ISSN 2543–5248
e-ISSN: 2543–8077

Tom 7 | Numer 4 | Rok 2022

Biuletyn Polskiego Towarzystwa Onkologicznego

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Nowotwory. Journal of Oncology – indeksacja:
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ISSN 2543–5248
e-ISSN: 2543–8077

21-0502.004.001

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Spis treści

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Edytorial

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 249

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Polskie Towarzystwo Onkologiczne – kontynuacja działań i nowe wyzwania

Zdjęcie: archiwum

Polskie Towarzystwo Onkologiczne (PTO) to największe i najstarsze polskie towarzystwo naukowe w onkologii, które jednoczy wiele specjalności medycznych. Jest to również Towarzystwo czynnie działające na rzecz zmian organizacyjnych w polskiej opiece onkologicznej i te działania bezwzględnie będą kontynuowane.

Po pierwsze, PTO będzie wspierać realizację Narodowej Strategii Onkologicznej jako największej kompleksowej reformy polskiej onkologii. Po drugie, niezwykle ważne jest większe zaangażowanie członków PTO w jego działania, w tym zwiększenie kontaktów z zarządem Towarzystwa. Tworzymy grupy tematyczne do reprezentacji stanowisk PTO w różnych dziedzinach. Ponadto zwiększymy działalność edukacyjną PTO, m.in. poprzez dwie coroczne konferencje *Onkologia precyzyjna w praktyce klinicznej* (która miała miejsce 23 czerwca) i *Wytyczne w onkologii* (która odbędzie się 29 września). Rozbudowujemy newsletter kliniczny i prasowy PTO, który wydaje się najlepszym tego rodzaju informatorem z zakresu onkologii w Polsce. Zachęcamy również do korzystania ze środków komunikacji elektronicznej: strony internetowej (pto.med.pl) i twittera (@OnkologiaPolska). Planujemy rozwój stypendiów zjazdowych i nagród naukowych PTO.

Realizujemy bieżące projekty, np.:

- bezpieczeństwo chorego na nowotwór poddawanego immunomodulującemu leczeniu systemowemu (współpraca z innymi towarzystwami naukowymi, m.in. Polskim Towarzystwem Kardiologicznym czy Pulmonologicznym),
- wytyczne postępowania u chorych z zaburzeniami odporności w sytuacji przedekspozycyjnej i zakażenia SARS-CoV-2,
- minimalne wytyczne dla klinicystów dotyczące diagnostyki molekularnej nowotworów.

Wspieramy również prace Ministerstwa Zdrowia w zakresie rozwoju profilaktyki nowotworów – chcemy, aby w niedalekiej przyszłości działania profilaktyczne były zintegrowane z Internetowym Kontem Pacjenta.

Wspieramy także bieżącą działalność ośrodków onkologicznych – właśnie kupiliśmy 8 translatorów, które ułatwią komunikację z pacjentami onkologicznymi z Ukrainy lub innych krajów, którzy nie porozumiewają się w języku polskim, i przekazujemy je do regionalnych ośrodków onkologicznych.

Na koniec chciałbym zaprosić wszystkich polskich onkologów do współpracy w ramach Polskiego Towarzystwa Onkologicznego, bo po prostu warto.

Piotr Rutkowski
Przewodniczący Zarządu Głównego Polskiego Towarzystwa Onkologicznego

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Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 250–257

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Cyclooxygenase-2 and Bcl-2 expression in patients with triple-negative breast cancer

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Introduction. Triple-negative breast cancer (TNBC) is a rare type of breast cancer associated with lack of expression of estrogen and progesterone receptors and the HER2 protein. It is characterized by a poor outcome and chemotherapy resistance. Cyclooxygenase-2 (COX-2) is a constitutional enzyme responsible for prostaglandin synthesis, present in neoplastic cells and premalignant lesions. The B-cell lymphoma 2 (Bcl-2) protein is considered one of the most potent apoptosis-regulating agents, assuring body homeostasis.

Material and methods. The aim of the present study was to evaluate the immunohistochemical (IHC) profile of COX-2 and Bcl-2 expression in patients suffering from TNBC in order to obtain more detailed data on additional factors negatively influencing TNBC outcome. The IHC evaluation of COX-2 and Bcl-2 expression among 21 women with diagnosis of TNBC was performed.

Results. The most common histological subtype was invasive ductal cancer of no special type. COX-2 was present in all examined samples with moderate to strong expression detected in 20 of 21 cases. There was a positive correlation between histological grade (G) and COX-2 expression ($p = 0.002$). Bcl-2 was present in all examined samples. The analysis showed that tumours presenting highly positive expression of Bcl-2 accounted for the majority of examined cases (57.2%).

Conclusions. The achieved results might lead to a conclusion that COX-2 and Bcl-2 high expression in TNBC may be linked to tumour aggressiveness and poor overall survival. However, before their consideration as additional markers to be used in routine histological examinations and breast cancer grading, it will be necessary to undertake further studies.

Key words: Bcl-2, cyclooxygenase-2, immunohistochemistry, prognostic factors, triple-negative breast cancer

Introduction

Breast cancer is the most common type of cancer among women worldwide. This heterogeneous group of malignant neoplasms represents 22.2% of newly diagnosed cancer cases and 13.3% of cancer-related deaths. Unfortunately, its incidence is constantly on the rise [1]. Triple-negative breast cancer (TNBC) is a rare histological type of breast cancer characterized by a lack of presence of estrogen and progesterone receptors and the HER2 protein. A wide range of studies have shown its association with a poor outcome, low 5-year overall survival rate, chemotherapy resistance and co-existence with younger patients age [2].

Cyclooxygenase is a constitutional enzyme responsible for prostaglandin and thromboxane synthesis, occurring in two isoforms. Cyclooxygenase-2 (COX-2) is present in inflamed tissues, neoplastic cells and premalignant le-

Jak cytować / How to cite:

Liszcz-Tymoszuk A, Fudalej M, Deptała A, Badowska-Kozakiewicz AM. ***Cyclooxygenase-2 and Bcl-2 expression in patients with triple-negative breast cancer.*** *NOWOTWORY J Oncol* 2022; 72: 211–218.

sions. It enhances cellular proliferation, tissue invasion and angiogenesis, in addition to its anti-apoptotic effect [3], it subsequently provides prime conditions for developing a tumour. Epidemiological studies showed a relation between COX-inhibiting drugs (nonsteroidal anti-inflammatory drugs – NSAIDs) and reduced cancer risk of the gastrointestinal tract [3]. Studies conducted over the years showed that medications inhibiting COX-2 might act as possible chemopreventive agents in breast cancer, since increased expression of COX-2 in tumour samples was often observed [4, 5]. As a result of those findings, cyclooxygenase was also considered as a biochemical marker of poor prognosis.

Another fundamental aspect of neoplastic processes is evasion of programmed cell death. B-cell lymphoma 2 (Bcl-2) protein is a product of the *BCL-2* gene and is considered one of the most potent apoptosis-regulating agents, assuring body homeostasis. This protein prevents apoptosis by deterring cytochrome C and apoptosis inducing factor (AIF) in mitochondria, thus inhibiting the caspase-dependent apoptosis pathway [6]. Overexpression of Bcl-2 was observed in number of cancers; also in case of breast cancer. Moreover, expression of Bcl-2 was established as an independent risk factor of poorer breast cancer prognosis [6, 13, 30].

The aim of our study was to evaluate the immunohistochemical profile of COX-2 and Bcl-2 expression in patients suffering from TNBC in order to obtain more detailed data on additional factors negatively influencing TNBC outcome (fig. 1).

Material and methods

Patients

The patient population comprised 21 women with a diagnosis of triple-negative breast cancer. The material came from biopsies, excisional biopsies and modified radical mastectomies. They were fixed in 10% buffered formalin phosphate, dehydrated by a set of alcohols of increasing concentrations, embedded in paraffin and cut into serial sections of 4 µm thick. Then, the samples were rehydrated and stained with haematoxylin and eosine, allowing to classify them according to the WHO classification. Moreover, the samples allowed for an evaluation of the histological grade (G), tumour grade (T) and lymph node involvement (N) of the given tumours. Additionally, the expression of receptors for estrogen (ER), progesterone (PR) and HER2 receptors was assessed by means of immunohistochemical staining, using mouse monoclonal antibodies (DAKO: IR654. IR068 and K5204) and the DAKO EnVision™ system for visualisation of results. Stain intensity was assessed by a computed image analysis of a number of stained nuclei per 1000 neoplastic cells.

Detection of COX-2

Cyclooxygenase expression was determined using the Monoclonal Mouse Anti-Human COX-2 antibody. First, the samples were dewaxed using a set of alcohols of decreasing concentrations. Then, they were put info pH 6 buffer and put into a water bath for 30 minutes in 90°C for antigen retrieval. Subsequently, the preparations were left at room temperature for 20 minutes. Then, samples were rinsed twice in distilled water and then incubated with 3% hydrogen peroxide for 5 minutes in order to quench endogenous peroxidase activity. After that, they were washed in TRIS (Tris-Buffered Saline, pH 8, SIGMA) and then incubated with a primary antibody in a humidity chamber for 60 minutes at room temperature. In the next stage, samples were again washed in TRIS for 10 minutes and incubated with visualisation reagent for 30 minutes. Next, after being washed in TRIS, were incubated with 3.3-diaminobenidine (DAB) for a visualisation of staining results. The time of incubation was controlled in order to obtain the desired stain intensity. At the end of the procedure, preparations were counter-stained with haematoxylin. Stain intensity was assessed by computed image analysis of

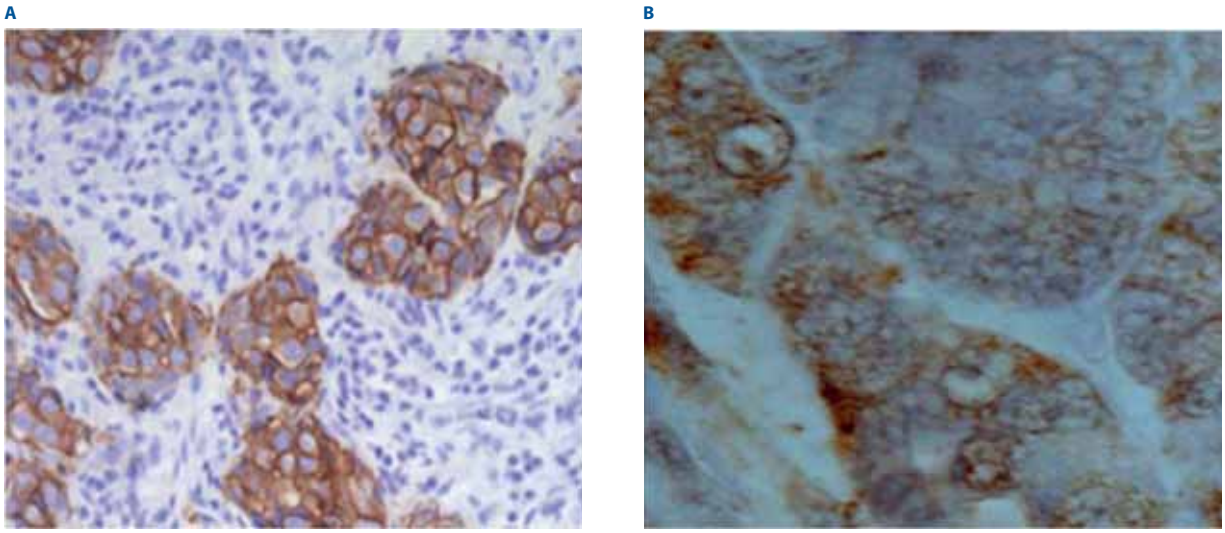

Figure 1. A histopathological image of invasive triple negative breast cancer (TNBC) (H&E): left (A) – positive immunohistochemical staining for Bcl-2 (original magnification 200×); right (B) – positive immunohistochemical staining for Cox-2 (original magnification 1000×)

a number of stained cytoplasm per 1000 neoplastic cells. The following score was adapted, similarly to Nam et al. and others' research [7, 18, 35]:

- none – less than 10% positively stained cells,
- weak – 10% positively stained cells,
- medium – from 10% to 30% positively stained cells,
- strong – over 30% positively stained cells.

Detection of Bcl-2

Bcl-2 expression was assessed using the monoclonal mouse anti-human Bcl-2 antibody. After dewaxing, the samples were incubated for 10 minutes in 1% hydrogen peroxide diluted in phosphate buffer saline (PBS) to quench endogenous peroxidase activity. Then, they were washed in PBS twice for 5 minutes. Next, they were incubated with 1.5% blocking serum in PBS for one hour at room temperature. Then they were incubated with a primary antibody diluted (1:50) in 1.5% blocking serum in PBS for 30 minutes at room temperature, and then washed thrice with PBS. Thereafter, sections were incubated for 30 minutes with a AB enzyme reagent (avidin + biotinylated rorseradish peroxidase [HRP]) and then washed with three changes of PBS for 5 minutes each. At the end, the samples were incubated with 3 drops of peroxidase substrate for 5 minutes, until the desired stain intensity developed. The process concluded with a counterstain with haematoxylin. Stain intensity was assessed by computed image analysis of a number of stained cytoplasm per 1000 neoplastic cells. The scoring method was modified from a score used by van Slooten et al. [8] and others [32–34] in their research, to emphasise different levels of stain intensity, and adapted as followed:

- none – less than 10% positively stained cells,
- weak – from 10% to 50% positively stained cells,
- medium – from 50% to 80% positively stained cells,
- strong – from 80% to 100% positively stained cells.

Statistical analysis

All the results were obtained using SPSS v. 12.0 PL Windows and the Statistica 13.1. Chi-square test and Fisher exact test were performed. Statistical significance was set at $p = 0.05$, however, for some of the calculations p was set at 0.008 (0.05/6) because Bonferroni correction was used to counteract the problem of multiple comparisons. In order to establish relations between COX-2 levels, Bcl-2 levels and patient age, the Spearman rang test was performed. An R value lesser then 0.2 is considered as without correlation.

Results

A pathological examination was performed on total of 21 female patients with confirmed diagnosis of TNBC. In the present study, we observed and analysed the expression and relationship of COX-2 and Bcl-2 with means of immunohistochemistry (tab. I). 14 out of 21 patients (66.7%) were above 50 years of age at the time of diagnosis (mean age 55.5 years old). The most common histological subtype was invasive ductal cancer of no special type (IDC-NST – 61.9%). The majority of samples were assessed as pT2 (57.1%). The lymph node involvement examination showed the dominance of pN1 stage, with 11 cases out of 21 (52.4%), followed by N0 (38.1%). Detailed pathological characteristics are included

Table I. Clinicopathological characteristics of the patients included in the study

Characteristics	Number of patients (n = 21), (%)
mean age	55.5
under 50 y.o.	7 (33.3%)
above 50 y.o.	14 (66.7%)
histological type	
IDC	6 (28.6%)
IDC-NST	13 (61.9%)
metaplastic	2 (9.5)%
tumour size (T)	
T1	4 (19.1%)
T2	12 (57.1%)
T3	3 (14.3%)
T4	2 (9.5%)
lymph node involvement (N)	
N0	8 (38.1%)
N1	11 (52.3%)
N2	1 (4.8%)
N3	1 (4.8%)
histological grade (G)	
G1	1 (4.8%)
G2	12 (57.1%)
G3	8 (38.1%)
COX-2 expression	
0	0
1	1 (4.8%)
2	9 (42.8%)
3	11 (52.4%)
Bcl-2 expression	
0	0
1	0
2	9 (42.8%)
3	6 (28.6%)
4	6 (28.6%)

Bcl-2 – B-cell lymphoma 2; COX-2 – cyclooxygenase 2; IDC – invasive ductal carcinoma, IDC-NST – invasive ductal carcinoma – no special type; y.o. – years old

in table I. The presence of distant metastases was not evaluated in the study.

The vast majority of examined tumours were assessed as moderately differentiated G2 (57.1%) and poorly differentiated G3 (38.1%), leaving only one sample with well differentiated cell architecture. Correlations between the histological grade, tumour size and lymph node status were examined, with no statistically significant relations.

As shown in table II, COX-2 was present in all examined samples with moderate to strong expression detected in 20 of 21 cases (staining intensity of 2 and higher).

Table II. IHC staining of COX-2 in studied samples

Percentage and degree of positively stained cells			TNBC samples with positive reaction
>10%	1	none	0
10%	2	weak	1 (4.8%)
>10–30%	3	medium	9 (42.9%)
>30%	4	strong	11 (52.3%)

COX-2 – cyclooxygenase 2; IHC – immunohistochemical; TNBC – triple negative breast cancer

There was a positive correlation between the histological grade (G) and COX-2 expression (p = 0.002). However, there was no statistically significant relationship between COX-2 presence, lymph node involvement (N) and the type of neoplasms. The relation between the patient's age and COX-2 levels was also not significant (R = 0.00). Considering the COX-2 expression, tumours were more likely to be identified as IDC-NST (tab. III).

Bcl-2 was present in all examined samples (tab. IV), demonstrating a moderate and higher level of cytoplasmic expression in nearly half of them (a staining intensity of 3 and higher – 12/21 of the analysed specimens). No correlation was found between the tumour stage, histological grade, lymph node involvement and the level of expression of Bcl-2 (tab. V). We identified no association between Bcl-2 expression and patients age (R = 0.167). Analysis has shown that tumours presenting a positive expression of Bcl-2 (of staining intensity of 3 and higher) accounted for the majority of examined cases (57.2%) and were more likely to be assessed as T2, N1 and G2.

Discussion

Breast cancer is one of the most frequently diagnosed neoplasms in developed countries, resulting in almost 15% of cancer-related deaths amongst women [1]. Triple-negative breast cancer is a very rare subtype of this type of cancer,

Table III. Relations between degree of COX-2 staining and clinicopathological features

	Degree of immunohistochemical expression of COX-2 in TNBC samples				
	None	Weak	Medium	Strong	p
histological type					
IDC-NST	0	1 (4.8%)	6 (28.6%)	6 (28.6%)	0.889
IDC	0	0	3 (14.3%)	3 (14.3%)	
metaplastic	0	0	1 (4.8%)	1 (4.8%)	
histological grade (G)					
G1	0	1 (4.8%)	0	0	0.002
G2	0	0	7 (33.5%)	5 (23.8%)	
G3	0	0	6 (28.6%)	2 (9.5%)	
tumour size (T)					
T1	0	0	2 (9.5%)	2 (9.5%)	0.828
T2	0	1 (4.9%)	5 (23.8%)	6 (28.6%)	
T3	0	0	2 (9.5%)	1 (4.8%)	
T4	0	0	0	2 (9.5%)	
lymph node involvement (N)					
N0	0	1 (4.8%)	1 (4.8%)	6 (28.6%)	0.130
N1	0	0	6 (28.6%)	5 (23.8%)	
N2	0	0	1 (4.8%)	0	
N3	0	0	1 (4.8%)	0	

COX-2 – cyclooxygenase 2; IDC – invasive ductal carcinoma; IDC-NST – invasive ductal carcinoma – no special type; TNBC – triple negative breast cancer

Table IV. IHC staining of Bcl-2 in studied samples

Percentage and degree of positively stained cells			TNBC samples with positive reaction
<10%	1	none	0
10–50%	2	weak	9 (42.8%)
50–80%	3	medium	6 (28.6%)
>80%	4	strong	6 (28.6%)

Bcl-2 – B-cell lymphoma 2; IHC – immunohistochemical; TNBC – triple negative breast cancer

Table V. Relations between the degree of Bcl-2 staining and clinicopathological features

Grade of IHC expression of Bcl-2 in TNBC samples					
	None	Weak	Medium	Strong	p
histologic type					
IDC-NST	0	4 (19.0%)	4 (19.0%)	5 (23.8%)	0.522
IDC	0	4 (19.0%)	1 (4.8%)	1 (4.8%)	
metaplastic	0	1 (4.8%)	1 (4.8%)	0	
histological grade (G)					
G1	0	0	0	0	1.0
G2	1 (4.8%)	5 (23.8%)	3 (14.3%)	4 (19.0%)	
G3	0	3 (14.3%)	3 (14.3%)	2 (9.5%)	
tumour size (T)					
T1	0	3 (14.3%)	0	1 (4.8%)	0.828
T2	0	4 (19.0%)	5 (23.8%)	3 (14.3%)	
T3	0	1 (4.8%)	1 (4.8%)	1 (4.8%)	
T4	0	1 (4.8%)	0	1 (4.8%)	
lymph node involvement (N)					
N0	0	5 (23.8%)	2 (9.5%)	1 (4.8%)	0.610
N1	0	4 (19.0%)	3 (14.3%)	4 (19.0%)	
N2	0	0	1 (4.8%)	0	
N3	0	0	0	1 (4.8%)	

Bcl-2 – B-cell lymphoma 2; IDC – invasive ductal carcinoma; IDC-NST – invasive ductal carcinoma – no special type; IHC – immunohistochemical; TNBC – triple negative breast cancer

characterized by the lack of expression of ER, PR and HER2, accounting for 15–20% of cases. Previous studies have shown that TNBC diagnosis is a negative prognostic factor in breast cancer [9, 10], as well as high COX-2 expression [11, 12] and Bcl-2 expression [13, 14]. Considering all of the above, we aimed to obtain more detailed data on additional factors that negatively influence TNBC outcome. The goal of the present study was to evaluate the immunohistochemical profile of COX-2 and Bcl-2 expression in patients suffering from TNBC.

COX-2 is known for its association with poor prognosis in breast cancer patients. In 2015, Xu et al. [14] conducted a meta-analysis including twenty-one studies with 6739 patients trying to evaluate the prognostic value of COX-2 and its association with clinicopathological characteristics. Their study proved that the expression of COX-2 predicts greater tumour size and presence of lymph node metastasis, whereas they indicated no significant correlation between ER, PR and HER2 status and COX-2 expression. The mechanism of detected association remained unclear and the role of COX-2 in TNBC was not widely discussed and examined.

In the present study there was no statistically significant relation between COX-2 presence and lymph node involvement, nevertheless this correlation was found in many previ-

ously conducted studies [14]. Some researchers try to explain the mechanism of this correlation. In 2017, Krishnamachary et al. [15] investigated the role of COX-2 expression by TNBC cells in shaping the structure and function of the tumour extra-cellular matrix (ECM), which may affect metastasis forming. In their study, COX-2 downregulation impacted the ECM structure by reducing collagen I (Col1) fiber volume, which then resulted in a reduced ability of TNBC cells to metastasize to lymph nodes. Col1 fiber density and orientation were previously linked to breast cancer metastasis in 2012 by Kakkad et al. as their pilot study [16] revealed statistically significant increases of Col1 fiber density in breast cancers with lymph node involvement.

Our results showed that the vast majority of TNBC cases were characterised by a highly positive expression rate of COX-2 (95.2% of cases). In a study performed by Chikman et al. [17], only 57.4% of patients were classified as COX-2-positive. They found a prognostic significance of COX-2 for TNBC – the 5-year disease-free survival rate reached 83.9% in COX-2-negative patients, whereas it was only 58.3% in COX-2-positive TNBC patients. No prognostic significance of COX-2 expression was proved for other types of breast cancer.

Molsapuria et al. investigated a cohort with similar clinicopathological characteristics (dominant T2, 31 TNBC cases), with positive association between COX-2 expression and both TNBC and high tumour grade, whereas in the present study the correlation was positive only with the histological grade [18]. However, Zhau et al. [19] showed no correlation between any of the clinicopathological characteristics. Similarly, Basudhar et al. [20] showed no correlation between COX-2 levels and the histological grade. Chickman et al. [17] presented a lack of correlation between any hormonal receptor status and COX-2 expression, and our results are in accordance to those findings. On the other hand, Ristmaki et al. [21] showed positive correlation between COX-2 expression levels and negative hormone status, a large tumour size, high histological grade, high proliferation rate (identified by Ki-67), high p53 expression, ductal type and axillary lymph node involvement, which is a well-known independent risk factor for poorer outcomes [22]. In the present study, positive nodal involvement was common, the majority of which assessed as N1, with no statistical significance.

Simonnson et al. carried out one of the largest studies evaluating COX-2 expression in breast cancer, where non-TNBC cancers were associated with a high COX-2 expression, lower, less aggressive tumour characteristics and increased age [23]. Moreover, in their study, TNBC correlated negatively with high COX-2 expression. In the present study, the results did not indicate any relation between age and moderate tumour malignancy.

Members of the Bcl-2 family belong to a group of pivotal arbiters of mitochondria-mediated apoptosis, consisting of anti-apoptotic and pro-apoptotic members. The role of Bcl-2 in apoptosis regulation seems to be well established, however its role in tumorigenesis remains unclear. Changes in the genome that lead to the overexpression of anti-apoptotic proteins like Bcl-2 or Bcl-xl are reported in a wide range of malignancies, including breast cancer [24]. Paradoxically, Bcl-2 protein expression in breast cancer is associated with a favourable phenotype of low-grade, ER-positive, that has more slowly proliferating breast tumours and better prognosis [25]. What it more, Bcl-2 was established as a marker that could improve the prognostic power of the Nottingham Prognostic Index [26].

One study found a correlation between increased COX-2 expression and Bcl-2 expression both in TNBC and non-TNBC patients [27]. The potential role of Bcl-2 as a prognostic factor for breast cancer has been examined in previous studies; nevertheless, its role in pathogenesis and the course of TNBC needs further research.

The frequency of Bcl-2 overexpression in TNBC varies significantly. In the present study, all examined samples presented strong Bcl-2 expression (of score 2 and higher), whereas Escórcio-Dourado et al. observed it in 40% of the 30 studied cases [28]. In 2013, Abdel-Fatah et al. described Bcl-2 as an independent prognostic marker of TNBC [29]. They observed a positive expression of Bcl-2 in 29.8% of the examined samples. Moreover, it was significantly associated with a high expression of p27, MDM4 and SPAG5. Taking into consideration only the Bcl-2-positive group, they found that G2 and G3 made up the largest percentage of cases – similarly to the present study. As far as tumour size is concerned, they observed T2 stage in 44.1% of cases comparable to 57.1% of studied cases; in both studies T2 tumours accounted for the largest group. Their study proved that loss of Bcl-2 considerably escalates the risk of both death and recurrence in TNBC.

In a study conducted by Abd El-Hafez et al. on a similar group of patients with TNBC, they observed Bcl-2 positive staining in 85% of invasive ductal carcinomas [30]. It is worth mentioning that they reported opposite results concerning patients' age and grading of the tumours. In the present study, 66.7% of patients were above 50 years old at the time of diagnosis, whereas Abd El-Hafez et al. reported that Bcl-2 was more frequently expressed in younger patients, accounting for 81.3% of all cases. Moreover, they correlated Bcl-2 expression with lower grading, whereas in the present research we did not observe the group of G0. These contradictory statements lead us to the conclusion that the role of Bcl-2 and its prognostic value in TNBC still seems unclear and needs further research on a wider group of patients.

Conclusions

All the aforementioned details may lead to the conclusion that COX-2 and Bcl-2 high expression in triple-negative breast cancer may be an interesting asset in routine histological examination and the grading of breast cancer, however further studies with a larger group is necessary. Moreover, as they are usually present in higher graded neoplasms, COX-2 and Bcl-2 may also serve as potential new targets for systemic treat-

ment. This approach could potentially reveal new methods in the therapy of triple-negative breast cancer. This is crucial, as hormonotherapy and HER2 targeting remain unavailable for those patients. The described association should be investigated further, as the group of patients was small, even though representing a rare histological subtype of breast cancer.

Conflict of interest: none declared

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Received: 16 Mar 2022
Accepted: 22 May 2022

References

1. Wojciechowska U, Didkowska J, Zatoński W. Prognosis of maliginant cancers' morbidity and mortality in Poland in 2025. In: Malignant tumors registration. , Warsaw 2009.
2. Dawood S. Triple-Negative Breast Cancer. Drugs. 2010; 70(17): 2247–2258, doi: 10.2165/11538150-000000000-00000.
3. Moris D, Kontos M, Spartalis E, et al. The Role of NSAIDs in Breast Cancer Prevention and Relapse: Current Evidence and Future Perspectives. Breast Care (Basel). 2016; 11(5): 339–344, doi: 10.1159/000452315, indexed in Pubmed: 27920627.
4. Ristimäki A, Sivula A, Lundin J, et al. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Res. 2002; 62(3): 632–635, indexed in Pubmed: 11830510.
5. Fornetti J, Jindal S, Middleton KA, et al. Physiological COX-2 expression in breast epithelium associates with COX-2 levels in ductal carcinoma in situ and invasive breast cancer in young women. Am J Pathol. 2014; 184(4): 1219–1229, doi: 10.1016/j.ajpath.2013.12.026, indexed in Pubmed: 24518566.
6. Yang J, Liu X, Bhalla K, et al. Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked. Science. 1997; 275(5303): 1129–1132, doi: 10.1126/science.275.5303.1129, indexed in Pubmed: 9027314.
7. Nam E, Lee SN, Im SA, et al. Expression of cyclooxygenase-2 in human breast cancer: relationship with HER-2/neu and other clinicopathological prognostic factors. Cancer Res Treat. 2005; 37(3): 165–170, doi: 10.4143/crt.2005.37.3.165, indexed in Pubmed: 19956498.
8. van Slooten HJ, Clahsen PC, van Dierendonck JH, et al. Expression of Bcl-2 in node-negative breast cancer is associated with various prognostic factors, but does not predict response to one course of perioperative chemotherapy. Br J Cancer. 1996; 74(1): 78–85, doi: 10.1038/bjc.1996.319, indexed in Pubmed: 8679463.
9. Qiu JD, Xue XY, Li R, et al. Comparison of Clinicopathological Features and Prognosis in Triple-Negative and Non-Triple Negative Breast Cancer. J Cancer. 2016; 7(2): 167–173, doi: 10.7150/jca.10944, indexed in Pubmed: 26819640.
10. Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. Cancer. 2007; 109(1): 25–32, doi: 10.1002/cncr.22381, indexed in Pubmed: 17146782.
11. van Nes JGH, de Kruijf EM, Faratian D, et al. COX2 expression in prognosis and in prediction to endocrine therapy in early breast cancer patients. Breast Cancer Res Treat. 2011; 125(3): 671–685, doi: 10.1007/s10549-010-0854-7, indexed in Pubmed: 20358279.
12. Kim T, Han W, Kim MK, et al. Predictive Significance of p53, Ki-67, and Bcl-2 Expression for Pathologic Complete Response after Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer. J Breast Cancer. 2015; 18(1): 16–21, doi: 10.4048/jbc.2015.18.1.16, indexed in Pubmed: 25834606.
13. Ozretic P, Alvir I, Sarcevic B, et al. Apoptosis regulator Bcl-2 is an independent prognostic marker for worse overall survival in triple-negative breast cancer patients. Int J Biol Markers. 2018; 33(1): 109–115, doi: 10.5301/ijbm.5000291, indexed in Pubmed: 28777433.
14. Xu F, Li M, Zhang C, et al. Clinicopathological and prognostic significance of COX-2 immunohistochemical expression in breast cancer: a meta-analysis. Oncotarget. 2017; 8(4): 6003–6012, doi: 10.18632/oncotarget.13990, indexed in Pubmed: 27999206.
15. Krishnamachary B, Stasinopoulos I, Kakkad S, et al. Breast cancer cell cyclooxygenase-2 expression alters extracellular matrix structure and function and numbers of cancer associated fibroblasts. Oncotarget. 2017; 8(11): 17981–17994, doi: 10.18632/oncotarget.14912, indexed in Pubmed: 28152501.
16. Kakkad SM, Solaiyappan M, Argani P, et al. Collagen I fiber density increases in lymph node positive breast cancers: pilot study. J Biomed Opt. 2012; 17(11): 116017, doi: 10.1117/1.JBO.17.11.116017, indexed in Pubmed: 23117811.
17. Chikman B, Vasyanovich S, Lavy R, et al. COX2 expression in high-grade breast cancer: evidence for prognostic significance in the subset of triple-negative breast cancer patients. Med Oncol. 2014; 31(6): 989, doi: 10.1007/s12032-014-0989-1, indexed in Pubmed: 24816739.
18. Mosalpuria K, Hall C, Krishnamurthy S, et al. Cyclooxygenase-2 expression in non-metastatic triple-negative breast cancer patients. Mol Clin Oncol. 2014; 2(5): 845–850, doi: 10.3892/mco.2014.327, indexed in Pubmed: 25054056.
19. Zhou L, Li Ke, Luo Y, et al. Novel prognostic markers for patients with triple-negative breast cancer. Hum Pathol. 2013; 44(10): 2180–2187, doi: 10.1016/j.humpath.2013.03.021, indexed in Pubmed: 23845466.
20. Basudhar D, Glynn SA, Greer M, et al. Coexpression of NOS2 and COX2 accelerates tumor growth and reduces survival in estrogen receptor-negative breast cancer. Proc Natl Acad Sci U S A. 2017; 114(49): 13030–13035, doi: 10.1073/pnas.1709119114, indexed in Pubmed: 29087320.
21. Ristimäki A, Sivula A, Lundin J, et al. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Res. 2002; 62(3): 632–635, indexed in Pubmed: 11830510.
22. Dings PJM, Elferink MAG, Strobbe LJA, et al. The prognostic value of lymph node ratio in node-positive breast cancer: a Dutch nationwide population-based study. Ann Surg Oncol. 2013; 20(8): 2607–2614, doi: 10.1245/s10434-013-2932-7, indexed in Pubmed: 23536053.
23. Simonsson M, Björner S, Markkula A, et al. The prognostic impact of COX-2 expression in breast cancer depends on oral contraceptive history, preoperative NSAID use, and tumor size. Int J Cancer. 2017; 140(1): 163–175, doi: 10.1002/ijc.30432, indexed in Pubmed: 27632554.
24. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers. Nature. 2010; 463(7283): 899–905, doi: 10.1038/nature08822, indexed in Pubmed: 20164920.
25. Ayadi EZ, Cherif B, Ben Hamed Y, et al. Prognostic Value of BCL2 in Women Patients with Invasive Breast Cancer. Asian Pac J Cancer Prev. 2018; 19(12): 3557–3564, doi: 10.31557/APJCP.2018.19.12.3557, indexed in Pubmed: 30583683.
26. Callagy GM, Pharoah PD, Pinder SE, et al. Bcl-2 is a prognostic marker in breast cancer independently of the Nottingham Prognostic Index. Clin Cancer Res. 2006; 12(8): 2468–2475, doi: 10.1158/1078-0432.CCR-05-2719, indexed in Pubmed: 16638854.
27. Sezgin Alikanoglu A, Yildirim M, Suren D, et al. Expression of cyclooxygenase-2 and Bcl-2 in breast cancer and their relationship with triple-negative disease. J BUON. 2014; 19(2): 430–434, indexed in Pubmed: 24965402.
28. Escórcio-Dourado CS, Martins LM, Simplício-Revoredo CM, et al. Bcl-2 antigen expression in luminal A and triple-negative breast cancer. Med Oncol. 2017; 34(9): 161, doi: 10.1007/s12032-017-1022-2, indexed in Pubmed: 28801774.
29. Abdel-Fatah TMA, Perry C, Dickinson P, et al. Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. Ann Oncol. 2013; 24(11): 2801–2807, doi: 10.1093/annonc/mdt277, indexed in Pubmed: 23908177.
30. Abd El-Hafez A, Shawky Mohamed AEA, Elesawy BH. Different prognostic factors correlate with Bcl-2 expression among triple negative and non-triple negative breast cancers. Asian Pac J Cancer Prev. 2013; 14(2): 1037–1041, doi: 10.7314/apjcp.2013.14.2.1037, indexed in Pubmed: 23621182.
31. Sicking I, Rommens K, Battista MJ, et al. Prognostic influence of cyclooxygenase-2 protein and mRNA expression in node-negative breast cancer patients. BMC Cancer. 2014; 14: 952, doi: 10.1186/1471-2407-14-952, indexed in Pubmed: 25511800.
32. Honma N, Horii R, Ito Y, et al. Differences in clinical importance of Bcl-2 in breast cancer according to hormone receptors status or adjuvant endocrine therapy. BMC Cancer. 2015; 15: 698, doi: 10.1186/s12885-015-1686-y, indexed in Pubmed: 26472348.

33. Lee KH, Im SA, Oh DY, et al. Prognostic significance of bcl-2 expression in stage III breast cancer patients who had received doxorubicin and cyclophosphamide followed by paclitaxel as adjuvant chemotherapy. BMC Cancer. 2007; 7: 63, doi: 10.1186/1471-2407-7-63, indexed in Pubmed: 17430582.
34. Brzozowa-Zasada M, Kurek J, Piecuch A, et al. Correlation study of GAPDH, Bcl-2, and Bax protein immunoexpression in patients with colorectal adenocarcinoma. Prz Gastroenterol. 2018; 13(4): 322–331, doi: 10.5114/pg.2018.79813, indexed in Pubmed: 30581507.
35. Solanki R, Agrawal N, Ansari M, et al. COX-2 Expression in Breast Carcinoma with Correlation to Clinicopathological Parameters. Asian Pac J Cancer Prev. 2018; 19(7): 1971–1975, doi: 10.22034/APJCP.2018.19.7.1971, indexed in Pubmed: 30051683.

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 258–264

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

The influence of surgery quality on the longtime results of gastric cancer combination therapy

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Introduction. The aim of this study was to analyze the influence of surgical center experience on the long term survival of patients with locoregionally advanced gastric adenocarcinoma undergoing primary surgery, followed by complementary chemoradiotherapy according to MacDonald regimen.

Material and methods. 154 patients treated surgically, including 75 (48.7%) at the Maria Sklodowska-Curie National Research Institute of Oncology (NIO-PIB) in Warsaw, and 79 (51.3%) outside this center. Both groups were retrospectively analyzed. The compared groups were statistically homogeneous. The following parameters were analyzed: age, gender, tumor differentiation, TNM VII (2010) staging, nodal index, radicality of surgical treatment, tumor type according to the Lauren classification, clinical stage, presence of prognostic factors, overall survival time.

Results. Among those patients operated on at NIO-PIB, 71 (94.7%) patients underwent radical resection, 4 (5.3%) cases were microscopically non-radical resection had. There were no macroscopically non-radical resections (0%). For patients operated on outside NIO-PIB, 60 (75.9%) R0 resections, 15 (19%) R1 resections and 4 (5.1%) R2 resections were performed. The percentage of radical resections was significantly higher at NIO-PIB ($p = 0.001$). In 77% of patients operated on at NIO-PIB, disease progression in terms of feature could be established. This percentage for patients operated on outside the NIO-PIB was 54% and was significantly lower ($p = 0.001$). The probability of 5-year survival was 41.6% in total, with 45.3% for the group of patients operated on in the NIO-PIB and 38.0% for the group of patients operated on outside the NIO-PIB, respectively ($p = 0.628$).

Conclusions. The quality of surgical treatment was significantly higher in NIO-PIB. The difference in 5-year overall survival (OS) between the compared groups is not statistically significant. Complementary treatment with chemoradiotherapy (CRT) according to MacDonald regimen reduces the shortcomings in the quality of surgical treatment in locoregionally advanced gastric adenocarcinoma.

Key words: gastric cancer, surgery, chemoradiotherapy

Introduction

Gastric cancer (GC), despite its long-term decline in incidence and mortality, remains the fourth most common cancer and the second cause of cancer-related deaths. Differences in gastric cancer incidence between populations are approximately 10-fold. The incidence is particularly high in East Asia (over 40/100,000), Eastern Europe (about 25/100,000), and Central America (30/100,000) and South America (20/100,000) [1]. The share of gastric cancer incidence in Poland has decreased almost 3-fold over the last 4 decades. In Poland, stomach can-

Jak cytować / How to cite:

Pierzankowski I, Dmitruk A, Rybski S, Wyrwicz L, Olesiński T. ***The influence of surgery quality on the longtime results of gastric cancer combination therapy.*** *NOWOTWORY J Oncol* 2022; 72: 219–225.

cer constitutes about 5% of all cancers in men and about 3% in women. It is the cause of about 7% of deaths in men and 5% in women. The 5-year survival rate in this group of patients increased slightly during the first decade of the 21st century, from 14.6% to 16.4% in men and from 18.2% to 19.8% in women. In total, it currently amounts to 17.6%. In Poland in 2010, the number of deaths due to gastric cancer among men was about 25% higher than the average for European Union countries (data from 2009), among women about 10% [1].

Although surgery remains the mainstay of treatment in gastric cancer, in view of its limited efficacy, increasingly more importance is being attached to combined treatment, especially for regionally advanced disease. Currently, the recommended treatment for patients with a stage above T1N0 is combination therapy, including perioperative chemotherapy, with the currently preferred quadruple FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel). This increases a patient's chance of a cure by up to 70% [2–4]. Of fundamental importance for the development of combination therapy for gastric cancer was the study by MacDonald et al. [5]. The scheme of treatment proposed by the researchers includes 1 cycle of chemoradiotherapy (CRT) consisting of FU at a dose of 425 mg/m^2/day for 5 days and calcium folinate 20 mg/m^2/day for 5 days, followed after 28 days by irradiation to a dose of 45 Gy (fractions of 1.8 Gy) together with CTH according to the scheme: FU 400 mg/m^2 together with calcium folinate 20 mg/m^2/day for the first 4 and for the last 3 days of irradiation – recommendations for the Diagnostic and Therapeutic Management of Malignancies – 2013. 132 irradiation, and one month after completion of radiotherapy (RTH), 2 consecutive cycles of CTH, at doses as in the first course, administered one month apart. The irradiation area should include the gastric lobe and regional lymph nodes. Critical of the results of the study, the researchers particularly raised the aspect of poor quality of surgical treatment in most of the analyzed cases (predominantly patients with limited or no lymphadenectomy), which could affect the final results, In our institution, complementary treatment according to MacDonald regimen in the years 2009–2012 was the treatment of choice for locally advanced gastric cancer. Since 2013, it has been used in a selected group of patients as an adjunct to standard combination treatment.

In this study, we retrospectively analyzed the long-term results of combined treatment, which included surgical intervention with the intention of cure and complementary therapy according to the MacDonald regimen. Medical records of 154 patients treated with the MacDonald regimen at the Maria Sklodowska-Curie National Research Institute of Oncology (NIO-PIB) in Warsaw between 2009 and 2012 were analyzed.

Aim of the study

The aim of this study was to analyze the influence of the experience of the surgical center on the distant results of gastric cancer treatment in a group of patients subsequently undergoing complementary treatment according to the MacDonald regimen.

Material and methods

Between 2009 and 2012, 154 patients, including 55 (35.7%) women and 99 (64.3%) men, after gastrectomy for GER were treated with the MacDonald regimen. The medical records of all patients were retrospectively analyzed. Detailed demographic and tumor type, differentiation degree, type and stage are presented in tables I and II.

Table I. Parameters of study group

Study group parametres	Number of patients (n = 154), (%)
age (median, standard deviation)	60 (±10.691)
sex	
women	55 (35.7%)
men	99 (64.3%)
tumor grade (G)	
G2	37 (24%)
G3	116 (75.3%)
MANEC	1 (0.7%)
anatomic stage of tumor	
Ia	0 (0 %)
Ib	18 (11.7%)
IIa	21 (13.6%)
IIb	28 (18.2%)
IIIa	32 (20.8%)
IIIb	39 (25.3%)
IIIc	16 (10.4%)
IV	0 (0%)
primary tumor advanced (T)	
T1a	0 (0%)
T1b	1 (0.6%)
T2	18 (11.7%)
T3	103 (66.9%)
T4a	28 (18.2%)
T4b	4 (2.6%)
regional stage (N)	
N0	26 (16,9%)
N1	39 (25,3%)
N2	33 (21,4%)
N3a	42 (27,3%)
N3b	11 (7,1%)
N3c	1 (0,6%)
tumor type according to Lauren classification	
I	17 (11%)
II	127 (82.5%)
III	10 (6.5%)

Table II. Comparison of parameters of subgroups: operated on in NIO-PIB and operated on outside NIO-PIB

Tested parameter	NIO-PIB operated group Number of patients (n = 75), (%)	Group operated outside NIO-PIB Number of patients (n = 79), (%)	Two-sided statistical significance level p
age (median, standard deviation)	62 (±10.331)	59 (±10,968)	0.181
sex			
women	30 (40%)	25 (31.6%)	
men	45 (60%)	54 (68.4%)	
grading (G)			
G1	0 (0.00%)	0(0.00%)	
G2	17 (22.7%)	20 (25.3%)	0.540
G3	57 (76%)	59 (74.7%)	
MANEC	1 (1.3%)	0 (0.00%)	
anatomic stage of tumor			
Ia	0 (0%)	0 (0%)	
Ib	8 (10.7%)	10 (12.7%)	
IIa	10 (13.3%)	11 (13.9%)	
IIb	17 (22.7%)	11 (13.9%)	0.882
IIIa	15 (20.0%)	17 (21.5%)	
IIIb	17 (22.7%)	22 (27.8%)	
IIIc	8 (10.7%)	8 (10.1%)	
feature T			
TIa	0 (0.00%)	0 (0.00%)	
TIb	0 (0.00%)	1 (1.3%)	
TII	5 (6.7%)	13 (16.5%)	0.321
TIII	53 (70.7%)	50 (63.3%)	
TIVa	15 (20.0%)	13 (16.5%)	
TIVb	2 (2.7%)	2 (2.5%)	
feature N			
N0	15 (20%)	11 (13.,9%)	
N1	23 (30.7%)	16 (20.3%)	
N2	11 (14.7%)	22 (27.8%)	0.196
N3a	20 (26.7%)	24 (30.3%)	
N3b	6 (8.0%)	5 (6.3%)	
N3c	0 (0.00%)	1 (1.3%)	
tumor type according to Lauren classification			
I	8 (10.7%)	9 (11.4%)	
II	60 (80.0%)	67 (84.8%)	
III	7 (9.3%)	3 (3.8%)	

G – grading; T – tumor; N – lymph nodes

Two subgroups were distinguished in the analyzed group:

- patients operated on in the NIO-PIB,
- patients operated on outside the NIO-PIB.

The following parameters were taken into consideration: age of patients, gender, tumor differentiation degree, tumor stage (according to TNM VII 2010 classification), nodal index, radicality of surgical treatment, tumor type according to Lauren classification, clinical stage, presence of prognostic factors. The overall survival time of the patients was defined as the period from diagnosis of the disease to the end of follow-up in April 2017, using the Kaplan-Meyer estimator.

Results

A group of 154 patients was retrospectively analyzed and divided into two homogeneous subgroups. The first was composed of those operated on at NIO-PIB (75–48.7%) and the second was those operated on outside (79–51.3%). Patients from both groups then underwent complementary CRT according to the MacDonald regimen. Among patients operated on in NIO-PIB, 71 (94.7%) patients underwent radical resection, in 4 (5.3%) cases it was microscopically non-radical resection. There were no macroscopically non-radical resections (0%). For patients operated on outside NIO-PIB, 60 (75.9%) R0 resections, 15 (19%) R1 resections and 4 (5.1%) R2 resections were performed.

Thus, the percentage of radical resections was significantly higher in NIO-PIB (p = 0.001). The number of lymph nodes in the evaluated specimen ranged from 2 to 64, with a median of 21 for the entire study group, 25 for patients operated on at NIO-PIB, and 10.5 for patients operated on outside NIO-PIB, respectively. The median number of lymph nodes involved by metastases was 4 for the whole group, with –2 for patients operated on in NIO-PIB and 5.5 for patients operated on outside NIO-PIB. In 77% of patients operated on in NIO-PIB, it was possible to establish the stage of the disease in terms of N feature (number of lymph nodes in the specimen >15). This percentage for patients operated on outside the NIO-PIB was 54% and was significantly lower (p = 0.001). In 19% of patients operated on in the NIO-PIB *vs.* 46% of patients operated on outside the NIO-PIB, the number of evaluated lymph nodes was 7–15, and for 4% of patients operated on in the NIO-PIB *vs.* 0% of patients operated on outside the NIO-PIB – between 0–6. Angioinvasion was noted in 134 (74%) patients and nerve trunk infiltration in 130 (71%). The median overall survival time was 38.5 (3–104) months, for patients with R1 resection it was 25.5 (7–104) months, and for R2 it was 8.5 (3–31) months (tab. I and II).

The evaluated parameters were statistically analyzed (Levene's test, t-test for equality of means, Pearson's test), which confirmed the homogeneity of the study groups. Based on the collected data, using the log-rank test and Kapplan-Meier estimator, the probability of 5-year survival was estimated for the group of patients studied and for the compared subgroups. It amounted to 41.6% in total, with 45.3% for the group of patients operated on in the NIO-PIB and 38.0% for those operated on outside the NIO-PIB, respectively (p = 0.628) (fig. 1 and 2).

Discussion

Over the past thirty years, there have been marked advances in the treatment of gastric cancer. In countries leading in the diagnosis and treatment of this cancer, this translates into a significantly better prognosis than in the past. In the Far East, the 5-year survival rate reaches 70%, in Western European countries it is 25% [1, 4, 6]. Unfortunately, in Poland the 5-year survival rate in this group of patients increased slightly during the first decade of the 21st century, from 14.6% to 16.4% in men and from 18.2% to 19.8% in women. The total is currently 17.6%, and the number of deaths in 2010 due to gastric cancer

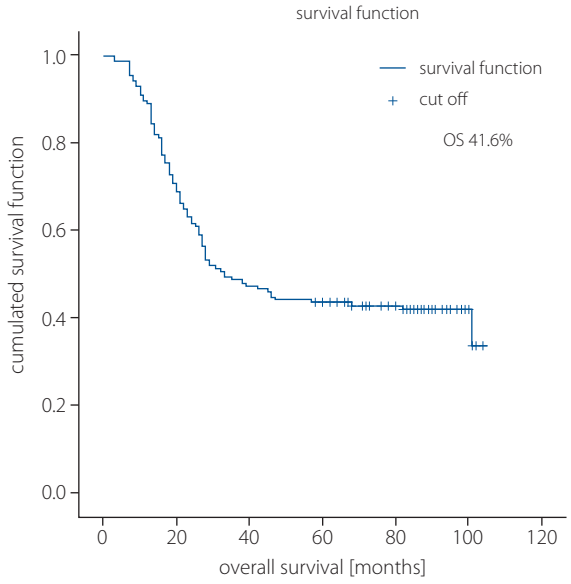

Figure 1. Survival function

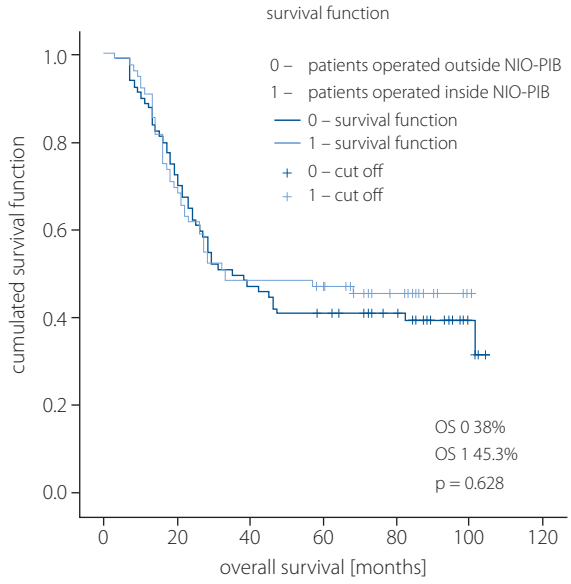

Figure 2. Survival functions by surgical site

was, by about 25% higher in men and 10% in women, than the average for European Union countries (data from 2009). Fortunately, the incidence of gastric cancer has decreased 3-fold over the past 40 years [1].

Gastric adenocarcinoma is a disease whose incidence, course and prognosis depend not only on tumor biology and stage, but also on geographic, cultural, and economic factors as well as the organization of the health care system [6]. The best results in the treatment of this cancer are achieved in highly developed countries of the Far East, where the high incidence has forced certain systemic measures (screening endoscopic examinations, centralization of treatment) to reduce the mortality associated with this disease. A more favorable tumor profile (intestinal type, distal localization), anthropometric parameters of the local population, and thus a significantly lower risk of complications during treatment, related, for example, to obesity and other civilization diseases, as well as the very high quality of surgery, are not without significance with regards to the better treatment outcomes being seen [6]. This is also reflected in the different, in relation to the European and American way, of combined treatment. The most common is surgical treatment, involving D2 lymphadenectomy and complementary chemotherapy (CT). The basis for this approach was provided by two randomized, multicenter studies ACTS-GC and CLASSIC [4], which confirmed a significantly higher percentage of overall survival (OS) and disease-free survival (DFS) in patients treated in a combined manner, compared with patients undergoing surgery alone.

The longstanding dominance of treatment based on surgery alone was interrupted by the MacDonald study. The authors presented the results of the study, which showed a significantly higher rate of survival in patients undergoing complementary CRT compared to patients who underwent surgery alone (36 months *vs.* 27 months) [5]. The conclusions of this report, as well as the results of The North American Intergroup – the 0116 trial – became the basis for the use of CRT in the United States for the adjuvant treatment of gastric cancer [4, 7]. Critics of the trial emphasized that only 9% of patients had curative surgery with D2 lymphadenectomy, and 54% had less than D1 lymphadenectomy [4, 7].

Thus, complementary CRT may have been primarily to compensate for the shortcomings of surgery. This was confirmed by the retrospective comparative Dutch D1D2 trial, which showed a lower rate of local recurrence after CRT, in patients after gastrectomy and D1 lymphadenectomy. For D2 lymphadenectomy, no benefit was observed [4]. Nevertheless, other reports suggest that patients after optimal lymphadenectomy also benefit from complementary CRT [4]. Studies in this area are currently ongoing. The current indications for complementary CRT are: inadequate extent of surgical treatment, its irreversibility, both microscopically (R1) and macroscopically (R2), the presence of locoregional lymph node metastases (especially when the nodal index exceeds 20%), nerve trunk infiltration and angioinvasion [7–9].

According to the ESMO recommendations, the currently recommended treatment is a combined therapy consisting of perioperative chemotherapy starting at stage IB and potentially curative surgery (gastrectomy, subtotal resection) accompanied by D2 lymphadenectomy [4]. This approach was based on the results of the UK MRC MAGIC trial, which demonstrated an improved 5-year survival after perioperative administration of 6 courses of ECF (epirubicin, cisplatin, 5-fluorouracil) compared with patients treated with surgery alone (36% *vs.* 23%). On the other hand, the German AIO study group showed a greater number of complete pathological responses in patients undergoing perioperative CT according to the FLOT4 regimen (5-fluorouracil, leucovorin, oxaliplatin, docetaxel) *vs.* ECF/X (15.6% *vs.* 5.8%), as well as a longer median survival (mOS), 50 *vs.* 35 months. These results have now become the basis for the implementation of the FLOT4 regimen into clinical practice [2, 4]. On the other hand, patients who did not receive preoperative chemotherapy and whose disease stage was determined to be at least IB, should undergo complementary treatment with CRT or CT [4, 7–11]. In contrast, the randomized phase III CRITICS trial showed that patients undergoing preoperative CT do not benefit from postoperative CRT over postoperative CT (OS 37 m. *vs.* 43 m., respectively) [12].

Current studies, which aim to optimize the combination treatment, are ongoing. In particular, this concerns the preoperative treatment period. In the multicenter TOPGEAR study, patients with resectable adenocarcinoma of the stomach or gastroesophageal junction are randomized to groups receiving, respectively: preoperative CT (3 courses of ECF) or preoperative RT followed by CT (2 courses of ECF), and after surgery in both groups CT (3 courses of ECF). Preliminary results of the study show no significant differences between the groups in terms of operability (90% CT *vs.* 85% CRT), grade III operative complications (according to Clavien-Dindo) were 22% in both groups, grade III toxicity, both hematologic and gastrointestinal, were also similar and were 50% CT *vs.* 52% CRT and 32% CT *vs.* 30% CRT, respectively [13]. In contrast, the phase II CRITICS study focuses on comparing the efficacy of neoadjuvant therapy based on, respectively: CT according to the DOC regimen (docetaxel, oxaliplatin, capecitabine) – 4 cycles, 2 cycles of CT according to the DOC regimen following CRT (45 Gy with paxitaxel and carboplatin) and CRT [14]. Given that 40–50% of patients do not receive postoperative treatment, the results of this study may be extremely.

The incidence of severe postoperative complications is also an important prognostic factor that depends directly on the quality of surgical treatment. Peng et al. compared two groups, a total of 239 patients undergoing gastrectomy with D2 lymphadenectomy, combined with neoadjuvant CT. The analysis took into account patient-dependent factors (gender, age, BMI,

comorbidities, previous abdominal surgery), tumor-dependent factors, as well as those determined by the surgical process (duration of surgery, blood loss, extent of surgery – e.g. multiorgan resections, type of surgical technique) and the length of hospital stay. The severity of complications was determined according to the Clavien-Dindo classification. Complications were observed in 24.7% of patients, and perioperative mortality was 0.8%. Grade I and II complications occurred in 9.2% of patients, and severe complications (grade III and IV) in 15.5%. The occurrence of postoperative complications was correlated primarily with age >55 years, BMI ≥25, operative time >200 min, and extent of surgery ($p < 0.05$). Both the 3-year overall survival and disease-free survival were significantly longer in patients who did not experience complications from groups III and IV ($p = 0.033$ and $p = 0.034$, respectively) [17].

In a study published in 2016, Datta and colleagues analyzed the impact of lymphadenectomy and the results of the histopathological evaluation of the removed lymph nodes on the choice of follow-up treatment. The study group included 3008 patients with gastric adenocarcinoma, grades IB–III treated surgically and then with complementary therapy, between 1998 and 2006. The analysis concluded that inadequate lymphadenectomy and the presence of lymph node metastases were strong predictors of increased mortality risk. Overall survival after CRT was significantly longer than after chemotherapy regardless of disease stage (OS CRT *vs.* OS CT 36.1% *vs.* 28.9 m., ($p < 0.0001$). This benefit decreases as the number of evaluated lymph nodes in the specimen increases. CRT improves overall survival in patients with lymph node metastases regardless of the extent of lymphadenectomy (29.8 *vs.* 22.2 months, $p < 0.001$). In patients without lymph node metastases, with normal extent of lymphadenectomy, no benefit of CRT over CT was observed. Patients without lymph node metastases, with inadequate lymphadenectomy, benefited from CRT [18]. In contrast, Dutch researchers took a closer look at the effect of CRT on the prognosis of patients after microscopically non-radical surgery. They compared two groups of patients – 361 patients after R1 resection without complementary CRT and 40 patients undergoing this procedure – using the Cox regression test and the extreme fitting method for statistical analysis. The disease progression in both groups did not show statistically significant differences. However, a significantly longer survival was observed in patients undergoing complementary CRT (24 months *vs.* 13 months) [19].

The retrospective data obtained during the analysis compared two practically homogeneous groups of patients treated in the NIO-PIB with complementary CRT. The factors that differentiated them were:

- percentage of radical operations,
- number of lymph nodes evaluated in the specimen.

It should be added here that in the group of patients treated outside the NIO-PIB, almost all patients were operated on in institutions of II and mainly III referral level. Thus, it should have been expected that the parameters determining the quality of surgical treatment and histopathological evaluation, such as the radicality of the surgical procedure and the number of lymph nodes evaluated in the examined specimen, should be similar. Nevertheless, both resection and the extent of lymphadenectomy were significantly different. However, the 8.6% higher 5-year OS in the group of patients operated on in NIO-PIB did not translate into statistical significance. The authors conclude that the use of adjuvant CRT effectively eliminated the differences in the quality of surgical treatment. Comparing the 5-year OS values with data from foreign centers, it should be noted that the results of surgical treatment of locoregionally advanced gastric cancer supplemented with CRT according to the MacDonald scheme, are similar to those achieved in American and Western European centers and slightly worse than those achieved in the Far East [6, 8, 9, 15, 16].

In summary, improvements in treatment outcomes resulting from advances in gastric cancer therapy will only occur if this cancer is diagnosed early enough [6] and treatment is concentrated in quality-assured facilities. In particular, this applies to the surgical stage of combined treatment and the adherence to protocols for the appropriate preparation of the specimens collected for histopathological examination, as well as the examination itself. A similar opinion is held by researchers gathered around the CRITICS project [20–22]. Much also depends on the awareness of the patients themselves, who should lobby for the introduction of endoscopic screening and avoid institutions where the proposed treatment differs from the commonly accepted one. A hope in this matter is increasing access to information and a social trend to be proactive in taking care of one's own health.

Conclusions

- The quality of surgical treatment, expressed both by the percentage of radical operations and the extent of lymphadenectomy, is significantly better at NIO-PIB compared to other centers.
- The difference in 5-year OS between the compared groups is not statistically significant.
- Complementary treatment with CRT according to MacDonald regimen reduces the shortcomings in the quality of surgical treatment in locoregionally advanced gastric adenocarcinoma.

Conflict of interest: none declared

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Received: 2 Feb 2022
Accepted: 15 Mar 2022

References

1. National Cancer Registry. http://onkologia.org.pl/nowotwory-żołądka.
2. Al-Batran SE, Hofheinz RD, Pauligk CI, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016; 17(12): 1697–1708, doi: 10.1016/s1470-2045(16)30531-9 , indexed in Pubmed: 27776843.
3. Olesiński T. Surgical treatment of gastric cancer: then and now. Nowotwory. Journal of Oncology. 2017; 66(5): 408–414, doi: 10.5603/njo.2016.0072.
4. Smyth EC, Verheij M, Allum W, et al. ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016; 27(suppl 5): v38–v49, doi: 10.1093/annonc/mdw350, indexed in Pubmed: 27664260.
5. MacDonald JS, Smalley SR, Benedetti JI, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastrooesophagal junction. N Engl J Med. 2001; 345(10): 725–730, doi: 10.1056/NEJMoa010187, indexed in Pubmed: 11547741.
6. Chelakkot PG, Ravind R, Sruthi K, et al. Treatment in resectable non-metastatic adenocarcinoma of stomach: Changing paradigms. Indian J Cancer. 2019; 56(1): 74–80, doi: 10.4103/ijc.IJC_375_18, indexed in Pubmed: 30950450.
7. Xu J, Zhu J, Wei Q. Adjuvant Radiochemotherapy versus Chemotherapy Alone for Gastric Cancer: Implications for Target Definition. J Cancer. 2019; 10(2): 458–466, doi: 10.7150/jca.27335, indexed in Pubmed: 30719140.
8. Aoyama T, Yoshikawa T. Adjuvant therapy for locally advanced gastric cancer. Surg Today. 2017; 47(11): 1295–1302, doi: 10.1007/s00595-017-1493-y, indexed in Pubmed: 28251375.
9. Zhou MLZ, Yang W, Wang YQI, et al. Adjuvant chemoreadiotherapy versus adjuvant chemotherapy for patients with N3 gastric cancer after D2/R0 resection: a retrospective study based on propen sity score analyses. Cancer ManagRes. 2019: 4855–4870.
10. Zhou ML, Kang M, Li GC, et al. Postoperative chemoradiotherapy versus chemotherapy for R0 resected gastric cancer with D2 lymph node dissection: an up-to-date meta-analysis. World J Surg Oncol. 2016; 14(1): 209, doi: 10.1186/s12957-016-0957-7, indexed in Pubmed: 27502921.
11. Xu J, Zhu J, Wei Q. Adjuvant Radiochemotherapy versus Chemotherapy Alone for Gastric Cancer: Implications for Target Definition. J Cancer. 2019; 10(2): 458–466, doi: 10.7150/jca.27335, indexed in Pubmed: 30719140.
12. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemioradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS):an international, open – label, randomized phase 3 trial. Lancer oncol. 2018; 19(5): 616–628.
13. Leong T, Smithers B, Haustermans K, et al. TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG. Ann Surg Oncol. 2017; 24(8): 2252–2258, doi: 10.1245/s10434-017-5830-6.
14. Slagter AS, Jansen EPM, van La, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. BMC Cancer. 2018; 18: 877, doi: 10.1186/s12885-018-4770-2, indexed in Pubmed: 30200910.
15. Kanhere H, Goel R, Finlay B, et al. Radical Gastrectomy: Still the Cornerstone of Curative Treatment for Gastric Cancer in the Perioperative Chemotherapy Era-A Single Institute Experience over a Decade. Int J Surg Oncol. 2018; 2018: 9371492, doi: 10.1155/2018/9371492, indexed in Pubmed: 29568650.
16. Nakamura Y, Yamanaka T, Chin K, et al. Survival Outcomes of Two Phase 2 Studies of Adjuvant Chemotherapy with S-1 Plus Oxaliplatin or Capecitabine Plus Oxaliplatin for Patients with Gastric Cancer After D2 Gastrectomy. Ann Surg Oncol. 2019; 26(2): 465–472, doi: 10.1245/s10434-018-7063-8, indexed in Pubmed: 30456678.
17. Yuan P, Wu Z, Li Z, et al. Impact of postoperative major complications on long-term survival after radical resection of gastric cancer. BMC Cancer. 2019; 19(1): 833, doi: 10.1186/s12885-019-6024-3, indexed in Pubmed: 31443699.
18. Datta J, McMillan MT, Ecker BL, et al. Implications of Lymph Node Staging on Selection of Adjuvant Therapy for Gastric Cancer in the United States: A Propensity Score-matched Analysis. Ann Surg. 2016; 263(2): 298–305, doi: 10.1097/SLA.0000000000001360, indexed in Pubmed: 26135687.
19. Stiekema J, Trip AK, Jansen EPM, et al. Does adjuvant chemoradiotherapy improve the prognosis of gastric cancer after an r1 resection? Results from a dutch cohort study. Ann Surg Oncol. 2015; 22(2): 581–588, doi: 10.1245/s10434-014-4032-8, indexed in Pubmed: 25164039.
20. Claassen YHM, de Steur WO, Hartgrink HH, et al. Surgicopathological Quality Control and Protocol Adherence to Lymphadenectomy in the CRITICS Gastric Cancer Trial. Ann Surg. 2018; 268(6): 1008–1013, doi: 10.1097/SLA.0000000000002444, indexed in Pubmed: 28817437.
21. Claassen YHM, Hartgrink HH, de Steur WO, et al. Impact of upfront randomization for postoperative treatment on quality of surgery in the CRITICS gastric cancer trial. Gastric Cancer. 2019; 22(2): 369–376, doi: 10.1007/s10120-018-0875-1, indexed in Pubmed: 30238171.
22. Claassen YHM, van Amelsfoort RM, Hartgrink HH, et al. Effect of Hospital Volume With Respect to Performing Gastric Cancer Resection on Recurrence and Survival: Results From the CRITICS Trial. Ann Surg. 2019; 270(6): 1096–1102, doi: 10.1097/SLA.0000000000002940, indexed in Pubmed: 29995679.

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 265–269

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Anatomy is the key to mastery in cancer and general surgery: the results of a survey on anatomical knowledge among surgeons

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Introduction. Cancer and general surgery is a medical field in which anatomical knowledge is crucial. The anatomy taught to medical students is based on a standardized model of the body, with no regard paid to anatomical variations which can result in serious difficulties and disorientation during surgical procedures.

Material and methods. Our goal was to assess anatomical knowledge, including anatomical variations, among surgeons. The questionnaire was administered among a group of 90 surgeons (general [69.7%] and oncological [20.2%]). The mean number of years in practice in their respective field was 12.9 ± 9.3.

Results. All participants were unanimous in declaring that anatomical knowledge was required in everyday surgical practice. The responses were also consistent in describing the role of knowledge of anatomical variations, declaring it "very important" and "important" in avoiding complications (76.4%). The majority of surgeons rated their anatomical aptitude as "good" (57.3%) or "very good" (13.5%).

Conclusions. The anatomical knowledge of Polish general and cancer surgeons is satisfactory.

Key words: anatomy, professional education, surgery, anatomic variation, medical errors

Introduction

Anatomy has been an indispensable component of medical school curricula for centuries, while also being the bane of medical students' education. Anatomical education not only represents a purely academic pursuit, but it remains a rite of passage for medical students on their journey to becoming clinicians [1–3]. A fundamental knowledge of anatomy seems to be essential in virtually every aspect of the diagnostic and therapeutic process – the physical exam, the diagnosis, the treatment strategy, and effective communication among specialists [1, 4].

Surgery is a medical field in which anatomical knowledge is of the utmost importance. Each surgical procedure is inextricable from the surrounding anatomy, whether it be variations in shape, size or configurations of the corresponding structures [1, 4]. Removal of malignancy requires the highest level of

Jak cytować / How to cite:

Kowalczyk KA, Majewski A, Wysocki WM, Tomaszewski K. ***Anatomy is the key to mastery in cancer and general surgery: the results of a survey on anatomical knowledge among surgeons.*** *NOWOTWORY J Oncol* 2022; 72: 226–230.

anatomical skills to achieve radicality of dissection, including regional lymphadenectomies, regardless of the location of the primary tumor; this is critical in reconstructive surgery following oncological resection. Lack of detailed knowledge of anatomical variations is an important risk factor for suboptimal dissection and subsequently decreased overall cancer surgery efficacy [5, 6].

Given the above, it becomes unsettling to discover the emergence of weakening standards of anatomical acumen among medical students, medical graduates, and even new surgeons [3, 4, 7–11]. A declining proficiency in anatomical knowledge may inevitably lead to surgical errors, eventually impacting patient satisfaction and resulting in legal action [4, 8, 12]. The percentage of procedural errors attributed to anatomical factors is as high as 20% to 35% [13–15]. Furthermore, the anatomy taught to medical students is based on a standardized model of the body, with no regard paid to anatomical variations. Medical students are thus ill-equipped to recognize clinically relevant variations, and this dearth of knowledge can result in serious difficulties and disorientation during surgical procedures [16, 17]. Taken together, these trends are especially disconcerting given that the field of medicine, including surgery, is evolving toward increasingly specialized disciplines that will require more training and knowledge in anatomy than previous generations of medical doctors [18]. Given the reports in foreign publications on the declining level of anatomical knowledge among surgeons, especially those new to the field, it was worth investigating the situation in Poland to address the lack of similar studies conducted in our country.

The main goal of our study was to assess the level of anatomical skills, including knowledge of anatomical variations, among surgeons.

Material and methods

Survey design

The study was conducted through an online questionnaire. The questionnaire was comprised of two parts. The first part involved open and closed questions, with both multiple choice and single choice (formulated according to the 5-item Likert scale) questions aimed at assessing the characteristics of the studied group and collecting feedback on the subjectively assessed utility of anatomical knowledge in everyday surgical practice including the most often consulted resources for anatomical information. The second part of the questionnaire was an evaluation of anatomical knowledge consisting of 8 multiple choice questions with a single correct answer; questions were referring to specific anatomical issues. The questionnaire (in Polish) is attached as supplementary material.

Survey administration

The questionnaire was distributed by e-mail and shared on social media platforms, including closed groups for surgeons only, between August and December 2020.

Statistical analysis

All data were analysed with Statsoft STATISTICA v.13. The results are presented as mean ± standard deviation (SD) or median with quartiles, when appropriate. The Shapiro-Wilk test was used to check for normal distribution of data. In the cases of quantitative variables, where no normal distribution was observed and when other requirements were not met, we used the Kruskal-Wallis or the Mann-Whitney U test depending on the number of subgroups. The results were considered statistically significant when the p-value was found to be less than 0.05.

Results

The questionnaire was administered among a group of 90 surgeons. One of the responders was excluded from analysis owing to the fact that their declared age and field of work was found to be factually inconsistent; thus, the final number of questionnaires analyzed was 89.

The study participants consisted mainly of general surgeons (69.7%) and oncological surgeons (20.2%) with varying years of experience. The mean number of procedures among general surgeons was found to be 197 ± 168.1, 252.3 ± 156.6 procedures among oncological surgeons, and 101.7 ± 55.6 procedures among the remaining participants. The mean number of years in practice in their respective fields was 12.9 ± 9.3 years. General surgeons reported 11.7 ± 9.0 years of experience in their field, while oncological surgeons reported 16.8 ± 9.9 year, and other surgeons reporting 14.4 ± 7.9 years. The cohort consisted of 23 (25.8%) women and 66 (74.2%) men. The mean age was 38.9 ± 9.2 years of age; the mean age of the female participants (34.3 ± 4.8 years) was significantly ($p = 0.0046$) different from their male counterparts (40.5 ± 9.8). The youngest respondent was 27 years old, while the most senior was 70 years old. The mean number of procedures performed in a year among the studied population was 199 ± 161.7. When separated by sex, the mean number of procedures performed among men was 202 ± 162.9 and 189.0 ± 161.8 among woman. The respondents were workers of university-affiliated institutions (39.3%), district hospitals (30.3%), and provincial hospitals (24.7%). Characteristics of respondents are included in table I.

All participants were unanimous in declaring that anatomical knowledge was required in everyday surgical practice, with 86.5% selecting "essential", and 13.5% selecting "useful". The responses were also consistent in describing the role of knowledge of anatomical variations in a given structure, declaring it "very important" and "important" in avoiding surgical complications (76.4%) or acknowledging that "anatomical variations are worth knowing" (23.6%). When asked about the nature of anatomical variants considered most important in their training, the study participants specified venous and organ variants (fig. 1).

As a main source of information for broadening their anatomical acumen, respondents most often endorsed manuals and atlases (92.1%), followed by multimedia resources which includes but is not limited to videos or virtual reality, (74.2%)

Table I. Group characteristics

Number of responders (n = 89), (%)	
• females, n (%)	23 (25.8%)
• males, n (%)	66 (74.2%)
mean age, years ± SD	38.9 ± 9.2
number of years worked in the profession, years ± SD	12.9 ± 9.3
Surgical field	
• general surgery	62 (69.7%)
• oncological surgery	18 (20.2%)
• others	9 (10.1%)
mean number of operations performed per year ± SD	199 ± 161.7
Workplace	
• university hospital	36 (39.3%)
• provincial hospital	22 (24.7%)
• district hospital	27 (30.3%)
• others	5 (5.6%)

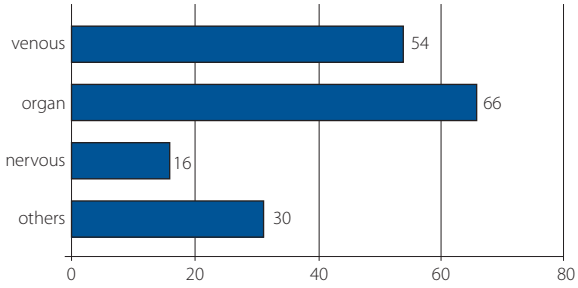

Figure 1. Which of the following classes of anatomical variations were includes in the program of your training so far? (More than one answer possible)

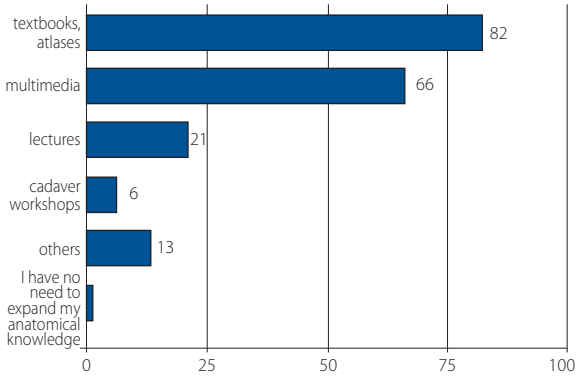

Figure 2. What sources do you mainly use to expand your knowledge of anatomy? (Multiple answers possible)

and cadaveric workshops (6.7%) (fig. 2). Among those who endorsed these workshops as a source of anatomical knowledge, the median score on the anatomical knowledge test was 4 (range 3 to 7), while the median score for those who did not make use of anatomical workshops was 5 (range 4 to 6).

The majority of surgeons rated their anatomical aptitude as "good" (57.3%) or "very good" (13.5%). 28.1% of respondents rated their knowledge as "neither good, nor bad" and only one as "bad" (1.1%). The amount of points earned on the anatomical skills evaluation did not differ among the respective groups who self-assessed their anatomical knowledge – the median was 5 points (for a maximum of 8 possible points on a knowledge assessment).The individuals in the group who assessed their anatomical knowledge as "very good" earned a slightly higher median score of 6 (tab. II). The mean amount of points earned on the evaluation of anatomical knowledge was 5.9 ± 1.64. These details are presented in table III (note that questions 1–8 in table III correspond to questions 12–19 in the questionnaire). No statistically significant difference was found in the number of points earned on the evaluation of anatomical knowledge among the groups specified by sex ($p = 0.958$), surgical specialty ($p = 0.235$), place of work ($p = 0.1428$), years of experience (less than or more than 10 years of experience) ($p = 0.7563$) or the approximate number of procedures performed within a year (less than or more than 100 procedures per year) ($p = 0.6849$) (tab. IV).

Discussion

The main findings of this study include the consensus among Polish general and oncological surgeons that knowledge of anatomy and its variations is important in their surgical practice, and that their main sources of knowledge are atlases and manuals, as well as medical multimedia resources. Most Polish surgeons self-assessed their own knowledge as either good or very good, with those in the latter group earning a slightly higher median score on the knowledge test. However, factors such as sex, surgical specialty, and years of experience had no significant effect on the results of the knowledge test.

Many studies have described the declining standard of foundational anatomical knowledge among surgeons and students [3, 4, 7–11]. Concurrently, there also exists a growing number of legal claims attributed to surgical errors, which cite insufficient knowledge as a contributing factor to the error [13–15, 19]. In the context of these well-established claims, it can be surmised that the level of anatomical knowledge among Polish surgeons is satisfactory, regardless of whether

Table II. Results of the anatomical knowledge test in accordance with belonging to the groups of anatomical knowledge self-assessment

	Number of responders (%)	Median sum (IQR)
very good	12 (13.5%)	6 (5.5–6.5)
good	51 (57.3%)	5 (4–6)
neither good nor bad	25 (28.1%)	5 (4–6)
bad	1 (1.1%)	5 (5–5)
very bad	–	–

Table III. The number of correct answers obtained in the anatomical knowledge test in each group

Correct answer								
	Question 1 [Question about the blood vessels of the liver]	Question 2 [Question about the portal vein]	Question 3 [Question about the gallblader]	Question 4 [Question about visceral vascularization]	Question 5 [Question about vascularization of the large intestine]	Question 6 [Question about anatomy of the duodenum]	Question 7 [Question about the arc of Buhler]	Question 8 [Question about the clinical significance of the arc of Buhler]
all, n (%)	70 (78.7%)	69 (77.5%)	67 (75.3%)	68 (76.4%)	38 (42.7%)	56 (62.9%)	62 (69.7%)	23 (25.8%)
sex								
females, n (%)	19 (82.6%)	15 (65.2%)	19 (82.6%)	19 (82.6%)	9 (39.1%)	15 (65.2%)	17 (73.9%)	5 (21.7%)
males, n (%)	51 (77.3%)	54 (81.8%)	48 (72.7%)	49 (74.2%)	29 (43.9%)	41 (62.1%)	45 (68.2%)	18 (27.3%)
surgical field								
general surgery	46 (74.2%)	48 (77.4%)	47 (75.8%)	48 (77.4%)	23 (37.1%)	37 (59.7%)	40 (64.5%)	14 (22.6%)
oncological surgery	17 (94.4%)	15 (83.3%)	16 (88.9%)	16 (88.9%)	10 (55.6%)	11 (61.1%)	15 (83.3%)	6 (33.3%)
others	7 (77.8%)	6 (66.7%)	4 (44.4%)	4 (44.4%)	5 (55.6%)	8 (88.9%)	7 (77.8%)	3 (33.3%)
workplace								
university hospital	29 (92.9%)	26 (75.3%)	25 (71.4%)	28 (80%)	17 (48.6%)	23 (65.7%)	25 (71.4%)	9 (25.7%)
provincial hospital	15 (68.2%)	18 (81.8%)	18 (81.8%)	13 (59.1%)	7 (31.8%)	11 (50%)	16 (72.7%)	5 (22.7%)
district hospital	21 (77.8%)	21 (77.8%)	19 (70.4%)	22 (81.5%)	12 (44.4%)	19 (70.4%)	17 (59.3%)	7 (25.9%)
others	5 (100%)	4 (80%)	5 (100%)	5 (100%)	2 (40%)	3 (60%)	5 (100%)	2 (40%)

Table IV. The average number of points obtained in the anatomical knowledge test in each group

Median sum (IQR)		p
females, n (%)	5 (4–6)	0.958
males, n (%)	5 (4–6)	
general surgery	5 (4–6)	0.235
oncological surgery	6 (5–7)	
others	5 (4–6)	
university hospital	5 (4–6)	0.1428
provincial hospital	6 (3–6)	
district hospital	5 (4–6)	
others	6 (6–7)	
>10 years of work	5 (4–6)	0.7563
<10 years of work	5 (4–6)	
approximate number of surgical procedures per year >100	5 (4–6)	0.6849
approximate number of surgical procedures per year <100	5 (4–6)	

he or she is beginning their career or has years of experience. In cancer surgery anatomical crucial landmarks and anatomical variations are of utmost importance, as the extent of cancer resection includes typically regional lymph nodes [5, 6] and often encompasses neighboring organs (multiorgan *en-bloc* resections). Appropriate care for oncological radically from one side and preservation of blood supply to the organs left in situ requires detailed anatomical aptitude; specific knowledge of anatomy is required in organ-sparing cancer surgery [20].

A very small subset of respondents in this study was found to take advantage of cadaveric workshops, which is in contrast to the results of studies conducted outside of Poland [9, 17]. Such workshops are considered to be the most effective method of learning anatomy [1, 4, 7, 17]. There was no statistically significant difference in test results between those participants who participated in cadaveric workshops and those who did not. Although other studies have described the advantage of these workshops, the lack of statistically significant results in our research could be due to the small sample size. This discrepancy may also be attributed to a lack of access to these resources in our country.

While the majority of respondents were able to give the correct answer (69.7% answered correctly) on an anatomical variant (question 7), the task of describing its clinical significance (question 8) proved to be more difficult, with 25.8% of respondents answering correctly. Given these findings, it may be worth investing in resources that can expand surgeons' knowledge of anatomical variants.

Limitations

This study was limited by the number of surgeons who were able to respond to the questionnaire. A more rigorous asses-

sment of anatomical knowledge could also be used to more accurately determine each participant's acumen.

Conclusions

According to the authors' knowledge, this is the first study of its kind conducted in Poland. To extract broader conclusions, it would be worthwhile to expand the number of study participants, and to administer a more advanced evaluation of anatomical knowledge. From this study, the authors can ascertain that the anatomical knowledge of Polish general and cancer surgeons is satisfactory. It may be beneficial to provide surgeons-in-training with access to cadaveric workshops, as this resource has been found to be the most effective method of learning anatomy, yet as this study has found, only a minority of the respondents take advantage of such opportunities. Finally, post-graduate medical education programs should consider placing more emphasis on anatomical variants as well as their clinical correlations, particularly for surgeons dealing with cancer patients, in whom it is often required to perform non-anatomical, multiorgan or – contrary – organ-preserving surgery, which requires the very highest level of anatomical mastery.

Acknowledgements

The authors would like to thank all the participants who took the time to complete the electronic survey.

Conflict of interest: none declared

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Received: 13 May 2022
Accepted: 17 May 2022

References

1. Turney BW. Anatomy in a modern medical curriculum. Ann R Coll Surg Engl. 2007; 89(2): 104–107, doi: 10.1308/003588407X168244, indexed in Pubmed: 17346399.
2. Netterstrøm I, Kayser L. Learning to be a doctor while learning anatomy! Anat Sci Educ. 2008; 1(4): 154–158, doi: 10.1002/ase.31, indexed in Pubmed: 19177402.
3. Staśkiewicz GJ, Walczak E, Torres K, et al. What do clinicians think of the anatomical knowledge of medical students? Results of a survey. Folia Morphol (Warsz). 2007; 66(2): 138–142, indexed in Pubmed: 17594673.
4. Singh R, Tubbs R. Should a Highly Skilled Surgeon be an Advanced Anatomist first? - A View Point. Basic Sciences of Medicine. 2015; 4(4): 53–57, doi: 10.5923/j.medicine.20150404.01.
5. Wysocki W, Libondi G, Juszczak A. Surgical anatomy of the breast revisited. Nowotwory J Oncol. 2020; 70(1): 26–28, doi: 10.5603/njo.2020.0005.
6. Cieśla S, Wichtowski M, Poźniak-Balicka R, et al. The surgical anatomy of the mammary gland. Vascularisation, innervation, lymphatic drainage, the structure of the axillary fossa (part 2. Nowotwory J Oncol. 2021; 71(1): 62–69, doi: 10.5603/NJO.2021.0011.
7. Waterston SW, Stewart IJ. Survey of clinicians' attitudes to the anatomical teaching and knowledge of medical students. Clin Anat. 2005; 18(5): 380–384, doi: 10.1002/ca.20101, indexed in Pubmed: 15971223.
8. Sharma G, Aycart MA, Najjar PA, et al. A cadaveric procedural anatomy course enhances operative competence. J Surg Res. 2016; 201(1): 22–28, doi: 10.1016/j.jss.2015.09.037, indexed in Pubmed: 26850180.
9. Mattar SG, Alseidi AA, Jones DB, et al. General surgery residency inadequately prepares trainees for fellowship: results of a survey of fellowship program directors. Ann Surg. 2013; 258(3): 440–449, doi: 10.1097/SLA.0b013e3182a191ca, indexed in Pubmed: 24022436.
10. Tayyem R, Qandeel H, Qsous G, et al. Medical Students' vs. Consultant Surgeons' View of Anatomy Knowledge. International Journal of Morphology. 2019; 37(4): 1475–1479, doi: 10.4067/s0717-95022019000401475.
11. Cottam WW. Adequacy of medical school gross anatomy education as perceived by certain postgraduate residency programs and anatomy course directors. Clin Anat. 1999; 12(1): 55–65, doi: 10.1002/(SICI)1098-2353(1999)12:1<55::AID-CA8>3.0.CO;2-O, indexed in Pubmed: 9890730.
12. Goodwin H. Litigation and surgical practice in the UK. Br J Surg. 2000; 87(8): 977–979, doi: 10.1046/j.1365-2168.2000.01562.x, indexed in Pubmed: 10931037.
13. Rogers SO, Gawande AA, Kwaan M, et al. Analysis of surgical errors in closed malpractice claims at 4 liability insurers. Surgery. 2006; 140(1): 25–33, doi: 10.1016/j.surg.2006.01.008, indexed in Pubmed: 16857439.
14. Somville FJ, van Sprundel M, Somville J. Analysis of surgical errors in malpractice claims in Belgium. Acta Chir Belg. 2010; 110(1): 11–18, doi: 10.1080/00015458.2010.11680558, indexed in Pubmed: 20306903.
15. Regenbogen SE, Greenberg CC, Studdert DM, et al. Patterns of technical error among surgical malpractice claims: an analysis of strategies to prevent injury to surgical patients. Ann Surg. 2007; 246(5): 705–711, doi: 10.1097/SLA.0b013e31815865f8, indexed in Pubmed: 17968158.
16. Raikos A, Smith JD. Anatomical variations: How do surgical and radiology training programs teach and assess them in their training curricula? Clin Anat. 2015; 28(6): 717–724, doi: 10.1002/ca.22560, indexed in Pubmed: 25974002.
17. Henry BM, Tomaszewski KA, Walocha JA. Methods of Evidence-Based Anatomy: a guide to conducting systematic reviews and meta-analysis of anatomical studies. Ann Anat. 2016; 205: 16–21, doi: 10.1016/j.aanat.2015.12.002, indexed in Pubmed: 26844627.
18. Ahmed K, Rowland S, Patel V, et al. Is the structure of anatomy curriculum adequate for safe medical practice? Surgeon. 2010; 8(6): 318–324, doi: 10.1016/j.surge.2010.06.005, indexed in Pubmed: 20950770.
19. Ellis H. Medico-legal Litigation and its Links with Surgical Anatomy. Surgery (Oxford). 2002; 20(8), doi: 10.1383/surg.20.8.0.14518.
20. Zubaryev M, Kim HS, Min BS. Local excision vs. radical surgery in treating rectal nets considering the biology of neuroendocrine tumors (NETs). Nowotwory J Oncol. 2021; 71(1): 9–16, doi: 10.5603/njo.a2021.0001.

VIA MEDICA

Artykuł przeglądowy / Review article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 270–280

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Principles of prevention and management of adverse events of immunomodulatory drugs in the treatment of multiple myeloma

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Over the past 15 years, significant progress has been made in understanding the biology and treatment of multiple myeloma (MM). This is due to the introduction of new therapies and new applications of known drugs associated with a better understanding of how to optimize treatment to patient and disease characteristics. Indeed, 15 new drugs have been approved over this time period. Immunomodulatory drugs (IMiDs) have been used in the treatment of MM for over 20 years. Initially, it was thalidomide, then analogues lenalidomide and pomalidomide; in the future, cereblon E3 ligase modulators CelMoDs, such as iberdomide and CC-480. Currently, IMiDs are mainly used as the backbone of multi-drug protocols, including in combination with monoclonal antibodies and proteasome inhibitors. Given the common utilization of IMiDs in the management of MM, it is relevant to review the safety profile of IMiDs and the management of adverse events (AEs).

Key words: adverse events, immunomodulatory drugs, lenalidomide, management, multiple myeloma, pomalidomide, thalidomide, treatment

Introduction

Immunomodulatory drugs (IMiDs) have significantly improved survival in patients with multiple myeloma (MM) over the past 20 years. That said, only 10–15% of MM patients meet or exceed life expectancy compared to the matched general population [1]. There are three IMiDs commonly used in clinical practice: thalidomide, lenalidomide, and pomalidomide. Immunomodulating drugs are oral drugs that have unique mechanisms of action, including anti-cancer and anti-inflammatory effects, and affect the human immune system [2].

The mechanism of action of IMiDs in MM cells was initially considered a process of anti-angiogenesis [3]. After that, direct and indirect anti-tumor activity was demonstrated by immunomodulation. In 2010, the anti-MM activity of the IMiDs was mediated by the inhibition of cereblon (CRBN), a protein that dictates the substrate specificity of CRL4CRBN E3 ubiquitin ligase [4–6]. By binding the CRL4CRBN E3 ligase, the proteins associated with the disease are ubiquitinated and degraded. The key neosubstrates in plasma cells (PCs) are transcription factors – the Ikaros (IKZF1) and Aiolos (IKZF3) proteins [7, 8]. IMiDs degrade Ikaros and Aiolos *via* CRBN-dependent ubiquitination, leading to the downregulation of IRF4 and MYC [9]. In addition to their direct anti-MM activity, IMiDs show indirect anti-MM activity, inhibiting the secretion of pro-in-

Jak cytować / How to cite:

Charliński G, Vesole DH, Jurczyszyn A. ***Principles of prevention and management of adverse events of immunomodulatory drugs in the treatment of multiple myeloma.*** *NOWOTWORY J Oncol* 2022; 72: 231–241.

flammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin (IL) – 1, IL-6, IL-12, and IL-16, which leads to the inhibition of proliferation and migration of neoplastic PCs and apoptosis [10]. Lenalidomide and pomalidomide induce malignant PCs apoptosis more potently by activating tumor suppressor genes than thalidomide. In preclinical studies, lenalidomide and pomalidomide were 300–1200 times more potent than thalidomide in T-cell costimulation [11, 12]. Both lenalidomide and pomalidomide increase the action of NK cells in destroying PCs. Lenalidomide additionally activates NKT cells [13, 14]. Cereblon E3 ligase modulators (CELMoDs), compared to IMiDs, have a greater affinity for CRBN and a more decisive influence on the degradation of Ikaros and Aiolos, which results in a stronger anti-MM and immunomodulatory effect [15, 16]. This is the fundamental difference between the two groups of drugs.

Despite the similarities in their chemical structure, the IMiDs differ in their adverse event (AE) profile and exhibit only moderate cross-reactivity, and can be used sequentially in subsequent lines of MM treatment. Currently, these drugs are considered a standard backbone in the induction therapy of transplant and non-transplant eligible patients, post-autologous stem cell transplantation (ASCT) consolidation and maintenance therapy, and in the treatment of relapsed/refractory MM (RRMM).

Thalidomide (α-N-phthalimido-glutarimide) has been used to treat MM for over 20 years [17]. Thalidomide shows synergy *in vitro* with other drugs and has become an integral component of many combinations of MM treatment. In the European Union (EU), the European Medicines Agency (EMA) approved thalidomide in combination with melphalan and prednisone (MPT), MPT with daratumumab (Dara-MPT), and with daratumumab, bortezomib, and dexamethasone (Dara-VTD) for the treatment of newly diagnosed MM (NDMM). The AEs observed during treatment with thalidomide favored the development of thalidomide analogs with greater immunomodulatory activity and a better safety profile [18]. A modification of the chemical structure led to the formulation of lenalidomide and pomalidomide.

Lenalidomide is an analogue of thalidomide that is commonly used in the treatment of MM. In the EU, the EMA approved lenalidomide in combination with dexamethasone (Rd), daratumumab and dexamethasone (Dara-Rd), bortezomib and dexamethasone (VRd), and melphalan and prednisone (MPR) for the treatment of NDMM. In Poland, lenalidomide can treat NDMM under the Ministry of Health drug program criteria based on the Rd and VRd chemotherapy protocols [19]. Lenalidomide monotherapy for maintenance treatment after ASCT is also EMA approved. In addition, the EMA approved lenalidomide for the treatment of RRMM, in combination with dexamethasone, and Rd in combination with carfilzomib (KRd), ixasomib (Ixa-Rd), Dara-Rd, and elotuzumab (Elo-Rd). In Poland, in the treatment of RRMM, lenalidomide treatment is approved following the criteria of the Ministry of Health drug program under the Rd, KRd, Ixa-Rd chemotherapy protocols [19].

Pomalidomide is another thalidomide analogue with direct antiproliferative, pro-apoptotic, and anti-angiogenic effects. It has a modulating effect on bone resorption and the immune system [20]. The EMA has approved pomalidomide and dexamethasone (Pd) remove for the treatment of RRMM in combination with bortezomib (PVd), isatuximab (Isa-Pd), and elotuzumab (Elo-Pd). In Poland, in the treatment of RRMM, the combination of Pd and PVd is approved under the Ministry of Health drug program [19]. A comparison of the chemical structure, dosing, and mechanism of action of IMiDs is presented in table I [21].

The AEs observed in patients with MM result from both the neoplastic disease and the anti-MM treatment used and comorbidities. For this reason, it is not easy to ascribe specific AEs to specific drugs. In clinical practice, the Common Terminology Criteria (CTC) for AEs classification is most often used to identify AEs [22]. Common to all IMiDs is their potential teratogenic effect, which can result in severe, life-threatening congenital malformations (e.g., phocomelia). For this reason, unless there is reliable evidence that they cannot become pregnant, all patients must meet the conditions of the pregnancy prevention program before starting treatment with IMiDs [23].

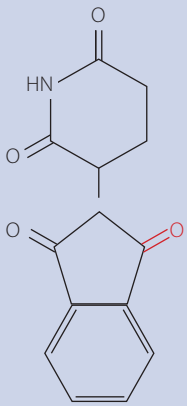
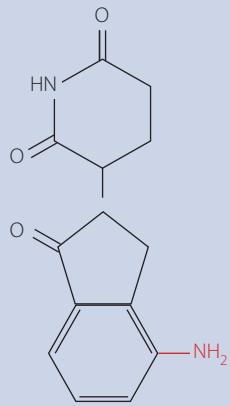
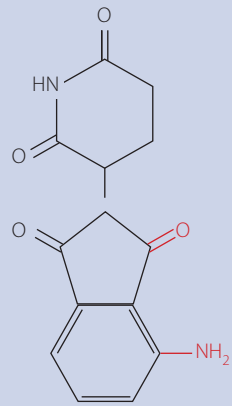
Due to the results of phase 3 clinical trials, IMiDs are currently used mainly in multi-drug combinations with new drugs, including monoclonal antibodies (daratumumab, elotuzumab, isatuximab) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib). We review the AEs reported in the latest phase 3 clinical trials and their management principles.

Thalidomide

So far, thalidomide has been the main IMiD used in the treatment of patients with NDMM in Poland. In ASCT eligible patients, thalidomide is used with bortezomib and dexamethasone (VTD) and VTD in combination with daratumumab. In the most recent EHA-ESMO recommendations issued in 2021, thalidomide is not recommended for patients with NDMM who are ineligible for ASCT [24].

The AEs of thalidomide depend on the dose and duration of treatment and the presence of comorbidities. The most common serious AEs of thalidomide include constipation, peripheral neuropathy (PN), somnolence, depression, and venous thromboembolism (VTE). Depending on the treatment regimen (monotherapy versus multi-drug combinations), the frequency of AEs is variable [25]. In randomized phase 3 clinical trials utilizing VTD induction therapy for NDMM before ASCT, the most common causes of hematological AEs, include neutropenia (15–19% of patients). In contrast, the most common non-hematological AEs are infections and PN [26, 27]. The combination of VTD and Dara-VTD in induction therapy before ASCT compared to VTD increases the incidence of serious hematological AEs, including neutropenia (grade 3–4: 28%

Table I. Comparison of the mechanisms of action and chemical structure of immunomodulatory drugs

	Thalidomide	Lenalidomide	Pomalidomide
chemical structure			
daily dose	50–200 mg	2.5–25 mg	1–4 mg
dose modification depending on RI	no dose modification needed	CrCl (ml/min) / daily dose: >60 / 25 mg; 30–59 / 10 mg; 15–29 / 15 mg every other day; <15 / 5 mg; on dialysis / 5 mg	no dose modification needed
relative potency ± potency factor of 10			
CD4+ and CD8+ T-cell co-stimulation	+	++++	+++++
tregs suppresion	–	+	+
Th1 cytokine production	+	++++	+++++
NK and NKT cell activation	+	++++	+++++
antibody-dependent cellular cytotoxicity	–	++++	++++
anti-angiogenesis	++++	+++	+++
anti-inflammatory properties	+	++++	+++++
anti-proliferative activity	+	+++	+++

CrCl – creatinine clearance; RI – renal impairment

vs. 15%) and thrombocytopenia (grade 3–4: 11% *vs.* 7%). There was no increase in the frequency of non-hematological serious AEs in the Dara-VTD group compared to the VTD group [28].

In patients not eligible for ASCT in first-line treatment, thalidomide is most often used in combination with melphalan and prednisone (MPT). The most common hematological AE was neutropenia, whereas the non-hematological AEs included infections, PN, VTE, and skin lesions (Stevens-Johnson syndrome and toxic epidermal necrolysis) [29, 30]. In some countries, thalidomide combined with cyclophosphamide and dexamethasone (CTD) was used as first-line treatment. The most frequently observed AEs in the phase 3 study, MRC Myeloma IX, were neutropenia (grade 3–4: 11%), infections (grade 3–4: 13%), and PN (grade 3–4: 7%) [31]. Table II summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of thalidomide for the treatment of NDMM. Thalidomide has been well studied as post ASCT maintenance therapy. The most common AEs are PN and constipation [32, 33], thus limiting their *se* for long term treatment.

Currently, the role of thalidomide in the treatment of RRMM is limited. In this indication, thalidomide has been used as monotherapy, combined with dexamethasone (TD) and triplet regimens. Regardless of the regimen, the most common side effects AE's were somnolence (11–57%), constipation (16–75%), PN (6–23%), skin rashes (3–21%), cardiovascular disorders (bradycardia, arrhythmias, 2%), and VTE (3–7%) [34, 35]. Thalidomide when combined with cyclophosphamide has the additional hematologic AEs including neutropenia (grade 3–4: 86%), thrombocytopenia (grade 3–4: 30%), infection (grade 3–4: 26%) [36].

Table II. Incidence of serious adverse events of thalidomide in treatment of newly diagnosed multiple myeloma identified in pivotal phase 3 clinical trials

Trial	Cavo et al. [26]		IFM2013-04 [27]		CASSIOPEIA [28]		Myeloma MRC IX [31]		The metanalysis of 6 randomized trials [30]	
regimen	TD	VTD	VCD	VTD	VTD	Dara-VTD	CTD	MP	MPT	MP
hematological adverse events, grade ≥3 (%)										
neutropenia	NA	NA	33	19	15	28	11	15	overall: 32	overall: 29
thrombocytopenia	0	5	11	5	7	11	NA	NA		
anemia	NA	NA	9	4	NA	NA	NA	NA		
non-hematological adverse events, grade ≥3 (%)										
febrile neutropenia										
infections	3	1	NR	NR	20	22	13	7	13	9
peripheral neuropathy	0	<1	grade 2–4: 12.9	grade 2–4: 21.9	9	9	7	2	15	3
venous thromboembolism	<1	<1	2	2	NA	NA	0	0	6	2
constipation	<1	<1	NA	NA	1	1	3	1.2	NA	NA
skin rash	<1	<1	NA	NA	NA	NA	2	<1	3	1
secondary malignancy (any grade)	NA	NA	NA	NA	2	2	NA	NA	NA	NA

CTD – cyclophosphamide, thalidomide, dexamethasone; Dara-VTD – daratumumab, bortezomib, thalidomide, dexamethasone; MP – melphalan, prednisone; MPT – melphalan, prednisone, thalidomide; NA – not available; TD – thalidomide, dexamethasone; VCD – bortezomib, cyclophosphamide, dexamethasone; VTD – bortezomib, thalidomide, dexamethasone

Management of AEs during treatment with thalidomide

The most common hematological AE in treatment with thalidomide is neutropenia. Anemia and thrombocytopenia are observed less frequently than neutropenia [23, 37]. For this reason, it is recommended to perform a blood count. When the absolute neutrophil count (ANC) is 0.5–1.0 G/L, reduce the thalidomide dose by 50% and consider the use of granulocyte colony-stimulating factor (G-CSF) when the ANC < 0.5 G/L treatment with thalidomide should be discontinued; if the ANC is more than 1.0 G/L, start treatment with a dose reduced by 50% with or without G-CSF [23]. Anemia and thrombocytopenia are less frequently observed than neutropenia [23, 37].

The most severe non-hematological undesirable effect of thalidomide treatment is PN. The incidence of PN is variable and is dependent on the dose and duration of therapy [38]. Some authors recommend treatment with thalidomide be limited to no more than six months [39]. Unfortunately, thalidomide-associated PN is often slow to resolve, if ever, and a substantial proportion of patients have some level of persistent PN. Therefore, during therapy with thalidomide, it is necessary to monitor for PN. Grade 1 PN does not require a reduction of the thalidomide dose; in grade 2, the dose of thalidomide should be reduced by 50%, and in grades 3 and 4, treatment with thalidomide should be discontinued until symptoms resolve or decrease to grade 1 [40].

The treatment for neuropathic pain is variable and challenging to manage, and the best management is to avoid the development of PN. One option is using agents which reduce neurotransmitter release: gabapentin (titrated up to 1200 mg three times daily) or pregabalin (titrated up to 300 mg twice daily). Alternative options include amitriptyline (10–100 mg daily), serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine), or anti-epileptic drugs (carbamazepine) [41]. Only 25% of patients completely recover from thalidomide-induced PN within 4–6 years [42].

Another non-hematological AEs of thalidomide (and all other IMiDs) treatment is VTE, which most often develops in the first three months and decreases after approximately 12 months [43]. During treatment with an IMiD, it is necessary to use anticoagulation prophylaxis adapted to the presence of risk factors, which include: age, immobility, obesity, history of VTE, presence of a central venous catheter, presence of comorbidities, hereditary thrombophilia, a large mass of MM tumor and treatment of high doses of dexamethasone, an anthracycline, or multi-drug chemotherapy [44]. According to the SAVED Score, the finding of at least two risk factors is an indication for treatment with enoxaparin 40 mg/day or warfarin (target International Normalized Ratio [INR]: 2–3). According to the SAVED Score, treatment with acetylsalicylic acid (ASA) 81–325 mg daily is recommended in patients with one risk factor [45–47]. Other drugs recommended are rivaroxaban 10 mg daily, apixaban 2.5 mg twice daily, and fondaparinux 2.5 mg daily.

A common side effect of thalidomide treatment is constipation, reported in 80–90% of patients. It develops early after

initiation of thalidomide treatment and most often affects elderly patients concomitantly treated with opioid analgesics. In patients starting thalidomide treatment, prophylactic use of low doses of stool softeners and/or laxatives is recommended. Should be adjusted treatment according to the severity of constipation. In the case of grade 3 or 4 constipation a 50% reduction in the daily dose of thalidomide is recommended. In constipation requiring the use of an enema, thalidomide treatment should be withheld until symptoms resolve. Prophylactic laxatives should be taken when treatment with thalidomide is resumed at a reduced dose [48, 49].

Common AEs of thalidomide include somnolence and fatigue. Mild drowsiness occurs in more than 75% of patients and severe (grade 3–4) in 5–10%. Daytime drowsiness may be reduced by taking the total daily dose of thalidomide in the evening. Hazardous tasks and the concomitant use of alcohol and medications that may make you feel drowsy should be avoided. If grade 3 somnolence interferes with normal activities of daily living, or if dementia, or a coma occurs, one should discontinue treatment until the toxicity has resolved. When re-treating, the daily dose of thalidomide should be reduced by 50%. Additionally, patients may report fatigue, weakness, difficulty concentrating, and mood changes [48].

Other non-hematological AEs include skin lesions observed in approximately 15% of patients, including about 1.5% of patients with grade ≥3 skin lesions [23]. The most common symptoms are pruritis and maculopapular rash. Alveolar lesions develop in 25% of patients treated with thalidomide in a dose >400 mg/day. Once the skin lesions have resolved, re-treatment of thalidomide may be considered at a reduced dose [23, 37]. After the skin lesions have resolved, may resume treatment with thalidomide at a reduced dose. If grade 1–2 dermatological AEs develops, treatment with thalidomide should be discontinued until the toxicity resolves or decreases to grade 1. Thalidomide should be suspended indefinitely in the event of severe exfoliative, macular, or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected. Medicines that may cause severe skin reactions, such as trimethoprim/sulfamethoxazole or allopurinol, should be avoided during treatment with thalidomide [23].

Renal impairment

Dexamethasone protocol is a highly effective and widely used treatment of NDMM with renal impairment (RI), mainly in Europe. The use of thalidomide in combination with a high dose of dexamethasone (TD) improves renal function in 55–75% of patients with NDMM and about 60% of patients with RRMM [50, 51]. The use of thalidomide in the treatment of MM with RI does not increase the incidence of AEs. Therefore, there is no need to adjust the dose of thalidomide depending on RI [52]. This also applies to patients requiring dialysis. Patients undergoing dialysis require close monitoring as they may develop hyperkalemia. It is necessary to remember the necessity to use antithrombotic prophylaxis in this group of patients [43]. Thalidomide dosing by creatinine clearance (CrCl) is presented in table I.

Lenalidomide

Lenalidomide is an IMiD that is approved for both NDMM and RRMM. Despite the high structural similarity to thalidomide, the two drugs have different safety profiles. The dominant AEs are hematological AEs resulting from the myelosuppressive effects of lenalidomide on the bone marrow [25]. Lenalidomide, unlike thalidomide, is renally cleared; therefore, RI increases the myelosuppressive effect of lenalidomide [53]. Unlike thalidomide, PN, constipation, and somnolence are rarely observed with lenalidomide treatment.

Lenalidomide may be associated with an increased risk of VTE. In a randomized phase 3 trial comparing Rd with lenalidomide in combination with high-dose dexamethasone (RD) in patients with NDMM, thromboprophylaxis was not mandatory until the first 266 patients were enrolled. More AEs were observed in the Rd group except grade 3–4 VTE, which was more common in the RD group (12% *vs.* 26%, respectively) [54]. Lenalidomide, when incorporated into multi-drug protocols, including in combination with dexamethasone and cyclophosphamide or liposomal doxorubicin, resulted in VTE in 14% and 9%, respectively) [55, 56].

The phase 3 FIRST study in NDMM compared lenalidomide in combination with dexamethasone for 18 cycles (Rd18) with continuous Rd – Rd(cont), and MPT [57]. In the group of patients treated with lenalidomide, hematological serious (grade 3–4) AEs were reported in the following proportion of patients: neutropenia in 26% and 30% of patients treated with Rd18 and Rd(cont), respectively; thrombocytopenia in 8% and 9% of patients, respectively, and neutropenia in 26%, and 30% of patients, respectively. The most common non-hematological serious (grade 3–4) AEs were infection (22% *vs.* 32%, respectively), VTE (4% *vs.* 5%, respectively) and pulmonary embolism (3% *vs.* 4%, respectively), thromboprophylaxis was included in the study), peripheral sensory neuropathy (<1% *vs.* 1%, respectively), diarrhea (3% *vs.* 5%, respectively) [57].

The use of VRd in NDMM compared to Rd does not increase serious (grade 3–4) hematological AEs but increases the risk of PN (grade 3–4: 35% *vs.* 11%, respectively) [58].

In the phase 3 MAIA trial, comparing Dara-Rd with Rd in transplant-ineligible NDMM, serious AEs were reported in 77% and 70% of patients, respectively. It is known that daratumumab is associated with neutropenia as a single agent. The most common serious (grade 3–4) AEs are neutropenia (54% *vs.* 37%, respectively), anemia (17% *vs.* 22%, respectively), lymphopenia (16% *vs.* 11%, respectively), and infections (32% *vs.* 23%, respectively) [59]. MPR compared with MPR with lenalidomide in maintenance therapy (MPR-R) in the treatment of NDMM is associated with a higher incidence of myelosuppression: neutropenia (grade 3–4) was found in 65% patients,

thrombocytopenia in more than 33%, and anemia in 25% patients [60]. Table III summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of lenalidomide for the treatment of NDMM.

In RRMM, two randomized phases 3 trials reported grade 3–4 AEs, including neutropenia (35%), anemia (11%), thrombocytopenia (13%), and infections (16%), atrial fibrillation (3%), and VTE (13%) The duration of use of lenalidomide in second-line treatment did not generally worsen the safety profile [61, 62].

There are several phase 3 studies comparing triplets with an Rd backbone to an Rd doublet, including combinations with carfilzomib, ixazomib, daratumumab, or elotuzumab. Most of the additions of a third drug, in general, resulted in a higher incidence of AEs [63–66]. In contrast, in these phase 3 studies which included mild to moderate RI, the myelosuppressive effect of lenalidomide was more pronounced, a significantly higher incidence of thrombocytopenia (grade 3–4) was found in patients with CrCl < 50 ml/min compared to CrCl ≥ 50 ml/min (14% *vs.* 5%) with no difference in grade 3 or 4 neutropenia [67]. Table IV summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of lenalidomide for the treatment of RRMM.

It is worth adding that the development of secondary neoplasms is observed in the treatment with lenalidomide in the context of recent melphalan therapy (e.g., MPR, or ASCT), post-ASCT, lenalidomide-maintenance therapy). In the treatment of NDMM, secondary primary malignancy were reported in 3–9% of NDMM and 4–17% of RRMM [61–66].

Management of AEs during treatment with lenalidomide

The myelosuppressive effect of lenalidomide is the most serious AE. Blood counts (CBCs) need to be routinely monitored, minimum monthly, to avoid severe infections and discontinuation of lenalidomide treatment. You should follow the EMA product information for dose restrictions, resumptions, and dose reductions. When the platelets (PLT) count drops to <25 G/L, should discontinue lenalidomide treatment until the PLT count has improved to ≥50 G/L, and lenalidomide should be given at a reduced dose of 15 mg/day. With each successive decrease in the PLT count <25 G/L, lenalidomide treatment should be discontinued and restarted when the PLT count increases ≥50 G/L, at a dose reduced by 5 mg compared to the previously used dose [68]. When the ANC < 0.5 G/L, lenalidomide treatment should be discontinued, G-CSF administered, and lenalidomide at the current dose resumed when the ANC increases ≥1.0 G/L. If ANC count returns to <1.0 G/L, lenalidomide treatment should be discontinued and restarted at a dose 5 mg lower when the ANC becomes ≥1.0 G/L [68]. In the case of

Table III. Incidence of serious adverse events of lenalidomide in treatment of newly diagnosed multiple myeloma identified in pivotal phase 3 clinical trials

Trial/author	MM-015 [60]			Rajkumar et al. [54]		FIRST [57]		SWOG S0777 [58]			MAIA [59]	
regimen	MPR-R	MPR	MP	RD	Rd	Rd(cont)	Rd18	MPT	Rd	VRd	Dara-Rd	Rd
hematological adverse events, grade ≥3 (%)												
neutropenia	67	64	29	12	20	30	26	45	21	19	50	35
thrombocytopenia	35	38	12	6	5	9	8	11	14	18	NA	NA
anemia	24	26	14	8	7	19	16	19	16	13	12	20
non-hematological adverse events, grade ≥3 (%)												
febrile neutropenia	5	1	0	NA	NA	1	3	3	NA	NA	NA	NA
infections	9	13	7	16	9	32	22	17	14	19	32	23
pneumonia												
peripheral neuropathy	NA	NA	NA	2	2	1	<1	9	11	35	NA	NA
venous thromboembolism	1	4	1	26	12	5	4	3	9	8	NA	NA
constipation	NA	NA	NA	NA	NA	2	2	5	NA	NA	2	<1
diarrhea	2	1	0	NA	NA	5	3	1	NA	NA	7	4
skin rash	5	5	1	NA	NA	NA	NA	NA	4	4	NA	NA
secondary malignancy (any grade)	NA	NA	NA	NA	NA	7	7	9	3	3	9	7

Dara-Rd – daratumumab, lenalidomide, dexamethasone; MP – melphalan, prednisone; MPR – melphalan, prednisone, lenalidomide; MPR-R – melphalan, prednisone, lenalidomide and maintenance lenalidomide; NA – not available; Rd – lenalidomide, low dose dexamethasone; RD – lenalidomide, high dose dexamethasone; Rd18 – lenalidomide, dexamethasone (18 cycles); Rd(cont) – lenalidomide, dexamethasone continues therapy; VRd – bortezomib, lenalidomide, dexamethasone

Table IV. Incidence of serious adverse events of lenalidomide in treatment of relapsed/refractory multiple myeloma identified in pivotal phase 3 clinical trials

Trial	ASPIRE [63]		TOURMALINE-MM1 [64]		POLLUX [65]		ELOQUENT-2 [66]	
regimen	Rd	KRd	Rd	Ixa-Rd	Rd	Dara-Rd	Rd	Elo-Rd
hematological adverse events, grade ≥3 (%)								
neutropenia	27	31	24	23	42	55	45	36
thrombocytopenia	13	17	9	19	16	15	21	21
anemia	17	19	13	9	21	18	21	20
non-hematological adverse events, grade ≥3 (%)								
febrile neutropenia	NA	NA	NA	NA	3	6	NA	NA
infections								
pneumonia	12	16.	NA	2	10	15	26	33
peripheral neuropathy	3	3	2	2	NA	NA	NA	NA
venous thromboembolism	NA	NA	3	2	NA	NA	NA	NA
constipation	<1	<1	<1	<1	<1	1	<1	1
diarrhea	4	5	NA	NA	4	10	5	6
skin rash	NA	NA	2	5	NA	NA	NA	NA
cardiac disorders	2.	4	2	3	NA	NA	8	5
secondary malignancy (any grade)	NA	NA	4	5	9	8	11	17

Dara-Rd – daratumumab, lenalidomide, dexamethasone; Elo-Rd – elotuzumab, lenalidomide, dexamethasone; Ixa-Rd – ixazomib, lenalidomide, dexamethasone; KRd – carfilzomib, lenalidomide, dexamethasone; NA – not available; Rd – lenalidomide, dexamethasone

anemia (hemoglobin [Hb] concentration <9.0 g/dl), treatment with erythropoiesis-stimulating agents (ESA) may be used.

Lenalidomide monotherapy has little effect on the development of VTE. This risk increases when lenalidomide is combined with high-dose dexamethasone and multi-drug combinations [54, 69]. VTE is more commonly found in the treatment of NDMM. Thromboprophylaxis is not recommended during treatment with lenalidomide monotherapy [46]. In other cases, the principles of thromboprophylaxis are the same as in therapy with thalidomide.

Other serious (grade 3–4) non-hematological AEs requiring a dose reduction of lenalidomide are infections (dose reduction 25–50%), asthenia (25–50%), grade 2 skin toxicity (50%), and grade 2 intestinal toxicity (50%). In the case of lenalidomide treatment with a high dose of dexamethasone, antibacterial prophylaxis is recommended in NDMM [67].

Skin rashes are observed in approximately 25% (grade 3–4: 3.5%) of patients, usually appearing in the first month of treatment and may last for several weeks [70]. Discontinuation of lenalidomide treatment and the use of antihistamines and systemic corticosteroids is recommended in the presence of grade 3–4 skin lesions. Retreatment once the rash has resolved is usually well tolerated [71]. The reappearance of skin lesions is a contraindication to further treatment with lenalidomide [72].

Constipation can be managed with a bowel regimen while continuing lenalidomide therapy. Diarrhea (defined as four or more bowel movements) is a common complication of lenalidomide treatment. Loperamide may be used to reduce the frequency of bowel movements [73, 74]. After several months of lenalidomide treatment, diarrhea may occur due to bile salt malabsorption syndrome [74].

Renal impairment

Lenalidomide is mainly eliminated renally. When lenalidomide is used to treat patients with MM with RI, care should be taken in dose selection and monitoring renal function. In patients with moderate, severe, or end-stage renal disease, dose adjustments of lenalidomide are recommended at treatment initiation and during treatment. No dose adjustment of lenalidomide is required during therapy in patients with mild RI [68]. Lenalidomide dosing by CrCl is presented in table I.

Pomalidomide

Pomalidomide is an IMiD currently used to treat RRMM. The safety profile of pomalidomide is similar to that of lenalidomide. Adverse events resulting from the myelosuppressive effect of pomalidomide dominate, mainly neutropenia, less often thrombocytopenia and anemia. Constipation, infection, fatigue, fever, peripheral edema, confusion, and VTE are the most

common non-hematological AEs. Peripheral neuropathy is uncommonly observed [75].

In the phase 3 clinical trial MM-003, patients were treated with Pd or with dexamethasone alone, neutropenia (grade 3–4) was reported in 48% of patients, most often developing in the first treatment cycles. Anemia (grade 3–4) was observed in 33% of patients and thrombocytopenia (grade 3–4) in 24% of patients. Febrile neutropenia was found in <10% of patients [76, 77]. In another phase, three studies in which Pd was combined with a third drug, i.e., bortezomib, daratumumab, isatuximab, elotuzumab, again predominantly hematological AEs were observed, including neutropenia in 41–85% of patients, thrombocytopenia 8–34% and anemia 10–35% of patients. Due to compulsory antithrombotic prophylaxis, VTE was observed in 2–4% of patients treated with Pd [78–81].

In the MM-002 study, although 73% of patients treated with Pd had a history of PN, no grade 3–4 PN was observed [82]. In study MM-003, 15% of Pd-treated patients had PN. Grade 1 PN was diagnosed in 52% of patients at baseline [76]. In the phase 3 study, OPTIMISMM, PN (grade 3–4) was reported in 8.5% of patients with RRMM treated with PVd and 4% of patients treated with bortezomib with dexamethasone (Vd) [78]. Table V summarizes the incidence of serious AEs from pivotal phase 3 clinical trials of pomalidomide for the treatment of RRMM.

Management of AEs during treatment with pomalidomide

Due to the risk of myelosuppression, CBC monitoring weekly is recommended for the first two treatment cycles. When the ANC drops to <0.5 G/L, pomalidomide should be discontinued. G-CSF may be administered until the ANC is ≥1.0 G/L; after that, treatment should be resumed with pomalidomide at a dose reduced by 1 mg/day compared to the previously used dose [83, 84]. Due to the increased risk of infection during treatment with pomalidomide, some authors recommend antimicrobial prophylaxis for at least the first three treatment cycles. In patients at high risk of infection and/or after infection, prophylactic antibiotics may be considered. A reduction in the PLT count <25 G/L indicates discontinuing pomalidomide therapy until the PLT count is increased ≥50 G/L.

Treatment should be resumed at a dose reduced by 1 mg/day compared to previous treatment [83, 84]. The principles of treating anemia with pomalidomide are the same as those with lenalidomide treatment. Thrombotic prophylaxis is recommended in all patients treated with pomalidomide when combined with dexamethasone, following the same guidelines as for lenalidomide. If grade ≥2, PN develops, withhold pomalidomide treatment until symptoms improve to grades 0–1. After that, pomalidomide should be taken at a reduced

Table V. Incidence of serious adverse events of pomalidomide in treatment of relapsed/refractory multiple myeloma identified in pivotal phase 3 clinical trials

Trial	MM-003 [76]		STRATUS [77]	OPTIMISMM [78]		APOLLO [79]		ICARIA-MM [80]		ELOQUENT-3 [81]	
regimen	Dex	Pd	Pd	Vd	PVd	Pd	Dara-Pd	Pd	Ixa-Rd	Pd	Elo-Pd
hematological adverse events, grade ≥3 (%)											
neutropenia	16	48	50	9	41	51	68	71	85	27	13
thrombocytopenia	26	21	24	29	28	18	17	25	34	5	8
anemia	37	33	33	14	14	21	17	29	35	21	20
non-hematological adverse events, grade ≥3 (%)											
febrile neutropenia	0	10	NA	NA	NA	3	9	NA	NA	20	10
infections	10	14	28	1	1	23	28	<1	5	22	13
pneumonia			13	7	11	7	13	21	23	9	5
peripheral neuropathy	NA	NA	<1	4	9	NA	NA	NA	NA	NA	NA
venous thromboembolism	NA	NA	<2	NA	NA	NA	NA	NA	NA	NA	NA
constipation	0.0	2	<1	<1	3	NA	NA	0	0	0	2
diarrhea	1	1	<1	4	7	1	5	1	2	0	0
skin rash	NA	NA	NA	NA	NA	NA	NA	NA	NA	2	0
cardiac disorders	NA	NA	NA	NA	NA	NA	NA	NA	NA	4	7
secondary malignancy (any grade)	NA	NA	2	NA	NA	NA	NA	NA	NA	22	2

Dara-Pd – daratumumab, pomalidomide, dexamethasone; Dex – dexamethasone; Elo-Pd – elotuzumab, pomalidomide, dexamethasone; Ixa-Pd – isatuximab, pomalidomide, dexamethasone; NA – not available; Pd – pomalidomide, dexamethasone; PVd – pomalidomide, bortezomib, dexamethasone; Vd – bortezomib, dexamethasone

dose. The occurrence of PN (grade 4) is an indication for discontinuing treatment with pomalidomide [83, 84]. Treatment of the rash and reduction of the daily dose of lenalidomide by 1 mg is recommended. Rash (grade 4) is an indication of permanent discontinuation of pomalidomide treatment [84]. If constipation and another grade ≥3 non-hematological AEs occur, it is recommended that pomalidomide treatment be interrupted until symptoms resolve to grade ≤2 and that treatment is resumed at a dose reduced by one dose level for the next cycle [83].

Renal impairment

Pomalidomide is metabolized in the liver and, unlike lenalidomide, only 2% of unmetabolized pomalidomide is excreted in the urine [47]. Based on study MM-013, patients with RRMM and moderate or severe RI, including those requiring hemodialysis, benefit from treatment with pomalidomide in combination with low-dose dexamethasone. The use of pomalidomide at a dose of 4 mg daily in combination with dexamethasone is an effective and safe treatment for patients with RRMM and moderate to severe RI, including patients who require hemodialysis [85]. Therefore, no dose reduction of pomalidomide is needed in patients with mild or moderate RI (CrCl ≥ 45 ml/min). Pomalidomide should be taken after hemodialysis on the patient's hemodialysis [47]. Pomalidomide dosing by CrCl is presented in table I.

Conclusions

One of the most important drugs used in the treatment of MM is IMiDs. The combination of IMiD, dexamethasone, and a third drug (proteasome inhibitor, monoclonal antibody, alkylating drug) is the cornerstone of treatment for NDMM and RRMM.

Immunomodulatory drugs have a predictable toxicity profile. The most important AEs of thalidomide are PN and VTE, while lenalidomide and pomalidomide are predominantly myelosuppressive. Close monitoring of their safety profile makes it possible to protect patients from AEs by reducing doses and/or discontinuing treatment with IMiDs. Table V summarizes the most common AEs observed during treatment with IMiDs in patients with MM. Maintaining clinical vigilance and timely dose modifications to AEs with the simultaneous use of the recommended prophylaxis will reduce the development of serious AEs, resulting in improved quality of life and longer treatment duration.

Conflict of interest: none declared

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Received: 19 Jan 2022
Accepted: 16 Mar 2022

References

1. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma - an IMWG Research Project. Blood Cancer J. 2018; 8(12): 123, doi: 10.1038/s41408-018-0155-7, indexed in Pubmed: 30470751.
2. Aragon-Ching JB, Li H, Gardner ER, et al. Thalidomide analogues as anticancer drugs. Recent Pat Anticancer Drug Discov. 2007; 2(2): 167–174, doi: 10.2174/157489207780832478, indexed in Pubmed: 17975653.
3. Davies F, Baz R. Lenalidomide mode of action: linking bench and clinical findings. Blood Rev. 2010; 24 Suppl 1: S13–S19, doi: 10.1016/S0268-960X(10)70004-7, indexed in Pubmed: 21126632.
4. Ito T, Ando H, Handa H, et al. Identification of a primary target of thalidomide teratogenicity. Science. 2010; 327(5971): 1345–1350, doi: 10.1126/science.1177319, indexed in Pubmed: 20223979.
5. Ito T, Handa H. Cereblon and its downstream substrates as molecular targets of immunomodulatory drugs. Int J Hematol. 2016; 104(3): 293–299, doi: 10.1007/s12185-016-2073-4, indexed in Pubmed: 27460676.
6. Sievers QL, Petzold G, Bunker RD, et al. Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN. Science. 2018; 362(6414), doi: 10.1126/science.aat0572, indexed in Pubmed: 30385546.
7. Lu G, Middleton RE, Sun H, et al. The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins. Science. 2014; 343(6168): 305–309, doi: 10.1126/science.1244917, indexed in Pubmed: 24292623.
8. John LB, Ward AC. The Ikaros gene family: transcriptional regulators of hematopoiesis and immunity. Mol Immunol. 2011; 48(9-10): 1272–1278, doi: 10.1016/j.molimm.2011.03.006, indexed in Pubmed: 21477865.
9. Chanan-Khan AA, Swaika A, Paulus A, et al. Pomalidomide: the new immunomodulatory agent for the treatment of multiple myeloma. Blood Cancer J. 2013; 3: e143, doi: 10.1038/bcj.2013.38, indexed in Pubmed: 24013664.
10. Castelli R, Cassin R, Cannavò A, et al. Immunomodulatory drugs: new options for the treatment of myelodysplastic syndromes. Clin Lymphoma Myeloma Leuk. 2013; 13(1): 1–7, doi: 10.1016/j.clml.2012.09.016, indexed in Pubmed: 23153925.
11. Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood. 2001; 98(1): 210–216, doi: 10.1182/blood.v98.1.210, indexed in Pubmed: 11418482.
12. Hayashi T, Hideshima T, Akiyama M, et al. Molecular mechanisms whereby immunomodulatory drugs activate natural killer cells: clinical application. Br J Haematol. 2005; 128(2): 192–203, doi: 10.1111/j.1365-2141.2004.05286.x, indexed in Pubmed: 15638853.
13. Noonan K, Rudraraju L, Ferguson A, et al. Lenalidomide-induced immunomodulation in multiple myeloma: impact on vaccines and antitumor responses. Clin Cancer Res. 2012; 18(5): 1426–1434, doi: 10.1158/1078-0432.CCR-11-1221, indexed in Pubmed: 22241792.
14. Matyskiela ME, Zhang W, Man HW, et al. A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. J Med Chem. 2018; 61(2): 535–542, doi: 10.1021/acs.jmedchem.6b01921, indexed in Pubmed: 28425720.
15. Hansen JD, Correa M, Nagy MA, et al. Discovery of CRBN E3 Ligase Modulator CC-92480 for the Treatment of Relapsed and Refractory Multiple Myeloma. J Med Chem. 2020; 63(13): 6648–6676, doi: 10.1021/acs.jmedchem.9b01928, indexed in Pubmed: 32130004.
16. Moreau P, San Miguel J, Sonneveld P, et al. ESMO Guidelines Committee. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017; 28(suppl_4): iv52–iv61, doi: 10.1093/annonc/mdx096, indexed in Pubmed: 28453614.
17. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999; 341(21): 1565–1571, doi: 10.1056/NEJM199911183412102, indexed in Pubmed: 10564685.
18. Richardson PG, Delforge M, Beksac M, et al. Management of treatment-emergent peripheral neuropathy in multiple myeloma. Leukemia. 2012; 26(4): 595–608, doi: 10.1038/leu.2011.346, indexed in Pubmed: 22193964.
19. https://www.gov.pl/web/zdrowie/choroby-onkologiczne (15.03.2022).
20. Lacy MQ, McCurdy AR. Pomalidomide. Blood. 2013; 122(14): 2305–2309, doi: 10.1182/blood-2013-05-484782, indexed in Pubmed: 23974193.
21. Quach H, Ritchie D, Stewart AK, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia. 2010; 24(1): 22–32, doi: 10.1038/leu.2009.236, indexed in Pubmed: 19907437.

22. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf (25.11.2021).
23. Ghobrial IM, Rajkumar SV. Management of thalidomide toxicity. J Support Oncol. 2003; 1(3): 194–205, indexed in Pubmed: 15334875.
24. Dimopoulos MA, Moreau P, Terpos E, et al. EHA Guidelines Committee. Electronic address: guidelines@ehaweb.org, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(3): 309–322, doi: 10.1016/j.annonc.2020.11.014, indexed in Pubmed: 33549387.
25. Cohen AD, Parekh S, Santomasso BD, et al. KEYNOTE-183 Investigators. Management of treatment-related adverse events in patients with multiple myeloma. Cancer Treat Rev. 2010; 36 Suppl 2(4): S24–S32, doi: 10.1016/S0305-7372(10)70009-8, indexed in Pubmed: 20472185.
26. Cavo M, Pantani L, Petrucci MT, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012; 120(1): 9–19, doi: 10.1182/blood-2012-02-408898, indexed in Pubmed: 22498745.
27. Moreau P, Hulin C, Macro M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016; 127(21): 2569–2574, doi: 10.1182/blood-2016-01-693580, indexed in Pubmed: 27002117.
28. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019; 394(10192): 29–38, doi: 10.1016/S0140-6736(19)31240-1, indexed in Pubmed: 31171419.
29. Kapoor P, Rajkumar SV, Dispenzieri A, et al. Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: a meta-analysis. Leukemia. 2011; 25(4): 689–696, doi: 10.1038/leu.2010.313, indexed in Pubmed: 21233832.
30. Palumbo A, Waage A, Hulin C, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: a meta-analysis of data from individual patients in six randomized trials. Haematologica. 2013; 98(1): 87–94, doi: 10.3324/haematol.2012.067058, indexed in Pubmed: 22875621.
31. Morgan GJ, Davies FE, Gregory WM, et al. National Cancer Research Institute Haematological Oncology Clinical Studies Group. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2012; 97(3): 442–450, doi: 10.3324/haematol.2011.043372, indexed in Pubmed: 22058209.
32. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinicals Trials Group Myeloma 10 Trial. Blood. 2013; 121(9): 1517–1523, doi: 10.1182/blood-2012-09-451872, indexed in Pubmed: 23297129.
33. Donk Nv, Holt Bv, Minnema M, et al. Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial. The Lancet Haematology. 2018; 5(10): e479–e492, doi: 10.1016/s2352-3026(18)30149-2.
34. Glasmacher A, Hahn C, Hoffmann F, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006; 132(5): 584–593, doi: 10.1111/j.1365-2141.2005.05914.x, indexed in Pubmed: 16445831.
35. Terpos E, Christoulas D, Kastritis E, et al. Greek Myeloma Study Group. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001; 12(7): 991–995, doi: 10.1023/a:1011132808904, indexed in Pubmed: 11521808.
36. Kropff MH, Lang N, Bisping G, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. Br J Haematol. 2003; 122(4): 607–616, doi: 10.1046/j.1365-2141.2003.04473.x, indexed in Pubmed: 12899716.
37. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008; 111(8): 3968–3977, doi: 10.1182/blood-2007-10-117457, indexed in Pubmed: 18245666.
38. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. Nat Rev Clin Oncol. 2009; 6(10): 596–603, doi: 10.1038/nrclinonc.2009.128, indexed in Pubmed: 19707193.
39. Reddy GK, Mughal TI, Lonial S. Optimizing the management of treatment-related peripheral neuropathy in patients with multiple myeloma. Support Cancer Ther. 2006; 4(1): 19–22, doi: 10.3816/SCT.2006.n.027, indexed in Pubmed: 18632462.
40. Tariman JD, Love G, McCullagh E, et al. IMF Nurse Leadership Board. Peripheral neuropathy associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs. 2008; 12(3 Suppl): 29–36, doi: 10.1188/08.CJON.S1.29-35, indexed in Pubmed: 18490255.
41. Jongen JL, Broijl A, Sonneveld P. Chemotherapy-induced peripheral neuropathies in hematological malignancies. J Neurooncol. 2015; 121(2): 229–237, doi: 10.1007/s11060-014-1632-x, indexed in Pubmed: 25326770.
42. Delforge M, Bladé J, Dimopoulos MA, et al. Treatment-related peripheral neuropathy in multiple myeloma: the challenge continues. Lancet Oncol. 2010; 11(11): 1086–1095, doi: 10.1016/S1470-2045(10)70068-1, indexed in Pubmed: 20932799.
43. Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. Ther Adv Drug Saf. 2012; 3(5): 255–266, doi: 10.1177/2042098612452291, indexed in Pubmed: 25083240.
44. Snowden JA, Ahmedzai SH, Ashcroft J, et al. Haemato-oncology Task Force of British Committee for Standards in Haematology and UK Myeloma Forum. Guidelines for supportive care in multiple myeloma 2011. Br J Haematol. 2011; 154(1): 76–103, doi: 10.1111/j.1365-2141.2011.08574.x, indexed in Pubmed: 21517805.
45. Minnema MC, Breitkreutz I, Auwerda JJA, et al. Prevention of venous thromboembolism with low molecular-weight heparin in patients with multiple myeloma treated with thalidomide and chemotherapy. Leukemia. 2004; 18(12): 2044–2046, doi: 10.1038/sj.leu.2403533, indexed in Pubmed: 15470485.
46. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008; 22(2): 414–423, doi: 10.1038/sj.leu.2405062, indexed in Pubmed: 18094721.
47. Fouquet G, Bories C, Guidez S, et al. Pomalidomide for multiple myeloma. Expert Rev Hematol. 2014; 7(6): 719–731, doi: 10.1586/17474086.2014.966074, indexed in Pubmed: 25265911.
48. NCCN Clinical Practice Guidelines in Oncology. Multiple myeloma. Version 4.2022.
49. Smith LC, Bertolotti P, Curran K, et al. IMF Nurse Leadership Board. Gastrointestinal side effects associated with novel therapies in patients with multiple myeloma: consensus statement of the IMF Nurse Leadership Board. Clin J Oncol Nurs. 2008; 12(3 Suppl): 37–52, doi: 10.1188/08.CJON.S1.37-51, indexed in Pubmed: 18490256.
50. Dimopoulos MA, Roussou M, Gkotzamanidou M, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013; 27(2): 423–429, doi: 10.1038/leu.2012.182, indexed in Pubmed: 22763386.
51. Rizzello I, Cavo M, Dozza L, et al. GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto Italian Myeloma Network), GIMEMA Italian Myeloma Network. Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. Eur J Haematol. 2004; 73(2): 98–103, doi: 10.1111/j.1600-0609.2004.00272.x, indexed in Pubmed: 15245508.
52. Alexander M, Kirsa S, Mellor JD. Thalidomide thromboprophylaxis in multiple myeloma: a review of current evidence. Asia Pac J Clin Oncol. 2012; 8(4): 319–324, doi: 10.1111/j.1743-7563.2011.01511.x, indexed in Pubmed: 22897571.
53. Niesvizky R, Jayabalan DS, Christos PJ, et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. Blood. 2008; 111(3): 1101–1109, doi: 10.1182/blood-2007-05-090258, indexed in Pubmed: 17989313.
54. Rajkumar SV, Jacobus S, Callander NS, et al. Eastern Cooperative Oncology Group. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol. 2010; 11(1): 29–37, doi: 10.1016/S1470-2045(09)70284-0, indexed in Pubmed: 19853510.
55. Morgan GJ, Schey SA, Wu P, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective

and tolerated regimen for myeloma patients. Br J Haematol. 2007; 137(3): 268–269, doi: 10.1111/j.1365-2141.2007.06538.x, indexed in Pubmed: 17408469.
56. Schey S, Morgan G, Ramasamy K, et al. CRD: A Phase 1 Dose Escalation Study to Determine the Maximum Tolerated Dose of Cyclophosphamide in Combination with Lenalidomide and Dexamethasone in Relapsed/Refractory Myeloma. Blood. 2008; 112(11): 3707–3707, doi: 10.1182/blood.v112.11.3707.3707.
57. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. Blood. 2018; 131(3): 301–310, doi: 10.1182/blood-2017-07-795047, indexed in Pubmed: 29150421.
58. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet. 2017; 389(10068): 519–527, doi: 10.1016/S0140-6736(16)31594-X, indexed in Pubmed: 28017406.
59. Facon T, Kumar S, Plesner T, et al. MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019; 380(22): 2104–2115, doi: 10.1056/NEJMoa1817249, indexed in Pubmed: 31141632.
60. Palumbo A, Gay F, Cavallo F, et al. MM-015 Investigators. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med. 2012; 366(19): 1759–1769, doi: 10.1056/NEJMoa1112704, indexed in Pubmed: 22571200.
61. Dimopoulos M, Spencer A, Attal M, et al. Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007; 357(21): 2123–2132, doi: 10.1056/NEJMoa070594, indexed in Pubmed: 18032762.
62. Weber DM, Chen C, Niesvizky R, et al. Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007; 357(21): 2133–2142, doi: 10.1056/NEJMoa070596, indexed in Pubmed: 18032763.
63. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. ASPIRE Investigators. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015; 372(2): 142–152, doi: 10.1056/NEJMoa1411321, indexed in Pubmed: 25482145.
64. Mateos MV, Masszi T, Grzasko N, et al. TOURMALINE-MM1 Study Group. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016; 374(17): 1621–1634, doi: 10.1056/NEJMoa1516282, indexed in Pubmed: 27119237.
65. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020; 34(7): 1875–1884, doi: 10.1038/s41375-020-0711-6, indexed in Pubmed: 32001798.
66. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol. 2017; 178(6): 896–905, doi: 10.1111/bjh.14787, indexed in Pubmed: 28677826.
67. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. International Myeloma Working Group. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008; 22(2): 414–423, doi: 10.1038/sj.leu.2405062, indexed in Pubmed: 18094721.
68. https://www.ema.europa.eu/en/documents/product-information/revlimid-epar-product-information_en.pdf (25.11.2021).
69. Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. Blood. 2009; 114(4): 772–778, doi: 10.1182/blood-2008-12-196238, indexed in Pubmed: 19471019.
70. Imbesi S, Allegra A, Calapai G, et al. Cutaneous adverse reactions to lenalidomide. Allergol Immunopathol (Madr). 2015; 43(1): 88–91, doi: 10.1016/j.aller.2013.07.005, indexed in Pubmed: 24998775.
71. Barley K, He W, Agarwal S, et al. Outcomes and management of lenalidomide-associated rash in patients with multiple myeloma. Leuk Lymphoma. 2016; 57(11): 2510–2515, doi: 10.3109/10428194.2016.1151507, indexed in Pubmed: 26943456.
72. Tinsley SM, Kurtin SE, Ridgeway JA. Practical Management of Lenalidomide-Related Rash. Clin Lymphoma Myeloma Leuk. 2015; 15 Suppl: S64–S69, doi: 10.1016/j.clml.2015.02.008, indexed in Pubmed: 26297281.
73. Vehreschild MJ, Vehreschild JJ, Hübel K, et al. German Society of Hematology and Oncology. Diagnosis and management of gastrointestinal complications in adult cancer patients: evidence-based guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). Ann Oncol. 2013; 24(5): 1189–1202, doi: 10.1093/annonc/mdt001, indexed in Pubmed: 23401037.
74. Pawlyn C, Khan MS, Muls A, et al. Lenalidomide-induced diarrhea in patients with myeloma is caused by bile acid malabsorption that responds to treatment. Blood. 2014; 124(15): 2467–2468, doi: 10.1182/blood-2014-06-583302, indexed in Pubmed: 25301337.
75. Richardson PG, Palumbo A, Schey SA, et al. Pomalidomide – an appraisal of its clinical development and role in the treatment of relapsed/refractory multiple myeloma. Eur Oncol Haematol. 2015; 11: 109–117.
76. Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013; 14(11): 1055–1066, doi: 10.1016/s1470-2045(13)70380-2.
77. Dimopoulos MA, Palumbo A, Corradini P, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. Blood. 2016; 128(4): 497–503, doi: 10.1182/blood-2016-02-700872, indexed in Pubmed: 27226434.
78. Richardson PG, Oriol A, Beksac M, et al. OPTIMISMM trial investigators. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol. 2019; 20(6): 781–794, doi: 10.1016/S1470-2045(19)30152-4, indexed in Pubmed: 31097405.
79. Dimopoulos MA, Terpos E, Boccadoro M, et al. APOLLO Trial Investigators. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021; 22(6): 801–812, doi: 10.1016/S1470-2045(21)00128-5, indexed in Pubmed: 34087126.
80. Attal M, Richardson PG, Rajkumar SV, et al. ICARIA-MM study group. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet. 2019; 394(10214): 2096–2107, doi: 10.1016/S0140-6736(19)32556-5, indexed in Pubmed: 31735560.
81. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. N Engl J Med. 2018; 379(19): 1811–1822, doi: 10.1056/NEJMoa1805762, indexed in Pubmed: 30403938.
82. Richardson PG, Siegel DS, Vij R, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood. 2014; 123(12): 1826–1832, doi: 10.1182/blood-2013-11-538835, indexed in Pubmed: 24421329.
83. Dimopoulos MA, Leleu X, Palumbo A, et al. Expert panel consensus statement on the optimal use of pomalidomide in relapsed and refractory multiple myeloma. Leukemia. 2014; 28(8): 1573–1585, doi: 10.1038/leu.2014.60, indexed in Pubmed: 24496300.
84. https://www.ema.europa.eu/en/documents/product-information/imnovid-epar-product-information_en.pdf (25.11.2021).
85. Dimopoulos M, Weisel K, van de Donk NW, et al. Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial. J Clin Oncol. 2018; 36(20): 2035–2043, doi: 10.1200/JCO.2017.76.1742, indexed in Pubmed: 29394124.

VIA MEDICA

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 281–285

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Tumor and normal tissue radiation side effects

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This paper presents the various side effects of radiation including tumor cure probability (TCP) accompanied with frequently severe but transient acute side effects in the surrounding normal (mainly epithelial) tissues and also the risk of late side effects in normal organs, confined to their partial or whole volumes. Besides the local side effects, unexpected exposure to low radiation doses results in the stochastic risk of mutagenic, teratogenic or cancerogenic side effects. In order to minimize the risk of various radiation side effects, some obligatory radiation protection constraints should be restrictively fulfilled.

Key words: TCP, acute and late side effects, teratogenesis, carcinogenesis

Particle and photon ionizing radiation produces various deterministic (both expected and unexpected) effects in malignant tumors and surrounding normal tissues (organs) in addition to undesirable stochastic effects in healthy people incidentally exposed to various types of radiation.

Tumor radiation effects (TRE)

Tumor response to the high energy of a single or fractionated dose of radiation (radiotherapy, brachytherapy) is usually beneficial due to cancer cells killed process. It is an obvious aim of radiotherapy (RT), and a probalistic event in its nature. At first glance, tumor response to radiation generally depends on their individual radiosensitivity. Lymphomas, seminomas as well as epithelial carcinomas, are classified as sensitive, whereas liposarcomas, neuro-, osteo- chondrosarcomas and parotid tumors are radioresistant in a larger or smaller degree. This latter group needs a significantly higher total radiation dose to achieve tumor cure probability (TCP) than the first one. This is often an obstacle to achieve with the use of RT only.

The major feature of the delivered fractionated dose is the random process of kill [1]. This means that some cells to be killed receive two or more hits of secondary electrons (or primary protons, neutrons), whereas other cells remain untouched. The probability of the TCP is an exponential function of the average number cells (e.g. survival of an average 0.1 cell/tumor results in the TCP = $e^{-0.1}$ = 0.9 (90%)), whereas an average 1 cell survived/tumor reduces TCP to $e^{-0.1}$ = 0.37. Such a "language of probability" does not satisfy patients who immediately raise the question: "Am I in the first (successfully treated) or in the second group (failures)?" Until now, there has been no reliable answer to such a question.

It is obvious that depending on the progression of the tumor size (stage), needs an increase in the higher fractionated total dose, however, only to a certain limit; above which a risk of severe late normal tissue complications outstrips the expected TCP [1, 2]. In such cases, radiotherapy loses its radical intent and becomes palliative in nature (fig. 1).

In order to intensify the radiation effects with regards to destroying cancer cells, some tests were performed, examining various altered dose fractionations and boost doses (brachytherapy), conformal techniques and concurrent chemoradiation, but only few of them have been successfully employed in the daily practice [1, 3, 4, 5]. During the last 20–25 years it has been well documented that a single process – accelerated repo-

Jak cytować / How to cite:
Maciejewski B. ***Tumor and normal tissue radiation side effects.*** *NOWOTWORY J Oncol* 2022; 72: 242–246.

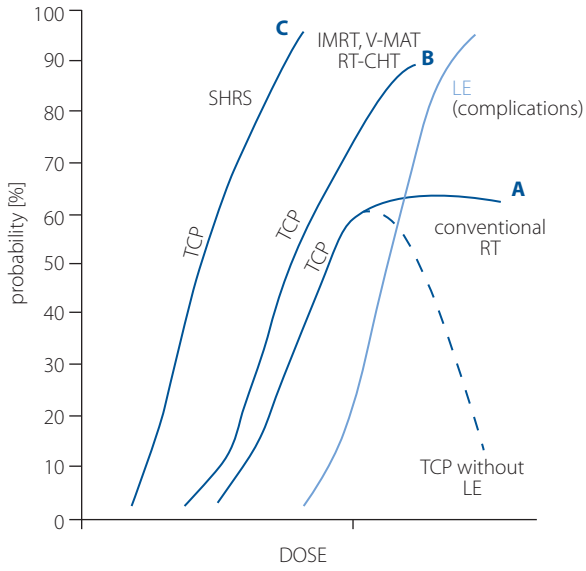


Figure 1. Dose-response (LTC, LE) as a function of dose (Gy) and dose intensity – DI (Gy/d) [TCP – tumor cure probability, LE – late effects (complications); (A) – TCP curve for conventionally fractionated, RT – effect *plateau* – further increase in the TD with extension time (OTT) does not result in higher TCP; (B) – LTC curve for conformal IMRT, V-MAT, chemo-radiotherapy; (C) – SHRS – stereotactic hypofractionated radiosurgery – high DI single dose or a few large fractions – very short OTT; dotted line – TCP without late complication]

pulation of the cancer cells which have survived consecutive dose fractions – significantly counterbalances cell kill effect [1, 3, 4–6]. For example, at the end of the 6th week of fractionated RT, accelerated repopulation effectively neutralizes cell kill effect of as much as 1.4 Gy of the 2.0 Gy fraction delivered within the therapy. Thus, overall treatment time (OTT) has been recognized as a pronounced or even major factor determining the treatment outcome (TCP). Therefore, it became clear that radiotherapy (and other combined therapies) should be completed within overall treatment time (OTT) as short as possible. For this recommendation, some hope is seen in the stereotactic hypofractionated radiosurgery (SHRS) which allows to deliver a high single dose or a few large fractions (fig. 1) within a very short time (OTT) [7–10] resulting in unexpectedly high TCP (85–90%). On the other hand, this method is limited to a relatively small, primary or metastatic tumors, whilst the TCP only a local effect only, not necessarily equivalent to a patient's curability. Generally, tumor radiosensitivity has an influence on the position of the TCP curve on the dose coordinate. An increase of the dose above a certain level carries an unacceptably high risk of various late complications, depending on the volume of normal tissues (organs) involved, and therefore the rate of the TCP free from any complication decreases (fig. 1).

Normal tissue acute radiation side effects

Total dose, even if it is precisely focused within the tumor bounds, also partly affects the surrounding normal tissues (organs). Normal tissue side effects are generally classified as acute and/or late.

Acute radiation side effects (ARSE) are usually epithelial or hematopoietic in their etiology. Characteristic attribute of the ARSE is that their intensity progressively increases during daily irradiation, but is transient, and according to Fletcher [2], often heals at the end of irradiation (if dose/fraction is below 2.0 Gy) or within a few weeks thereafter.

The kinetics, severity, duration and healing of the ARSEs depend on various factors and parameters, such as patient's age, epithelial atrophy, concomitant diseases (e.g. diabetes), smoking, alcohol abuse, energy of radiation, irradiation techniques (e.g. conformal IMRT, IART, V-MAT), the area of the irradiated epithelium, the size and duration of dose accumulated per week, and the turn-over time of the epithelial cells (e.g. mitotic activity).

There is some lag period (a few days) before the radiation begins to induce epithelial damage, which is expressed morphologically and depends on cell kinetic characteristics. Short cellular turn-over leads to an early manifestation of the epithelial defects. The intensity of the epithelial cells repopulation is much higher than in the case of the cancer cells (about 1.8 Gy/day). A gradual depletion of the successive epithelial layers continues [11–14], and the first morphological EORTC grade is the redness, followed by erythema, spotted and finally confluent mucositis (grade IV). These morphological side effects (fig. 2A) trigger off progressive functional disorders (pain, oedema, dysphagia, odynophagia), which become much less tolerable by the patients than morphological defects. Sometimes they are so severe that a few days' break is needed within irradiation process to reduce the severity of the ARSE. Supportive care (parenteral nutrition, analgetics, steroid and non-steroid agents, antibiotics) has been recognized as very useful and effective, because it significantly reduces dysfunctional symptoms and therefore improves the patient's tolerance. DISCHE grading system (a wide scale ranging from 0 to 20) more precisely quantitates both morphological and functional disorders than narrow the EORTC 4-grade scale (which is, however, still used in practice). The ARSEs and their severity are generally more or less predictable. Early appearance of the erythema or spotted mucositis during the first few days of irradiation, is a pronounced sign to turn to supportive care immediately, especially when radiation therapy is concurrently combined with chemotherapy.

Sometimes confluent mucositis (CM) becomes very severe as the result of almost complete denudation of residual reserve of the basic epithelial cells (stem cells). It leads the CM to progress into the so-called consequential late effect (CLE), etiology of which is an acute defect but which manifests morphologically as a late reaction (necrosis, pathological fracture, severe fibrosis). The CLE is mainly the result of too intensive weekly accumulated doses (AD). The CLE risk steeply increases when the AD is higher than 15 Gy/week and is continued for about 4–6 weeks. This definitively exceeds the limit of tolerance acceptable by the patients (fig. 2B, fig. 3).

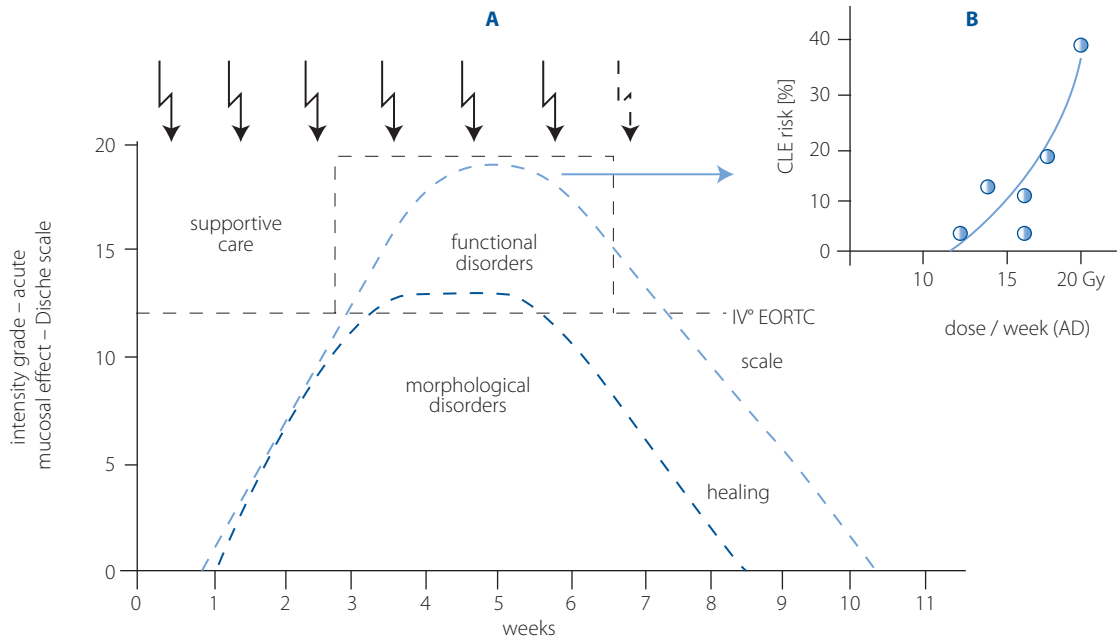
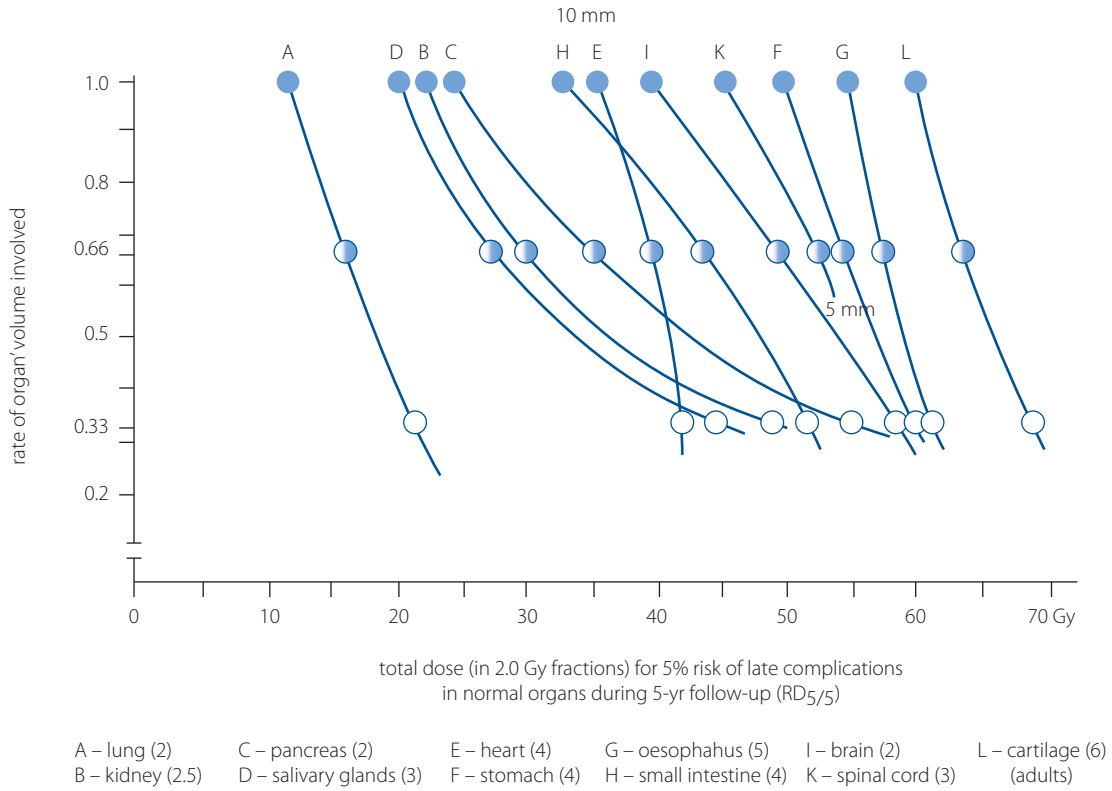


Figure 2. (A) Intensity and healing curves for acute mucosal reaction scored by Dische System as a function of treatment time (in weeks); (B) Risk of ◑ consequential late effect (CLE) as a function of dose accumulated per week – [AD in Gy/wk]



A – lung (2) B – kidney (2.5) C – pancreas (2) D – salivary glands (3) E – heart (4) F – stomach (4) G – oesophahus (5) H – small intestine (4) I – brain (2) K – spinal cord (3) L – cartilage (6) (adults)

Figure 3. Risk curves for late post radiation effects (complications) for various normal organs as a function of conventional total dose (given in 2.0 Gy/fractions) [risk: ○ – acceptable, ◑ – too high, ● – unacceptable]

Esophageal, gastrointestinal mucosa and hematopoietic tissues also demonstrate clinical signs of acute radiation damage. Although morphologically they remain similar to that occurred in the head and neck region but different functional disorders dominate (e.g. diarrhoea), especially when a large mucosal area is involved. In such cases supportive care plays substantial role.

Late radiation side effects

As opposed to the ARSEs, late side effects (complications – LRSE) are unpredictable a priori and they usually appear a few or even more years after completing the RT. They develop in highly differentiated and specialized tissues and organs in type F (flexible), whose cells lost proliferative (mitotic) activity and

accumulated potentially sublethal damage. Their metabolism and function, however, remain untouched until some environmental, microvascular and oxic conditions substantially worsen. Then sublethal damages lead to the cellular death. The LRSEs manifest clinically as a combination of many different pathological processes like atrophy, necrosis, atypia, dysplasia, aplasia, pathological structure, telangiectasia [1, 6, 11]. The risk of various LRSEs (constraints) which are generally acceptable are about 5% within 5 year follow-up ($RD_{5/5}$) but not more than 1% for spinal cord (paraplegia or hemiplegia). The range of the $RD_{5/5}$ doses is quite wide depending on type of the organ (tissue) and the irradiated area involved (fig. 3).

The weakness of the immune system reduces and lengthens the repair mechanisms in some of the normal organs and the LRSEs severity can progressively increase (avalanche effect). In case of the rare genetic disorders as ataxia telangiectasia, retinoblastoma, Fanconi anemia, Bloom, Sjogren, Nijmegen syndromes, progeria (progressive senility) normal tissues radiosensitivity is extraordinarily higher. In such rare mutations, fractionated dose deposited in the surrounding normal tissues should be much lower and very carefully planned [11].

A favorable feature of the stereotactic hyper-fractionated radiosurgery (SHRS) is that this high-tech method allows to focus many (over 100) pencil beams within the tumor volume (GTV), with the sharp-down dose gradient in the surrounding normal tissues. This property allows to deliver a much higher single or a few large fractional doses to the tumor. The tolerance dose consequently increases [7], but the current knowledge on the late SHRS side effects is not detailed enough and therefore these side effects are still rather guessed than precisely estimated because of inefficient clinical data available so far. Nevertheless, some of them listed in table I can provide some guideline for a daily practice.

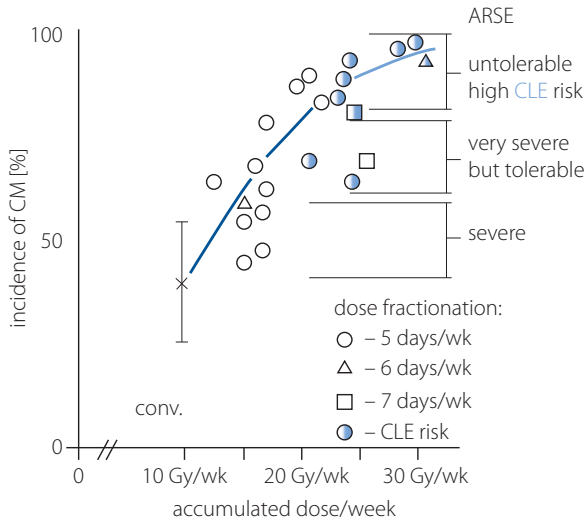


Figure 4. Incidence of acute confluent mucositis (CM) and the risk of CLE (consequential late effects) related to weekly accumulated dose (AD/wk) [red area within symbols corresponds with the CLE risk (based on ref. 15)]

Other than radiotherapy side effects

Radiotherapy which radiation effects are deterministic and depend on the dose threshold value below which no damage occurs. Stochastic radiation, in turn, damages display no threshold dose and even a very small dose of radiation may result in some events which are classified as induced cancers and/or hereditable genetic mutagenic side effects.

Induced cancers

After the exposure to even small doses of radiation practically all human organs can transform into a malignant lesion. In the past, medical staff (radiologists) exposed to small doses of the X-ray diagnostics frequently developed leukemia or severe

Table I. Physical (TD) and biological equivalent dose (BED TD x [1 + di/α/β]) constraints for stereotactic hypo-fractionated radiosurgery (SHRS)

Organ	Dose constraints				Volume limits
	single		fractionated		
	physical (Gy)	BED (Gy α/β)	physical (Gy)	BED (Gy α/β)	
brain	10–13	≤98	3 x 8 Gy 5 x 6 Gy	≤120	≤1.0 cc
optic chiasm	8–10	<60	3 x 6.5 Gy 5 x 5 Gy	83–88	≤0.2 cc
spinal cord	10–13	≤98	3 x 7 Gy 5 x 5 Gy	≤70	≤0.35 cc
lung	9	48	3 x 5 Gy 5 x 3 Gy	50–55	≤4 cc
heart	22	131	3 x 10 Gy 5 x 7.5 Gy	110–116	≤15 cc
liver	12	58	3 x 6.6 Gy 5 x 4 Gy	56	≤170 cc
kidney	11	48	3 x 6.2 Gy 5 x 4.6 Gy	58	<200 cc

skin necrosis, but this phenomenon was documented till 1930 only, when a new X-ray machines became fully protected against radiation.

In 1984 and, later in 1991, the International Commission on Radiological Protection [16] has defined admissible dose limits of 20 mSv (Sievert) per year (100 mSv in 5 years) with an additional dose limit which should not exceed 50mSv within one year, and dose limits of 150 mSv for the lens of the eye and 500 mSv for hands. Nevertheless, it was quite well documented (in the case of nuclear disasters in Hiroshima, Nagasaki, Tschernobyl and also the exposure to unusually high natural radiation in Kerala (India), the Rocky Mountain (USA), China or Japan) that small doses can induce cancer development (hormesis). Bowel, lung, skin, breast, ovary, bladder, thyroid cancer and bone marrow dysplasia and atypia have been documented as the most frequent events induced by radiation. Their latent period takes on average 10 years, but only 2 years to develop leukemia. Even the dose of 0.5 cGy can induce chromosome damage in about a half of human lymphocytes.

Ionizing radiation and some other environmental (teratogenic) factors induce mutations (chromosome breaks, translocations, etc.) in germ cells depending on their phase of development. In the embryo during preimplantation period, blastogenesis is the most sensitive process, reacting to as little as 0.5 cGy. During organogenesis, after an exposure to low doses of radiation the risk of organs and growth deformities increases dramatically. Disorders within the central nervous system are the most prominent, and the risk of severe mental retardation is about 0.4%/1 cGy. The fetus in the utero is also very sensitive to radiation cancerogenesis. Although stochastic low-dose damage cancer or teratogenic effects do not appear early, the current reports document an increasing rate of the thyroid abnormalities and cancer.

Radiotherapy can also induce delayed secondary primary cancers (brain and connective tissue) even after moderate primary doses (30–40 Gy). Lung, breast, stomach, lung, bone narrow, thyroid and soft tissues belong to the organs at risk. Generally, the risk of secondary tumors is low of about 2% in male and 1.5% in female in age >60 years and about 9% in age 40–50 years. Children, whose malignant tumors were cured in the past by radiotherapy are exposed on the 5% risk of post radiation secondary cancer (thyroid, breast, central nervous system) developing within about 12 years after a latency period.

Conclusions

Summarizing, patients are generally endangered on radiation side effects. Some of these effects are local and beneficial as local cancer curability TCP) accompanied with deterministic predictive local acute normal tissue effects which are sometimes severe, but usually transient and heal at the end of radiotherapy or shortly thereafter. Late local radiation induced complications are usually unpredictable and sometimes they are life threatening. Beside local side effects, some of patients cannot avoid unpredictable stochastic exposure on low dose radiation which may lead to the risk of various mutagenic, teratogenic, or cancerogenic side effects. Therefore, it is obligatory that all radiation protection constraints should be restrictively fulfilled.

Conflict of interest: none declared

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Received: 6 May 2022
Accepted: 7 Jun 2022

References

1. McBride WH, Withers HR, Schaue D. Biological basis of radiation therapy. In: Perez CA, Brandy LW. ed. Principles and Practice of Radiation Oncology. VII ed. Wolters-Kluwer, Philadelphia 2018: 87–111.
2. Fletcher GH. Textbook of Radiotherapy. I, II and III eds. Lea and Febiger, Philadelphia 1966, 1973, 1980.
3. Maciejewski B, Miszczyk L, Tarnawski R, et al. How the game is played--challenge between therapeutic benefit and acute toxicity in fractionated radiotherapy. Front Radiat Ther Oncol. 2002; 37: 174–184, doi: 10.1159/000061315, indexed in Pubmed: 11764660.
4. Maciejewski B, Suwiński R, Withers HR, et al. To boost or not to boost in radiotherapy. Nowotwory J Oncol. 2004; 54(5): 446–458.
5. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 1988; 27(2): 131–146, doi: 10.3109/02841868809090333, indexed in Pubmed: 3390344.
6. Maciejewski B, Withers HR, Taylor JM, et al. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx. Part 2. Normal tissue responses: acute and late effects. Int J Radiat Oncol Biol Phys. 1990; 18(1): 101–111, doi: 10.1016/0360-3016(90)90273-m, indexed in Pubmed: 2298613.
7. Maciejewski B, Blamek S, Składowski K, et al. Radiobiological rationale for stereotactic hypofractionated radiosurgery Part II. Normal tissue tolerance — dose constraints. Nowotwory. Journal of Oncology. 2018; 68(2): 79–86, doi: 10.5603/njo.2018.0012.
8. Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol. 2008; 18(4): 215–222, doi: 10.1016/j.semradonc.2008.04.001, indexed in Pubmed: 18725106.
9. Rubin P, Constine LS, Williams JP. Late effect of cancer treatment. In: Perez CA, Brady Lw. ed. Principles and Practice of Radiation Oncology. Lippincott-Raven Publ, Philadelphia 1998: 155–212.
10. Rubin P. Clinical Oncology. A Multidisciplinary Approach. WB Saunders, Philadelphia 1993.
11. Maciejewski B, Suwiński R, Blamek S. Radiobiologia kliniczna w radioonkologii. Med Prak, Kraków 2019: 25–124.
12. Kaanders J, Kogel Av, Ang KK. Altered fractionation: limited by mucosal reactions? Radiotherapy and Oncology. 1999; 50(3): 247–260, doi: 10.1016/s0167-8140(99)00012-2.
13. Denham J, Walker Q, Lamb D, et al. Mucosal regeneration during radiotherapy. Radiotherapy and Oncology. 1996; 41(2): 109–118, doi: 10.1016/s0167-8140(96)01830-0.
14. Denham JW, Hamilton CS, Simpson SA, et al. Acute reaction parameters for human oropharyngeal mucosa. Radiotherapy and Oncology. 1995; 35(2): 129–137, doi: 10.1016/0167-8140(95)01545-r.
15. Maciejewski B, Miszczyk L, Składowski K. Which normal tissue reactions could be considered as dose limiting for altered radiotherapy in head and neck cancer? Medimond Inc 2022: 714–730.
16. ICRP Publication 60. Documentations of the International Commission on Radiobiological Protection. Pergamon Press, Oxford, New York 1991.

VIA MEDICA

Artykuł redakcyjny na zaproszenie / Invited editorial

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 286–287

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Are we ready to change treatment planning for left-side breast cancer radiotherapy?

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Comment on "What new dose distribution statistics may be included in the optimization of dose distribution in radiotherapy for post-mastectomy patients" by Piotr Mężyński and Paweł Kukołowicz [NOWOTWORY J Oncol 2021; 71(5): 267–273]

The standard treatment for breast cancer is either breast-conserving surgery or, in high-risk patients, mastectomy. Surgery is typically followed by adjuvant whole breast radiotherapy [1, 2]. Breast irradiation is intended to deliver a high therapeutic dose to the entire breast, minimising the doses in healthy tissues, defined as organs at risk (OARs). Previously, the fundamental law of radiobiology [3] postulated that highly differentiated organs with a low mitotic index are radioresistant and therefore described the heart as the quintessential radioresistant organ. Multiple studies on breast cancer treatment have refuted this claim, demonstrating a significant cardiac risk when portions of the heart are irradiated [4]. Routinely, the whole heart is considered as a single OAR. It is based on findings of the population-based case-control study published by Darby et al. [5], where a linear relationship between radiation dose and heart disease was defined. Darby's group showed that each additional 1 Gy of mean heart dose (MHD), predicted a 7.4% increase in a major coronary event over 20 years with no threshold below which there was no risk. Even though MHD has since become the prime restrictor of doses to the heart, numerous studies have shown that the impact of the radiation dose also depends on the heart substructures and, thus, dose restrictions should be modified accordingly [6]. One of these substructures is the left anterior descending coronary artery (LAD). Atkins et al. found the importance of limiting the dose to this substructure [7]. Because of its close proximity to the anterior chest wall, LAD is often exposed to high doses during breast irradiation and is a significant predictor of heart complications. Generally, the mean LAD dose is monitored as a surrogate predictor of cardiotoxicity.

Recently, Mężyński and Kukołowicz [8] presented an interesting planning study where they evaluated the doses delivered to various heart substructures and calculated normal tissue complication probability (NTCP) for the intensity modulation radiotherapy (IMRT) irradiated group of left-sided post-mastectomy patients. The study's conclusion recommends contouring cardiac substructures for a reliable assessment of the dose distribution as the MHD is not sufficient for cardiac risk evaluation for modern radiotherapy techniques. The LAD was one of all delineated substructures in this study where doses and NTCP were analysed. The authors found that below 30 Gy of the mean LAD dose, the NTCP seems to be negligible (the average value of LAD toxicity was below 0.2%). Nevertheless, their findings were based on a relatively small group (30) of patients. The study performed by Zureick et al. [9] was based on a more representative group (375) of patients treated with the 3D conformal technique, and investigated whether dose to LAD correlates with adverse cardiac events. The median

Jak cytować / How to cite:
Piotrowski T, Malicki J. ***Are we ready to change treatment planning for left-side breast cancer radiotherapy?*** *NOWOTWORY J Oncol* 2022; 72: 247–249.

follow-up time in this study was 48 months. 36 patients experienced some cardiac event, and 23 patients experienced a major cardiac event. The analysis showed that the increased mean and maximum LAD and mean heart doses were associated with an increased risk of some cardiac event and a major event. Based on the ROC (receiving operator curve) analysis, the authors identified the thresholds of 2.8, 6.7, and 0.8 Gy for the mean and max LAD dose, and MHD, respectively.

Another issue that could affect Mężyński and Kukołowicz's results was the difficulty in precise contouring of the heart substructures (especially LAD). As shown by Biedka and Żmuda [10], contouring the LAD is complicated due to its volume and location. Nevertheless, based on the analysis performed on the group of 50 patients, the authors of this study delivered valuable tips that could be helpful during the manual contouring of the LAD. To reduce the probability of wrong contouring (contour does not cover structure), applying a 1 cm margin to the contoured structure is recommended [10]. Current technology in structure segmentation based on artificial intelligence automatically produces contours of heart substructures. The recent study by van Velzen et al. [11] develops and validates an auto segmentation algorithm for the whole heart and its substructures and evaluates the association between heart dose, hospitalisation, and death due to heart disease in a large clinical dataset. In general, van Velzen et al. found that the risk of heart disease requiring hospitalisation was higher in patients receiving a high dose to cardiac substructures than in patients who had lower doses. Unfortunately, they could not distinguish the effects of MHD from dose to respective substructures on the risk of developing heart disease. A similar problem for predicting cardiac complications exists in lung cancer treatment [12]. Inability to establish such a relation may be due, in our opinion, to the multifactorial nature of radiation-induced cardiovascular disease. The disease can be associated with damage caused by doses deposited in multiple heart substructures. The role of several substructures would also support the hypothesis that IMRT offers better treatment than the 3D conformal option by giving a low dose to a large volume of the heart instead of a high dose to a small volume.

Most studies on this subject were focused on conformal 3D techniques including Zureick et al. [9]. Only Mężyński and Kukołowicz performed their analysis on breast treatment realised by IMRT. Unfortunately, their study is based on a relatively small group of patients, and we recommend a larger patient cohort investigation. Also, it would be interesting to include the data on LAD motion in different patients as an important factor in the correct contouring of this OAR [13].

We currently lack strong evidence demonstrating that heart avoidance by high doses using dose constraints for cardiac substructures rather than MHD improves clinical outcomes. This remains especially true in an era when 3D treatments are being replaced by IMRT and thus we need more data. Meanwhile, MHD should continue to be the standard of care in routine practice until the relationship of cardiac complications is unequivocally linked to the selected heart substructures.

Conflict of interest: none declared

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Received: 1 Jun 2022
Accepted: 7 Jun 2022

References

1. Poitevin-Chacón A, Chávez-Nogueda J, Prudencio RR, et al. Dosimetry of the left anterior descending coronary artery in left breast cancer patients treated with postoperative external radiotherapy. Rep Pract Oncol Radiother. 2018; 23(2): 91–96, doi: 10.1016/j.rpor.2018.01.003, indexed in Pubmed: 29681771.
2. Bukovszky B, Fodor J, Mátri Z. et l. Rdiotherpy insted of xillry lymph node dissection: evlution of xillry lymph node dose coverge with whole brest rdiotherpy. Rep Pract Oncol Radiother. 2022; ahead of print, doi: 10.5603/RPOR.a2022.0043.
3. Vogin G, Foray N. The law of Bergonié and Tribondeau: a nice formula for a first approximation. Int J Radiat Biol. 2013; 89(1): 2–8, doi: 10.3109/09553002.2012.717732, indexed in Pubmed: 22856587.
4. Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005; 366(9503): 2087–2106, doi: 10.1016/S0140-6736(05)67887-7, indexed in Pubmed: 16360786.
5. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013; 368(11): 987–998, doi: 10.1056/NEJMoa1209825, indexed in Pubmed: 23484825.
6. Sardaro A, Petruzzelli MF, D'Errico MP, et al. Radiation-induced cardiac damage in early left breast cancer patients: risk factors, biological mechanisms, radiobiology, and dosimetric constraints. Radiother Oncol. 2012; 103(2): 133–142, doi: 10.1016/j.radonc.2012.02.008, indexed in Pubmed: 22391054.
7. Atkins K, Bitterman D, Chaunzwa T, et al. Mean Heart Dose Is an Inadequate Surrogate for Left Anterior Descending Coronary Artery Dose and the Risk of Major Adverse Cardiac Events in Lung Cancer Radiation Therapy. Int J Radiat Oncol Biol Phys. 2021; 110(5): 1473–1479, doi: 10.1016/j.ijrobp.2021.03.005.
8. Mężeński P, Kukołowicz P. What new dose distribution statistics may be included in the optimization of dose distribution in radiotherapy for post-mastectomy patients. NOWOTWORY J Oncol. 2021; 71(5): 267–273, doi: 10.5603/njo.a2021.0047.
9. Zureick AH, Grzywacz VP, Almahariq MF, et al. Dose to the Left Anterior Descending Artery Correlates With Cardiac Events After Irradiation for Breast Cancer. Int J Radiat Oncol Biol Phys. 2022 [Epub ahead of print], doi: 10.1016/j.ijrobp.2022.04.019, indexed in Pubmed: 35483540.
10. Biedka M, Żmuda E. Contouring of the left anterior descending coronary artery in patients with breast cancer – the radiation oncologist's view. NOWOTWORY J Oncol. 2020; 70(2): 60–64, doi: 10.5603/NJO.2020.0014.
11. van Velzen SGM, Gal R, Teske AJ, et al. AI-Based Radiation Dose Quantification for Estimation of Heart Disease Risk in Breast Cancer Survivors After Radiation Therapy. Int J Radiat Oncol Biol Phys. 2022; 112(3): 621–632, doi: 10.1016/j.ijrobp.2021.09.008, indexed in Pubmed: 34624460.
12. Zhang TW, Snir J, Boldt RG, et al. Is the Importance of Heart Dose Overstated in the Treatment of Non-Small Cell Lung Cancer? A Systematic Review of the Literature. Int J Radiat Oncol Biol Phys. 2019; 104(3): 582–589, doi: 10.1016/j.ijrobp.2018.12.044, indexed in Pubmed: 30630029.
13. El-Sherif O, Yu E, Xhaferllari I, et al. Assessment of Intrafraction Breathing Motion on Left Anterior Descending Artery Dose During Left-Sided Breast Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016; 95(3): 1075–1082, doi: 10.1016/j.ijrobp.2016.02.026, indexed in Pubmed: 27130788.

VIA MEDICA

Artykuł redakcyjny na zaproszenie / Invited editorial

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 288–295

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Evaluation of postoperative complications in the older population

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Evaluation of the frequency and severity of postoperative complications is an integral part of establishing the clinical utility of a specific treatment. They define the possible consequences resulting from the chosen method of treatment, and thus the potential risks associated with this choice. Thanks to the analysis of complications, it is possible to evaluate patients' safety, identify a problem in the course of surgery within a given hospital and surgical team or carry a financial analysis. Not only is the frequency of occurrence important, but so is the severity of complications. Therefore, in recent years we have seen the development of several new tools for assessing postoperative complications such as the Clavien-Dindo scale, the Accordion Severity Grading System, the Postoperative Morbidity Index or the Comprehensive Complication Index. Analysis of the above-mentioned scales may contribute to the development of clear algorithms for the management of older patients at increased risk of severe complications and higher mortality, which subsequently may lead to increased efficacy and safer treatment in this population.

Key words: postoperative complications, elderly, Accordion Severity Grading System, Postoperative Morbidity Index, Comprehensive Complication Index

Evaluation of the frequency and severity of postoperative complications is an integral part of establishing the clinical utility of a specific treatment. They define the possible consequences resulting from the chosen method of treatment, and thus the potential risks associated with this choice. Thanks to the analysis of complications, it is possible to evaluate patients' safety, identify a problem in the course of surgery within a given hospital and surgical team or carry out a financial analysis [1]. Not only is the frequency of occurrence important, but so is the severity of complications. Moreover, in the long term, for a proper analysis of a given operating procedure and its modifications, it is important to report on complications in a repeatable manner [2]. In this way the decision-making process is based on evidence of higher quality. Unfortunately, for many years, scientific studies on postoperative complications focused on various data and, in many cases, did not provide information on the severity of a given complication [1, 3]. This often chaotic and, above all, inconsistent way of informing has eliminated the possibility of comparing results between work carried out on the same procedures.

Chronological age alone is no longer recognized as a reliable factor predicting the postoperative course. Significantly more important are elements of the Comprehensive Geriatric Assessment such us: functional activity, the presence of comorbidities, polypragmasia, nutritional, cognitive, and psychosocial status, which can allow one to determine the frailty status

Jak cytować / How to cite:
Sitkowski M, Kenig J. ***Evaluation of postoperative complications in the older population.*** *NOWOTWORY J Oncol* 2022; 72: 250–257.

(being a surrogate of biological age) [4–7]. During surgery it is essential to limit the extent of trauma: conducting scheduled surgery, positioning the patient in a safe way, using minimally invasive surgical techniques, limiting intraoperative blood loss (even at the expense of prolonged surgical time), avoiding hypothermia and many more [5, 8]. These elements are particularly important in the older population with cancer, where the most important factors determining overall survival are the pathological stage of the cancer and the occurrence and severity of complications [9]. Therefore, understanding the role of the complication and their proper evaluation is crucial across this population [10].

Clavien-Dindo scale

The first notable attempt at standardization of reporting complications was proposed in the 1990s in Toronto by Clavien et al. [11]. Negative results of surgery were divided into complications, sequelae, and failures to cure. In terms of severity, the grades were distinguished depending on the treatment method needed due to the complication, and the incidence of permanent disability or death [12]. The authors did not try to create a numerical scale. The Toronto 1992 complication grading system (T92) was a 4-grade scale with the grade 2 divided into levels A and B (pharmacological or surgical treatment needed). The first grade included all complications that could be resolved by interventions at the patient's bedside, without the need to intervene in the operating theater. The second grade had two subcategories and featured potentially life threatening complications. In the case of complications that left a permanent mark on the patient, they were classified into the third grade. In the event of a patient's death, the case was allocated to grade 4 [11].

The above scale was the first attempt at organizing a way of communicating the severity of complications; the proposed system became widespread. Unfortunately, due to the imprecise definitions and unclear descriptions in these classification systems, much of the work published in the past are difficult to compare or unreliable. Researchers in various fields of surgery modified the T92 scale and adapted it to a specific procedure, a patient's disease, or type of complication. However, T92 modified scales differ significantly and through the multiplicity of cut-off points, comparisons between studies are often impossible [12].

The development of the Clavien-Dindo scale led to clearer structuring on this issue. The 5-grade classification includes 7 levels of severity of complications (tab. I) [12, 13]. The refinement of the T92 scale consisted of additional information on the need to use general anesthesia in the treatment required to deal with the complication, and whether it was necessary to admit to the Intensive Care Unit (ICU) due to organ failure [12, 13]. This modification significantly improved the reporting of postoperative complications, but the obvious drawbacks of this scale should also be noted. The Clavien-Dindo scale only reports one, i.e. the most serious, complication of a patient after treatment [3, 14]. Other, less serious complications are ignored and the patient's picture after treatment is incomplete. Similar modifications by various researchers, as with the T92 scale, were made to the Clavien-Dindo scale [2]. The most common modification reduced the number of severity levels to make it simpler and less complex, or to adapt it to a particular disease. Moreover, only recently scales were proposed which would provide statistical information about the severity of complications, however, there is still no consensus on the common use of the selected scale.

Defining an appropriate tool for assessing postoperative complications in patients, regardless of their health status or age group, remains a research problem. As research shows, the demand for a universal tool in this matter is growing, which can be seen in the number of citations of publications on the scales of postoperative complications. The demand for such a tool is great across multiple fields, not only general surgery, but in every operational field with many scientific publications

Table I. Dindo et al. Classification of Surgical Complications [7]

Grade		Definition
I		Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions.
II		Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications. Blood transfusions and total parenteral nutrition are also included.
III	a	Requiring surgical, endoscopic or radiological intervention not under general anesthesia.
	b	Requiring surgical, endoscopic or radiological intervention under general anesthesia.
IV	a	Life-threatening complications (including CNS complications) requiring IC/ICU management. Single organ dysfunction (including dialysis).
	b	Life-threatening complication (including CNS complications) requiring IC/ICU management. Multi-organ dysfunction.
V		Death of the patient.
suffix d		If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

CNS – central nervous system, IC – intensive care, ICU – intensive care unit

reporting on a demand in urology and gynecology [12, 15, 16]. When considering the universality of a given scale, it is fundamental for it to be possible to use both in large studies and in those with a smaller number of patients or complications so that the results are comparable. For this reason, in recent years we have seen the development of several new tools for assessing postoperative complications such as the Accordion Severity Grading System (ASGS), the Postoperative Morbidity Index (PMI) or the Comprehensive Complication Index (CCI).

Accordion system

In a 2009 study, Strasberg et al. proposed a new scale based on the modification of the T92 and Clavien-Dindo classifications under the name the Accordion Severity Grading System. Since the introduction of the two previous scales, their use has steadily increased over time, but reporting in individual studies was often inconsistent. Due to the authors' observations of the studies published in the past, they noted the frequent tendency to combine the levels or even shorten the Clavien-Dindo or T92 scales, which often correlated with the number of patients or their complications included [12, 17, 18]. Therefore, the Accordion system is slightly different, depending on the sample size. The contracted version for smaller studies includes 4 grades: mild, moderate, severe, death (tab. II). The expanded classification for larger studies, often with more complex operating procedures in the research, includes 6 grades. The difference comes from dividing grade 3 (severe complication) into 3 additional categories: invasive procedure without general anesthesia, invasive procedure under general anesthesia, organ system failure (tab. III) [12].

In order to simplify the scales, both versions of Accordion do not contain separate levels, which was often omitted in previously published scientific papers. The authors also proposed a graphical version of the scale presentation in the form of a table to facilitate clarity and standardize the format of reporting the severity of complications. A clear limitation of the table, as the authors noted, is that it is only feasible in single arm studies [12].

Accordion was the first response to the previous widely used and recognized classifications: T92 and Clavien-Dindo. It focused on introducing solutions that were more concise and adapted to the type and size of the study, hence the name of the scale – Accordion. In successively published papers, the ASGS turned out to be a good tool in assessing the severity of complications, and thanks to the systematization of the reporting method, it enabled reliable comparisons between them [19]. Its positive correlation with the length of hospital stay and the economic aspects of treatment was also assessed [20]. It is necessary to note some disadvantages of this classification. It is a system that evaluates the severity of complications based on the required form of treatment to counter the complication – similar to the previous scales. It is not a quantitative classification in which the complication can be assigned a numerical value. Even though it is difficult not to match the appropriate form of treatment, its initiation depends on the subjective assessment of the patient's phy-

Table II. Accordion Severity Classification of Postoperative Complications: Contracted Classification [6]

Mild complication	Requires only minor invasive procedures that can be done at the bedside, such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, drainage of wound infections. Physiotherapy and the following drugs are allowed – antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy.
Moderate complication	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
Severe complication	All complications requiring endoscopic or interventional radiologic procedures or re-operation as well as complications resulting in failure of one or more organ systems.
Death	Postoperative death.

Table III. Accordion Severity Classification of Postoperative Complications: Expanded Classification [6]

Mild complication	Requires only minor invasive procedures that can be done at the bedside such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, drainage of wound infections. Physiotherapy and the following drugs are allowed – antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy.
Moderate complication	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
Severe: invasive procedure without general anesthesia	Requires management by an endoscopic, interventional procedure or re-operation without general anesthesia.
Severe: operation under general anesthesia	Requires management by an operation under general anesthesia.
Severe: organ system failure	Such complications would normally be managed in an increased acuity setting, but in some cases patients with complications of lower severity might also be admitted to an ICU.
Death	Postoperative death.

sician [20]. One of the ways to deal with the situation was proposed by Jung et al. [17]. Due to the precise determination of complications after gastrectomy due to gastric cancer, with the appropriate assignment of the method used to eliminate adverse effects, the possible ambiguity of the choice of the procedure by the surgeon was eliminated. It should be noted that the system can be adapted to many procedures in the field of surgery. It is better defined than its predecessors, but it cannot be specified as a fully universal scale.

An attempt to modify the Accordion Severity Grading System towards the quantitative scale was made by Porembka et al. using the severity weighting method before the actual publication of the original Accordion classification [18]. Questionnaires were sent to surgical outcome experts at US hospitals, containing 12 cases, corresponding to 6 levels of the expanded ASGS (2 cases for each level). As the system was not published then, experts were not able to follow it. They were asked to rate the cases on a scale of 0–100 (0 no complication, 100 death). After analyzing the returned questionnaires, it was decided to revise the Accordion scale due to the identification of a false-positive type error [18]. In their responses, the experts did not distinguish between single organ system failure and a need for reoperation under general anesthesia in a statistically significant manner. Thus, the criteria for grade 4 were improved and single-organ failure was included in it. It should be noted that the severity weighting method did not affect the interpretation of the contracted Accordion scale.

The study describing the modification of the expanded Accordion scale initiated the development of the Postoperative Morbidity Index (PMI). This revised system was still not a fully quantitative scale, but only a refinement of the Accordion Severity Grading System, another stage before the creation of a fully numerical scale.

Postoperative Morbidity Index

In another publication, Strasberg et al, based on deriving utility weights, proposed a new classification: the Postoperative Morbidity Index. In their study, they recommended the Index as a useful tool in the quantitative assessment of morbidity for surgical procedures [21]. Based on five surgical procedures and their possible extensions, the use of PMI was assessed. A selection of 636 cases were analyzed by 2 independent reviewers and complications were assessed based on the modified expanded Accordion Severity Grading Scale. The analysis included the following procedures: hernia repair, appendectomy, laparoscopic colectomy, hepatectomy, and pancreaticoduodenectomy. PMI scores were respectively: 0.005, 0.031, 0.082, 0.145, 0.150 [21]. The extension of the procedures had a significant impact on the change in the index value. When a hepatectomy was performed with a colectomy, the PMI increased to 0.468. It is worth mentioning that two reviewers evaluating the complications from selected cases using the Accordion Severity Grading System had an initial concordance above 98%. The very process of calculating the index is to match the grade to a given complication, taking into account its weight assigned to each of the 6 accordion levels (tab. IV).

Table IV. Accordion Classification System with Severity Weights [14, 17]

grade 1	0.110
grade 2	0.260
grade 3	0.370
grade 4	0.600
grade 5	0.790
grade 6	1.000

There are two ways to calculate and interpret the PMI. In the first case, the weights of complications of all patients of a given procedure are summed up and divided by the number of patients; in the second case, they are divided by the number of patients who had any complications at all. As a result, the first method informed us of chance of developing a complication after a given operation per case. The second method informed us of the estimated percentage of cases that might develop a complication, and, when it does occur, its severity is X [21].

PMI also facilitates observing the difference between surgical procedures, which differ both in the frequency of occurrence of a given complication as well as their severity for a given operation. Thanks to this new index, it is possible to identify trends in the occurrence of complications in given procedures and thus compare the quality of treatment within a given hospital over time [22]. It can also indicate the direction of successive studies due to differences in its values, as in the case of the modification of a procedure. Appropriate analysis and knowledge of the index scores by the attending physician gives a better opportunity to present to the patient the potential risk resulting from a given operation [23]. It was the first semi-quantitative scale which was not achieved in the previously described tools. M.K. Lee et al., who analyzed PMI in patients undergoing distal pancreatectomy, showed that the incidence of postoperative complications does not necessarily reflect the severity of these complications [24]. Thanks to the countability of this index, the results can be presented in a transparent manner.

Following the publication of the revised expanded ASGS and PMI, an implementation evaluation in urology procedures was undertaken. Based on the evaluation of complications in 654 cases from 11 urological procedures, using the expanded Accordion Severity Grading System, the PMI was calculated for each procedure. Beilan et al. positively verified the possibility of using the PMI as a tool to assess the severity of postoperative complications within their institution [25]. They also pointed to the opportunity of using this as a signaling factor for the need for further studies to determine the causes of complications in transurethral prostatectomy.

Despite the positive feedback, PMI still has some limitations. It still takes into account only the highest grade of complication per patient. Thus, there is a possibility of misinterpretation of PMI in patients with many different complications. It is also not a tool that sufficiently assesses the risk and possible severity of a given complication in an individual patient. Remember that the index is based on the ACS-NSQIP system, which only reports complications of the procedure entered into the system as a template, and does not necessarily report all actual complications [26]. Moreover, possible differences in the characterization of complications between ACS-NSQIP and the institutional database have been demonstrated [27]. An attempt to interpret it in terms of a different type of surgery carries the risk of the subjective assessment of those persons conducting the study. Risk adjusted PMI may help to verify the reasons for the change in the index results, like the characteristics of patients or even the improvement of the quality of provided treatment.

Comprehensive Complication Index

The newly created scale proposed by Slankamenac et al. is the Comprehensive Complication Index (CCI) [28]. It is a system based on the Clavien-Dindo classification. Severity, unlike previous studies, has been analyzed and revised by both patients and doctors using the given questionnaires. Based on 30 selected cases, 227 patients and 245 doctors rated severity using a numerical analogue scale from 0 (best) to 100 (worst). Cases corresponded to the five most common complications in the Clavien-Dindo grades I–IVb. Grade V, with is the patient's death, which was omitted in the questionnaires.

The two main reasons for developing the CCI are for the scale to be fully quantitative rather than ordinal and to include all complications in a single patient. The second reason is to distinguish it from previously created scales, such as the Clavien-Dindo, Accordion or PMI. One of the main problems was trying to create an appropriate mathematical formula. It would have to differentiate between the series of moderate complications of a given case and the severity of single complication but with greater health consequences. For this purpose, a method known from economic sciences was used: "operation risk index" [28]. In using this method to assess the severity of postoperative complications, more severe complications were assigned higher severity values than lesser complications. The index was created from the summed values. Due to the theoretically countless possible number of complications and thus the high values that CCI could achieve, which would definitely reduce the usefulness and ease of reporting of the scale, the authors decided to transform it so that it was within the limits of 0–100. After all the modifications, the formula for calculating CCI is as follows: $CCI = \sqrt{(CW1 + CW2 \ldots + CWX)}/2$, where CW means complication weight. An online calculator to calculate CCI is available at https://www.assessurgery.com/about_cci-calculator/.

Slankamenac et al. validated the CCI from four different perspectives. The results presented in the study demonstrated that the CCI significantly differentiates patients with complications of varying frequency. The authors also postulate the usefulness of CCI in complications observed over a longer period of time in the case of studies in which the follow-up was taken into account, and not only complications during hospital observation. The structure of the CCI makes it possible to add in a way and to take into account complications occurring later. This is not possible for other classifications because they take into account only the most serious complication, which can potentially dramatically change the perception of a given procedure. If the complication was more severe than previously reported, the entire index changes its character, however, in the case of a less significant complication, it is not taken into account when it comes to other systems.

As with the previously described scales, the CCI can be used as a tool to assess the quality of treatment within an institution or between different centers. If it is used for benchmarking, risk-adjustment is also necessary. In some centers specialized in carrying out given procedures, the characteristics of patients admitted may affect the interpretation of the CCI.

Previous studies also proved the usefulness of CCI as a more sensitive tool than traditional endpoints in detecting between-group differences [29]. Based on the 3 RCTs developed in accordance with the CONSORT guidelines, the CCI was found to be a more sensitive tool in assessing the necessary sample size to demonstrate differences than the traditional primary end points. It was shown that CCI significantly correlated with length of hospital stay and ICU stay. The possibility of using CCI to estimate the costs of potential complications was also presented.

Several of the above opinions about CCI turned out to be controversial, especially the validation methodology was questioned. Of the 3 RCTs on which the CCI was validated, only 1 used overall morbidity as the primary end point, the rest were limited to the assessment of a specific complication. Booney et al. adequately pointed out that the scales that take into account all possible complications in a given patient may, in a way, mask the results of particular specific complications in different groups [30]. The statement concerned only the CCI scale, but this may be true in relation to all collective scales reporting complications.

In subsequent years, research studies have proven a better correlation of CCI with the length of hospital stay compared to the Clavien-Dindo scale [31], the usefulness of the CCI assessment in predicting the costs of abdominal surgery [32, 33], and the increased usefulness of CCI in assessing particularly extensive surgery over a longer period of observation of patients (up to 3 months) [34].

The CCI is the first fully quantitative scale proposed to assess the severity of complications. The authors also propo-

sed a scale that takes into account all complications of the patient. Its modification is much easier and takes into account a patient's treatment course from the very beginning. Despite the controversy in validation, CCI is the first classification to significantly change the way of reporting postoperative complications and their severity.

Postoperative complications and the use of scales in older patients

Consistency in reporting postoperative complications and their severity is particularly important in older patients. Biological age alters both the frequency and severity of complications. In patients with frailty syndrome, the force of a potentially harmless complication can initiate a significant disruption of body homeostasis (p6, p7). Postoperative complications are a better predictor of mortality than perioperative complications, further emphasizing the need for scales. The mere occurrence of a postoperative complication affects the health status and survival of the patient even months after surgery [37]. Many papers in the past have reported prolonged hospitalization, increased perioperative mortality, increased investigations and subsequent treatments due to complications, which obviously carried over to the burden of additional costs [38, 39]. According to the literature reviewed, 25–40% of elderly patients have postoperative complications [40–42]. The most common significant complications are neurological disorders, mainly postoperative delirium as well as pulmonary complications and renal impairment [36, 41, 43]. Prolonged recovery of activity or, in many cases, some degree of loss of organ function definitely affects the organism with reduced physiological reserves. Tahiri et al. showed that only 68% of patients with postoperative complications returned to preoperative function after 6 months [40]. A comparable result was reported by Lawrence et al. who showed 63% of patients returned to preoperative performance after 6 months [44]. Postoperative complications affect the subsequent functioning of the patient, unfortunately often with varying degrees of disability and thus a reduced subjective quality of life for the patient [45]. For this reason, the assessment of the elderly patient should be done on an individual basis with an in-depth analysis of comorbidities and preoperative activity [46, 47]. The analysis of the above-mentioned scales may contribute to the development of clear algorithms for the management of patients at increased risk of severe complications and higher mortality, thereby leading to increased efficacy and safety of treatment.

Currently, few studies address the use of the scales described above in patients with frailty syndrome. Artiles-Armas et al. demonstrated the correlation of frailty and CCI [48]. They also indicated efficacy in predicting the emergence of additional complications of greater severity when complications were initially present. The correlation of CCI with long-term overall survival in patients 65 years of age and older undergoing colorectal cancer resection has also been demonstrated [49]. In the same study, CCI was shown to have a similar predictive value for long term overall survival as that of CDC. Carli et al. used CCI to evaluate postoperative complications in frail patients when comparing the implementation of a prehabilitation program versus postoperative rehabilitation in patients undergoing resection for colorectal cancer [50]. It is necessary to include the follow-up in the reporting of surgical complications. If the assessment of complication frequency and severity is closed after the hospital stay, data on complications resulting from the implemented intervention are lost. Ommundsen et al. in their study indicated that if had it not been for a 30-day follow-up, they would not have known about the 19% of frail patients who had complications only after the end of their ward stay while expressing no symptoms during hospitalization [51]. Further studies and applications of indexes in frail patients are needed to compare their effectiveness. The next step should also be to determine the magnitude or ratio of intraoperative and postoperative complication scales. Such attempts have already been made, where Kinaci et al. found the predictive value of intraoperative complications described by the CLASSIC (Classification of Intraoperative Complications) scale relative to the postoperative complications described by the ASGS. The correlation was particularly pronounced in the higher grades [52]. The use of appropriate scales of postoperative complications and their severity unifies reporting and thus contributes to increased knowledge of the risks associated with a given operation. This is particularly important in frail patients, where the margin for error is even smaller and may be associated with irreversible functional deterioration in such a patient.

Conflict of interest: none declared

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Received: 15 Jun 2022
Accepted: 29 Jun 2022

References

1. Krosch TCK, D'Cunha J. Comparing apples to apples: a call for unification of complication reporting across health systems. Semin Thorac Cardiovasc Surg. 2010; 22(4): 271–273, doi: 10.1053/j.semtcvs.2011.01.002, indexed in Pubmed: 21549265.
2. Martin RCG, Brennan MF, Jaques DP. Quality of complication reporting in the surgical literature. Ann Surg. 2002; 235(6): 803–813, doi: 10.1097/00000658-200206000-00007, indexed in Pubmed: 12035036.
3. Brennan MF. Postoperative complication reporting: more than mortality and morbidity. Ann Surg. 2013; 258(1): 8–9, doi: 10.1097/SLA.0b013e318297a1e7, indexed in Pubmed: 23728279.
4. Kenig J. Oncogeriatrics (part 2.). Normal and pathological ageing. Nowotwory. Journal of Oncology. 2019; 69(3-4): 146–149, doi: 10.5603/njo.2019.0027.
5. Fried TR, Van Ness PH, Byers AL, et al. Changes in preferences for life-sustaining treatment among older persons with advanced illness. J Gen Intern Med. 2007; 22(4): 495–501, doi: 10.1007/s11606-007-0104-9, indexed in Pubmed: 17372799.

6. Kenig J. Oncogeriatrics (part 4.) Pre-operative assessment of elderly patients with cancer. Nowotwory. Journal of Oncology. 2020; 70(1): 16–19, doi: 10.5603/njo.2020.0003.
7. Skorus U, Kenig J. Oncogeriatrics (part 5.) The role of comorbidities in older patients with cancer. Nowotwory Journal of Oncology. 2020; 70(2): 54–59, doi: 10.5603/NJO.2020.0013.
8. Kristjansson SR, Nesbakken A, Jordhøy MS, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. Crit Rev Oncol Hematol. 2010; 76(3): 208–217, doi: 10.1016/j.critrevonc.2009.11.002, indexed in Pubmed: 20005123.
9. Kenig J. Oncogeriatrics (part 1.). Frailty in older adults with cancer. Nowotwory. Journal of Oncology. 2019; 69(2): 55–57, doi: 10.5603/njo.2019.0010.
10. Kenig J. Oncogeriatrics (part 3.) Influence of surgical trauma on older patients. Nowotwory. Journal of Oncology. 2019; 69(5-6): 163–167, doi: 10.5603/njo.2019.0030.
11. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery. 1992; 111(5): 518–526, indexed in Pubmed: 1598671.
12. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg. 2009; 250(2): 177–186, doi: 10.1097/SLA.0b013e3181afde41, indexed in Pubmed: 19638919.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2): 205–213, doi: 10.1097/01.sla.0000133083.54934.ae, indexed in Pubmed: 15273542.
14. Li J, Moustafa M, Freiwald-Bibiza E, et al. Is It Feasible to Standardize a Composite Postoperative Complication Reporting System for Liver Resection? J Gastrointest Surg. 2020; 24(12): 2748–2755, doi: 10.1007/s11605-019-04457-w, indexed in Pubmed: 31792904.
15. Mitropoulos D, Artibani W, Biyani CS, et al. Validation of the Clavien-Dindo Grading System in Urology by the European Association of Urology Guidelines Ad Hoc Panel. Eur Urol Focus. 2018; 4(4): 608–613, doi: 10.1016/j.euf.2017.02.014, indexed in Pubmed: 28753862.
16. Radosa MP, Meyberg-Solomayer G, Radosa J, et al. Standardised Registration of Surgical Complications in Laparoscopic-Gynaecological Therapeutic Procedures Using the Clavien-Dindo Classification. Geburtshilfe Frauenheilkd. 2014; 74(8): 752–758, doi: 10.1055/s-0034-1382925, indexed in Pubmed: 25221343.
17. Jung MiR, Park YK, Seon JW, et al. Definition and classification of complications of gastrectomy for gastric cancer based on the accordion severity grading system. World J Surg. 2012; 36(10): 2400–2411, doi: 10.1007/s00268-012-1693-y, indexed in Pubmed: 22752074.
18. Porembka MR, Hall BL, Hirbe M, et al. Quantitative weighting of postoperative complications based on the accordion severity grading system: demonstration of potential impact using the american college of surgeons national surgical quality improvement program. J Am Coll Surg. 2010; 210(3): 286–298, doi: 10.1016/j.jamcollsurg.2009.12.004, indexed in Pubmed: 20193891.
19. Low DE, Kuppusamy M, Hashimoto Y, et al. Comparing complications of esophagectomy and pancreaticoduodenectomy and potential impact on hospital systems utilizing the accordion severity grading system. J Gastrointest Surg. 2010; 14(11): 1646–1652, doi: 10.1007/s11605-010-1325-5, indexed in Pubmed: 20824376.
20. Carrott PW, Markar SR, Kuppusamy MK, et al. Accordion severity grading system: assessment of relationship between costs, length of hospital stay, and survival in patients with complications after esophagectomy for cancer. J Am Coll Surg. 2012; 215(3): 331–336, doi: 10.1016/j.jamcollsurg.2012.04.030, indexed in Pubmed: 22683069.
21. Strasberg S, Hall B. Postoperative Morbidity Index: A Quantitative Measure of Severity of Postoperative Complications. J Am Coll Surg. 2011; 213(5): 616–626, doi: 10.1016/j.jamcollsurg.2011.07.019.
22. Tahkola K, Väyrynen V, Kellokumpu I, et al. Critical evaluation of quality of hepatopancreatic surgery in a medium-volume center in Finland using the Accordion Severity Grading System and the Postoperative Morbidity Index. J Gastrointest Oncol. 2020; 11(4): 724–737, doi: 10.21037/jgo.2020.04.03, indexed in Pubmed: 32953156.
23. Datta J, Lewis RS, Strasberg SM, et al. Quantifying the burden of complications following total pancreatectomy using the postoperative morbidity index: a multi-institutional perspective. J Gastrointest Surg. 2015; 19(3): 506–515, doi: 10.1007/s11605-014-2706-y, indexed in Pubmed: 25451733.
24. Lee MK, Lewis RS, Strasberg SM, et al. Defining the post-operative morbidity index for distal pancreatectomy. HPB (Oxford). 2014; 16(10): 915–923, doi: 10.1111/hpb.12293, indexed in Pubmed: 24931404.
25. Beilan J, Strakosha R, Palacios DA, et al. The Postoperative Morbidity Index: a quantitative weighing of postoperative complications applied to urological procedures. BMC Urol. 2014; 14: 1, doi: 10.1186/1471-2490-14-1, indexed in Pubmed: 24383457.
26. American College of Surgeons NSQIP Data User Guide 2015.
27. Epelboym I, Gawlas I, Lee JA, et al. Limitations of ACS-NSQIP in reporting complications for patients undergoing pancreatectomy: underscoring the need for a pancreas-specific module. World J Surg. 2014; 38(6): 1461–1467, doi: 10.1007/s00268-013-2439-1, indexed in Pubmed: 24407939.
28. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg. 2013; 258(1): 1–7, doi: 10.1097/SLA.0b013e318296c732, indexed in Pubmed: 23728278.
29. Slankamenac K, Nederlof N, Pessaux P, et al. The comprehensive complication index: a novel and more sensitive endpoint for assessing outcome and reducing sample size in randomized controlled trials. Ann Surg. 2014; 260(5): 757–62; discussion 762, doi: 10.1097/SLA.0000000000000948, indexed in Pubmed: 25379846.
30. Boney O, Moonesinghe R, Grocott M. Reply to Slankamenac et al's Comprehensive Complication Index Validation Study. Ann Surg. 2016; 264(2): e11, doi: 10.1097/SLA.0000000000001288, indexed in Pubmed: 26079896.
31. Kim TH, Suh YS, Huh YJ, et al. The comprehensive complication index (CCI) is a more sensitive complication index than the conventional Clavien-Dindo classification in radical gastric cancer surgery. Gastric Cancer. 2018; 21(1): 171–181, doi: 10.1007/s10120-017-0728-3, indexed in Pubmed: 28597328.
32. de la Plaza Llamas R, Hidalgo Vega Á, Latorre Fragua RA, et al. The Cost of Postoperative Complications and Economic Validation of the Comprehensive Complication Index: Prospective Study. Ann Surg. 2021; 273(1): 112–120, doi: 10.1097/SLA.0000000000003308, indexed in Pubmed: 30985367.
33. Smeyers KM, Slankamenac K, Houben B, et al. Comparison of the Clavien-Dindo and Comprehensive Complication Index systems for grading of surgical complications after colorectal resections. Acta Chir Belg. 2021 [Epub ahead of print]: 1–8, doi: 10.1080/00015458.2021.1920682, indexed in Pubmed: 33910493.
34. Clavien PA, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI®): Added Value and Clinical Perspectives 3 Years "Down the Line". Ann Surg. 2017; 265(6): 1045–1050, doi: 10.1097/SLA.0000000000002132, indexed in Pubmed: 28486288.
35. Kenig J, Mituś J, Rapacz K. Oncogeriatrics (part 6.). The usefulness of routine preoperative investigations in the qualification of an older patient for elective surgery. Nowotwory. Journal of Oncology. 2020; 70(3): 101–104, doi: 10.5603/njo.2020.0022.
36. Kenig J, Szabat K. Oncogeriatrics (part 7.). Geriatric assessment for older patients with cancer. Nowotwory. Journal of Oncology. 2020; 70(4): 153–157, doi: 10.5603/njo.2020.0031.
37. Story DA. Postoperative complications in elderly patients and their significance for long-term prognosis. Curr Opin Anaesthesiol. 2008; 21(3): 375–379, doi: 10.1097/ACO.0b013e3282f889f8, indexed in Pubmed: 18458558.
38. Sieber FE, Barnett SR. Preventing postoperative complications in the elderly. Anesthesiol Clin. 2011; 29(1): 83–97, doi: 10.1016/j.anclin.2010.11.011, indexed in Pubmed: 21295754.
39. Gani F, Hundt J, Makary MA, et al. Financial Impact of Postoperative Complication Following Hepato-Pancreatico-Biliary Surgery for Cancer. Ann Surg Oncol. 2016; 23(4): 1064–1070, doi: 10.1245/s10434-015-5042-x, indexed in Pubmed: 26714947.
40. Tahiri M, Sikder T, Maimon G, et al. The impact of postoperative complications on the recovery of elderly surgical patients. Surg Endosc. 2016; 30(5): 1762–1770, doi: 10.1007/s00464-015-4440-2, indexed in Pubmed: 26194260.
41. Story DA, Leslie K, Myles PS, et al. REASON Investigators, Australian and New Zealand College of Anaesthetists Trials Group. Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study. Anaesthesia. 2010; 65(10): 1022–1030, doi: 10.1111/j.1365-2044.2010.06478.x, indexed in Pubmed: 20731639.
42. Hamel MB, Henderson WG, Khuri SF, et al. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005; 53(3): 424–429, doi: 10.1111/j.1532-5415.2005.53159.x, indexed in Pubmed: 15743284.
43. Serafim RB, Dutra MF, Saddy F, et al. Delirium in postoperative non-ventilated intensive care patients: risk factors and outcomes. Ann

Intensive Care. 2012; 2(1): 51, doi: 10.1186/2110-5820-2-51, indexed in Pubmed: 23272945.
44. Lawrence VA, Hazuda HP, Cornell JE, et al. Functional independence after major abdominal surgery in the elderly. J Am Coll Surg. 2004; 199(5): 762–772, doi: 10.1016/j.jamcollsurg.2004.05.280, indexed in Pubmed: 15501119.
45. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. JAMA Surg. 2015; 150(12): 1134–1140, doi: 10.1001/jamasurg.2015.2606, indexed in Pubmed: 26352694.
46. Kenig J. Oncogeriatrics (part 8.). Frailty screening tools. Nowotwory. Journal of Oncology. 2020; 70(5): 184–186, doi: 10.5603/njo.a2020.0039.
47. Kenig J, Krzeszowiak J, Kupniewski K. Postoperative functional results of older patients after pancreas and liver surgery. Nowotwory. Journal of Oncology. 2022; 72(3): 202–206, doi: 10.5603/njo.2022.0029.
48. Artiles-Armas M, Roque-Castellano C, Conde-Martel A, et al. The Comprehensive Complication Index is Related to Frailty in Elderly Surgical Patients. J Surg Res. 2019; 244: 218–224, doi: 10.1016/j.jss.2019.06.011, indexed in Pubmed: 31301477.
49. Wang D, Zhang J, Bai Z, et al. Associations of Postoperative Complications Assessed by Clavien-Dindo Classification and Comprehensive Complication Index with Long-Term Overall Survival in Elderly Patients after Radical CRC Resection. Clin Interv Aging. 2020; 15: 1939–1949, doi: 10.2147/CIA.S271969, indexed in Pubmed: 33116448.
50. Carli F, Bousquet-Dion G, Awasthi R, et al. Effect of Multimodal Prehabilitation vs Postoperative Rehabilitation on 30-Day Postoperative Complications for Frail Patients Undergoing Resection of Colorectal Cancer: A Randomized Clinical Trial. JAMA Surg. 2020; 155(3): 233–242, doi: 10.1001/jamasurg.2019.5474, indexed in Pubmed: 31968063.
51. Ommundsen N, Nesbakken A, Wyller TB, et al. Post-discharge complications in frail older patients after surgery for colorectal cancer. Eur J Surg Oncol. 2018; 44(10): 1542–1547, doi: 10.1016/j.ejso.2018.06.024, indexed in Pubmed: 30037638.
52. Kinaci E, Sevinc MM, Bayrak S, et al. Is the classification of intraoperative complications (CLASSIC) related to postoperative course? Int J Surg. 2016; 29: 171–175, doi: 10.1016/j.ijsu.2016.03.068, indexed in Pubmed: 27063858.

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Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 296

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

QTc prolongations as a result of drug interactions of CD4/6 inhibitors

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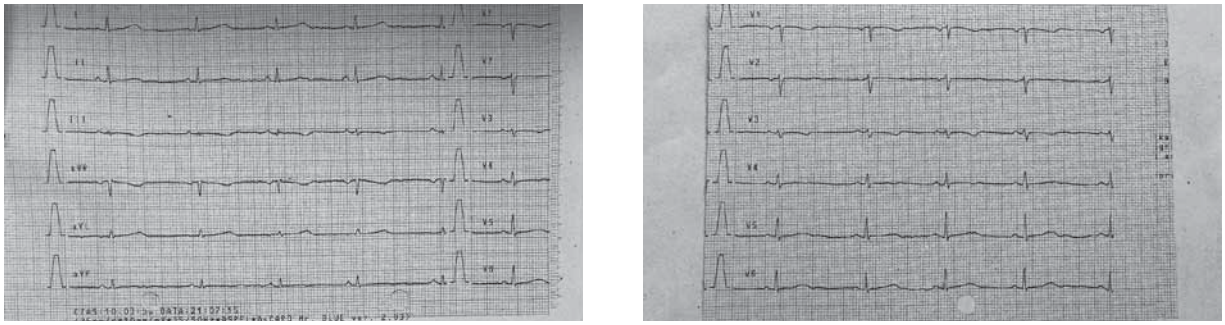

Figure 1. EKG (15.07.21): sinus bradycardia 54/min. Intermed. heart axis. The interval P-R: 130 ms, QTc – 520 ms, flat T in V2, shallow negative T in V3, flat T in V4

A 45-year-old woman was diagnosed with metastatic breast cancer with dissemination to the bones and mediastinal lymph nodes of the breast. Taking into account the biological type (luminal B, *HER2*-negative) and the low dynamics of the disease, the best therapeutic option was to use hormone therapy in combination selective oestrogen receptor downregulator – fulvestrant with the cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor. The therapy was initiated in July 2021. The pre-treatment electrocardiogram (ECG) was normal. On day 15 the control ECG showed heart rate 54/min and QTc – 520 ms. During therapy, mycoses of the esophagus were diagnosed and fluconazole 50 mg tabletes QD were ordered. Due to persisting dysphagia, antifungal agents were continued for the next 10 days, together only with hormonal therapy. A control ECG 3 weeks later was normal and the CDK 4/6 therapy was restarted. Conclusion: protein kinase inhibitors used in molecularly-targeted oncology drugs are cardiotoxic and can cause various disorders of the cardiovascular system. This group of agents includes CDK 4/6 inhibitors that occasionally prolong the QTc interval [1]. Cyclin-dependent kinase 4/6 inhibitors are metabolized by CYP3A enzymes and inhibit CYP3A themselves. Co-administration with a strong CYP3A inhibitor increases cardiotoxicity of CDK 4/6 inhibitors and should be avoided [2].

References

1. Grela-Wojewoda A, Pacholczak-Madej R, Adamczyk A, et al. Cardiotoxicity Induced by Protein Kinase Inhibitors in Patients with Cancer. Int J Mol Sci. 2022; 23(5): 2815, doi: 10.3390/ijms23052815, indexed in Pubmed: 35269958.
2. Rascon K, Flajc G, De Angelis C, et al. Ribociclib in HR+/HER2- Advanced or Metastatic Breast Cancer Patients. Ann Pharmacother. 2019; 53(5): 501–509, doi: 10.1177/1060028018817904, indexed in Pubmed: 30522347.

Jak cytować / How to cite:

Grela-Wojewoda A, Puskulluoglu M, Lompart J, Ziobro M, Konduracka E. ***QTc prolongations as a result of drug interactions of CD4/6 inhibitors***. *NOWOTWORY J Oncol* 2022; 72: 258.

VIA MEDICA

Genetyka i onkologia / Genetics and oncology

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 297–302

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Wilms tumor (nephroblastoma) – clinical and genetic aspects

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Nephroblastoma (Wilms tumor – WT) is the most common kidney tumor among the pediatric population, fifth among malignant neoplasms and third among solid tumors. The most common type of WT is sporadic and unilateral. WT occurs either as an isolated, nonsyndromic WT or as syndromic one belonging to the spectrum of a variety of genetic syndromes. Molecular genetic testing should be considered in nonsyndromic WT and include a multigene panel or whole exome sequencing (WES); in syndromic cases single-gene testing, DNA methylation panel and chromosomal microarray. Outcomes of treatment in WT patients remain very good, but there are still subgroups with poor prognosis and increased relapse rates, especially in the blastemic and disseminated anaplasia types. WT survivors have increased risk of chronic kidney disease (CKD). They need further follow-up, not only by oncologists but also by nephrologists, to preserve kidney function or slow down CKD progression.

Key words: Wilms tumor, genetics clinical, presentation, nephrological control

Introduction

Nephroblastoma (Wilms tumor – WT) is the most common kidney tumor in the pediatric population, fifth among malignant neoplasms and third among solid tumors (after brain tumors and neuroblastoma) [1]. WT accounts for 5% of childhood malignancies and 80% of all diagnosed kidney tumors in children and adolescents [2]. WT occurs in 7 per 1,000,000 children below 15 years of age, and the median age at diagnosis is 5 years. Most patients are diagnosed with localized disease, but in approximately 5% of patients distant metastases are present at the time of diagnosis [4]. The tumor is most often located unifocally in the lower or upper pole of the kidney, less often multifocally. In 5–8% of cases, it occurs bilaterally, most often in cases with co-existing nephroblastomatosis, which is defined as disturbed, incomplete maturation of primary nephrogenic cells [5].

Pathogenesis

The fetal kidney is formed from mesodermal blastemic cells, epithelial cells, and mesenchymal tissue [3]. The causes of tumor development are not fully explained. The most common type of WT is sporadic, unilateral, less frequently sporadic, bilateral tumor occurs. Family predisposition was confirmed in 1–2% of children [6]. WT can coexist with congenital defects in 10% of cases (tab. I), genetic syndromes (tab. II) and nephroblastomatosis [7].

Jak cytować / How to cite:
Janeczko-Czarnecka M, Ślęzak R, Pietras W, Kiliś-Pstrusińska K. ***Wilms tumor (nephroblastoma) – clinical and genetic aspects.*** *NOWOTWORY J Oncol* 2022; 72: 259–264.

Table I. Congenital defects coexisting with Wilms tumor

System/organ	Type of defect
genitourinary system	cryptorchidism, hypocrisy, gonadal dysgenesis, pseudohermaphroditism, renal hypoplasia, horseshoe kidney, ectopic kidney, kidney cysts
osteoarticular system	hemihypertrophy, fusion of fingers, fusion of ribs, focomelia
sense organs	aniridia
other	cardiovascular defects, hemihypertrophy, neurofibromatosis

Genetics

Wilms tumor occurs either as an isolated, nonsyndromic WT or as syndromic one belonging to the spectrum of a variety of genetic syndromes. In isolated, nonsyndromic WT cases, single gene mutations are found in approximately 10–15% of tumors. These mutations were most frequently observed in genes such as: *WT1, WT2, CTNNB1, NYNRIN, CDC73, TRIM28, FANCD1 (BRCA2), REST, TRIP13, POU6F2, H19, DIS3L2, DICER1, FBXW7, TP53, KDM3B*. Ongoing studies on the genetic etiology of nonsyndromic WT have shown that loss of heterozygosity in loci 1p, 7p, 16q, 17p, and 19q is also associated with an increased risk of Wilms tumor. An increased risk of WT development is observed in a variety of genetic syndromes such as:

- congenital malformation syndromes, e.g. sex-reversal gonadal dysgenesis (Denys-Drash, WAGR [Wilms tumor, aniridia, genitourinary anomalies, mental retardation], Meecham syndrome),
- overgrowth syndromes (Beckwith-Wiedemann, Sotos, Perlman, Simpson-Golabi and PIC3CA-related syndrome), microsomic syndromes (mulibrey nanism, Bohring-Opitz syndrome, mosaic variegated aneuploidy),
- chromosomal aneuploidy syndromes (e.g. Edwards syndrome), but also in hereditary cancer predisposition syndromes (e.g. Fanconi anaemia, Bloom syndrome, Li-Fraumeni syndrome).

Genetic aetiology as well as mode of inheritance of these syndromes are heterogenous (tab. II).

Clinical presentation of Wilms tumor

Most often, the first symptom of the disease is a painless abdominal tumor (60–70%). The lesion is characterized by slow growth, which is the reason for an initially asymptomatic course of the disease [8]. Approximately 35% of patients have other clinical symptoms, which include (in order of frequency):

- haematuria (26%),
- hypertension (25%) due to compression of the renal artery by the tumor,
- fever (18%),
- loss of appetite (14%),
- abdominal pain (3%),
- malaise,
- anemia caused by extensive subcapsular haemorrhage,
- recurrent urinary tract infections and constipation [9].

The general condition of the patient remains good, despite the large size of the tumor. The neoplasm destroys the kidney parenchyma, invades the kidney capsule, surrounding adipose tissue and adjacent organs. Metastases spread through the continuity after crossing the renal capsule, and then the tumor invades adjacent organs, blood vessels and the peritoneal cavity. The tumor's tendency to grow into venous vessels (renal vein, inferior vena cava) is characteristic. The neoplastic mass initially covers the renal vessels, then the inferior vena cava, sometimes reaching the right atrium of the heart [10]. The ease of spreading at punctures or incisions during a biopsy or surgical procedure is significant. At diagnosis, metastases are present in 15% of patients. Most often they include lungs (85%), liver (15%), less frequently the central nervous system and bones. Regional lymph nodes are often involved in tumors with an unfavorable histological structure, disseminated anaplasia, and imply a worse prognosis.

Diagnostics

Diagnostics of WT is based on a detailed history, including a family history, a thorough physical examination, laboratory blood and urine tests, and imaging studies, which include ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) of the abdominal cavity with intravenous contrast agent administration [11]. A chest X-ray and CT scan are used to exclude the presence of lung metastases. According to the European protocol, preoperative chemotherapy is administered based on the characteristic features in the imaging tests. Definitive diagnosis and qualification to the prognostic group are made after surgery and a pathomorphological examination.

The patient's qualification to the appropriate prognostic group is based on the degree of local advancement (I–V) and a histopathological examination (LOW, INT, HR). The clinical and histopathological classification according to the SIOP (International Society of Pediatricians and Oncologists) includes five local stages (I–V) [12]. In stage I, the tumor is limited to the kidney; in stage II, it penetrates the kidney capsule and invades the adjacent organs. Patients with incomplete tumor excision, capsule rupture, tumor rupture, peritoneal implants and open biopsy prior to treatment are qualified to stage III. Stage IV presents with distant metastases, and stage V is reserved for bilateral Wilms tumors.

Table II. Genetic syndromes characterized by an increased risk of Wilms tumor development

Syndromes	Gene	Inheritance	Clinical characteristics	Risk of WT development	Other malignancies
Beckwith--Wiedemann syndrome	*CDKN1C* uniparental disomy (UD) for 11p15	AD, UD	macrosomia, macroglossia, umbilical hernia, omphalocele, hemihyperplasia, tongue hyperplasia, hepatomegaly, splenomegaly, neonatal hypoglycemia, defects of the urinary-genital system, hypertrophy of adrenal cortex cells	5%	hepatoblastoma, adrenal carcinoma, neuroblastoma, rhabdomyosarcoma
Sotos syndrome	*NSD1*	AD	overgrowth, macrocephaly, advanced bone age, cardiac anomalies, joint hyperlaxity, renal anomalies, scoliosis, seizures, learning disability, speech delays, behavior problems, unique facial features	<3%	sacrococcygeal teratoma, neuroblastoma, presacral ganglioma, acute lymphoblastic leukemia
Simpson--Golabi--Behmel syndrome	*GPC3, GPC4*	XL	macrosomia, macrocephaly, coarse facial features, large forehead, nose, lips and tongue, macrostomia, macroglossia, and palatal abnormalities, intellectual disability, supernumerary nipples, umbilical and diaphragmatic hernia, congenital heart defects, genitourinary defects, gastrointestinal anomalies, skeletal anomalies	4–9%	hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, hepatocellular carcinoma, medulloblastoma
Perlman syndrome	*DIS3L2*	AR	fetal and neonatal macrosomia, facial dysmorphism, defects of the genitourinary system	65%	renal hamartomas
PIK3CA-related overgrowth spectrum	*PIK3CA*	S	segmental or focal overgrowth, ***v***ascular and lymphatic malformations, ventriculomegaly**,** epidermal nevi, ***s***keletal anomalies, hypoglycemia, intellectual disability	1–2%	nephroblastomatosis
osteopathia striata with cranial sclerosis	*AMER1 (WTX)*	XL	macrocephaly, palate anomalies, deafness, facial dysmorphism, sclerosis of skull base, ophtalmoplegia, intellectual disability	5%	colorectal cancer
Bohring-Opitz syndrome	*ASXL1*	AD	growth deficiency, IUGR, microcephaly, characteristic facial features, distinct posture, seizures, intellectual disability, developmental delay, cardiac anomalies	7%	medulloblastoma
mulibrey nanism	*TRIM37*	AR	fetal growth delay (IUGR), characteristic facial features, microsomia, macrocephaly, hypotonia, hepatomegaly, heart disease, skeletal anomalies, yellow discoloration of the eyes	6%	ovarian tumors, endometrial carcinoma, renal papillary, papillary and medullary thyroid carcinoma, pheochromocytoma lymphoblastic leukemia
mosaic variegated aneuploidy	*BUB1B, CEP57, TRIP 13*	AR	fetal growth delay (IUGR), microcephaly, intellectual disability, postnatal growth deficiency, microcephaly, dysmorphic features	10–85%	rhabdomyosarcoma, acute lymphoblastic leukemia, nephroblastoma
Denys-Drash syndrome	*WT1*	AD	46,XY sex reversal, gonadal dysgenesis, ambiguous genitals, congenital nephropathy, nephrotic syndrome	>90%	gonadoblastoma
Meecham syndrome	*WT1*	AD	46,XY sex reversal, ambiguous genitals, diaphragmatic abnormalities, genital defects and cardiac malformations, nephrotic syndrome	high risk	gonadoblastoma
WAGR	*WT1, PAX6* 11p13 deletion	AD	Wilms tumor (W) anridia (A), congenital defects of the urinary system (G), mental retardation (R), ambiguous genitals (sex reversal in 46,XY) mental retardation, cataract, glaucoma, duplicated ureters, horseshoe kidney, obesity	30–50%	gonadoblastoma
Fanconi anemia	*FANCD1 (BRCA2) PALB2*	AR	short stature, skeletal malformations of the limbs, microcephaly, ophthalmic and genitourinary tract anomalies, abnormal skin pigmentation	20–60%	myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), medulloblastoma, breast and ovarian cancer
Bloom syndrome	*BLM*	AR	growth deficiency, immune deficiency, diabetes, immune abnormalities, sensitivity to sunlight, insulin resistance	6%	acute myelogenous leukemia, lymphoma, pharyngeal, breast, tonsils, lung, gastrointestinal tract, uteri and skin carcinoma
Edwards syndrome (trisomy 18)	chromosome 18 trisomy	S	hypotonia, developmental delay, characteristic facial feature, growth retardation, cardiac, pulmonary and gastrointestinal defects, microcephaly, intellectual disability,	increasing risk	hepatoblastoma

AD – autosomal dominant; AR – autosomal recessive; S – sporadic; XL – X-linked; UD – uniparental disomy; IUGR – intrauterine growth restriction

Histopathological qualification to the prognostic group takes into account the type of tissue forming Wilms tumor. The main part includes the primary blastemic mesenchymal tissue [4]. Other histopathological components include epithelial tissue, the stroma, the blastemic part, and the anaplastic lesions. We distinguish:

- low-risk neoplasms (LOW) – mesoblastic nephroblastoma, the cystic type and completely necrotic type,
- intermediate-risk (INT) neoplasms – epithelial, stromal, mixed, regressive type, with focal anaplasia,
- high-risk neoplasms (HR) – blastemic type, with disseminated anaplasia, clear cell sarcoma of the kidney (CCSK).

More recent studies indicate that the Wilms tumor risk stratification system, based only on histology and local stage, is not optimal for identifying all patients at risk of relapse. Research to develop new clinical, genetic, and molecular risk factors for recurrence and unfavorable prognosis is ongoing [13]. They include i.e mutations of the *TP53* gene, reported in patients with a poorly prognostic anaplastic type, and mutations of the *TRIM28* gene in patients with an epithelial form of WT [14–16].

Molecular genetic testing should be considered in nonsydromic Wilms tumor and include a multigene panel or whole exome sequencing (WES), and in syndromic cases single--gene testing, DNA methylation panel and chromosomal microarray.

Treatment

Wilms tumor is a type of solid tumor in which the best response to treatment can be observed. The therapy implemented in Poland is based on the European strategy according to the SIOP-RTSG (Renal Tumour Study Group of the International Society of Pediatric Oncology) and includes combination therapy with induction (preoperative) and postoperative chemotherapy, surgery and radiotherapy in selected clinical situations [17]. The following agents are used in chemotherapy: vincristine, actinomycin D, doxorubicin, cyclophosphamide, carboblatin and vepesid. Autologous haematopoietic stem cell transplantation remains a salvage treatment for patients not responding to standard therapy or who have relapsed with WT. The American strategy, according to the Children's Oncology Group (COG), begins with the surgical removal of the tumor with the kidney and ureter. COG suggests that only the initiation of the treatment with surgery allows precise assessment of the local advancement stage and the histopathological type of the tumor, which is crucial for the selection of the type and intensity of postoperative treatment. The treatment results in both groups are comparable [18].

Prognosis

Outcomes of treatment in patients with Wilms tumor are very good, but there are still subgroups with poor prognosis and increased relapse rates, especially in the blastemic and disseminated anaplasia types. The identification of these subgroups is extremely important in improving treatment outcomes, and can reduce the early and late complications of chemotherapy. The results of molecular research and targeted therapy are promising. The curability rate for patients with localized disease is 85%. In stage IV, HR usually reaches 50–60% [16, 19]. For 5 years after the end of treatment, regular clinical check-ups are performed at increasing intervals, the most intensive ones shortly after the end of treatment.

Nephrological care of children with Wilms tumor

In children with suspected WT, renal function blood tests, urinalysis, urine culture and blood pressure measurements should be performed. Any abnormalities found must be taken into account in the therapy of the neoplastic disease.

Wilms tumor survivors have increased risk of chronic kidney disease (CKD). In the National Wilms Tumor Study (NWTS), the 20-year cumulative overall incidence of kidney failure, the most advanced stage of CKD, was 1.3% for unilateral WT patients and 15% for bilateral WT [20]. Nephrectomy, radiation, and nephrotoxic chemotherapy are each associated with a potential increased risk of CKD [21, 22]. Moreover, significantly higher rates of kidney failure were found among WT patients with associated syndromes or genitourinary anomalies due to constitutional *WT1* pathogenic variants [23, 24]. It has been reported that 74% of Denys-Drash patients, 36% of WAGR patients, and 7% of hypospadias or cryptorchidism patients had kidney failure after 20 years of follow-up, compared with only about 1% of non-syndromic children [20]. Therefore, prior knowledge of the presence of a constitutional *WT1* pathogenic variant and its subtype may have important implications in predicting the risk and rate of deteriorating function of the remaining nephrons [25, 26]. On the other hand, Falcone et al. [27] described long-term kidney function in 25 children with WT and *WT1* pathogenic variants and noted kidney survival in 72% of them at median follow-up of 9 years. Only 28% of patients required hemodialysis at 5.6 years (median; range: 0–16) after WT diagnosis. The observations may be useful for making a decision between either a complete resection of WT to optimize tumor control, or the performing of nephron-sparing surgery to preserve kidney function.

The above data indicate that survivors of WT should be monitored, not only by oncologists but also by nephrologists, to preserve kidney function or slow down CKD progression. Chu et al. [28], based on the findings of their study, recommend annual outpatient visits with blood tests for kidney function and electrolytes, urinalysis and a blood pressure check. They also suggest screening with 24-hour ambulatory pressure monitoring (ABPM). A study of 32 WT survivors (without genetic syndromes associated with WT, median age 13.5 years), at a median of 8.7 years after completion of treatment showed an estimated glomerular filtration rate (eGFR) <90 ml/min/1.73 m^2 in 34% of patients, abnormal urinary

epidermal growth factor/creatinine ratio in 69% and elevated casual blood pressure in 53% of participants. In addition, any ABPM abnormality was found in up to 76% of children. In another study performed on 40 adults after treatment for unilateral non-syndromic WT without radiation (an average of 28.8 years of age and 26.9 years post-diagnosis of WT) and with radiation (an average of 33.7 years and 30.1 years, respectively), without exposition to nephrotoxic chemotherapy, renal function was not significantly impaired [29]. Nobody had an eGFR below 60 ml/min/1.73 m^2 based on serum creatinine only or on serum creatinine and cystatin C. Hypertension was identified in 25% of un-irradiated survivors and in 35% of irradiated WT survivors. It was more prevalent in patients treated with nephrectomy, regardless of radiation status, suggesting that nephrectomy contributes to its pathogenesis.

To sum up, currently it is not entirely clear which factors may indicate a higher risk of deterioration of kidney function in patients treated for WT. Survival of WT has improved in the last few decades due to advances in treatment. As a result, current management of WT patients should focus more on preventing chronic kidney disease and optimizing long-term health. Wilms tumor survivors require monitoring of renal function, urine tests, abdominal ultrasonography and blood pressure measurements, as well as the elimination of conditions that may impair renal function. Further research on the clinical and genetic determinants of the disease's course is needed to personalize and optimize therapy.

Conflict of interest: none declared

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Received: 23 May 2022
Accepted: 7 Jun 2022

References

1. Bhutani N, Kajal P, Sharma U. Many faces of Wilms Tumor: Recent advances and future directions. Ann Med Surg (Lond). 2021; 64: 102202, doi: 10.1016/j.amsu.2021.102202, indexed in Pubmed: 33747498.
2. Nelson MV, van den Heuvel-Eibrink MM, Graf N, et al. New approaches to risk stratification for Wilms tumor. Curr Opin Pediatr. 2021; 33(1): 40–48, doi: 10.1097/MOP.0000000000000988, indexed in Pubmed: 33394739.
3. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006; 56(2): 106–130, doi: 10.3322/canjclin.56.2.106, indexed in Pubmed: 16514137.
4. van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, et al. International Society of Paediatric Oncology — Renal Tumour Study Group (SIOP–RTSG). Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol. 2017; 14(12): 743–752, doi: 10.1038/nrurol.2017.163, indexed in Pubmed: 29089605.
5. Han Q, Li K, Dong K, et al. Clinical features, treatment, and outcomes of bilateral Wilms' tumor: A systematic review and meta-analysis. J Pediatr Surg. 2018; 53(12): 2465–2469, doi: 10.1016/j.jpedsurg.2018.08.022, indexed in Pubmed: 30274708.
6. Ruteshouser EC, Huff V. Familial Wilms tumor. Am J Med Genet C Semin Med Genet. 2004; 129C(1): 29–34, doi: 10.1002/ajmg.c.30025, indexed in Pubmed: 15264270.
7. Dumoucel S, Gauthier-Villars M, Stoppa-Lyonnet D, et al. Malformations, genetic abnormalities, and Wilms tumor. Pediatr Blood Cancer. 2014; 61(1): 140–144, doi: 10.1002/pbc.24709, indexed in Pubmed: 23970395.
8. Seseke F, Gutjahr P, Kremens B. [Wilms tumor]. Urologe A. 2006; 45 Suppl 4: 235–238, doi: 10.1007/s00120-006-1199-z, indexed in Pubmed: 16933117.
9. Irtan S, Ehrlich PF, Pritchard-Jones K. Wilms tumor: „State-of-the-art" update, 2016. Semin Pediatr Surg. 2016; 25(5): 250–256, doi: 10.1053/j.sempedsurg.2016.09.003, indexed in Pubmed: 27955727.
10. Siegel MJ, Chung EM. Wilms' tumor and other pediatric renal masses. Magn Reson Imaging Clin N Am. 2008; 16(3): 479–97, vi, doi: 10.1016/j.mric.2008.04.009, indexed in Pubmed: 18585600.
11. Watson T, Oostveen M, Rogers H, et al. The role of imaging in the initial investigation of paediatric renal tumours. Lancet Child Adolesc Health. 2020; 4(3): 232–241, doi: 10.1016/s2352-4642(19)30340-2.
12. Janeczko M, Niedzielska E, Pietras W. Evaluation of Renal Function in Pediatric Patients After Treatment for Wilms' Tumor. Adv Clin Exp Med. 2015; 24(3): 497–504, doi: 10.17219/acem/43768, indexed in Pubmed: 26467140.
13. Davidoff A. Wilms' tumor. Curr Opin Pediatr. 2009; 21(3): 357–364, doi: 10.1097/mop.0b013e32832b323a.
14. Termuhlen AM, Tersak JM, Liu Qi, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2011; 57(7): 1210–1216, doi: 10.1002/pbc.23090, indexed in Pubmed: 21384541.
15. Deng C, Dai R, Li X, et al. Genetic variation frequencies in Wilms' tumor: A meta-analysis and systematic review. Cancer Sci. 2016; 107(5): 690–699, doi: 10.1111/cas.12910, indexed in Pubmed: 26892980.
16. Vujanić GM, Gessler M, Ooms AH, et al. International Society of Paediatric Oncology–Renal Tumour Study Group (SIOP–RTSG). The UMBRELLA SIOP-RTSG 2016 Wilms tumour pathology and molecular biology protocol. Nat Rev Urol. 2018; 15(11): 693–701, doi: 10.1038/s41585-018-0100-3, indexed in Pubmed: 30310143.
17. Pietras W. Advances and changes in the treatment of children with nephroblastoma. Adv Clin Exp Med. 2012; 21(6): 809–820, indexed in Pubmed: 23457141.
18. Chen H, Yang S, Qian C. Effectiveness of Nephron Sparing Surgery and Radical Nephrectomy in the Management of Unilateral Wilms Tumor: A Meta-Analysis. Front Oncol. 2020; 10: 1248, doi: 10.3389/fonc.2020.01248, indexed in Pubmed: 33014769.
19. Groenendijk A, Spreafico F, de Krijger RR, et al. Prognostic Factors for Wilms Tumor Recurrence: A Review of the Literature. Cancers (Basel). 2021; 13(13), doi: 10.3390/cancers13133142, indexed in Pubmed: 34201787.
20. Breslow NE, Collins AJ, Ritchey ML, et al. End stage renal disease in patients with Wilms tumor: results from the National Wilms Tumor Study Group and the United States Renal Data System. J Urol. 2005; 174(5): 1972–1975, doi: 10.1097/01.ju.0000176800.00994.3a, indexed in Pubmed: 16217371.
21. Interiano RB, Delos Santos N, Huang S, et al. Renal function in survivors of nonsyndromic Wilms tumor treated with unilateral radical nephrectomy. Cancer. 2015; 121(14): 2449–2456, doi: 10.1002/cncr.29373, indexed in Pubmed: 25832759.
22. Daw NC, Gregornik D, Rodman J, et al. Renal function after ifosfamide, carboplatin and etoposide (ICE) chemotherapy, nephrectomy and radiotherapy in children with Wilms tumour. Eur J Cancer. 2009; 45(1): 99–106, doi: 10.1016/j.ejca.2008.09.017, indexed in Pubmed: 18996004.
23. Diller L, Ghahremani M, Morgan J, et al. Constitutional WT1 mutations in Wilms' tumor patients. J Clin Oncol. 1998; 16(11): 3634–3640, doi: 10.1200/JCO.1998.16.11.3634, indexed in Pubmed: 9817285.
24. Scott RH, Stiller CA, Walker L, et al. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet. 2006; 43(9): 705–715, doi: 10.1136/jmg.2006.041723, indexed in Pubmed: 16690728.
25. Wilde JCH, Godzinski J, Heij H, et al. Nephron sparing surgery (NSS) for unilateral wilms tumor (UWT): the SIOP 2001 experience. Pediatr Blood Cancer. 2014; 61(12): 2175–2179, doi: 10.1002/pbc.25185, indexed in Pubmed: 25156758.
26. Cost NG, Sawicz-Birkowska K, Kajbafzadeh AM, et al. A comparison of renal function outcomes after nephron-sparing surgery and radical nephrectomy for nonsyndromic unilateral Wilms tumor. Urology. 2014; 83(6): 1388–1393, doi: 10.1016/j.urology.2014.01.051, indexed in Pubmed: 24768019.

27. Falcone MP, Pritchard-Jones K, Brok J, et al. Long-term kidney function in children with Wilms tumour and constitutional WT1 pathogenic variant. Pediatr Nephrol. 2022; 37(4): 821–832, doi: 10.1007/s00467-021-05125-5, indexed in Pubmed: 34608521.
28. Chu DI, Ehlayel AM, Ginsberg JP, et al. Kidney Outcomes and Hypertension in Survivors of Wilms Tumor: A Prospective Cohort Study. J Pediatr. 2021; 230: 215–220.e1, doi: 10.1016/j.jpeds.2020.12.005, indexed in Pubmed: 33290810.
29. Green DM, Wang M, Krasin MJ, et al. Long-term renal function after treatment for unilateral, nonsyndromic Wilms tumor. A report from the St. Jude Lifetime Cohort Study. Pediatr Blood Cancer. 2020; 67(10): e28271, doi: 10.1002/pbc.28271, indexed in Pubmed: 32706494.

VIA MEDICA

Varia

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 303–311

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Dostosowanie zgody pacjenta na znieczulenie do standardu prostego języka

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Wprowadzenie. W artykule opisujemy proces redagowania i walidacji dokumentów, na podstawie których pacjent wyraża świadomą zgodę na znieczulenie przed operacją. Naszym celem było dostosowanie takiej dokumentacji do standardu prostego języka, dzięki czemu będą one przystępne dla przeciętnego pacjenta.
Materiał i metody. Stworzyliśmy dwa dokumenty: *Informacja o znieczuleniu* i *Zgoda na znieczulenie*. W procesie redagowania wykorzystaliśmy opracowane dla języka polskiego zasady prostej polszczyzny.
Wyniki. Zebraliśmy dostępne w polskich placówkach medycznych analogiczne dokumenty. Do walidacji porównywanych tekstów wykorzystaliśmy nową w Polsce formułę *readability*: Plain Language Index. Algorytm ten mierzy 10 cech stylu i na tej podstawie ocenia w procentach prostotę tekstu.
Wnioski. Oba zaprojektowane przez nas dokumenty osiągnęły normę prostego języka (PLI 50% i więcej). Okazały się też najprzystępniejsze ze wszystkich badanych tekstów.

Słowa kluczowe: prosty język, czytelność, świadoma zgoda, znieczulenie

Wprowadzenie

Problem jakości informacji udzielanych pacjentowi jest dość często poruszany w orzecznictwie polskiego Sądu Najwyższego [1–5]. W artykule tym omawiamy językowy aspekt dokumentów, na podstawie których dorosły pacjent wyraża świadomą zgodę na znieczulenie do planowej operacji. Naszym celem jest opracowanie i zweryfikowanie dokumentacji spełniającej wymagania międzynarodowego standardu prostego języka (w momencie powstawania tego tekstu niemal gotowa była norma ISO określająca standard prostego języka: https://www.iso.org/standard/78907.html).

Przegląd literatury

W ochronie zdrowia świadoma zgoda jest dokumentem ważnym zarówno dla nadawcy, jak i odbiorcy. Dobrze poinformowani pacjenci dokonują świadomych wyborów w zakresie własnego zdrowia. Mają też bardziej realistyczne oczekiwania, większą satysfakcję po zabiegu, a ponadto wykazują się lepszą współpracą w trakcie leczenia [6]. Z drugiej strony, wysokie koszty ubezpieczenia od potencjalnych błędów wymuszają na placówkach świadczących usługi medyczne precyzyjne i skuteczne poinformowanie pacjentów o procedurze medycznej, która związana jest z ryzykiem wystąpienia powikłań zdrowotnych.

Z tego powodu w wielu krajach urzędy odpowiedzialne za służbę zdrowia tworzą standardy redagowania świadomych zgód [7–9]. W innych krajach to przepisy prawa narzucają dostosowanie języka informacji medycznych do poziomu wykształcenia przeciętnego obywatela, zwykle na poziomie 6–8 lat edukacji [10]. Wobec tego uzasadnione wydaje się także przygotowanie

Jak cytować / How to cite:
Romanik W, Piekot T, Tymiński R. ***Adaptation of informed consent for anaesthesia to plain language standard.*** *NOWOTWORY J Oncol* 2022; 72: 265–273.

tych informacji w języku polskim w sposób, który umożliwi ich zrozumienie przez jak najszersze grono pacjentów.

Niestety, badania z zakresu *health literacy* wskazują, że umiejętność rozumienia informacji medycznych jest w wielu krajach słaba lub zbyt zróżnicowana. Badania WHO w Europie wykazały, że w 10 krajach odsetek osób z nieodpowiednim lub problematycznym poziomem kompetencji czytelniczych mieści się w przedziale między 30% (Niderlandy) a 60% (Bułgaria) – średnia to ok. 48% [11].

Niski poziom *health literacy* w populacji nie jest jedynym problemem. Powszechnie przyjmuje się, że niezrozumiałość świadomych zgód wynika także ze sposobu ich przygotowania jako dokumentów dla pacjentów [12]. Badania potwierdzają, że świadome zgody mają bardzo niski poziom *readability* [13–15], nie przekazują wszystkich wymaganych informacji (zwłaszcza w zakresie ryzyka) [16], a sami pacjenci tuż po ich lekturze są z informacji zadowoleni, ale niewiele z treści pamiętają [17–18]. Trudny język, rozwlekłość i zła kompozycja powodują, że pacjentom brakuje motywacji do wnikliwej lektury [19]. W pewnym stopniu skuteczna okazuje się zmiana semiotycznej postaci dokumentu, czyli odejście od formy werbalnej na rzecz komunikacji multimedialnej, a zwłaszcza wizualnej [20].

W artykule tym opisujemy proces redagowania i walidacji polskojęzycznych dokumentów, które przekazują pacjentowi wymagane informacje medyczne, zgodnie ze standardem prostego języka, tzn. przystępnie i w sposób ustrukturyzowany. Zakładamy przy tym, że tego typu teksty powinny być zrozumiałe dla przeciętnego w sensie statystycznym pacjenta [21].

Kontekst prawny

Przepisy polskiego prawa przewidują konieczność udzielenia przez pacjenta zgody na wykonanie świadczenia zdrowotnego, choć wskazują również, że formy tej zgody mogą być różne: pisemna, ustna, a nawet dorozumiana [22]. W przypadku zabiegów operacyjnych oraz zabiegów o podwyższonym ryzyku prawo nakazuje uzyskać od pacjenta zgodę pisemną [23].

W praktyce medyczno-prawnej nie budzi wątpliwości, że zgoda pacjenta na znieczulenie do zabiegu wymaga formy pisemnej. Stanowisko to wynika z treści przepisów rozporządzenia Ministra Zdrowia z 16 grudnia 2016 r. w sprawie standardu organizacyjnego opieki zdrowotnej w dziedzinie anestezjologii i intensywnej terapii, które nakazują dołączenie do historii choroby „dokumentu zawierającego zgodę pacjenta na znieczulenie" [24]. Stąd konieczne jest sporządzanie dokumentów zgody na znieczulenie.

Co więcej – przepisy polskiego prawa w pewnym stopniu precyzują wymogi, którymi musi cechować się zgoda pacjenta, żeby zostać uznaną za prawnie skuteczną. I tak, na podstawie analizy sfery *de lege lata* można stwierdzić, że zgoda jest skuteczna, jeżeli pacjent:

- jest osobą uprawnioną do jej wyrażenia,
- wyraził ją przed zabiegiem, którego zgoda dotyczy,
- wyraził ją świadomie,
- wyraził ją w sytuacji umożliwiającej swobodne powzięcie decyzji [25–26].

W rozważaniach istotnych z punktu widzenia tematyki naszego artykułu szczególnie istotny jest aspekt świadomości pacjenta, który został sprecyzowany prawnie. Jak bowiem wynika z przepisów prawa, przed wyrażeniem zgody pacjent musi być poinformowany o „rozpoznaniu, proponowanych oraz możliwych metodach diagnostycznych i leczniczych, dających się przewidzieć następstwach ich zastosowania albo zaniechania, wynikach leczenia oraz rokowaniu" [27–28].

Co istotne, przepisy wprost statuują także wymóg sformułowana zgody w sposób przystępny [27–28]. Prawidłowe poinformowanie pacjenta przed zabiegiem ma pierwszorzędne znaczenie, ponieważ w orzecznictwie sądowym podkreśla się, że sama aprobata pacjenta dotycząca dokonania zabiegu, uzyskana w sytuacji braku uprzedniego udzielenia mu przystępnej informacji, nie może być traktowana jako zgoda w rozumieniu art. 32 i 34 ustawy z 1996 r. o zawodzie lekarza i dentysty [3, 29].

Pojęcie „przystępności" informacji nie doczekało się jak dotąd szerszych rozważań w piśmiennictwie prawniczym, choć większość autorów podkreśla, że chodzi o sposób przekazania informacji przez lekarza, który musi być dostosowany do konkretnego odbiorcy, znajdującego się w określonej sytuacji zdrowotnej [26, 30]. Ważne jest bowiem to, żeby pacjent przekazaną mu informację zrozumiał. Tym samym, przedstawiając informację, lekarz powinien uwzględnić nie tylko stan zdrowia pacjenta (np. wpływ bólu na świadomość pacjenta), lecz także jego wykształcenie, stan psychiczny czy też rodzaj i charakter zabiegu [26, 30].

Mając powyższe na uwadze, wyszliśmy z założenia, że sednem obowiązku informowania pacjenta przed procedurą medyczną jest uzyskanie przez pacjenta świadomości co do jej: potrzeby, przebiegu, ryzyka i możliwych alternatyw. Zgodnie jednak z wytycznymi formułowanymi w piśmiennictwie prawniczym, „wszelkie informacje pozyskane do celu przygotowania formularzy, powinny być przetworzone tak, aby były one zrozumiałe, nawet dla osoby posiadającej ograniczoną wiedzę, medyczną, biologiczną, fizyczną itd." [31].

Mamy przy tym świadomość, że nawet najlepiej napisane dokumenty nie są w stanie zastąpić rozmowy lekarza z pacjentem, mają za to jednak znaczenie dowodowe, tj. wykazują zakres informacji, które zostały pacjentowi udzielony.

Kontekst anestezjologiczny

Znieczulenie wymagane jest do przeprowadzenia wielu zabiegów operacyjnych. Przed każdą operacją odbywa się standardowo konsultacja anestezjologiczna, której celem jest kwalifikacja pacjenta do znieczulenia. Przed rozmową z anestezjologiem, pacjent wypełnia ankietę dotyczącą stanu zdrowia oraz zapoznaje się z pisemną informacją o znieczuleniu. Rozmowa z lekarzem kończy się zazwyczaj podpisaniem przez pacjenta zgody na ustalony sposób znieczulenia.

Opisana procedura stanowiąca szkielet standardowego postępowania przedoperacyjnego może być w dużym stop-

niu oraz w wielu punktach modyfikowana i dostosowywana do potrzeb i charakterystyki danego podmiotu medycznego. W związku z tym zarówno ankieta, informacja, jak i sam formularz świadomej zgody są często opracowywane przez poszczególne jednostki. Niemniej wspólnym mianownikiem tych dokumentów jest specjalistyczne słownictwo oraz związane z nim zagadnienia medyczne.

Ze względu na założony cel, należy ustrukturalizować w świadomości pacjenta przekazywane informacje o znieczuleniu przez czytelne tytułowanie kolejnych akapitów, ich logiczne powiązanie i spójność wywodu. Piszemy o tym w dalszej części artykułu. W informacji o rodzajach znieczulenia, należy zrezygnować np. z drobiazgowego tłumaczenia różnicy pomiędzy znieczuleniem podpajęczynówkowym i zewnątrzoponowym. Od strony pacjenta opis wykonania obu znieczuleń jest podobny, co dotyczy również znacznej liczby możliwych powikłań. Jeśli anestezjolog przewiduje możliwość wykonania danego znieczulenia, w czasie obligatoryjnej rozmowy powinien dokładnie zaznajomić pacjenta ze szczegółami wybranej procedury. Szczegółowe opisywanie przebiegu obu wymienionych wyżej rodzajów znieczulenia znacznie ogranicza możliwość zrozumienia i na tym etapie wydaje się niepotrzebne.

Brak zrozumienia staje się zauważalny, gdy podany tekst „zmusza" pacjenta do interakcji. Dzieje się tak np. w przypadku wypełniania ankiety medycznej. Wielokrotnie można spotkać się z brakiem odpowiedzi, zaznaczeniem fałszywej informacji czy błędnym zrozumieniem poleceń. Takie sytuacje jednoznacznie pokazują konieczność rozmowy lekarza z pacjentem i wyjaśnienia problematycznych fragmentów przed podpisaniem zgody na działania anestezjologiczne.

Z naszej praktyki wynika, że najtrudniejszą do zrozumienia dla odbiorcy częścią informacji o znieczuleniu jest opis ryzyka, w tym lista możliwych powikłań i działań niepożądanych. Bardzo trudno wytłumaczyć laikowi wiele zwrotów medycznych, nie uciekając się do złożonych opisów. Poza tym liczba możliwych powikłań, stopień ich wpływu na stan zdrowia oraz prawdopodobieństwo wystąpienia stawiają przed projektantami dokumentacji kolejne wyzwania. Co więcej, podczas znieczulenia używanych jest wiele leków, z których każdy posiada własną listę działań niepożądanych. Oznacza to, że niemożliwe jest zapoznanie i wytłumaczenie pacjentowi każdego możliwego powikłania [32].

Zaleceniem godnym uwagi, wskazywanym przez praktyków, jest ujmowanie stopnia prawdopodobieństwa wystąpienia powikłań w postaci procentowej lub ułamkowej [33]. Niektóre podręczniki czy broszury anestezjologiczne idą krok dalej – poza oceną procentową, podają sytuacje z życia, które odpowiadają danej wartości, np. jedna osoba na duże miasto, szansa wyrzucenia szóstki przy rzucie kostką, szansa wylosowania nagrody w loterii. Nie do przecenienia jest dodawanie w tym aspekcie infografik, które zwiększają możliwości zrozumienia tekstu [34].

Raz jeszcze podkreślamy, że informacja pisemna pozostaje tylko narzędziem, dzięki któremu stopień uświadomienia pacjenta może być wyższy. Niezbędny jest jednak osobisty kontakt lekarza z pacjentem. Biorąc pod uwagę wyżej wspomniane problemy, wydaje się, że kluczem do ich rozwiązania jest rozmowa anestezjologa z pacjentem. Rozmowa zindywidualizowana, w trakcie której jest czas na analizę odpowiedzi z ankiety, czas na zadanie pytań przez pacjenta, czas na udzielenie wyjaśnień oraz czas na dobranie optymalnej formy znieczulenia dla konkretnej osoby i danego zabiegu. Dobrze skonstruowana informacja o znieczuleniu jest punktem wyjścia do rozmowy z pacjentem, który może zadać pytania adekwatne do swoich indywidualnych cech osobowościowych, stanu zdrowia i potrzeb poznawczych. Zadanie przedstawienia ostatecznych informacji, zwłaszcza odnośnie do rodzaju znieczulenia i jego ryzyka, pozostaje w gestii anestezjologa, który zapoznał się ze stanem jego zdrowia, historią medyczną oraz badaniami dodatkowymi [35].

Od sprawności komunikacyjnej lekarza, od jego doświadczenia, od czasu, który poświęci na rozmowę z pacjentem zależy to, w jakim stopniu ten pacjent będzie miał poczucie zaspokojenia potrzeby informacji, potrzeby bezpieczeństwa, potrzeb emocjonalnych i poczucia kontroli. Lekarz powinien także pamiętać, że pozawerbalne elementy budujące relację z pacjentem, tj. dystans, pozycja ciała, spojrzenia, dotyk, gesty i mimika, mają niebagatelny wpływ na poczucie zrozumienia i szacunku, przekonanie o kompetencji lekarza oraz zaufanie do zaproponowanego leczenia [36].

Materiał i metody

Wstępne założenia

Naszym celem było zaprojektowanie i zredagowanie dokumentacji anestezjologicznej zgodnej z wymaganiami standardu prostego języka. Będzie ona adresowana do dorosłych pacjentów oczekujących na planową operację, posługujących się językiem polskim.

Przed rozpoczęciem prac redakcyjnych przyjęliśmy kilka istotnych założeń.

1. Dokumentacja tego typu powinna się składać z dwóch tekstów:
   - informacji – czyli opisu działań podejmowanych wobec pacjenta w związku ze znieczuleniem,
   - zgody – czyli formalnego oświadczenia woli, w którym pacjent potwierdza uzyskanie wszystkich podanych informacji i akceptuje proponowane działania anestezjologiczne.
2. Z projektowanej dokumentacji wyłączyliśmy ankietę medyczną, ponieważ nie ma ona charakteru ciągłego tekstu, co uniemożliwia przeprowadzenie wiarygodnych badań ilościowych.
3. Wynikające z przeglądu literatury wnioski skłoniły nas do zastosowania radykalnego podejścia językowego. Wyraża je przekonanie, że niewystarczające będzie skorzystanie z powszechnej w studiach z zakresu prostego języka i w praktyce medycznej metody upraszczania istniejącego tekstu [37–38]. Przeredagowywanie oryginału wywoła-

łoby efekt powierzchniowego tłumaczenia, a zatem nie rozwiązałoby problemów z nieudaną kompozycją tekstu czy przesadnie formalną relacją: lekarz–pacjent. Przygotowanie skutecznej świadomej zgody wymaga zaprojektowania tekstu od podstaw – z uwzględnieniem problemów strukturalnych i relacyjnych.

4. Ostatecznie zrezygnowaliśmy z kryterium wykształcenia jako czynnika weryfikującego komunikatywność języka opracowywanej dokumentacji. W Polsce odsetek osób z wykształceniem wyższym szybko rośnie, nie poprawiają się jednak dane dotyczące czytelnictwa. W 2009 roku w Polsce było 9,9% osób z wykształceniem wyższym, w 2011 – 16,8%, a w roku 2020 odsetek ten wynosił 39% (u osób w wieku 25–54). Mimo to czytelnictwo książek utrzymuje się od 2008 roku na tym samym poziomie (7 i więcej książek czyta 9–12% populacji) [39–41]. Rozbieżność taka stawia pod znakiem zapytania stosowane wzory oparte na wykształceniu, które w Polsce wydają się niezbyt wiarygodnym wskaźnikiem umiejętności czytania ze zrozumieniem.
5. Nowe dokumenty przygotowaliśmy zgodnie z modelem prostej polszczyzny opracowanym na Uniwersytecie Wrocławskim.

Metoda redagowania tekstu

Redagując tekst informacji oraz zgody, stosowaliśmy trzy strategie prostego języka. Każdej z nich podporządkowane były szczegółowe techniki redakcyjne. Metodę tę opracowała Pracownia Prostej Polszczyzny na Uniwersytecie Wrocławskim [42–43]. Stosują ją z powodzeniem nie tylko najważniejsze polskie urzędy, ale też banki, firmy ubezpieczeniowe, a nawet autorzy tekstów naukowych [44–45].

Strategia pierwsza polega na przygotowaniu tekstu do wielokrotnego przeglądania w poszukiwaniu potrzebnych informacji. Na tym poziomie wprowadziliśmy więc zasady efektywnej strukturyzacji tekstu, takie jak śródtytuły, wyliczenia w formie list, tabele itp.

Strategia druga polega na upodobnieniu gramatyki tekstu do tekstów najpopularniejszych, tzn. czytanych w czasie wolnym (np. popularne serwisy internetowe, dzienniki i tygodniki). Owa językowa akomodacja dotyczy przede wszystkim długości zdania i frekwencji form gramatycznych typu strona bierna, nominalizacja czy imiesłowy.

Strategia trzecia prowadzi do wzmocnienia relacyjnego wymiaru tekstu. Celowi temu służą zwroty bezpośrednie do czytelnika, użycie formy 1 os. l. mn. (my), a także różne zabiegi leksykalne, np. unikanie słownictwa urzędowego na rzecz codziennego czy użycie wyrażeń empatycznych.

Szczegółową listę technik redakcyjnych odpowiadającą poszczególnych strategiom prezentujemy w tabeli I. Zastosowane przez nas techniki ilustrujemy przykładami z tekstu.

Wyniki

Metoda walidacji dokumentów

Kolejnym etapem po zredagowaniu obu tekstów była weryfikacja przystępności ich języka. Użyliśmy do tego Plain Language Index (dalej: PLI), tj. wskaźnika, który ocenia, w ilu procentach

Tabela I. Strategie i techniki prostego języka zastosowane w trakcie redagowania nowych dokumentów

Strategia prostego języka	Techniki redagowania tekstu	Przykład
Tekst redaguj tak, by czytelnik mógł go łatwo przeglądać	1. Dokument rozpocznij od edukacyjnego wstępu.	*Niedługo masz operację. W tym dokumencie znajdziesz najważniejsze informacje o znieczuleniu. Przeczytaj go uważnie. Nie musisz wszystkiego zapamiętywać. Po prostu zachowaj ten dokument, by w razie potrzeby do niego zajrzeć. Miej go przy sobie w trakcie rozmowy z anestezjologiem.*
	2. Śródtytułom nadaj formę pytań.	*Co to jest znieczulenie?* *Kim jest anestezjolog?* *Jak się przygotować do spotkania?* *Jakie możesz mieć powikłania po transfuzji?*
	3. Złożone zdarzenia prezentuj jako chronologiczne procesy.	Treści w podrozdziale pt. *Jak wygląda znieczulenie ogólne?* podzieliliśmy na trzy etapy: *Przed operacją*, *W trakcie operacji*, *Po operacji*.
	4. Prozę zamieniaj na tabele.	W jednej tabeli porównaj powikłania po obu typach znieczulenia (porządkuj je prawdopodobieństwem występowania).
	5. Prozę zamieniaj na listy numerowane.	W informacji lista pojawia się średnio raz na stronę. Cały tekst zgody jest zredagowany w formie listy – z ciągłą numeracją.
Naśladuj gramatykę tekstów chętnie czytanych w czasie wolnym	6. Twórz krótkie zdania (poniżej 16 wyrazów). Jedną myśl zamykaj w jednym zdaniu.	*Zmyj makijaż. Nie nakładaj nowego. Nie nakładaj kremu na twarz ani na ręce. Zmyj lakier z paznokci.*
	7. Unikaj zjawisk gramatycznych typowych dla bezosobowych stylów formalnych (np. urzędowego).	*wyrazić zgodę -> zgodzić się* *w celu wybrania znieczulenia -> aby wybrać znieczulenie* *zostaniesz zawieziony -> pielęgniarka zawiezie Cię*
	8. Wzmacniaj spójność międzyzdaniową – pokazuj relacje logiczne (używaj zaimków, spójników, wyrazów nawiązujących).	*Niektóre drobne zabiegi i badania możemy wykonywać bez znieczulenia. Lekarze powiedzą Ci o takiej możliwości. Możesz wtedy wybrać, czy chcesz otrzymać znieczulenie. Większość zabiegów i operacji wymaga jednak znieczulenia.*

→

Tabela I. cd. Strategie i techniki prostego języka zastosowane w trakcie redagowania nowych dokumentów

Strategia prostego języka	Techniki redagowania tekstu	Przykład
Naśladuj gramatykę tekstów chętnie czytanych w czasie wolnym	9. Unikaj terminów medycznych lub je definiuj.	*Czasem w trakcie operacji możesz stracić dużo krwi. Trzeba Ci będzie wtedy zrobić transfuzję krwi (inaczej: przetoczenie krwi, podanie krwi). Transfuzja to wstrzyknięcie nowej krwi do żyły przez kroplówkę. Czasem wstrzykuje się też inne preparaty z krwi.*
	10. Unikaj terminów 2-wyrazowych o szyku rzeczownik + przymiotnik.	*W dniu operacji pielęgniarka zaprowadzi Cię na salę operacyjną. Może też zaproponować, że zawiezie Cię na wózku szpitalnym. Na sali operacyjnej położysz się na łóżku operacyjnym.* ->*W dniu operacji pielęgniarka zaprowadzi Cię na salę operacyjną. Może też zaproponować, że zawiezie Cię na szpitalnym wózku. Na sali położysz się na łóżku operacyjnym.*
Dbaj o relacje interpersonalne	11. Często zwracaj się do czytelnika bezpośrednio.	*Tuż przed operacją lekarz anestezjolog poda Ci do oddychania maskę tlenową. Od tej chwili rozpoczniesz przyjmowanie narkozy. Zaśniesz kilka chwil później. Lekarz włoży wtedy Ci przez usta rurkę do oddychania. Aparat do znieczulenia będzie oddychał za Ciebie. Otrzymasz konieczne lekarstwa.*
	12. Unikaj generycznego rodzaju męskiego. Pisz językiem neutralnym płciowo.	*będziesz potrzebował -> będą Ci potrzebne* *będziesz mógł wybrać -> będzie można wybrać* *nie będziesz niczego czuł -> nie będziesz niczego czuć*
	13. O swojej instytucji pisz per „my".	*Badania naukowe pokazują, że niektóre powikłania zdarzają się częściej, inne rzadziej, a niektóre bardzo rzadko. Opisujemy tu większość znanych powikłań. Nie robimy tego, by Cię przestraszyć. Po prostu chcielibyśmy Cię o nich uprzedzić.*
	14. Unikaj słownictwa formalnego (urzędowego).	*Jestem świadom, że reakcja mojego ciała na ww. znieczulenie jest nieprzewidywalna. ->* *Rozumiem, że nikt nie może przewidzieć reakcji mojego ciała na to znieczulenie.*
	15. Pisz szczerze i empatycznie.	*Gdyby Ci coś dolegało, powiedz o tym personelowi. Personel jest po to, aby przynieść Ci ulgę i opiekować się Tobą. Po pewnym czasie pielęgniarki zawiozą Cię na oddział chirurgiczny.*

badany tekst spełnia wymagania prostej polszczyzny. Wskaźnik PLI mierzy 10 cech stylu, przy czym osiągnięcie normy przez każdą cechę, oznacza przyznanie tekstowi 10 punktów procentowych. PLI ocenia teksty w języku polskim i dostępny jest w aplikacjach Logios (https://logios.dev/). Wynik procentowy PLI wyliczany jest na podstawie 10 cech stylu:

Dobór słów

1. Urzędyzmy (FORMAL) – parametr ten pokazuje, jak dużo jest w tekście wyrazów urzędowych. To one sprawiają, że styl staje się formalny i urzędowy.
2. Terminologizacja stylu (TERMS) – parametr ten pokazuje, jak dużo jest w tekście 2-wyrazowych wyrażeń specjalistycznych o szyku: rzeczownik + przymiotnik. To one sprawiają, że tekst staje się niezrozumiały dla nieprofesjonalisty.
3. Wyrazy najczęstsze (TOP100) – parametr ten oblicza, jak dużo jest w tekście słów najczęstszych (z listy frekwencyjnej 100 wyrazów). To one sprawiają, że tekst ma łatwą tematykę.
4. Wyrazy trudne (DWORDS) – parametr ten pokazuje, jak dużo jest w tekście słów rzadkich i jednocześnie długich. Ich obecność zwiększa mglistość języka.
5. Zaimkowość (PRON) – parametr ten mierzy w tekście odsetek zaimków. Wysoka frekwencja tej części mowy sprawia, że język jest naturalny, a tekst spójny.

Budowa zdań

6. Rzeczownikowość stylu (N/V) – parametr ten wskazuje, czy styl tekstu jest czasownikowy (cecha pożądana) czy rzeczownikowy (cecha niepożądana). Czasowniki są informacyjnym sercem zdania, więc w tekście powinno być ich jak najwięcej.
7. Nienaturalna gramatyka (GRAM) – parametr ten zlicza, ile nazw czynności występuje w tekście w postaci imiesłowów, strony biernej, rzeczowników odczasownikowych i form bezosobowych.
8. Długość zdania (ASL) – parametr ten oblicza średnią długość zdania, czyli liczbę wyrazów w zdaniu. W atrakcyjnych tekstach nie spotykamy zbyt wielu zdań dłuższych niż 15 wyrazów.

Relacje

9. Obecność nadawcy (SENDER) – parametr ten pokazuje, jak często nadawca ujawnia w tekście swoją obecność. Mogą to być zaimki (ja, mnie, nasz) lub czasowniki (proszę,

witam) pierwszej osoby. Im więcej nadawcy, tym tekst bardziej relacyjny.

10. Obecność odbiorcy (RECEIVER) – parametr ten pokazuje, jak często w tekście nadawca zwraca się bezpośrednio do odbiorcy. Mogą to być zaimki (Ty, Ciebie, Wasz, Pan, Pani) lub czasowniki (prześlij, weź) drugiej osoby. Im więcej takich zwrotów, tym tekst jest bardziej relacyjny.

Zredagowane przez nas tekst pod względem wskaźnika PLI i jego 10 składowych porównaliśmy z analogicznymi tekstami używanymi obecnie w Polsce w publicznych i niepublicznych placówkach medycznych. Za pomocą wyszukiwarki Google zebraliśmy 20 informacji edukacyjnych oraz 15 zgód. Jedną ze zgód wyłączyliśmy z badanej próby ze względu na niewystarczającą długość tekstu (poniżej 30 wyrazów). Ostatecznie zbadaliśmy więc 20 informacji i 14 zgód.

Wnioski

Informacja o znieczuleniu

Analiza przystępności informacji o znieczuleniu wskazuje, że obecnie używane teksty w niewielkim stopniu realizują standard prostego języka (tab. II). Wyrażona medianą typowa informacja uzyskuje 10% PLI, a najprostsza informacja o znieczuleniu: 28% PLI (Szpital 3). Zredagowany przez nas tekst osiągnął PLI na poziomie 50%, to akceptowalny poziom prostoty (który definiuje się na poziomie co najmniej 40%). W naszej wersji normy prostego języka osiągnęło pięć z dziesięciu cech: zaimkowość, stosunek rzeczowników do czasowników, nieprzystępna gramatyka i zwroty do czytelnika. Pozostałe cechy nie uzyskały wymaganych przez standard prostego języka wartości, choć wypadły dużo lepiej niż typowa informacja (wyrażona medianą wyliczoną dla badanych dokumentów).

Tabela II. Ranking przystępności informacji o znieczuleniu. Zestawienie zawiera Plain Language Index (PLI) i jego 10 składowych. Skróty w nagłówkach tabeli objaśnione są powyżej (część: Materiał i metody)

Tekst	PLI	FORMAL	TERMS	TOP100	DWORDS	PRON	N/V	GRAM	ASL	SENDER	RECEIVER
nasza wersja	50%	3,55%	39,40%	40,60%	8,42%	4,02%	1,61	16,60%	8,51	1,12%	10%
szpital 3	28%	9,07%	63,10%	30,70%	16,30%	1,05%	2,09	48,40%	17,1	0,26%	2%
szpital 1	24%	8,22%	53,40%	30,30%	15,40%	0,77%	2,41	49,70%	14,2	0,39%	2,57%
szpital 11	20%	7,46%	53,50%	32,30%	12,30%	1,22%	2,27	44,20%	18,6	1,37%	1,29%
szpital 2	20%	5,68%	47,10%	33,30%	14,50%	0%	2,09	40,90%	12,4	0,46%	0,68%
szpital 6	17%	7,98%	59%	26,90%	16,40%	0,50%	2,49	51,90%	15	0,82%	2,23%
szpital 9	17%	7,93%	54,50%	28,20%	17,90%	1,01%	2,16	48,30%	16,7	0%	0%
szpital 16	16%	8,72%	55,80%	28,70%	15,80%	0,54%	2,45	49,40%	16,9	0,86%	2,21%
szpital 4	15%	7,71%	52,10%	30,10%	13,60%	1,15%	2,51	46,50%	18,6	0%	0,53%
szpital 12	11%	8,60%	58,80%	30,90%	15,30%	0,46%	2,32	48%	15,1	0,53%	1,70%
szpital 17	10%	9,64%	53,20%	28,60%	18,10%	0,53%	2,02	52,10%	16,4	0,60%	0,30%
szpital 18	10%	12,30%	63,30%	24,70%	20,80%	1,39%	3,41	56,90%	16	0%	0%
szpital 10	6%	8,54%	56,90%	27,70%	15,10%	0,36%	2,48	46,50%	16	0,62%	0,41%
szpital 19	6%	9,90%	54%	27,60%	17,10%	0,17%	2,48	53,70%	15,7	0%	0,39%
szpital 20	6%	8,89%	58,50%	30,90%	14,10%	0,28%	2,44	50,80%	17,4	0,48%	0,64%
szpital 7	6%	6,69%	59,10%	29,80%	13%	0,55%	2,47	46,60%	18,7	0,63%	1,03%
szpital 8	5%	5,61%	57%	28,80%	13,30%	0,41%	2,52	40%	16,1	0,64%	0,48%
szpital 15	4%	7,93%	56,70%	27,10%	17,80%	0,18%	2,56	52,40%	19,7	0%	0,10%
szpital 14	3%	8,35%	49,50%	31,10%	15,80%	0,78%	2,71	52%	17,9	0,76%	1,39%
szpital 13	0%	6,46%	58%	28,20%	13,30%	0,53%	3,19	43,90%	19,9	0,12%	0,85%
szpital 5	0%	7,96%	61,70%	26,80%	15,20%	0,58%	2,98	56,40%	19,2	0,90%	0,11%
średnia	11,2%	8,2%	56,3%	29,1%	15,6%	0,6%	2,5	48,9%	16,9	0,5%	0,9%
mediana	10,0%	8,1%	56,8%	28,8%	15,4%	0,5%	2,5	48,9%	16,8	0,5%	0,7%

Dane w tabeli posortowaliśmy malejąco według wartości Plain Language Index (PLI). Przy naszej wersji tekstu informacji o znieczuleniu (pierwszy wers tabeli) wyróżniamy (podkreśleniem) wartości, które osiągnęły normy prostego języka. Średnia i mediana obliczone są dla porównywanych tekstów: szpital 1–szpital 20.

Tabela III. Ranking przystępności zgód na znieczulenie. Zestawienie zawiera Plain Language Index (PLI) i jego 10 składowych. Skróty w nagłówkach tabeli objaśnione są powyżej (część: Materiał i metody)

Placówka	PLI	FORMAL	TERMS	TOP100	DWORDS	PRON	N/V	GRAM	ASL	SENDER	RECEIVER
nasza wersja	50%	6,55%	24,00%	43,90%	10%	2,17%	1,95	34%	12,6	10,90%	0,87%
szpital 10	45%	14,10%	42,90%	33,80%	11,30%	3,53%	1,05	45,80%	14,2	12,70%	2,82%
szpital 9	43%	13,60%	28,60%	33,90%	13,60%	1,41%	0,818	39,10%	14,8	16,90%	0%
szpital 3	38%	8,25%	44,40%	39,20%	10,30%	3,54%	1,58	40,90%	13,6	9,28%	0%
szpital 12	36%	10,80%	33,30%	36,50%	16,20%	2,38%	1,73	57,90%	18,5	10,80%	0%
szpital 8	35%	9,03%	50%	33,30%	16%	2,37%	2,04	48,30%	14,1	9,03%	0%
szpital 1	30%	10,20%	46,70%	40,60%	14,20%	4%	1,15	37,80%	25,4	13,40%	0%
szpital 11	30%	13,70%	37,50%	36,60%	14,90%	2,53%	1,87	55,30%	21,1	7,43%	0%
szpital 13	30%	11,10%	52,90%	34,40%	19,40%	1,30%	1,65	55,20%	16,9	10,30%	0%
szpital 14	30%	11,70%	40%	41,70%	16,70%	3,55%	1	42,50%	17,1	15,80%	0%
szpital 6	30%	9,29%	41,20%	40,40%	14,20%	3,30%	1,43	42,60%	17,4	11,90%	0%
szpital 7	30%	9,33%	53,30%	42%	19,20%	3,03%	1,21	48,30%	17,5	13%	0%
szpital 2	27%	8,80%	60%	28%	22,40%	1,31%	2,43	59,30%	15,6	6,40%	0%
szpital 4	27%	11,60%	45,80%	33,50%	13,40%	1,02%	1,68	51,20%	18,2	10,40%	0%
szpital 5	27%	15,70%	52,40%	30,90%	21,90%	1,46%	2,38	56,40%	17,4	6,18%	0%
średnia	32,7%	11,2%	44,93%	36,06%	15,98%	2,48%	1,57	48,61%	17,27	10,97%	0,20%
mediana	30,0%	11,0%	45,1%	35,5%	15,5%	2,5%	1,62	48,3%	17,25	10,6%	0,0%

Dane w tabeli posortowaliśmy malejąco według wartości Plain Language Index (PLI). Przy naszej wersji tekstu zgody na znieczulenie (pierwszy wers tabeli) wyróżniamy (podkreśleniem) wartości, które osiągnęły normy prostego języka. Średnia i mediana obliczone są dla analizowanych tekstów: szpital 1–szpital 14.

Zgoda na znieczulenie

Różnice między analizowanymi tekstami zgód w porównaniu z tekstem naszej zgody nie są tak duże (tab. III). Wyrażona medianą przeciętna zgoda osiąga 30% PLI, jednak dwie najlepsze zgody uzyskały zadowalający poziom prostoty (PLI 40%), tj. 43% (szpital 9) i 45% (szpital 10). Opracowana przez nas zgoda znajduje się na pierwszym miejscu rankingu z wynikiem PLI 50%.

W porównaniu do informacji – nasza zgoda osiągnęła normy prostego języka w odniesieniu do terminologii i obecności nadawcy, a gorzej wypadła pod względem nieprzystępnej gramatyki i zwrotów do czytelnika. Różnice te są jednak wytłumaczalne. Tekst zgody jest oświadczeniem woli, a zatem podlega rygorowi formalnemu większemu od edukacyjnego tekstu informacji o znieczuleniu. Stąd prawie o połowę wyższy poziom nienaturalnej gramatyki (informacja: 16,6% GRAM, zgoda: 34% GRAM). Specyfiką gatunku należy też wyjaśnić niespełnienie norm relacyjnych zwrotów do czytelnika. Ponieważ wyrazicielem zgody jest sam pacjent, tekst jest pisany z perspektywy 1 os. lp. (ja). Nie jest zatem możliwe częste zwracanie się do pacjenta.

Dyskusja

Zredagowane zgodnie ze standardem prostego języka dokumenty anestezjologiczne okazały się wystarczająco przystępne. Co więcej, zarówno informacja, jak i zgoda uzyskały podobny poziom prostoty języka. W porównaniu z analizowanymi dokumentami używanymi obecnie przez polskie placówki medyczne udało nam się znacznie uprościć przede wszystkim tekst informacji o znieczuleniu (50% PLI *vs.* mediana analizowanych tekstów: 10% PLI). Różnica 40 p.p. PLI obiecuje dobrą skuteczność nowego tekstu.

Wysoka wartość Plain Language Index nie oznacza jednak, że są zredagowane przez nas teksty są zrozumiałe. Zrozumiałości, czy szerzej – skuteczności tego typu dokumentów nie da się badać bez użytkowników. Docenienie w pełni jego walorów będzie możliwe po weryfikacji klinicznej. Kolejnym etapem walidacji powinno być zatem przeprowadzenie testów z potencjalnymi oraz rzeczywistymi pacjentami. Przydatne mogłyby się tu okazać metoda odpamiętywania (przywoływania treści z pamięci) i testy zadaniowe.

Kolejnym etapem projektowania badanych dokumentów powinno być upełnienie tekstu informacji o inne kody semiotyczne typu infografika czy ilustracja, dobranie odpowiedniej wielkości i rodzaju czcionki, zastosowanie podkreśleń, wyróżnień, ramek oraz ostateczny układ graficzny. Połączenie naszego tekstu z wymienionymi komponentami wizualnymi powinno stać się przedmiotem odrębnych badań.

Osobnym celem powinno być radykalne uproszczenie opracowanych dokumentów tak, by były one zrozumiałe przez osoby ze specjalnymi potrzebami komunikacyjnymi. Mamy tu

na myśli chociażby afazję, demencję czy niepełnosprawność intelektualną. Zasady komunikacji z tak zróżnicowaną grupą odbiorczą reguluje odrębny standard (tzw. *easy language*), a w Polsce – ustawa o zapewnieniu dostępności [46]. Z tej perspektywy zarówno informacja, jak i zgoda powinny występować w dwóch wariantach. Pierwszym jest standard prostego języka, drugim zaś – języka łatwego.

Dokumenty służące uzyskaniu świadomej zgody powinny podlegać okresowej aktualizacji i weryfikacji przez kompetentne gremia interdyscyplinarne. Współcześnie medycyna rozwija się nie tylko na płaszczyźnie technicznej i merytorycznej (np. *evidenced based medicine* [EBM] – medycyna oparta na faktach), ale również pod względem komunikacji medycznej (np. świadomość istotnej wagi kompetencji miękkich) oraz holistycznego i indywidualnego podejścia do pacjenta (czego przykładami mogą być multidyscyplinarne zespoły Heart Teams), jak również organizacji opieki zdrowotnej (np. protokół kompleksowej opieki okołooperacyjnej dla poprawy wyników leczenia [*enhanced recovery after surgery* – ERAS]). Daje to nadzieję, zwłaszcza pacjentom i ich rodzinom, na lepsze efekty leczenia, wsparcie emocjonalne i wypełnienie luki informacyjnej.

Konflikt interesów: nie zgłoszono

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Otrzymano: 23 lutego 2022
Zaakceptowano: 16 Marca 2022

Piśmiennictwo

1. Wyrok SN z 18.01.2013. IV CSK 431/12. LEX nr 1275006.
2. Wyrok SN z 24.09.2015. V CSK 738/14. LEX nr 1796881.
3. Wyrok SN z 20.05.2016. II CSK 654/15. LEX nr 2067781.
4. Wyrok SN z 31.06.2017. V CSK 619/16. LEX nr 2389607.
5. Wyroki SN z 24.09.2020. IV CSK 49/19. LEX nr 3057399.
6. Kessler TM, Nachbur BH, Kessler W. Patients' perception of preoperative information by interactive computer program-exemplified by cholecystectomy. Patient Educ Couns. 2005; 59(2): 135–140, doi: 10.1016/j.pec.2004.10.009, indexed in Pubmed: 16257617.
7. Yentis SM, Yentis SM, Hartle AJ, et al. AAGBI: Consent for anaesthesia 2017: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2017; 72(1): 93–105, doi: 10.1111/anae.13762, indexed in Pubmed: 27988961.
8. ANZCA. PS26 Guidelines on Consent for Anaesthesia or Sedation: Australian and New Zealand College of Anaesthetists. 2005. http://www.anzca.edu.au/documents/ps26-2005-guidelineson-consent-for--anaesthesia-or (22.02.2022).
9. AANA. Informed consent for anesthesia care, policy and practice considerations: American Association of Nurse Anesthetists. 2016. http://www.aana.com/resources2/professionalpractice/Pages/Informed--Consent-for-Anesthesia-Care.aspx (30.05.2017).
10. Plain Language at AHRQ. 2022. https://www.ahrq.gov/policy/electronic/plain-writing/index.html (22.02.2022).
11. Europe, WHO. Health literacy—the solid facts. WHO Regional Office for Europe: Geneva, Switzerland. 2013. https://www.euro.who.int/__data/assets/pdf_file/0008/190655/e96854.pdf.
12. Foe G, Larson E. Reading Level and Comprehension of Research Consent Forms. J Empir Res Hum Res Ethics. 2016; 11(1): 31–46, doi: 10.1177/1556264616637483, indexed in Pubmed: 27106889.
13. Paasche-Orlow MK, Taylor HA, Brancati FL. Readability standards for informed-consent forms as compared with actual readability. N Engl J Med. 2003; 348(8): 721–726, doi: 10.1056/NEJMsa021212, indexed in Pubmed: 12594317.
14. Eltorai AEM, Naqvi SS, Ghanian S, et al. Readability of Invasive Procedure Consent Forms. Clin Transl Sci. 2015; 8(6): 830–833, doi: 10.1111/cts.12364, indexed in Pubmed: 26678039.
15. Hopper KD, TenHave TR, Tully DA, et al. The readability of currently used surgical/procedure consent forms in the United States. Surgery. 1998; 123(5): 496–503, doi: 10.1067/msy.1998.87236, indexed in Pubmed: 9591001.
16. Loughran D. Surgical consent: the world's largest Chinese Whisper? A review of current surgical consent practices. J Med Ethics. 2015; 41(2): 206–210, doi: 10.1136/medethics-2013-101931, indexed in Pubmed: 25205390.
17. Tait A, Voepel-Lewis T, Gauger V. Parental Recall of Anesthesia Information. Anesthesia & Analgesia. 2011; 112(4): 918–923, doi: 10.1213/ane.0b013e31820a9193.
18. Sherlock A, Sherlock A, Brownie S. Patients' recollection and understanding of informed consent: a literature review. ANZ J Surg. 2014; 84(4): 207–210, doi: 10.1111/ans.12555, indexed in Pubmed: 24812707.
19. Lavelle-Jones C, Byrne DJ, Rice P, et al. Factors affecting quality of informed consent. BMJ. 1993; 306(6882): 885–890, doi: 10.1136/bmj.306.6882.885, indexed in Pubmed: 8490411.
20. Nishimura A, Carey J, Erwin PJ, et al. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Med Ethics. 2013; 14: 28, doi: 10.1186/1472-6939-14-28, indexed in Pubmed: 23879694.
21. Schenker Y, Fernandez A, Sudore R, et al. Interventions to improve patient comprehension in informed consent for medical and surgical procedures: a systematic review. Med Decis Making. 2011; 31(1): 151–173, doi: 10.1177/0272989X10364247, indexed in Pubmed: 20357225.
22. Art. 17 ust. 1, ust. 4 ustawa z dnia 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta (t.j. Dz. U. z 2020 r., poz. 849 ze zm.).
23. Art. 18 ust. 1. ustawy z dnia 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta (t.j. Dz. U. z 2020 r., poz. 849 ze zm.).
24. § 9 pkt 8 rozporządzenia Ministra Zdrowia z dnia 16 grudnia 2016 r. w sprawie standardu organizacyjnego opieki zdrowotnej w dziedzinie anestezjologii i intensywnej terapii (t.j. Dz. U. z 2020 r. poz. 940 ze zm.).
25. Baron K. Zgoda pacjenta. Prokuratura i Prawo. 2010(9): 45.
26. Lis W. Zgoda pacjenta na czynność medyczną w polskim porządku prawnym. Zeszyty Naukowe KUL. 2020; 61(3): 39–58, doi: 10.31743/zn.2018.61.3.39-58.
27. Art. 18 ust. 2 ustawy z dnia 6 listopada 2008 r. o prawach pacjenta i Rzeczniku Praw Pacjenta (t.j. Dz. U. z 2020 r., poz. 849 ze zm.).
28. Art. 31 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (t.j. Dz. U. z 2021 r. poz. 790 ze zm.).
29. Wyrok SN z 16.05.2012. III CSK 227/11. LEX nr 1211885.
30. Tymiński R. Informacja lekarska w praktyce. Medycyna Praktyczna, Kraków 2012: 42.
31. Siwiec M. Formularz zgody pacjenta na udzielenie świadczenia zdrowotnego – zasady tworzenia. 2021. https://sip.lex.pl/komentarze--i-publikacje/komentarze-praktyczne/formularz-zgody-pacjenta-na-udzielenie-swiadczenia-470076460.
32. Dunn HP. Etyka dla lekarzy, pielęgniarek i pacjentów. Biblos, Tarnów 1997: 59.
33. Tymiński R. Zgoda na zabieg planowy pacjenta pełnoletniego, świadomego. 2020. https://prawalekarzy.pl/artykuly/zgoda-na-zabieg-planowy-pacjenta-pelnoletniego-swiadomego-420.
34. The Royal College of Anaesthetists. O znieczuleniu. 2020. https://rcoa.ac.uk/media/14486.
35. Jurgielaniec E. Jakie korzyści daje prawidłowo wyrażona zgoda i jak ją uzyskać. 2020. https://paragrafbezznieczulenia.pl/jakie-korzysci-daje-prawidlowo-wyrazona-zgoda-i-jak-ja-uzyskac/.
36. Barański J, Waszyński E, Steciwka A. Komunikowanie się lekarza z pacjentem. Astrum, Wrocław 2000: 90–91.
37. Zimmermann A, Pilarska A, Gaworska-Krzemińska A, et al. Written Informed Consent-Translating into Plain Language. A Pilot Study. Healthcare (Basel). 2021; 9(2), doi: 10.3390/healthcare9020232, indexed in Pubmed: 33672624.
38. Moroń E. (Świadoma) zgoda pacjenta. Jak realnie zwiększyć alfabetyzm zdrowotny w polskiej służbie zdrowia. Oblicza Komunikacji. 2020(12).

39. Czubkowska S. Wykształcenie Polaków: studia przestały być furtką do społecznego awansu. 2014. https://forsal.pl/artykuly/799385,wyksztalcenie-polakow-studia-przestaly-byc-furtka-do-spolecznego-awansu.html.
40. Bankier.pl. Coraz mniej osób kończy studia. Polska w połowie europejskiej stawki. 2021. https://www.bankier.pl/wiadomosc/Wyksztalcenie-wyzsze-w-2020-r-Polska-w-polowie-europejskiej-stawki-8142230.html.
41. Biblioteka Narodowa. Stan czytelnictwa w Polsce w 2020 roku. 2021. Pobrano z: bn.org.pl https://www.bn.org.pl/raporty-bn/stan-czytelnictwa-w-polsce/stan-czytelnictwa-w-polsce-w-2020-r.
42. Piekot T. W poszukiwaniu uniwersalnej metody upraszczania pism urzędowych i decyzji administracyjnych. Poznańskie Studia Polonistyczne. Seria Językoznawcza. 2021; 28(1): 109–122, doi: 10.14746/pspsj.2021.28.1.8.
43. Piekot T, Zarzeczny G. Upraszczanie tekstu użytkowego jako (współ) działanie. Perspektywa prostej polszczyzny. In: Niebrzegowska-Bartmińska S, Nowosad-Bakalarczyk M, Piekot T. ed. Działania na tekście. Przekład – redagowanie – ilustrowanie. Wydawnictwo UMCS, Lublin 2015: 99–116.
44. Wrzesień A, Piekot T, Wysocki W. Dlaczego artykuły naukowe warto pisać prostym językiem. Biuletyn PTO NOWOTWORY. 2021; 6(1): 78–79.
45. Wrzesień A, Piekot T, Wysocki WM. Językowa mgła w tekstach naukowych. Biuletyn PTO NOWOTWORY. 2021; 6(2): 157–159.
46. Ustawa z dnia 19 lipca 2019 roku o zapewnianiu dostępności osobom ze szczególnymi potrzebami (Dz.U. 2019, poz. 1696 z późn. zm.).

Z kalendarium Zarządu PTO

maj – czerwiec 2022

Wybrano nowy Zarząd Główny PTO na kadencję 2022–2026

Dwudziestego trzeciego czerwca 2022 r. w Warszawie odbyło się Walne Wyborcze Zgromadzenie Członków Polskiego Towarzystwa Onkologicznego. Udzielono absolutorium ustępującemu Zarządowi Głównemu kadencji 2018–2022 oraz wybrano – na kadencję 2022–2026 – nowy Zarząd Główny PTO, Redaktora Naczelnego czasopisma *Nowotwory. Journal of Oncology*, Główną Komisję Rewizyjną, a także Sąd Koleżeński.

Odchodzącym członkom Zarządu Głównego PTO składamy serdeczne podziękowania za działalność na rzecz Towarzystwa. W szczególności dziękujemy za zaangażowanie w ważne zmiany systemowe w opiece onkologicznej, uczestnictwo w dziesiątkach spotkań w Ministerstwie Zdrowia, parlamencie polskim i parlamencie europejskim, udział w licznych konferencjach, debatach organizowanych przez towarzystwa naukowe, związki lekarskie, organizacje pacjentów oraz media.

Docenienia wymagają wszelkie aktywności w postaci wystosowania setek pism w istotnych dla środowiska onkologicznego sprawach, w szczególności opiniowanie projektów ustaw i rozporządzeń związanych z onkologią. Nie mniej ważna dla ustępującego Zarządu była także współpraca międzynarodowa, m.in. w ramach inicjatywy iPAAC czy z Niemieckim Towarzystwem Onkologicznym. Ponadto, Zarząd kadencji 2018–2022 kontynuował tradycje naukowe PTO, realizując konferencje naukowe, w tym V Kongres Onkologii Polskiej, oraz publikując liczne raporty czy wydając zalecenia i rekomendacje. Dzięki tej działalności Polskie Towarzystwo Onkologiczne stało się znaczącym partnerem debaty publicznej i świata naukowego.

Źródło: www.pto.med.pl

Wywiady i artykuły

Kraska: ustawa o krajowej sieci onkologicznej od 1 stycznia 2023 roku

Minister Waldemar Kraska zapowiedział, że w planach jest uruchomienie w całym kraju od 1 stycznia 2023 r. pilotażu Sieci Onkologicznej, który działa już w kilku województwach – dolnośląskim, świętokrzyskim, podlaskim i pomorskim. – Krajowa Sieć Onkologiczna ma główny cel, aby w całym kraju, obojętnie gdzie mieszkamy, dostęp do leczenia onkologicznego była na takim samym, bardzo dobrym poziomie (...). Chcemy, aby ta terapia była od postawienia diagnozy po rehabilitację w jednym ośrodku, choć oczywiście nie zawsze się to udaje – podsumował wiceminister zdrowia.

Źródło: www.pulsmedycyny.pl

Międzynarodowy Onkologiczny Okrągły Stół: koordynacja to priorytet

Nie ma obecnie ważniejszego priorytetu niż wprowadzenie koordynacji w onkologii, która poprawi dostęp pacjentów do leczenia i opieki onkologicznej w całym kraju. A taki efekt może przynieść jedynie Krajowa Sieć Onkologiczna (KSO) – przetestowana, przygotowana do wdrożenia i przy tym rekomendowana przez UE koncepcja systemu onkologicznego – mówi prof. Adam Maciejczyk. Jak podkreśla uczestnik okrągłego stołu, prof. Adam Maciejczyk, dyrektor Dolnośląskiego Centrum Onkologii we Wrocławiu, najważniejszy, wskazany przez jego uczestników cel to wdrożenie Krajowej Sieci Onkologicznej, której istotnym zadaniem jest zapewnienie powszechnego dostępu do kompleksowej opieki onkologicznej. W tym celu konieczne będzie uruchamianie kolejnych unitów narządowych. – Główną osią KSO jest unifikacja standardów diagnostyki i leczenia onkologicznego oraz wdrożenie systemu monitorującego jakość tych działań. Wdrożenie KSO powinno być komplementarne do uruchamiania kolejnych unitów narządowych i te działania powinny być realizowane równolegle i konsekwentnie – wskazuje.

Źródło: www.cowzdrowiu.pl

Polską onkologię zapoczątkował Instytut Radowy

Dyrektor Narodowego Instytutu Onkologii (NIO), prof. Jan Walewski, przypomniał, że polską onkologię zapoczątkował Instytut Radowy w Warszawie, oficjalnie otwarty 29 maja 1932 r. W uroczystości tej uczestniczyła Maria Skłodowska-Curie, dla której był on spełnieniem marzeń. Dwukrotna polska noblistka przekazała wtedy instytutowi pierwszy gram radu o wartości ponad pół miliona ówczesnych złotych (ofiarowany przez kobiece stowarzyszenia polonijne w USA i Kanadzie). Instytut powstał dzięki ofiarom Polaków w kraju i za granicą. 9 marca 1923 r. Polski Komitet do Zwalczania Raka powołał Komitet Daru Narodowego im. Marii Skłodowskiej-Curie w celu zbudo-

wania Instytutu Radowego w Warszawie. W tym samym roku zwrócono się do społeczeństwa polskiego z apelem o składanie datków na budowę. – Od tego czasu zatrudniono cztery pokolenia pracowników instytutu, pierwsze było pionierskie, a jego gwiazdą była właśnie Maria Skłodowska-Curie – powiedział Dyrektor Narodowego Instytutu Onkologii. Drugie pokolenie dźwigało ośrodek ze zgliszcz wojennych. Już w listopadzie 1945 r. w Ministerstwie Zdrowia i Opieki Społecznej zapadła decyzja o odbudowie Instytutu Radowego w Warszawie. Jego działalność została wznowiona w 1947 r. – W kolejnych latach dostosowywano ośrodek do wymogów nowoczesnej nauki, a także potrzeb naszego społeczeństwa – zaznaczył prof. Jan Walewski.

Źródło: www.termedia.pl

Koordynacja, ośrodki specjalistyczne i profilaktyka potrzebne w onkologii

Przyszłością onkologii są wyspecjalizowane ośrodki, zapewniające pacjentom kompleksową opiekę i dostęp do nowoczesnych metod leczenia chorób nowotworowych. Konieczna jest ścisła współpraca wiodących, wielospecjalistycznych jednostek. Ważnym wyzwaniem jest nie tylko dobra organizacja i zarządzanie procesem terapii, ale także profilaktyka, edukacja pacjentów i sprawny system badań przesiewowych – to najważniejsze wnioski z dyskusji ekspertów podczas konferencji *Onkologia – w trosce o pacjenta – nowe terapie, nowe możliwości*. Dyrektor Dolnośląskiego Centrum Onkologii, Pulmonologii i Hematologii, prof. Adam Maciejczyk, zrelacjonował trudności przy zbieraniu danych do pilotażowego programu Krajowej Sieci Onkologicznej, a dyrektor USK, Jakub Berezowski, podkreślił ogromny potencjał szpitala w leczeniu chorób onkologicznych – W regionie jest miejsce zarówno dla dużego ośrodka onkologicznego, jak i dla onkologii w wielospecjalistycznym szpitalu, jakim jest USK.

Źródło: www.mzdrowie.pl

Więcej pacjentów i z bardziej zaawansowanymi nowotworami. Pandemia zwiększyła dług onkologiczny w Polsce

– Pandemia nie miała wpływu na zachorowalność na nowotwory, lecz na ich zgłaszalność. I teraz podstawowym problemem nowych pacjentów onkologicznych jest wydłużony czas oczekiwania na wstępną diagnostykę oraz rozpoczęcie leczenia, np. przy raku prostaty to aż dwa miesiące – mówi Adam Maciejczyk, dyrektor Dolnośląskiego Centrum Onkologii. W Dolnośląskim Centrum Onkologii, Pulmonologii i Hematologii, choć cały czas intensywnie działamy w celu zaopatrzenia jak największej liczby pacjentów onkologicznych, również nie jesteśmy w stanie w krótkim okresie nadrobić powstałych we wszystkich jednostkach zaległości. Obecnie pracujemy od rana do wieczora, często przez siedem dni w tygodniu. Bloki operacyjne działają do godziny 19. Zorganizowaliśmy dodatkowe przychodnie, a badania rezonansem magnetycznym odbywają się od godziny 6 do 23 przez sześć dni w tygodniu. W czasie pandemii ściśle monitorowaliśmy liczbę odwiedzających nasz szpital pacjentów. Liczba ta przekraczała 1600 osób dziennie. Obecnie pacjentów zgłasza się jeszcze więcej. To pokazuje poziom wyzwań, z którymi się codziennie mierzymy. Bardzo istotna w takiej sytuacji jest właściwa koordynacja i tu dużą rolę odgrywa onkologiczna infolinia, umożliwiająca pacjentowi sprawniejsze dotarcie do specjalisty.

Źródło: www.wroclaw.wyborcza.pl

Przybywa pacjentów onkologicznych z Ukrainy. Gdzie szukać pomocy?

Nawet o jedną czwartą wzrosła liczba pacjentek z nowotworem piersi w polskich szpitalach onkologicznych. To najczęściej kobiety, które uciekły przed wojną z Ukrainy. Wskazują na to dane Polskiego Towarzystwa Onkologicznego. Lekarze podkreślają, że uchodźcy z Ukrainy, którzy potrzebują leczenia, mogą korzystać ze specjalnych infolinii. Są dwie opcje: jedna to generalna infolinia Narodowego Funduszu Zdrowia, druga to infolinie ośrodków onkologicznych, gdzie w większości mamy osoby mówiące w językach ukraińskim i rosyjskim – podkreśla profesor Rutkowski. Główny problem to dostęp do dokumentacji medycznej i tłumaczenia, mamy oczywiście na szczęście tłumaczy, którzy pomagają, tłumaczą dokumenty. Wspierają nas psychoonkolodzy. Jest trudniej, bo pacjenci są w niesłychanie stresującej sytuacji. Nie jest to lawina nowych pacjentów, jest to dodatek kilkunastoprocentowy, a w raku piersi jest to jedna czwarta – dodaje profesor Piotr Rutkowski.

Źródło: www.twojezdrowie.rmf24.pl

Konferencje i wydarzenia

- 14 maja 2022 r. odbyła się konferencja naukowo-szkoleniowa *Rak stercza – wielodyscyplinarne podejście do terapii po niepowodzeniu leczenia miejscowego i w chorobie z przerzutami* z udziałem Adama Maciejczyka.
- 17 maja 2022 r. w Kielcach miała miejsce VI Ogólnopolska Konferencja *Ewidencja świadczeń zdrowotnych podstawą bezpieczeństwa prawno-finansowego placówki medycznej* pod patronatem Polskiego Towarzystwa Onkologicznego.
- W dniach 19–21 maja 2022 r. trwały obchody 75-lecia Instytutu Onkologii w Gliwicach.
- W dniach 20–21 maja 2022 r. pod patronatem Polskiego Towarzystwa Onkologicznego odbyły się I Zachodniopomorskie Dni Onkologiczne.
- W dniach 26–27 maja 2022 r. obchodzono 90-lecie Narodowego Instytutu Onkologii im. Marii Skłodowskiej-Curie – Państwowego Instytutu Badawczego w Warszawie.
- 30 maja 2022 r. Medyczna Racja Stanu zorganizowała debatę *Bezpieczeństwo Zdrowotne Polski – Nowe Wyzwania dla Idei Solidarności Europy.*
- W dniach 6–8 czerwca 2022 r. w Rzymie odbyła się konferencja *Polska i Włochy wobec kryzysów i wyzwań w sektorze ochrony zdrowia – praktyka i doświadczenia*. Uczestniczył w niej Adam Maciejczyk.

- 9 czerwca 2022 r. miało miejsce webinarium *Advances in therapy of non-melanoma skin cancers*, które prowadził Piotr Rutkowski.
- 20 czerwca 2022 r. odbyło się Forum Pacjentów Onkologicznych zorganizowane przez Polską Koalicję Pacjentów Onkologicznych.
- 21 czerwca 2022 r. redakcja *Dziennika Gazety Prawnej* zorganizowała debatę *Dług zdrowotny i co dalej?* z udziałem Adama Maciejczyka.
- 23 czerwca 2022 r. odbyła się konferencja *Onkologia precyzyjna w praktyce klinicznej* zorganizowana przez Narodowy Instytut Onkologii – Państwowy Instytut Badawczy w Warszawie oraz Polskie Towarzystwo Onkologiczne. Konferencja będzie miała charakter cykliczny.

VIA MEDICA

Journal Club

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 315–320

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer

Tie J., Cohen J., Phil M. i wsp.
Engl. J. Med., 2022; 386: 2261–2272

Rola uzupełniającej chemioterapii u chorych na raka jelita grubego w II stopniu zaawansowania nie została dotąd ustalona. Obecność krążącego nowotworowego DNA (*circulating tumour* DNA – ctDNA) po zabiegu operacyjnym może świadczyć o krótszym przeżyciu wolnym od nawrotu, natomiast jego brak – o małym ryzyku nawrotu. Nie jest jednak pewne, czy chorzy z obecnym ctDNA odnoszą korzyść z uzupełniającej chemioterapii.

Metody. Badanie przeprowadzono, aby ocenić, czy uzależnienie sposobu postępowania od obecności ctDNA może ograniczyć zastosowanie uzupełniającej chemioterapii bez zwiększenia ryzyka nawrotu choroby. Chorych na raka jelita grubego w II stopniu zaawansowania klinicznego nowotworu przydzielano losowo (w stosunku 2:1) do leczenia zależnie od obecności ctDNA lub do standardowego postępowania uwzględniającego cechy histopatologiczne guza. W grupie, w której leczenie zależało od obecności ctDNA, wykrycie tego czynnika we krwi w 4. lub 7. tygodniu po zabiegu operacyjnym była wskazaniem do wdrożenia chemioterapii zawierającej oksaliplatynę lub wyłącznie fluoropirymidynę. Chorzy, u których nie potwierdzono obecności ctDNA nie byli leczeni. Pierwszorzędowym punktem końcowym było przeżycie wolne od wznowy w ciągu 2 lat, a drugorzędowym – zastosowanie uzupełniającej chemioterapii.

Wyniki. Spośród 455 chorych biorących udział w badaniu 302 przydzielono losowo do leczenia zależnie od obecności ctDNA, a u 153 zastosowano standardowe postępowanie. Mediana obserwacji wyniosła 37 miesięcy. Mniej chorych w grupie leczonej na podstawie obecności ctDNA otrzymało uzupełniającą chemioterapię niż w grupie standardowego postępowania (15% *vs* 28%; ryzyko względne [*hazard ratio* – HR] 1,82; 95% przedział ufności [*confidence interval* – CI] 1,25–2,65). Częstość 2-letnich przeżyć wolnych od nawrotu nie była mniejsza w grupie leczonej zależnie od obecności ctDNA w porównaniu z grupą leczoną standardowo (odpowiednio: 93,5% i 92,4%; różnica bezwzględna 1,1 punktu procentowego; 95% CI –4,1–6,2 [margines równoważności –8,5%]). Udział 3-letnich przeżyć wolnych od nawrotu wyniósł 86,4% u chorych poddanych uzupełniającej chemioterapii na podstawie obecności ctDNA oraz 92,5% u chorych, u których nie stwierdzono obecności ctDNA.

Wnioski. Leczenie chorych na raka jelita grubego w II stopniu zaawansowania zależnie od obecności ctDNA zmniejszyło częstość stosowania chemioterapii i nie spowodowało zwiększenia ryzyka dotyczącego skrócenia przeżycia wolnego od nawrotu.

Pembrolizumab *versus* placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial

Luke J., Rutkowski P., Queirolo P. i wsp.
Lancet, 2022; 399: 1718–1729

Zastosowanie pembrolizumabu wydłuża czas wolny od progresji, czas całkowitego przeżycia oraz czas wolny od nawrotu u chorych na czerniaka w III stopniu zaawansowania po zabiegu operacyjnym. W badaniu KEYNOTE-716 oceniano zastosowanie pembrolizumabu w uzupełniającym leczeniu chorych na czerniaka wysokiego ryzyka w II stopniu zaawansowania po zabiegu operacyjnym. Przedstawiono wyniki z planowanej pierwszej i drugiej okresowej analizy przeżycia wolnego od nawrotu.

Metody. W podwójnie zaślepionym badaniu III fazy z grupą kontrolną stosującą placebo wzięło udział 160 ośrodków akademickich i szpitali w 16 krajach (Australia, Belgia, Brazylia, Kanada, Chile, Francja, Niemcy, Izrael, Włochy, Japonia, Polska, Południowa Afryka, Hiszpania, Szwajcaria, Wielka Brytania i Stany Zjednoczone). W badaniu brali udział chorzy w wieku co najmniej 12 lat na nowo rozpoznanego czerniaka w stopniu IIB oraz IIC (wg TNM w stopniu zaawansowania T3b oraz T4 z ujemnymi wynikiem biopsji węzła wartowniczego) po doszczętnym zabiegu operacyjnym. Uczestników przydzielano losowo, w stosunku 1:1, z uwzględnieniem stopnia zaawansowania cechy T (3b, 4a *vs* 4b) i wieku (12.–17. r.ż. *vs.* ≥18. r.ż.), do leczenia pembrolizumabem 200 mg (2 mg/kg mc. u chorych pediatrycznych) lub do stosowania placebo. Lek i placebo podawano co 3 tygodnie do 17 cykli albo do wystąpienia nawrotu choroby lub nieakceptowalnej toksyczności leczenia. Badanie było zaślepione dla chorych, badaczy oraz analityków. Pierwszorzędowym punktem końcowym było przeżycie wolne od nawrotu (określone jako czas od randomizacji do nawrotu lub zgonu) w grupie zgodnej z intencją leczenia (wszyscy chorzy włączeni do badania). Pierwszorzędowy punkt końcowy uznawano za spełniony, jeśli przeżycie wolne od nawrotu było dłuższe wśród leczonych pembrolizumabem

niż u otrzymujących placebo w pierwszej okresowej analizie (po stwierdzeniu około 128 zdarzeń u chorych) lub w drugiej okresowej analizie (po 179 zdarzeniach). Bezpieczeństwo oceniono u wszystkich chorych, którzy otrzymali przynajmniej jedną dawkę leku.

Wyniki. Od 23 września 2018 roku do 4 października 2020 roku spośród 1182 chorych poddanych badaniom przesiewowym, 976 przydzielono losowo do leczenia pembrolizumabem (n = 487) lub placebo (n = 489). Mediana wieku wyniosła 61 lat (IQR 52–69), 387 chorych (40%) było płci żeńskiej, a 589 (60%) – męskiej, 874 spośród 976 chorych (90%) należało do rasy białej, a 799 (82%) nie było narodowości hiszpańskiej ani latynoskiej. Przydzielone postępowanie wdrożono u 483 spośród 487 chorych (99%) otrzymujących pembrolizumab oraz u 486 spośród 489 chorych (99%) w grupie otrzymujących placebo. W pierwszej okresowej analizie (odcięcie danych 4 grudnia 2020 roku) mediana obserwacji wyniosła 14,4 miesiąca (IQR 10,2–18,7) w grupie leczonej pembrolizumabem oraz 14,3 miesiąca (10,1–18,7] – w grupie placebo. U 54 spośród 487 chorych (11%) w grupie leczonej pembrolizumabem oraz u 82 spośród 489 (17%) z grupy placebo stwierdzono nawrót choroby lub zgon (HR 0,65 [95% CI 0,46–0,92]; p = 0,0066). W drugiej okresowej analizie (odcięcie danych 21 czerwca 2021 roku; mediana obserwacji 20,9 miesiąca [16,7–25,3] w grupie leczonej pembrolizumabem i 20,9 miesiąca [16,6–25,3] w grupie placebo) u 72 chorych (15%) leczonych pembrolizumabem i u 115 (24%) w grupie placebo stwierdzono nawrót choroby lub zgon (HR 0,61 [95% CI 0,45–0,82]). Mediana przeżycia wolnego od progresji nie została osiągnięta w żadnym punkcie czasowym. W pierwszej okresowej analizie zaobserwowano działania niepożądane związane z leczeniem w stopniu 3.–4. u 78 spośród 483 chorych (16%) w grupie leczonej pembrolizumabem w porównaniu z 21 spośród 486 chorych (4%) w grupie placebo. W pierwszej okresowej analizie odnotowano zgon czterech chorych z powodu zdarzeń niepożądanych – wszyscy należeli do grupy otrzymującej placebo – z powodu zapalenia płuc, zakażenia COVID-19, popełnienia samobójstwa oraz nawrotu choroby; w drugiej okresowej analizie zmarł jeden chory z powodu zdarzenia niepożądanego (zapalenie płuc związane z zakażeniem COVID-19). Nie stwierdzono zgonów związanych z leczeniem.

Wyniki. Trwające rok uzupełniające leczenie pembrolizumabem chorych na czerniaka w stopniu zaawansowania IIB lub IIC znamiennie zmniejszyło ryzyko nawrotu choroby lub zgonu w porównaniu z użyciem placebo, a profil bezpieczeństwa pozostał akceptowalny.

The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial

Pollack A., Karrison T., Balogh A. i wsp.
Lancet, 2022; 399: 1886–1901

U chorych poddanych usunięciu gruczołu krokowego, z wykrywalnym stężeniem antygenu gruczołu krokowego (*prostate-specific antigen* – PSA) ratująca radioterapia na obszar loży po usuniętym gruczole krokowym (*prostate bed radiotherapy* – PBRT) zmniejsza ryzyko progresji nowotworu o 70% w ciągu 5 lat. Przeprowadzono trójramienne badanie, aby ocenić korzyść z dodaniau do PBRT 4–6-miesięcznej blokady androgenów (*androgen deprivation therapy* – ADT) oraz krótkoterminowej ADT i radioterapii na obszar węzłów chłonnych (*prostate lymph nodes radiotherapy* – PLNRT).

Metody. Międzynarodowe wieloośrodkowe badanie SPPORT z grupą kontrolną przeprowadzono w 283 ośrodkach radioterapii w Stanach Zjednoczonych, Kanadzie oraz Izraelu. Włączano do niego chorych (wiek ≥18. r.ż.), w stanie sprawności 0–1 według skali Zubroda, po zabiegu operacyjnym z powodu gruczolakoraka gruczołu krokowego (stopień zaawansowania pT2 lub pT3, stopień złośliwości ≤9 w skali Gleasona), u których stwierdzono utrzymujące się wykrywalne stężenie całkowitego PSA lub wzrastające, po wcześniej niewykrywalnym, do 0,1–2,0 ng/ml, niezależnie od wcześniejszego usunięcia węzłów chłonnych (N0/Nx), jeżeli nie stwierdzono cech klinicznego ani patologicznego ich zajęcia. Chorych przydzielano losowo do wyłącznej PBRT w dawce 64,8–70,2 Gy po 1,8 Gy w dawce frakcyjnej codziennie (grupa 1.), PBRT z krótką ADT (grupa 2.), oraz PLNRT (45 Gy po 1,8 Gy w dawce frakcyjnej z późniejszym zmniejszeniem planowanej objętości tarczowej do dawki 19,8–25,2 Gy) z PBRT oraz krótką ADT (grupa 3.). Pierwszorzędowym punktem końcowym był czas wolny do progresji, określonej jako wznowa biochemiczna według definicji Phoenix (PSA ≥2 ng/ml powyżej nadiru PSA), kliniczna progresja (miejscowa, regionalna lub odległa) albo zgon z jakiejkolwiek przyczyny. W planowanej okresowej analizie dla 1191 chorych z minimalnym czasem obserwacji 5 lat zastosowano granicę skuteczności wyznaczoną metodą Haybittle–Peto p < 0,001 dla porównania 5-letnich wskaźników braku progresji pomiędzy leczonymi grupami.

Wyniki. Od 31 marca 2008 roku do 30 marca 2015 roku 1792 chorych przydzielono losowo do jednej z trzech grup: 592 do

grupy 1. (wyłączna PBRT), 602 do grupy 2. (PBRT z krótkoterminową ADT), i 598 do grupy 3. (PLNRT z PBRT oraz krótką ADT). Spośród nich 76 chorych nie spełniało kryteriów włączenia i zostało wyłączonych z analizy, zatem oceniana grupa obejmowała 1716 chorych. W okresowej analizie (n = 1191 chorych, odcięcie danych 23 maja 2018 roku), granica skuteczności wyznaczona metodą Haybittle–Peto została przekroczona dla 5-letniego czasu wolnego od progresji przy porównaniu grupy 1. z 3. (różnica 17,9%, SE 2,9%; p < 0,0001). Różnica pomiędzy grupą 2. i 3. nie była znamienna (p = 0,0063). Po dłuższym czasie obserwacji (odcięcie danych 26 maja 2021 roku), mediana obserwacji wyniosła 8,2 roku (IQR 6,6–9,4), udział 5-letnich przeżyć wolnych od progresji dla 1716 chorych stanowił 70,9% (95% CI 67,0–74,9) w grupie 1., 81,3% (78,0–84,6) w grupie 2., i 87,4% (84,7–90,2) w grupie 3. Czas wolny od progresji był dłuższy w grupie 3. w porównaniu z grupami 1. i 2. Wczesne (≤3 miesięcy od radioterapii) działania niepożądane co najmniej 2. stopnia znamiennie częściej występowały w grupie 3. (246 spośród 563 chorych [44%]) niż w grupie 2. (201 spośród 563 [36%]; p = 0,0034), najrzadziej natomiast występowały one w grupie 1. (98 spośród 547 [18%]; p < 0,0001). Podobne zależności zaobserwowano dla działań niepożądanych co najmniej 3. stopnia. Różnice pomiędzy grupami w częstości występowania późnych działań niepożądanych (>3 miesięcy od radioterapii) nie były znamienne, jedynie zaburzenia dotyczące krwi i szpiku kostnego co najmniej 2. stopnia stwierdzano częściej w grupie 3. w porównaniu z grupą 2. (p = 0,0060), co było związane z dodaniem PLNRT.

Wnioski. Wyniki badania z losowym doborem chorych wskazują na korzyści z dołączenia krótkoterminowej ADT do PBRT w celu zapobieżenia progresji raka gruczołu krokowego. Jest to pierwsze badanie, w którym wykazano, że rozszerzenie ratującej radioterapii na obszar węzłów chłonnych miednicy w połączeniu z krótkoterminową ADT znamiennie zmniejsza ryzyko progresji u chorych na raka gruczołu krokowego po zabiegu operacyjnym.

Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in *de novo* metastatic castration-sensitive prostate cancer (PEACE-1): a multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

Fizazi K., Foulon S., Carles J. i wsp.
Lancet, 2022; 399: 1695–1701

Obecny standard leczenia chorych na rozsianego raka gruczołu krokowego wrażliwego na kastrację obejmuje blokadę androgenów, leczenie systemowe z zastosowaniem docetakselu, hormonoterapię drugiej generacji lub radioterapię. Celem prezentowanego badania była ocena skuteczności i bezpieczeństwa dołączenia do standardowego postępowania podawania abirateronu z prednizonem oraz radioterapii.

Metody. Otwarte badanie III fazy przeprowadzono w 77 szpitalach w Belgii, Francji, Irlandii, Włoszech, Rumunii, Hiszpanii i Szwajcarii. Chorych (w wieku co najmniej 18 lat) na potwierdzonego histologicznie lub cytologicznie rozsianego *de novo* gruczolakoraka gruczołu krokowego, w stanie sprawności 0–1 (lub 2 z powodu bólu kości) według Eastern Cooperative Oncology Group przydzielano losowo (1:1:1:1) do: standardowej opieki (wyłączna hormonoterapia lub leczenie systemowe z zastosowaniem docetakselu w dawce 75 mg/m^2 raz na 3 tygodnie), standardowej opieki w połączeniu z radioterapią, standardowej opieki wraz z abirateronem (doustnie 1000 mg abirateronu raz na dobę z dodatkiem doustnie stosowanego prednizonu w dawce 5 mg dwa razy na dobę) lub do standardowej opieki wraz z radioterapią i stosowaniem abirateronu. Badacze i chorzy znali przydział do leczenia. Pierwszorzędowymi punktami końcowymi były: przeżycie bez progresji radiologicznej oraz przeżycie całkowite. Skuteczność abirateronu oceniano najpierw w całej grupie, a następnie w grupie, w której zastosowano blokadę androgenów wraz z docetakselem (grupa będąca przedmiotem zainteresowania).

Wyniki. Od 27 listopada.2013 roku do 20 grudnia 2018 roku 1173 chorych (spośród których jeden wycofał zgodę na analizę swoich danych) przydzielono losowo do standardowej opieki (n = 296), standardowej opieki w połączeniu z radioterapią (n = 293), standardowej opieki w połączeniu z abirateronem (n = 292) lub standardowej opieki w połączeniu z radioterapią i abirateronem (n = 291). Mediana czasu obserwacji wyniosła 3,5 roku (IQR 2,8–4,6) dla przeżycia bez progresji radiologicznej i 4,4 roku (3,5–5,4) dla przeżycia całkowitego. Skorygowane modelowanie regresji Coxa nie wykazało interakcji pomiędzy abirateronem a radioterapią, umożliwiając zbiorczą analizę skuteczności abirateronu. W całej grupie przeżycie bez progresji radiologicznej (HR 0,54, 99,9% CI 0,41–0,71; p < 0,0001) i przeżycie całkowite było dłuższe (0,82, 95,1% CI 0,69–0,98; p = 0,030) wśród przydzielonych do leczenia z użyciem abirateronu (n = 583) w porównaniu z pozostałymi chorymi (n = 589). Wśród leczonych blokadą androgenów w połączeniu z docetakselem (n = 355 zarówno w grupie z abirateronem, jak i bez) wartości HR były zgodne (przeżycie bez progresji radiologicznej 0,50, 99,9% CI 0,34–0,71; p < 0,0001; przeżycie całkowite 0,75, 95,1% CI 0,59–0,95; p = 0,017). Wśród chorych, u których zastosowano blokadę androgenów w połączeniu z docetakselem zdarzenia niepożądane stopnia 3. lub wyższego wystąpiły u 217 spośród 347 chorych (63%) leczonych z użyciem abirateronu i u 181 spośród 350 (52%) nieotrzymujących tego leku; największa różnica dotyczyła nadciśnienia tętniczego (odpowiednio 76 chorych [22%] i 45 [13%]). Dodanie abirateronu do blokady androgenów i docetakselu nie zwiększyło częstości występowania neutropenii, gorączki neutropenicznej, zmęczenia lub neuropatii w porównaniu z osobami poddanymi blokadzie androgenów w połączeniu z przyjmowaniem docetakselu.

Wnioski. Połączenie blokady androgenów, docetakselu i abirateronu u chorych na rozsianego *de novo* raka gruczo-

łu krokowego wrażliwego na kastrację wydłużyło przeżycie całkowite i przeżycie wolne od progresji radiologicznej przy umiarkowanym wzroście toksyczności (głównie nadciśnienia tętniczego). To potrójne leczenie mogłoby się stać standardem opieki w tej grupie chorych.

Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer

Forde P.M., Spicer J., Lu S. i wsp.
N. Engl. J. Med., 2022; 386:1973–1985

Indukcyjna lub uzupełniająca chemioterapia przynosi niewielkie korzyści u chorych na operacyjnego niedrobnokomórkowego raka płuca w porównaniu z wyłącznym zabiegiem operacyjnym. W badaniach wczesnej fazy indukcyjne leczenie z użyciem niwolumabu wykazało obiecującą aktywność kliniczną. Potrzebne są dane z badań III fazy, aby potwierdzić te wyniki.

Metody. W otwartym badaniu III fazy chorych na operacyjnego niedrobnokomórkowego raka płuca (stopień zaawansowania IB–IIIA) przydzielano losowo do indukcyjnego leczenia niwolumabem w skojarzeniu z chemioterapią zawierającą pochodną platyny lub do wyłącznej chemioterapii. Pierwszorzędowymi punktami końcowymi były: przeżycie wolne od zdarzeń i całkowita odpowiedź patologiczna (0% żywych komórek nowotworowych w wyciętym guzie płuca i węzłach chłonnych), oceniane w niezależnym, zaślepionym przeglądzie. Przeżycie całkowite było głównym drugorzędowym punktem końcowym. Bezpieczeństwo oceniano u wszystkich leczonych.

Wyniki. Mediana przeżycia wolnego od zdarzeń wyniosła 31,6 miesiąca (95% CI 30,2–nie osiągnięto) w grupie otrzymującej niwolumab z chemioterapią i 20,8 miesiąca (95% CI 14,0–26,7) wśród poddanych wyłącznie chemioterapii (współczynnik ryzyka progresji, nawrotu lub zgonu 0,63; 97,38% CI 0,43–0,91; p = 0,005). Udział chorych z patologiczną, całkowitą odpowiedzią wyniósł odpowiednio 24,0% (95% CI 18,0–31,0) i 2,2% (95% CI 0,6 –5,6) (iloraz szans 13,94; 99% CI 3,49–55,75; p < 0,001). Wyniki dotyczące przeżycia wolnego od zdarzeń i całkowitej odpowiedzi patologicznej przemawiały w większości podgrup na korzyść niwolumabu skojarzonego z chemioterapią. W pierwszej określonej analizie pośredniej współczynnik ryzyka zgonu wyniósł 0,57 (99,67% CI 0,30–1,07) i nie spełnił kryterium znamienności. Udział przeprowadzonych zabiegów operacyjnych wśród chorych przydzielonych losowo do leczenia wyniósł 83,2% w grupie otrzymującej niwolumab z chemioterapią i 75,4% w grupie poddanej wyłącznie chemioterapii. Częstość związanych z leczeniem zdarzeń niepożądanych 3. lub 4. stopnia wyniosła 33,5% dla otrzymujących niwolumab z chemioterapią i 36,9% wśród poddanych wyłącznie chemioterapii.

Wnioski. Indukcyjne leczenie niwolumabem w skojarzeniu z chemioterapią wiązało się ze znamiennie dłuższym przeżyciem bez zdarzeń i większym udziałem całkowitych odpowiedzi patologicznych u chorych na operacyjnego niedrobnokomórkowego raka płuca. Dodanie niwolumabu do indukcyjnej chemioterapii nie zwiększyło częstości występowania zdarzeń niepożądanych ani nie wpłynęło na wykonalność zabiegu operacyjnego.

Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer

Palefsky J.M., Lee J.Y., Jay N. i wsp.
N. Engl. J. Med., 2022; 386: 2273–2282

Częstość występowania raka odbytu jest znacznie większa wśród chorych zakażonych ludzkim wirusem niedoboru odporności (*human immune-deficiency virus* – HIV) niż w ogólnej populacji. Podobnie jak rak szyjki macicy, rak odbytu jest poprzedzony zmianami śródnabłonkowymi o wysokim stopniu złośliwości (*high-grade squamous intraepithelial lesion* – HSIL). Leczenie stanów przednowotworowych szyjki macicy zmniejsza ryzyko progresji do raka szyjki macicy. Brakuje danych z prospektywnych badań dotyczących leczenia HSIL odbytu w celu zapobiegania rozwojowi raka odbytu.

Metody. Przeprowadzono badanie III fazy w 25 regionach w USA. Zakażonych HIV w wieku 35 lat lub starszych, u których stwierdzono HSIL odbytu, przydzielano losowo (w stosunku 1:1) do leczenia, które trwało do całkowitego ustąpienia HSIL lub do aktywnego monitorowania bez leczenia. Leczenie obejmowało zabiegi ablacyjne wykonywane w gabinecie, ablację lub wycięcie w znieczuleniu albo miejscowe podawanie fluorouracylu lub imikwimodu. Pierwszorzędowym punktem końcowym była progresja do raka odbytu w analizie czasu do zdarzenia. U wszystkich chorych wykonywano anoskopię wysokiej rozdzielczości przynajmniej co 6 miesięcy; biopsję wykonywano również w przypadku podejrzenia przetrwałego HSIL w grupie leczonej, corocznie w grupie objętej aktywnym monitorowaniem lub zawsze, gdy istniała obawa zachorowania na raka.

Wyniki. Spośród 4459 uczestników przydzielonych losowo do leczenia 4446 (99,7%) włączono do analizy czasu do progresji do raka. Po obserwacji o medianie wynoszącej 25,8 miesiąca rozpoznano 9 przypadków raka odbytu w grupie leczonej (173 na 100 000 osobolat; 95% CI 90–332) i 21 przypadków w grupie aktywnego monitorowania (402 na 100 000 osobolat; 95% CI 262–616). Udział progresji do raka odbytu był niższy o 57% w grupie leczonej niż w grupie aktywnego monitorowania (95% CI 6–80; p = 0,03 w teście *log-rank*).

Wnioski. Wśród chorych z potwierdzonym HSIL odbytu ryzyko wystąpienia raka było znamiennie niższe w przypadku zastosowania leczenia HSIL odbytu w porównaniu z chorymi poddanymi wyłącznie aktywnej obserwacji.

PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer

Cercek A., Lumish M., Sinopoli J. i wsp.
N. Engl. J. Med., 2022; 386: 2363–2376

Przedoperacyjna radioterapia i chemioterapia poprzedzająca zabieg operacyjny jest standardowym postępowaniem w przypadku chorych na miejscowo zaawansowanego raka odbytnicy. Część nowotworów odbytnicy jest spowodowana zaburzeniami w genach naprawy DNA (*deficient* DNA *mismatch repair* – dMMR). Rozsiany rak jelita grubego dMMR reaguje na blokadę receptora programowanej śmierci typu 1 (PD-1). Założono, że blokada punktu kontroli może być skuteczna u chorych na miejscowo zaawansowanego raka odbytnicy dMMR.

Metody. W prospektywnym badaniu II fazy chorym na raka gruczołowego odbytnicy dMMR w II i III stopniu zaawansowania podawano przeciwciało anty-PD-1, dostarlimab, co 3 tygodnie przez 6 miesięcy, następnie planowano standardową radiochemioterapię oraz zabieg operacyjny. Chorych, u których uzyskano z całkowitą odpowiedź po dostarlimabie nie kwalifikowano do dalszego leczenia. Pierwszorzędowym punktem końcowym było utrzymanie klinicznej całkowitej odpowiedzi po leczeniu dostarlimabem przez 12 miesięcy lub całkowita patologiczna odpowiedź po leczeniu dostarlimabem z radiochemioterapią lub bez niej oraz całkowita odpowiedź na przedoperacyjne leczenie dostarlimabem z radiochemioterapią lub bez.

Wyniki. Leczenie dostarlimabem ukończyło 12 chorych, których poddano co najmniej 6-miesięcznej obserwacji. U wszystkich 12 chorych (100%; 95% CI 74–100) stwierdzono całkowitą odpowiedź bez podejrzenia choroby nowotworowej w rezonansie magnetycznym, pozytonowej tomografii emisyjnej, ocenie endoskopowej, badaniu *per rectum* czy biopsji. W chwili opisywania badania żaden chory nie rozpoczął radiochemioterapii oraz nie przeprowadzono zabiegu operacyjnego, nie stwierdzono również progresji choroby czy nawrotu podczas obserwacji (zakres 6–25 miesięcy). Nie odnotowano działań niepożądanych 3. lub wyższego stopnia.

Wnioski. Miejscowo zaawansowany rak odbytnicy z dMMR był wysoce wrażliwy na blokadę PD-1. Konieczna jest dłuższa obserwacja, aby ocenić czas trwania odpowiedzi u chorych na miejscowo zaawansowanego raka odbytnicy dMMR.

Oncolytic DNX-2401 virus for pediatric diffuse intrinsic pontine glioma

Pérez-Larraya J.G., Garcia-Moure M., Labiano S. i wsp.
N. Engl. J. Med., 2022; 386: 2471–2481

Chorzy na rozlanego glejaka mostu (*diffuse infiltrating pontine glioma* – DIPG) <18. r.ż. mają złe rokowanie, a mediana przeżycia nie przekracza roku. Onkolityczne leczenie wirusowe oceniano u chorych na glejaki dziecięce umiejscowione w innych częściach mózgu, ale brakuje danych dotyczących tego leczenia u chorych na DIPG.

Metody. Przeprowadzono jednoośrodkowe badanie z eskalacją dawki DNX-2401 – onkolitycznego adenowirusa, który selektywnie namnaża się w komórkach nowotworowych u chorych na nowo rozpoznane DIPG. Chorzy otrzymali pojedynczy wlew wirusa przez cewnik umieszczony w nasadzie móżdżku, a następnie radioterapię. Głównym celem była ocena bezpieczeństwa i profilu zdarzeń niepożądanych DNX-2401, a drugorzędowymi – ocena wpływu DNX-2401 na przeżycie całkowite i jakość życia, określenie udziału chorych z obiektywną odpowiedzią oraz pobranie próbek z biopsji guza i krwi obwodowej do oceny zależności pomiędzy cechami molekularnymi DIPG a immunologiczną odpowiedzią przeciwnowotworową.

Wyniki. Łącznie 12 chorych (w wieku od 3 do 18 lat) na nowo rozpoznanego DIPG otrzymało 1×10^{10} (pierwszych 4 chorych) lub 5×10^{10} (kolejnych 8 chorych) cząstek wirusa DNX-2401, a 11 zostało następnie poddanych radioterapii. Zdarzenia niepożądane obejmowały ból głowy, nudności, wymioty i zmęczenie. Niedowład połowiczy i tetrapareza rozwinęły się u jednego chorego. W okresie obserwacji o medianie 17,8 miesiąca (zakres 5,9–33,5) u 9 chorych stwierdzono zmniejszenie guza na podstawie rezonansu magnetycznego, u 3 – odpowiedź częściową, a u 8 – stabilizację choroby. Mediana czasu przeżycia wyniosła 17,8 miesiąca. Dwóch chorych żyło w chwili sporządzania niniejszego raportu, a u jednego nie stwierdzono progresji nowotworu po 38 miesiącach. Badanie próbki guza uzyskanej podczas autopsji od 1 chorego oraz badania krwi obwodowej wykazały zmiany w mikrośrodowisku guza i limfocytach T.

Wnioski. Poprzedzające radioterapię podanie onkolitycznego wirusa DNX-2401 do guza spowodowało zmiany w aktywności limfocytów T i zmniejszenie lub stabilizację wielkości guza u niektórych chorych na DIPG <18. r.ż., ale było związane z działaniami niepożądanymi.

Ibrutinib plus bendamustine and rituximab in untreated mantle-cell lymphoma

Wang M.L., Jurczak W., Jerkeman M. i wsp.
N. Engl. J. Med., 2022; 386: 2482–2494

Ibrutynib, inhibitor kinazy tyrozynowej Brutona, w skojarzeniu z bendamustyną i rytuksymabem, może przynosić korzyści kliniczne u starszych chorych na nowo rozpoznanego chłoniaka z komórek płaszcza, leczonych następnie podtrzymująco rytuksymabem.

Metody. Chorych w wieku 65 lat lub starszych przydzielono losowo do stosowania ibrutynibu (560 mg, podawany doustnie raz dziennie do wystąpienia progresji chłoniaka lub nieakceptowalnych działań niepożądanych związanych z leczeniem) lub placebo, w połączeniu z 6 cyklami bendamustyny

(90 mg/m^2) z rytuksymabem (375 mg/m^2). Chorzy, u których stwierdzono obiektywną odpowiedź na leczenie (całkowitą lub częściową) otrzymywali leczenie podtrzymujące rytuksymabem, podawanym co 8 tygodni do 12 dodatkowych dawek. Pierwszorzędowym punktem końcowym było przeżycie bez progresji oceniane przez badaczy. Oceniono również całkowite przeżycie i bezpieczeństwo terapii.

Wyniki. Spośród 523 chorych 261 przydzielono losowo do leczenia z użyciem ibrutynibu, a 262 do grupy otrzymującej placebo. Przy medianie okresu obserwacji 84,7 miesiąca mediana przeżycia wolnego od progresji wyniosła 80,6 miesiąca w grupie ibrutynibu i 52,9 miesiąca w grupie placebo (współczynnik ryzyka progresji choroby lub zgonu 0,75; 95% CI 0,59–0,96; p = 0,01). Udział chorych, u których uzyskano całkowitą odpowiedź wyniósł 65,5% w grupie ibrutynibu i 57,6% w grupie placebo (p = 0,06). Całkowite przeżycie było podobne w obu grupach. Częstość występowania działań niepożądanych 3. lub 4. stopnia podczas leczenia wyniosła 81,5% w grupie ibrutynibu i 77,3% w grupie placebo.

Wnioski. Leczenie ibrutynibem w skojarzeniu ze standardową chemioimmunoterapią znacząco wydłużyło przeżycie bez progresji choroby u chorych na nowo rozpoznanego chłoniaka z komórek płaszcza. Profil bezpieczeństwa leczenia skojarzonego był zgodny ze znanymi profilami poszczególnych leków.

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Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 4, 321

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

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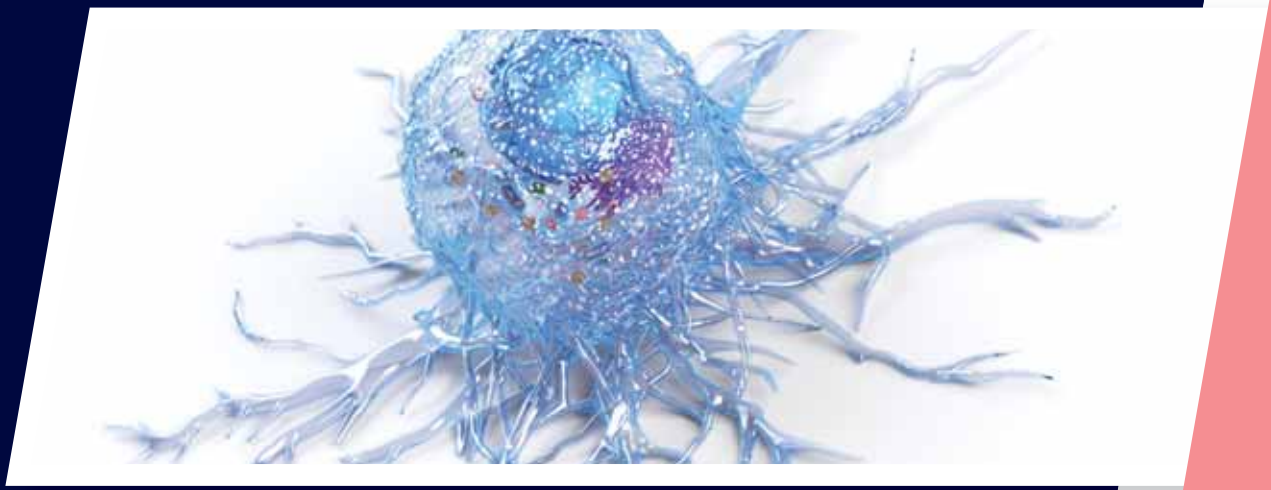

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22-8426.001.012

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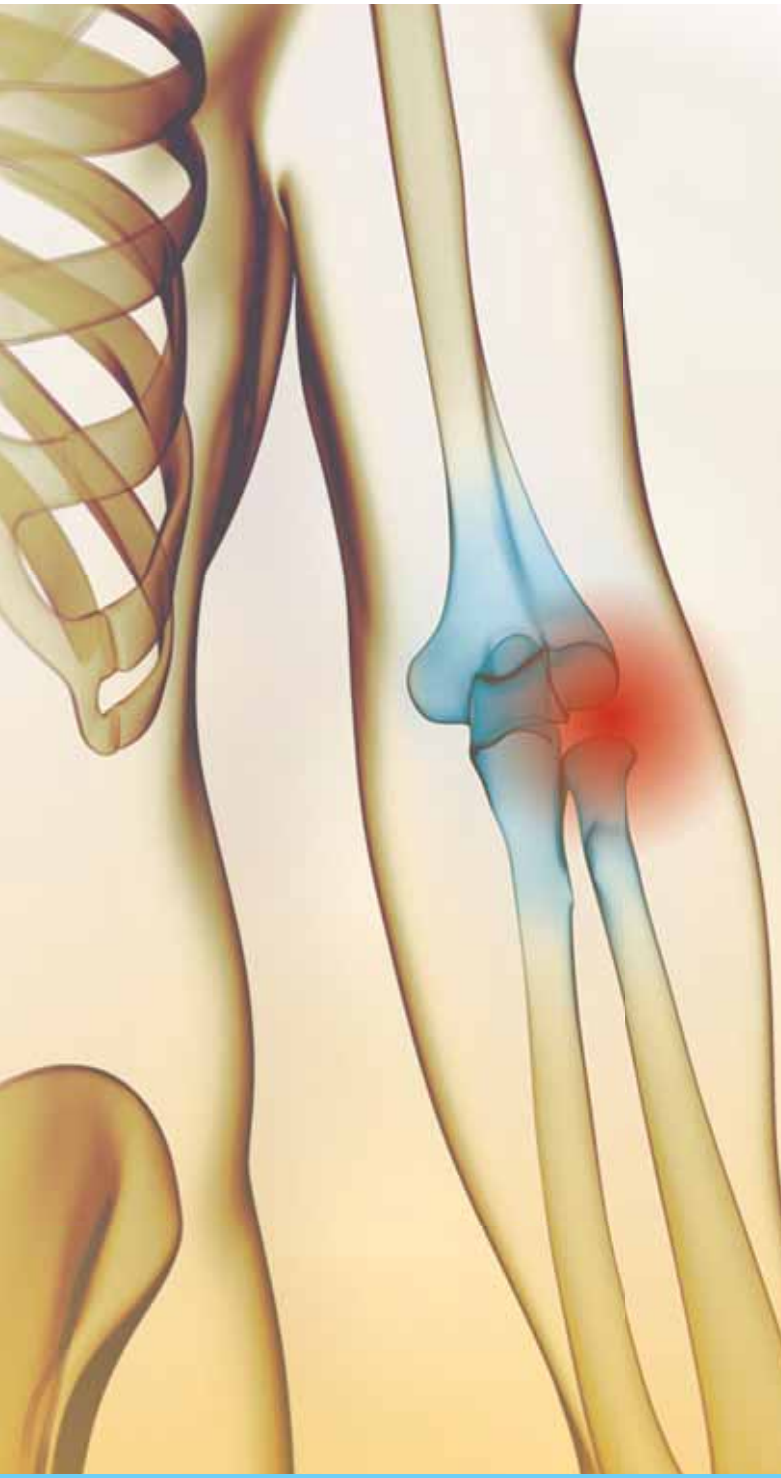

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