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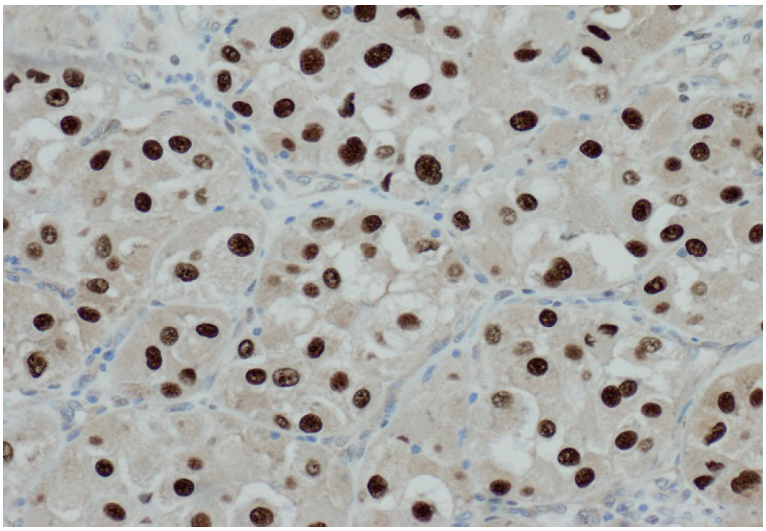

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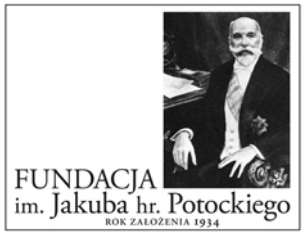

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Contents

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What was supposed to be the role of a coordinator of oncological treatment, and what is it really like?

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Introduction. Due to the multidisciplinary nature of oncological treatment, it is necessary to coordinate it properly. In response to this need, an idea emerged to create a new profession in the system of oncological care, the so-called oncological treatment coordinator. The aim of the study was to assess the actual role of coordinators in hospitals in Poland.
Material and methods. The study was carried out by means of a questionnaire among persons employed as coordinators and persons who act as coordinators within additional duties.
Results. The study involved 95 coordinators from various centers in Poland, half of which were recruited on purpose as coordinators. Less than half (40%) have received training on their work. The main task of the coordinators is to ensure that the documentation related to the patient's Diagnostic and Oncological Treatment Card (DiLO) is complete, to set appointments for diagnostic tests and visits to doctors' offices and to cooperate with medical statistics departments. Only half of the coordinators inform or provide non-medical support to the patient. Coordinators face very different difficulties in their work.
Conclusions. Coordinators are a valuable professional group in the Polish oncological care system. However, there is a lack of clearly defined tasks, systematic training and support.

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Key words: coordinator, oncology package, cancer patient care system

Introduction

Advances in technology and medicine have led in recent years to the introduction of various new methods, both diagnostic and therapeutic, for the diagnosis and treatment of cancer patients. Diagnostics and treatment of cancer have become more complex, require the participation of many specialists, and often require diagnostics and treatment in different – sometimes distant – centers. This brings new challenges for oncological care, including the need for proper integration and coordination of diagnosis and treatment.

This problem was noticed many years ago. In oncological centers in Poland, attempts have been made to coordinate oncological activities in many ways, e.g. by arranging so-called "multidisciplinary meet-ups", creating organ clinics, assigning specialists to treat particular types of tumors. Thanks to the work of many specialists from the oncological community, a document entitled *Strategia walki z rakiem w Polsce 2015–2024* (Strategy for Combating Cancer in Poland 2015–2024) was created in 2014, which, among other things, included the idea of creating a new profession in the system of oncological

care, the so-called coordinator of oncological treatment. The role of the coordinator of oncological treatment was to be a comprehensive and individual help for the patient to move efficiently in the health care system and quickly pass through the successive stages of oncological diagnosis and treatment. It is well known that a person who is suspected or has already been diagnosed with cancer faces various problems, not only of a medical nature, but also of an organizational, social, legal, psychological or spiritual character. Thus, a patient suffering from cancer requires not only efficient and timely diagnostics and prompt implementation of proper oncological treatment, but also care and support in non-medical areas at individual stages of diagnosis and treatment.

The coordinated model of oncological care was to create a new quality in the Polish healthcare system. The role of the coordinator of oncological treatment was to support a patient with cancer during diagnostics and oncological treatment, both in organizational terms and to provide them with help and support in the remaining areas of life, which are significantly affected by the suspicion and diagnosis of cancer. Therefore, such a person should not only have the skills and appropriate competence to organize oncological care, but should also have basic medical, legal, administrative, psychological and social knowledge and support skills in these areas. The persons acting as coordinators of oncological treatment should therefore be covered by an appropriate training program developed by a team consisting of representatives of various disciplines: medical, social, legal and psychooncological ones. Such training was to take place at the faculties of public health at medical faculties of universities.

The *Regulation of the Minister of Health of October 20, 2014 amending the Regulation on guaranteed services in the field of hospital treatment* introduced the obligation *to appoint a so-called Coordinator [...], whose tasks include in particular providing the patient with information about the organization of the treatment process and its coordination, including ensuring cooperation between entities within the framework of comprehensive patient care*. However, the Regulation did not specify the specific tasks and competences assigned to the coordinating function. Other solutions introduced at the same time – in particular the rules of accounting and handling the Diagnostic and Oncological Treatment Card (DiLO) – required the providers to carry out a number of administrative activities, which the hospitals have just handed over to their coordinators. It seems that, as a result, the role of the majority of coordinators appointed to operate in hospitals in accordance with the Regulation has in practice been reduced to an informational and administrative role only.

The aim of the work was to assess what is the real role of persons called coordinators in hospitals in Poland, what their duties are, who they are by profession, where they get the knowledge needed to perform those duties and what difficulties they encounter while performing their work.

Material and methods

The study was conducted among persons employed as coordinators and persons who act as coordinators within additional duties while being employed in other positions. In the first stage of the study, a list of centers in Poland which have concluded an agreement for the provision of oncology package services was drawn up based on data from the National Health Fund (NFZ) and the Ministry of Health – Health Needs Maps. 361 hospitals were then contacted by phone and it was verified whether individual centers actually provided services as part of the oncology package and whether there were persons employed as coordinators. One hundred and nine centers were excluded due to the fact that the services of the oncology package are provided sporadically or not at all and there were no person acting as coordinator in these centers. In 117 centers the coordinators could not be contacted or did not agree to participate in the study. In the remaining 135 hospitals, the coordinators agreed to take part in the study, eventually 95 coordinators from 75 centers returned the completed questionnaire or participated in a telephone interview. Among the above 75 centers, there were 15 multi-profile centers (which provide services in oncological surgery, radiotherapy and systemic treatment) and 60 single or dual-profile centers where no radiotherapy was performed. Thirty-two respondents (34%) are coordinators working in multi-profile oncology centers, 63 respondents (66%) are coordinators from smaller centers. The first stage of the study, consisting in drawing up a list of centers, was carried out from May to June 2019, while the study was conducted from July to October 2019.

The study was carried out by means of a questionnaire drawn up for the purpose of this study. The questionnaire was sent by e-mail directly to the coordinators who agreed to the participate in the study and sent back to the researcher or completed by the researcher during a telephone conversation with the coordinator. The study was voluntary and anonymous.

The analysis of the data was carried out using descriptive statistics and the chi2 test was used to compare proportions in subgroups. The statistical significance level of $p < 0.05$ was assumed. The statistical analysis was carried out using STATISTICA software, version 13.3. The project was implemented and financed within the statutory activities of the Fundacja Onkologia 2025.

Results

The study covered all centers which provide services within the scope of oncology package in Poland. The participation in the study was approved by the persons acting as coordinators in 135 out of 361 centers identified as the oncology package implementers. Finally, 95 coordinators representing all voivodeships returned the questionnaires (Fig. 1.).

Half of the examined coordinators (49 persons, 52%) were recruited on purpose as coordinators, the remaining 46 per-

Figure 1. The number of coordinators who took part in the survey in particular voivodeships in Poland

sons (48%) perform the coordinator's tasks as part of additional duties, working in other jobs. This group consists mainly of nurses (18 persons, 39%), administrative staff (16 persons, 35%) and medical secretaries/medical admissions clerk (11 persons, 24%). In one case, it was a physician (Fig. 2.).

In multi-profile centers, significantly more often than in single or dual-profile ones, persons were deliberately employed as coordinators (75% *vs.* 40%; p = 0.001).

Less than half of the coordinators surveyed (38 persons, 40%) have received any training concerning their work: 23% of all the coordinators have either received training conducted by the NFZ (National Health Fund) or received professional assistance from the NFZ employee, 29 people (31%) have taken part in internal/on-the-job training organized by the employer. Almost half of the coordinators (49%) stated that they gained knowledge on their own on a trial-and-error basis, 41 people (43%) declared that they gained knowledge mainly from the exchange of experience with coordinators of other centers, or from physicians who took part in case consultations in various hospitals and therefore had more experience and

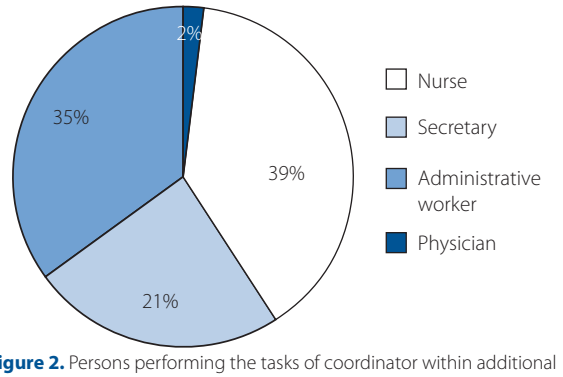


Figure 2. Persons performing the tasks of coordinator within additional duties, employed in other positions

knowledge. The coordinators surveyed assessed that drawing on the experience of others was for them the most valuable form of gaining knowledge about how to perform the function of coordinator (Fig. 3.).

It turned out that individual coordinators carried out similar activities as part of their duties. Their main task is to ensure that the documentation related to the DiLO card is complete, e.g. they record in the medical records the case consultation and its decisions, they set appointments for diagnostic tests and visits to doctors' offices, they cooperate with medical statistics departments in order to properly account for oncological services (Fig. 4.).

These tasks did not differ depending on the type of center (multi-profile centers *vs.* single or dual-profile ones), except for the coordinator's participation in case consultations. Indeed, more often than not, coordinators were present at case consultations in multi-profile centers (p = 0.03) (Tab. I).

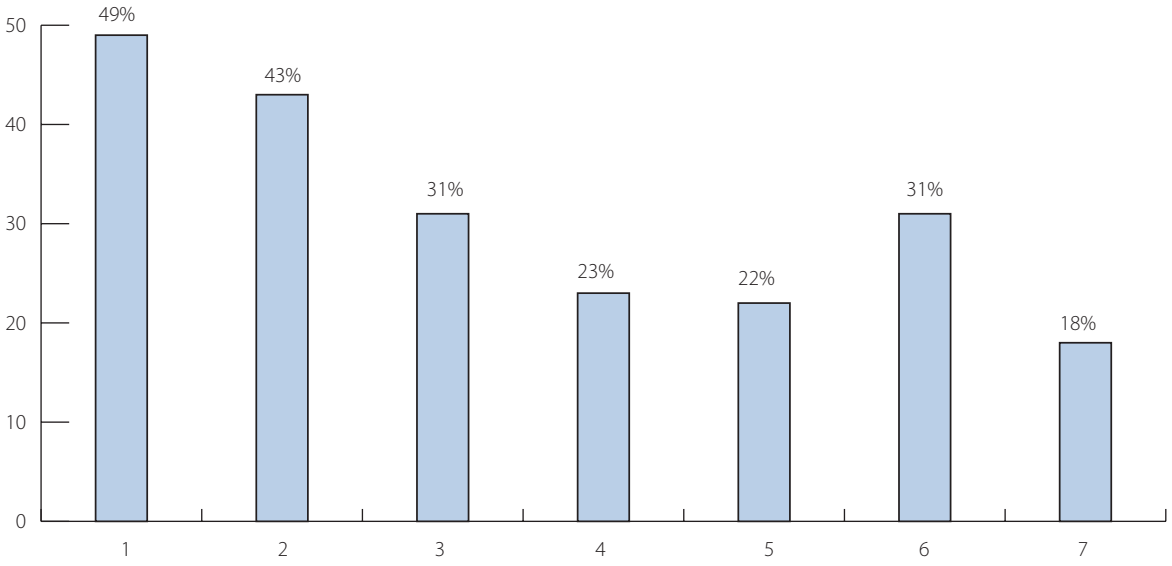
Almost all coordinators (97%) have contact with patients. Most often this contact includes informing patients in person or by phone about fixed dates of diagnostic tests, dates of doctors' visits, a date commencing the treatment (81%) and providing practical advice on tests/treatment (71%). Only half of the coordinators (51%) provide patients with information about the possibility of obtaining non-medical support, e.g. from a social worker, the same number (51% of respondents) provide any non-medical support on their own (Fig. 5.).

There were no significant differences in the frequency and type of contact between the coordinator and the patients depending on the type of center (multi-profile centers *vs.* single or dual-profile ones).

A coordinator devotes 2 to 51 hours per week (on average 26.4 ± 13.9 hours, median 36 hours) to work. In the surveyed centers, a case consultation takes place at a frequency from 1 to 2 weeks to 6 times a week (average 2 times a week, median once a week). The duration of one case consultation depends on the number of patients and lasts from 0.5 to 7 hours (average 2.4 ± 1.4 hours, median 2 hours).

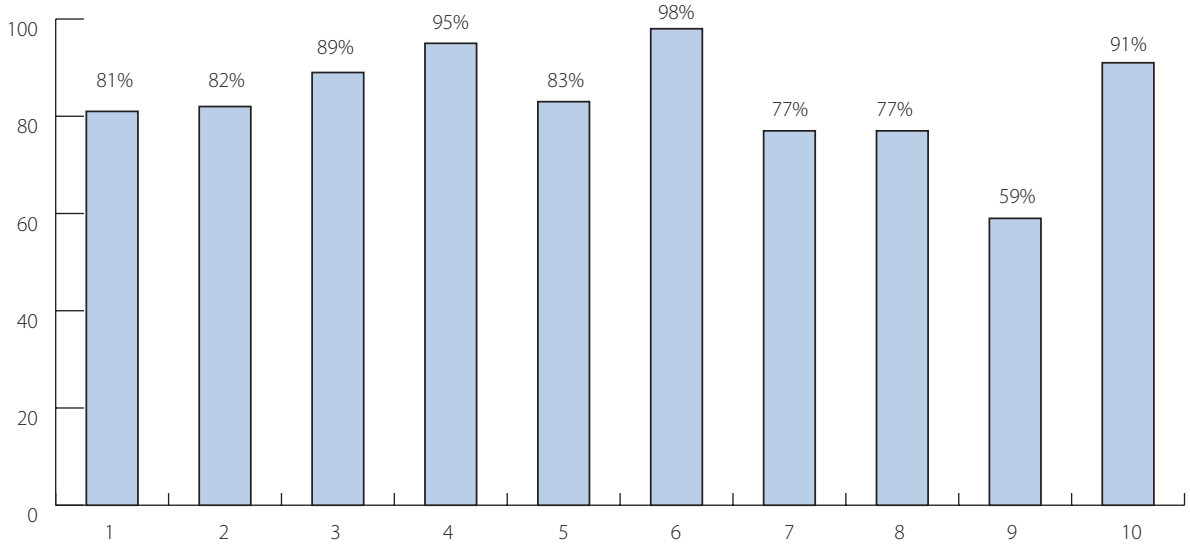
Only one third of the respondents (34%) receive an additional remuneration for performing the duties of a coordinator, e.g. in the form of a bonus, of which 12 people (24.5%) employed as a coordinator and 20 people (43.5%) perform the duties of a coordinator within additional duties.

Coordinators face very different difficulties in their work. A quarter of the respondents indicated difficulties in cooperation with medical personnel, i.e. "indifference" of other employees, low interest of physicians in the subject of DiLO card, lack of respect for DiLO rules by physicians. Fourteen percent of persons indicated problems at the primary care level, such as incorrect issuing of DiLO cards, incorrect informing patients about the purpose of issuing the DiLO card, wrongly informing patients about centers that have a contract to provide services as part of an oncology package or a refusal to issue the DiLO card. The problem at the level of cooperation between



1. Trial and error principle
2. **Consultation with other coordinators**
3. Independent search for information
4. Initial training by NFZ/Assistance of an NFZ employee
5. Previous employee/coworker/RUM accounting department
6. Internal/on-the-job training organized by the employer
7. External training organized by third party companies

Figure 3. Sources of coordinators' knowledge

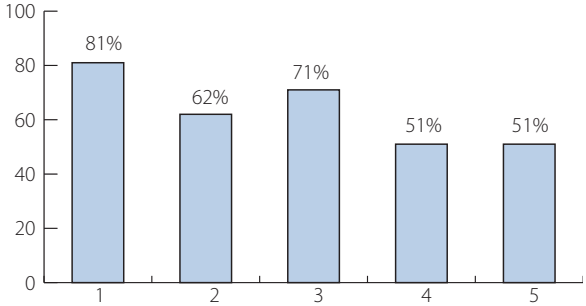


1. Setting up DiLO cards
2. Attendance at case consultations
3. Coordinating the patient's treatment plan established by the case consultation (setting appointments, examinations, notifying the patient of dates)
4. Ensuring that the documentation related to the patient's diagnosis and treatment card is complete
5. Providing the patient with information related to oncological treatment
6. Cooperation with medical personnel and other organizational units in the designated area
7. Recording the course of the case consultation to the hospital's electronic records
8. Recording the decision of the case consultation and possibly "initiating treatment" in the electronic EMS system
9. Referral of closed DiLO cards to the GP doctors indicated by patients
10. Cooperation with the Medical Statistics/RUM Department in order to properly account for oncological services

Figure 4. Scope of activities performed by the coordinators

Table I. Tasks performed by the coordinators

	CENTER		
	Multi-profile	Single or dual-profile	p
	33.7%	66.3%	
Setting up DiLO cards			
no	21.9%	17.5%	0.60
yes	78.1%	82.5%	
Participating in case consultations			
no	6.3%	23.8%	0.03
yes	93.8%	76.2%	
Coordinating the patient's treatment plan established by the case consultation			
no	9.4%	11.1%	0.79
yes	90.6%	88.9%	
Ensuring that the documentation related to the patient's diagnosis and treatment card is complete			
no	6.3%	6.3%	0.99
yes	93.8%	93.7%	
Providing the patient with information related to oncological treatment			
no	15.6%	19.0%	0.68
yes	84.4%	81.0%	
Cooperation with medical personnel and other organizational units in the designated area			
no	0.0%	4.8%	0.21
yes	100.0%	95.2%	
Recording the course of the case consultation to the hospital's electronic records			
no	12.5%	28.6%	0.08
yes	87.5%	71.4%	
Recording the decision of the case consultation meeting and possibly "initiating treatment" in the electronic EMS system			
no	18.8%	27.0%	0.38
yes	81.2%	73.0%	
Referral of closed DiLO cards to the GP doctors indicated by patients			
no	43.8%	39.7%	0.70
yes	56.2%	60.3%	
Cooperation with the Medical Statistics/RUM Department in order to properly account for oncological services			
no	12.5%	9.5%	0.66
yes	87.5%	90.5%	



1. Informing about fixed test/treatment dates
2. Informing about the nature of tests/treatment
3. Providing practical advice on tests/treatment
4. Informing about the possibility of obtaining support, e.g. from a social worker
5. Independent providing non-medical support to the patient

Figure 5. The role of coordinators as regards contacts with patients

different oncology centers was indicated by 25 persons (26%). This problem included locking individual stages, reluctance to change the stages of DiLO cards, extending the duration of individual stages, refusal to close an incorrectly issued card. The respondents pointed to problems with meeting the prescribed test dates in the oncology package by diagnostic laboratories. One third of the respondents pointed out the difficulties of coordination due to e.g. lack of possibility to view cards issued in other centers, lack of "centralized" collection/registration of issued DiLO cards. More than one third of the respondents (37%) indicated a lack of flexibility of AP-DiLO application and various system limitations. Moreover, it turned out that in Poland there are significant differences in the interpretation of the rules of proper handling of the oncology package by both individual oncological centers and NFZ Departments.

Discussion

A patient using a complex system of diagnostics and oncological care requires appropriate guidance and support. This system covers different elements of healthcare, such as: GP, diagnostic laboratories, various outpatient and oncological wards, centers providing rehabilitation, palliative care and psychooncological support. The task of individual components of this system is efficient diagnostics and quick undertaking of appropriate therapeutic actions, which will result in curing the patient and improve/maintain a patient's quality of life. It is also important to reduce costs, make good use of local (basic) healthcare resources and relieve the burden on specialists in oncology centers.

Programs to "coordinate" the diagnosis and treatment of cancer patients have already been introduced in various countries. The first such coordination program was designed in 1990 by Harold P. Freeman at Harlem Hospital in New York. The program was addressed to the group of African-Americans, because in this group of patients, according to the analysis, cancer was detected at a more advanced stage (only 6% of patients were at the 1st stage), which resulted in high mortality (5-year survival was estimated at 39%) [1]. It has been noted that women who were found to have a suspicious change in their breasts in the screening test, and who were "coordinated", were more often and more likely to have a breast tumor biopsy compared to 'uncoordinated' women (respectively: 87.5% *vs.* 56.6%) [1]. The next steps were to coordinate the process of diagnosis and treatment of women undergoing screening mammography. The study involved 325 women who were suspected on the basis of mammography and subsequently diagnosed with breast cancer – the 5-year total survival in this group increased to 70% compared to the 5-year survival rate of 39% before the introduction of the above intervention [2]. Also, in the USA, a project was introduced which aimed to improve the treatment results of patients with a low level of education, low income, without social support by eliminating obstacles to rapid diagnosis and treatment of cancer, shortening the time of waiting for diagnosis and therapy [3, 4]. A key figure in this program was the coordinator, whose role was to coordinate visits to doctors' surgeries, hospitals, clinics, contacting the insurer and patient support organizations, emotional support for patients, contacting their family doctor, ensuring the availability of relevant medical records at scheduled visits, providing access to clinical trials, facilitating access to financial support and assisting with formal matters, organizing transport and/or care for a child or elderly family member, and organizing interpreter services, as well as monitoring patient satisfaction with the oncology care system. Thanks to this program, including the work of the coordinators, the screening efficiency of mammography has been improved, the degree of cancer severity at the time of detection has been slightly reduced, times of waiting for diagnosis and treatment have been shortened, the access to healthcare has been improved, the cost effectiveness has been reduced and patient satisfaction has improved. Harold P. Freeman and Rian L. Rodriguez [4], drawing on 20 years of experience, have created the general principles for the proper functioning of the oncological care coordination model. The basic principle of this model is a patient's smooth and timely passage through the various stages of diagnosis and treatment, including rehabilitation and control tests.

In Poland, the coordination of the "patient pathway" in the system is formally established only from the moment of the case consultation to the end of treatment. In principle, coordinators do not take part in the earlier stages of diagnosis (screening, cancer suspicion, initial and in-depth diagnostics). The lack of effectiveness of our patient coordination system may result from the lack of patient support at the beginning of the path to cancer diagnosis, at the time of suspected cancer and at the first stage of diagnosis (to obtain a histopathological diagnosis). The coordinators also do not participate in the stage of broadly understood patient rehabilitation (physical, social, professional) and in the organization of follow-up examinations after the end of treatment (both after the treatment of the patient and in case of progression/recovery of the disease).

The second principle of proper functioning of the oncological care coordination model is to eliminate accessibility barriers to all stages that a patient goes through in the healthcare system. This is possible with properly planned/organized activities of diagnostic and treatment centers and individual patient coordination.

The third principle for the proper functioning of the oncological care coordination model is to clearly define the responsibilities, role and responsibilities of the coordinator. It is emphasized that the role of a coordinator is sometimes naturally performed by oncological nurses who, due to their function, are in close relationship with the patient and often provide not only medical and nursing support, but also psychological, dietary, informational, social and legal one [5–9].

The oncology package, introduced in Poland in 2015, includes the DiLO card as a tool to manage a rapid oncology therapy package and oncology care coordinators whose function has not been precisely defined. According to the National Health Fund, the coordinator supervises the process of treatment of a patient from the moment of referral to a case consultation until the end of treatment, supports the patients in terms of information, administration and organization, and helps them to communicate with physicians. After completing the oncological treatment and closing the DiLO card, the patient goes under the care of a primary care physician (GP). According to the NFZ [10], the tasks of a coordinator include: attendance at case meetings, coordinating the patient's treatment plan established by the case meeting, ensuring that the documentation related to the DiLO card is complete, providing the patient with information related to oncological treatment, cooperation with medical personnel and other organizational units in the designated area introducing the conciliation in the

hospital system, supplementing the case consultation decision on further treatment in the DiLO system, sending closed DiLO cards back to GPs. The provider is obliged to comply with the conditions imposed by the NFZ and usually only fulfils the recommendations to which it is obliged. Any additional activities that would be beneficial to the patient, but are not required by the payer, do not have to and are not performed by providers mainly due to additional costs. Despite the lack of guidelines for the implementation of support for non-medical needs of the patient, in our study, some coordinators show empathy for patients and half of them provide, for example, information about the possibility of receiving non-medical support from, among others, a psychologist, a social worker, and even provide such assistance themselves. At the same time, the problems faced by the coordinators are generated more by the system itself than the organizational, clinical and social challenges associated with cancer. Excessive administrative work, resulting from the negligence of the system, takes time and creates understandable frustration – coordinators would prefer to devote this time to patients.

Another issue identified by Freeman is the need for training and acquisition of skills necessary for the work of the coordinator. In Poland, there is no structural support for coordinators in the area of knowledge, competence improvement, tools, basic assistance in solving current problems. The results of the survey show that the coordinators most often learn by exchanging experience with other coordinators or try to solve problems on a trial and error basis. The authors of various papers stress the importance of the level of skills, knowledge and experience of persons acting as oncological treatment coordinators and point out that such duties should not be fulfilled by persons without appropriate qualifications [5, 9]. The Minister of Health in the National Oncological Strategy declares the development of a post-graduate education program for the coordinator of oncological care. Oncological care coordinator is not a separate profession in Poland.

In view of the different tasks faced by coordinators, they should have particular aptitudes, knowledge and skills. According to our survey, half of the coordinators were deliberately hired for the position of coordinator, but there are no specific criteria for selecting such people for the above position, the requirements they should meet (profession, education, skills), and there is no proper training of candidates for coordinators. Nearly 40% of the persons who perform the coordinator's tasks within additional duties are employed as nurses, who have to organize the work themselves and often do not have enough time for patients. A majority of persons who have been assigned a coordinating role as additional work are administrative staff or medical secretaries. It can be assumed that the large number of administrative and accounting duties related to the oncology package induces hospitals to entrust the function of coordinator to persons experienced in administrative work rather than in contact with the patient.

Another principle of proper functioning of the oncological care coordination model is to define the points from which the patient coordination process will start and end. It should be remembered that the path of a cancer patient does not end with the completion of basic oncological treatment; patients require rehabilitation, follow-up and diagnostic tests, often the implementation of oncological re-treatment due to progression or relapse of the disease or palliative care. It is emphasized that comprehensiveness, integration of the treatment plan is an important factor which increases the availability of various methods of treatment and thus affects the survival of patients [11]. Good coordination reduces stress, fatigue and improves the quality of patients' life [12, 13]. Swanson [14] demonstrated a significantly statistical decrease in stress levels among cancer patients receiving support from the coordinating nurse. A randomized, controlled study by Kevin Fiscell [15] showed that the introduction of a coordination program has improved healthcare satisfaction in patients with breast and colorectal cancer. Similarly, in a study by Carroll [16], it turned out that patients who were properly coordinated received adequate psychological support, assistance in information needs and problem solving.

In Canada, a program of coordination in oncological care between family doctors and specialists has been introduced at both the systemic and individual levels. Effective and timely transfer of medical information about a patient between medical care units as well as clearly defined roles for each provider are essential for good oncological care coordination. Despite technological progress, there are still communication challenges that may lead to serious consequences for clinical decision making [17]. A meta-analysis conducted in the USA showed that the coordination of oncological care improves the process of diagnosis, treatment and terminal care of patients [18].

However, there is still a lack of appropriate tools to test and validate the effectiveness of the patient coordination program [5]. Similarly, in Poland, we do not have any system for evaluating the changes introduced in the system, nor do we have tools to check the level of patients' satisfaction with the quality of oncological coordination.

Conclusions

The coordinators in the Polish system of oncological care are a new, undoubtedly extremely valuable and with great potential, professional group. However, there is a lack of clearly defined tasks to be undertaken. In addition, oncology coordinators do not receive systematic training, they lack support.

Conflict of interest: none declared

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From the Editorial Office

The paper raises an issue important for the healthcare system in Poland. However, it is the duty of the Editorial Office to draw attention to significant reservations concerning chiefly the methodology of the conducted research, which – independently of each other – were pointed out by both reviewers. However, the Editorial Office recognizes the importance of the problem for the organization of oncological care in our country and despite the reservations of the reviewers (largely explained by the Authors in the submitted amendments) decided to publish the paper in *Nowotwory. Journal of Oncology*.

The results of the study and data cited in the paper come from the report by Onkologia 2025 Foundation (January 2020) entitled *Koordynatorzy. Kim są i jaką funkcję pełnią koordynatorzy pacjenta onkologicznego? Wyniki badania ankietowego* (Coordinators. Who are the coordinators of an oncological patient and what is their function? Results of the survey).

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Review article

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What is new when it comes to acute and chronic radiation-induced dermatitis in head and neck cancer patients?

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Head and neck cancer is a serious clinical and social problem. Surgery and radiotherapy play the most important role in treatment and give the chance of cure. Optimal treatment of patients with head and neck cancer should provide for the maximum destruction of cancerous tissue, saving as much healthy tissue as possible. Despite this, due to radiotherapy still almost 90% of patients develop skin symptoms. It seems that the mechanism of radiodermatitis is quite clear, but studies assume that its pathogenesis is not fully understood and there is much to be clarified. Acute and chronic dermatitis caused by radiotherapy is usually diagnosed according to clinical criteria. It seems that it would be useful to have a photographic classification that would facilitate and unify the clinical evaluation. In this article we shall summarize the current knowledge about the mechanisms of formation, risk factors, clinical classifications and methods for the prevention and treatment of acute and chronic radiation dermatitis. We have included clinical photos that depict individual stages according to the clinical classification of RTOG.

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Key words: acute and chronic radiation-induced dermatitis

Introduction

Head and neck cancer is a serious clinical and social problem. The major reason for poor treatment results is the advanced stage of disease at diagnosis. Surgery and radiotherapy are the main treatment options that give a chance of a complete cure [1]. Radiotherapy utilizes ionizing radiation that usually covers relatively large volumes of tissue surrounding the tumor [2]. The optimal treatment of patients with head and neck cancer involves a compromise between destroying as much cancerous tissue as possible, and saving as much healthy tissue as possible [3]. Radiotherapy should be carried out with the use of modern technologies, such as conformal 3D radiation, and, in particular, intensity-modulated radiation therapy (IMRT) [1]. This method allows for a significant reduction in tissue volume subject to the high radiation dose, and in the intensity of acute radiation-related reactions of these tissues. Despite this, still almost 90% of patients develop skin symptoms after radiotherapy [4]. Radiation-induced reactions can be divided into early and late as regards the time of their appearance in the relation to radiotherapy. Acute (early) ones appear during radiotherapy and usually disappear a few weeks after the completion of the treatment. Late reactions appear months after radiotherapy and may leave chronic results [5]. In turn, as far as the extent of radiation is concerned, reactions can be local or generalized [2, 3].

Pathogenesis

According to the Michalowski and Wheldon classification, proliferative tissues can be divided into "hierarchical" and "flexible",

and consequently, the course of radiation injury differs in these two groups [6]. The skin belongs to hierarchical tissues and is made of mature cells, maturing cells and stem cells. Radiotherapy causes cells, 70% of which is composed of water, to become ionized [6]. Hydrolysis of water and the formation of free radicals, be it direct or indirect, causes breaks in the DNA and cell death. The lethal effect mainly pertains to stem cells and, to some extent, to maturing cells [3]. Consequently, the balance between normal cell production at skin's basal layer and cell destruction at skin surface is disrupted [3]. The radiation-induced skin reaction reflects the degree of cell damage. Its intensity depends on the radiation dose, and increases with the number of stem cells that die. The first phase, transient erythema, may occur 24 hours after radiotherapy, with vessels becoming wider and more permeable [5]. Inflammatory cytokines, prostaglandins, and many other mediators are secreted [3, 5]. This inflammatory reaction causes the development of a secondary erythematous response. Immune cells, keratinocytes, fibroblasts and other cells are stimulated. Subsequent radiation doses create a vicious circle and correlate with the degree of radiodermatitis [7]. In the next phase, dry exfoliation usually occurs, which results from the disturbed balance between the division of new cells and the exfoliation of the old ones. In the final stage, stem cells are lacking and the skin has no material from which to rebuild individual layers. Wet exfoliation and exudates occur [7]. The inflammation that started in the epidermis after the beginning of irradiation lasts for months, and even years. Inflammatory cytokines are secreted, including interleukin IL-1α, IL-1β, tumor necrosis factor TNF-α, TGF-β, IL-6, IL-8 [7]. The secretion of TGF-β, which is a central mediator of fibrogenesis, increases following the exposure to ionizing radiation, and it is proportional to the radiation dose delivered [8, 9]. Huang and Glick summarize the knowledge about major genes and polymorphisms, and delineate the role of TGF-β as a peptide protein gene associated with an immune response that plays an important role in both early and late dermatitis [10]. Studies using the rat and mice model show that those less equipped with this protein are not as sensitive to radiotherapy as wild rats [9, 11].

Despite this knowledge, the studies at the National Jewish Health Biological Resource Center assumed that pathogenesis of radiodermatitis is not fully understood. Using mouse models in their project, the researchers at the Center discovered that the transient receptor potential melastatin 2 (TRPM2) ion channel plays a major role in developing radiation injury. They suggest that TRPM2 may be a potential target for a systemic medicine which would inhibit this channel and reduce the severity of radiodermatitis [12]. However, other researchers who have also used mouse models say that plasminogen plays a major role in the development of radiation injury. Among other things, it participates in the activation of many inflammatory factors, such as TGF-β. Fallah et al. used tranexamic acid, postulating that inhibiting plasminogen could be used as treatment or as a preventive option in the future [13]. The pathogenesis of bio-radiation dermatitis differs from that associated with radiotherapy alone. Inhibition of the EGFR pathway results in a disruption of physiological processes associated with the migration and proliferation process, and the development of inflammation in the skin. The type of response depends on the degree of interaction between the inhibitor of EGFR pathway and radiotherapy [14]. The multitude of reports on factors that may be involved in the development of acute and chronic radiation-induced dermatitis is certainly attributable to the fact that many studies are still needed to find out the actual pathogenesis of this process.

Risk factors

The risk factors associated with the development of radiodermatitis can be divided into patient- and treatment-related [3, 7], where the letter include the type and energy of irradiation, the dose per fraction, the duration of treatment, and the total radiation dose [3]. An additional factor associated with the treatment may be concurrent chemotherapy. Researchers have shown that chemotherapy improves the therapeutic effect [15–17], but also increases the intensity of radiodermatitis [18]. EGFR inhibitor – cetuximab given during radiotherapy increases the intensity more seriously compared to radiotherapy alone [14]. Concomitant diseases, a patient's age, past injuries and surgeries in the irradiated area should be considered as the main patient-related factors [3]. Patients with genetic disorders, such as ataxia-telangiectasia or the Nijmegen syndrome, show a genetically determined susceptibility to the development of radiation damage. Consequently, their normal cells are hypersensitive to the radiation-related damage [3].

The neoplastic tissue itself is a constant factor affecting the severity and development of radiodermatitis. It secretes factors that increase the number of cells that divide both cancerous and healthy tissues [3]. Undoubtedly, the study conducted by Huang and Glick shows how many risk factors are associated with human genetic material and how many factors affect the development of radiodermatitis [10]. Kawamura et al. present a new radiation dermatitis scoring system. The results of their study show that radiation dose, concurrent chemotherapy, age and body mass index (BMI) have a predictive significance. On this basis, they constructed a score system combining the above parameters [18]. Apart from this, there are no other commonly used score systems that allow predicting the risk and intensity of acute and late skin reactions in patient before radiotherapy.

Clinical classification

In clinical practice, various clinical scales are applied in the assessment of acute and chronic radiodermatitis. The Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC), Common Terminology Criteria for Adverse Events (CTCAE), and the Late

Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENTSOMA) scales are used most often [19]. RTOG/EORTC scale is dedicated to assessing early and late post-radiation reactions (Tab. I) [20].

LENTSOMA scores only late reactions [4]. In turn, CTCAE does not describe the late effect, but only its acute phase [19] (Tab. II).

Generally, RTOG scale refers to various tissues and organs. At grade 0, no skin reactions are observed. Reactions of different intensities are scored between grades I to IV, with death due to dermatitis at grade V [20]. In our review, we include figures presenting the individual grades in line with the RTOG classification.

At grade I, erythema of moderate intensity is observed. Hair loss and dry exfoliation may also occur (Fig. 1) [20]. At grade II, usually, tender or bright erythema is visible with moist desquamation. This is accompanied by moderate swelling (Fig. 2) [20]. At grade III, erythema is accompanied by swelling and moist exfoliation, which includes areas outside the skinfolds (Fig. 3) [20]. Grade IV is characterized by ulceration, bleeding

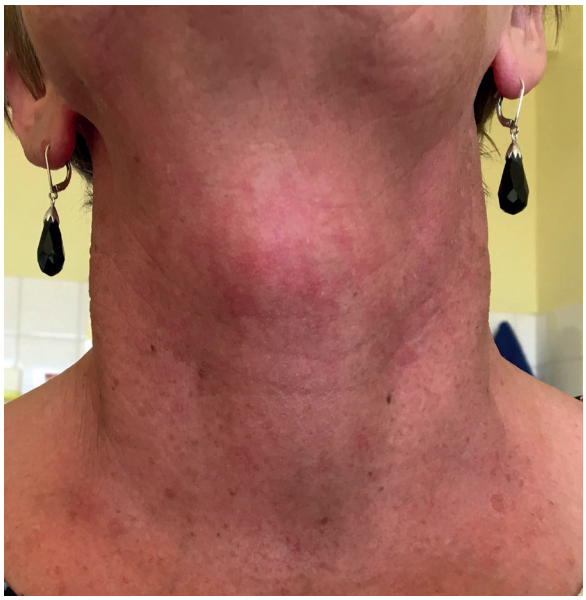

Figure 1. Follicular dull erythema with epilation and red dermographism in the course of acute radiodermatitis, RTOG/EORTC grade I

Table I. Early and late post-radiation reactions

	Grade I	Grade II	Grade III	Grade IV
Acute radiodermatitis	follicular, faint or dull erythema, epilation, dry desquamation, decrease sweating	tender or bright erythema, patchy moist desquamation, moderate edema	confluent, moist desquamation other then skin folds, pitting edema	ulceration, hemorrhage, necrosis
Chronic radiodermatitis	slight atrophy, pigmentation change, some hair loss	patchy atrophy, moderate teleangiectasia, total hair loss	marked atrophy, gross teleangiectasia	ulceration

Table II. Late post-radiation reactions – proposed modifications

	Grade I	Grade II	Grade III	Grade IV
NCI-CTCAE v 4.03 radiation dermatitis	faint erythema or dry desquamation	moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Proposed modifications	faint erythema or dry desquamation	moderate to brisk erythema and/or dry desquamation; patchy moist desquamation, **or nonhemorrhagic crusts mostly confined to skin folds and creases**	moist desquamation **or hemorrhagic crusts; nonhemorrhagic crusts other** than in skin folds and mostly confined to skin folds and creases; bleeding induced by minor trauma or abrasion; **superinfection requiring oral antibiotics**	life-threatening consequences; **extensive confluent hemorrhagic crusts or ulceration (>50% of involved field); extensive spontaneous bleeding from involved site (>40% of the involved site); skin necrosis or ulceration of full-thickness dermis or any size ulcer with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures with or without full-thickness skin loss; skin graft indicated; ulceration associated with extensive superinfection with i.v. antibiotics indicated**

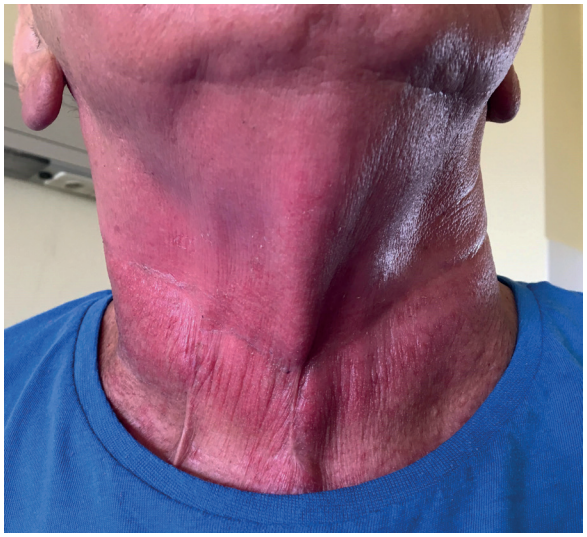

Figure 2. Tender and bright erythema with moderate edema-within the irradiated area in the course of acute radiodermatitis, RTOG/EORTC grade II

and necrosis [20]. In contrast to the acute cutaneous reaction after radiation therapy, chronic dermatitis occurs not earlier than 90 days from completing radiotherapy and may develop even a few years after irradiation [5]. It is clinically characterized by moderate (Fig. 4) to severe atrophy (Fig. 7) accompanied by telangiectasia (Fig. 4–7), as well as ulceration (Fig. 7) (grade IV) [20]. RTOG, CTCAE and LENTSOMA are descriptive scales, with a risk of subjective evaluation and classification of acute and chronic radiation dermatitis [21]. Zenda et al. provide an atlas of radiodermatitis with pictures showing grades from I to IV according to CTCAE. A photographic classification could be useful in supporting and unifying the clinical one [21]. Acute and chronic dermatitis caused by radiotherapy is usually diagnosed based

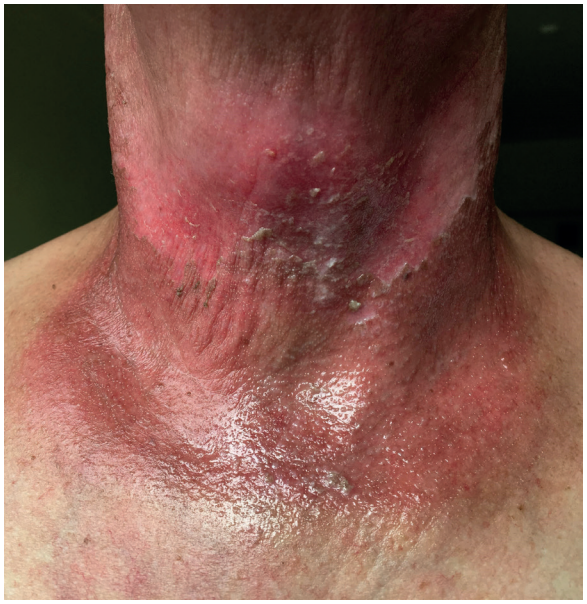

Figure 3. Sharp demarcated, exacerbated erythema accompanied by swelling and moist exfoliation, expanding to non-irradiated neighbouring areas in the course of acute radiodermatitis, RTOG/EORTC grade III

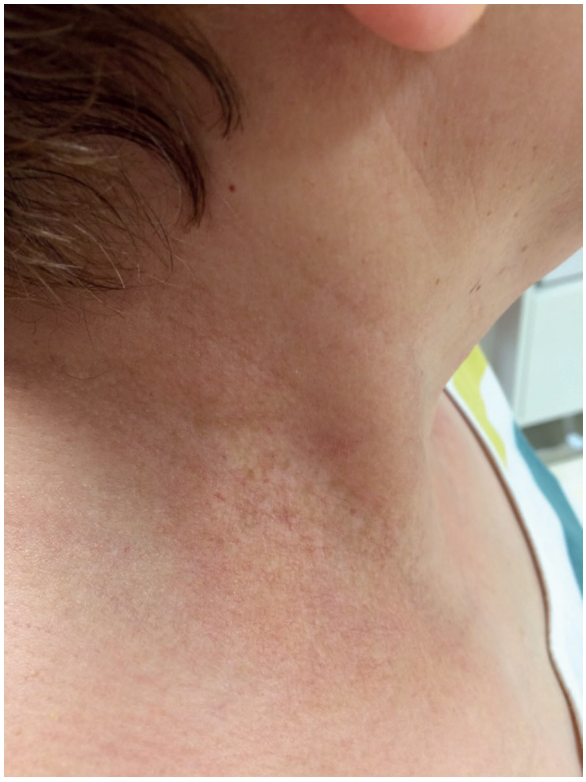

Figure 4. Slight atrophy, poikilodermic pigmentation (mainly depigmentation) with permanent hair loss and several thin telangiectasias in the course of chronic radiodermatitis, RTOG/EORTC grade I

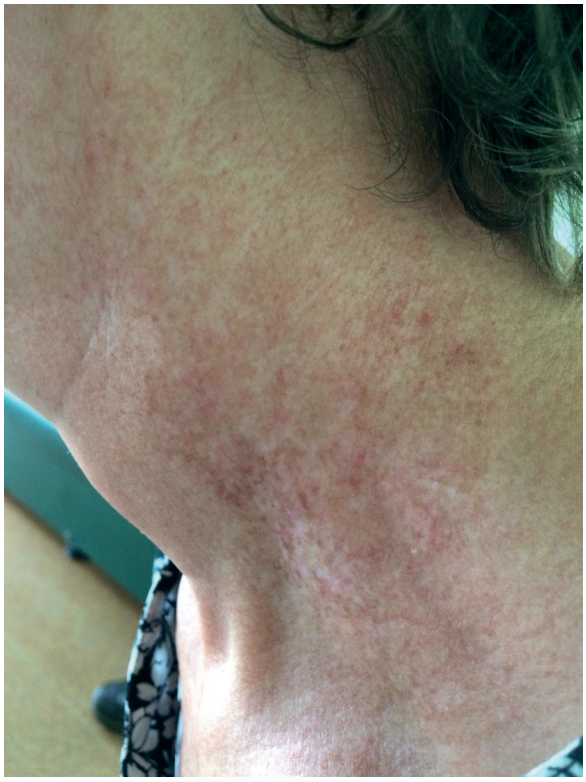

Figure 5. Patchy atrophy areas with thin, moderate telangiectasias accompanied by total hair loss and skin discoloration (depigmented and brownish spots) in the course of chronic radiodermatitis, RTOG/EORTC grade II

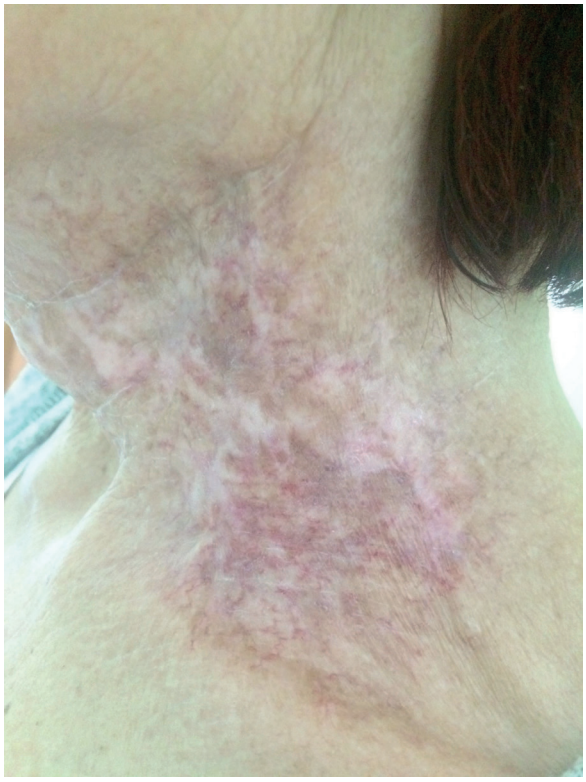

Figure 6. Marked skin atrophy presented as multiple whitish scarred lines with multiple gross telangiectasias in the course of chronic radiodermatits, RTOG/EORTC grade III

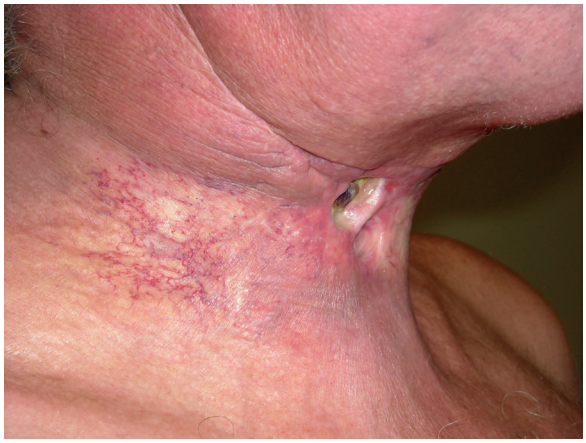

Figure 7. Advanced atrophy with multiple gross telangiectasias and desquamation of the skin. Diffused white atrophy with multiple thick telangiectasias also observed. Thinning of the skin of epidermis also seen in the course of chronic radiodermatitis, RTOG/EORTC grade IV

on the above-mentioned clinical criteria. CTCAE 4.0 appears to be the most commonly used scale during clinical assessment, but it is not a unified, unambiguous system for the assessment of post-radiation reactions [19]. It is worth mentioning that the combined treatment involving concomitant radiotherapy and EGFR inhibitor may result in reaction called bio-radiation dermatitis [22]. This type of reaction has a different pathogenesis and clinical characteristics [14]. Bernier et al. propose guidelines on the classification and treatment of bio-radiation dermatitis. These would help clinicians to properly assess and manage it. The treatment could be optimized, and there would be a greater chance of a good clinical outcome [14, 23]. Table II shows the changes proposed by Bernier et al. in relation to CTCEA. In grades II–IV, the change in type and extent of crusting can be observed. Infections may influence the intensity of bio-radiation and therefore appropriate local or systemic treatment should be considered (Tab. II) [14]. The extent of spontaneous bleeding is concerned at grade IV (Tab. II) [14].

Prevention and treatment

The latest recommendation on prevention and treatment was published in 2013 by the Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity Study Group [19], and showed that randomized studies have confirmed that skin hygiene with the use of water, with or without gentle soap, and the use of antiperspirants is recommended. A positive effect of using topical glucocorticosteroids has also been shown [19].

In 2015 O'Donnovan carried out an anonymous online survey in Europe and in the United States [24]. It turned out that there is a large discrepancy between the clinical management, prevention and treatment of acute radiodermatitis, and what has been confirmed in scientific studies. Many of the commercially available products have no scientific support [24].

In 2017 Lucey et al. began another such study in the United States. They conclude that there is a considerably wide variety in the prevention and treatment of acute radiodermatitis [25]. At the same time, this type of research shows that, in fact, no recommendations are available yet. However, since clinical experience shows that this process yields some effects, it requires confirmatory research. Lucey et al. show that aloe vera, gentle soap, and topical glucocorticosteroids are most commonly used for the prevention of acute radiation injury [25]. When it comes to treatment, it is correlated with the degree of the development of radiodermatitis [25]. Dry desquamation is mostly treated with emollients and aloe vera [25]. For grade II and III, silver sulfadiazine cream is most commonly used. A comparison of procedures at different centers in the country showed that the procedures result from observation in 89% of cases, and only in 51,4% from scientifically confirmed studies [25]. There is evidently a need to carry out tests confirming the effectiveness of individual intervention. In 2018 a randomized Radiotherapy Related Skin Toxicity (RAREST-01) study commenced [26]. It compares standard care and Mepitel Film (gentle, transparent, breathable dressings) in patients with locally advanced squamous-cell carcinoma of the head and neck receiving radiotherapy or radiochemotherapy [26]. One of the surveys done in China confirmed the effectiveness of Mepitel Film dressings and it decreases acute radiation injury in head and neck cancer patients [27].

At the same time, the third phase of the study protocol of J-SUPPORT 1602 (TOPICS study) began, comparing topical glucocorticosteroids with placebo as prevention of radiation

injury [28]. Zhang et al. used red light therapy and it turned out that such an intervention may accelerate wound healing, reduce pain, and improve the patient's life [29]. Ferreira et al. published a review of 13 randomized studies. Intervention with trolamine, aloe vera, allantoin, Lianbai liquid (Chinese remedy), sucralfate, Na-sucrose octasulfate, olive oil, hyaluronic acid, and dexpanthenol did not show any benefits in prevention and treatment of radiation injury [30]. At the same time, there was no difference between the control group using institution routine, aqueous cream, mild soap, water thermal gel, placebo, and no intervention [30]. Regarding bio-radiation dermatitis, Bonomo et al. confirmed the effectiveness of calcium dressing for moist exfoliation [22]. Side effects like radiodermatitis which is particularly visible may significantly impair the quality of life. Non-pharmacological recommendations and patient education should not be forgotten [31].

It is very important to minimize the risk of infection using an appropriate standard of hygiene and choose the right cosmetics and cleaning products that are clinically tested and adapted to this group of patients. In addition, patients should remember about photoprotection [31]. Experts believe that in the interests of patient's well-being, the use of deodorants and non-irritating perfumes can be part of daily routine [31]. It is very important to conduct regular dermatological follow-ups due to the fact that chronic radiation dermatitis predisposes patients to secondary malignant tumors [32, 33].

Conclusions

At this time, there is a lot of reports on factors that may be involved in the pathogenesis of acute and chronic radiodermatitis. Further studies are still needed to confirm and find out the actual nature of the pathogenesis of this process. Clinical assessment is carried out using various clinical scales. There is no one unified system which would make our assessments uniform, and thanks to which we could subsequently proceed with treatment. There is a good chance that the photographic atlas presenting the selected grade of acute and chronic radiodermatitis may unify the clinical evaluation.

Currently, apart from one study, there are no specific prognostic factors and predictors that could indicate the dynamics and severity of acute dermatitis caused by radiotherapy or prognostic factors related to the late reaction of skin. Genetic susceptibility testing and the determination of the final pathogenesis pathway in the future may bring the target for treatment and prevention. Currently, the last recommendations come from 2013; they were published by MASCC Skin Toxicity Study Group [17]. By 2019, no new recommendations have been issued, and the clinics today are based on observation in 89% of cases and only in 51.4% on clinically confirmed results [23].

Appropriate assessment of the severity of acute and chronic radiation induced skin injury makes it possible to decide how to proceed with patients, especially with such groups for which the cosmetic effect has special importance for personal, social and professional reasons.

Conflict of interest: none declared

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Oncogeriatrics (part 4.)

Pre-operative assessment of elderly patients with cancer

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Older patients comprise a highly heterogeneous group, and chronological age, comorbidities, or the type of surgical procedure performed cannot adequately describe the risk of adverse post-operative outcomes. Therefore, current routine pre-operative assessment also cannot adequately identify patients at risk. The Comprehensive Geriatric Assessment, the mean life expectancy and the treatment goals of a patient must be included in the pre-operative evaluation. The Comprehensive Geriatric Assessment helps to determine the primary status of an older patient, to diagnose frailty syndrome and to identify how to optimize a patient's condition before surgery. Surgery is one of the primary triggers for disability in older patients. In this age group, being independent is more important than prolonging life. This is particularly true in patients with frailty syndrome, or decreased physiological reserves, which arise from cumulative deficits in several physiological systems and result in a diminished resistance to stressors. Therefore, a standardized pre-operative diagnostic approach, individualized surgical technique selection and tailored post-operative care are essential for successful treatment of elderly patients.

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Key words: older patient, pre-operative assessment, comprehensive geriatric assessment

In geriatric surgery, the key element is to recognize that an elderly patient is not simply an "older adult", and that routine procedures reserved for younger adults may not bring the expected outcomes. In this age group, it is essential to standardize pre-operative diagnostic processes and to personalize treatment and post-operative care. A key factor in geriatric care is the pre-operative assessment, which should be extensive and consider all changes associated with both physiological and pathological ageing. The surgical procedure technique, itself, does not currently differ extensively from accepted standards. However, an increasing number of institutions are introducing modifications to the existing oncological guidelines, especially for patients with frailty syndrome. In addition, there is enough evidence that elderly cancer patients benefit when they undergo minimally invasive surgical and/or endoscopic procedures performed by experienced professionals [1, 2]. The wide availability of various surgical platforms and techniques provides an unprecedented opportunity to offer elderly patients alternative possibilities for their surgeries.

This necessity for personalized care arises from the substantial heterogeneity within the ageing population. Chronological and biological age are different, and with increasing age, these differences become more pronounced. The speed of ageing is unique to individuals and may even differ in separate organs and systems of a single patient. Thus, it is a grave mistake to make decisions on the extent and method of surgery for an elderly patient based solely on chronological age, medical history, physical examination, basic biochemical and imaging tests, as well as consultations. An increasing number of studies show that the surgeon's assessments for surgery eligibility are largely subjective. For example, a large proportion of surgeons associate frailty syndrome with multiple morbidities and/or disability. Fried et al. studied the relationship between these factors and concluded that only 21.5% of patients were diagnosed with multiple morbidities, disability and frailty syndrome

and most patients had only one of these factors. They found that 6% of frailty syndrome patients were disabled (defined as dependency in daily activities on others), while 46% had multiple morbidities (defined as the presence of two or more accompanying illnesses). The most important observation from this study was that 27% of patients with frailty syndrome were not disabled and did not have multiple morbidities at all [3].

Routine examinations often lead to a discontinuation of therapy in patients who may potentially qualify for such treatments, and conversely, to seemingly healthy patients being qualified for extensive surgical procedures. Commonly, older patients are disqualified from radical treatments based on an information card containing a long list of diagnoses. However, it may turn out that none of these diseases are a marker illness, and they may not have a significant effect on the post-operative period. However, the opposite may also be true, where a patient reports for surgery without any comorbidities and with documentation showing no counter-indications for surgery. Nonetheless, this patient also has not been adequately assessed prior to the surgical procedure.

Another key aspect in the pre-operative assessment in elderly patients is to define the treatment goal. For young adults, the aim is to achieve all elements, such as curing the illness, preventing complications, alleviating symptoms, prolonging life, maintaining an appropriate level of physical activity, and improving the quality of life. For older patients, the situation is not as obvious. Studies indicate that ensuring a suitable quality of life is significantly more important than prolonging it and maintaining independence in the post-operative period should be a priority [4]. These facets to the treatment goals are also increasingly being noticed by scientists studying cancer. Five-year survival, disease- and complication-free survival are no longer the only endpoints in assessing elderly cancer patients. Other factors that are increasingly being discussed are those that are critical for elderly patients, such as quality of life in the post-operative period and return to pre-operative physical and mental capacity. We need to be aware that often the doctor's goals in designing the treatment do not align with the patient's goals. Additional factors that may prove helpful in better understanding the patient's expectations and what can be offered to them, include: Comprehensive Geriatric Assessment (CGA), knowledge of the remaining average lifespan relative to physical health, and defining the short- and long--term goals of the patient. A study is currently being conducted which aims to answer some basic questions involved in the process of returning to health following surgery:

- How long does an elderly patient need to return to everyday activity?
- How long will they be reliant on others for care?
- What will their mental capacity be after treatment?

Knowing the answers to these questions will allow elderly patients to be offered more personalized treatment plans and will allow the patients to give informed consent to such plans. A patient's perception of their own health, mood, and ability to cope with their illness also varies by individual and with time. The same goal does not always suit everyone. A healthy, elderly person will have different goals than a bedridden patient with frailty syndrome. For the first, a key outcome will be staying active, while for the second, it will be alleviating symptoms and the possibility of independently going about their daily activities.

Comprehensive Geriatric Assessment (CGA) is a multidirectional, integrated diagnostic process whose goal is to establish the extent of impairment of welfare [5]. A detailed review of CGA is beyond the scope of this article, so only the most basic information necessary for understanding the process will be discussed here. CGA is a set of diagnostic tools that evaluate everyday:

- functionality,
- physical fitness,
- level of nutrition,
- existing comorbidities,
- risk of depression,
- cognitive function,
- polypharmacotherapy,
- social support.

Its goals are to assess the baseline condition of the patient, identify previously unknown health issues, and diagnose frailty syndrome. This in turn leads to pre-operative "optimization" of the patient's state and may be useful in selecting a treatment strategy. It is estimated that CGA allows for the identification of previously unidentified health issues in up to 40% of older patients qualifying for surgical treatment [6]. Studies in many different specialties have shown that frailty syndrome is an independent risk factor for poor treatment outcomes in elderly patients [7–9].

Studies conducted at our department showed that a deficit-accumulation model was the most beneficial model for pre-operative patient assessment. The sum of the diagnostic tools, and not their separate individual results, was an independent risk factor of 30-day mortality and post-operative complications. Additionally, the number and type of assessment tools employed had a great effect on how frequently frailty syndrome was identified. A CGA consisting of diagnostic tools measuring functionality, physical and cognitive capacity, levels of depression, level of nutrition, polypharmacotherapy and comorbidities turned out to be the most precise measure predicting post-operative complications and mortality [10].

A large obstacle to the widespread use of CGA is that it requires experience, it is time-consuming, and it is not necessary for all elderly patients. However, in terms of the time consumption, devoting an additional 40–60 minutes to a patient prior to surgery may result in a decreased risk of complications and decreased dependence on others, and could allow the patient to return to physical and cognitive fitness sooner. Financially, there are benefits as well. The cost of care

frequently multiplies when complications occur and could cause the patient to require prolonged dependence on others and/or being moved to a nursing/caring facility.

An alternative to using the full CGA may be to use a screening study. The current literature contains at least a dozen diagnostic tools dedicated to this. In our studies, we compared six of the most commonly used tools. The abbreviated CGA (aCGA) and the G8 test were the best tools for elderly patients with a cancer diagnosis who were qualified for a surgical procedure; the G8 showed the highest sensitivity and negative predictive value, while the aCGA was better for general assessment [11]. On the other hand, for *ad hoc* procedures, the best screening test was the Vulnerable Elderly Survey 13 (VES-13). It had the highest sensitivity and negative predictive value in assessing the risk of complications and mortality during the post-operative period. While these approaches require further study, they can already offer clinicians additional information that may be used for post-operative treatment optimization of high-risk elderly patients [12]. One should be aware that screening tools aim to merely identify patients requiring additional geriatric assessments, and they do not allow for reliable identification of problems in individual domains, which in turn prevents planning the appropriate pre-rehabilitation. These tools also have variable efficacy in different populations, which is why it is recommended to analyze the potential usefulness according to one's needs.

Another important consideration to pre-operative assessment in the elderly is that surgical procedures are the single greatest risk factor for disability and dependence on others for care, especially in patients with frailty syndrome. It is therefore worthwhile to briefly discuss the legal aspects. Often, elderly cancer patients are offered a standardized treatment model geared toward younger adults by their doctors, who do so from the fear of being accused of incorrect oncological treatment. In this context, it may be useful to surgeons to highlight the Supreme Court verdict from September 24, 2015 (V CSK 738/14 – the extent of obligation to provide information by doctors), discussed in the article by Dr. Radosław Drozda from the Department of Forensic Medicine at the Wrocław Medical University [13]. It concluded that "the choice between alternative treatment methods belongs to the patient, and the clinician should present the patient with all available treatment options that are possible in their physical condition – at most with an indication as to which of these options is the most beneficial according to the doctor…"and "…it is the patient – despite a lack of medical training – who should make the decision on the surgical method that they will be subjected to. The role of the doctor is to convince the patient why (and for what medical reasons) it would be worth to undergo a riskier procedure. The patient however has the right (driven by personal reasons or even superstition) to pick a method that would be less invasive and is likely to have a lower efficacy than the method proposed by the clinician" [13].

Currently, evidence-based medical decision-making in this age group is met with great difficulty. This is caused in part by the large number of low- and medium-quality publications and in part by the dearth of scientific evidence. The best example of this is a study by Schiphorst et al., which analyzed the involvement of elderly patients in studies of laparoscopic surgeries, performed due to colorectal cancer. As highlighted by the authors, in 85% of the cases the average age was below 65 years old, and 44% of studies excluded elderly patients [14]. Extrapolating results from studies conducted on younger patients is a significant error. However, in analyzing the number of new publications devoted to the topic of elderly patients, one can hope that many questions will be answered by increasingly well-designed studies.

In conclusion, in order to improve treatment outcomes, it is necessary to consider issues specific to older populations in the pre-operative patient assessment. The questions presented below can help in this decision-making process:

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

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Adjuvant radiation therapy after immediate implant-based breast reconstruction

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The role of radiotherapy in the postmastectomy setting with substantial lymph node burden or locally advanced disease has been well described. In the last decade, the indications for postmastectomy radiotherapy (PMRT) have expanded in light of a measurable disease-free survival benefit, even in T1–2N1-patient subgroup. Concurrently, immediate breast reconstruction (IBR) rates after mastectomy are rapidly increasing. Optimal integration of IBR and PMRT is challenging, as PMRT has a known deleterious effect on reconstruction outcomes and IBR has been reported to pose challenges to PMRT delivery. Implant-based reconstruction is the most common type of IBR performed nowadays. This article reviews the current problems regarding integration of the implant-based IBR with optimum radiation delivery and discusses the advantages and disadvantages of each reconstruction method with PMRT.

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Key words: adjuvant radiotherapy, alloplastic reconstruction, immediate breast reconstruction, implant-based reconstruction, postmastectomy radiotherapy

Introduction

Immediate breast reconstruction (IBR) rates have continued to increase over time, concurrently with expanded indications for postmastectomy radiation therapy (PMRT) resulting from evidence that PMRT reduces recurrences and breast cancer mortality not only in patients with substantial lymph node burden or locally advanced disease, but also in pT1–2N1--patient subgroup [1, 2]. Although surgeons used to anticipate receipt of PMRT to guide decision-making regarding recommendations for IBR, nowadays a tendency for women with more advanced tumors to be less likely offered IBR due to their overall poorer prognosis and very high likelihood of receiving PMRT is gradually decreasing [3]. Optimal integration of IBR and PMRT is challenging, as PMRT has a known deleterious effect on reconstruction outcomes [4–6] and IBR has been reported to pose challenges to PMRT delivery [7]. The implant-based IBR (IB-IBR) is usually preferable in the majority of patients with breast cancer facing PMRT due to its preservation of autologous tissue for salvage and often acceptable outcomes, whereas most guidelines do not routinely recommend autologous reconstruction in patients who will definitely need PMRT [8, 9]. In current practice, reconstruction with tissue expander (TE) followed by PMRT and subsequent permanent reconstruction with prosthesis is prevalent [10].

The aim of this article is to review the current problems regarding integration of IB-IBR with optimum radiation delivery and to discuss the advantages and disadvantages of each reconstruction method with PMRT. Several questions will be addressed, such as oncological safety, cosmetic outcomes, and some technical radiotherapy issues, like target volume definitions depending on the reconstruction methods and disease stage, a problem of administering a boost and of using bolus material, the volume of fluid within the TE – i.e. deflation or inflation before PMRT, and the impact of an internal magnetic metallic port within TE on radiotherapy dose distribution.

PMRT in patients after IB-IBR – is oncological safety compromised?

IBR improves quality of life and self-perceived body image [11]. However, a concern remains that the procedure may have an impact on disease control, resulting from the risk of delaying PMRT due to surgical complications and from the influence of IBR on the optimization of PMRT, compromising dose coverage of the clinical target volume (CTV), i.e. of the volume of tissues that contains subclinical malignant disease at a certain probability level, and thus has to be treated adequately. There are no data from prospective randomized trials on the oncological safety of IBR followed by PMRT. Two meta-analyses have reported that local recurrence rates [12], overall survival and disease-free survival [13] did not differ between patients with or without IBR. However, not more than 30% of the patients included in these meta-analyses were treated with PMRT, detailed data about RT were missing in several included studies, most of the patients included had the early stage of disease (clinical stage I–II) and patients with IB-IBR constituted the minority of patients in these meta-analyses.

Results of a matched control study where the population consisted of 128 IB-IBR patients (all with retropectoral implants, one third irradiated with TE) and 252 controls without IBR, aiming to evaluate the CTV dose coverage and to investigate the safety of IB-IBR in terms of recurrence and survival compared to patients without an implant, showed that PMRT after IB-IBR lead to minor under-dosage of the CTV. However, recurrence and survival rates were equally distributed among patients with IB-IBR and controls, indicating that the overall treatment protocol is safe [14]. Again, patients with locally advanced breast cancer (LABC), i.e. pT3 disease, constituted less than 10% of the whole cohort, and patients who received neoadjuvant chemotherapy constituted only 24.2% of the IB-IBR group.

In a population-based propensity score matched analysis comparing the survival outcomes in LABC patients (pT1–4N2–3M0) receiving PMRT with and without IBR, that included 1732 patients from the Surveillance, Epidemiology, and End Results (SEER) database, there was comparable breast cance r specific survival and overall survival between patients who received IBR or mastectomy alone followed by PMRT. In this study, 36.8% of patients received autologous IBR, 36.3% received IB-IBR, and 26.8% had reconstruction that was not otherwise specified or combined with tissue and implant reconstruction. pT1–T2 patients constituted 70% of the matched cohort [15].

With the increasing rates of prepectoral reconstructions being performed, often without the use of acellular dermal matrix (ADM) due to reimbursement policy in Poland, the problem emerged regarding the positional uncertainty of the target during PMRT, which is much higher in case of prepectoral TEs without ADM, due to higher range of both their inter- and intrafraction motion. It seems that anatomical position of prepectoral TEs without ADM is far less stable than retropectoral TE/implants and prepectoral implants with ADM. This may cause additional delays in PMRT as well as unplanned treatment breaks resulting from the need for re-planning of these patients whose initial target positioning cannot be reproduced during PMRT (Fig. 1). Such delays may have a negative impact on the oncological outcomes, as prolongation of the overall treatment time was confirmed as a cause of treatment failure in early breast cancer patients [16].

In conclusion, IB-IBR followed by PMRT seems safe for early stage patients (pT1–2N1), for whom the minor under-dosage of the CTV may be acceptable. However, caution should be paid when offering IB-IBR to the patients with locally advanced breast cancer, because data on the oncological safety are scarce, and there is virtually no data on patients with pT4-disease treated with IB-IBR followed by PMRT.

Cosmetic outcomes

Surgical techniques for IB-IBR continue to develop with the aim of improving cosmetic outcomes. However, in patients undergoing PMRT, adverse events must be considered, including the risk of reconstruction failure or major complications, such as capsular contracture or implant exposure [17, 18].

Reconstruction failure rates, being consistently reported at the level of about 20%, are clinically significant when considering IB-IBR in the setting of PMRT [4, 18]. Capsular contracture is a well-recognized complication of IB-IBR, which can occur in the absence of PMRT, because all breast implants become surrounded by scar tissue or fibrosis, and in some cases, excessive fibrosis re-

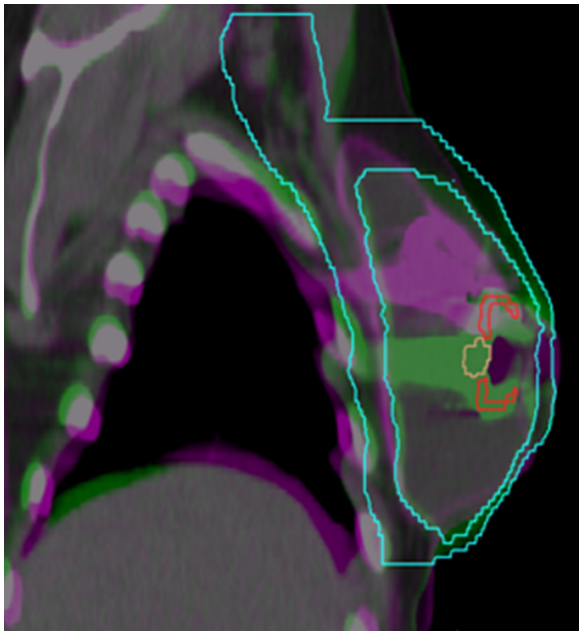

Figure 1. Anatomical position of prepectoral tissue expanders without acellular dermal matrix is not stable. Initial target positioning may be unreproducible, which results with additional delays or unplanned breaks in post-mastectomy radiation therapy due to the need for re-planning. Localization computed tomography image (pink) fused with the reference image (green). Clinical target volume – blue; magnetic metallic port – red and orange. The lack of reproducibility is clearly seen

sults in a shrinkage of the scar tissue ("capsular contracture") and noticeable distortion of the reconstructed or augmented breast. PMRT increases the frequency and worsens the degree of capsular contracture, as tissue fibrosis is a well known late normal tissue effect of radiotherapy [19]. Severe capsular contracture, where revisional surgery in the form of capsulotomy or capsulectomy with implant exchange is usually required, is reported at the level of more than 30% after IB-IBR and PMRT [4, 19]. Another major complications, i.e. requiring revisional surgery, are reported in one-third of patients after IB-IBR and PMRT [4].

Irradiated patients have an inferior cosmetic outcomes of IB-IBR: good or excellent cosmetic result attainable in about 90% of patients with IB-IBR alone, decreases to 57% after PMRT [20]. In two-stage prosthetic reconstruction, any sequence of PMRT (i.e. radiation to the TE, or to the permanent implant) negatively impacts the final aesthetic outcome and long-term implant survival. In this setting, the risk of reconstructive failure is significantly higher for patients with PMRT to the TE compared to patients with PMRT to permanent implant (six-year predicted failure rates of 32% *vs.* 16.4%, $p < 0.01$), but the final aesthetic results and capsular contracture rates are slightly better [21].

The impact of PMRT on the cosmetic outcomes after prepectoral versus retropectoral IB-IBR has not been clearly defined to date. With the increasing rates of prepectoral reconstructions being performed, it is important to assess the outcomes in the setting of PMRT, to ensure that morbidity rates are not higher, as these patients undergo PMRT without the presence of vascularized muscle over the implants [22]. There is a growing body of evidence from retrospective data to suggest that prepectoral reconstruction is an effective technique in the setting of PMRT, with morbidity rates similar or even better than those experienced with complete submuscular or dual-plane (partial submuscular) coverage techniques with PMRT [22, 23]. However, the use of ADM seems crucial for these patients, because it is believed that ADM may protect against capsular contracture after IB-IBR in the non-irradiated and PMRT settings, and the risk of extensive soft-tissue damage and expander exposure is greater in patients with prepectoral reconstruction without ADM [23, 24].

In summary, patients should be appropriately counseled about all the aforementioned risks and consequences of potential complications so they could make fully informed decisions.

Target volume definitions with respect to the reconstruction methods and disease stage

Most of the local recurrences after mastectomy occur at the level of the skin and subcutaneous tissue (about 75%) and within the pectoral muscle, especially near the primary tumour site (about 25%) [25]. Thus, European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines for target volume delineation in the setting of PMRT recommend that in case of retro-pectoral implants the CTV of the chest wall should be positioned ventral (anterior) to the major pectoral muscle [26]. In case of the retro-pectoral implants with partial coverage by the pectoral muscle and supportive material in the lower part, for patients with adverse factors or with the tumour localised close to the dorsal fascia, the ESTRO guidelines [26] recommend to include in the CTV the part of the chest wall that was initially not covered by the major pectoral muscle, taking into account the muscle's pre-surgical position (which preferably should be marked with surgical clips). After IBR using a prepectoral implant, the CTV is composed of 2 parts: the ventral part between the skin and the implant, containing the subcutaneous lymphatic plexus and eventual residual glandular tissue and the dorsal part between the implant and the pectoral muscle or the chest wall, containing eventual residual glandular tissue. This second part should be included in case of the presence of adverse tumour factors. In case of rib cage invasion, the ribs/intercostal muscles should also be included in the CTV, irrespectively of the reconstruction technique, however the guidelines emphasize that IBR is generally not advised in these patients. For selected patients with LABC considered for IBR, the CTV should be based on the discussion in a multidisciplinary team conference and carefully individually adapted per case, according to the high-risk areas for remaining subclinical tumour deposits. In case of ambiguities, it's recommended to include the entire mastectomy site including the implant [26]. Such a design of the CTV often results with less optimal dose distribution, and the risk for higher doses in normal tissues. The transplanted tissues (skin, fat, muscle) and synthetic materials (implant, TE, ADM) are not part of the CTV [26].

Boost dose and the use of bolus

According to the ESTRO guidelines [26], the use of a "tumour-bed" boost (i.e. additional radiotherapy dose) is not recommended, unless the surgeon has placed clips to mark anticipated and subsequently confirmed involved resection margins that cannot be removed surgically.

Bolus, i.e. the tissue equivalent material, is used in radiotherapy to provide build-up of dose to the skin surface. The main indication for the use of bolus after IB-IBR is skin involvement. As long as patients with skin involvement were not offered skin-sparing mastectomy, most of the European radiation oncologists did not use bolus [7], however nowadays the need for using bolus increases and up to two-thirds of radiation oncologists declare that they do not use bolus "unless the skin is involved" [10]. This may impact the aesthetic outcomes of IB-IBR, as the use of bolus was recognized as the only "technical" radiotherapy factor negatively influencing cosmetic results [27].

In patients with skin involvement who underwent IB-IBR, the use of bolus poses specific challenges, because to be able to fulfill its function, bolus material should adhere tightly to the skin. This is very often difficult or even impossible to achieve on the curved-shaped reconstructed breast (Fig. 2), resulting in the underdosage of the skin within the target volume, thus possibly influencing local control of the tumour. Offering the IB-IBR to the patients with skin involvement puts them at hi-

gher risk of local relapse that might be avoided if the patient underwent mastectomy with breast reconstruction delayed after completion of oncological treatment.

Tissue expander – deflated or inflated?

The volume of fluid within the implant affects radiation dose distribution and can make radiation treatment planning challenging [7]. On the other hand – expansion of the TE after completion of PMRT is usually not possible due to radiation--induced early and late normal tissue effects. Thus, the approach to the patients for whom IB-IBR and PMRT follows the neoadjuvant chemotherapy involves rapid expansion of the TE within 6 weeks and start of radiation to the TE within 8 weeks post-surgery [8]. This usually means the moderate volume of fluid within the TE, as pushing the inflation to the maximal volume within this short period of time would mean very thin and tightened skin and subcutaneous tissues, more prone to radiation damage. In particular situations, radiation oncologists would ask reconstructive surgeons to adjust the TE volume to facilitate PMRT planning or to improve the predicted reproducibility of the target positioning, but it should be kept in mind that PMRT to the completely deflated TE could make it impossible to expand the TE in the future. In patients with bilateral IB-IBR with TEs, most of the radiation oncologists will request that the TE be deflated in the contralateral unaffected breast to minimize radiation dose to this breast [7, 28]. Of note, the volume of fluid within the TE (or both TEs in case of bilateral IB-IBR) has to remain the same during the whole course of PMRT, starting on the day when the computed tomography for radiation treatment planning is performed.

The air-filled expanders (Fig. 3) are not suitable for irradiation, as the thin rim of tissues surrounded with air lies entirely within the build-up region (i.e. the layer between the surface and the depth of dose maximum; energy deposition increases gradually beneath the surface, reaching the equilibrium at a finite depth), so the dose distribution would be unacceptable, with significant underdosage of the CTV.

Tissue expander – the impact of an internal magnetic metallic port

Frequently used TEs contain the internal metallic ports with a strong magnet, through which the fluid is injected. The metallic port magnet is made of high-Z, high-density, rare-earth metal which results in artefacts in imaging and perturbation in dose distribution around the port when receiving PMRT to TE.

Dose is attenuated in the "shadow" of the TE port in patients receiving PMRT, with an average reduction of 7–13% in dose *in vivo* to skin surface, when compared with that predicted by the treatment planning system (TPS) [29–31]. This level of attenuation is considered likely to be clinically insignificant for most patients, but each centre should undertake its own appropriate measurements before utilizing TPS predictions [29].

Another dose perturbation is the increase in dose upstream of the metallic disk caused by backscatter and the dose beside the magnet caused by side scatter radiation. Backscatter measurements [30] showed that when the port is in the parallel orientation, i.e. parallel to the central axis of the beam, there is a 4% increase in dose close to the edge of the disk compared to the dose without the metallic disk, but this difference decreases rapidly farther from the disk edge and at distances greater than 3 mm there is no significant effect on

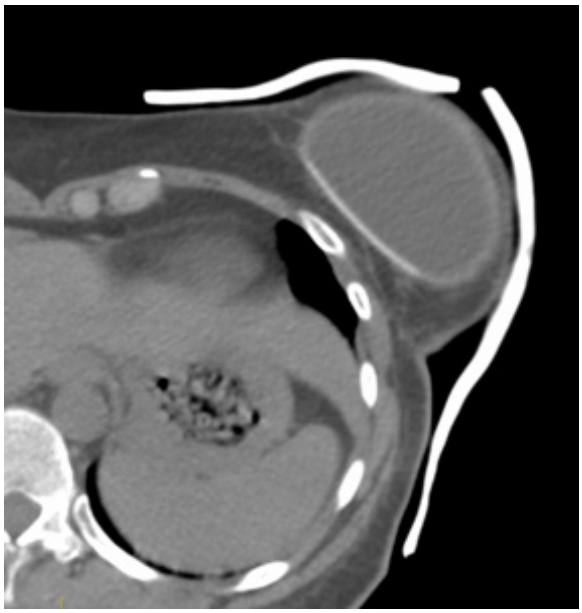

Figure 2. A bolus is a layer of tissue-equivalent material placed on the patient's skin during treatment that assists in providing the optimal dose of radiation. Bolus should adhere tightly to the skin, which is often difficult or even impossible on the curved-shaped reconstructed breast, resulting in underdosage of the skin within the target volume, thus possibly influencing local control of the tumour in patients with skin involvement

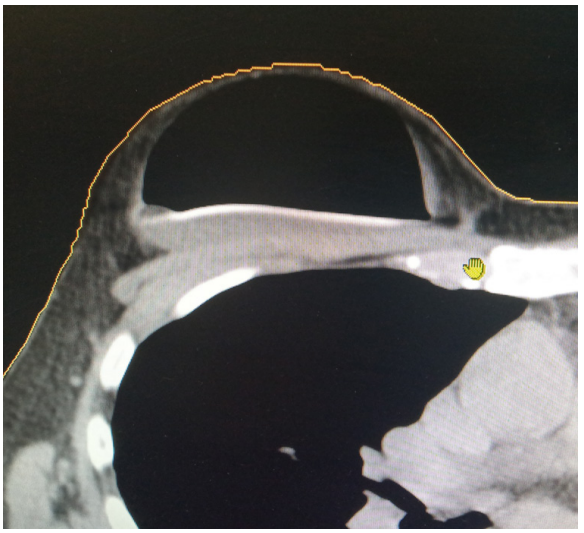

Figure 3. The air-filled expanders are not suitable for irradiation. The dose distribution would be unacceptable in the thin rim of tissues surrounded with air, with significant underdosage of the clinical target volume which in that case would be located within the build-up region

the dose. This port setup is similar to the way the TE might be irradiated in a patient with a parallel-opposed pair tangential beam arrangement. When the port is perpendicular to the central axis of the beam (one of the possible positions of the port during an arc-therapy delivery), the increase in dose is larger: 11% at the disk edge, but again this decreases sharply away from the disk edge so that there is no effect on the dose beyond 5 mm. Side scatter measurements [30] showed that there is an increase in dose of 2.75% compared to the dose without the metallic disk at the edge of the disk, decreasing to 0% at 7 mm away from the disk. Thus, the percentage increase in dose due to the scatter radiation is within the range acceptable in the treatment planning, and in case of the TE with an internal metallic port, the range of these secondary electrons scattered back from the implant is no more than 5 mm and should not result in an increase in dose to breast tissue, being absorbed in the silicone elastomer shell and saline components of the TE [30].

Conclusion

The complexity of integrating IB-IBR and PMRT underscores the need for close communication in multidisciplinary team to best prospectively coordinate and deliver patient-centered breast cancer care. Decision-making regarding the possibility of IB--IBR belongs to the surgeon and is based on the assessment of feasibility, the patient's characteristics and wishes, as well as the surgeon's skill and expertise, however – to offer breast cancer patients best outcomes in terms of disease control, toxicity, cosmesis and quality of life after reconstruction – surgeons and radiation oncologists need to develop "shared views" on risks and priorities for the particular patient. Thus, a radiation oncologist should always be present at the pre-surgery clinical meetings that plan breast reconstructions. Patients must be well informed, not only regarding potential benefits of IB-IBR, but also on the possibility of an increased risk of complications in the PMRT setting.

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Surgical anatomy of the breast revisited

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With the advent of breast conservation options in the 1970s, as well as wider acceptance of breast reconstruction in cancer patients in 1980/1990, ending up with evolution of oncoplastic concepts in the early 2000s, detailed surgical anatomy of the breast became important. This short article reviews surgical anatomy of breast with particular emphasis on innervation and blood supply to the skin and nipple-areolar complex, as well as points out the concept of compartmental breast cancer anatomy. Meticulous dissection and avoidance of transection of major vessels and nerves constitutes the crucial factor for satisfactory results of surgery in terms of preservation of sensation as well as appropriate vitality of skin.

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Key words: breast, surgery, anatomy, blood supply, innervation

Introduction

Definition of breast in English language dictionary is straightforward – a gland located on the anterior wall of female's thorax [1]. Detailed anatomy of the breast was for many years regarded as of marginal importance for surgical oncologists (apart from axilla anatomy). This could be mainly attributed to the fact that since Halsted's innovative concept in the end of 19th century, the breast surgery in cancer patients was only ablative and radical – the standard treatment was a radical mastectomy [2].

With the advent of breast conservation options in the 1970s [3–5], as well as wider acceptance of breast reconstruction in cancer patients in 1980/1990, ending up with evolution of oncoplastic concepts in the early 2000s, detailed surgical anatomy of the breast became important. Special attention was paid to the innervation of skin covering the gland (and to the innervation of nipple-areolar concept) and to the blood supply of the breast skin and – mainly – nipple/areola complex.

This short article reviews surgical anatomy of breast with emphasis on innervation and blood supply to the skin and nipple-areolar complex, as well as points out new concept of compartmental breast cancer surgery.

Breast blood supply

Breast blood supply comes from three main sources:

1. **Internal mammary (aka thoracic) artery (IMA/ITA)**, which is a branch of subclavian artery; it supplies mainly the medial portion of the breast (by its **anterior and posterior perforating branches**). Internal mammary artery delivers about 60% of total breast blood flow.
2. **Lateral thoracic artery (LTA)**, which arises from axillary artery or thoracoacromial artery or subscapular artery and supplies mainly the lateral and upper outer portions of the breast; lateral thoracic artery represents circa 30% of total blood flow in healthy female.
3. The remaining breast blood flow is provided by **the 2nd to 6th intercostal artery perforators**. The intercostal arteries arise directly from aorta; the 5th and 6th perforators serve as the blood supply of the inferior pole of the breast.

The second to fourth internal mammary artery perforators exit intercostal spaces approximately 2 cm laterally to the sternum; these vessels at that anatomical area during surgical dissection should be preserved, if possible. Anterior branches continue to run within the subcutaneous tissue of the breast and are found usually 0.5 to 1 cm deeper, from the medial

surface of the skin, reaching the nipple/ areola complex from the medial part. The importance of ITA branches for breast cancer surgery results from the following facts:

- these perforators are dominating blood suppliers to the breast (~60% of total blood supply to the breast),
- higher blood filling pressure in these branches (close next),
- well-developed anatomoses between these vessels and neighbouring vessels.

That is why pedicled oncoplastic reconstructions based on these vessels is safe and effective. Moreover these perforators are used as an alternative recipient vessels in microsurgical breast reconstruction [6–10].

Lateral thoracic artery branches are frequently found from 1 to 2.5 cm from the skin surface (i.e. deeper compared to ITA branches), as more subcutaneous tissue is present in the lateral quadrants of the breast as opposed to its medial parts. That is why as the areola is approached, vessels climb more and more superficial. Peripheral branches of LTA course infero-medially within the subcutaneous tissue to finally anastomose with branches of the ITA/IMA and intercostal arteries in the NAC area [6–9].

A minor blood supply derives from the perforators of the pectoral branch of the thoracoacromial artery, a branch of the axillary artery.

Nipple-areola complex main blood supply is provided by branches of both ITA/IMA and LTA, which communicate with each other behind the areola. Small branches deriving from these communicating vessels run upward, toward nipple and surrounding areola. Minor vessels reach the base of the nipple and give off even finer vessels travelling to the areolar skin, and ascending into the nipple; vessels arborize in the upper and middle thirds of the nipple [6–9].

Moreover from the surgical point of view it is important to emphasize that the skin of the breast and the NAC are supplied by a continuous vascular plexus formed by the anastomoses of the aforementioned vessel; it is mainly a subdermal plexus running between the superficial fascia of the breast and the subcutaneous fat of the skin and its viability is mainly influenced by the surgical technique [11].

Breast sensory innervation

Sparing the nipple and areola during breast oncoplastic and reconstructive surgery serves virtually no purpose, if the nipple is insensate postoperatively.

Sensory innervation of the breast skin comes from **lateral cutaneous branches** of the 2nd through 6th intercostal nerves and **anterior cutaneous branches** of the 2nd through 6th intercostal nerves. Lateral branches of the intercostal nerves exit the intercostal spaces at the anterior attachment sites of serratus anterior muscle; afterwards these branches cross breast parenchyma (deep branches) and reach nipple-areolar complex from behind. Anterior branches of the intercostal nerves run superficially within subcutaneous tissue beneath the skin, do not cross breast parenchyma (this is opposite to the lateral branches, which crosses the parenchyma) and approach nipple-areolar complex from the medial aspect of areola.

It is important to underline, that 2nd and 3rd intercostal nerves give rise only to cutaneous branches to the very superior aspect of the breast. Additionally limited region over the upper portion of the breast supplied by the cervical plexus (i.e. anterior or medial branches of the supraclavicular nerve). Innervation of the remaining breast comes mainly from the 4th, 5th and 6th intercostal nerves. All these nerves convey sympathetic fibers to the breast and overlying skin and influence:

- flow of blood through vessels,
- secretory function of the sweat glands. Secretory function of the gland is regulated by hormonal axis [6–9].

Nipple innervation relies solely on branches of 4th intercostal nerve: it is assessed that over 90% of innervation of the nipples comes from deep branches of lateral cutaneous nerve (arising from the 4th intercostal nerve), and for circa 7% of nipple innervation superficial branches of lateral cutaneous nerve (arising from the 4th intercostal nerve) are responsible. These nerves are best protected if surgical resection starts at the base of the breast and skin incisions at the medial edge of the areola are avoided [6–9,12]. Table I sums up the data on nipple-areola complex innervation.

Lateral branch of the 2nd intercostal nerve is of special significance because it gives away fibres to a large nerve – intercostal brachial nerve. It has limited functional significance, but if injured, patient losses cutaneous sensation from the upper medial aspect of arm and axilla floor [6–9, 12].

Compartmental breast concept

Würinger et al. described concept of horizontal fibrous septum dividing the breast parenchyma into upper and lower portions. It contains major vessels and nerves climbing up to the NAC. It extends medially from the sternum to the lateral edge of

Table I. Nipple-areola complex innervation

Lateral branches	Anterior branches
usually transected during mastectomy	usually transected during mastectomy
often partially transected during majority of WLE/LE	often transected in medial quadrants WLE/LE
by meticulous planning and dissection **deep and or superficial fibres of lateral branches should be preserved** (mainly peripherally located tumors)!	meticulous planning and dissection to avoid transection

pectoral minor muscle, curving upwards at the lateral and medial border, reaching the level of 2nd rib. On its horizontal part at the thoracic wall it follows the 5th rib. The horizontal (transverse) septum serves as suspensory scaffolding for the breast [13, 14]. Recently vertical septum was described, running from the infra-mammary crease centrally to the NAC, joining the horizontal septum and dividing lower portion of the breast into two parts [15]. These transverse and vertical septa create altogether compartmental breast structure and are directly linked to the anatomy of the breast vessels and nerves pathways, therefore are important in breast surgery planning.

Conclusions

Detailed knowledge of breast skin innervation and blood supply is mandatory for surgical oncologists performing breast surgery – reconstructive and oncoplastic resections. Meticulous dissection and avoidance of transection of major vessels and nerves is crucial factor for satisfactory results of surgery in terms of preservation of sensation as well as appropriate vitality of skin.

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VIA MEDICA

Short review

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Should adjuvant radiotherapy be used in patients with early stage Hodgkin's lymphoma? A vote for yes

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Hodgkin's lymphoma (HL) belongs to the most radiosensitive and chemosensitive cancers. Combined modality therapy is the preferred treatment for patients with classical favorable early-stage HL. However, late toxicity still remains an issue. A modern approach in HL radiotherapy includes implementation of sophisticated and dedicated delivery techniques together with the lower doses and smaller fields, which allow for reduction of early and late toxicity. In recent years, the question on the need for complementary radiotherapy in the early stages of Hodgkin's lymphoma has been increasingly raised. The aim of the present review is to discuss the current role of radiotherapy and its potential future developments, with a focus on major clinical trials.

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Key words: Hodgkin's lymphoma, chemotherapy, radiotherapy, combined modality treatment

Introduction

Hodgkin's lymphoma (HL) belongs to the most radiosensitive and chemosensitive cancers. Most frequently young persons, 20–40 years old, suffer from it [1]. In most patients, however, the disease is diagnosed in early stages, which allows for effective recovery and long-term survival.

The key role in the therapy of early stages Hodgkin's lymphoma is played by radiotherapy. Historically, it was the first method of treatment for this disease. Demonstrating the advantage of combined treatment for many years has established a scheme of standard treatment of this disease. The role of chemotherapy alone at early stages has not been precisely defined and has been the subject of endless discussions for many years.

Review of the main studies on the combined treatment of early stage Hodgkin's lymphoma

Research by the German Lymphoma Group – German Hodgkin Study Group (GHSG), has established standards of management in stage I and II according to the Ann Arbor classification. On the basis of HD10 trial it was found that in patients with favorable prognostic factors 2 cycles of ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) with adjuvant involved field radiotherapy (IF-RT) at the dose of 20 Gy are equally effective and less toxic than 3 cycles of ABVD with radiotherapy at the dose of 30 Gy [2]. In turn in patients with adverse prognostic factors, a scheme consisting of 4 ABVD cycles or in younger patients (under 60 years of age) – also chemotherapy according to BEACOPP (bleomycin, etoposi-

de, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and IF-RT at a dose of 30 Gy is the recommended standard of treatment [3].

According to the recommendations of the European Society for Medical Oncology (ESMO), the standard procedure is combined treatment, including chemotherapy with radiotherapy [1]. Modern methods of treatment provide very high percentage of cured patients in this group. Therefore, late treatment complications are an increasing therapeutic problem. Late complications of radiotherapy are widely known, mainly in the context of secondary cancers. In turn, data on the long-term toxicity of systemic treatment are less known. The introduction of modern, highly effective and less toxic chemotherapy schemes makes radiotherapy appear to be an old-fashioned method. Hence the question: can we give up the adjuvant irradiation in early stage Hodgkin's lymphoma patients?

Chemotherapy alone versus combined treatment

The first reports comparing chemotherapy alone with combined treatment showed better control of the disease in patients treated with radiotherapy [4–6]. According to some, such a difference applies only to patients at an early stage with favorable prognostic factors, according to others it is true only in patients with unfavorable prognosis [4–6]. An unquestionable disadvantage of early research in this field are the outdated methods of treatment. These include the previously used large irradiation fields and the lack of PET diagnostic imaging, both during the initial assessment of the progress and to evaluate the metabolic response after chemotherapy. The data obtained from the above-mentioned studies are quite ambiguous and have opened a debate on the necessity of adjuvant radiotherapy in patients with early Hodgkin's lymphoma, a debate that is still ongoing.

Several recent studies have attempted to make a contribution to this discussion [7–9]. An integral part of the protocol was the PET imaging, which was used to assess the stage of the disease and to evaluate early cancer treatment response. In the experimental arm of those studies were patients with complete remission after 2–3 cycles of systemic treatment, who were randomized to chemotherapy alone or combined treatment. According to the above scheme 3 large, randomized trials were conducted: RAPID (UK NCRI), HD16 (GHSG) and H10F/U (EORTC/GELA/FIL) [10]. And while the main concept of these trials was similar, they differed in several details.

Firstly, none of them applied the current standard of treatment as the control arm. Secondly, the H10 trial introduced a limited irradiation volume, namely the involved-node radiotherapy (IN-RT). In addition, other studies used a conservative method of radiotherapy, i.e. involved-field radiotherapy (IF-RT). All of them also differ in terms of the doses used and, importantly, only in the GHSG HD16 trial the "modern" radiation therapy doses were used, i.e. 20 Gy in patients with favorable prognostic factors. Differences also apply to chemotherapy. Only in the HD16 trial the patients with favorable prognostic factors received 2 ABVD cycles. In other cases, patients received at least 3 cycles of chemotherapy according to the ABVD scheme.

In the group of patients treated with chemotherapy alone, a significant difference in time free from progression was shown. In case of the RAPID study, after 3 years of observation, the difference was 3.8% in favor of combined treatment. In the H10 study, the 5-year time free from progression was 99% and 87.1%, respectively, in the group treated with combined treatment vs. chemotherapy alone. It should be emphasized that the increased risk of relapse did not translate in both studies to worse overall survival in the group of patients treated with chemotherapy alone. No HD16 results have been published so far, but early analyses presented in 2018 in the form of an abstract at the convention of the American Society of Hematology suggest similar results.

In 2017 Cochrane's meta-analysis of combined treatment for patients with early Hodgkin's lymphoma was published [11]. Its main conclusions are comparable to the results of the above-mentioned studies. Namely, when an identical number of courses of chemotherapy was administered in both arms, no difference was observed in overall survival (OS) in patients treated with chemotherapy alone compared to patients treated with combined treatment. In patients treated with chemotherapy alone a shorter progression free survival (PFS) was observed. Significantly, there were no differences in mortality rates associated with infections, secondary cancers and cardiological diseases. As a different number of chemotherapy courses were applied in both arms, it is difficult to draw clear conclusions about PFS and OS due to poor quality of scientific evidence and heterogeneity of studies. In a subgroup of patients with early Hodgkin's lymphoma and with a favorable prognosis, the advantage of combined therapy in the context of PFS was demonstrated. However, in patients with adverse prognostic factors, such an advantage has not been demonstrated.

The above-mentioned studies have not been designed in an optimal way, i.e. in a way that would allow to draw a clear conclusion that chemotherapy alone is equally effective in comparison with current standards of combined treatment in patients with early Hodgkin's lymphoma with a favorable prognosis.

The role of PET

At this point, it is also important to mention the key role of PET imaging as a tool to assess the response to treatment. The value of metabolic regression assessment after 2–3 courses of chemotherapy in patients with early stage without risk factors is unclear and retrospective analyses provide contradictory results. However, the majority of scientists are of the opinion that such a study should be performed in this group of patients

[12–16]. In contrast, in patients with more advanced stages (stage II with adverse prognostic factors and stages III and IV according to Ann Arbor), interim PET after 2–4 cycles of chemotherapy is a sensitive prognostic factor [17, 18].

It is also worth noting that in large randomized trials, the evaluation of PET scans was verified by a panel of experts. In everyday practice, the standard is to rely on an independent description of a nuclear medicine specialist, which may cause some differences in the interpretation of results. Is this a sufficient parameter to assess the severity of the disease? It turns out that not necessarily, because more and more data published in the literature proves that other parameters, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), can also be more objective indicators [19].

Innovations in radiotherapy and strategies to reduce radiation toxicity

As for the modern approach to radiotherapy, which consists of reducing the size of irradiation fields and reducing doses of ionizing radiation, these have resulted in lower expected toxicity of the treatment. Extended field radiotherapy (EF-RT) techniques have been replaced by the techniques of irradiating the region of originally involved lymph nodes, involved field radiotherapy (IF-RT), which provided comparable results while reducing toxicity [20, 21]. Currently, in accordance with the recommendations of the International Lymphoma Radiation Oncology Group (ILROG), only the area of the originally involved sites should be irradiated: involved site radiotherapy (ISRT) [22]. To date, there are no prospective randomized studies comparing ISRT with IFRT, although more and more reports suggest that field size reduction does not adversely affect the risk of relapse [22]. The ongoing GHSG HD17 study, for which recruitment closed at the end of 2019, is likely to provide an answer to this question. The current guidelines, both by European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), recommend using ISRT.

In recent years we have also witnessed an extremely rapid development of radiotherapy. Current techniques allow not only to precisely determine the target volume (fusion of localization tomography with MR or PET scan), but also to precisely locate the irradiated area (image-guided radiotherapy, IGRT). IGRT techniques include imaging obtained by using electronic portal imaging device (EPID) systems, 2D-2D kV, KV- CBCT, MV--CBCT, MVCT or ultrasound examination. One of the modern radiotherapy technique is also 4D radiotherapy, where the fourth dimension is time. An incredible advantage of this method, especially in the case of lesions located in the chest area, is the adaptation to the change of the target volume position during a treatment session. And what is additionally important, over the last dozen or so years the method of radiotherapy treatment has also changed: a traditional 3D-CRT conformal technique (conformal radiotherapy) is being replaced by IMRT (intensity modulated radiotherapy) techniques.

All these techniques enabled more conformal dose distribution to the target volume and reduction of doses in critical organs, which directly translated into lower toxicity of radiotherapy [23].

Summary

It should be emphasized that patients diagnosed with relapse require intensive second line treatment, often with autologous hematopoietic cells transplantation. Such treatment may result in significant early and late toxicity, often exceeding that of the primary combined treatment. It is estimated that only half of them will achieve long-term remission of the disease.

In conclusion, due to the lack of convincing proofs to support chemotherapy alone, the standard of treatment of the early stages of Hodgkin's lymphoma is still combined therapy. ESMO guidelines for the early stages of Hodgkin's lymphoma recommend combined therapy. NCCN guidelines, on the other hand, allow for chemotherapy alone only in a narrow group of patients who meet all favorable prognosis criteria. Although modern radiotherapy techniques have the potential to reduce the risk of late complications, longer observations are still necessary, if only to confirm this thesis. And, equally importantly, whenever possible, patients should be allowed to participate in prospective randomized clinical trials.

Conflict of interest: none declared

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We are presenting one of the voices in the debate. The other participant in the debate has not presented their article.

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VIA MEDICA

Case report

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Malignant granular cell tumor of the lumbar region – a case report and review of the criteria for diagnosis

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We report an unusual case of a malignant granular cell tumor of the left lumbar region in 63-year old woman – diagnosed, consulted and treated with surgical resection (R1) and radiotherapy, followed up for 2 years with lung metastases after 22 months. Furthermore, we discuss histopathological differential diagnosis and current criteria for malignancy, as well as available options for systemic treatment in view of cytogenetic and molecular genetic characteristics of the tumor.

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Key words: granular cell tumor, malignant granular cell tumor, differential diagnosis, immunophenotype

Introduction

Granular cell tumor (GCT) was first described in 1926 by Abrikossoff as myoblastoma, although it is now believed that tumor cells are of Schwannian origin [1]. Malignant granular cell tumor (MGCT) was first reported in 1945 by Ravich et al. and comprises 0.5–2% of all GCT cases [2]. The current literature review includes no more than 100 MGCT case descriptions. MGCTs are usually larger and faster-growing than their benign counterparts, the female-to-male ratio is lower and they are more often located in the skin (which can ulcerate) or soft tissue of extremities and trunk rather than head and neck region or gastrointestinal tract. Most importantly, they exhibit metastatic potential. The classification for malignancy is still debatable, and there persists the gray zone, where lesions have the vague potential for local recurrence or distant metastases.

In 1998, Fanburg-Smith et al. proposed subsequent criteria for histopathological MGCT, based on their study of 73 cases: necrosis, at least 3 mitoses per 10 high power fields (HPF, 400 x magnification), pleomorphism, spindling of the tumor cells, increased nuclear to cytoplasmic ratio, vesicular nuclei with prominent nucleoli [3]. According to the suggested criteria, at least 3 out of 6 features are required to confirm the malignancy; 1 or 2 suggest uncertain behavior (atypical GCT); only focal pleomorphism strongly advocates for a benign tumor. Curtis et al. classified MGCT in 3 categories:

1. tumors with both malignant behavior and malignant histology,
2. tumors with atypical histology that are clinically aggressive but not metastatic,
3. tumors with aggressive clinical behavior that are histologically benign [4].

In 2011 Nasser et al. suggested other criteria for malignancy: confirmed metastasis – as being the only accurate – and histological and cytological characteristics (necrosis and/or mitoses present) – only indicative of the malignant potential of the lesion (GCT-UMP) [5].

Due to the rare occurrence of MCGT, regardless of its further biological behavior, the pathologist is obliged to differentiate the lesion from a list of mimickers. For tumors with histologically atypical features, sarcomatoid carcinoma, melanoma, epithelioid malignant peripheral nerve sheath tumor (MPNST), alveolar soft part sarcoma (ASPS), dermatofibrosarcoma (DFSP), angiosarcoma and leiomyosarcoma must be excluded.

We present a case report of a 63-year old Caucasian female with MGCT (classified according to Fanburg-Smith criteria) in the lumbar region and discuss the classification, differential diagnosis, and treatment.

Case presentation

A 63-year old female with lumbar pain for 6 months underwent radiographic imaging with magnetic resonance scan revealing soft tissue, hypodense, poorly circumscribed, solid mass of 10 x 8 x 8 cm, infiltrating lumbar muscles (Fig. 1 – A.1). The initial diagnosis made by open biopsy sampling outside our center was of Abrikossoff tumor with features suspicious for malignancy and a histopathological consultation was evaluated in the Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw.

Pathology findings

Biopsy showed sheets of spindled, polyhedral and focally pleomorphic cells with abundant, granular, eosinophilic cytoplasm with focal condensations of intracytoplasmic hyaline-like globules and vesicular nuclei with prominent nucleoli. Necrosis was present as well as mitotic activity of 3/10 HPF. Tumor displayed immunopositivity with S100 (nuclear and cytoplasmic, diffuse and strong), TFE3 (nuclear, strong), SOX10 (nuclear, strong), CD56 (membrane and cytoplasmic, diffuse and strong), CD68KP1 (cytoplasmic, focal, weak), NSE (cytoplasmic, diffuse, weak), Nestin (cytoplasmic and membrane, diffuse, weak) and negative for CKAE1/AE3, SMA, HMB-45, NF, GFAP mono, Inhibin, Calretinin, Desmin, MITF, Melan-A. The pathological findings are presented in figure 1 – A.2.

Treatment and follow-up

Excision of the tumor was undertaken in the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw. The excised specimen was non-encapsulated, white-tan, firm, homogenous tumor of 9 x 8.5 x 8 cm with focal necrosis (5% of the tumor mass), which was located mostly above and partially under the fascia of lumbar muscle. The margins were involved by the tumor (microscopically R1 resection). Microscopic examination confirmed the initial diagnosis of malignant granular cell tumor. The patient underwent adjuvant radiotherapy [VHAT with CBCT, 6MV, 30 fractions per 2 Gy, total dose 60 Gy] and remains under close observation. After 22 months from the operation the patient developed local recurrence and distant metastases and was referred to regional hospital for chemotherapy (Adriamycin – 15 mg/m^2, Dacarbazine – 150 mg/m^2, Cyclophosphamide – 100 mg for 5 days every 21 days).

Discussion

The importance of depicting cases with malignant features lies in the poor prognosis for metastatic disease (60% survival in 3 years). Due to the low number of cases, guidelines for staging, treatment, and follow-up are still lacking. A wide excisional margin is optimal because of the infiltrative pattern of growth and the tendency to recur. It has been described that MGCTs can result from malignant transformation of benign GCT, so margins preservation is highly recommended also for benign-appearing lesions [6–8].

Macroscopic sampling is one of the key points in diagnostics, especially when the lesion is 4 cm or larger; following the standard protocol for soft tissue sarcoma processing is advised. Differential diagnosis of the cases with malignant features (necrosis, >2 mitoses/ 10 HPF, high nuclear to cytoplasmic ratio, polymorphism, spindling of the cells, vesicular nuclei with prominent nucleoli) should include melanoma, MPNST, DFSP, spindle cell carcinoma [9]. The broad panel of immunohistochemical stainings is needed. Briefly, melanomas are usually positive for more than one melanocytic markers, i.e. HMB-45, Melan-A, and MITF; MPNST shows weaker and focal expression of S100 in comparison to GCT/MGCT, DFSP is positive for CD34 and carcinomas more often express cytokeratins. In difficult cases, the panel needs to be extended according to

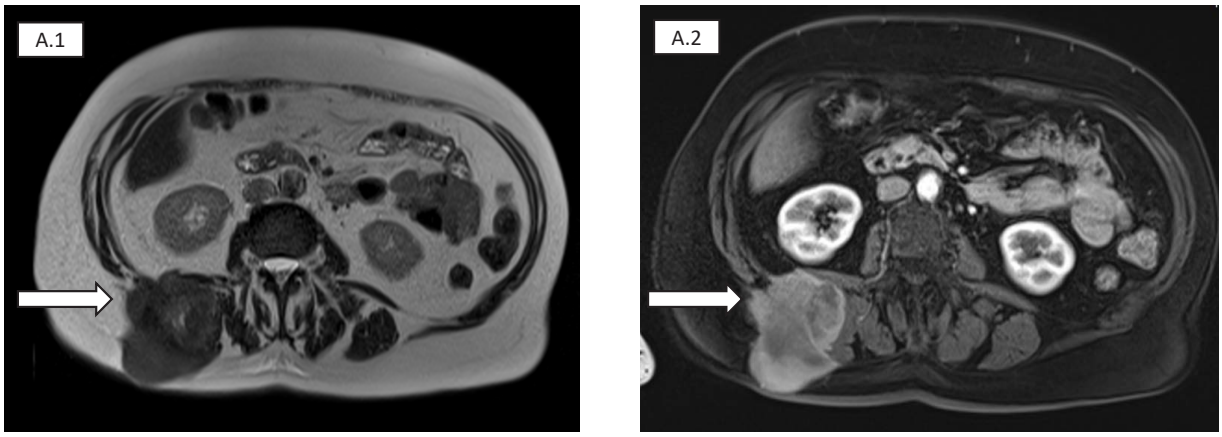

Figure 1. Magnetic resonance scan revealing soft tissue, hypodense, poorly circumscribed, solid mass (arrows) of 10 x 8 x 8 cm, infiltrating lumbar muscles (A.1 & A.2)

morphological features and results of initial immunophenotypisation. In the presented case, TFE3 was strongly positive, but no PAS/D granules were found, which helped to exclude ASPS. Moreover, the additional "neural" panel of consecutive stains was evaluated including GFAP, NF, NSE, CD56, SOX10, and Nestin; it tends to be positive in MPNST and negative in ASPS [9–11]. The immunohistochemical characteristics with differential diagnosis were depicted in table I.

The pathologist should always highlight the possibility of aggressive behavior, based on recognized histological features (especially necrosis and mitosis) and high Ki-67 ratio (>10% is a poor prognostic factor). It is debatable if "malignant granular cell tumor" can be a histopathological diagnosis rather than a clinical one (confirmed metastasis) and if a designation of "granular cell tumor with uncertain malignant potential" seems to be more accurate, especially in the setting of rapidly-growing or large tumor (>4 cm). The diagnostic criteria of MGCT according to Fanburg-Smith et al. and Nasser et al. are presented in figure 2 [3, 5].

The diagnosis of GCT-UMP requires continuous observation of the patient. Wide excision margins remain the best possible option, as the role of chemotherapy or radiation therapy remains indefinite. In MGCT, adjuvant radiotherapy on the tumor bed can be delivered with the aim of reducing local recurrence risk [11]. In our case, due to R1 resection of the lesion, the patient underwent postoperative radiotherapy. The two-year follow-up showed aggressive tumor behavior with local recurrence and local metastases.

The results of genetic studies on GCT/MGCT are scarce (based on single cases), but have revealed the heterogeneity of the alterations with no specific karyotype and the absence of most of the alterations described in schwannomas and

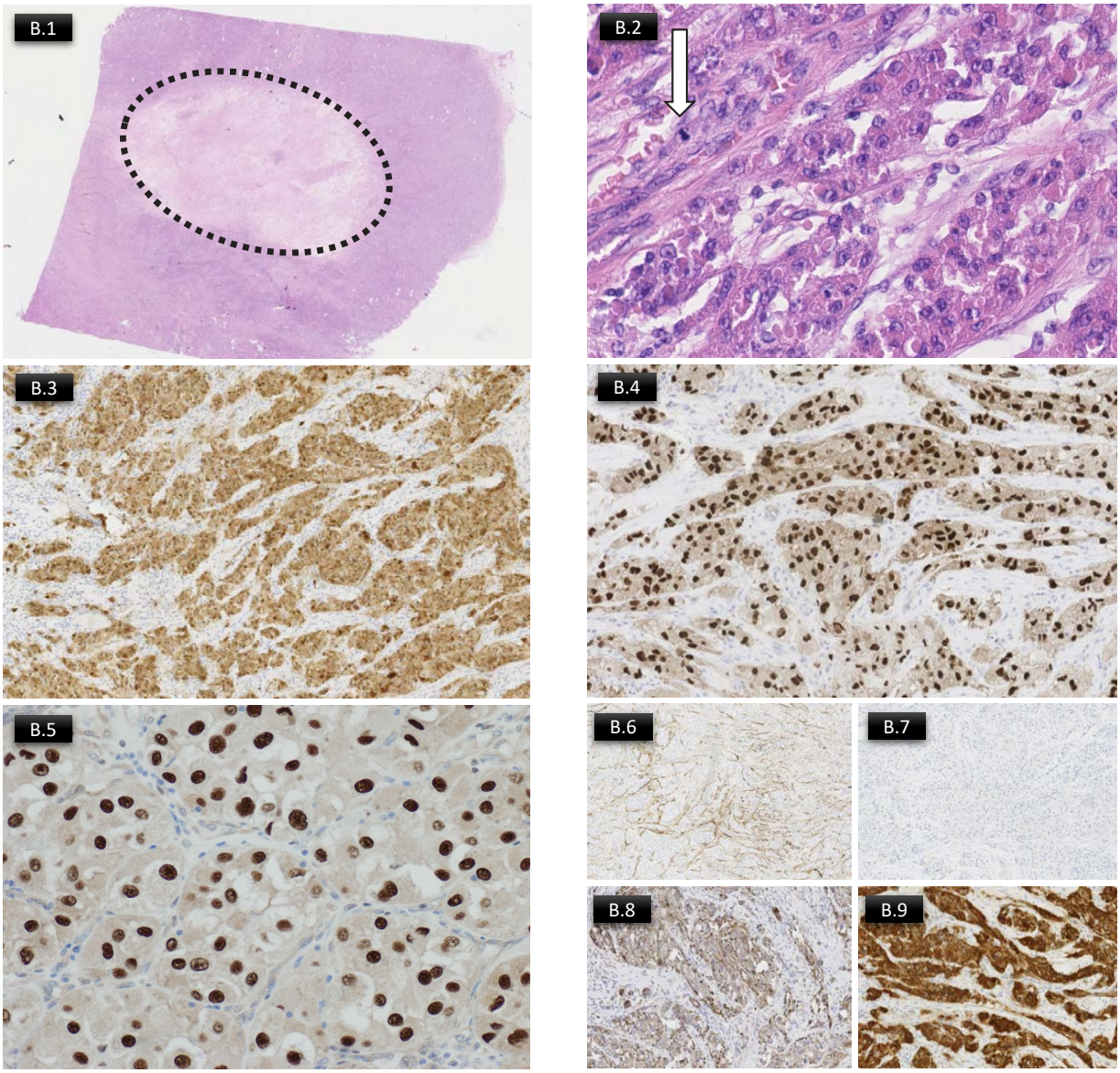

Figure 2. B.1: Hematoxylin and eosin staining (HE, 40x) with marked necrosis (circle); **B.2**: HE (200x) with visible mitotic activity (arrow); **B.3**: S100 (100x); **B.4**: SOX10 (100x); **B.5**: TFE3 (400x); **B.6**: SMA (100x); **B.7**: HMB-45 (100x); **B.8**: Nestin (100x); **B.9**: CD56 (100x magnification)

Table I. Immunohistochemical differential diagnosis of granular cell tumor/ / malignant granular cell tumor (GCT/MCGT – granular cell tumor/ malignant granular cell tumor; EMPNST – epithelioid malignant peripheral nerve sheath tumor; ASPS – alveolar soft part tumor; MM – malignant melanoma; CA – cancer); blue – positive, navy – negative, white – positive in limited number of cases

Marker	Type of maliganancy				
	GCT/MGCT	EMPNST	ASPS	MM	CA
PAS/D					
S100					
Inhibin					
SOX10					
Nestin					
Calretinin					
TFE3					
CK					
HMB45 or Melan-A					
CD68					

MPNST. Overall, the sequencing results indicate that the abnormalities of ASXL1-, Notch2-, and PARP4-mediated pathways are possibly involved in the disease initiation and progression of MGCT [12, 13]. Moreover, single studies showed metabolic response to treatment with pazopanib – a small-molecule inhibitor of vascular endothelial growth factor receptor-1, -2 and -3, platelet-derived growth factor receptor-α and -β, and c-kit, which is an approved drug in the treatment of soft tissue sarcomas and there are first reports that this targeted therapy allows for improvement of progression-free survival [13–16].

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