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Journal of Oncology



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

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

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## Tumor and normal tissue radiation side effects

*B. Maciejewski*

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

*T. Piotrowski, J. Malicki*

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

Anna Liszcz-Tymoszuk<sup>1,2</sup>, Marta Fudalej<sup>1</sup>, Andrzej Deptała<sup>1</sup>, Anna M. Badowska-Kozakiewicz<sup>1</sup>

<sup>1</sup>Department of Cancer Prevention, Medical University of Warsaw, Warsaw, Poland

<sup>2</sup>Students' Scientific Organization of Cancer Cell Biology, Department of Cancer Prevention, Medical University of Warsaw, Warsaw, Poland

**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].

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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 lesions. 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

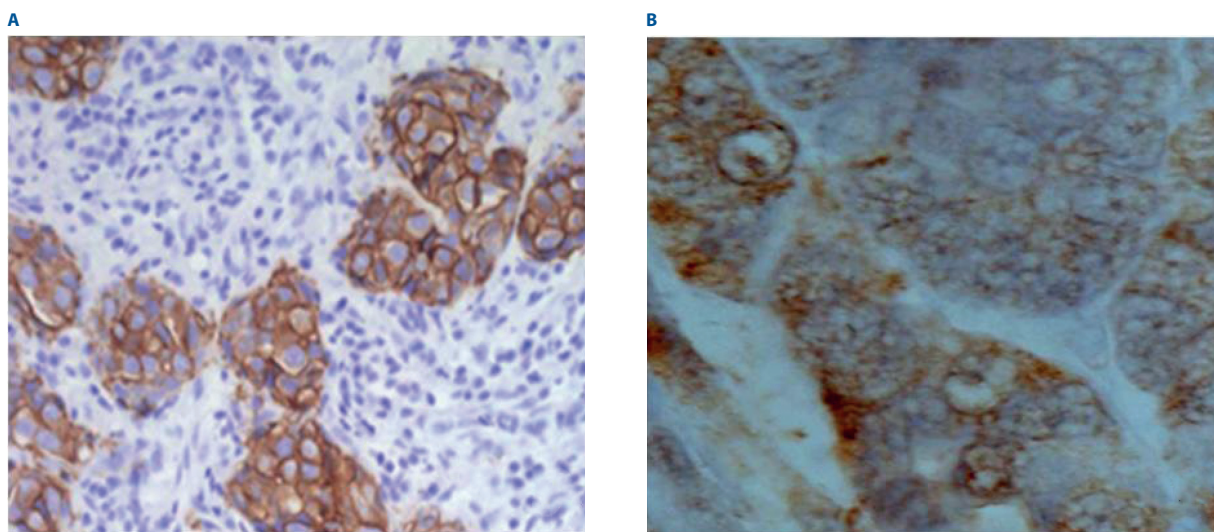
### Patients

The patient population comprised 21 women with a diagnosis of triple-negative breast cancer. The material came from biopsies, excisional biopsies and modified radical mastecto-

mies. 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 into 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-diaminobenzidine (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



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

haematoxylin. Stain intensity was assessed by computed image analysis of 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 rorsradish 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 emphasize 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 than 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

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

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

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



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

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

	Degree of immunohistochemical expression of COX-2 in TNBC samples				p
	None	Weak	Medium	Strong	
<b>histological type</b>					
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%)	
<b>histological grade (G)</b>					
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%)	
<b>tumour size (T)</b>					
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%)	
<b>lymph node involvement (N)</b>					
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

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 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				p
	None	Weak	Medium	Strong	
<b>histologic type</b>					
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	
<b>histological grade (G)</b>					
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%)	
<b>tumour size (T)</b>					
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%)	
<b>lymph node involvement (N)</b>					
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.

Simonsson 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, how-

ever 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 hormone therapy 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

**Anna M. Badowska-Kozakiewicz**

*Medical University of Warsaw*

*Department of Cancer Prevention*

*ul. Erazma Ciołka 27*

*01-445 Warszawa, Poland*

*e-mail: aliszcz@hotmail.com abadowska@wum.edu.pl*

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

Ireneusz Pierzankowski<sup>1</sup>, Adam Dmitruk<sup>1</sup>, Sebastian Rybski<sup>2</sup>, Lucjan Wyrwicz<sup>3</sup>, Tomasz Olesiński<sup>1</sup>

<sup>1</sup>*Clinic of Surgery of Gastrointestinal Cancers and Neuroendocrine Tumors, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

<sup>2</sup>*Department of Oncology Math, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

<sup>3</sup>*Clinic of Oncology and Radiotherapy, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

**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 Skłodowska-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

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## 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 cancer 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 21<sup>st</sup> 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<sup>2</sup>/day for 5 days and calcium folinate 20 mg/m<sup>2</sup>/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<sup>2</sup> together with calcium folinate 20 mg/m<sup>2</sup>/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 inter-

vention 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 Skłodowska-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

**Table I.** Parameters of study group

Study group parametres	Number of patients (n = 154), (%)
<b>age (median, standard deviation)</b>	60 (±10.691)
<b>sex</b>	
women	55 (35.7%)
men	99 (64.3%)
<b>tumor grade (G)</b>	
G2	37 (24%)
G3	116 (75.3%)
MANEC	1 (0.7%)
<b>anatomic stage of tumor</b>	
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%)
<b>primary tumor advanced (T)</b>	
T1a	0 (0%)
T1b	1 (0.6%)
T2	18 (11.7%)
T3	103 (66.9%)
T4a	28 (18.2%)
T4b	4 (2.6%)
<b>regional stage (N)</b>	
N0	26 (16.9%)
N1	39 (25.3%)
N2	33 (21.4%)
N3a	42 (27.3%)
N3b	11 (7.1%)
N3c	1 (0.6%)
<b>tumor type according to Lauren classification</b>	
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
<b>age (median, standard deviation)</b>	62 (±10.331)	59 (±10.968)	0.181
<b>sex</b>			
women	30 (40%)	25 (31.6%)	
men	45 (60%)	54 (68.4%)	
<b>grading (G)</b>			
G1	0 (0.00%)	0 (0.00%)	0.540
G2	17 (22.7%)	20 (25.3%)	
G3	57 (76%)	59 (74.7%)	
MANEC	1 (1.3%)	0 (0.00%)	
<b>anatomic stage of tumor</b>			
Ia	0 (0%)	0 (0%)	0.882
Ib	8 (10.7%)	10 (12.7%)	
IIa	10 (13.3%)	11 (13.9%)	
IIb	17 (22.7%)	11 (13.9%)	
IIIa	15 (20.0%)	17 (21.5%)	
IIIb	17 (22.7%)	22 (27.8%)	
IIIc	8 (10.7%)	8 (10.1%)	
<b>feature T</b>			
T1a	0 (0.00%)	0 (0.00%)	0.321
T1b	0 (0.00%)	1 (1.3%)	
TII	5 (6.7%)	13 (16.5%)	
TIII	53 (70.7%)	50 (63.3%)	
TIVa	15 (20.0%)	13 (16.5%)	
TIVb	2 (2.7%)	2 (2.5%)	
<b>feature N</b>			
N0	15 (20%)	11 (13.9%)	0.196
N1	23 (30.7%)	16 (20.3%)	
N2	11 (14.7%)	22 (27.8%)	
N3a	20 (26.7%)	24 (30.3%)	
N3b	6 (8.0%)	5 (6.3%)	
N3c	0 (0.00%)	1 (1.3%)	
<b>tumor type according to Lauren classification</b>			
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



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. 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-Meier 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 Kaplan-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).

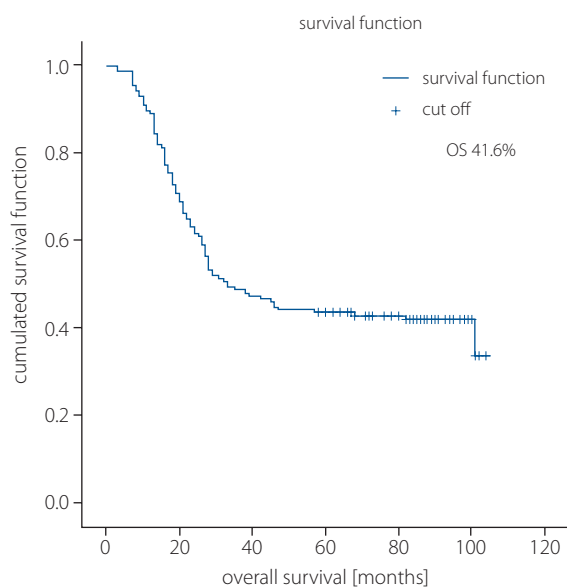


Figure 1. Survival function

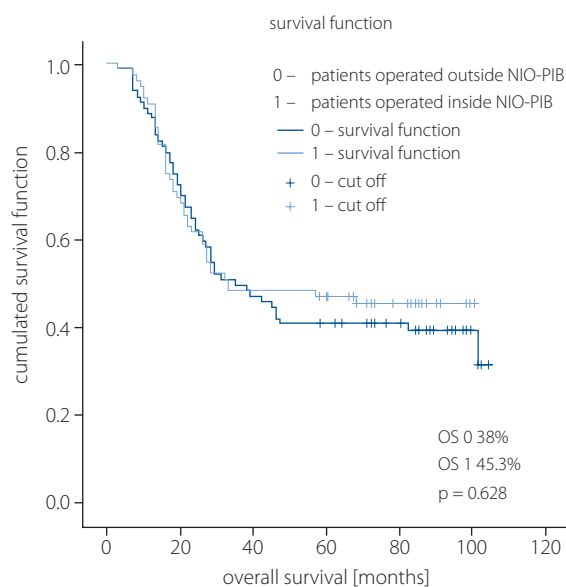


Figure 2. Survival functions by surgical site

## 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 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 con-

firmed 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 paclitaxel 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  $\geq$ 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.

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**Ireneusz Pierzankowski**

*Maria Skłodowska-Curie National Research Institute of Oncology  
ul. Roentgena 5*

*02-781 Warszawa, Poland*

*e-mail. i.pierzankowski@gmail.com*

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

Katarzyna A. Kowalczyk<sup>1, 2, 3</sup>, Adrianna Majewski<sup>4</sup>, Wojciech M. Wysocki<sup>1, 2, 5</sup>,  
Krzysztof Tomaszewski<sup>2, 3, 6</sup>

<sup>1</sup>Department of General, Oncological and Vascular Surgery, 5<sup>th</sup> Military Clinical Hospital in Krakow, Krakow, Poland  
<sup>2</sup>Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland  
<sup>3</sup>Department of Anatomy, Jagiellonian University Medical College, Krakow, Poland  
<sup>4</sup>Jagiellonian University Medical College, Krakow, Poland  
<sup>5</sup>Maria Skłodowska-Curie National Research Institute of Oncology, Scientific Editorial Office, Warsaw, Poland  
<sup>6</sup>Scanmed St. Raphael Hospital, Krakow, Poland

**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  $12.9 \pm 9.3$ .

**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 inextricably

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cable 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 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  $\pm$  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

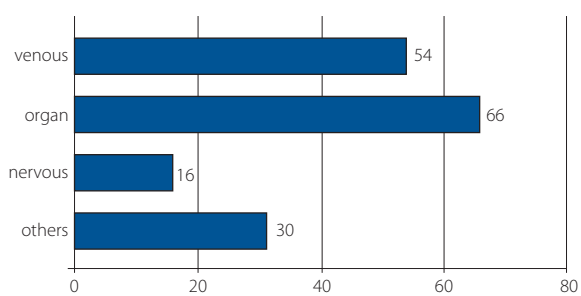
The questionnaire was administered among a group of 90 surgeons. One of the responders was excluded from analysis owing to the fact that their declared age and field of work was found to be factually inconsistent; thus, the final number of questionnaires analyzed was 89.

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  $197 \pm 168.1$ ,  $252.3 \pm 156.6$  procedures among oncological surgeons, and  $101.7 \pm 55.6$  procedures among the remaining participants. The mean number of years in practice in their respective fields was  $12.9 \pm 9.3$  years. General surgeons reported  $11.7 \pm 9.0$  years of experience in their field, while oncological surgeons reported  $16.8 \pm 9.9$  years, and other surgeons reporting  $14.4 \pm 7.9$  years. The cohort consisted of 23 (25.8%) women and 66 (74.2%) men. The mean age was  $38.9 \pm 9.2$  years of age; the mean age of the female participants ( $34.3 \pm 4.8$  years) was significantly ( $p = 0.0046$ ) different from their male counterparts ( $40.5 \pm 9.8$ ). 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  $199 \pm 161.7$ . When separated by sex, the mean number of procedures performed among men was  $202 \pm 162.9$  and  $189.0 \pm 161.8$  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.

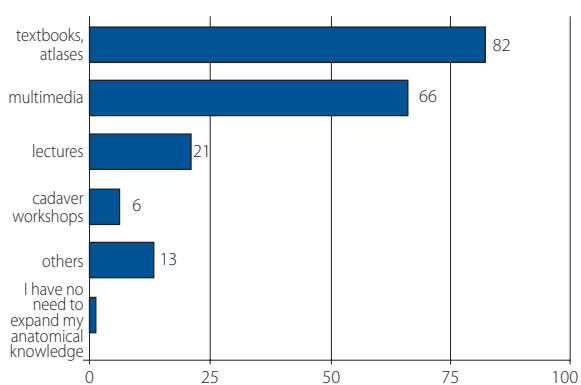
All participants were unanimous in declaring that anatomical knowledge was required in everyday surgical practice, with 86.5% selecting "essential", and 13.5% selecting "useful". The responses were also consistent in describing the role of knowledge of anatomical variations in a given structure, declaring 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

**Table I.** Group characteristics

Number of responders (n = 89), (%)	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 included 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)

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%) 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  $5.9 \pm 1.64$ . 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 stu-

**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 ves- sels of the liver]	Question 2 [Question about the portal vein]	Question 3 [Question about the gallblader]	Question 4 [Question about visce- ral vasculari- zation]	Question 5 [Question about va- scularization of the large intestine]	Question 6 [Question about ana- tomy of the duodenum]	Question 7 [Question about the arc of Buh- ler]	Question 8 [Question about the clini- cal 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%)
<b>sex</b>								
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%)
<b>surgical field</b>								
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%)
<b>workplace</b>								
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 (%)	0.958
males, n (%)	
general surgery	0.235
oncological surgery	
others	
university hospital	0.1428
provincial hospital	
district hospital	
others	
>10 years of work	0.7563
<10 years of work	
approximate number of surgical procedures per year >100	0.6849
approximate number of surgical procedures per year <100	

dents [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 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 assessment 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.

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## Katarzyna A. Kowalczyk

*5<sup>th</sup> Military Clinical Hospital in Krakow  
Department of General, Oncological and Vascular Surgery  
ul. Wrocławska 1/3  
30-901 Kraków, Poland  
e-mail: katarzyna.anna.kowalczyk@gmail.com*

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

Grzegorz Charliński<sup>1</sup>, David H. Vesole<sup>2,3</sup>, Artur Jurczynszyn<sup>4</sup>

<sup>1</sup>Department of Hematology, Medical Faculty, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland

<sup>2</sup>Department of Hematology/Oncology, Medstar Georgetown University Hospital, Washington, United States

<sup>3</sup>John Theurer Cancer Center at Hackensack Meridian School of Medicine, Hackensack, United States

<sup>4</sup>Plasma Cell Dyscrasias Center, Department of Hematology, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland

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].

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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-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- $\alpha$ ), 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 ( $\alpha$ -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 (Ixa-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].

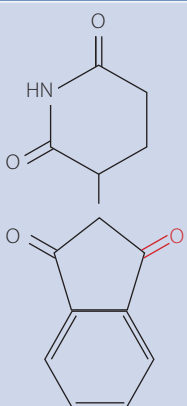
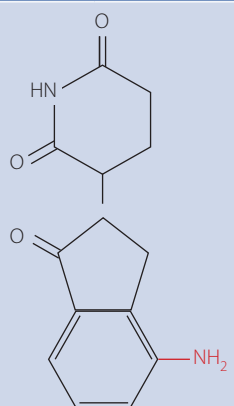
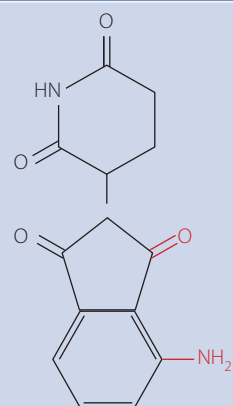
Due to the results of phase 3 clinical trials, IMiDs are currently used mainly in multi-drug combinations with new drugs, including monoclonal antibodies (daratumumab, elotuzumab, isatuximab) and proteasome inhibitors (bortezomib, carfilzomib, ixasomib). We review the AEs reported in the latest phase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

**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	<table border="1"> <tr> <th>CrCl (ml/min)</th> <th>daily dose</th> </tr> <tr> <td>&gt;60</td> <td>25 mg</td> </tr> <tr> <td>30–59</td> <td>10 mg</td> </tr> <tr> <td>15–29</td> <td>15 mg every other day</td> </tr> <tr> <td>&lt;15</td> <td>5 mg</td> </tr> <tr> <td>on dialysis</td> <td>5 mg</td> </tr> </table>	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
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														
relative potency ± potency factor of 10															
CD4+ and CD8+ T-cell co-stimulation	+	++++	+++++												
tregs suppression	–	+	+												
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

mon 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% 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 use 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 AEs 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].

**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]	
	TD	VTD	VCD	VTD	VTD	Dara-VTD	CTD	MP	MPT	MP
<b>hematological adverse events, grade ≥3 (%)</b>										
neutropenia	NA	NA	33	19	15	28	11	15		
thrombocytopenia	0	5	11	5	7	11	NA	NA	overall: 32	overall: 29
anemia	NA	NA	9	4	NA	NA	NA	NA		
<b>non-hematological adverse events, grade ≥3 (%)</b>										
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

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].

### 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  $\geq 3$  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 VdRd 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, resummptions, 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, lenalido-

**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]	
	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]	
	Rd	KRd	Rd	Ixa-Rd	Rd	Dara-Rd	Rd	Elo-Rd
<b>hematological adverse events, grade <math>\geq 3</math> (%)</b>								
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
<b>non-hematological adverse events, grade <math>\geq 3</math> (%)</b>								
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

mid treatment should be discontinued, G-CSF administered, and lenalidomide at the current dose resumed when the ANC increases  $\geq 1.0$  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  $\geq 1.0$  G/L [68]. In the case of 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 sys-

temic 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  $\geq 1.0$  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  $\geq 50$  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

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

Trial regimen	MM-003 [76]		STRATUS [77]	OPTIMISMM [78]		APOLLO [79]		ICARIA-MM [80]		ELOQUENT-3 [81]	
	Dex	Pd	Pd	Vd	PVd	Pd	Dara-Pd	Pd	Ixa-Pd	Pd	Elo-Pd
<b>hematological adverse events, grade <math>\geq 3</math> (%)</b>											
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
<b>non-hematological adverse events, grade <math>\geq 3</math> (%)</b>											
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

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  $\geq 2$ , PN develops, withhold pomalidomide treatment until symptoms improve to grades 0–1. After that, pomalidomide should be taken at a reduced 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  $\geq 3$  non-hematological AEs occur, it is recommended that pomalidomide treatment be interrupted until symptoms resolve to grade  $\leq 2$  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  $\geq 45$  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.

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### Grzegorz Charliński

University of Warmia and Mazury in Olsztyn

Medical Faculty

Department of Hematology

ul. Wojska Polskiego 37

10-228 Olsztyn, Poland

e-mail: grzegorz.charlinski@uwm.edu.pl

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## Tumor and normal tissue radiation side effects

Bogusław Maciejewski

*Div. Research Programmes, Maria Skłodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland*

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 probabilistic 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 kil-

led 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).

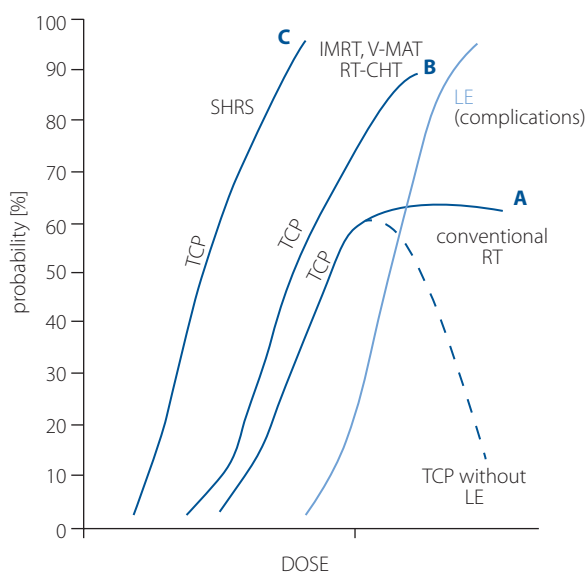
In order to intensify the radiation effects with regards to destroying cancer cells, some tests were performed, examining various altered dose fractionations and boost doses (brachytherapy), conformal techniques and concurrent chemoradiation, but only few of them have been successfully employed in the

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**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, chemoradiotherapy; (C) – SHRS – stereotactic hypofractionated radiosurgery – high DI single dose or a few large fractions – very short OTT; dotted line – TCP without late complication]

daily practice [1, 3, 4, 5]. During the last 20–25 years it has been well documented that a single process – accelerated repopulation 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 6<sup>th</sup> 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

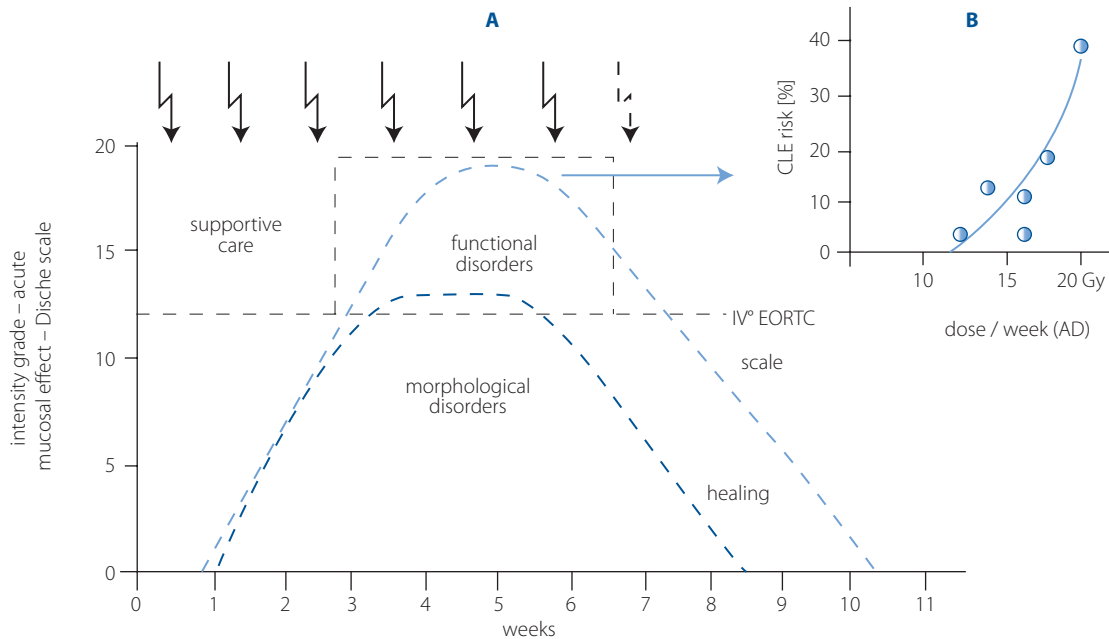
(organs). Normal tissue side effects are generally classified as acute and/or late.

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.

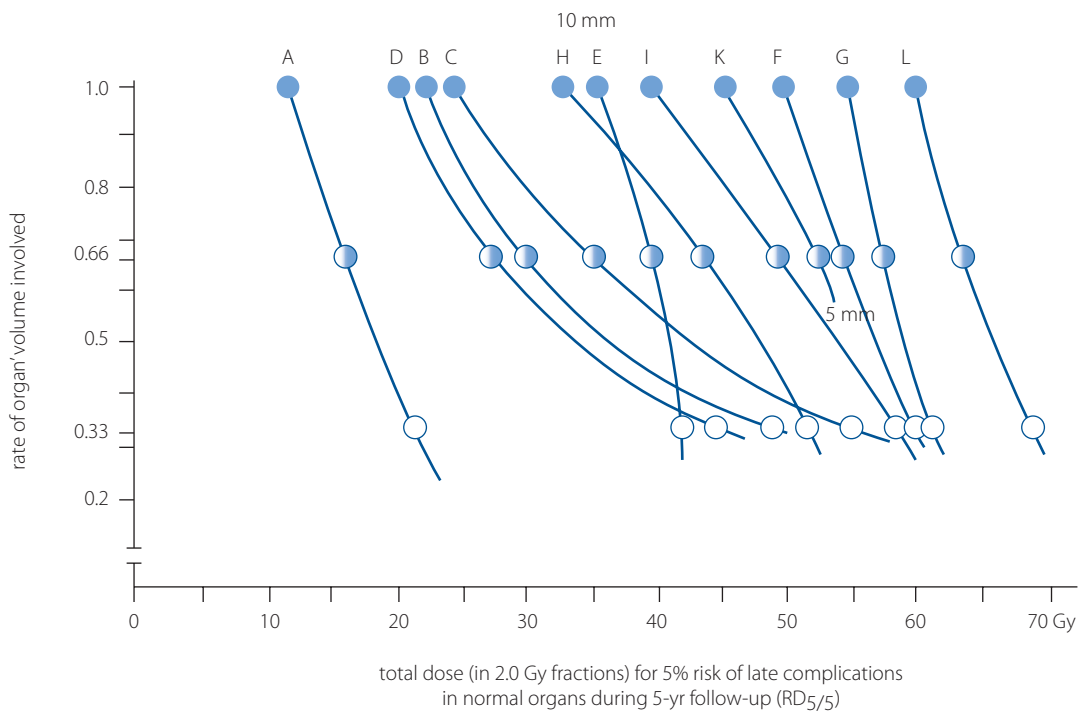
The kinetics, severity, duration and healing of the ARSEs depend on various factors and parameters, such as patient's age, epithelial atrophy, concomitant diseases (e.g. diabetes), smoking, alcohol abuse, energy of radiation, irradiation techniques (e.g. conformal IMRT, IART, V-MAT), the area of the 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



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

about 4–6 weeks. This definitely exceeds the limit of tolerance acceptable by the patients (fig. 2B, fig. 3).

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

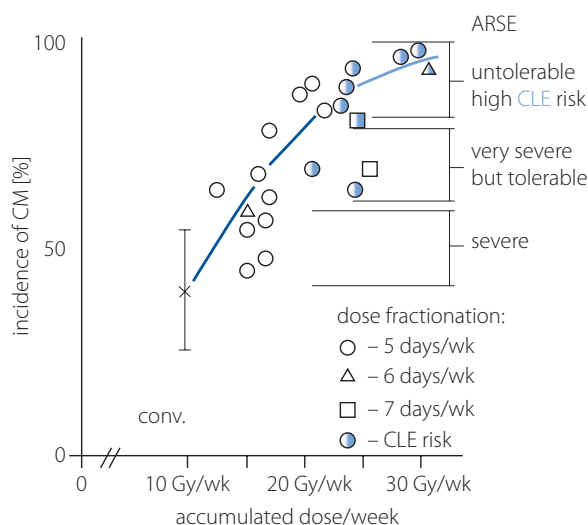
more years after completing the RT. They develop in highly differentiated and specialized tissues and organs in type F (flexible), whose cells lost proliferative (mitotic) activity and accumulated potentially sublethal damage. Their metabolism and function, however, remain untouched until some environmental, 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.

**Table I.** Physical (TD) and biological equivalent dose (BED  $TD \times [1 + di/\alpha/\beta]$ ) constraints for stereotactic hypo-fractionated radiosurgery (SHRS)

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



**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 hereditary 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 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 marrow, 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.

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**Bogusław Maciejewski**

*Maria Skłodowska-Curie National Research Institute of Oncology  
Gliwice Branch  
Div. Research Programmes  
Wybrzeże Armii Krajowej 15  
44-102 Gliwice, Poland  
e-mail: Boguslaw.Maciejewski@io.gliwice.pl*

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

Tomasz Piotrowski<sup>1, 2</sup>, Julian Malicki<sup>1, 2</sup>

<sup>1</sup>Department of Medical Physics, Greater Poland Cancer Centre, Poznan, Poland

<sup>2</sup>Department of Electroradiology, Poznan University of Medical Sciences, Poznan, Poland

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.

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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 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.

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**Tomasz Piotrowski**

*Greater Poland Cancer Centre*

*Department of Medical Physics*

*ul. Garbary 15*

*61-866 Poznań, Poland*

*e-mail: tomasz.piotrowski@me.com*

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# Evaluation of postoperative complications in the older population

Mateusz Sitkowski<sup>1,2</sup>, Jakub Kenig<sup>3</sup>

<sup>1</sup>Doctoral School in Medical and Health Sciences, Jagiellonian University Medical College, Krakow, Poland

<sup>2</sup>III Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

<sup>3</sup>Department of General, Gastrointestinal, Oncologic Surgery and Transplantology, I Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

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

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more important are elements of the Comprehensive Geriatric Assessment such as: functional activity, the presence of comorbidities, polypragmasia, nutritional, cognitive, and psychosocial status, which can allow one to determine the frailty status (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

**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

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 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

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

<b>Mild complication</b>	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.
<b>Moderate complication</b>	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
<b>Severe complication</b>	All complications requiring endoscopic or interventional radiologic procedures or re-operation as well as complications resulting in failure of one or more organ systems.
<b>Death</b>	Postoperative death.

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

<b>Mild complication</b>	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.
<b>Moderate complication</b>	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
<b>Severe: invasive procedure without general anesthesia</b>	Requires management by an endoscopic, interventional procedure or re-operation without general anesthesia.
<b>Severe: operation under general anesthesia</b>	Requires management by an operation under general anesthesia.
<b>Severe: organ system failure</b>	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.
<b>Death</b>	Postoperative death.



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 physician [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 Porem-bka 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

**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

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).

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:  $CCI = \sqrt{(CW1 + CW2 \dots + CWX)/2}$ , where CW means complication weight. An online calculator to calculate CCI is available at [https://www.assessurgery.com/about\\_cci-calculator/](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 proposed 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. Artilles-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.

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**Mateusz Sitkowski**

*Jagiellonian University Medical College*

*III Chair of General Surgery*

*ul. Prądnicka 35–37*

*31-202 Kraków, Poland*

*e-mail: mateusz.sitkowski@yahoo.com*

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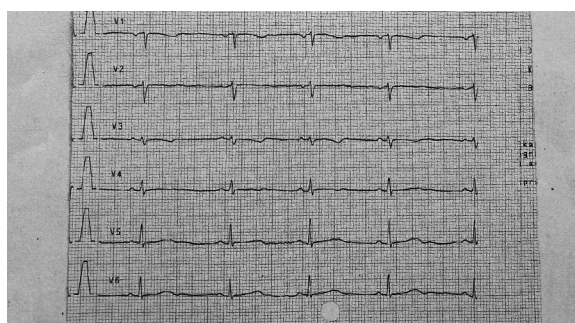
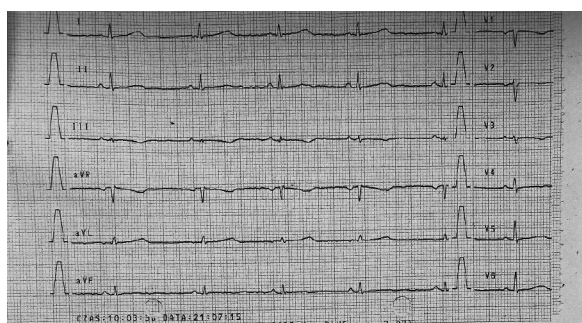


## QTc prolongations as a result of drug interactions of CD4/6 inhibitors

Aleksandra Grela-Wojewoda<sup>1</sup>, Mirosława Puskulluoglu<sup>1</sup>, Joanna Lompart<sup>1</sup>, Marek Ziobro<sup>1</sup>, Ewa Konduracka<sup>2</sup>

<sup>1</sup>Department of Clinical Oncology, Maria Skłodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland

<sup>2</sup>Department of Coronary Disease and Heart Failure, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland



**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].

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## Wilms tumor (nephroblastoma) – clinical and genetic aspects

Małgorzata Janeczko-Czarnecka<sup>1</sup>, Ryszard Ślęzak<sup>2</sup>, Wojciech Pietras<sup>1</sup>,  
Katarzyna Kiliś-Pstrusińska<sup>3</sup>

<sup>1</sup>Clinical Department of Paediatric Bone Marrow Transplantation, Oncology and Haematology, Faculty of Medicine, Wrocław Medical University, Wrocław, Poland

<sup>2</sup>Department of Genetics, Faculty of Medicine, Wrocław Medical University, Wrocław, Poland

<sup>3</sup>Clinical Department of Paediatric Nephrology, Faculty of Medicine, Wrocław Medical University, Wrocław, Poland

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,

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**Table I.** Congenital defects coexisting with Wilms tumor

System/organ	Type of defect
genitourinary system	cryptorchidism, hypospadias, 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

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].

### 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*, *CTNBN1*, *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

**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	<i>CDKN1C</i> 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	<i>NSD1</i>	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	<i>GPC3, GPC4</i>	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	<i>DIS3L2</i>	AR	fetal and neonatal macrosomia, facial dysmorphism, defects of the genitourinary system	65%	renal hamartomas
<i>PIK3CA</i> -related overgrowth spectrum	<i>PIK3CA</i>	S	segmental or focal overgrowth, vascular and lymphatic malformations, ventriculomegaly, epidermal nevi, skeletal anomalies, hypoglycemia, intellectual disability	1–2%	nephroblastomatosis
osteopathia striata with cranial sclerosis	<i>AMER1 (WTX)</i>	XL	macrocephaly, palate anomalies, deafness, facial dysmorphism, sclerosis of skull base, ophthalmoplegia, intellectual disability	5%	colorectal cancer
Bohring-Opitz syndrome	<i>ASXL1</i>	AD	growth deficiency, IUGR, microcephaly, characteristic facial features, distinct posture, seizures, intellectual disability, developmental delay, cardiac anomalies	7%	medulloblastoma
mulibrey nanism	<i>TRIM37</i>	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	<i>BUB1B, CEP57, TRIP 13</i>	AR	fetal growth delay (IUGR), microcephaly, intellectual disability, postnatal growth deficiency, microcephaly, dysmorphic features	10–85%	rhabdomyosarcoma, acute lymphoblastic leukemia, nephroblastoma
Denys-Drash syndrome	<i>WT1</i>	AD	46,XY sex reversal, gonadal dysgenesis, ambiguous genitals, congenital nephropathy, nephrotic syndrome	>90%	gonadoblastoma
Meecham syndrome	<i>WT1</i>	AD	46,XY sex reversal, ambiguous genitals, diaphragmatic abnormalities, genital defects and cardiac malformations, nephrotic syndrome	high risk	gonadoblastoma
WAGR	<i>WT1, PAX6</i> 11p13 deletion	AD	Wilms tumor (W) aniridia (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	<i>FANCD1 (BRCA2)</i> <i>PALB2</i>	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	<i>BLM</i>	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

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.

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 nonsyndromic 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, carboplatin 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<sup>2</sup> 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<sup>2</sup> 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

**Katarzyna Kiliś-Pstrusińska**

*Wroclaw Medical University*

*Faculty of Medicine*

*Clinical Department of Paediatric Nephrology*

*ul. Borowska 213*

*50-556 Wrocław, Poland*

*e-mail:* katarzyna.kilis-pstrusinska@umw.edu.pl

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# Adaptation of informed consent for anaesthesia to plain language standard

Wojciech Romanik<sup>1</sup>, Tomasz Piekot<sup>2</sup>, Radosław Tymiński<sup>3</sup>

<sup>1</sup>2<sup>nd</sup> Department of Anesthesiology and Intensive Care, Medical University of Warsaw, Warsaw, Poland

<sup>2</sup>Plain Polish Lab, University of Wrocław, Wrocław, Poland

<sup>3</sup>The Law Firm Radosław Tymiński, Warsaw, Poland

**Introduction.** The paper describes the process of editing and validating documents on the basis of which a patient gives their informed consent for anaesthesia before surgery. Our objective was to adapt such documents to plain language standards, thanks to which they will be more accessible to an average patient.

**Material and methods.** Two documents were drafted: *Information about anaesthesia* and *Informed consent for anaesthesia*. Within the editing process, we applied the principles of Plain Polish worked out for the Polish language.

**Results.** Similar documents available in Polish medical institutions were collected. For the comparison of the texts, the readability formula – Plain Language Index (PLI) – recently available in Poland was used. This algorithm assesses 10 properties of the style and, based on these, it measures the simplicity of the text.

**Conclusions.** Both documents which we designed obtained the standard of plain language (PLI 50% and more). They turned out to be the most accessible out of all the texts examined.

**Key words:** plain language, readability, informed consent, anaesthesia

## Introduction

The quality of the information communicated to a patient is frequently addressed in the rulings of the Supreme Court of Poland [1–5]. This paper discusses the linguistic aspect of those documents to which an adult patient gives their informed consent for a planned surgery. Our objective was to plan and then verify the documentation that meets the requirements of the international standard for plain language (while this text was being written, the ISO standard for plain language was almost ready: <https://www.iso.org/standard/78907.html>).

## Literature overview

In healthcare, informed consent is an important document both for the author and the recipient. Well-informed patients make conscious decisions with respect to their own health. They have also more realistic expectations, more satisfaction after a procedure, and, moreover, they tend to be more co-operative during the treatment [6]. On the other hand, high insurance costs against potential errors force the healthcare services providers to inform the patients about planned medical procedures connected with some risk of health complications, in a precise and effective manner.

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For this reason, in many countries, the institutions responsible for healthcare create the standards for drafting the informed consent forms [7–9]; yet, in some other countries, the adaptation of language to the level of education of an average citizen, with the status of 6–8 years of education on average, is imposed by legal regulations [10]. Therefore, it seems justified to prepare this information in Polish in such a way as to allow communication to be understood by the largest possible group of patients.

Unfortunately, research in the field of *health literacy* points to the fact that in many countries, the ability to understand medical information is poor or too diversified. The WHO research conducted in Europe, showed that in 10 countries, the rate of people with inadequate or problematic levels of reading competencies varies between 30% (Netherlands) and 60% (Bulgaria) – with a mean of approx. 48% [11].

The low level of *health literacy* in a population is not the sole problem. It is generally assumed that the incomprehensibility of informed consent is also the outcome of the manner in which these documents have been prepared for the patients [12]. The research confirms that the informed consents have a very low level of *readability* [13–15], failing to communicate all the required information (also in the field of language) [16]; that said, after reading, the patients themselves are satisfied with the information provided, yet they remember very little of the contents [17–18]. Difficult language, verbosity and poor composition result in the patients' lack of motivation to read the communications thoroughly [19]. In some way, it might be more effective to change the semiotic form of the document from verbal to a multimodal communication – especially, a more visual one [20].

This paper describes the process of drafting and validating the Polish-language documents which communicate the required medical information to the patient, in accordance with the plain language standard, i.e. in an accessible and structured manner. We also assume that such texts should be understandable for the average patient [21].

### **Legal context**

Regulations of Polish law require the patient to grant informed consent for a medical procedure, but they also stipulate that the forms of this consent may vary: written, oral or even implied [22]. In the case of surgical procedures and the procedures bearing an increased risk, it is required by law to obtain written consent from a patient [23].

In legal medical practice, it is unquestionable that a consent of a patient for anaesthesia before a medical procedure requires a written form. This standpoint is also the outcome of content of the regulation of the Minister of Health of 16<sup>th</sup> December 2016 on the organisational standard in anaesthesiology and intensive care, which stipulate that “a document containing the patient's consent to anaesthesia” must be included in the patient's medical file [24]. Hence it is necessary to draft the document of a consent for anaesthesia.

What is more – the regulations of Polish law, in some way, stipulate the requirements for the patient's consent in order to make it effective. And therefore, on the basis of the analysis of the sphere of *de lege lata*, the consent may be regarded as effective, provided that:

- the patient is authorised to grant the consent,
- the consent was granted before the procedure covered by the consent,
- the consent was granted consciously,
- The patient granted the consent in a situation that allowed for making a free decision [25–26].

What is especially vital for consideration and significant from the point of view of this paper, is the aspect of the patient's awareness, which was defined in legal terms. As it stems from the law, before giving consent, the patient must be informed about the *diagnosis, proposed and possible diagnostic and treatment methods, the outcomes which can be predicted once these methods are applied or abandoned, the treatment results and prognosis* [27–28].

What matters here is that the law directly requires that the consent be stipulated in an accessible manner [27–28]. Informing the patient in an appropriate way before the procedure has primary significance, as in court judicial practice, it is emphasised that the patient's very consent for a procedure, granted in such a situation when no accessible information was provided, cannot be treated as consent as defined by articles 32 and 34 of the Act of 1996 on the profession of a doctor and a dentist [3, 29].

The notion of *accessibility* of information so far has not received any extensive consideration in legal literature, although the majority of authors emphasise that the issue concerns the method of communicating information to the patient by a doctor, which must be adapted to the specific recipient in a specific health situation [26, 30]. What matters here is that the patient should understand the delivered information. Therefore, when communicating the information, a doctor should not only take into consideration the health condition of the patient (e.g. the effect of pain on the patient's awareness), but also their educational status, mental condition or the type and character of procedure [26, 30].

Given the above, the authors made the assumption that the essence of the obligation to inform a patient before a medical procedure is to make them aware of its necessity, course, risk and possible alternatives. However, in accordance with the guidelines formulated in the legal publications, *all the information obtained for the preparation of the consent forms, should be processed in a way that makes them understandable – even for a person with limited knowledge in medical, biological, physical and other fields* [31].

Also, the authors are aware that even the best wording of documents cannot replace a conversation between a doctor and a patient, yet they have the evidentiary significance, i.e. they point to the scope of information which was presented to the patient.



### **Anaesthesiologic context**

Anaesthesia is required for many surgical procedures. Before any surgery, a patient is consulted by an anaesthesiologist in order to be fully qualified for anaesthesia. Before the conversation with the anaesthesiologist, the patient fills in a questionnaire concerning their health status and reads some written information about anaesthesia. The conversation with the doctor is usually completed by the patient signing their consent for the agreed method of anaesthesia.

The described procedure, which makes up the core of standard preoperative procedures, may be modified to a large degree in many aspects and adapted to the needs and characteristics of a specific medical institution. That is why, both the questionnaire and the informed consent form are often prepared by the specific healthcare centres. Nevertheless, a common feature of these documents is specialist vocabulary and related medical issues.

On account of the assumed objective, the communicated information about the anaesthesia must be structured in the patient's mind – which can be done by means of legible titles given to specific paragraphs, their logical connection and the comprehensibility of reasoning. This issue is discussed in a further part of the paper. In the information about the types of anaesthesia, one must abandon, for example, a detailed explanation of the difference between a subarachnoid and epidural anaesthesia. From the patient's point of view, the description of both types of anaesthesia is similar, which also concerns a significant number of possible complications. If an anaesthesiologist predicts which type of anaesthesia will be applied, they should, during the obligatory talk with the patient, introduce to them the details of the specific procedure. A detailed description of both types of anaesthesia will significantly reduce the possibilities of understanding and seems to be unnecessary at this stage.

A lack of understanding seems to be noticeable when the submitted text *forces* the patient for interaction. It happens, for example, when a medical questionnaire is filled in. Frequently, no answers are provided, wrong information is ticked or the instructions are misunderstood. Such situations definitely point to the necessity of a talk with a doctor and the need for an explanation of the problematic issues before signing the consent for anaesthesiologic procedures.

Our practice shows that the most difficult part of the information about anaesthesia is the description of the risk involved, including the list of possible complications and adverse reactions. It is quite difficult to explain to a lay person many medical expressions, without complex descriptions. Apart from this, the number of possible complications and the degree of their influence on the health condition and probability of occurrence pose the next challenges for the authors of medical documents. What is more, during anaesthesia, a lot of medication is used, with each of them having their own list of possible adverse reactions. This means that it is impossible to present and explain all the possible complication to a patient [32].

A recommendation worth paying attention to, observed by practitioners, is the expression of the degree of probability of a specific complication relayed in the form of percentages or fractions [33]. Some anaesthesiologic coursebooks or brochures go one step further than a percentage evaluation, providing situations from real life, which correspond to a given value, such as a one person per a large city, the chance of throwing a six with a dice in a game, the chance of winning the jackpot. Infographics added to the text, could improve its understandability [34].

We would like to stress once again that written information remains merely a tool thanks to which the level of patient information may be higher; that said, personal contact between a doctor and a patient is necessary. Given the above challenges it seems that the key to solving them is the conversation between the anaesthesiologist and the patient. The talk should be personalised with time devoted to the analysis of the answers in the questionnaire, for questions to be asked by the patient, for explanations and for the selection of an optimal type of anaesthesia and procedure. Well-constructed information about the anaesthesia should be the starting point for the talk with the patient who may then ask questions which are suitable for their particular personality, health condition and cognitive needs. The task to present the final information, in particular referring to the type of anaesthesia is at the anaesthesiologist's discretion, as they are familiar with the patient's condition, medical history and results of the additional tests [35].

The patient's needs for information, safety, emotional and control depend on the communicative skills of the doctor, their experience and the amount of time devoted to the conversation with the patient. A doctor should always remember that non-verbal elements can foster the relationship with the patient, i.e. physical distance, body posture, look, touch, gestures and facial expressions all have an important influence on the sense of understanding and respect, belief in the doctor's competencies and the confidence in the proposed treatment [36].

## **Material and methods**

### **Initial objectives**

The authors' objective was to design and draft an anaesthesiologic set of documents which is compliant with plain language standards, addressed to adult patients expecting elective surgery, who are Polish speakers.

Before the works on editing a few significant assumptions were made.

1. The set of documents should consist of two texts:
  - informative part – i.e. a description of the procedures performed on the patient in connection with the anaesthesia,
  - consent part – i.e. a formal declaration of intent in which the patient confirms the receipt of all the communicated information and accepts all the proposed anaesthesiologic procedures.

- The medical questionnaire was excluded from the designed set of documents as this questionnaire does not have a form of a continuous text, making it impossible to perform any reliable quantitative research.
- Conclusions resulting from the literature review convinced the authors to use a more radical linguistic approach, expressed by the opinion that the use of the method simplifying the existing text, with the method generally accepted in the studies of plain language and medical practice will not be sufficient [37–38]. Re-editing the original text would cause an effect of superficial explanation, and so it would not solve the problem with an inadequate text composition or excessively formal relations between a doctor and the patient. Working out an effective consent from requires designing a text from the start – taking into consideration structural and relational problems.
- Finally, the authors decided to give up defining education as the factor verifying the communicativeness of the language of documentation. In Poland, the rate of persons with higher education increases quickly, yet the data concerning literacy have not been improving. In 2009, in Poland, 9.9% of people had higher education status, in 2011 – 16.8%, whilst in 2020, this rate was 39% (among people aged 25–54). In spite of this, book readership has remained at the same level since 2008 (7 and more books are read by 9–12% population) [39–41]. This disparity puts a question mark next to the readability formulas based on education, which, in Poland, do not seem to be a credible indicator of literacy.
- New documents were prepared in accordance with the plain Polish language model worked out at the University of Wrocław.

### The methods of text editing

When editing the text with procedure information and consent, we used three strategies of plain language, with special editing techniques ascribed to each of them. This method was prepared by the Plain Polish Lab at the University of Wrocław [42–43] and was used successfully not only by the major Polish offices, but also banks, insurance companies and even authors of scientific texts [44–45].

The first strategy consists of the preparation of a text for multiple browsing in search of necessary information. At this level, the principle of effective text structuring was introduced, such as headings, listings, tables, etc.

The second strategy consists of using grammar patterns that makes the text similar to the most popular texts, i.e. those read in one's free time (e.g. popular Internet services, daily and weekly papers). This linguistic accommodation concerns first of all the length of a sentence and the frequency of grammatical structures, such as passive voice, nominalisation or participles.

The third strategy leads to enhancing the interpersonal dimension of the text, which is obtained by direct reference to the reader and the use of the first person plural, and also various lexicography choices, for example the avoidance of official language and its substitution with everyday expressions or the use of empathic expressions.

A detailed list of editing techniques corresponding to specific strategies is presented in table I. The techniques are illustrated with examples from the text.

## Results

### Documents validation method

The next stage, after editing the documents, was the verification of their simplicity with the use of the Plain Language Index (PLI),

**Table I.** Plain language strategies and techniques applied for editing new documents

Plain language strategy	Text editing technique	Example (in English)
The text should be edited in such a way that a patient could browse it quickly.	1. The document should begin with an educational introduction.	<i>You are going to have a surgery soon. This document contains the most important information about the anaesthesia. Please, read the document carefully. You don't have to remember all the information. Just keep the copy to be able to refer to it later. Keep with you during the consultation with an anaesthesiologist.</i>
	2. Headings should have the form of questions.	<i>What is an anaesthesia? Who is an anaesthesiologist? How do I get prepared for the consultation? What kind of complications can occur after transfusion?</i>
	3. Complex events should be presented as chronological processes.	The text of the chapter: <i>What is general anaesthesia like?</i> were divided into three parts: Before the surgery, During the surgery, After surgery.
	4. Lengthy texts should be changed into tables.	In one table the complications after the two types of anaesthesia are compared (they are ordered with regards to the probability of occurrence).
	5. Lengthy texts should be changed into lists with numbers.	The information leaflet contains one list per page on average. The entire text of the consent has a form of a list with consecutive numbers.
Imitate the grammar of the texts which are read for pleasure.	6. Write short sentences (below words). One idea should be contained in one sentence.	<i>Remove your make-up. Do not put new make-up. Do not apply cream on the face or hands. Remove nail polish.</i>
	7. Avoid grammar constructions typical of impersonal and formal style (official language).	<i>to give consent -&gt; to agree in order to select an anaesthesia -&gt; to choose anaesthesia you will be taken -&gt; the nurse will take you</i>

**Table 1. cont.** Plain language strategies and techniques applied for editing new documents

Plain language strategy	Text editing technique	Example (in English)
Imitate the grammar of the texts which are read for pleasure.	8. Increase cohesion between sentences – show logical relations (use pronouns, conjunctions, words of reference).	<i>Some small procedures and exams may be performed without anaesthesia. Doctors will tell you about such an option. You can choose if you want to get anaesthesia. The majority of procedures and surgeries require anaesthesia.</i>
	9. Avoid medical terminology or explain it.	<i>Sometimes during a surgery you may lose a lot of blood. Then you will need a transfusion (in other words: you will have to get blood). Transfusion means giving new blood through an infusion (in a drip). Sometimes other blood products are given.</i>
	10. Avoid 2-word terms consisting of an adjective + noun.	<i>On the surgery day a nurse will take you to the operating room. She can propose to take you there on a wheeled stretcher. In the operating room you will lie down on an operating bed.</i> -> <i>On the surgery day a nurse will take you to the operating room. She can propose to take you there on a wheeled stretcher. In the operating room you will lie down on an operating bed.</i>
Ensure interpersonal relations.	11. Address the reader directly.	<i>Just before the surgery the anaesthesiologist will give you an oxygen mask to breathe. From this moment you will begin getting anaesthesia. You will fall asleep a few moments later. Then the doctor will put a tube for breathing through your mouth. The anaesthesia machine will do the breathing for you. You will get the necessary drugs.</i>
	12. Avoid using male gender. Use neutral language.	specific for Polish
	13. When speaking about your institution, write "we".	<i>The research shows that some complications are more frequent, and others occur very rarely. Here we describe the majority of complications. <u>We do not do</u> this to scare you. <u>We simply want</u> to warn you.</i>
	14. Avoid formal (official) vocabulary.	<i>I am aware that the reaction of my body to anaesthesia is unpredictable.</i> -> <i>I understand that it is not possible to predict the reaction of my body to anaesthesia.</i>
	15. Speak openly and with compassion.	<i>If you have any complaints, please tell the medical staff about it. They are here to give you relief and to take care of you. After some time, the nurses will take you to the surgical department.</i>

i.e. the index which assesses the percentage degree in which the examined text meets the requirements of Plain Polish Standard. The PLI index measures 10 properties of style, whilst meeting the standard by each of the properties, means scoring 10 percentage points by the text. PLI assesses texts written in Polish and it is available with Logios applications (<https://logios.dev/>).

The PLI percentage score is calculated on the basis of 10 properties of style.

#### Vocabulary selection

1. Formal words (FORMAL) – this parameter shows how many formal words there are in the text. These words make the style formal and official.
2. Terminology (TERMS) – this parameter shows how many 2-word specialist expressions, such as: adjective + noun there are in the text. They make the text incomprehensible for non-professionals.
3. Most frequent words (TOP100) – this parameter calculates how many of the most frequent words there are in the text (from the frequency list of 100 words). They make the subject matter of the text easier to understand.
4. Difficult words (DWORDS) – this parameter shows how many infrequent and at the same time long words there are in the text. Their presence increases the vagueness of the language.

5. Pronouns (PRON) – this parameter measures the rate of pronouns in the text. A high frequency of this part of speech makes the language sound natural and the text coherent.

#### Sentence construction

6. Verbalization (N/V) – this parameter shows whether the style of the text is more verb-oriented (a desired property) or noun-oriented (undesired property). The verbs are the informative core of a sentence so there should be as many verbs in the text as possible.
7. Confusing grammar (GRAM) – this parameter shows how many names of actions are present in the text in the form of participles, passive voice, gerunds and impersonal verbs.
8. Sentence length (ASL) – this parameter calculates the mean sentence length, i.e. the number of words within a sentence. Attractive texts do not contain sentences which are longer than 15 words.

#### Relations

9. The presence of the sender (SENDER) – this parameter shows how often the sender reveals their presence in the sentence. In Polish this can be manifested by the use of pronouns (I, me, our) or verbs (I would like to ask, I welcome

you) referring to the first person. The larger presence of the sender, the more relational the text is.

- The presence of the receiver (RECEIVER) – this parameter shows how often the sender addresses the receiver directly. In Polish this can be done with the use of pronouns (you, your) or verbs (send, take) referring to the second person. The more such expressions are used, the more relational the text is.

The text designed by the authors was compared, with reference to the PLI index and its 10 components, to analogous texts currently used in Poland in public and non-public healthcare centres. With the Google search engine, we collected 20 educational information leaflets and 15 consent forms. One of the consent forms was excluded from the study on account of its inadequate text length (less than 30 words). Finally, 20 educational information leaflets and 14 consent forms were collected.

## Results

### Information leaflets about anaesthesia

The analysis of the readability of the information concerning anaesthesia shows that the texts which are currently used, realise only to a minor degree, the plain language standard (tab. II). The typical information, as expressed with median value, obtains 10% PLI, whilst the simplest information about the anaesthesia: 28% PLI (hospital 3). The text designed by the authors, obtained a PLI of 50%, which is an acceptable level of plain language (defined as a level of at least 40%). In our version, the plain language standards were obtained by five out of ten features: pronoun presence, noun to verb ratio, inaccessible grammar and addressing the reader. Other properties did not reach the standard values of plain language, although they ranked much higher than typical information leaflets (as expressed by the median calculated for the examined documents).

**Table II.** The ranking list of the accessibility of information concerning anaesthesia. The table presents Plain Language Index (PLI) and its 10 constituents

Text	PLI	FORMAL	TERMS	TOP100	DWORDS	PRON	N/V	GRAM	ASL	SENDER	RECEIVER
our version	50%	3,55%	<u>39.40%</u>	40.60%	8.42%	<u>4.02%</u>	<u>1.61</u>	16.60%	<u>8.51</u>	<u>1.12%</u>	10%
hospital 3	28%	9.07%	63.10%	30.70%	16.30%	1.05%	2.09	48.40%	17.1	0.26%	2%
hospital 1	24%	8.22%	53.40%	30.30%	15.40%	0.77%	2.41	49.70%	14.2	0.39%	2.57%
hospital 11	20%	7.46%	53.50%	32.30%	12.30%	1.22%	2.27	44.20%	18.6	1.37%	1.29%
hospital 12	20%	5.68%	47.10%	33.30%	14.50%	0%	2.09	40.90%	12.4	0.46%	0.68%
hospital 6	17%	7.98%	59%	26.90%	16.40%	0.50%	2.49	51.90%	15	0.82%	2.23%
hospital 9	17%	7.93%	54.50%	28.20%	17.90%	1.01%	2.16	48.30%	16.7	0%	0%
hospital 16	16%	8.72%	55.80%	28.70%	15.80%	0.54%	2.45	49.40%	16.9	0.86%	2.21%
hospital 4	15%	7.71%	52.10%	30.10%	13.60%	1.15%	2.51	46.50%	18.6	0%	0.53%
hospital 12	11%	8.60%	58.80%	30.90%	15.30%	0.46%	2.32	48%	15.1	0.53%	1.70%
hospital 17	10%	9.64%	53.20%	28.60%	18.10%	0.53%	2.02	52.10%	16.4	0.60%	0.30%
hospital 18	10%	12.30%	63.30%	24.70%	20.80%	1.39%	3.41	56.90%	16	0%	0%
hospital 10	6%	8.54%	56.90%	27.70%	15.10%	0.36%	2.48	46.50%	16	0.62%	0.41%
hospital 19	6%	9.90%	54%	27.60%	17.10%	0.17%	2.48	53.70%	15.7	0%	0.39%
hospital 20	6%	8.89%	58.50%	30.90%	14.10%	0.28%	2.44	50.80%	17.4	0.48%	0.64%
hospital 7	6%	6.69%	59.10%	29.80%	13%	0.55%	2.47	46.60%	18.7	0.63%	1.03%
hospital 8	5%	5.61%	57%	28.80%	13.30%	0.41%	2.52	40%	16.1	0.64%	0.48%
hospital 15	4%	7.93%	56.70%	27.10%	17.80%	0.18%	2.56	52.40%	19.7	0%	0.10%
hospital 14	3%	8.35%	49.50%	31.10%	15.80%	0.78%	2.71	52%	17.9	0.76%	1.39%
hospital 13	0%	6.46%	58%	28.20%	13.30%	0.53%	3.19	43.90%	19.9	0.12%	0.85%
hospital 5	0%	7.96%	61.70%	26.80%	15.20%	0.58%	2.98	56.40%	19.2	0.90%	0.11%
mean	11.2%	8.2%	56.3%	29.1%	15.6%	0.6%	2.5	48.9%	16.9	0.5%	0.9%
median	10.0%	8.1%	56.8%	28.8%	15.4%	0.5%	2.5	48.9%	16.8	0.5%	0.7%

The abbreviations in the headings are explained in section Material and methods. The data in the table were sorted from the highest to the lowest according to the value of the Plain Language Index (PLI). With our version of the text about the anaesthesia (the first line in the table) the values which reached the standards of the plain language are underlined. The mean and median values are calculated for the compared texts: hospital 1 to hospital 20.

**Table III.** The ranking list of the accessibility of consents for anaesthesia. The table presents Plain Language Index (PLI) and its 10 constituents

Institution	PLI	FORMAL	TERMS	TOP100	DWORDS	PRON	N/V	GRAM	ASL	SENDER	RECEIVER
our version	50%	6.55%	<u>24.00%</u>	43.90%	10%	<u>2.17%</u>	<u>1.95</u>	34%	<u>12.6</u>	<u>10.90%</u>	0.87%
hospital 10	45%	14.10%	42.90%	33.80%	11.30%	3.53%	1.05	45.80%	14.2	12.70%	2.82%
hospital 9	43%	13.60%	28.60%	33.90%	13.60%	1.41%	0.818	39.10%	14.8	16.90%	0%
hospital 3	38%	8.25%	44.40%	39.20%	10.30%	3.54%	1.58	40.90%	13.6	9.28%	0%
hospital 12	36%	10.80%	33.30%	36.50%	16.20%	2.38%	1.73	57.90%	18.5	10.80%	0%
hospital 8	35%	9.03%	50%	33.30%	16%	2.37%	2.04	48.30%	14.1	9.03%	0%
hospital 1	30%	10.20%	46.70%	40.60%	14.20%	4%	1.15	37.80%	25.4	13.40%	0%
hospital 11	30%	13.70%	37.50%	36.60%	14.90%	2.53%	1.87	55.30%	21.1	7.43%	0%
hospital 13	30%	11.10%	52.90%	34.40%	19.40%	1.30%	1.65	55.20%	16.9	10.30%	0%
hospital 14	30%	11.70%	40%	41.70%	16.70%	3.55%	1	42.50%	17.1	15.80%	0%
hospital 6	30%	9.29%	41.20%	40.40%	14.20%	3.30%	1.43	42.60%	17.4	11.90%	0%
hospital 7	30%	9.33%	53.30%	42%	19.20%	3.03%	1.21	48.30%	17.5	13%	0%
hospital 2	27%	8.80%	60%	28%	22.40%	1.31%	2.43	59.30%	15.6	6.40%	0%
hospital 4	27%	11.60%	45.80%	33.50%	13.40%	1.02%	1.68	51.20%	18.2	10.40%	0%
hospital 5	27%	15.70%	52.40%	30.90%	21.90%	1.46%	2.38	56.40%	17.4	6.18%	0%
mean	32.7%	11.2%	44.93%	36.06%	15.98%	2.48%	1.57	48.61%	17.27	10.97%	0.20%
median	30.0%	11.0%	45.1%	35.5%	15.5%	2.5%	1.62	48.3%	17.25	10.6%	0.0%

The abbreviations in the headings are explained in section Material and methods. The data in the table were sorted from the highest to the lowest according to the value of the Plain Language Index (PLI). With our version of the text with the consent for anaesthesia (the first line in the table) the values which reached the standards of the plain language are underlined. The mean and median values are calculated for the compared texts: hospital 1 to hospital 14.

### Consent for anaesthesia

In the case of consents for anaesthesia, the differences between the analysed texts of consent forms in comparison with the text of our consent form are not that large (tab. III). An average consent, as expressed by the median, obtains 30% PLI, whilst two best consent documents obtained the satisfactory level of simplicity (PLI 40%), i.e. 43% (hospital 9) and 45% (hospital 10). The consent form edited by the authors ranks first with a PLI at a level of 50%.

In comparison with the information leaflet – our consent gained the plain language standard in reference to the terminology and the sender's presence, scoring worse with regards to confusing grammar and addressing the reader. The differences, however, are easy to explain. The text of the consent form is a declaration of intent and therefore is subject to a formal requirement which is greater than in the text of information about anaesthesia. Hence the level of confusing grammar is higher (information: 16.6% GRAM, consent: 34% GRAM). The specifics of this type of text also explains the failure to meet the standard to the relational forms in addressing the reader. As the consent is granted by the patient themselves, the text is written from the perspective of the first person singular (me). Therefore, frequent addressing the patient directly is not possible.

### Discussion and conclusions

Anaesthesiologic documents edited in accordance with the plain language standards, turned out to be accessible enough. What is more, both the information document and the consent had similar levels of plain language. In comparison with the analysed documents used currently by Polish medical institutions, we managed to simplify the text about the anaesthesia (50% PLI vs. median of the analysed texts: 10% PLI). Difference of 40 p.p. PLI guarantees a good readability of text.

The high value of the Plain Language Index does not mean, however, that the texts edited by the authors are understandable. Understandability, or rather the efficiency of such documents, cannot be examined without the users. Understandability can be appreciated only after clinical verification. The next step of the validation should therefore be the tests with potential and real patients. The method of recalling text from memory and solving tasks may be promising.

The next stage in designing the examined documents should be completing the text of the information leaflet with some other semiotic codes, such as infographics or illustrations, the selection of appropriate font size and type and final graphic layout. The connection of our text with the visual

graphic elements listed here should become the subject of separate studies.

A separate objective should be the radical simplification of the processed documents in a way they can be understandable for persons with special communication needs, such as people with aphasia, dementia or intellectual impairment. The principles of communication with such a diverse group of recipients are regulated by dedicated standard: *easy language*, and in Poland – the act on guaranteeing accessibility [46]. From this perspective, both information and the consent should be presented in two variations, with the first being the plain language standard and the other – easy language.

The documents used for obtaining informed consent should be periodically updated and verified by competent interdisciplinary teams. Currently, medicine is developing not only in technical and substantive terms (evidence based medicine – EBM), but also with respect to medical communication (e.g. the awareness of the significance of soft competencies) as well as an holistic and individual approach to a patient (evidenced for example by the multidisciplinary Heart Teams), or the healthcare organisations (enhanced recovery after surgery protocol [ERAS] – a comprehensive form of perioperative care for the improvement of the treatment results). This gives hope, especially for patients and their families, for better results of treatment, emotional support and filling in the often confusing information gap.

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**Tomasz Piekot**

University of Wrocław  
Plain Polish Lab  
pl. Uniwersytecki 1  
50-148 Wrocław, Poland  
e-mail: tomasz.piekot@uwr.edu.pl

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