplastic and immediate autologous reconstructions was 27% and 4%, respectively, and after delayed alloplastic and delayed autologous reconstructions it was 37% and 5%, respectively. The authors summed up that in patients who required irradiation, reconstruction with implants as the most popular method of breast reconstruction was burdened with the risk of serious complications [52].

Comparison of immediate autologous reconstructions followed by radiotherapy and delayed autologous reconstructions (after radiotherapy)

The research shows that there are no significant differences in the rate of complications in patients after autologous reconstructions (either immediate or delayed) [1, 57, 58]. The meta-analysis made by Hershenhouse et al. [57], based on 44 studies, analysed the history of 1927 patients after immediate autologous reconstructions with radiotherapy and 1546 after delayed autologous reconstructions with radiotherapy. The rate of early complications was assessed, comprising fat necrosis, thrombosis, seroma, hematoma, infections, dehiscence of the wound edges, loss of the flap; and delayed complications: fibrosis, significant asymmetry, hyperpigmentation, volume decrease of the musculocutaneous flap. A comparable rate of complications was observed with the exception of the risk of seroma which was more frequent in the case of delayed reconstructions (2.6% after immediate reconstruction and 10.5% after delayed reconstruction, $p = 0.04$). Both methods were regarded as comparable with regards to the risk of complications and the risk of flap loss in both groups was lower than 2%.

The meta-analysis of Heiman et al. [58] also compared the rate of complications after the reconstructions with native tissues: immediate with radiotherapy (729 patients) and delayed with radiotherapy (868 patients). It was shown that the risk of complete flap loss (2.4% *vs.* 0.9%, $p = 0.004$) or partial flap loss (4.6% *vs.* 1.9%, $p = 0.01$) was slightly higher after a delayed autologous reconstruction whilst the risk of infections – after immediate autologous reconstructions. The risk of other complications was comparable. The authors did conclude though that an immediate autologous reconstruction is more beneficial for tissue survival than delayed autologous reconstruction. That is why it should be proposed to patients who require radiotherapy [58].

An evaluation of patient satisfaction following various types of reconstruction

The BREAST-Q and BODY-Q questionnaires allow for an evaluation of patient satisfaction after breast reconstruction procedures as well as satisfaction with their psychosocial and sexual life, an evaluation of the physical appearance of the breasts and of the donor site of the musculocutaneous flap as well as satisfaction in general. In 6 papers, [53, 55, 59–62] the patient satisfaction was studied with regards to the quality of life and aesthetic effects following various types of breast reconstruction. In all the studies, better results were observed in patient opinion after autologous breast reconstructions.

The best type of breast reconstruction with regards to the risk of complications in irradiated patients – analyses results

The analyses presented above point to the fact that from the point of view of the risk of complications, the most beneficial reconstruction for a patient requiring radiotherapy is immediate autologous breast reconstruction, whilst a delayed autologous breast reconstruction (i.e. performed a few months / years following primary oncological treatment with radiotherapy) ranks second. A significantly larger number of complications occur after immediate alloplastic reconstructions with radiotherapy onto the permanent implant, whilst immediate alloplastic reconstruction with radiotherapy onto the expander seems even less beneficial (it gives fewer fibrosis but a higher risk of implant loss than radiotherapy into the permanent implant). Prepectoral reconstructions with radiotherapy give slightly fewer complications than subpectoral reconstructions with radiotherapy. The highest risk of complications is observed after delayed reconstructions with implants and therefore this method is not recommended in breast cancer patients after pervious radiotherapy.

Tables I and II present the risk of reconstruction failure (RF), defined as the loss of the implant or the musculocutaneous flap, depending on the type of breast reconstruction in patients undergoing radiotherapy. The RF rate following immediate autologous reconstruction and radiotherapy varies 0–4.4%, and following delayed autologous reconstruction (after previous irradiation) – 1.8–7%; following immediate implant-based reconstruction and radiotherapy – 4.5–37%; and following a delayed implant-based reconstruction (after previous irradiation) – 37–56%.

Why does clinical practice differ from the results of the studies? The advantages and disadvantages of autologous and alloplastic reconstructions

In 2021 a panel of Italian experts published current data concerning breast reconstruction and radiotherapy (Italian Expert Delphi Consensus Statement) [19]. It confirmed that in patients requiring radiotherapy, the lowest complication rate and the best cosmetic effect is observed following an immediate autologous reconstruction. Contrary to these findings, implant based reconstruction (one-stage or two-staged) is the most frequently method used in this patient group [19].

Why do oncological centres in the majority of cases perform an implant reconstruction if radiotherapy is planned in spite of scientific evidence pointing to a lower risk of complications following autologous reconstructions? This is especially the case since autologous reconstructions keep evolving significantly, and together with progress in microsurgery, this allows for a further decrease in the complication rate in the donor site and reconstruction area [15]. It seems that as much as the rate of complications influences the type of reconstruction planning, the final decision depends also on other factors, such as the preferences of the surgeon concerning the treatment technique, the patient's preferences with respect to the method and her approval of a higher risk for a selected method, the possibilities of complex plastic surgeries in

Table I. The risk of reconstruction failure in irradiated patients depending on the type of reconstruction

Individual original papers and metanalyses	The number of irradiated patients	Type of reconstruction with irradiation, treatment sequence	The rate of implant / flap loss
Tanos G. [51]	114	immediate: • TE/I -> RT • AR -> RT	 37% 0
Chetta M.D. [52]	4781	immediate: • TE/I -> RT • AR -> RT delayed: • RT -> TE/I • RT -> AR	 27% 4% 37% 5%
Jagsi R. [53]	2247 (482 RT)	immediate: • TE/I -> RT • AR -> RT	 18.7% 1%
Manyam B.V. [54]	204	immediate: • AR -> RT • TE/I -> RT delayed: • RT -> AR • RT -> TE/I	 4.4% 22% 7% 56%
Reinders F.C.J. [55]	109	immediate: • TE/I -> RT • AR -> RT	 21.3% 0
Naoum G.E. [56]	1286 (407 RT)	immediate: • TE -> RT -> I • I -> RT	 9.1% 2.9%
Thuman J.M. [11]	 44 141	immediate: • TE/I -> RT prepectoral subpectoral	 4.5% 14.9%
metanalysis Ricci J.A. [23]	 1479 869	immediate: • TE -> RT -> I • TE -> I -> RT	 20% 13.4%
metanalysis Heiman A.J. [58]	729 868	immediate: • AR -> RT delayed: • RT -> AR	 0.9% 2.4%
metanalysis Hershenhouse K.S. [57]	1927 1546	immediate: • AR -> RT delayed: • RT -> AR	 1% 1.8%
metanalysis O'Donnell J.P.M. [48]	1914	immediate: • TE -> RT -> I • TE -> I -> RT • TE -> RT -> AR • AR -> RT delayed: • RT -> AR • RT -> TE -> I	 OR = 1 OR = 0.42 OR = 0.27 OR = 0.1 OR = 0.16 OR = 0.74

TE – expander; I – permanent implant; AR autologous reconstruction; RT – radiotherapy; OR – odds ratio; TE/I -> RT – first immediate reconstruction with expander/implant, followed by radiotherapy; AR -> RT – first immediate autologous reconstruction, followed by radiotherapy; RT -> TE/I – radiotherapy during primary oncological treatment followed by delayed reconstruction with an implant; RT -> AR – radiotherapy during primary oncological treatment followed by delayed autologous reconstruction; TE -> RT -> I – 2-stage immediate reconstruction with radiotherapy onto the expander, followed by exchange into permanent implant; TE -> RT -> AR – 2-stage immediate reconstruction with radiotherapy onto the expander, and in the second stage – autologous reconstruction; I -> RT – 1-stage immediate reconstruction with radiotherapy onto the permanent implant

Table II. The summary of the risk of reconstruction failure on the basis of publications presented in table I [11, 23, 48, 51–58]

Type of breast reconstruction with radiotherapy	The rate of implant / flap loss
immediate autologous breast reconstruction followed by radiotherapy	0–4.4%
delayed autologous breast reconstruction (following previous radiotherapy)	1.8–7%
immediate breast reconstruction with an implant, 1- or 2-stages, followed by radiotherapy onto the expander or permanent implant	4.5–37%, mainly about 20%
delayed breast reconstruction with an implant, 1- or 2-stages, (following previous radiotherapy)	37–56%

a given oncological centre (microvascular anastomoses) and other advantages and disadvantages of specific reconstruction methods. Table III presents a comparison of the benefits and drawbacks of reconstruction with the use of native tissues and implants.

An advantage of an autologous reconstruction is the natural look of the breasts, natural contours and inframammary fold, the natural position of the nipple-areolar complex, a lower rate of complications and increased patient satisfaction with the surgery followed by radiotherapy after long-term follow-up [13, 14, 53, 59, 63]. The downsides of autologous surgeries comprise:

- more extensive type of surgery,
- the level of technical difficulty,
- frequent numerous stages of surgery,
- more pain,
- requirement of a surgical team performing microvascular anastomoses,
- longer recovery period,
- possible complications of the donor site and reconstruction site,
- it is a more expensive procedure than implant reconstruction; and in the case of reconstruction failure, there is little chance of salvage surgery with the use of the patient's own tissues [15, 31, 33, 60].

As opposed to autologous reconstructions, the greatest benefits in the use of prostheses is the shorter treatment time, the immediate treatment effect as perceived by the patients, lower treatment costs and the possibility to use native tissues in the salvage surgery after the loss of the implant [13, 16, 49].

In 2019, after a meeting of the expert panel from 20 countries of the Oncoplastic Breast Consortium (OPBC) [64] the most significant issues which required an urgent solution in oncoplastic surgery with radiotherapy were published. The experts believe that currently the decision about the type of breast reconstruction depends more on the doctor than on the patient. That is why studies of the values of specific reconstruction methods with radiotherapy should be performed, taking into consideration the point of view and feelings of the patients. The results of these studies might help patients in the selection of the most beneficial procedure methods. Moreover, currently the following clinical studies with randomisation have been carried out: Primary Radiotherapy And DIEP flAp Reconstruction Trial (PRADA), DBCG RT Recon Trial, and PREPEC OPBC-02 studies, which are hoped to solve the presented problems with breast reconstruction and radiotherapy [65].

Conclusions

On the basis of the presented literature, it can be concluded that in the setting of postmastectomy radiotherapy, immediate autolgous breast reconstruction gives fewer complications and guarantees a better quality of life than immediate implant-based reconstruction (both prepectoral and subpectoral). Hence immediate autologous reconstruction really should be one of the available reconstructive options in selected oncological centres. The individual choice of the breast reconstructive method still remains a subject of debate as each of the reconstructive methods has its advantages and disadvantages.

A still very short follow-up period after breast reconstruction performed with the new techniques and a relatively high rate of complications after reconstructions with radiotherapy result in the fact that each patient opting for breast reconstruction should be advised, at the very beginning of their oncological treatment, about the advantages and disadvantages and complication rate in the case of specific reconstructive methods.

The above literature overview and conclusions refer solely to breast reconstructions in patients undergoing radiotherapy.

Table III. The comparison of immediate breast reconstructions with native tissues (autologous) and with synthetic material (implant-based, alloplastic)

	Autologous reconstructions	Alloplastic reconstructions
pros	• preservation of the natural look and contour of the breasts, natural inframammary fold and natural position of the nipple-areolar complex, • scars are less visible with the progress of time, • larger patient satisfaction in case of radiotherapy, • reduction of the excess fat tissue from abdominal integuments (TRAM) – donor site, • lower rate of complications following radiotherapy	• technically simpler procedure, • does not require the ability to make microvascular anastomoses, • shorter treatment period, • shorter recovery time, • fewer complaints, • immediate treatment effect as perceived by the patient, • lower treatment costs, • in the case of implant loss it is possible to make a salvage surgery with the use of patient's native tissues
cons	• more extensive and more difficult surgery, often performed in many stages, • requires the ability to make microvascular anastomoses, • more painful surgery, • may lead to complications in the donor and reconstruction site, • longer hospital stay and recovery, • more expensive than implant reconstruction, • in case of failure it is not possible to make a salvage surgery with native tissues	• significantly larger rate of complications following radiotherapy, • unnatural look of the breasts, • poorer aesthetic effect after radiotherapy in comparison with the autologous reconstruction followed by radiotherapy, • lower patient satisfaction with the procedure followed by radiotherapy

In breast cancer patients who do not require adjuvant irradiation, the indications for specific reconstruction techniques and complication rates differ from those presented in this paper.

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The effect of physical activity on sex hormone levels in women. Implications for breast cancer risk

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Breast cancer is the most commonly diagnosed neoplastic disease in women, which leads to a significant deterioration in the quality of life and a reduction in the ability of women to function normally in everyday life. The main risk factor for breast cancer in both premenopausal and postmenopausal women is exposure to high levels of endogenous estrogen. It takes many years for neoplasia to develop, but lowering estrogen levels has been observed to reduce the risk of both a new diagnosis and recurrence of breast cancer. Observational studies have found that exercise reduces the level of bioavailable sex hormones, and thus may reduce the risk of developing breast cancer. Currently available evidence clearly shows that adequate levels of physical activity are associated with a 25–30% reduction in the average risk of breast cancer in women and play a role in its treatment.
This review summarizes the data available in the literature on the effect of physical activity on the level of sex hormones in women, while presenting the biological mechanisms underlying the relationship between physical activity and the development of breast cancer. This issue requires further research, but already now, extensive educational campaigns are needed which can be aimed at young women to inform them on the possibility of significantly reducing their risk of breast cancer by introducing physical activity into their everyday lives.

Key words: exercise, gonadal steroid hormones, estrogen, risk factors, breast cancer

Physical activity and sex hormone levels

The results of many observational and experimental studies confirm that there is a relationship between lifestyle and the occurrence of many diseases, including cancer, and their prognosis [1, 2]. The American Cancer Society's recommendations for a healthy lifestyle include a healthy eating pattern, at least 150 to 300 minutes of moderate-intensity exercise per week, limiting sedentary behavior, maintaining a healthy body weight and avoiding drinking alcohol [3]. Among women, one of the most common cancers is breast cancer and in 2020 it accounted for 25.4% of all newly diagnosed cancers. [4, 5].

Breast cancer risk factors

There are a few modifiable factors that influence the risk of breast cancer, including: being overweight or obese [6], improper diet and alcohol consumption [7], lack of physical activity [8] and prolonged exposure to steroid hormones [9]. Non-modifiable or less modifiable risk factors include: age, reproductive factors [10], such as early age of first menstruation, late age of menopause, late age of first term pregnancy, infertility [11, 12], as well as a family history of breast cancer [13].

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The role of sex hormones in the development of breast cancer

As the risk of breast cancer in women increases with early first menstruation and late menopause, estrogen and progesterone are believed to play a major role in breast carcinogenesis [14]. Endogenous sex hormones, especially estrogens, appear to be involved in cancer initiation, promotion and progression [12, 15], therefore long-term exposure to high hormone levels is considered one of the major risk factors. The role of progesterone in the development of breast cancer is less clear-cut, but there is evidence that progesterone may augment the mitogenic effects of estradiol [16].

It is also considered that progesterone has an antiproliferative effect on breast cells in premenopausal women. The results of research on animal models indicate that progesterone contributes to the proliferation of the endothelial gland and sensitizes cellular cancer cells to growth factors [17–19]. The results of the Million Women Study survey show that women who used progesterone combined with estrogen as hormone replacement therapy had a significantly higher risk of breast cancer compared with women taking only estrogen [20]. There are also epidemiological data indicating the protective action of progesterone in the development of breast cancer [18, 20].

In addition, sex hormone binding globulin (SHBG) is also considered to play a role in breast carcinogenesis. It regulates the bioavailability of estradiol and testosterone [22], inhibits cell growth and counteracts apoptosis in breast cancer cells that have estrogen receptors (ER+) [23].

Biological mechanisms

Current evidence indicates that physical activity is associated with a 25–30% reduction of the average breast cancer risk in women [1, 24]. Underlying biologic mechanisms mediating the association between physical activity and breast cancer are not fully understood, but there are several likely biological mechanisms at play. It is assumed that physical exercise can lead to a reduction in breast cancer risk through both hormonal and non-hormonal mechanisms. Physical activity reduces the level of biologically available sex hormones, which can lead to a reduction in the risk of tumors associated with hormones, including breast cancer. Physical exercise also affects glucose metabolism, reducing the concentration of other hormones and growth factors, including insulin and insulin-like growth factor (IGF-1) [25, 26]. Inter-population variation in ovarian steroid levels and exposure to estrogens throughout life is associated with a variation of breast cancer risk. The causes of such variation are differences in physical activity and energy expenditure [27].

In the prevention of breast cancer, body weight control is particularly important. Physical activity helps to reduce the total body weight and intra-abdominal fat. In addition, it strengthens immunological functions, inhibiting tumors, increases the number of macrophages, NK cells and cytokines, and also regulates the activity of free radical inhibitors and increases the concentration of biogenic antioxidants [28].

Physical activity and the level of hormones in women before menopause

To date, several studies on breast cancer have examined healthy premenopausal women [29]. However, it is suspected that the hormonal exposition before menopause has an impact on the risk of incidence of breast cancer after menopause [30, 31], and the risk of breast cancer increases with an early first menstruation and late menopause [14]. This suggests that the exposure to high concentrations of sex hormones during this period can play an important role in the initiation and development of breast cancer.

Moderate physical activity

The physical activity in adulthood is associated with a reduced risk of breast cancer, even with a moderate level of physical activity, including occupational physical activity [32, 33]. In a study of young women with premenstrual syndrome, it was observed that the level of estradiol and progesterone decreased by 23.9% and 41.2% respectively when compared to the control group after a series of 3-month aerobic training [34]. The risk of breast cancer is also smaller in women who have practiced recreational physical activity before, as well as among women who were more active than their peers at the age of 10–12 [35].

Physical activity combined with a caloric deficit

Exercise interventions that are accompanied by the energy deficit, lead to changes in the circulation of estrogens in women before menopause [36]. Research results show that moderate aerobic physical activity in combination with calorie limitation may result in a significant reduction in exposure to estrogens and progesterone and transient increase in SHBG [37]. In one study, young women before menopause perform moderate aerobic exercises for 16 weeks after 150 minutes for week, but without changing weight. Sex hormone or SHBG levels have not changed significantly. However, the reason for the lack of the expected effect could be slight changes in body composition. Perhaps a longer exercise intervention would have had different results. It is also possible that the detection of changes would be possible when collecting samples to analyze closer to the ovulation date when the estradiol level is higher. [38].

However, there is also evidence that work-related energy expenditure does not have to lead to a negative energy balance to cause inhibiting reproductive functions in women. Even in women whose body weight does not change as a result of intensive training, there may be disorders in cycles [36, 39, 40]. In addition, in meta-analyzes of randomized control trials on the impact of physical activity on the level of sex hormones in women, it was observed that a decrease in total estradiol was associated with weight loss after intervention; a drop in free

estradiol was not associated with weight loss. This result suggests that physical activity without associated weight loss, can also lead to the suppression of estradiol levels in women [41].

It also assumes that a certain level of activity is needed to induce a protective effect in relation to breast cancer. The relationship between training load and ovarian function was observed and it suggests that the hormonal response also depends on the type and intensity of the workout. In addition, the amount of the energy deficit is linearly related to the overall frequency of the occurrence of menstruation disorders [42, 43].

The role of estrogen metabolites in carcinogenesis

Estrogen metabolites can initiate the carcinogenesis process, which is why they are considered as breast cancer risk markers. In many studies, it was found that a higher 2-OHE1 ratio to 16-OHE1 is associated with a reduced risk of breast cancer [44, 45]. In addition, women before menopause, who declared a higher level of physical activity, had a higher ratio of the estradiol metabolites 2-OHE1 and 16-OHE1 than women who declared that they exercised less [46]. However, in some studies, improving oxygen capacity (V_{O2max}) and slight changes in the composition of the body did not have a significant impact on estrogen metabolites [47, 48].

Physical activity and the level of sex hormones in women taking part in high intensity training

Physical activity can cause hypomenorrhoea and amenorrhea, which is observed in 6–79% of women-athletes [49, 50]. It can also cause anovulatory cycles and/or a reduction of sex hormone concentrations without affecting the regularity of the cycles. Nutrition disorders, irregular menstruation, and bone loss are part of the clinical condition called "triad of women--athletes"[51]. Insufficient calorie consumption in relation to energy expenditure during exercise leads to energy deficiency and stimulates compensation mechanisms, such as weight loss or energy saving, causing inhibiting reproductive functions, including a reduced level of estrogen [52]. The intensity of exercises is the decisive factor. In many studies, participants who intensively trained, suffered significant dips in estrogen and progesterone levels, sometimes leading to the lack of menstruation. [53, 54].

In 70% of officers' training participants who had regular menstruation, as a result of training menstruation became more irregular. The levels of the tested hormones, including estradiol, decreased after training, but did not differ between participants with normal menstruation and those with irregular menstruation [55].

The effect of physical activity on women at increased risk of breast cancer and breast cancer survivors

Physical activity, both before diagnosis of primary breast cancer and after diagnosis, has a beneficial effect on the survival of women [56]. There was an inverse relationship between increased levels of physical activity after diagnosis and all-cause mortality and death from breast cancer, as well as a higher risk of death among women who had decreased levels of physical activity after diagnosis. Women who increased their physical activity after diagnosis had a 45% lower risk of death compared to inactive women both before and after diagnosis [57, 58]. Observational studies have also shown that women with breast cancer who are overweight or who gain weight after diagnosis are at a higher risk of breast cancer recurrence and death compared to women who are not overweight [59].

The results of meta-analyzes of prospective cohort studies confirm that adequate physical activity may be an important intervention to reduce the number of deaths and recurrences of breast cancer in women [60, 61].

There is also growing evidence of the active role of adipose tissue in tumor initiation and growth. The local production of estrogen in the tumor is believed to stimulate the growth of hormone-dependent breast cancer. In addition, estrogen metabolism is regulated differently in the adipose tissue of women with or without cancer. In one study, the concentration of estradiol in breast adipose tissue was lower in women with cancer than in the control group, while the levels of serum hormones did not differ [62].

A 6-month lifestyle intervention was performed in overweight or obese women who were at high risk of breast cancer and included dietary modification and exercise. As a result of the intervention, a reduction in obesity was accompanied by a reduction in serum estrogen levels. However, statistically significant decreases in serum estradiol and estrone levels were not detected in the period of active adipose tissue loss, but instead 3 months after the intervention, in the period of body weight stabilization [63].

Studies have also shown that in healthy premenopausal women at high risk of breast cancer, the levels of estradiol and progesterone decrease or remain unchanged due to exercise [64].

Lifestyle and the risk of breast cancer

Habitual physical activity

Habitual physical activity includes daily physical activity, work, housework, childcare, walking and exercise, and according to research results, it is significantly related to the concentration of estradiol in saliva. In women with low habitual physical activity, mean estradiol levels are 21% higher than in the group of highly active women and almost 18% higher than in women with moderate activity [27] [65]. Also, seasonal increases in the intensity of physical work by Polish women living in the countryside may be associated with a decrease in the level of progesterone by almost 25% [39]. It has also been observed that postmenopausal women who have never used hormone replacement therapy had a reduced risk of exercise-related

breast cancer. These results suggest that daily, moderate-intensity physical activity, such as walking, may protect against breast cancer [66].

Healthy lifestyle

In a study assessing the relationship of a healthy lifestyle, which included smoking, diet, and physical activity, a significant inverse relationship was found between a healthy lifestyle, assessed using validated questionnaires, and the chance of developing breast cancer. This relationship was significant in postmenopausal women, but no relationship was found in the group of premenopausal women [67].

Metabolic profile

Low serum HDL-C cholesterol is associated with increased levels of free, biologically active estradiol throughout the menstrual cycle. Moreover, it was observed that women with high BMI (≥23.6 kg/m^2) and relatively high serum LDL/HDL-C ratio (≥2.08) were exposed to significantly higher levels of free estradiol than other women [68]. For this reason, HDL-C levels may be a biomarker of breast cancer risk, especially useful in overweight and obese women.

Tea and coffee consumption

Catechins and theaflavins are the main ingredients of tea. It inhibit aromatase, an enzyme that catalyzes the conversion of androgens to estrogens, and as a result, estradiol production may be reduced in women of childbearing age who consume large amounts of tea. According to studies, women with a higher average daily intake of black tea have lower salivary estradiol levels compared to women who drink less black tea [69]. Coffee ingredients also exhibit estrogenic activity. Many studies have noted the potential uses of coffee in the treatment and prevention of cancer. Derivatives of cinnamic acid, terpenoids, and alkaloids contained in coffee, by inducing apoptosis, have a cytotoxic effect on breast cancer cells [70, 71].

Birth weight and adult body composition

In a study of young healthy women with regular menstrual cycles, it was shown that low birth weight (<3.530 g) combined with a large adult waist circumference (>84 cm) was associated with a 33% increase in free estradiol levels throughout the menstrual cycle compared with women of higher birth weight with the same waist circumference in adulthood. These results confirm that birth weight, which is a marker of pre-fetal conditions, in combination with energy availability and metabolism during growth and development, affect estrogen levels in the premenopausal period [72].

Regular sleep

Increased exposure to light at night, for example due to night shift work or shorter sleep times, can suppress melatonin production, which in turn can increase sex hormone levels. It was shown that the average level of estradiol in women who slept regularly was 60% lower compared to women with greater variability in their sleep schedule. These results suggest that sleep variability is significantly correlated with estradiol levels, while sleep duration does not show a statistically significant relationship [73, 74]. High estradiol levels may also be associated with poorer sleep quality [75].

Sedentary lifestyle

The role of a sedentary lifestyle in estrogen metabolism has yet to be established, but existing evidence suggests that prolonged time spent sitting may lead to negative metabolic consequences, including increased central obesity and higher levels of endogenous estrogen [76, 77].

Physical activity before menarche

The date of the menarche is to some extent a modifiable feature. Studies have shown that competitive sport between the ages of 13–16 was associated with a later first menstruation compared to girls who did not exercise at that age. [78]. A meta-analysis of studies conducted on a group of athletes and people not practicing sports showed that in people practicing sports professionally in adolescence, the first menstruation occurred on average more than 1 year later compared to people not practicing sports [79].

Physical activity and hormone level in postmenopausal women

Menopause occurs, on average, around the age of 50 and is characterized by numerous hormonal changes. The postmenopausal period is associated with estrogen deficiency [80] and an increase in androgens [81]. There is also a reduction in urinary excretion of progesterone metabolites [82, 83]. These changes can lead to a rapid loss of muscle strength and bone mineral density, reduced aerobic capacity and weight gain. There is also an increased risk of developing a number of chronic diseases, including breast cancer [84].

The regulatory effect of exercise on women's hormone metabolism varies between pre- and postmenopausal women, and the mechanisms responsible for the protective effects of exercise are not yet well understood. It is believed that physical activity may lower the levels of circulating parent estrogens, estradiol and estrone [85]. In a study evaluating the relationship between physical activity and a sedentary lifestyle and postmenopausal estrogen metabolite levels, higher mean activity was significantly associated with lower urine estrogen levels and selected estrogen metabolites, while longer sitting time was significantly associated with higher estrogen levels and their metabolites [85].

Epidemiological studies compared hormone levels in women diagnosed with breast cancer to healthy controls. The results of these studies suggest that postmenopausal women with breast cancer had higher levels of estradiol and estrone than healthy postmenopausal women [86].

The role of adipose tissue in the formation of estrogens

In postmenopausal women, endogenous estrogen formation occurs mainly in adipose tissue by aromatizing the adrenal androgens to estrone – the main circulating estrogen – which is then metabolized [87]. There is convincing evidence that obesity, resulting in higher endogenous estrogen levels than in lean women, increases the risk of breast cancer in postmenopausal women [88, 89]. This mechanism is biologically insignificant in the premenopausal period, when the ovaries are the main source of estrogen, and estrogen levels are many times higher than in the postmenopausal period.

In healthy, overweight, and obese postmenopausal women, higher levels of estrogens and androgens and lower concentrations of SHBG have been observed compared with lower body weight women [90, 91]. It also seems that the relationship of body mass index (BMI) with breast cancer risk is largely limited to ER1/PR1-dependent tumors. With the increase in body weight in the postmenopausal period, a significantly increased risk of hormone-dependent ER1/PR1 breast tumors was observed [92].

Moreover, excess adipose tissue, especially abdominal fat, is positively correlated with insulin resistance. Prolonged hyperinsulinemia reduces the level of bioavailable sex-hormone-binding globulin (SHBG) and increases the levels of circulating estrogens and androgens, which may further contribute to the formation of neoplasms [90, 93].

The authors of a meta-analysis of prospective observational studies estimated that in postmenopausal women, with an increase in body mass index (BMI) by 5 kg/m^2, the risk of developing breast cancer increases by 12% [94]. Abdominal obesity as assessed as waist to hip circumference ratio (WHR) also shows a strong positive correlation with the risk of postmenopausal breast cancer [95].

In the analysis of the anthropometric measurements, including measurements of estrogen and serum estrogen metabolite levels, strong positive associations were found between the present BMI and estrogens in postmenopausal women who do not use hormone replacement therapy [96].

Women's knowledge about breast cancer prevention

The credibility of messages promoting physical activity as a factor preventing heart disease and breast cancer was tested depending on the level of physical activity reported by participants. According to the surveyed women, it is easier to prevent and control heart disease than breast cancer. Moreover, physically active women are more susceptible to messages and prophylactic actions concerning the influence of physical activity on the prevention of breast cancer, compared to women who do not exercise. For this reason, innovative ways of reaching people who are not interested in physical activity need to be found [97].

Conclusions

Although the mechanism underlying the relationship between exercise and breast cancer risk remains unclear, the majority of randomized controlled trials conducted in healthy women showed a marked decrease in estradiol and progesterone induced by exercise. To date, evidence suggests that higher levels of endogenous estrogen are associated with an increased risk of breast cancer in both premenopausal and postmenopausal women; therefore, exercise contributes to reducing the risk of breast cancer and plays a key role in breast cancer management.

In summary, exercise decreases circulating sex hormones and reduces breast tumor growth by promoting changes in apoptosis and cell proliferation, and is therefore a safe intervention with undeniable benefits for women – regardless of the status of menopause and exercise-induced weight loss.

Current recommendations for physical activity include 150 to 300 minutes of moderate-intensity physical activity per week, or 75 to 150 minutes of high-intensity physical activity and some muscle-strengthening activity for at least 2 days a week [3]. Based on the available literature, a comprehensive and multidisciplinary approach is recommended that should include physical activity, weight control, a high fruit and vegetable intake, and a reduced dietary fat intake.

The process of carcinogenesis and the subsequent development of human neoplasia takes many years, so educational campaigns are needed to inform young women about the risk of breast cancer and how they can reduce it in the future. Prevention programs are also needed to motivate women to engage in health protective behaviors, including physical activity, to reduce their risk of breast cancer. It may be helpful to find innovative ways to target people who are not interested in physical activity [97].

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Management of hepatocellular carcinoma with novel immunotherapeutic agents and prospects for the future

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The most frequent type of primary liver cancer is hepatocellular carcinoma (HCC). Although HCC is not the most frequent cancer, it is characterized by high mortality – the 5-year survival rate is 6,9%. In recent decades there was only one molecule available in treatment (sorafenib). However, in the past few years there have been advances in treatment. Nowadays, new generation tyrosine kinase inhibitors, check point inhibitors and anti-angiogenesis drugs are available. All those studies were analyzed outcome in context of monotherapy or combined therapies. In this review we made an attempt to compare results from different studies. Even though, many studies are undergoing final stages of clinical trials, it seems that combined therapies should be the next step in treatment advances.

Key words: hepatocellular carcinoma, targeted therapy, immunotherapy

Introduction

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer. Globally, each year approximately 750,000 new cases are diagnosed, so it constitutes 7% of all neoplasms [1]. Although HCC is not the most frequent cancer, it is characterized by high mortality – the 5 year survival rate is only 6,9% [2]. Cirrhosis is the most important risk factor and is observed in 70–90% of patients [3].

Other factors are hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcoholism and aflatoxin B1. While the exposition of HBV infection in high incidence areas appears in at least 50% cases of HCC, HCV infection is more common in lower incidence HCC areas like Eastern Europe and North America [4, 5]. It has also been suggested that non-alcoholic fatty liver disease (NAFLD), occurring as a consequence of obesity and diabetes, can be the cause of an increasing number of HCC cases [6].

The most widely used staging system for HCC is the Barcelona Clinic Liver Cancer algorithm (fig. 1). Cancer is classified as an early-stage when patients have single liver tumors or as many as 3 nodules measuring 3 cm or less. They are treated by resection, transplantation or ablation. Intermediate-stage cancer concerns greater tumor burden confined to the liver without any symptoms and chemoembolization can be a beneficial treatment method. Advanced-stage cancer is when HCC symptoms are present and/or extrahepatic cancer and/

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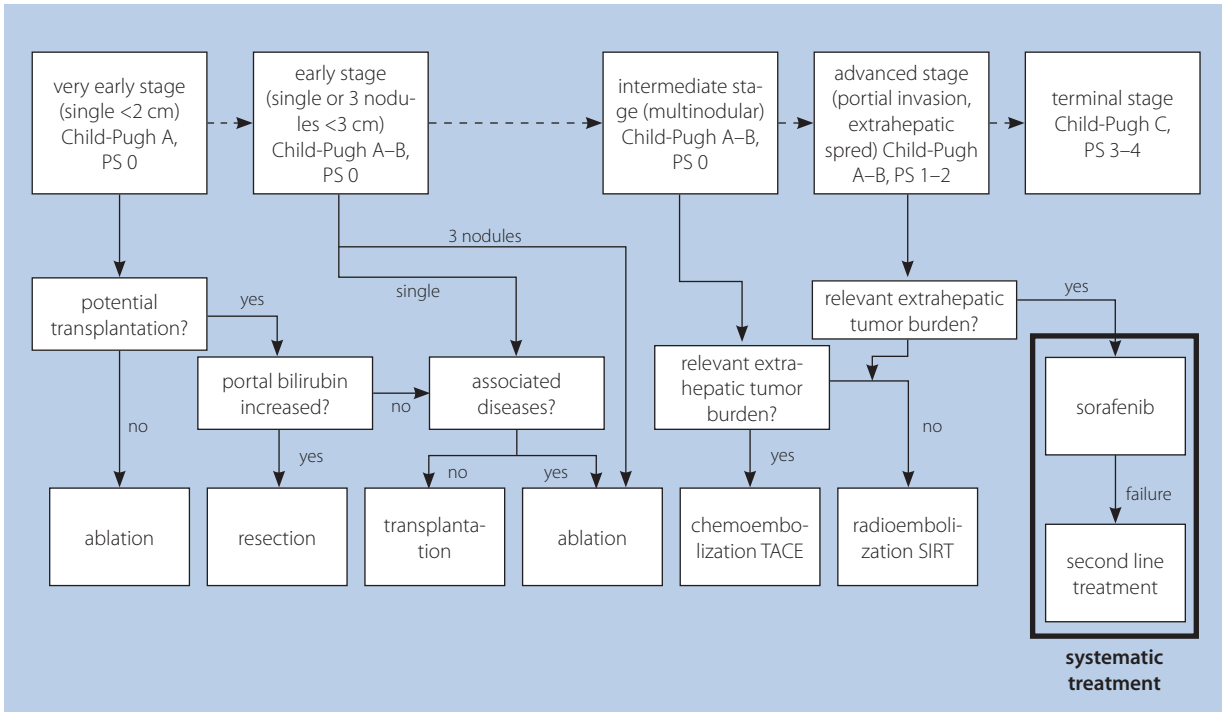

Figure 1. Barcelona Clinic Liver Cancer (BCLC) for HCC and available treatment strategies. In advanced stages, SIRT can be offered, if patients have no prognostically relevant tumor burden. Systemic therapy with sorafenib as a treatment by choice is recommended. In case of failure (clinical progression or intolerable toxicity), second-line treatment should be introduced [7]

or vascular invasion is/are diagnosed. The treatment of choice is the kinase inhibitor sorafenib [7].

The use of multi-kinase inhibitors and anti--angiogenic drugs in first-line treatment

Sorafenib has been used in HCC treatment for more than a decade. It is also used in renal cell carcinoma (RCC) and differentiated thyroid cancer (DTC) [8]. The mechanism of action is based on the inhibition of the vascular endothelial growth factor receptor, the platelet-derived growth factor receptor (PDGFR) angiogenesis through targeting the mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPK/ERK) pathway and receptor tyrosine kinases [9]. The role of sorafenib in HCC treatment is still being analyzed. The multicenter, double-blind, placebo-controlled trial of J.M. Llovet et al. focused on the differences in treatment of advanced HCC by sorafenib (at a dose of 400 mg twice daily) and placebo. They found that the median overall survival (OS) rate was 10.7 months in the sorafenib group, and 7.9 months in the placebo group with no significant difference in the median time in symptomatic progression. The median time in radiologic progression was 2.7 months longer in the sorafenib group [10]. A similar result was presented by J. Bruix et al. as they found that sorafenib improved median OS and the disease control rate (DCR) compared to the control group [11]. Another study showed that the efficacy of hepatic arterial infusion chemotherapy (HAIC) with cisplatin followed by sorafenib does not improve the survival rate in comparison with sorafenib alone; the median OS period in the HAIC group was 10 months and in the sorafenib group 15.2 months [12].

Lenvatinib is another drug used as a first-line treatment of HCC. Its mechanism is based on an inhibition of multiple receptor tyrosine kinases, including the vascular endothelial growth factor receptor 1 (VEGFR1), the vascular endothelial growth factor receptor 2 (VEGFR2) and the vascular endothelial growth factor receptor 3 (VEGFR3). It also impacts on angiogenesis, tumor growth and cancer progression by fibroblast growth factor receptors: FGFR1, FGFR2, FGFR3, FGFR4 and the platelet derived growth factor receptor alpha (PDGFRα) inhibition. Although there is no comprehensive comparison of both drugs in terms of OS, lenvatinib is considered as an alternative for sorafenib as there is significant improvement in OS (lenvatinib – 13.6 [95% CI: 12.1–14.9] months *vs.* sorafenib – 12.3 [95% CI: 0.4–13.9] months), longer progression-free survival (PFS) (7.4 [95% CI: 6.9–8.8] *vs.* 3.7 [95% CI: 3.6–4.6]) and time to progression (TTP) (8.9 [95% CI: 7.4–9.2] *vs.* 3.7 [95% CI: 3.6–5.4]) [13].

Second-line treatment

It is estimated that up to one-third of patients with advanced HCC qualify for second-line therapy. The necessity to change treatment options results from the failure of first-line therapeutics due to their high toxicity, disease progression or resistance to therapy of primary or adaptive mechanisms [14]. A study by Fung et al. on 730 Canadian patients showed that only 13.1% of patients would qualify for second-line treatment with

regorafenib, cabozantinib or ramucirumab after using strict eligibility criteria (SEC). In turn, applying modified eligibility criteria (MEC) increased the size of the group under therapeutic treatment by more than half, reaching 31.7% [15]. Tivantinib, brivanib, and everolimus were considered promising candidates for inclusion as second-line systemic therapy for HCC. Unfortunately, in the third phase of clinical trials, they did not show any significant benefit in terms of OS compared to the placebo [16–18].

Regorafenib

Until recently, patients treated with sorafenib who had not yet completed therapy due to progression or tolerance, could not count on any alternative form of systemic treatment. Bruix et al. (2016) published the results of their RESORCE study. They proved the effectiveness of using regorafenib as a second-line treatment in patients previously treated with sorafenib [19]. Regorafenib is an orally administered inhibitor of a set of multiple kinases responsible for angiogenesis (including vascular endothelial growth factor receptors 1–3 (VEGFR 1–3), tyrosine kinase with immunoglobulin-like and epidermal growth factor--like domains 2 (TIE2), fibroblast growth factor receptors 1–2 (FGFRs 1–2), the formation of metastases [VEGFR 2–3, PDGFR]) or the development of tumor immunity (colony-stimulating factor-1 receptor [CSF-1R]). These processes play a crucial role in the development of cancer and its progression [20]. In addition to second-line treatment, it is also used in therapy of refractory metastatic colorectal cancer (mCRC) and advanced gastrointestinal stromal tumors (GIST) [20, 21].

Cabozantinib

Cabozantinib is an orally administered tyrosine kinase inhibitor [TKI]. Its scope of action includes antagonistic effects against VEGFR 2, MET, KIT, RET, and AXL [22]. The MET tyrosine kinase receptor is the receptor for the hepatocyte growth factor (HGF). Their cooperation in a physiologically developing organism is important for processes such as the proper proliferation of cells or their motility [23]. However, in the case of HCC, melanoma, pancreatic, prostate, or ovarian tumors this mechanism is used by the tumor for its own benefit including growth and spread [22, 24]. HGF and MET antagonism, in turn, results in inhibition of tumor growth [25]. It is also believed that targeted MET and HGF therapies can overcome the barrier of HCC resistance to sorafenib treatment [26].

Based on the phase 3 results of the CELESTIAL study, cabozantinib was included in second-line standard of care for patients who had previously received sorafenib and had progressed. Abou-Alfa et al. conducted a randomized double-blinded trial including 707 patients with advanced HCC. The group was divided in a 2:1 ratio and the majority of patients received cabozantinib orally while the rest of the group received placebo. The initial dose was 60 mg and was decreased successively to 40 mg and 20 mg if necessary due to adverse events. The primary endpoint was OS while the secondary end points were PFS and objective ORR. Cabozantinib significantly increased the median of OS compared to placebo (respectively 10.2 months for cabozantinib and 8.0 months for placebo; HR 0.76; 95% CI: 0.63–0.92; p = 0.005). The median PFS was 5.2 months for cabozantinib and 1.9 months for placebo (HR 0.44; 95% CI: 0.36–0.52; p <0.001). Among the adverse events during therapy, the most frequent were palmar-plantar erythrodysesthesia (17% with cabozantinib and 0% in the placebo group), hypertension (16% and 2%, respectively), increased aspartate aminotransferase level (12% and 7%, respectively), fatigue (10% and 4%), and diarrhea (10% and 2% respectively) [27].

Ramucirumab

Ramucirumab is a recombinant human IgG1 monoclonal antibody that impairs angiogenesis which is essential for tumor development due to its VEGFR 2 antagonistic activity [28]. In a randomized double-blinded third phase REACH trial by Zhu et al., the efficacy of ramucirumab compared to a placebo was determined in patients with advanced HCC who had previously received sorafenib treatment. Initially there was no significant improvement in OS in ramucirumab-treated patients compared to placebo. Median OS of ramucirumab was 9.2 months vs 7.6 months with placebo administration (95% CI: 0.717–1.046; p = 0.1391) [29]. However, subsequent data analysis showed that ramucirumab significantly improved the OS score in patients with α-fetoprotein (AFP) ≥400 ng/mL [30]. The REACH II study included patients with advanced HCC (AFP values ≥ 400 ng/mL) and Child-Pugh class A liver disease treated only with sorafenib. 197 out of 292 subjects received ramucirumab therapy at a dose of 8 mg/kg intravenously every 14 days while 95 of them received placebo. The results showed that the median OS of ramucirumab treated patients was 8.5 months vs 7.3 months in the placebo group (HR of 0.71 [95% CI: 0.53–0.95]) while the PFS for ramucirumab was 2.8 months *vs.* 1.6 months for placebo (p < 0.0001). The most common adverse effects included hypertension (13% with ramucirumab *vs.* 5% with placebo), hyponatremia (6% *vs.* 0%, respectively), and increased aspartate aminotransferase (3% *vs.* 5%, respectively) [31].

Immunotherapeutic agents

One of the major problems in tumor management is their ability to escape from the immune system's range of action. Immunoediting, which is a key aspect of immune evasion, is based on tumor-immune system interactions and Darwinian selection leading to decreased immunogenicity of the neoplastic cells. This in turn makes them invulnerable to the immune response. Attempts have been made to counteract those effects with immunotherapy. Experimental immunotherapy consists of two approaches: inducement of a new immune response and enhancement of the existing one [32]. Strategies of the *de novo* response stimulation include the usage of antigen targeting

antibodies coupled with the immune cells, e.g. anti glypican 3 antibodies [33] and anti alpha-fetoprotein antibodies [34] conjugated with T cells or NK cells. Other examples are adoptive cell therapy using the chimeric antigen receptor expressing T cells (CAR-T cells) [35], cytokine induced killer cells (CIK cells) [36] or natural killer cells (NK cells) [37] and vaccine therapies with dendritic cell vaccines [38] or peptide vaccines [39].

The reinforcement of the existing immune response is based mainly on the pre-existing reactivity to neoplastic cells impeded by the microenvironmental components of the immune-edited tumor. One of the techniques aims at immune-inhibitory cytokines such as transforming growth factor beta (TGF-β) secreted by the neoplasm. The most relevant approach though, nowadays, is connected with the inhibition of immune checkpoints which is crucial in cancer immune evasion processes [40, 41].

Programmed death receptor 1 (PD1) is a surface protein expressed mainly by Tc lymphocytes but also by Th lymphocytes, Treg lymphocytes, B lymphocytes, NK cells, and some myeloid cells [32,33] which binds with its ligand PD-L1 (programmed cell death ligand 1). This triggers the metabolic cascade resulting in the inhibition of immune response by increasing the number and activity of Treg cells [42], inactivation of CD28 and downregulation of TCR in Tc cells [43] or their apoptosis [42, 44]. There are a number of clinical trials of PD1 inhibitors.

Nivolumab

Nivolumab is used for the treatment of patients with confirmed HCC and previously unsuccessfully treated with sorafenib. This indication was approved by the U.S. FDA in 2014 under accelerated approval due to its high efficacy and manageable safety profile demonstrated in CheckMate 040 open-label non-comparative phase ½ dose escalation and expansion trial in advanced HCC [45]. During both dose-escalation (n = 48) and dose-expansion (n = 214) phases (3 mg/kg), nivolumab showed acceptable tolerability. Although 46 of the dose-escalation patients (96%) discontinued treatment, 42 cases (88%) were due to disease progression. In the dose-expansion phase, the objective response (assessed using RECIST 1.1) was 20% (95% CI: 15–26) and in the dose-escalation phase it turned out to be 15% (95% CI: 6–28). The median OS rate was about two months longer (16.39 months) compared with sorafenib-treated patients (14.69 months). CheckMate 459, a phase III study on nivolumab in HCC (NCT02576509) is already in progress and results have not been published yet [46].

Camrelizumab

Camrelizumab is a humanized high-affinity IgG_4-kappa antibody PD-1 inhibitor used for the treatment of various neoplasms [47]. It has already received its first conditional approval in China for relapsed or refractory classical Hodgkin's lymphoma treatment in patients after receiving at least two systemic chemotherapies. Its safety and efficacy in patients with pretreated advanced HCC was evaluated in a multicenter open-label parallel-group and randomized phase 2 clinical trial [48]. The objective of the partial response evaluated by blinded independent central review (BICR) according to RECIST 1.1 was achieved in 32 of 217 patients (14,7%; 95% CI: 10.3–20.2). The 6-month OS probability was 74,4% (95% CI: 68–79.7), the 12-month OS was 55.9% (95% CI: 48.9–62.2) and the median OS turned out to be 13.8 months (95% CI: 11.5–16.6). The rate of treatment-related adverse events was relatively low and manageable (grade 3 or 4 in 22% of patients). Phase III studies on camrelizumab in HCC (NCT03605706) and other malignancies such as non-smalll-cell lung carcinoma (NSCLC), gastric / oesophageal cancer, nasopharyngeal carcinoma are pending or ongoing [49].

Pembrolizumab

Pembrolizumab is a humanized monoclonal IgG4 kappa antibody that acts as a PD1 inhibitor indicated for a variety of neoplasms besides HCC, such as melanomas, NSCLCs, head and neck squamous cell carcinomas (HNSCCs), several type of lymphomas and others. The usage of pembrolizumab in HCC was approved by the FDA under accelerated approval based on tumor response rate and durability of the response shown in the KEYNOTE-240 study [50]. KEYNOTE-224 is a single-arm non-randomized multicenter open-label phase 2 trial [51] on 104 patients after disease progression, on or after sorafenib therapy and who had measurable disease and Child-Pugh class A liver impairment. 18 of the 104 patients displayed an objective response (17%; 95% CI: 11–26) including 1 complete and 17 partial responses. Treatment-related adverse events of grade 3 or worse were reported in 27 (26%) participants and grade 4 and grade 5 events affected 1 patient each. The results of further assessment in phase III trial KEYNOTE-240 were consistent with those of KEYNOTE-224, although OS and PFS measurements did not reach their co-primary endpoints and statistical significance per specified criteria. There are a number of trials studying other PD-1 inhibitors such as sintilimab (NCT03794440) [52], or tislelizumab (NCT03412773) [53]. Meta-analysis by Voutsadakis carried out with trials of selected PD-1 inhibitors showed no dissimilarities in effectiveness with other systemic therapies for HCC [54].

Durvalumab

Durvalumab is a monoclonal human immunoglobulin G1 kappa. The safety and efficacy of this PD-L1 inhibitor in relation to HCC was assessed in phase 1/2, a multicenter open-label study in patients with advanced solid tumors (NCT01693562). Grade 3–4 treatment-related adverse events occurred in 20% of patients and antitumor activity measured in ORR was calculated to be 10.3% (95% CI: 2.9–24.2) with a median OS of 13.2 months (95% CI: 6.3–21.1) [55].

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) is another receptor that acts as an important immune checkpoint

that through various mechanisms (e.g. inhibition of cytotoxic T lymphocytes, dendritic cells, activation of regulatory T cells etc. [56, 57]) contributes to the tumor immune evasion. The only CTLA4-inhibitor tested on HCC patients was tremelimumab – the results of the phase I trial displayed a partial response rate of 17.6% without major safety concerns [58]. HIMALAYA, a phase III study on tremelimumab in HCC (NCT03298451), is already in progress as well [59]. Other immune checkpoints potentially relevant in HCC therapy (and oncology in general) are TGF-beta (e.g. NIS793 with PD-1 inhibitor spartalizumab – NCT02947165) [60], T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) (e.g. anti-TIM-3 and PD-1 – NCT03680508) [61] or lymphocyte activation gene 3 (LAG-3) (e.g. relatlimab and nivolumab – NCT01968109) [62].

Tremelimumab

As for other immunotherapeutics, with regards to worth mentioning is the combination of tremelimumab which is a human monoclonal antibody anti-CTLA-4 with ablative therapies that tend to induce peripheral immune responses [63–65]. According to a clinical trial by Duffy et al., in 19 patients who underwent tremelimumab administration and subtotal radiofrequency ablation or chemoablation, a confirmed partial response was observed in five subjects (26.3%; 95% CI: 9.1–51.2). Those patients received the infusion at two dose levels (3.5 and 10 mg/kg *i.v.*) given every 4 weeks for a total of 6 doses followed by 3-monthly administrations until the fulfillment of off-treatment criteria. In the study group, the median PFS was 7.4 months (95% CI: 4.7–19.4 months) and OS – 12.3 months (95% CI: 9.3–15.4 months) [66]. What is more, tremelimumab shows a significant activity in patients with HCC and chronic HCV infection and these conjectures were confirmed both in the study mentioned above [66], but also in the results of the clinical trial of Sangro et al. In the second case given, no ablative treatment was used and also the drug dose was different – 15 mg/kg *i.v.* every 90 days until progression or toxicity occurrence. Median TTP was 6.48 months (95% CI: 3.95–9.14) and a significant drop in the viral load provoked by the anti-HCV increased immune response was confirmed [58].

Combined therapies

Studies are underway to show the efficacy of a combination of anti-cancer drugs in the treatment of HCC. Combinations of anti-angiogenesis drugs with inhibitors of immune checkpoints (PD-1, PD-L1) used primarily in the treatment of lung cancer are being tested.

Atezolizumab and bevacizumab

In recent months, anti-PD-L1 activity has gained prominence in HCC treatment due to its anti-proliferative activity. The aim of the GO30140 study was to investigate the significance of atezolizumab (anti-PD-L1) alone and in combination with bevacizumab (anti-VEGF) in unresectable HCC. In a group of patients receiving the combined therapy of atezolizumab (1200 mg) and bevacizumab (15 mg/kg) with a median follow-up of 12.4 months, a confirmed objective response was observed in 37 (36%; 95% CI: 26–46) out of 104 patients; while for PFS, with a median follow-up of 6,6 months, it was 5.6 months (95% CI: 3·6–7·4). In the group receiving only atezolizumab in monotherapy, the median PFS was 3.4 months (1.9–5.2; hazard ratio 0.55; 80% CI: 0.40–0.74; $p = 0.011$) [67]. Hack et al. compared also the HR for death – 0.58 (95% CI: 0.42–0.79; $p < 0.001$), OS at 12 months being 67.2% (95% CI: 61.3–73.1) *vs.* 54.6% (95% CI: 45.2–64.0) and PFS – 6.8 months (95% CI: 5.7–8.3) *vs.* 4.3 months (95% CI: 4.0–5.6); this was in atezolizumab plus bevacizumab and sorafenib-receiving groups with unresectable HCC with no prior systemic treatment. The results showed significantly better OS and PFS outcomes in atezolizumab + bevacizumab than sorafenib-receiving patients. According to the NCT04102098 study results, the PFS (in months) in the atezolizumab and bevacizumab group was even longer – 6.8 (5.7–8.3) [68].

Nivolumab and ipilimumab

As for other immunotherapeutic possibilities, there is much more to discover. In a Checkmate 040 randomized clinical trial in group A (obtaining nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks [4 doses] and then followed by nivolumab 240 mg every 2 weeks), the objective response rate (ORR) was 32% (95% CI: 20–47). In group B (obtaining nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks (4 doses)) ORR was 27% (95% CI: 15–41) and in group C (with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg administration every 6 weeks) – 29% (95% CI: 17–43). In groups B and C, the median duration of response was, respectively: 15.2 months (4.2–29.9+) and 21.7 months (2.8–32.7+) while in group A it was not reached until the end of the study period and this therapeutic pattern was approved in the US concerning the results and the good safety profile [69].

Tremelimumab and durvalumab

According to the results of the NCT02519348 clinical trial, tremelimumab (anti-CTLA-4 antibody) administered in a single dose of 300 mg combined with durvalumab (anti-PD-L1) in a dose of 1500 mg showed promising clinical activity and tolerance in patients with HCC with median OS of 18.73 months (10.78–27.27) and median ORR of 24% (95% CI: 14.9–35.3) with an acceptable safety profile. Tremelimumab-durvalumab combination remains evaluated in a phase III trial (HIMALAYA, NCT03298451) [70].

Ramucirumab and durvalumab

A 25-center study led by Bang [71] investigated the effectiveness of combined therapy with ramucirumab (IgG1, anti-VEGFR2) and durvalumab (IgG1, anti-PD-L1). The research subjects consisted of 28 patients diagnosed with HCC who had already been tre-

ated before. In the course of the study it was possible to obtain a partial tumor response to treatment in 3 out of 28 patients, of which two showed high PD-L1 expression. In contrast, 24 patients experienced treatment-related adverse events (TRAE). The most common were diarrhea (n = 8), fatigue (n = 6) and increased blood pressure (n = 4). Two patients died during the study due to complications: acute hepatitis (TRAE) and acute respiratory distress syndrome (considered unrelated to treatment). It was assessed that the side effects of the combination of these two drugs do not go beyond the known complications of using each of them separately.

Pembrolizumab and lenvatinib

The effectiveness of the combination of pembrolizumab (anti-PD-1 antibodies) and lenvatinib (inhibitor of VEGFR1, VEGFR2 and VEGFR3 kinases) was investigated by Finn et al. [72]. A total of 100 patients received the combination of pembrolizumab and lenvatinib for an average of 7.5 months. Treatment efficacy was measured by the Modified Solid Tumor Response Criteria (mRECIST). The objective response rate (ORR) was 46.0% (95% CI: 36.0–56.3). The median duration of response (DOR) was 8.6 months (95% CI: 6.9 months to not estimable [NE]), the time to respond (TTR) – 1.9 months and PFS – 9.3 months (95% CI: 5.6–9.7 months). Median OS was 22 months (95% CI: 20.4 months to NE). The shrinkage of the tumor size was observed in 89% of the subjects. Almost all patients (99%) experienced side effects and the vast majority (95%) reported more than one. The most common ones were: hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%) and hypothyroidism (25%). 13 patients died during the course of study while 3 of the deaths were considered treatment-related. This study also did not find any side effects that would be different from those of the two drugs administered alone.

While in the above study the combination of pembrolizumab and lenvatinib is used as the first-line treatment, there are isolated reports of patients successfully treated with combination therapy after using sorafenib [73] or pembrolizumab as monotherapy [74]. Not to mention the promising results of studies testing the effectiveness of this treatment in the therapy of endometrial cancer [75, 76], stomach [77] or kidney [78].

Avelumab and axitinib

Another variant of combination therapy is the combination of avelumab (anti-PD-L1 immunoglobulin) and axitinib (a selective VEGFR kinase inhibitor). This therapy has been shown to be effective in the treatment of kidney cancer [79, 80].

A study by Masatoshi Kudo et al. [81] involved 22 HCC patients who were administered these two drugs. A reduction in tumor size was noted (according to mRECIST) in 16 patients and ORR was 31.8% (95% CI: 13.9–54.9). Side effects such as hypertension (50% of the respondents), hypothyroidism (31.8%), and hand-foot syndrome (22.7%) were observed.

Bevacizumab and erlotinib

An alternative version of combination therapy is the combination of a VEGFR inhibitor with a drug that inhibits EGFR tyrosine kinase. A study verifying the effectiveness of such treatment was carried out by M. B. Thomas et al. [82]. 90 subjects with advanced HCC were randomized into two groups and treated with a combination of bevacizumab (anti-VEGFR immunoglobulin) and erlotinib (n = 45) or sorafenib in monotherapy (n = 45). The median OS was identical for both treatments and reached 8.5 months (95% CI: 7.00–13.9 for bevacizumab+erlotinib *vs.* 95% CI: 5.69–12.2 for sorafenib). However, the duration of event free survival (EFS) favored the combination treatment (median – 4.37 months, 95% CI: 2.99–7.36) over monotherapy (median – 2.76 months, 95% CI: 1.84–4.80). Side effects were more frequent in the sorafenib group but also in this group the treatment was discontinued much more often due to the occurrence of serious complications.

The researchers, led by Liyun He, also came to similar conclusions. Their study included 342 patients with HCC and showed that bevacizumab and erlotinib therapy is as effective as sorafenib therapy and is associated with lower toxicity and better tolerance by patients [83]. However, this combined therapy does not show significant efficacy in second-line treatment [84] or treatment of residual disease [85]. Table I shows sorafenib and second-line treatment options.

Discussions

Multi-kinase inhibitors and anti-angiogenic drugs have been the most commonly applied therapeutic options in HCC treatment, including sorafenib, as the treatment by choice in advanced HCC. Unfortunately, these options present certain disadvantages. Their high toxicity and frequent cases of disease progression as well as possible therapy-tolerance development cause a high number of failures in HCC therapy.

Among the drugs that can be used in HCC therapy after unsuccessful first-line treatment are lenvatinib, regorafenib, and cabozantinib, while tivantinib, brivanib, and everolimus were rejected in this regard. Regorafenib has proven effectiveness after previous treatment with sorafenib failure due to progression or in tolerance. Cabozantinib, in turn, is effective to some degree in patients with tumor progression.

However, disadvantages and limitations of therapy cause a pressing need for development of innovative therapeutic strategies in HCC treatment. Among the others, some immunotherapeutic agents are highly prospective.

A relatively high number of clinical trials and some meta-analyzes involved PD-1 inhibitors of immune checkpoints (PD-1, PD-L1), including nivolumab, camrelizumab, pembrolizumab, durvalumab, and tremelimumab. Existing data concerning immunotherapy indicate various efficacy, but good tolerance of most of the agents and their generally acceptable safety profile. So far, clinical trials of nivolumab show a longer median survival rate than in sorafenib groups, making the

Table I. Overall response rate (ORR), overall survival (OS), time to progression (TTP) / progression-free survival (PFS) – sorafenib and second-line treatment options

	ORR	Median OS (months)	Median TTP / PFS (months)	Citation
sorafenib		10.7 (*vs.* 7.9 placebo)	2.7 (TTP)	[10, 11]
		10.0 (*vs.* 15.2 sorafenib + cisplatin)	3.9 (TTP)	[12]
cabozantinib		10.2 (*vs.* 8.0 placebo)	5.2 (PFS)	[27]
ramucirumab		9.2 (*vs.* 7.6 placebo)		[29] [31]
		8.5 (*vs.* 7.3 placebo)	2.8 (PFS)	
nivolumab		16.39 (*vs.* 15.69)		[45, 46]
camrelizumab		13.8		[49]
durvalumab		13.2		[55]
tremelimumab		12.3	7.4 (PFS)	[66]
atezolizumab + bevacizumab			5.6 (PFS)	[63]
atezolizumab + bevacizumab			6.8 (PFS)	[64]
nivolumab + ipilimumab	27–32%			[65]
tremelimumab + durvalumab	24%	18.73		[66]
pembrolizumab + lenvatinib	46%			[68]
avelumab + axitinib	31.8%			[77]
bevacizumab + erlotinib		8.5		[78]

immunotherapeutic agents both a possible alternative for sorafenib and a therapeutic option for second-line treatment. Camrelizumab research, in turn, indicates a median survival rate shorter compared to nivolumab, but without serious adverse effects during the therapy.

Another group of therapies involve combinations of anti-angiogenesis drugs with inhibitors of immune checkpoints effective against lung cancer. Among them nivolumab and ipilimumab, tremelimumab and durvalumab, as well as ramucirumab and durvalumab combinations are characterized by at least an acceptable safety profile and tolerance, while neither the combinations of pembrolizumab with lenvatinib, nor ramucirumab with durvalumab show other side effects than the drugs used alone. Some of the combinations, including avelumab and axitinib have proven efficacy in tumor size reduction, while, bevacizumab and erlotinib combine treatment present duration of EFS better than monotherapy.

Conclusions

The promising results of cancer immunotherapy may offer new hope for patients diagnosed with HCC. In those with advanced cancer, some immunotherapeutic agents may be a safe and an effective alternative for chemotherapy; alternatively they can constitute medications to be applied as a part of second-line treatment after the failure of previous options mentioned earlier. Particularly good results have already been achieved in combined therapy clinical trials.

A serious weakness of the studies existing so far is that they are often based on isolated reports or have other crucial limitations. Only a few immunotherapeutic agents have been already approved or are undergoing the final stages of clinical trials, while others remain highly experimental. Research projects aiming to gain more clinical data concerning the efficacy and safety of both drugs used in monotherapies or in combined therapies are already underway.

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Legal aspects of teleservices in oncology

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The use of teleinformatic tools and other means of communication in specialist care, including oncological care, is completely admissible and in accordance with currently binding law. Key legal acts on principles of providing health services, including the Act on the Profession of Doctor and Dentist and the Act on Medical Activity, allow adjudicating on a patient's health status and providing all activities of a health service nature with the use of teleinformatic means and other communication systems. No organizational standards on televisits in specialist care have been established to date, imposing *per analogiam* use of the regulations on organizational standards of teleservices in primary health care. However, such a solution should be considered temporary and imprecise, therefore the regulation dedicated to providing televisits within specialist care, including its specificity areas, is essential. Simultaneously, it is necessary to eliminate the use of announcements and guidelines of the National Health Fund which refer to the admissibility of televisits as a binding legal form. Announcements, guidelines, recommendations and positions may only serve as advice for proceeding with special care and this should be eventually reflected in the current law.

Key words: telemedicine, teleconsultation, distance services, teleoncology, e-health

Introduction

Telemedicine is one of the novel forms to provide health services, replacing on many levels classic diagnostic and therapeutic process involving physician's and patient's personal contact. In the literature there are many terms defining telemedicine. In the 90s, P.F. Granade, J.H. Sander [1], among others, attempted to define telemedicine, being the first authors to refer to the issue of responsibility for damages related to health services "at a distance". According to the WHO, telemedicine is "the delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies (ICT) for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of health care providers, all in the interests of advancing the health of individuals and their communities" [2].

Communication from the Commission to the European Parliament defines telemedicine as "the provision of healthcare services, through use of ICT, in situations where the health professional and the patient (or two health professionals) are not in the same location. It involves secure transmission of medical data and information, through text, sound, images or other forms needed for the prevention, diagnosis, treatment and follow-up of patients" [3]. Furthermore, the communication emphasizes that advantages of ICT use in health care include, among others, specialist care access improvement in areas with hindered access to health care or with insufficient number of specialists. In case of numerous services, including for example teleradiology, teleconsultations may contribute

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to waiting lists reduction, resource use optimization and efficiency gain [4].

Telemedicine is undoubtedly immanent component of e-health concept which involves the use of technologies for medicine in the health sector. There is no doubt that telemedicine tools have been supporting both the process of diagnosis and consultation, and the process of monitoring the state of health of chronically ill patients for many years [5–8].

Material and methods

The materials used in this paper are the provisions of Polish law directly referring to providing health services with the use of ICT or other means of communication. The additional material comprised content of current Polish Court Case Law as well as positions grounded in the doctrine. The authors used method of analysis for reviewing and interpreting binding provisions, positions of the doctrine and judicature.

The main objective of the paper is to assess the admissibility of teleinformatic communication means or other means of communication (ICT) used to initiate and continue health services in oncology, including the diagnosis, treatment and monitoring of patients' health. An additional objective is to analyze the scope of duties of medical professionals performing health services "at a distance".

Admissibility of health services with the use of information and communications technology

Before the act from 9.10.2015 on the amendment of the act on information systems in health care (…) came into force on 12.12.2015, only single legal regulations and documents on ethics and medical deontology referred to the use of ICT for health services [9]. Direct admissibility of the use of teleinformatic tools in the treatment process was foreseen by the Medical Code of Ethics whose art. 9 states that a physician can only initiate treatment after examining the patient, excluding cases in which medical advice can only be provided at a distance [10]. Even though the Medical Code of Ethics is not a normative act but a set of ethical principles, the literature emphasizes that "ethical norms can be incorporated by the legal acts into the binding legal system. The Act on Medical Chambers made such incorporated of the Medical Code of Ethics' norms. The norms of this code specified the content of legal norms included in the Act on Medical Chambers (…)" [11]. Therefore, applying the provisions of the Medical Code of Ethics in the context of providing health services that exclude personal contact with a patient is justified in exceptional cases whose assessment depends each time on a physician's individual decision. Although telemedicine was the subject of residual legal regulations, these issues were analyzed in literature from the last decade, among others, in the context of teleconsultations in cases of severe poisoning, cardiac rehabilitation and also the monitoring of health status in diabetic patient [12–14].

According to revised art. 42 section 2 of the Act on the Profession of Doctor and Dentist of 5.12.1996 "a physician adjudicates on the health state of a particular person after examination of this person performed in-person or examining this person performed with the use of teleinformatic systems or communication systems" [15]. The term "a physician adjudicates" should be identified twofold. Firstly, this term refers to the possibility of performing an assessment of the state of health, to diagnose, which constitutes a formal statement on health status and the potential need for treatment. Secondly, the above term stands for issuing an opinion or a certificate in the form of a document – i.e. "adjudication" in the material sense [16].

Before the revision of the Act on the Profession of Doctor and Dentist (…) [15] provisions, there were statements in judicature claiming that the use of telemedicine tools should not be identified with health care services. The Voivodship Administrative Court in Krakow, in a judgement from 23.06.2015, emphasized that [17]:

"telemedicine services provided with the use of the Internet are in fact provision of advice, lectures, constitute recommendations on performing exercises, their assessment and monitoring, as well as consultations in health education. These activities cannot be deemed as medical care (…)". Taking into consideration the current wording of art. 42 section 1 of the Act on the Profession of Doctor and Dentist it should be deemed that the use of teleinformatic means during the provision of health services unquestionably constitutes executing a form of medical care activity whose purpose can be diagnosis, treatment, monitoring process, as well as constant monitoring of a patient.

When analyzing providing health services "at a distance", the difference between the notions: "personal contact" and "direct contact" should be emphasized. The ICT used by a physician to contact a patient does not prevent direct contact, but only personal contact understood as physical people meeting at the same place and time. Proper comprehension of the notion of "direct contact" has a major impact pursuant to, among others, the Act of 25.06.1999 on cash social insurance benefits in the event of sickness and maternity [18]. According to art. 55 section 4 point 1 of the act cited above "deciding on temporary incapacity for work due to illness, hospitalization (…) or on the need to provide care to an ill family member follows a direct examination of the state of health of the insured person or ill family member".

Direct examination cannot be identified with personal examination performed as a result of initiating physical contact of a physician with a patient, but only with the need for a heath state assessment, e.g. remotely or with the use of ICT. An exception that allows the use of teleinformatic means in the patient's health state decision process, determines art. 11 section 1 of the Mental Health Protection Act [19] which states that "decision on the state of health of a person with mental disorders, opinion or referral to another physician or psycho-

logist or healthcare entity may only be issued by a physician based on a previous personal examination of this person". The literal wording of art. 11 section 1 of the Mental Health Protection Act results in necessary requires an obligatory personal examination in order to assess the patient's state of health or issue referral to further treatment.

General ICT use admissibility is foreseen by art. 3 section 1 of the Act on Medical Activity of 15.04.2011 stating that "medical activity involves providing medical services. These services may be provided through teleinformatic systems or communication systems" [20]. It should be mentioned that the wording of art. 2 section 1 point 10 of the Act on Medical Activity defines the notion of health services as "(…) activities aimed to maintain, rescue, regain or improve health, and all other medical activities related to the process of medical treatment or separate regulations on the principles for performing these activities" [20]. The definition indicates that health services are any activities performed by medical professionals aimed at enhancing, sustaining or improving health regardless of the specificity, scope and specialization of provided services.

Undoubtedly health services "at a distance" gained popularity during the COVID-19 pandemic, nevertheless this form of delivering services was already present before the epidemiological threat manifested. For the purpose of this paper, delivering health services "at a distance" is identified with the televisit which should be clearly distinguished from teleadvice. The latter should be identified with a service provided through teleinformatic systems or other communication systems due to suspicion of, or infection with SARS-CoV-2 or a COVID-19 case. According to no longer binding art. 7 section 4 of the COVID Act [21]: "a physician's and dentist's (…) may provide health services in relation to COVID-19 prevention through teleinformatic systems provided by a unit subordinated to the minister competent for matters of health, appropriate in the field of information systems in health care, further called 'teleadvice' (…)". All services provided by healthcare professionals using ICT, which are related to other health problems, should be cataloged as a televisit, i.e. health services provided without personal contact between the medical personnel and the patient.

It should be emphasized that all legal regulations referring to providing health services using ICT concern publicly funded services. The above, however, does not exclude proper application of these regulations to commercially provided services. Currently, the law refers directly to ICT means used for providing primary health care services as well as certain specialist services.

In March 2020, the Central Office of the National Health Fund (NHF) issued an announcement indicating possible "execution and settlement of specialist advice provided under the contracts for providing health care services within outpatient specialist services with the use of teleinformatic systems or other communication systems" excluding services listed in appendix 1a and c to the resolution of 31.12.2019 no 182/2019/DSOZ of the President of the National Health Fund on specifying the conditions of conclusion and implementation of the contracts for providing outpatient specialist services [22]. At the same time the announcement emphasized that televisits can be provided "only in a situation when a health state assessment and scope of the necessary activities to be provided for a patient does not require the personal presence of healthcare professionals" [23]. It should be emphasized that appendix no 1a to the resolution no 182/2019/DSOZ of the President of the NHF enumerates, among others, services within oncology which are provided by specialist clinics, including, among others, gynecologic oncology clinic, oncology clinic, chemotherapy clinic and radiotherapy clinic [22].

Considering the above, it should be deemed that the NHF announcements of March 2020 excluded possible use of ICT tools for provision of outpatient oncological services. At the same time, no legal regulations allowing providing health services with the use of ICT were established as the above-mentioned art. 42 section 1 of the Act on the Profession of Doctor and Dentist [15] and art. 3 section 1 of the Act on Medical Activity [20], both allowing providing health services "at a distance", were still in force.

The issue of providing remote services was also referred to by the announcements of the NHF which allowed ICT use in home parenteral nutrition and home enteral nutrition when it concerns:

1. previously planned follow-up visits,
2. patients in a stable state [23].

On 24.03.2020, the National Health Fund also issued an announcement on the execution and settlement of health teleservices in the form of hospital treatment – drug programs and chemotherapy hospital treatment [23]. The announcement emphasized that teleconsultation is only possible in patients continuing treatment, in line with the specified therapeutic plan, accordingly to the current patient's clinical state. According to recommendations included in the announcement, follow-up visits for patients in a stable state may be performed by phone consultation with the use of teleinformatic systems or other communication systems. A patient's medical record should include appropriate notation on the way the service was provided. Furthermore, the provider is obliged to report on data in line with the provisions of the regulation on principles of settlement for services of a given type. Subsequent updates of the ICD-9 dictionary include reporting codes with their effective dates – i.e. code 89.0099 – medical advice through teleinformatic systems or communication systems (since 1.03.2020) and code 94.483 – a consultation with the use of teleinformatic systems (since 17.03.2020).

Since 17.04.2020, providing advice and visits with the use of teleinformatic systems or other communication systems was approved in home hospice care, provided that such form does not constitute a risk to the patient's health[23]. According to the

announcement of the Central Office of the NHF of 17.03.2020, remote services can be provided within:

- the order no 45/2018/DSOZ of the President of the NHF of 30.05.2018 on specifying conditions of conclusion and implementation of contracts in care and nursing allowance within long term care,
- long term home care for mechanically ventilated patients,
- long term home care for mechanically ventilated children,
- long term home nursing care,
- the order no 74/2018/DSOZ of the President of the NHF of 31.07.2018 on specifying conditions of conclusion and implementation of contracts in palliative and hospice care,
- home hospice services,
- pediatric home hospice services.

It should be emphasized that all NHF announcements on ICT admissibility were issued due to the need to minimize risk of COVID-19 infection transmission through limiting personal contact with patients. Therefore, communication refers to exceptional situations and does not apply to treatment processes provided in conditions unrelated to the COVID-19 pandemic.

It should be noted that the announcements issued by the NHF are not normative in nature and therefore are only an indication of proceedings whose eventual application treatment depends on the decision of the health care entity. Obligatory proceedings were included in the legal acts on ICT use in the process of providing health care services.

When analyzing the law on ICT use in health care services, it is necessary to indicate the regulation of the Minister of Health of 06.04.2020 amending the regulation on guaranteed services in outpatient specialist care [24], under which the possible use of teleinformatic systems or communication systems in providing services by dialysis unit physicians was added. The list of services which can be provided with the use of teleinformatic systems include, among others, peritoneal dialysis, dialysis with 24-hour care and hemodiafiltration (HDF).

On 9.04.2021, the regulation amended the regulation on guaranteed services in outpatient specialist care came into force [25] allowing the use of teleinformatic systems in diagnostics and monitoring in complex oncological care in patients with colorectal cancer. ICT tools can also be used for cooperation with the colorectal cancer treatment center which guarantees: the possibility to schedule or reschedule routine checkups and to utilize specialist consultations or advice.

Organizational standards of televisits

Although the pandemic led to the increased use of televisits, only limited provisions of the law referring to implementation and reporting standards for such visits were established. It should be emphasized that the Act on Medical Activity includes authorization for the Minister of Health to issue organizational standards in particular fields of medicine or in the case of the implementation of precisely specified services. According to art. 22 section 5 of the Act on Medical Activity [20]: "the minister competent for health issues can specify, through a regulation, health care organizational standards in chosen fields of medicine or in specified medical entities, following the need to ensure appropriate quality of health services". Organizational standards issued in the form of a regulation are strictly binding and mandatory as a result of their normative character. A medical entity is obliged to apply organizational standards in health care in providing health services, if they were issued based on art. 22 section 5 for the field of medicine covered by the scope of health services provided in this medical entity, or for the type of medical activity performed.

Until now, standards of proceedings in providing services within telemedicine were specified in the regulation of the Minister of Health on organizational standards in radiology and diagnostic imaging performed with the use of teleinformatic systems [26]. On 29.08.2020, organizational standards for a primary health care televisit came into force [27]. Based on art. 22 section 5 of the Act on Medical Activity [20], however, no provisions for the televisit within specialist health care were established. Taking into consideration the lack of provisions directly dedicated to televisits within specialist health care, the authors indicate that it is necessary to apply the provisions pertaining to the televisit in primary health care to specialist teleconsultation.

Organizational standards refer to formal aspects related to the implementation of the televisit and these are undoubtedly common for primary and specialist health care services. The common denominator applies to: principles concerning qualification to distant services, a mode in which a televisit is performed, verification of a patient's identity, cancellation of the appointment as well as medical entity's responsibility for the damage related to delivered service.

When analyzing the fundamental principles for implementation of the televisit, it is necessary to indicate the need to confirm the patient's identity in line with the principles specified in art. 50 section 2–2b of the Act on Healthcare Benefits Financed from Public Funds. The patient's identity can be confirmed by presenting an identity card, passport, driving license, school card or with the use of electronic document by presenting the document on the screen of the mobile device to the person confirming identity, or based on data transferred by the patient through the teleinformatic systems used to deliver the service. A patient may confirm his identity and declare eligibility for health care services through the electronic patient health account created as a result of personally confirmed identification or by the use of electronic identification means issued in the electronic identification system.

Another issue concerns verification of eligibility to health care services financed from public funds. In the case of "at a distance" services, verbal verification of eligibility to services is possible through a patient's verbal statement during the televisit. According to art. 50 section 7 of the Act on Health

Care Services Financed from Public Funds [28], a patient should make the following statement: "I am entitled to use health care services financed from public funds". Information on a patient's statement of eligibility to services financed from public funds should be reported in the individual medical record which should also include annotations, among others, on:

- the fact that the service was provided through teleinformatic systems or other communication systems,
- the fact that the patient was informed about the limitations related to teleconsultation,
- indication that providing a service through teleconsultation does not constitute a risk to the patient's health and the scope of the performed activities does not require the physical presence of medical personnel,
- postponement of an examination (for example diagnostic) with an explanation stating that it applies to a patient in a stable state in whom no need for such an examination was determined,
- informing a patient on the need to report to the physician or emergency room in person in case of a deterioration in their state of health or a change in the nature of the reported ailment,
- visit cancellation due to inability to connect with a patient despite 3 attempts to connect at intervals no shorter than 5 minutes,
- giving instructions on the use of the e-prescription and e-referral service, performing activities comprising provided health services, including the determination that a televisit is sufficient for the health problem that is the subject of the visit or informing the patient on the need to provide health service in personal contact with a doctor.

It should be emphasized that one of the changes introduced into the organizational standards of a televisit in primary health care [29] was limiting remote services provided to children under the age of 6, with the exclusion of routine services resulting from previously initiated treatment. Using the analogy on formal aspects of providing remote services in primary care and specialist care, it should be acknowledged that teleoncology services should only apply to patients aged 6 and older, excluding cases in which the televisit aims at monitoring the treatment plan or initiating routine activities affecting the quality of implemented procedure.

At the same time, in line with analogy to the regulation of 5.03.2021 [27], a teleservice in specialist care should not be provided in cases where:

- a patient or a patient's statutory representative does not consent to service "at a distance",
- the medical visit aims at obtaining a certificate (a document),
- a visit concerns a chronically ill patient experiencing worsening or changing symptoms.

It should be stressed that the entity providing the televisit is obliged to keep medical records in line with the principles specified in the regulations on type, scope and format of medical records and method of their processing [30] and archive it for the period of time indicated in art. 29 section 1 points 1–4 of the Act on Patients' Rights and Patients' Spokesman Rights [31], depending on the type of produced document. As a side note, it is worth reiterating that recording audio and vision during teleadvice does not replace a medical record whose scope and management was specified in the regulation indicated above.

Conclusions

The research papers developed several years ago already emphasized that the use of teleinformatic means in the process of treatment directly impacts the inclusion of financial and organizational efficiency criteria, hence a reduction in the health care cost [32, 33]. The papers published during the pandemic indicate the significant role of telemedicine in the reduction of SARS-CoV-2 transmission and the increased safety of the oncological patient [34]. At the same time, numerous authors indicate that teleoncology, which developed during the pandemic, will soon be introduced into the everyday clinical practice scheme [35]. The literature emphasizes that ICT tools provide a source of preliminary selection of oncological patients, including identifying those for whom visits "at a distance" may be more beneficial due to the limited need for physical examination [36, 37].

The authors engaged in the area of teleoncology indicate not only the positive aspects of ICT tool implementation for diagnostics and consultations, but also the drawbacks resulting from the use of this solution [38]. Among the negative aspects, the researchers indicate the unstable regulatory situation, problems related to settlement of services and the risk of diagnostic errors due to the lack of personal contact with the patient.

Taking into consideration the analysis of the regulatory environment of telemedicine in Poland, it should be emphasized that the use of ICT in specialist care, including oncology, is completely admissible and in accordance with currently binding law. It is becoming crucial that both the Act on Medical Activity and the Act on the Profession of Doctor and Dentist allow for assessing patients' state of health and providing any activities characterized as health services within the meaning of art. 2 section 1 point 10 of the Act on Medical Activity [20] with the use of teleinformatic means and other communication systems.

At the same time, it should be stressed that until now no organizational standards for televisits within specialist care were established, which necessitates the application of the provisions referring to organizational standards in teleservices within primary health care in this respect. This solution, however, should be deemed temporary and imprecise. The authors indicate that the regulation dedicated to providing televisits within specialist care, including its specificity areas, is necessary. Simultaneously, it is essential to eliminate the use of announcements and guidelines as a binding legal form. Announcements, guidelines, recommendations and positions may only serve as advice for

proceeding, which should be eventually reflected in the current law. Regardless of the announcements on the admissibility of televisits within oncology issued by the NHF, such activities are completely justified and in accordance with the provisions on the general principles of providing health care services.

In conclusion, it should be reiterated that services with the use of ICT in oncology are admissible in light of the law and thereby can be provided with the use of such tools in every case where the patient's health state and the specificity of the service allow replacing personal contact with remote contact. Furthermore, the use of ICT tools may lead to a reduction in the number of patients waiting lists for consultation.

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Guidelines and recommendations

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Systems for grading the strength of recommendations in clinical practice guidelines in oncology

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Introduction. In order to improve the applicability of clinical practice guidelines, their authors assign recommendations with grades denoting the degree of conviction regarding their practical application. Nevertheless even within one branch of medicine, significant differences between the grading systems arise.

Material and methods. To identify these systems, websites of societies and institutions publishing oncology guidelines were searched. Only high-quality, regularly updated guidelines were included.

Results. Five systems were analysed – all incorporate quality of evidence and strength of recommendation, but vary in the methods of their assessment and structure of the scales.

Discussion. The described systems depend on the review of data, the quality of which supports the ascribed strength. Systems differ with regard to the methods of assessing the quality, quantity and consistency of evidence, potentially leading to assigning different grades of strength to recommendations based on the same studies.

Conclusions. The introduction of unified grading systems across each branch of medicine could aid the development of unambiguous recommendations that are easy to introduce within the healthcare system.

Key words: grading system, guidelines, recommendation, quality of evidence, strength of recommendation

Introduction

Increasingly often, decisions concerning diagnostics and treatment in contemporary medicine are made in accordance with the paradigm of evidence-based medicine (EBM). However, due to the increasing number of clinical studies conducted and published, as well as the need to adapt the quality and effectiveness of health care to changing conditions, it has become necessary to systematize the gathered knowledge and make it more accessible. Various documents such as clinical practice guidelines (sets of recommendations) or healthcare standards are being developed in response to these needs.

In this work, the significance of the "strength of recommendation" parameter in the practical implementation of guidelines is thoroughly discussed. As the clinical practice guidelines employ varied methods of characterizing the strength of recommendation, the aim of this work is to present the grading systems most frequently used in the area of oncology. This study does not exhaust the broad subject of methodology of clinical practice guideline development, but it does constitute a review of the most popular grading systems used in oncology guidelines.

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Clinical practice guidelines

According to the definition by the American Institute of Medicine, clinical practice guidelines (CPGs) constitute a summary of scientific evidence "that are informed by a systematic review and an assessment of the benefits and harms of alternative care options" [1]. The CPGs are not only aimed at facilitating the decisions made in specific clinical situations, but they also influence the effectiveness and quality of diagnosis and therapy. The keynote of the guideline development process lies in the strict relationship between the recommendations and the gathered evidence. The process itself consists of many stages, is systematized, consistent with specific quality criteria, and based on a systematic review of literature. In addition to that it involves an assessment of quality and selection of the scientific evidence that will serve as a basis for development of recommendations [2].

From the perspective of the user of such recommendations, proper interpretation of the degree of trust in their content and confidence in the rationale for their application are of key importance. Therefore, methodologically correct guidelines for clinical practice should transparently present methods for the development and assessment of recommendations, as well as the logical connection between alternative care options and health results, plus an appraisal of the quality of evidence and strength of recommendations [1].

Quality of evidence and strength of recommendation

While determining the extent of authors' acceptance for the content of the recommendation (the strength of recommendation), four components are taken into consideration: the quality of scientific evidence (for a single study), the quality of overall evidence gathered, the strength of intervention and the benefit-risk balance. It is a complex process, which makes it necessary to distinguish between the following concepts:

- **The quality of evidence for a single study** referring to the impact of the methodological structure of a clinical trial upon the uncertainty of estimation of intervention results for a specific endpoint in a specific population in a single study.
- **The quality of evidence** describing the quality of the overall evidence gathered on the clinical profile of the intervention in relation to the defined endpoint. It defines the degree of certainty that the available scientific evidence reflects the true dimensions and direction of effects in the context of the target healthcare system's conditions. It is also referred to as strength, certainty or level of evidence.
- **The strength of intervention** refers to the effectiveness of the intervention; it illustrates the magnitude of the achievable effect of the new intervention in comparison to other available options in the population subject to the recommendation.
- **The balance of benefits and harms** – a description of magnitude of benefits in relation to damages/side effects/threats associated with a given intervention.

In the context provided above, **the strength of recommendation** defines the degree of authors' conviction that the content of the recommendation should be applied in clinical practice taken the conditions of the target healthcare system. The process for determining the strength of recommendations is based on quality of evidence, absolute and relative strength of intervention and the degree of consensus with regard to implementation in clinical practice.

Appraisal of evidence, or description of the degree of certainty that conclusions based on the collected evidence are reliable, constitutes one of the most significant factors, though not the only one, necessary to determine the ascribed strength of recommendation. It is based on the type of clinical trials included in the overall evidence. In accordance with the hierarchy of scientific evidence applied by the World Health Organization, systematic reviews and meta-analyses of RCTs are considered to be of the highest quality, while descriptive studies and expert opinions – of the lowest [3]. In this regard, it is key to appraise the internal and external reliability of the studies by considering other factors that may influence the quality of evidence, such as the risk of bias or inaccurate estimation of effects [4]. These factors – assessed using approved tools (i.a. AMSTAR2, RoB 2.0) – may result in lowering or raising the preliminary quality score determined by the study type. Hence the established quality of gathered scientific evidence, serving as a basis for recommendations, is known as the quality of evidence.

While clinical effectiveness of a given intervention, considering the uncertainty of study results, should be the main factor determining the strength of recommendation [5], the authors, when assigning the strength to each of the recommendations, consider various interrelated factors, such as:

- the quality of evidence justifying the recommendation,
- the strength of intervention,
- applicability of the evidence to the target clinical conditions,
- certainty in relation to basic risk (the occurrence of a given outcome (event) when a standard procedure is applied).

However, this process also accounts for various other aspects, such as uncertainty in relation to the values and preferences of patients and the significance of the effects of a given intervention – patients' expectations and objectives in terms of quality of life, or experience with the illness – as well as social equality and justice, costs, available resources, acceptability of recommendations and possibilities of utilising alternative treatments. In order to determine the strength of recommendation, it is necessary to provide a full and transparent summary of all the indicated components and to identify the potential effects of the CPGs' implementation. Among the desirable effects, health improvement significant to the patient

or cost reduction are of the greatest importance. Whereas, the unfavourable effects include, i.e. adverse effects, a significant increase in organisational or cost burden resulting from application of the procedure compliant with the guideline [6].

The systems for grading strength of recommendation in diagnostics and therapy therefore combine two aspects: the quality of evidence, based on the objective and precise process of appraisal of the research methodology, and the authors' certainty regarding the presence of reasonable grounds to apply the guideline in practice.

In general, evidence of high quality should result in strong recommendations. However, considering the balance of favourable and unfavourable effects of the intervention, or possible differences between the settings and conditions in the trials and those under consideration, as well as other factors, a recommendation might be assigned a much lower strength. As a result, recommendations may be weak despite a reliable estimation of the clinical effect, or strong despite the poor quality of the estimations, the reason being the need (or even the necessity) to consider prerequisites other than analytical data when developing the guidelines [6].

Due to the multitude of factors which should be considered in the process of recommendation assessment, a risk of discrepancies in the systems employed in various guidelines arises. Such situations may lead to a substantial weakening of the CPGs' implementation potential. Therefore, most organisations utilise commonly known appraisal systems or develop their own methodologies for grading the strength of recommendation to ensure its reliability. The common feature of all these documents lies in the transparency of factors considered during their development, relying upon the EBM principles and utilising systematic reviews of evidence as a basis.

Material and methods

The review of the systems for grading recommendations has been prepared on the basis of selected CPGs developed worldwide by oncology societies and governmental organisations. The thematic scope has been limited due to the legal conditions in Poland, which state that the Minister of Health announces, in the form of a notification, the guidelines for the diagnostic and therapeutic procedure regarding cancer treatment. Additionally, most oncology guidelines treat the process holistically – from prevention and screening to rehabilitation and follow-up – and include recommendations addressed to service providers, patients and their caregivers.

In order to identify the applied grading systems, a review was conducted involving 11 websites of science societies and organisations publishing oncology recommendations. Selection was conducted considering the societies recognized by clinical experts in Poland, which systematically publish new guidelines and update the older ones based on the most recent scientific evidence and global trends, as well as publish the methodology of guideline development. The documents analysed had to be of high quality as characterised by the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation II) [7]. Only systems published in English were included. Systems based solely on appraisal of research quality were excluded.

In the case of each of the systems included in this study, the methodology was described as presented in handbooks for authors and "Guidelines for guidelines" documents. Afterwards, the factors considered when defining and determining the strength of recommendations in the individual systems were compared.

Results

The analysis took into consideration the grading systems applied by the following groups of methodologists, scientific societies and organisations:

- Grading of Recommendations Assessment, Development and Evaluation (GRADE),
- National Comprehensive Cancer Network (NCCN),
- National Institute for Health and Clinical Excellence (NICE),
- European Society for Medical Oncology (ESMO),
- Scottish Intercollegiate Guidelines Network (SIGN).

Grading of Recommendations Assessment, Development and Evaluation

Grading of Recommendations Assessment, Development and Evaluation (GRADE) offers a transparent and organised process for developing and presenting summaries of scientific evidence for the purpose of:

- preparation of systematic reviews,
- determination of healthcare standards,
- development of CPGs [8].

One of the main objectives of the GRADE group was to eliminate misunderstandings caused by different methods of appraising evidence and classifying recommendations used in healthcare. For this purpose a transparent approach to assess the quality of evidence and strength of recommendation was developed, which includes some strictly defined criteria for estimation of the strength of recommendation, as presented in table I.

To facilitate the development of recommendations, the authors of GRADE propose to categorise the quality of evidence gathered for a given endpoint using four grades: high, moderate, low and very low. It should be kept in mind that these are not purely quantitative; they also involve some quality-based decisions (fig. 1), which require experience not only in conducting systematic reviews and analysis of scientific evidence, but also clinical knowledge concerning a given health problem. The preliminary grade of quality of evidence may be either high or low, depending on the design of the studies informing the recommendation.

In order to facilitate the interpretation and application of recommendations, the GRADE introduced a descriptive four-step designation of quality of evidence (certainty of effect estimation) and a two-step designation of strength of

Table I. The criteria that contribute to the strength of a recommendation according to GRADE

Domain	Comment
balance between desirable and undesirable outcomes (trade-offs) taking into account: • best estimates of the magnitude of effects on desirable and undesirable outcomes • importance of outcomes (estimated typical values and preferences)	the larger the differences between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted
confidence in the magnitude of estimates of the effect of the interventions on important outcomes (overall quality of evidence for outcomes)	the higher the quality of evidence, the more likely a strong recommendation is warranted
confidence in values and preferences and their variability	the greater the variability in values and preferences, or uncertainty about typical values and preferences, the more likely a weak recommendation is warranted
resource use	the higher the costs of an intervention (the more resources consumed), the less likely a strong recommendation is warranted

The term "outcome" is used in accordance with the original source, although it does not fully correspond to the differentiation between terms "outcome" and "endpoint" employed in this work

Source: Andrews J.C. et al. (2013). *GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation's direction and strength*

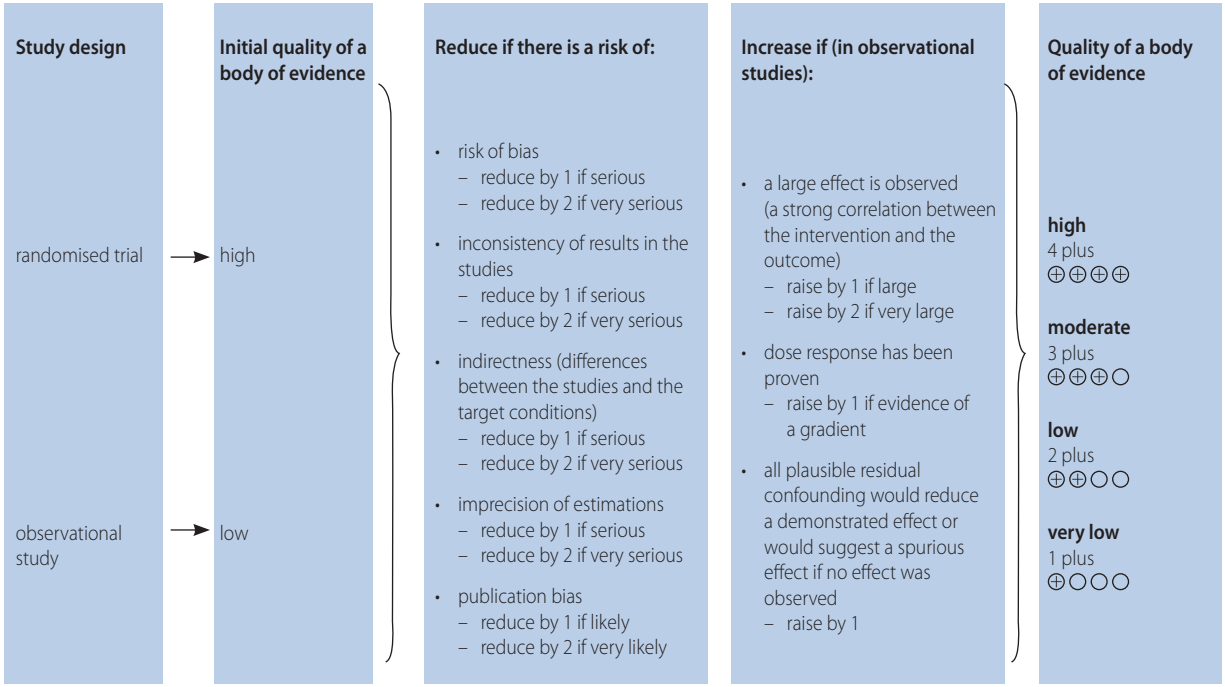

Figure 1. The GRADE approach to rating the quality of a body of evidence – factors influencing the appraisal of quality of evidence

Source: Table compiled based on Leśniak W. (2015). *Od danych naukowych do praktycznych zaleceń – tworzenie wytycznych według metodologii GRADE,* and Balshem H. (2011). *GRADE guidelines: 3. Rating the quality of evidence*

recommendation, recognising two grades: strong or weak (conditional). Although the division into separate grades requires arbitrary decisions, GRADE assumes that this approach has more merits than detriments; among other things, it provides precise instructions for patients, physicians and healthcare system managers. As a result, recommendations can be classified as presented in table II.

Basically, a **strong** recommendation means that the authors are convinced that beneficial (adverse) effects of the intervention substantially outweigh the adverse (beneficial) effects; evidence in this regard (of appropriately high quality) is available. A **weak** (**conditional**, **optional**) recommendation means that while the evidence weighs in favour/against the intervention, the authors are not convinced of the significant advantage (disadvantage) of the intervention, either due to insignificant differences in effects, lack of data or low quality of data. In general, high-quality evidence should provide strong recommendations; however, other factors, such as cost effectiveness or opinions of patients may lead to a weak recommendation. Also, in the case of low quality of evidence, additional factors may justify increasing the strength [8].

It should be underlined that the strength of a recommendation is not equivalent to high priority of such recommendation [8], which is particularly true when more than one

Table II. Description of quality of evidence and strength of recommendation according to GRADE

Quality of evidence	
high	we are very confident that the true effect lies close to that of the estimate of the effect
moderate	we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
low	our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
very low	we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
strong recommendation	in favour of the intervention
	against the intervention
weak recommendation	in favour of the intervention
	against the intervention

Source: Guyatt G. et al. (2013). *GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes,* and Andrews J.C. et al. (2013). *GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation's direction and strength*

recommendation is developed in order to consider co-morbidities or ethnic origin.

The main advantages of the GRADE system include:

- a clear grading of quality of evidence and strength of recommendation,
- a straightforward evaluation of significance of effects of alternative interventions,
- comprehensive criteria for lowering and raising the grades of evidence quality,
- a transparent process of moving from evidence to recommendations,
- recognition of values and preferences of stakeholders,
- an explicit, pragmatic interpretation of strong and weak recommendations for both clinicians, patients and decision-makers.

Due to its comprehensiveness and clarity, the GRADE methodology is presently recognised as a standard for the guideline development process. It is used by the World Health Organisation, the Guidelines International Network, scientific societies, state agencies responsible for guideline development and HTA, e.g., in the United States, Canada, Belgium, and Germany.

The GRADE methodology is mainly applicable for evaluation of drug technologies, as well as surgery or radiotherapy procedures. It may be used for evaluation of other non-drug technologies; however, certain limitations should be expected during evaluation of quality of evidence. When defining the key questions in the assessment of quality of evidence for diagnostic technologies, it is necessary to differentiate clearly between selection of endpoints referring to accuracy of the diagnostic test and results which are of significance to the patients [11]. Moreover, to warrant reliability of evaluation, clear and accurate definition of the assessment criteria, and analysts' experience in application of GRADE methodology are of key significance, since they might cause discrepancies in the interpretation of data and lead to diversified grades with little coherence between individual analysts [12].

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) is a non-profit organisation dedicated to improving the quality, effectiveness and efficiency of healthcare. Its CPGs are aimed at facilitating the decision-making processes in cancer care [13].

According to NCCN, a significant diversity of clinical study types in oncology – from big RCT trials to small retrospective studies – has made it necessary to place greater attention on the experience and opinion of specialists and clinical experts, and take them into account in the course of evaluating scientific evidence. To do so, the NCCN develops its recommendations based on the critical assessment of evidence, combined with the expertise and consensus of a multidisciplinary expert panel, especially in situations where high-quality evidence is lacking. Additionally, since most interventions in cancer treatment have adverse effects, the panel is obliged to evaluate them with attention to efficacy, utility, safety and toxicity [14].

The NCCN categories for recommendations (tab. III), which serve to denominate the strength of recommendation, are determined on the basis of quality of scientific evidence (single studies and overall evidence) and the stance (consensus) of the panel with regard to validity of the intervention. The panel consensus is determined based on voting on incorporating the recommendation. A uniform consensus, allowing the recommendation to be categorised as category 1 or 2A, requires the support of at least 85% of panel members. Consensus leading to the recognition of a recommendation as category 2B requires at least 50% of votes to support the recommendation. On the other hand, recommendations which are associated with substantial differences in opinions with regard to their validity must obtain at least 25% of votes to be included in the guidelines as category 3 [14]. All NCCN recommendations are considered appropriate and the guidelines do not indicate the interventions which in authors' opinions should not be used in the clinical practice, e.g. due to poor balance of benefits and harms.

Table III. NCCN categories for recommendations and categories of preference

NCCN categories for recommendations	
category 1	based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
category 2A	based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
category 2B	based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
category 3	based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
NCCN categories of preference	
preferred intervention	interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
other recommended intervention	other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes
useful in certain circumstances	other interventions that may be used for select patient populations (defined with recommendation)

Source: The National Comprehensive Cancer Network. *Development and Update of the NCCN Guidelines®*

Some of the documents developed by the NCCN, apart from the categories of recommendation, also classify interventions in terms of the categories of preference (tab. III). The scale has been developed, firstly – to describe institutional preferences and those of the panel, thus providing users with information on which recommendations are considered to be of choice; secondly – to describe the scope of the recommended interventions, which address various clinical situations and preferences of patients [14]. However, the NCCN methodology fails to transparently specify how the values and preferences of patients are taken into account during recommendation development.

Undoubtedly, the NCCN guideline process allows for a quick development of detailed recommendations on complex health problems such as neoplasms. However, the factors that allow the guidelines to be kept up-to-date are also their main limitation, with the documents lacking formal and transparent review and assessment of available trials. Thus, Wayant [15] suggests that, while panel members determine the quality of evidence in some fields, in order to enhance the objectivism, applicability and comparability of the NCCN guidelines, the GRADE approach should be adopted. At the same time, the recommendations include only a limited description of the assessed efficacy, safety, quality and consistency of evidence, and financial impact, which are additionally ascribed solely to the systemic therapy.

National Institute for Health and Clinical Excellence

National Institute for Health and Clinical Excellence (NICE) is a British agency responsible, among other things, for publishing guidance in four areas:

- use of both new and existing health technologies by the National Health Service (NHS),
- clinical practice (diagnosis and treatment),
- promotion of health and prophylaxis,
- social care.

The process of development of CPGs published by NICE is mainly informed by the appraisal of intervention's efficacy and cost effectiveness, considering existing circumstances, clinical conditions and patient preferences. Depending on the assessment of these factors, the recommendations can be ascribed a different level of authors' conviction regarding their strength (validity) – some of them can be established on the basis of evidence of higher quality and greater certainty as to the positive effect of the treatment. As a result, NICE guidelines can be ascribed one of three grades of strength of recommendation [16]:

- interventions which must be applied (or must not be applied),
- interventions which should be applied (or should not be applied),
- interventions which can be applied.

According to the NICE methodology, the guidelines are considered to be "strong" if most experts and patients would choose this specific intervention – mostly due to the positive effects of therapy outweighing the adverse ones in relation to the cost effectiveness of a given intervention. However, if the balance of benefits and harms is not that clear, and many patients would not choose a given intervention, although some could decide to do so, the recommendation will be a weak one [16] (tab. IV).

The grading system applied by the NICE, based on the development of recommendations using the appropriate verbs (particularly modal verbs) and grammatical forms, is distinguished by its simplicity and ease of use; still, it only defines the degree of authors' certainty with regard to the application of the intervention. The NICE recommendations do not refer directly to the quality of evidence gathered, although, all of the scientific evidence identified is assessed using the GRADE methodology, and the results of this process are published in an annex to the guidelines [16]. At the same time, despite being very straightforward in its form, one needs to remember that every language is characterized by ambiguity, so the

Table IV. Examples of strength of recommendation designation used by the NICE

Examples of recommendations with different strength of recommendation
recommendations on interventions which must or must not be applied: • provide treatment without undue delay for people who have lung cancer that is suitable for radical treatment or chemotherapy, or who need radiotherapy or ablative treatment for relief of symptoms
recommendations on interventions which should or should not be applied: • offer surgery to people with rectal cancer (cT1–T2, cN1–N2, M0, or cT3–T4, any cN, M0) who have a resectable tumour
recommendations on interventions which could be applied: • consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome

recommendations may not be considered that unequivocal to their user.

European Society for Medical Oncology

European Society for Medical Oncology (ESMO) publishes its guidelines with the aim of enhancing the quality and effectiveness of cancer care. The system for grading recommendations adopted in the ESMO guidelines is based on the Infectious Diseases Society of America-United States Public Health Service Grading System [17]. Determination of the quality of evidence and strength of recommendation is mandatory for every statement, but the methodology does not require a systematic review; instead, it allows for the recommendations to be based on both the evidence gathered in a non-systematic review and expert opinions.

The quality of evidence (referred to by ESMO as the level of evidence) points to the quality of research reports collected (e.g., clinical studies, case / control studies, expert opinions), answering a clinical question and more specifically the number of included studies, their sample size, methodology, risk of bias and heterogeneity. According to ESMO, the strength of recommendation (known as grade of recommendation) considers both the quality of evidence and the significance / magnitude of the effect of the intervention (tab. V). This grade may be either positive (a recommended procedure) or negative (a non-recommended procedure). In order to avoid any interpretation difficulties, every recommendation must be expressed as a positive statement and assigned a strength of recommendation (indicating whether the procedure is to be applied or not). Negative statements are not to be used when formulating the recommendations.

While simplicity is definitely an advantage of the grading system used by ESMO, the limitations of this methodology must be underlined – firstly, there is no obligation to hold a systematic review, thus the recommendations are formulated on the basis of subjectively selected studies, as well as expert knowledge and experience. Secondly, appraisal of the quality of scientific evidence is limited to determination of the study type and, possibly, assessment of the risk of bias (although the tools or criteria applied for this purpose have not been defined). Additionally, the ESMO methodology fails to include any formal procedure of patient involvement or collecting information on patient preferences [18].

Scottish Intercollegiate Guidelines Network

Scottish Intercollegiate Guidelines Network (SIGN) main objective of the SIGN is to improve healthcare by limiting the diversity in both clinical practice and the effects of diagnostic and therapeutic procedures. To achieve this, SIGN develops and disseminates the CPGs describing effective interventions

Table V. The ESMO grading of recommendations

Levels of evidence	
I	evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses well-constructed randomised trials without heterogeneity
II	small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity
III	prospective cohort studies
IV	retrospective cohort studies or case-control studies
V	studies without a control group, case reports, expert opinions
Grades of recommendation	
A	strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	strong or moderate evidence for efficacy but with limited clinical benefit, generally recommended
C	insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	moderate evidence against efficacy or for adverse outcome, generally not recommended
E	strong evidence against efficacy or for adverse outcome, never recommended

Source: The ESMO Guidelines Committee. (2020). *Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores*

based on current scientific evidence. Methods used by SIGN are founded on the GRADE methodology (especially, the appraisal of quality of evidence and strength of recommendation) and follow the quality standards for CPGs described in AGREE II instrument [7]. In order to develop recommendations in accordance with the EBM paradigm, that are both implementable and take into account the patient opinions, SIGN uses the Evidence-to-Decision framework grounded in GRADE [19].

As the guidelines are developed on the basis of consistent evidence, the ultimate wording of the recommendations is usually reached by informal consensus. When this cannot be reached, the evidence is interpreted by an independent supervision team involving external experts, leading to assigning strength to the recommendations, which can be either "strong" or "conditional".

A strong recommendation is made when:

- the evidence is of high quality,
- estimates of the effects of the intervention are precise (that is, there is certainty that the effects will be achieved in practice),
- the intervention assessed has a limited number of negative factors,
- there is a high level of acceptance of the intervention among patients [19].

A recommendation is conditional if:

- the evidence is of low quality,
- there are doubts with regard to the magnitude of the effect that can be achieved in practice,
- the benefits and harms of the therapy must be balanced out,
- the acceptance of the intervention varies among patients [19].

Nevertheless, the particular quality of evidence does not automatically lead to a particular strength of recommendation. High-quality evidence should be associated with strong recommendations, but a consideration of the applicability of published evidence to the target population, its relevance to the NHS and patients, and the balance of benefits and harms may lead to a much lower strength being assigned. Similarly, under some circumstances, when evidence is of lower-quality, but the intervention is characterized by low risk of harm and the problem is sufficiently significant, a strong recommendation can be justified [19]. Where equality, justice and co-morbidities should be accounted for, the authors may prepare several recommendations answering that particular question – one for each subpopulation. Regardless of the circumstances, the ultimate recommendation strength must be specified using one of the grades presented in table VI.

The strong correlation between the SIGN guidelines and requirements of the public payer (the guidelines translate directly to the conditions of provision of benefits) is one of the main factors that determine their high applicability and treatment effects. That said, it is also possibly the main limitation to the guidelines; by assessing the impact of the recommendations on the budget, they may marginalise the significance

Table VI. The SIGN grading for recommendations

The levels of evidence	
1^{++}	high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1^{-}	meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	high-quality systematic reviews of case-control studies or cohort studies. high-quality case-control studies or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	case-control or cohort studies with high risk of confounding or bias and a significant risk that the relationship is not causal
3	non-analytic studies, e.g. case reports, case series
4	expert opinion

Forms of recommendation	
Judgement	**Recommendation**
undesirable consequences clearly outweigh desirable consequences	strong recommendation against
undesirable consequences probably outweigh desirable consequences	conditional recommendation against
balance between desirable and undesirable consequences is closely balanced or uncertain	research is recommended and, possibly, a conditional recommendation for use in clinical studies
desired consequences probably outweigh undesirable consequences	conditional recommendation for
desirable consequences clearly outweigh undesirable consequences	strong recommendation for
Good-practice points	
recommended best-practice based on the clinical experience of the guideline development group	

Source: SIGN (2019). SIGN 50: a guideline developer's handbook

of the intervention for the target population and their impact on the patient's quality of life [20].

Discussion

As presented above, the common characteristics of all grading systems include:

- transparency of determinants influencing the strength of recommendation,
- following the EBM principles,
- being informed by a thorough review of evidence.

Thus, the basic aspects influencing the strength of recommendation are the quality of body of evidence, consistency of results, the type and magnitude of the effects, as well as the level of authors' certainty towards the effect. The approaches vary in terms of the recognition of the authors' support for recommendations and the conditions of the local healthcare system, which is of particular significance in the case of guidelines developed by state agencies. Table VII presents a summary of the factors that can determine the strength of recommendation, as considered in the analysed grading systems.

To add to the confusion, the same designations used in the grading systems may refer to different aspects – for instance, in some guidelines, letters of the alphabet refer to the quality of evidence, in others – to the strength of the recommendation. Additionally, the grading systems also differ in the number of grades in a scale, e.g. quality of evidence scale may vary – from four grades (according to GRADE) to eight (according to SIGN). Regardless of the above, the highest grade is commonly assigned to meta-analyses and RCTs, which constitute the highest methodological standard for original studies. Discrepancies between the recommendations formulated by different groups and the assigned strength of recommendation are related to additional factors and use of varying scales to grade the quality of evidence. As a result, on the basis of the same study, different authors may develop recommendations which will vary in terms of strength.

Conclusions

The role of CPGs is to verify the quality of the most recent scientific evidence and to assess the benefits and harms of a given diagnostic and treatment process (the strengths of individual interventions), instead of imposing a universal approach to patient care, like clinical care standards would.

However, the increasing number of guidelines published impedes proper interpretation and comparison of these documents. The number of available grading systems requires the user to have a thorough knowledge of the methods of their development and factors influencing the recommendations to ensure informed decisions on his(her) part.

The diversity of systems used to grade the strength of recommendation and describe the quality of evidence makes it difficult to compare recommendations developed by different authors – even within one branch of medicine. At the same time, guideline users may have doubts as to the meaning of the applied grades of strength of recommendation. They may believe that the assigned grading refers to the significance of the recommendation, and not to the certainty of the evidence informing it.

To tackle these uncertainties and create a transparent and unambiguous set of recommendations within each healthcare system, it would be advisable to introduce a unified grading system for all the guidelines across each branch of medicine. This would account for the key factors in the target healthcare settings.

Table VII. Factors considered in determination of strength of recommendation by various groups developing guidelines

Factors that determine the strength of recommendation		Organisation				
		GRADE	NCCN	NICE	ESMO	SIGN
quality of body of evidence	study design	+	+	+	+	+
	number of studies / sample size	–	+	–	+	–
	quality of evidence	+	risk of bias	+	risk of bias	+
	consistency of the results	+	+	+	+	+
assessment of effectiveness of the intervention		+	+	+	+	+
balance of benefits and harms / positive or negative effect of the intervention		+	+	+	+	+
degree of the group support for the recommendation		–	+	–	–	–
unanimous consensus of the guideline development group		+	–	+	+	+
level of certainty of the authors of a positive impact of the intervention		+	+	+	+	+
cost effectiveness		+	–	+	–	+
conditions of the target healthcare system		+	–	+	–	+
patients' acceptance of the intervention		+	–	+	–	+

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Pictures in oncology

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The heart as a rare colorectal cancer metastases location

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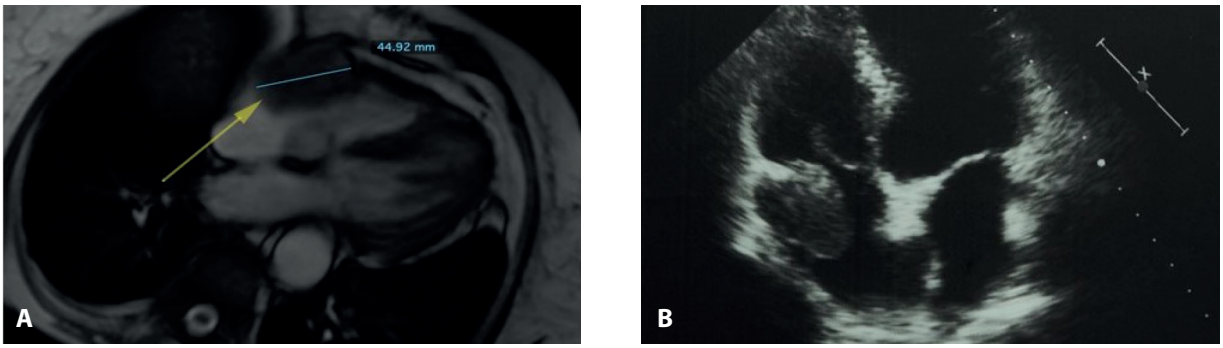

Figure 1. A. MRI: tumor mass with no signs of fat suppression seems strongly connected with the lateral and inferior wall of the right atrium, **B.** ECHO: right atrium tumor mass 50 x 28 mm connected with the lateral wall of the atrium

The most common cardiac primary tumor is the left atrial myxoma. Secondary malignant tumors of the heart are 40–100 times more common than the primary and originate from the lungs, breast, or kidney [1, 2]. A 72-year-old woman with disseminated adenocarcinoma of the colon was admitted to the hospital. An initial hemicolectomy and ablation of liver metastases was performed. Control CT performed after 3 months showed further progression in the liver and new mass in the right atrium. She was referred to 5FU-based chemotherapy. She had no symptoms except nausea. The lab test including Troponin and NT-proBNT were in normal ranges except for the elevated CEA. The ECG was normal. Two-dimensional echocardiography (supp. video) performed routinely before chemotherapy showed a rounded mass adjacent to the wall of the right atrium. Despite chemotherapy, no regression of the cardiac tumor was observed in the echocardiography and the MRI (fig. 1). Only a few cases of colon cancer with right atrium cardiac metastases have been described in the literature. Due to the increasing incidence of malignant neoplasms, metastases to the heart will be more common. Imaging diagnostics is aimed at diagnosing and assessing the advancement of the disease.

Supp. video: Echocardiography of the right atrium mass – see on www.nowotwory.edu.pl

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Invited editorial

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A change in the approach to pancreatic head cancer resection?

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In recent years, we have seen an improvement in the outcome of pancreatic cancer treatment. This is due to a change in the approach to both adjuvant and surgical treatment. Recent advances in systemic treatment, such as the use of FOLFIRINOX regimens (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel, as well as the optimization of local treatment, e.g., stereotactic body radiation therapy (SBRT), have led to an increase in the proportion of patients where a resection is possible. This is especially true for the subgroup of patients with borderline resectable tumors [1].

Moreover, modifications have been made to surgical treatment. These are due to the fact that the status of the mesenteric head resection margin (R0-none *vs.* R1-present tumor cells in the resection margin) is a strong predictor of survival after resection of pancreatic head adenocarcinoma (PHC) [2].

Therefore, a more radical approach has been proposed for the final stage of the pancreatoduodenectomy (PD) performed for PHC. In classical PD, the final stage of the resection part of the procedure (fig. 1) is to ligate and cut the small vessels running between the pancreatic uncinatum process and the superior mesenteric vein (SMV) and the superior mesenteric artery (SMA). Elements of connective tissue, lymph nodes, and nerve plexuses in this area that may be infiltrated by cancer cells are also removed. However, the cutting plane between the pancreas and the mesenteric vessels follows the right edge of the SMV and portal vein [3].

The final stage of PHC resection, performed as described above, is currently controversial for many surgeons. There have been opinions that guiding the cutting plane on the right side of the SMV and portal vein does not allow a complete resection of the tissues located in the space between the left edge of the pancreatic head and the SMA, called the mesopancreas. This space contains fatty tissue, nerve plexuses and ganglia, blood and lymph vessels, and lymph nodes. Moreover, this space has no fibrous capsule or fascia, making it invisible and very difficult to identify during surgery [4].

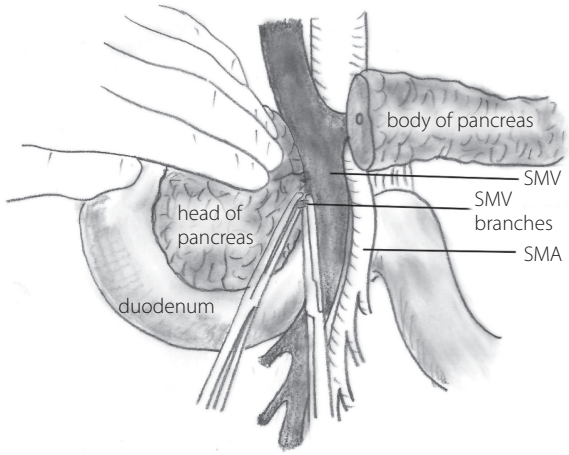

Figure 1. The final step of the dissection requires isolation, division, and ligation of the vascular supply and retroperitoneal attachments at the head of the pancreas. The venous tributaries to the superior mesenteric vein (SMV) are readily identified by retracting the pancreatic head gently to the right and the vein to the left. SMA – superior mesenteric artery [3] (author's modification)

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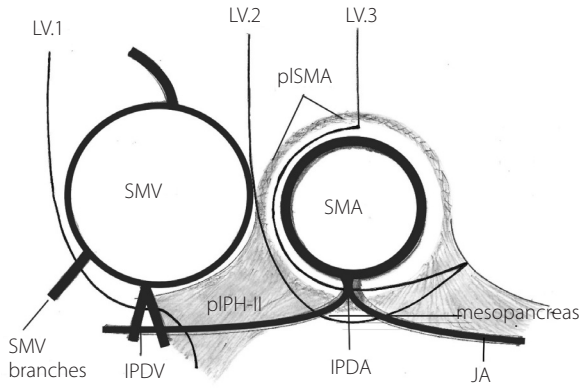

Figure 2. The anatomy and concept of systematic mesopancreas dissection using the supracolic anterior approach [5]. The dissection lines of each dissection level are indicated (own modification). LV.1 – level 1: simple mesopancreas division without nympho node (LN) dissection; LV.2 – level 2: *en bloc* LNs dissection in the mesopancreas by the central vessel ligation technique; LV.3 – level 3: *en bloc* mesopancreas resection with right hemicircumferential pl-SMA dissection for invasive pancreatic head tumor; IPDA – Inferior pancreatoduodenal artery; IPDV- inferior pancreatoduodenal vein; JA – jejunal artery; plSMA – nerve plexus around the SMA; plPH-II – second nerve plexuses of the pancreas head; SMA – superior mesenteric artery; SMV – superior mesenteric vein

In 2015, Japanese surgeons proposed that the extent of mesopancreas excision should be divided into 3 levels depending on the type of tumor (fig. 2). In the first, the preparation plane is on the right side of the SMV. The nerve plexuses around the SMA (pl-SMA), the small arterial and venous branches running to the intestine and the entire mesojejunum are preserved. The indication for level 1resection is that no lymph nodes need to be resected, which is the case for tumors of low malignancy (carcinoma in situ, pancreatic metastases or tumor cysts). At level 2, the mesopancreas is excised in its entirety together with the lymph nodes, plexuses and ganglion (plPH-I) located on the right side of the visceral trunk (VT), with the inferior pancreaticoduodenal artery ligated at the outlet. The line of preparation is on the right side of the SMA, but its periarterial nerve plexus is left intact (plPh-II). The indications for resection at level II are tumors of the papilla of Vater, the distal bile duct, and the duodenum. At level 3, the preparation plane of the SMA is moved even further to the left, so that *en block* with the entire mesopancreas, the periarterial nerve plexus (plPh-II) on its right side is additionally removed in an area of approximately 180 degrees of vessel circumference. This plane of resection is dedicated to ductal carcinoma of the pancreas or locally advanced bile duct cancer [5].

Recently, many surgeons have introduced several advanced modifications of the PD technique in order to improve the distant results of PHC treatment by shifting the pancreatic cut-off to the SMA-VT axis, e.g.,"artery first", "processus uncinatus first", triangle operation, periarterial divestment [6].

Whether shifting the cutting plane from the right side of the superior mesenteric vein to the SMA-VT axis improves the distant results of PHC treatment will be seen in the future after randomized clinical trials have been completed. This does not change the fact that, despite significant advances in multimodal treatment, the search for the optimal technique for PHC resection is still needed.

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Genetics and oncology

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Phacomatoses, genetic testing for personalisation of clinical management (part 1.)

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Genetically determined disorders of tissue development, which are derived from the ecto-, endo- and mesoderm and develop in the early stages of foetal life, referred to as phacomatoses, constitute a large group of diseases predisposing to development of neoplasms. Early diagnosis, including identification of mutations and clinical evaluation, enables introduction of multidisciplinary care for patients with a confirmed diagnosis. Thus, the long-term prognosis and quality of patients' life can be improved. The most common phacomatoses include neurofibromatosis types 1 and 2 and schwannomatosis.

Key words: phacomatoses, neurocutaneous diseases, neurofibromatosis 1, neurofibromatosis 2

Introduction

Phacomatoses, also known as neurocutaneous diseases, constitute a heterogeneous group of genetically determined disorders of development of tissues derived from three germ layers: ecto-, endo- and mesoderm. They are manifested by skin, nervous and vascular lesions. Phacomatoses are associated with a significant increase in the risk of cancer [1]. Management of patients with a diagnosed phacomatosis involves multidisciplinary supervision with particular emphasis on the early detection of neoplastic changes. The most common phacomatoses include neurofibromatosis (neurofibromatosis types 1 and 2) and less frequent disorders, such as the following syndromes: Sturge-Weber, von Hippel-Lindau, ataxia–telangiectasia, Klippel-Trenaunay, Gorlin-Goltz, Schimmelpennin-Feuerstein-Mims, tuberous sclerosis and Osler-Weber-Rendu disease.

Neurofibromatosis

The historical classification (Carey et al.) of 1986 distinguished:

- type 1 neurofibromatosis (NF1),
- type 2 neurofibromatosis (NF2) – acoustic type,
- type 3 neurofibromatosis (NF3) – segmental type,
- type 4 neurofibromatosis (NF4) – familial type,
- type 5 neurofibromatosis (NF5) – the Noonan phenotype [2].

Nowadays, the neurofibromatosis group is defined to include neurofibromatosis type 1, 2 and schwannomatosis, with neurofibromatosis type 1 accounting for 96% of all diagnoses [1].

Neurofibromatosis type 1

Type 1 neurofibromatosis (NF1, MIM # 162200), historically known also as von Recklinghausen disease (after Friedrich Daniel von Reklinghausen, who described two cases of symptoms corresponding to NF1 in 1882), is an autosomal dominant condition with a prevalence of 1 in 3000 worldwide [2].

Clinical symptoms include skin, bone and vascular lesions, which display particular tendency to form benign and malignant tumours.

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Pigmentation disorders are pathognomonic for NF1, but their severity may vary considerably between patients, even within the same family. Typical lesions include *café au lait* spots and excessive pigmentation of the armpits and groin (freckling in axillary and inguinal regions). *Café au lait* spots occur in 95–99% of patients with NF1 [1]. They are often present at birth, and their number and size increase with age. Finding more than 6 spots of a diameter greater than 0.5 cm before puberty or greater than 1.5 cm after puberty is one of the diagnostic criteria for NF1 established at National Institute of Health (NIH) conference in 1988, which are still used as guidelines for the diagnosis of neurofibromatosis [3, 4]. Histopathological examination of pigmented lesions shows hyperpigmentation of the basal layer of the epidermis with macromelanosomes present [1]. These changes are not cancerous, but they constitute a visible cosmetic defect that reduces the patients' quality of life.

Neurofibromas

Neurofibromas occur in 60% of patients with NF1 [1]. These are benign tumours originating in the peripheral nerves' sheath, which may undergo malignant transformation. They proliferate from Schwann cells, epithelial cells, as well as from macrophages, mast cells, fibroblasts and pericytes and are divided into:

- cutaneous neurofibromas,
- subcutaneous/internal neurofibromas,
- plexiform neurofibromas.

Cutaneous neurofibromas appear as soft, sometimes painful and itchy growths that are skin-coloured or purple, can be unifocal or multiple, and cover a large part of the body's surface. Apart from the skin, neurofibromas may develop along the dorsal roots of the spinal cord or arise from nerve plexuses. By expanding and clustering (so-called plexiform neurofibromas – PN), they can compress adjacent anatomical structures and lead to neurological deficits, deformation of bone structures and structural and functional changes in internal organs.

They may transform into a tumour – malignant peripheral nerve sheath tumour (MPNST). The risk of MPNST in patients with NF1 is 1000 times higher in comparison to the general population [5, 6]. The molecular basis of the transformation of plexiform nevi (PN) into MPNST has not been clearly explained, but it has been shown to be influenced by dysregulation of the RAS/MAPK signalling pathway (mitogen-activated protein kinase) and PI3K-AKT-mTOR [7, 8]. Schwann cells accumulated in the tumour mass are stimulated to malignant proliferation by growth factors secreted from the surrounding cells: mast cells, macrophages, and fibroblasts. A trauma – influencing the migration of mast cells – may stimulate neoplastic transformation [7].

The precancerous form of conversion of PN into MPNST is atypical neurofibroma (ANF) [5, 6]. The basic form of treatment for ANF and MPNTS is surgical resection. MPNST develops in 8–13% of patients and is the main cause of death in the course of NF1 [7, 9]. Surgical treatment with a large margin of the area around the tumour does not fully prevent local recurrence, which occurs in 25–37% of patients [10]. Pharmacological treatment of MPNST is ineffective. However, using doxorubicin, etoposide and ifosfamide in selected groups of patients may effectively reduce disease progression in metastatic and inoperable forms [11]. Inhibitors of the mTOR pathway, which are currently studied, seem to be promising [12]. The efficacy of other drugs used in clinical trials has not been demonstrated: tyrosine kinase inhibitors, erlotinib, sorafenib [13].

Cancers

Patients with NF1 have an increased risk of developing brain tumours compared to the general population. Brain tumours occurring in patients with NF1 are most often optic nerve gliomas (15–20% of patients), gliomas of the brain stem, diencephalon and cerebellum [14].

Pilocytic astrocytoma (astrocytoma pilocyticum) is a low-grade tumour (WHO I) which may undergo spontaneous remission in patients with NF1. During the time of the patient's development, so-called unidentified bright objects (UBO) may be observed, which are non-cancerous changes in the brain and dynamically arise and disappear. Their occurrence may influence the behavioural disorders of the ADHD type, mental retardation or epilepsy observed in patients [15].

Other cancers include:

- endocrine tumours, such as pheochromocytoma of the adrenal gland found in 5% of patients with NF1 compared to below 1% in the general population [1]. Key clinical symptoms of phaeochromocytoma are arterial hypertension, arrhythmias, sudden flushing,
- gastrointestinal stromal tumours (GIST) occur in approximately 20% of patients with NF1 [16]. They originate from the mesenchyme and arise from Cajal cells. Often small, long asymptomatic, they are detected during endoscopic and imaging examinations of the abdomen,
- endocrine tumours of the gastrointestinal tract that may occur in the course of NF1 include somatostatinoma and gastrinoma [16].

In childhood juvenile myelomonocytic leukemia (JMML), Wilms' tumour or rhabdomyosarcoma may also appear, as the risk is 20 times higher in patients with NF1 compared to the general population [1].

Ocular symptoms

Ocular symptoms include hamartomata-like Lisch nodules, which derive from pigment cells, fibroblasts and mast cells, presenting with characteristic irregularities of the iris in shades of brown [2]. These changes do not affect visual acuity and occur in over 90% of adult patients (the number increases with age). Optic gliomas (cancers of the anterior segment of the visual pathway) are an important manifestation of NF1. They are manifested by atrophy of the optic nerve and progressive loss of vision, as well as exophthalmia, nystagmus (described as

see-haw nystagmus) and symptoms that result from increased intracranial pressure. Optic nerve gliomas occur in about 15% of patients with NF1 and association of the tumour with NF1 accounts for 50% of all cases of this type of cancer [14]. Histologically, it is most often pilocytic astrocytoma. Its location limits the possibility of surgical intervention. Other ophthalmic symptoms found in NF1 include choroidal nevi and congenital glaucoma [17].

Skeletal symptoms

Skeletal symptoms include scoliosis, mainly of the cervico-thoracic region, pseudo-joints of long bones and bone dysplasia. Patients' height may be reduced due to bone deformities, and bone fractures are common. The mechanism of development of these changes has not been clarified, however, insufficient levels of vitamin D_3 and lower bone density compared to the general population were observed in patients with NF [1, 18].

Cardiovascular symptoms

Cardiovascular changes include, but are not limited to, narrowing of the pulmonary trunk, cerebral and renal arteries, which can lead to hypertension, myocardial infarction, and heart failure.

Treatment of neoplasms diagnosed in the course of type 1 neurofibromatosis is based on therapeutic protocols for forms unrelated to NF.

Diagnostic criteria for neurofibromatosis type 1

For diagnosis of type 1 neurofibromatosis, at least two of the following symptoms must be present [18]:

- six or more skin lesions of the *café au lait* type of a diameter greater than 5 mm in a child before puberty and greater than 15 mm after puberty,
- increased pigmentation of the armpits and groin,
- optic nerve glioma,
- two or more neurofibromas or one plexiform neurofibroma,
- first degree relative with neurofibromatosis type 1,
- two or more Lisch nodules (pigmented haemartomatous nodules of the retina) visible on a slit lamp examination,
- characteristic bone changes (dysplasia of the sphenoid bone, thinning of the cortex of long bones with or without pseudoarthrosis).

Genetics

Pathogenic variants of the *NF1* gene constitute the molecular basis for the development of neurofibromatosis type 1. The *NF1* gene is located on the long arm of chromosome 17 (*locus* q11.2) and encodes a 2818-aminoacid cytoplasmic protein, of 320kDa in mass, neurofibromin 1 (NF1, MIM * 613113) [19]. This gene contains 61 exons, 5 of which are subject to alternative splicing (9a, 10a-2, 23a, 43 and 48a), thus leading to the formation of different isoforms of neurofibromin. There are five isoforms of the protein known and their expression is characteristic for specific cells and / or tissues [20]. Neurofibromin is a multifunctional protein involved in numerous signalling pathways which regulates a number of cellular processes and plays a significant role in embryogenesis [21]. The presence of neurofibromin is detected in most cells of the body, but its highest expression is observed in cells of the nervous system such as astrocytes, oligodendrocytes and Schwann cells [20].

The main function of neurofibromin is to negatively regulate the Ras pathway by negative feedback through the activation of GTPase (GTPase activating protein – GAP). GAP regulation involves acceleration of the hydrolysis of GTP (guanosine-5'-triphosphate) associated with *Ras* to GDP (guanosine-5'-diphosphate) – by increasing the intrinsic activity of Ras GTApase. This "switches" the *Ras* oncogene to its inactive form [19]. Ras pathway proteins are encoded by the *HRAS*, *KRAS* and *NRAS,* genes and their protein products play a key role in such cellular processes as apoptosis, cell cycle, proliferation, differentiation, or migration of cells [20]. Because of its function, *NF1* was classified in the group of suppressor genes (antioncogenes). Deficiency of the functional NF1 protein (NF1–/–) leads to a disturbance of cell homeostasis and lack of control over the Ras pathway, and consequently to uncontrolled proliferation. This in turn, may contribute to the initiation of the neoplastic transformation process. The catalytic activity of the *NF1* depends on the central part of the protein, referred to as the GAP-related domain (GRD) [22].

The heterozygous mutation of the *NF1* is responsible for approximately 95% of NF1 cases. In about half of the cases, the pathogenic mutation is inherited from one of the parents (in an autosomal dominant manner), while in the remaining 50% it is a *de novo* mutation [23]. The *NF1* gene has the greatest mutation rates among human genes and to date, more than 2600 pathogenic variants thereof are known [23]. The NF1 mutations are characterised by complete penetration to adulthood and variable expression as a very wide spectrum of its expression is observed even in members of the same family (clinical symptoms, phenotype).

With a few exceptions, there are no data to show a correlation between the type of mutation and the clinical course of NF1 (genotype-phenotype correlation). The course of NF1 is extremely diverse, not only among members of the same family (having the same mutation), but even in individual patients at different times of their lives. There are some exception from the presented above:

- the group of patients with a large deletion that includes the *NF1* gene and the adjacent regions. Their phenotype is more severe than in patients with mutations within the gene. Facial dysmorphic features, somatic hypertrophy, cognitive impairment, ADHD and the early appearance of a large number of cutaneous neurofibromas are observed [24],
- the group of patients with deletion of three base pairs in exon 17 (c.2970-2972 delAAT), which is associated with

a milder disease course. Characteristic pigmentation features are observed, but cutaneous and plexus neurofibromas are absent [25],

- the group of patients with several variants of missense mutations contributing to substitution of other amino acids replacing arginine at codon 1809. These patients have *café au lait* spots, learning disabilities, shortness and lung stenosis, but no cutaneous neurofibromas and no clinically visible plexus neurofibromas [26].

There is also a form of NF1 that only affects certain parts of the body. This is called the segmental form. *NF1* mutations are confined to the symptomatic areas of the body only. Therefore, there is no constitutional mutation in lymphocytes or fibroblasts, but only in cells from the segment affected by the disease. Most often, this form results from the appearance of the *de novo* mutation during embryogenesis (mosaicism) and usually does not affect germ cells (no risk of transmission of the disease). This disease is very difficult to diagnose [27].

Genetic testing

Diagnosis of NF1 is basically a clinical one, but genetic tests which allow identification of a mutation within the *NF1* gene play an increasing role, especially for patients with suspected disease who do not meet the clinical criteria.

The recommended method is analysing the genome DNA (gDNA) sequence or only encoding sequence (cDNA) performed together with an analysis of rearrangements (microdeletion of individual exons) and/or deletion of the entire *NF1* [28]. This approach identifies 95% of pathogenic *NF1* variants in people meeting the NIH (US National Institutes of Health) diagnostic criteria. Pathogenic variants may occur throughout the whole *NF1* gene (no hot spots). They vary, ranging from, among others, single nucleotide substitutions, small insertions to deletions (which may alter the reading frame or not), and also, approximately 22–30% of the mutations affect splicing. Therefore, the methods of cDNA analysis seem to be more valuable in terms of diagnostics [28, 29]. In cases of clinical suspicion of a microdeletion phenotype, identification of the *NF1* gene deletion can be achieved using the following tests: FISH (with a specific probe), MLPA, qPCR or an array comparative genomic hybridisation test (aCGH). The loss of the *NF1* gene may be caused by chromosomal aberrations, which are detected in the cytogenetic test (most often translocations or inversions of chromosome 17 with the break point at q11.2). Chromosomal aberrations are responsible for NF1 in less than 1% of those affected by the disease [28].

Application of various algorithms allows identification of changes at a different level of effectiveness [28]:

- classic cytogenetic test – the aberration is detected in about 1% of patients,
- deletion analysis of the entire *NF1* gene or its part – about 10%,
- gDNA mutation analysis – 60–90%,
- algorithm consisting of cDNA and gDNA analysis and rearrangement / deletion of the *NF1* gene – above 95%.

It is also worth mentioning that recent years have brought enormous development in genetic research and access to next-generation sequencing (NGS) platforms is increasingly easy, which allows for quick diagnostics. Currently, many companies offer gene panels for the analysis of various forms of phacomatoses, which means that several genes of key importance are sequenced simultaneously, e.g., *NF1*, *NF2*, *SMARCB1*, *SPRED1*, *VHL*, *TSC1* or *TSC2*.

Genetic counselling

Identification of the pathogenic variant of the *NF1* gene is extremely important for people in childbearing age, as it enables reproductive and family counselling – prenatal and preimplantation diagnostics are possible. Anyone carrying a *NF1* mutation has a 50% risk of passing it on to their offspring. However, if a child from a previous pregnancy was diagnosed with *NF1* mutation, but no such change was found in the parents, the risk of having another child with the disease is low [30]. On the other hand, germline mosaicism in one of the parents cannot be ruled out (mutation present only in germ cells). This involves significantly higher risk of another child's having the disease. Prenatal molecular tests can be performed on DNA isolated from trophoblast villi or amniocytes.

Genetic counselling is crucial for couples who decide to undergo prenatal NF1 testing due to the wide spectrum of symptoms and variable expression of the disease [30]. Life expectancy of patients with NF1 is about 8 years shorter than in the general population, especially due to the development of malignant neoplasms and vasculopathy [28].

Type 2 neurofibromatosis

Type 2 neurofibromatosis (MIM # 101000) is an autosomal dominant disease of a frequency of 1:25,000–50,000 [31]. In 50% of cases NF2 mutation is inherited, and the other 50% are *de novo* mutations. The frequently observed mosaicism affects clinical symptoms of the disease.

Type 2 neurofibromatosis, like NF1, is a predisposing condition to neoplasms. The clinical picture is dominated by symptoms related to formation of schwannomas within the cranial, spinal and peripheral nerves, meningiomas, which may be located intracranially and intra-vertebrally, and ependymomas.

Bilateral auditory nerve vestibular neuroma (*vestibular schwannoma*) is pathognomonic for type 2 neurofibromatosis and occurs in 90% of patients [1]. Tinnitus, progressive retrocochlear hearing loss, dizziness and vertigo are the predominant symptoms in these patients. In the late stage of the disease, nausea and vomiting may occur. NF2 vestibular neuroma differs from neuromas that occur sporadically with polyclonal hyperplasia originating from distinct neoplastic cell lines that present a distinct type of *NF2* mutation. This

leads to lobularity identified in radiological examinations [32]. The increasing tumour mass causes progressive hearing loss, and if it enlarges significantly, it may compress the brain stem and trigger symptoms related to involvement of the facial nerves. Surgical treatment, which is the mainstay of the therapy, is technically difficult, and the number of relapses is more frequent in hereditary than in the sporadic form – 44% *vs.* 1.3% [1]. In the case of NF2-associated schwannoma, there is an increased risk of malignant transformation in response to radiotherapy, which limits the possibility of using this type of treatment [1]. There are attempts at using bevacizumab in chemotherapy, which is an inhibitor of vascular endothelial growth factor (VEGF) [33].

Schwannomas of other intracranial and peripheral nerves lead to paresis, e.g., facial muscles paresis (Bell's palsy), strabismus and sensory disturbances. In children, symptoms of the polio type with lower limb involvement can be observed [31]. Intracranial tumours, i.e., meningioma, glioma, ependymoma, may cause focal symptoms, convulsions, headaches, excessive drowsiness, vomiting with increasing intracranial pressure - mass effect. Meningiomas occur in approximately 50% of NF2 patients, largely in childhood, when the coexistence of meningiomas and NF2 is approximately 20% [1]. Ependymomas, which are relatively rare compared to other types of neoplasms in NF2, are located mainly intramedullary in the cervical region and form characteristic corals (string of pearl) in the radiographic image [1].

Cranial neuromas and meningiomas are reported in about 50% of patients, neuromas of spinal nerves and peripheral trunks – In 40% of patients [1]. While meningiomas significantly worsen the prognosis and are a common cause of death of patients with neurofibromatosis, ependymomas remain asymptomatic for a long time and are detected during periodic examinations in people with this disease.

Visual disturbances in patients with NF2 result from presence of optic nerve meningiomas, hamartoma-type tumours of the retinal pigment epithelium and posterior subcapsular cataract. On the other hand, skin lesions of neurofibroma character are less frequent than in NF1, and they characteristically grow hair. Subcutaneous neurofibromas, like *café au lait* spots are not numerous or may not occur at all.

Diagnostic criteria for neurofibromatosis type 2 – Manchester criteria

Leading criteria:

- bilateral tumour of the VIII nerve (shown in imaging – MR / CT or confirmed histologically),
- first degree relative with neurofibromatosis type 2 and unilateral tumour of the VIII nerve,
- first-degree relative with neurofibromatosis type 2, and finding two of the following: neurofibromas, meningiomas, schwannomas, gliomas, juvenile posterior subcapsular lens opacities.

Additional criteria:

- unilateral tumour of nerve VIII and any of the following: meningioma, glioblastoma, neurofibroma, schwannoma, posterior subcapsular lens opacities,
- multiple meningiomas (two or more) and unilateral tumour of the VIII nerve or any of the following: glioma, neurofibroma, schwannoma, cataract [1].

Genetics of neurofibromatosis type 2

The *NF2* gene is located on the long arm of chromosome 22 (*locus* q12.2), encodes the protein called merlin (other names schwannomin, neurofibromin 2, MIM * 607379) composed of 595 amino acids weighing 70 kDa. The gene contains 17 exons, one of which is alternatively spliced. There are at least 8 different isoforms of this protein known [34]. Merlin is an acronym for moezin-ezrin-radixin-like protein, because this protein displays high homology with the cytoskeleton-related protein family 4.1. Merlin is involved in the formation of the submembrane cellular cytoskeleton, it connects actin fibres with the cell membrane or membrane glycoproteins. Like the *NF1* gene, *NF2* is a suppressor gene and its function is to inhibit cell proliferation (negative growth regulator), and to weaken adhesion and migrations, which are characteristic of neoplastic processes. Merlin is expressed in many tissues, especially in neurons and Schwann cells [35].

The genetic background of NF2 involves pathogenic alterations of the NF2 gene. NF2 is inherited as an autosomal dominant and fully penetrant disease. About 50% of people with NF2 have an affected parent, and the other 50% develop the disease as a result of a *de novo* pathogenic variant. Mosaicism is frequently observed in NF2, affecting 30–60% of cases with the *de novo* mutation. This means that only some of the patient's cells have the pathogenic lesion (mutated and wild-type alleles) and some have normal form of the gene (both wild-type alleles) [36]. Therefore, such a change may remain unidentified in standard genetic tests. The mosaic form is associated with a milder course of the disease and may be confined to certain areas of the body. In such a case, the risk of passing the change on to offspring is lower than 50%. It depends on the number of reproductive cells with the pathogenic variant. However, if the change is passed on to the offspring, a more severe phenotype will be observed than that of the parent due to the fact that the child has mutations in all cells of the body [36–38]. A mosaic genotype can be detected by analysing the DNA from the tumour. If the same lesion is found in two tumours, the patient's offspring can then be tested for this genetic change [37]. As in NF1, after identifying the pathogenic variant of *NF2* in the family, prenatal testing and genetic testing before implantation are possible.

Regarding the genotype-phenotype correlation, it was found that patients with NF2 caused by constitutional nonsense mutations (premature stop codon) or frame shift mutations (which lead to a shortening of the protein product)

have a more severe disease compared to those with missense mutations (protein product of correct length) and to people with gene deletion (no protein product) [39]. Further, the differentiated phenotype is influenced by mutations at the splice sites. Patients with 5 'mutations have a more severe disease course compared to patients with mutations in 3' region. The type of mutation affects the relative risk of death, too. On the other hand, patients with missense mutations have a lower risk of death compared to patients with nonsense changes or frame shift [38].

Genetic testing

As in the case of NF1, a diagnostic approach to identifying the underlying NF2 lesion requires many steps. Depending on the phenotype, one can analyse the sequence of a single gene or a panel of several key genes, or use aCGH, exome sequencing, exome arrays or genome sequencing [40].

Differential diagnosis

When differentiating phacomatoses, it is necessary to take into account syndromes of phenotype similar to neurofibromatosis, including characteristic skin changes and a tendency to neoplastic growth.

Legius syndrome is an autosomal dominant genetic disorder. It is characterised by skin pigmentation disorders with no accompanying features as in NF1. Difficulties in early diagnosis result from the similarity of both diseases and the varied expression of NF1 phenotypic traits in individuals. In Legius syndrome, skin manifestations include spots of the *cafe au lait* type (at least six), the number of which increases with age, and increased pigmentation of the armpits and groin. Macrocephaly, shortness, chest deformities, cognitive deficits, ADHD and retarded development may occur, too. However, neurofibromas, Lisch nodules and gliomas of the visual pathway – typical of NF1 – are not found. Correct differentiation of Legius syndrome from neurofibromatosis 1 is extremely important due to differences in prognosis, which is significantly better in the case of Legius syndrome compared to NF1 [40, 41]. The genetic background of Legius syndrome involves mutations in the *SPRED1* gene located on the long arm of chromosome 15 (locus q13.2). Similarly as in NF1, the SPRED1 protein is a negative regulator of the RAS-MAPK pathway [41, 42].

Among other diseases that require differentiation from neurofibromatosis 1 and which include manifestation of *cafe au lait* spots, the following should be mentioned:

- constitutional mismatch repair deficiency (mismatch repair genes – *MMR*, *MLH1*, *MSH2*, *MSH6*, *PMS1*),
- multiple familial *café au lait* spots,
- syndromes:
  - McCune-Albright (*GNAS* gene),
  - Noonan (*PTPN11*, *SOS1*, *RAF1*, *KRAS* genes),
  - Noonan with multiple lentigines (genes *PTPN11*, *RAF1*),
- multiple benign neoplasms, including hamartoma type tumours in syndromes:
  - Proteus (*AKT1* gene),
  - Cowden (*PTEN*, *KLLN*, *WWP1* genes)
  - numerous orbital lesions of the neurofibroma type.

People with a suspicion of these diseases require genetic diagnosis, and if the diagnosis is confirmed, the entire family should obtain genetic counselling.

In Poland, from 15 June 2020, a pilot program is implemented in the field of coordinated medical care for patients with neurofibromatosis and related rasopathies based on the regulation of the Minister of Health. The objective of the programme is to improve effectiveness of diagnostics and treatment as well as early detection of health problems characteristic for this group of patients. Patients included in the program receive comprehensive care from a team of specialist physicians, including neurologists, psychiatrists, endocrinologists, otolaryngologists, surgeons, orthopaedists and others – depending on individual needs.

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