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02-781 Warszawa, Poland

Address for correspondence:
Krakowska Akademia im. Andrzeja Frycza-Modrzewskiego
ul. Gustawa Herlinga-Grudzińskiego 1
30-705 Kraków, Poland
room 309
phone: 512 177 774

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Quality of life at 3 to 5 years after surgical treatment of renal cell carcinoma – a pilot cross-sectional study

Magdalena Tarkowska[1], Iwona Głowacka-Mrotek[2], Damian Peterson[1], Michał Jankowski[3], Beata Pilarska[1], Łukasz Leksowski[2], Dorota Ratuszek-Sadowska[2], Anna Lewandowska[2], Piotr Jarzemski[1]

[1]*Department of Urology, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland*
[2]*Department of Rehabilitation, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland*
[3]*Department of Surgical Oncology, Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland*

Introduction. Predicted distant health-related quality of life is one of the key elements in the long-term assessment of the effectiveness of therapy, and a factor to be taken into account when deciding upon the choice of therapeutic options in modern cancer surgery. To assess the quality of life of patients having undergone surgical treatment for renal cell carcinoma.

Material and methods. This cross-sectional study was carried out in a group of 44 (17 radical nephrectomy [RN], 27 nephron-sparing surgery [NSS]) patients having received surgical treatment for renal cell carcinoma at the Department of Urology of the University Hospital no. 2 in Bydgoszcz. The control group consisted of 24 subjects within a matching age range. The standardized WHOQOL-BREF questionnaire was used as the study tool.

Results. No statistically significant differences ($p > 0.05$) were observed with regard to the subjectively assessed quality of life depending on the type of surgery performed, i.e. RN *vs.* NSS. A positive correlation was observed between the higher scores within the social ($p = 0.0453$) and environmental ($p = 0.0156$) domains and the laparoscopic approach. Lower scores within the somatic ($p = 0.0023$), environmental ($p = 0.0189$) and emotional ($p = 0.0356$) scale domains were observed in female patients. A statistically significant inverse relationship was observed between the cancer stage and the self-assessed overall health scores ($p = 0.0025$).

Conclusions. Minimally invasive surgical techniques open up the potential for the achievement of better quality of life of patients after surgery. Clinical and demographic variables influence the long-term health-related quality of life scores.

Key words: cancer, nephrectomy, nephron-sparing surgery, quality of life

Introduction

Renal cell carcinoma accounts for 3% of all malignancies diagnosed among adult patients in Poland. Epidemiological data indicate that the disease most frequently develops between 50 and 70 years of age. It contributes to approximately 3% and 2% of deaths in male and female subpopulations, respectively. The multifactorial etiology of renal cell carcinoma points to the genetic and environmental background

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of the disease [1, 2]. Surgery including complete (radical nephrectomy – RN) or partial (nephron-sparing surgery – NSS) resection of the kidney is the primary treatment method. Radical nephrectomy involves the resection of the kidney, perirenal fat, lymph nodes, and adrenal glands. This approach had been the standard of treatment for many years; however, nephron-sparing surgeries involving tumor enucleation or partial nephrectomy have been used with increasing frequencies in recent years. The development of minimally invasive surgical techniques has resulted in the laparoscopic approach becoming the most common treatment as being associated with shorter convalescence [3–5].

Regardless of its location, cancer may be responsible for numerous adverse changes in the daily functioning of patients, affecting the physical, emotional, and social domains of their lives [6]. The diagnosis and the need for immediate treatment are by themselves stress factors that impair the health-related quality of life (HRQOL) [5]. Therefore, due to the continuously increasing rates of 5-year survival in patients with urogenital cancers, the predicted HRQOL is taken into account as one of the key elements in the assessment of therapeutic effectiveness when deciding upon the choice of therapeutic options. Sociodemographic and clinical variables such as postoperative complications, time since the procedure, and cancer stage strongly influence numerous facets of patient's functioning, and therefore it is extremely important that they be taken into account in research planning [7, 8]. The main objective of this study was to assess the quality of life of patients having undergone unilateral complete or partial resection of the kidney due to renal cell carcinoma cancer 3 to 5 years after surgery, as compared to the control group of healthy subjects.

Material and methods

This cross-sectional study was carried out in a group of 44 patients with the diagnosis of renal cell carcinoma who had received surgical treatment at the Department of Urology of the University Hospital no. 2 in Bydgoszcz in the years 2016–2018. The patients were divided into 2 groups, depending on the type of surgical procedure: 17 patients had been subjected to unilateral RN, while the other 27 patients had been qualified for NSS. All patients had normal contra lateral kidney function. The quality of patients' life was assessed 3 to 5 years after the surgery. A control group was also established, which consisted of 24 people of similar age and with no history of the aforementioned procedures. The control group was recruited from among the students of the Third Age University at the WSG University in Bydgoszcz. A diagnostic survey method was used to collect study data, with the validated WHOQOL-BREF questionnaire being used as the research tool.

The WHOQOL-BREF questionnaire is a tool designed to assess health-related quality of life – regardless of the disease entity. It can be used in both sick and healthy individuals. In this paper, a brief version of the questionnaire was used, consisting of 26 questions assessing the physical, environmental, social, and emotional functioning as well as the overall quality of life and health of patients. The respondents provided answers to individual questions using a scale of 1 to 5 points. Summary scores were calculated separately for each of the domains, with the minimum and maximum scores amounting to 4 and 20 points, respectively. With regard to the interpretation of the results, the higher the mean score, the better the patients' subjective assessment of the quality of life within a particular domain. In addition, a proprietary questionnaire had been developed to evaluate demographic variables, i.e. age, gender, educational background, area of residence, number of children, marital status, and economic status of patients. The medical documentation of patients was analyzed to collect clinical data. Information on body weight, height, body mass index (BMI), laterality of the surgery, postoperative complications, cancer stage, type of surgery, and the duration of hospital stay were extracted from medical documentation for the purposes of statistical analysis. The research project was approved by the Bioethics Committee at the Nicolaus Copernicus University in Torun (no. 179/2022). Participation in the study was voluntary. Each participant was informed about the study purpose, method, and conditions.

Inclusion and exclusion criteria had been defined to establish a homogeneous study group.

The inclusion criteria included:

- written consent to participate in the study,
- histopathologically confirmed stage I–IV renal cell carcinoma,
- overall Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 at the time of the study,
- history of unilateral complete or partial resection of kidney due to renal cell carcinoma as performed 3–5 years prior to the study at the Department of Urology of Biziel University Hospital No. 2 in Bydgoszcz,
- age of 18 or above at the time of qualification for the surgery.

The exclusion criteria included:

- an active cancer disease,
- uncontrolled mental disorders,
- other serious diseases (ASA IV),
- other invasive, abdominal, surgical procedures in observed time,
- other malignant tumorsin observed time.

In the years 2016–2018, a total of 108 complete unilateral kidney resections and 151 unilateral partial kidney resections were performed at the Department of Urology of Biziel University Hospital No. 2 in Bydgoszcz. Telephone contact was obtained with 144 patients (RN: 63, NSS: 81); 91 of these patients expressed willingness to participate in the project, and a total of 79 patients reported at a predefined date to take part in the study combined with a follow-up visit at the Department

of Urology of Biziel Hospital in Bydgoszcz. The inclusion criteria were met by 44 patients (17 RN, 27 NSS). Overall, 44 patients constituting the study group and 24 subjects constituting the control group were included in the statistical analysis.

Statistical analysis

Statistical analyses were carried out using the PQStat software package (version 1.8.4.152). Fisher's exact test was used in the analysis of the qualitative scale scores within the compared groups. Quantitative scale scores were compared between the study groups using the Kruskal–Wallis test and the post-hoc Dunn's test with the Bonferroni correction. The Mann–Whitney U-test was used in the analysis of hospital stay times. For $k = 2$, the quality of life within the compared groups was analyzed using the Man–Whitney U-test, whereas the Kruskal–Wallis test and the post-hoc Dunn test with the Bonferroni correction as well as the Jonckheere trend test were used for $k > 2$. A probability value of $p < 0.05$ was used as the significance level and $p < 0.01$ was used as the high significance level.

Results

The study sample was characterized interms of demographic variables, i.e.:

- age,
- weight,
- height,
- BMI,
- educational background,
- area of residence,
- employment status,
- number of children,
- marital status,
- sociodemographic status,
- gender.

Statistical analysis revealed no statistically significant differences ($p > 0.05$) between the study groups with respect to all the demographic variables with the exception of gender, height, and area of residence.

The distribution of the area of residence was significantly related to the study group ($p = 0.2526$). Urban residents accounted for 66.67% of the RN group as compared to 94.12% in the NSS group and 95.83% in the control group. Height was significantly higher in patients with complete resection than in the control group ($p < 0.01$). Gender distribution was also significantly dependent on the study group ($p < 0.01$), with female patients accounting for 22.22%, 52.94%, and 87.5% of subjects within the RN, NSS, and control groups, respectively. Detailed results are presented in tables I and II.

The study sample was also characterized using selected clinical data, such as the laterality of the surgery, postoperative complications, cancer stage, type of surgery, body weight, height, BMI, and hospital stay duration. Statistically significant differences ($p < 0.05$) were observed between the groups in relation to cancer stage and type of surgery.

A significant difference ($p = 0.0334$) was noted between the study groups in relation to cancer stage. In the NSS group, stage I cancer accounted for 88.24% of cases, whereas stage II cancer accounted for the remaining 11.76% of cases. In the RN group, stage I cancer accounted for 48.15% of cases, stage II cancer for 18.50%, stage III for 18.52%, and stage V cancer for 14.81% of cases.

A significant difference ($p = 0.0298$) was also noted between the study groups in relation to the type of surgical approach. In the NSS group, laparoscopic surgery was performed in 82.35% of patients as compared to 48.15% of patients in the RN group (tab. III, IV).

Next, the quality of life of patients within the study groups was assessed using the WHOQOL-BREF questionnaire. Deta-

Table I. Age and body build within the compared groups

RN		Age			Body weight			Height			BMI		
		NSS	K	RN	NSS	K	RN	NSS	K	RN	NSS	K	
M		66.0	60.3	66.5	84.4	81.4	74.9	169.0	165.3	163.8	29.5	29.9	28.0
Me		67	66	68	83	78	76.5	170	163	160	29.4	29.9	27.0
SD		9.5	14.2	7.3	18.9	11.0	11.5	6.2	9.05	7.2	6.2	4.2	4.8
Kruskal–Wallis test	df		2			2			2			2	
	H		1.1248			3.429			9.6665			1.768	
	p		0.5698			0.1801			0.008			0.4131	
post-hoc Dunn–Bonferroni	RN		1	1		1	0.2272		0.0897	0.0099		1	1
	NSS	1		0.933	1		0.5856	0.0897		1	1		0.5521
	K	1	0.933		0.2272	0.5856		0.0099	1		1	0.5521	

M – arithmetic mean; Me – median; SD – standard deviation; RN – radical nephrectomy; NSS – nephron-sparing surgery; K – control group; p – statistical significance; df – degrees of freedom; H – test statistics

Table II. Sociodemographic characteristics of the compared treatment groups

		Group						Fisher's exact test
	RN		NSS		K			
	N	%	N	%	N	%		
educational background	vocational	6	35.29%	7	25.93%	2	8.33%	p = 0.3381
	higher	4	23.53%	7	25.93%	8	33.33%	
	secondary	7	41.18%	12	44.44%	14	58.33%	
	elementary	0	0%	1	3.7%	0	0%	
area of residence	rural	9	33.33%	1	5.88%	1	4.17%	p = 0.0117
	urban	18	66.67%	16	94.12%	23	95.83%	
employment status	own business	1	3.7%	0	0%	1	4.17%	p = 0.2526
	regular job	6	22.22%	6	35.29%	2	8.33%	
	disability pension	1	3.7%	1	5.88%	0	0%	
	retirement	19	70.37%	10	58.82%	20	83.33%	
	unemployed	0	0%	0	0%	1	4.17%	
number of children	4	2	7.41%	0	0%	0	0%	p = 0.6423
	3	5	18.52%	2	11.76%	2	8.33%	
	2	14	51.85%	7	41.18%	13	54.17%	
	1	4	14.81%	5	29.41%	7	29.17%	
	0	2	7.41%	3	17.65%	2	8.33%	
marital status	single	4	14.81%	2	11.76%	7	29.17%	p = 0.3587
	in a relationship	23	85.19%	15	88.24%	17	70.83%	
socioeconomic status	poor	0	0%	1	5.88%	1	4.17%	p = 0.1395
	medium	9	33.33%	11	64.71%	10	41.67%	
	good	17	62.96%	4	23.53%	11	45.83%	
	excellent	1	3.7%	1	5.88%	2	8.33%	
gender	male	21	77.78%	8	47.06%	3	12.5%	p < 0.0001
	female	6	22.22%	9	52.94%	21	87.5%	

RN – radical nephrectomy; NSS – nephron-sparing surgery; K – control group; p – statistical significance

iled results on the overall global quality of life, self-assessed health status, and scores within the somatic, emotional, social and environmental domains are presented in figure 1. No statistically significant differences ($p > 0.05$) were observed in the statistical analysis in relation to the type of surgery performed, i.e. RN *vs*. NSS.

In the next stage, the impact of demographic and clinical variables on the quality of life was analyzed within all domains of the BREF questionnaire. Patients' gender was the only demographic variable responsible for significant differences as observed in RN *vs.* NSS groups in the QOL scores within the somatic ($p = 0.0023$), environmental ($p = 0.0189$), and emotional ($p = 0.0356$) scale domains. Lower results, and thus poorer self-assessed quality, were reported in these domains by female subjects. With regard to clinical variables, the clinical stage of cancer had a highly significant ($p = 0.0025$) impact on the differences in the overall health scores as reported by study groups; the differences followed a highly significant inverse trend, i.e. the higher the stage of the disease, the lower the health scores. In addition, significant differences were observed within the social ($p = 0.0453$) and environmental ($p = 0.0156$) domains depending on the surgical approach: laparoscopic *vs.* open surgery. Better scores translating to better quality of life were significantly correlated with the laparoscopic method. Detailed results are presented in figures 2 and 3.

Table III. Clinical data recorded within the compared treatment groups

		Group				Fisher's exact test
		RN		NSS		
		N	%	N	%	
laterality	bilateral	0	0%	2	11.76%	p = 0.0605
	right-sided	14	51.85%	4	23.53%	
	left-sided	13	48.15%	11	64.71%	
post-procedural complications	yes	3	11.11%	3	17.65%	p = 0.6619
	no	24	88.89%	14	82.35%	
stage	IV	4	14.81%	0	0%	p = 0.0334
	III	5	18.52%	0	0%	
	II	5	18.52%	2	11.76%	
	I	13	48.15%	15	88.24%	
surgical approach	open	14	51.85%	3	17.65%	p = 0.0298
	laparoscopic	13	48.15%	14	82.35%	

RN – radical nephrectomy; NSS – nephron-sparing surgery; p – statistical significance

Table IV. Duration of hospital stays in the compared treatment groups

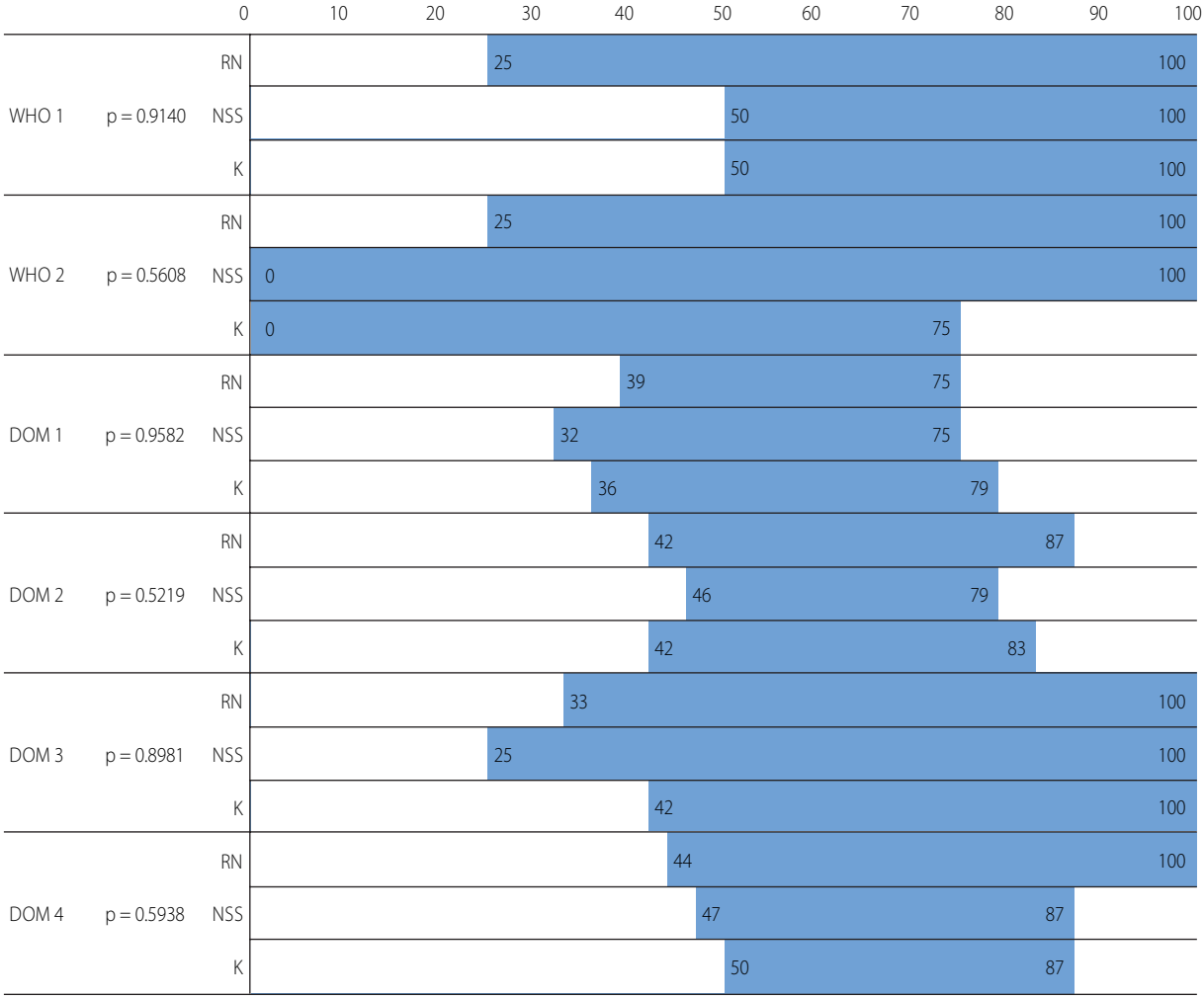
		Group		
		RN	NSS	K
M		7.963	9.3529	–
Me		7	8	–
SD		3.4248	3.8881	–
Mann–Whitney U-test	Z		1.1281	
	p		0.2593	

M – arithmetic mean; Me – median; SD – standard deviation; RN – radical nephrectomy; NSS – nephron-sparing surgery; K – control group; p – statistical significance; Z – Z-statistic

Discussion

The present study assesses health-related quality of life among patients operated on for renal cell carcinoma 3–5 years after surgery. The effect of the clinical and demographic variables on the subjective health-related quality of life (HRQOL) scores was also analyzed. Included in this cross-sectional study were patients having undergone complete renal resection and partial renal resection (NSS). An age-matched group of healthy controls was also included. The study tools included the standardized WHOQOL-BREF questionnaire as well as a proprietary form to evaluate socioeconomic variables. Clinical data as extracted from the medical documentation of patients were also included in the statistical analysis.

Many authors have pointed out the need for appropriate studies assessing the quality of life of patients with a diagnosis of renal cell carcinoma who were subjected to various therapeutic options [9–11]. Our study revealed no statistically significant differences within the environmental, emotional, social, and physical dimensions of health-related quality of life, as well as the overall subjective health and quality of life assessments among patients subjected to total and partial renal resection; this is in line with the results previously obtained by other authors [8, 12]. The purpose of NSS was to preserve kidney function, and it is this preservation rather than the mere difference in the surgical option (RN *vs*. NSS) that has been pointed out by other authors as a factor with a significant impact on HRQOL scores [12]. On the other hand, other studies had provided evidence of the somatic symptoms, such as i.e. fatigue, insomnia and pain(being less severe), and the scores within the physical domain being higher in patients after NSS [8,10], including as late as 4 years after the procedure [13]. The perioperative and distant benefits of NSS were also confirmed by the results of a systematic review by MacLennan et al. who highlighted the impact of "non-oncological" QOL related outcomes on patients' satisfaction with the medical care received [14].



WHO 1– overall quality of life score; WHO 2 – overall health score; DOM 1 – somatic domain; DOM 2 – emotional domain; DOM 3 – social domain; DOM 4 – environmental domain; NSS – nephron-sparing surgery; RN – radical nephrectomy; K – control group; p – statistical significance

Figure 1. Quality of life in the compared treatment groups as based on the WHOQOL-BREF scores

Maximization of the health-related quality of life in patients undergoing treatment for renal cell carcinoma is possible owing to our understanding of factors which closely intervene in the process. The increased awareness of the determinants of poor HRQOL may facilitate customized support being provided to high-risk patients [8, 14]. In our study, the impact of clinical and demographic variables on the distant quality of life was assessed. Minimally invasive surgical techniques were shown to open up the potential for the achievement of better quality of life within the social and environmental domains. Other authors had shown that laparoscopic surgery was associated with significantly less pain in the early postoperative period, as well as faster (42 *vs.* 62 days) return to daily activities when compared to the open method (p = 0.04). This difference was not observed several months after the procedure [15]. In addition to the physical component, the positive impact of a laparoscopy *vs.* open method was demonstrated in relation to subjective emotional health assessments [16]. The beneficial effect of a laparoscopy on the multifaceted HRQOL self-assessment was also confirmed by other studies which had proven that the technique was associated with shorter hospitalization times, lower blood loss, and faster recovery. However, no statistically significant relationships were observed with regard to the incidence of postoperative complications, pain levels, and physical functioning [17]. The perioperative and distant benefits of minimally invasive surgical techniques were also demonstrated in a meta-analysis of 37 studies as published in 2017 [18]. MacLennan et al. confirmed that laparoscopy was associated with better perioperative outcomes while no evidence could be provided for any difference between the retroperitoneal and transperitoneal access [14].

According to Rossi et al., in patients undergoing surgical treatment for renal cell carcinoma, clinical variables such as tumor size, clinical stage, age, BMI, occupational status, education level, and comorbidities are the determinants of health-related quality of life [8]. In our study, similar results were obtained, revealing that in addition to the open *vs.* laparoscopic method, the clinical stage of cancer at the time of surgery had also a significant impact on the long-term quality of life assessment. A statistically significant relationship between

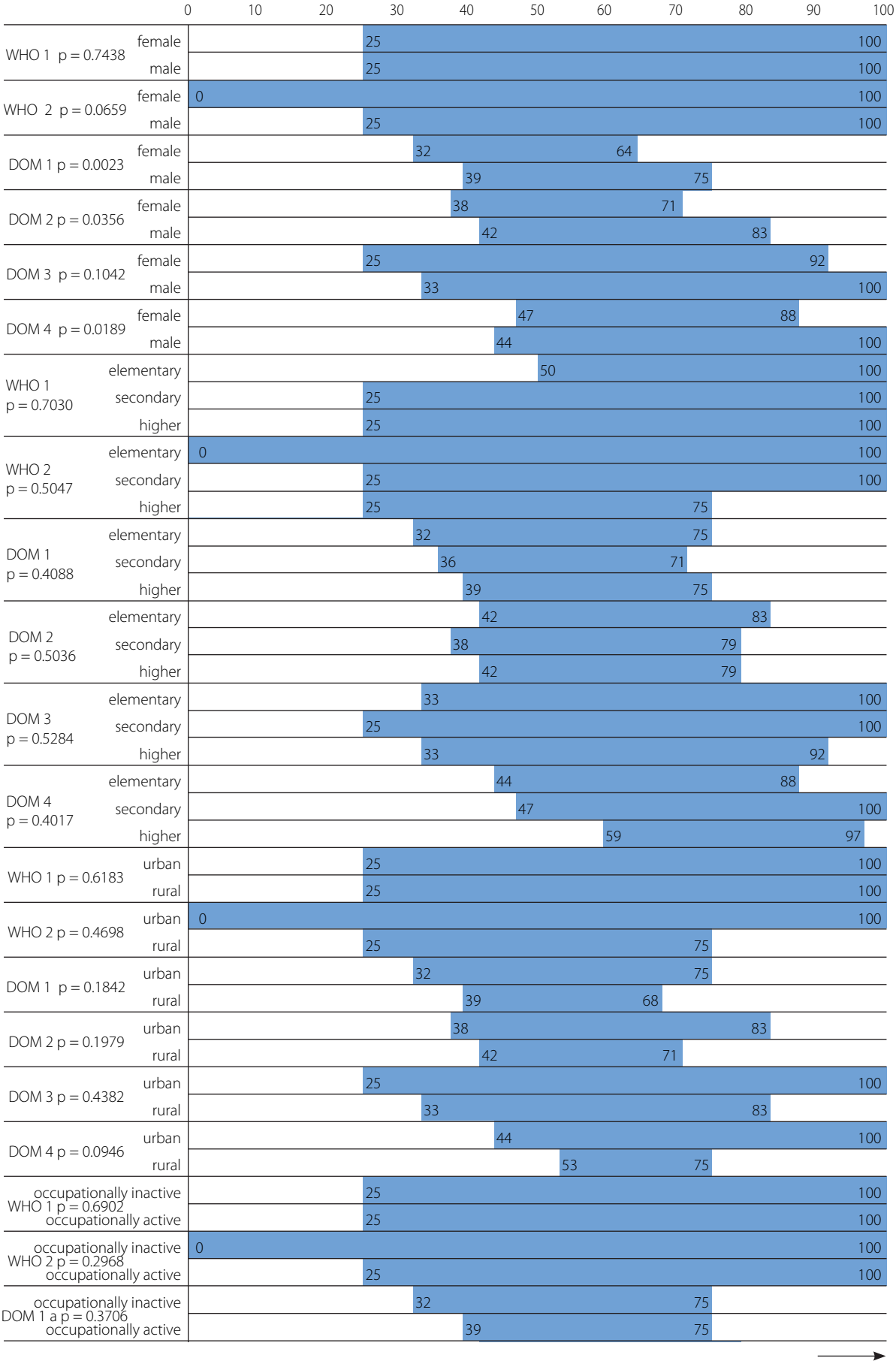
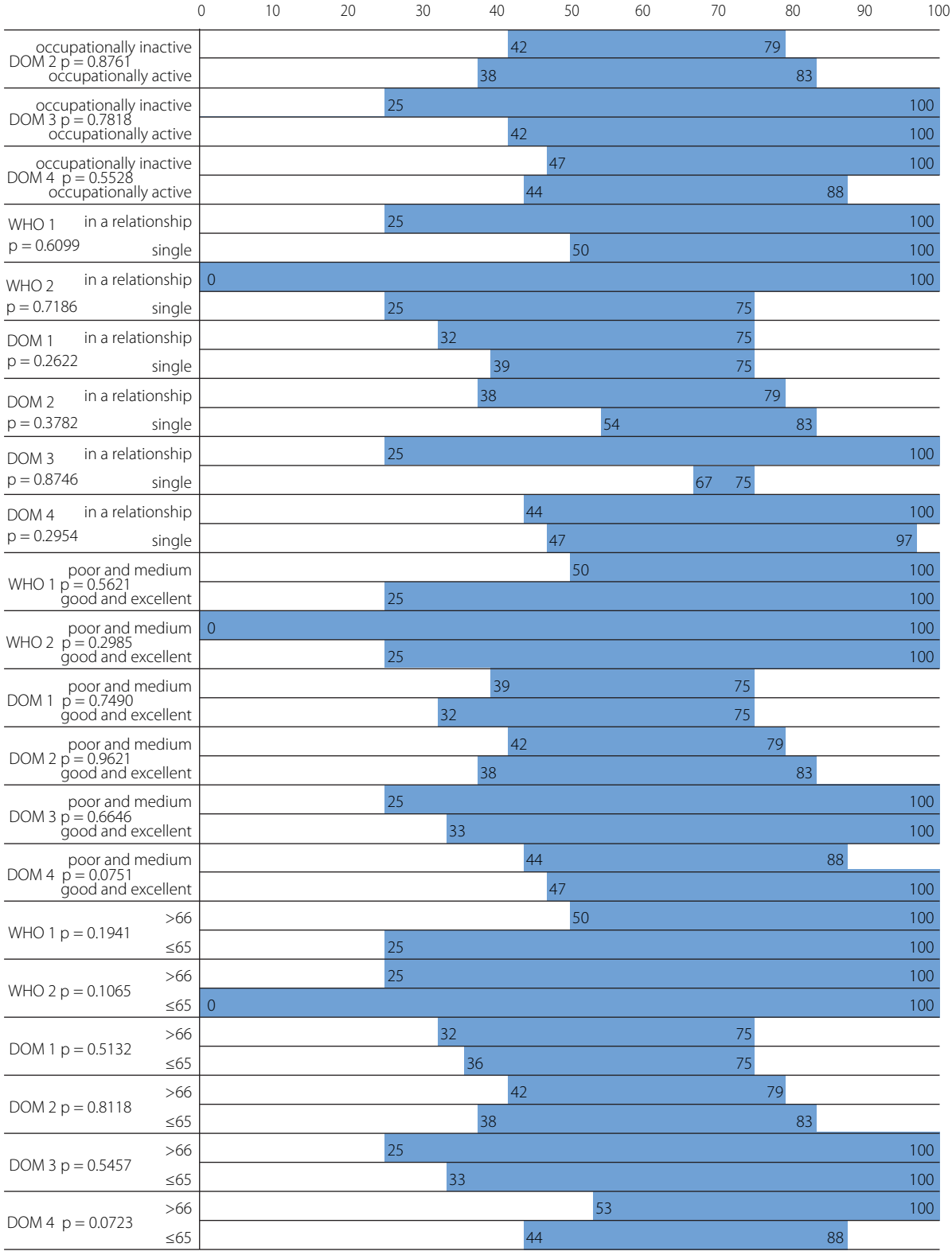


Figure 2. The impact of demographic variables on the quality of life within the compared groups



WHO 1– overall quality of life score; WHO 2 – overall health score; DOM 1 – somatic domain; DOM 2 – emotional domain; DOM 3 – social domain; DOM 4 – environmental domain; p – statistical significance

Figure 2. cont. The impact of demographic variables on the quality of life within the compared groups

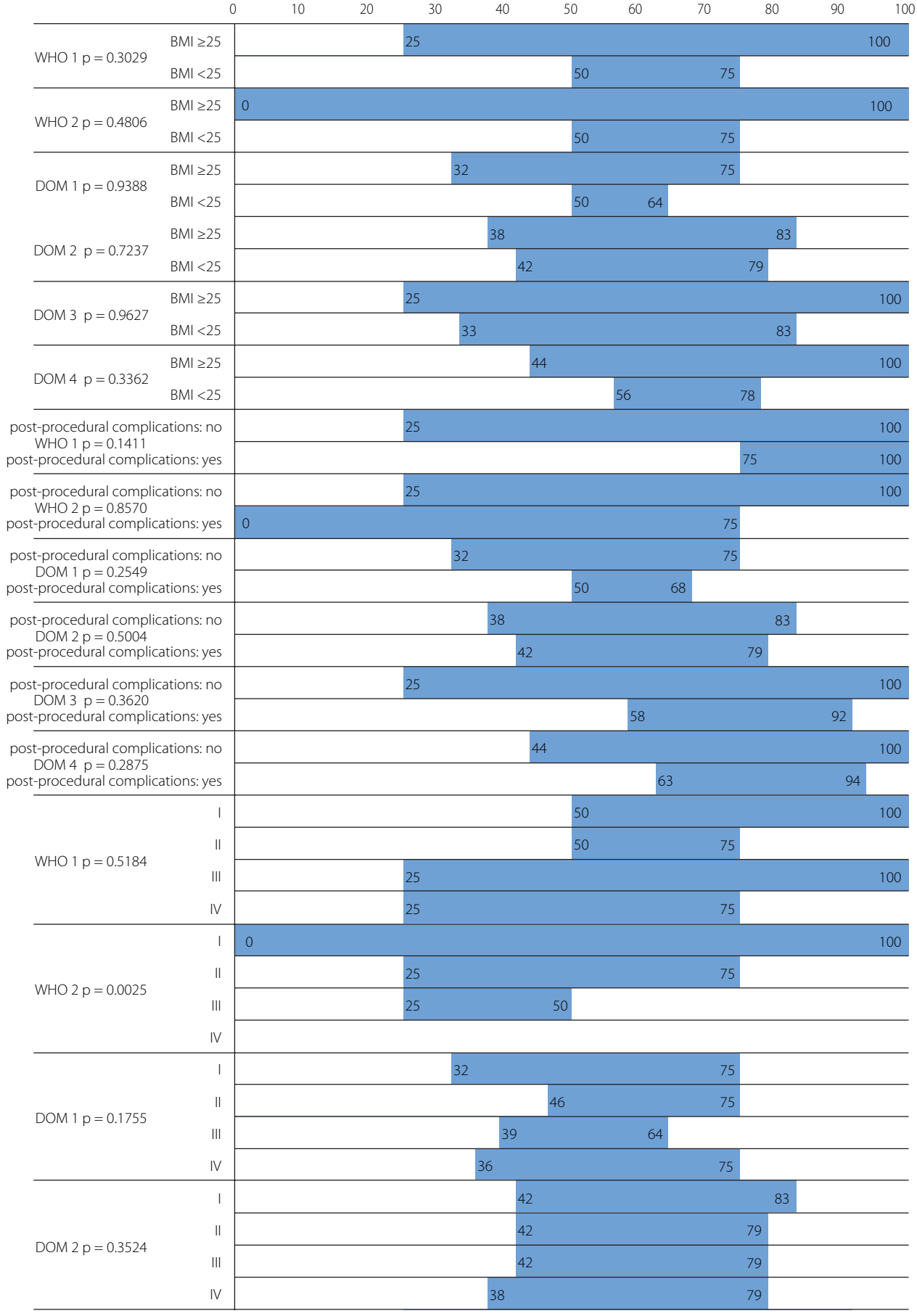
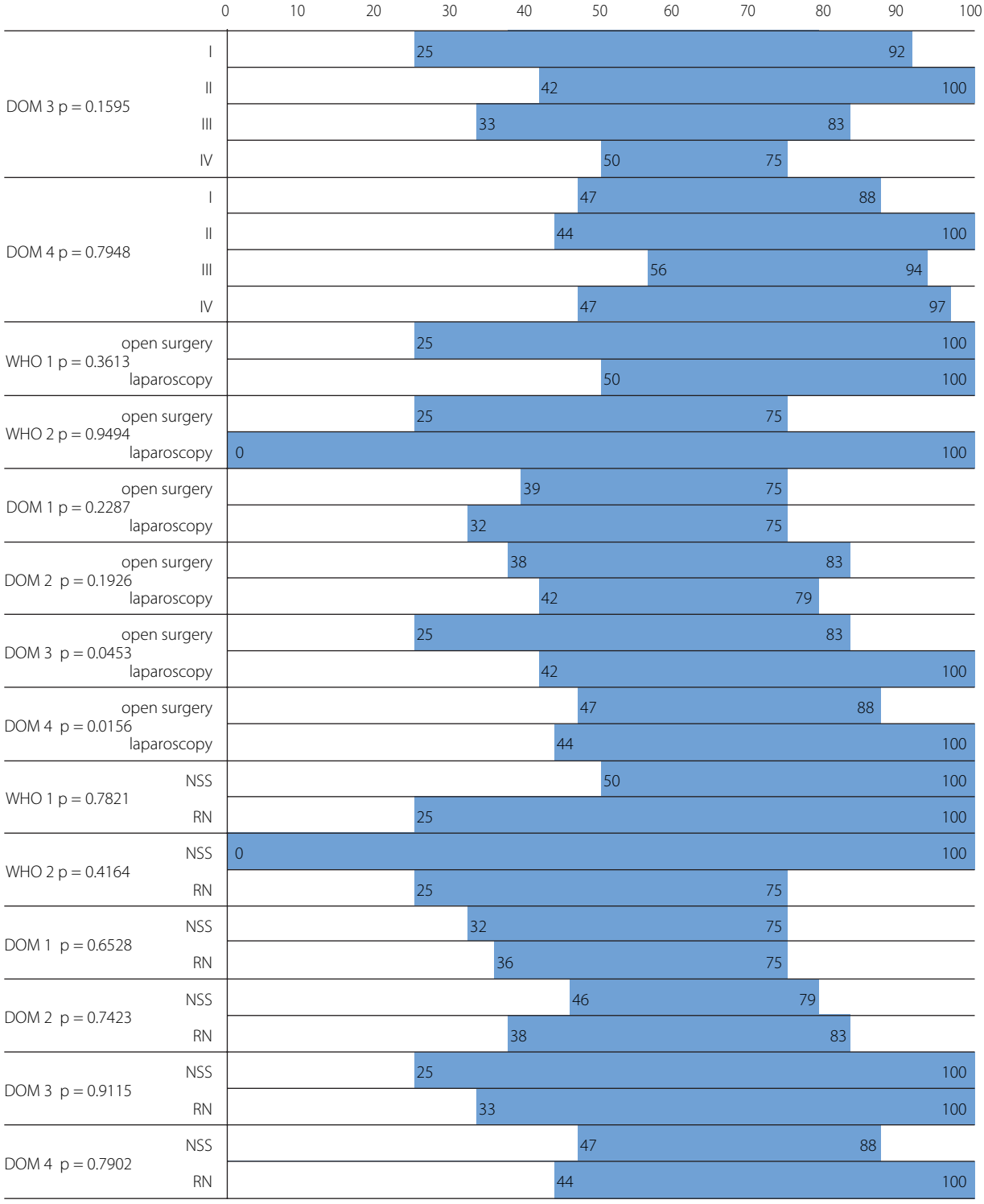


Figure 3. The impact of clinical variables on the quality of life within the compared groups



WHO 1– overall quality of life score; WHO 2 – overall health score; DOM 1 – somatic domain; DOM 2 – emotional domain; DOM 3 – social domain; DOM 4 – environmental domain; p – statistical significance; RN – radical nephrectomy

Figure 3. cont. The impact of clinical variables on the quality of life within the compared groups

the higher stages of cancer and lower self-assessed overall health scores was confirmed despite the lack of distant metastases or the recurrence of the disease.

Another aspect of the statistical analysis consisted in the determination of the relationship between demographic variables and the assessment of the quality of life within all dimensions of the BREF questionnaire. There was a statistically significant relationship between reduced health-related quality of life within the somatic, emotional, and environmental scales and the female gender. Quderi et al. also demonstrated

a significant relationship between the female gender and the lower HRQOL scores in the course of oncological treatment [19]. The conclusions of the 2020 study carried out by Beisland indicate that demographic and psychological variables, including personality traits and educational background, may be predictive of the quality of life scores, whereas factors related to cancer itself appear to be of secondary importance [11]. Other studies also confirm the impact of demographic and clinical variables on the quality of life of patients undergoing cancer treatment regardless of the location and stage of cancer [20, 21]. Prehabilitation also seems to be an important issue in oncological surgery, which not only aims to improve physical condition through rehabilitation and nutritional support, but also focuses on the psychological aspects of the recovery process. This is of considerable importance in the self-assessment of health-related quality of life [22, 23].

The strengths of our research consist in the use of a standardized, international research tool and in a thorough analysis of the medical documentation of patients and a fact, that all patients were operated in single, specialized center. In addition, few studies on the long-term outcomes of renal cell carcinoma are available in the literature. However, despite the unquestionable epistemic value, the study has been fraught with some limitations. Firstly, these include the retrospective character of the study, making it impossible to establish the baseline quality of life levels for re-measurement and comparison after the surgery in a pretest-posttest design. Notably, the available literature on this subject is also mainly retrospective, and includes studies conducted in small, heterogeneous samples. Secondly, this was a pilot study in which the size of the sample had not been established so as to achieve good external validity. Inclusion of other centers and a design including prospective measurements of a single variable at different stages of cancer treatment would be helpful in order to be able to generalize the results to the entire population of patients with renal cell carcinoma.

Conclusions

1. The type of procedure, namely RN *vs.* NSS, is not a factor differentiating the subjective health-related quality of life assessments.
2. However, even after all this time, laparoscopic surgery is associated with an opportunity to achieve better quality of life scores, particularly within social and environmental aspects 3 to 5 years after operation.
3. The analysis of correlations with clinical data 3 to 5 years after surgical treatment revealed a significant relationship between the stage of cancer and the subjective assessment of the quality of life within the overall health domain. The higher the cancer stage, the worse the subjective sense of physical well-being.
4. Demographic variables affect the long-term QOL results. A statistically significant impact on reduced health-related quality of life within the somatic, emotional, and environmental scales was demonstrated for the female gender.

Conflict of interest: none declared

Magdalena Tarkowska
Nicolaus Copernicus University in Torun
Collegium Medicum in Bydgoszcz
Department of Urology
ul. Jagiellońska 13–15
85-094 Bydgoszcz, Poland
e-mail: m.tarkowska@cm.umk.pl

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Mental adjustment to cancer in patients with colorectal cancer

Angelina P. Kaleta-Pilarska, Kamil Barański

Department of Epidemiology, Faculty of Medical Sciences, Medical University of Silesia in Katowice, Katowice, Poland

Introduction. Exploration of the psychological aspects of cancer may play a key role in the disease's progression. Active mental strategies have been associated with a better prognosis. Due to these associations, the aim of this study is to assess the prevalence and elucidate determinants influencing mental adjustment in patients with colorectal cancer.

Material and methods. A cross-sectional study identifying 200 patients with colorectal cancer. The mental state of patients was measured with an adaptation the of mini-MAC questionnaire.

Results. Constructive determinants influencing the occurrence of mental adaptation to colorectal cancer are the presence of the disease in the family, fitness status and smoking status. Education level is an important destructive determinant influencing the occurrence of mental adaptation to colorectal disease.

Conclusions. Among the patients with colorectal cancer, the destructive and constructive style of mental adaptation occurs with a similar frequency (26.5% and 22.5%).

Key words: colorectal cancer, mental adjustment, constructive style, destructive style, cancer

Introduction

Cancer diseases remain a significant health and social problem. The diagnosis of cancer is a source of long-term stress for the patient. Because of the treatment and associated side effects, the disease can impact the patient for prolonged periods. The disease is associated with decreased quality of life, decreased ability to work and reduced frequency of social relations. Aside from the physical symptoms, the patient can be exposed to a profound range of mental problems [1–3]. The mental attitude adopted by the patient towards the disease directly affects their quality of life and may also be a determinant in the efficacy of the final therapeutic effects [2, 4].

The stage of the disease is defined by the reaction on presented information about cancer and may change over time depending on the phase of treatment [5]. Axiomatically, mental adaptation to the disease is a process aimed at restoring the patient's psychological balance, as well as reducing their emotional discomfort [6]. Mental adjustment to the disease is most often measured in 4 strategies:

- anxious preoccupation,
- helplessness-hopelessness,
- fighting spirit,
- positive redefinition.

Combining the strategy of anxious preoccupation and helplessness-hopelessness creates a destructive style of managing

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with the disease characterized by a lack of willingness to fight the disease. Fighting spirit and positive redefinition represents the constructive style that encourages the patient to fight the disease [7, 8].

Colorectal cancer in Poland is one of the most common cancers among both sexes [9], as well as one of the most common causes of cancer deaths. Consequently, it is important from a public health perspective to elucidate the psychological factors that may affect the course of the disease. Defining the strategy of mental adaptation to the disease may present both cognitive values and practical dimensions in the form of improving the methods of monitoring mental health in the progression of colorectal cancer, and perhaps also in the form of improving preventive recommendations.

Taking into consideration the research needs, this study assesses frequency of occurrence and elucidates factors that may influence mental adaptation to cancer in patients with colorectal cancer in the period immediately preceding the surgical intervention.

Material and methods

The cross-sectional study was conducted on 200 patients with diagnosed colorectal cancer in two medical centers' departments of surgery and oncology and in the department of oncological surgery of Zagłębiowski Center of Oncology in Dąbrowa Górnicza. All patients signed informed consent forms. Participation in the study was voluntary. The statistical analysis covered patients aged between 24–85 years of age. The study was conducted between May 2018 and June 2020. The protocol of the study was approved by the Bioethical Commission of the Medical University of Silesia in Katowice (decision no KNW/0022/KB59/18). The following criteria were identified for inclusion to the study:

- diagnosed colorectal cancer,
- hospitalization in medical centers selected for the purpose of the study and planned surgery for cancer removal,
- the signed informed consent of the patient to participate in the study.

The questionnaire was used *via* direct interview at the place of hospitalization. The patients answered the questions in a separate room in a face-to-face meeting with the researcher. The final dataset was anonymized. The interview was performed preceding surgical intervention.

During the interview, the author's questionnaire was used, as well as the Polish version of psycho-oncological diagnosis of patients' attitudes towards cancer (mini-MAC). The authors questionnaire included 26 questions which included anthropometric and social and economic variables. The questions also included detail related to the suspicion and diagnosis of colorectal cancer.

The mini-MAC questionnaire is an adaptation of Z. Jurczyński [10] and is constructed with 29 claims. The adaptation measures four strategies in managing with the disease. These are:

- anxious preoccupation,
- fighting spirit,
- helplessness-hopelessness,
- positive redefinition.

In each claim the responded uses a 4 answer scale (1 – definitely no, 2 – rather no, 3 – rather yes, 4 – definitely yes). The results are calculated for each strategy separately.

Each category is constructed with 7 claims. The higher the score in strategy, the more intense the behavior characterized for each strategy. Anxious preoccupation and helplessness-hopelessness represents the destructive style of managing the disease, fighting spirit and positive redefinition represents the constructive style. After totaling the points obtained in the relevant strategies, the scores are converted into sten units and interpreted as high, low or average results. A result between 1–4 for a sten score is interpreted as a low score, 5–6 as average and 7–10 as high. The high score is interpreted as the presence of the specific style of managing with the disease [10].

The statistical analysis included descriptive and analytical methods. In the case of quantitative variables, the mean, standard deviation, median and range were used for description. The normality of quantitative variables was assessed with the Shapiro-Wilk test. The numbers and percentage were used to describe qualitative variables. The study assessed the statistical significance of differences in anthropometric and socio-economic characteristics using the alpha level <0.05. For this purpose, the Mann–Whithey U-test was performed for the analysis of quantitative variables, while the Chi^2 test, with the Yates correction and the Fisher's exact test were performed for the analysis of qualitative variables. The non-parametric Mann–Whithey U-test was used as the distribution of quantitative variables analysed in the study differed from the normal distribution (Shapiro-Wilk test result).

The variables from the mini-MAC questionnaire (anxiety absorption, fighting spirit, helplessness-hopelessness and positive redefinition) were transformed due to the key importance of three diagnoses:

- constructive style,
- destructive style,
- undefined style.

The results of univariable analyses were verified using logistic regression. The regression coefficients and the p-value were calculated from full model (fully adjusted). Additionally, the stepwise procedure was employed. In this analysis, the predictors of the dependent variable were identified using a criterion of statistical significance at the level of $p < 0.1$. Here the odds ratio (OR) and 95% confidence interval (CI)were calculated. Analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

Results

The analysis included 200 patients (89 females and 111 males) with a diagnosis of colorectal cancer. The participants were 65

Table I. Age, weight and height of subjects

Variable	Mean and standard deviation		Median		Range		p value
	Females	Males	Females	Males	Females	Males	
age (years)	63.4 ± 12.4	66.3 ± 10.3	64.0	69.0	24.0–85.0	32.0–82.0	0.06
age during the diagnosis of colorectal cancer (years)	62.8 ± 12.4	66.0 ± 10.3	64.0	69.0	24.0–85.0	29.0–82.0	0.04
body mass (kg)	68.8 ± 15.2	79.1 ± 15.6	68.0	82.0	42.0–105.0	44.0–120.0	<0.001
height (cm)	164.4 ± 5.7	173.0 ± 5.2	165.0	173.0	150.0–175.0	157.0–190.0	<0.001
BMI (kg/m^2)	25.5 ± 5.7	26.3 ± 4.7	24.6	26.9	15.2–41.1	15.2–37.5	0.11

* Mann–Whithey U-test

± 11,3 aged (range: 24–85). The mean age when the participants were diagnosed with cancer was 64.6 ± 11.4 years. Table I presents the characteristics of patients regarding anthropometric variables.

Most of the respondents (55.5%) were men. The majority of the participants were living in cities (91.0%). The most frequently declared education level was secondary education (41.0%). In the majority of the individuals participating in the study (54.5%), the detection of neoplastic disease was made by visiting a doctor after noticing disturbing symptoms of the disease. In around 44% of patients, colorectal cancer had not been identified in their family history. Chronic cardiovascular disease was the most frequent comorbidity (43.0% of the respondents). Women and men who participated in the study did not differ according to distribution of age and body mass index (BMI). The significant differences were found according to the age when the diagnosis of cancer was confirmed ($p = 0.04$), body mass ($p < 0.001$) and height ($p < 0.001$).

Table II presents the four strategies of mental adjustment to cancer disease of participants of the study. The highest percentage of respondents presents the strategy of positive redefinition (90.0%), the least frequent in this group is the strategy of helplessness-hopelessness (38.0%).

Table II. Strategies of mental adjustment to cancer in patients with colorectal cancer

Variable		N; %
anxious preoccupation	yes	95 (47.5%)
	no	105 (52.5%)
fighting spirit	yes	132 (66.0%)
	no	68 (34.0%)
helplessness-hopelessness	yes	76 (38.0%)
	no	124 (62.0%)
positive redefinition	yes	180 (90.0%)
	no	20 (10.0%)

The analysis of mental adjustment to cancer disease confirmed that in 51.0% of patients, it was impossible to describe the type of mental adjustment to the disease. The constructive style and destructive style occurred almost at the same frequency, i.e. 22.5% and 26.5% respectively.

Among the circumstances accompanying the presence of a constructive style of mental adaptation to cancer, statistical significance was found for the following variables:

- education ($p < 0.001$),
- family support ($p = 0.02$),
- circumstances of suspicion of cancer ($p = 0.004$),
- physical fitness ($p < 0.001$),
- smoking before the diagnosis of colorectal disease ($p = 0.03$).

The remaining variables did not have a statistically significant relationship with the occurrence of the constructive style (Chi^2 test result). The results of univariable analyses were verified using multivariable analysis in a logistic regression model with respect to the defined dependent variable – constructive style.

Table III shows the results of the analysis of the logistic regression model. The statistical significance in the analysis of the logistic regression model for determinants in developing the constructive style of mental adjustment to cancer revealed the following variables:

- sex ($p = 0.02$),
- educational level ($p = 0.004$),
- financial status ($p = 0.047$),
- the occurrence of colorectal cancer in the family previously ($p = 0.03$).

Done stepwise procedure. In the final model the following variables have been selected as predictors:

- sex (female *vs.* male) – OR = 0.40 (95% CI: 0.16–0.99),
- education level (below high school *vs.* high school and master's degree) – OR = 0.25 (95% CI: 0.10–0.62),

Table III. The results of the analysis of a logistic regression from full model (fully adjusted) for the circumstances accompanying the presence of a constructive style of mental adjustment to cancer

Variable	Regression coefficient	p value
sex (female *vs.* male)	–0.61	0.02
place of residence (city *vs.* country)	–0.58	0.09
education level (lower than secondary level *vs.* secondary and higher education)	–0.71	0.004
marital status (in a relationship *vs.* single)	0.03	0.94
employment (working person *vs.* unemployed person)	0.03	0.90
belief (believer *vs.* unbeliever)	0.15	0.63
housing conditions (alone *vs.* with a family member)	0.47	0.42
support from family (no *vs.* yes)	0.20	0.96
financial status (satisfactory *vs.* non-satisfactory)	–0.96	0.047
circumstances of cancer diagnosis (by a patient *vs.* by a doctor)	0.29	0.23
a family history of colorectal cancer (yes *vs.* no)	–1.03	0.03
satisfaction with medical care (yes *vs.* no)	0.38	0.49
occurrence of chronic disease – without mental disease (yes *vs.* no)	0.09	0.71
occurrence of other cancers diseases (yes *vs.* no)	–0.14	0.85
fitness status (*vs.* worse)	0.65	0.06
nutritional status (unchanged *vs.* worse)	–0.24	0.27
smoking status before being diagnosed with cancer (no *vs.* yes)	0.44	0.09
consuming alcohol before being diagnosed with cancer (no *vs.* yes)	0.20	0.56

- financial situation (satisfying *vs.* non satisfying) – OR = 0.22 (95% CI: 0.05–0.96),
- occurrence of colorectal cancer in family (yes *vs.* no) – OR = 3,33 (95% CI: 1.44–7.89),
- physical condition (not worse *vs.* worse) – OR = 4.94 (95% CI: 1.67–14.62),
- smoking status before diagnosis of cancer disease (no *vs.* yes) – OR = 2.43 (95% CI: 1.01–5.83).

Among the circumstances for the presence of the destructive style in managing cancer, the significant variables were educational level (p = 0.048). The other variables were not significantly associated with occurrence of the destructive style (Chi² test result). The results of univariable analysis were verified with multivariable analysis, in the logistic regression model, regarding the occurrence of the destructive style as a dependent variable.

Table IV shows the results of the analysis of the logistic regression model. In the logistic regression model for the assessment of the occurrence of the destructive style of mental adjustment to cancer, there were no significant variables noted. In further analysis, a stepwise selection was performed. The final predictive variable for occurrence of the destructive style of mental adjustment to cancer was educational level (below high school *vs.* high school + master's degree) – OR = 1.85 (95% CI: 0.97–3.55).

The multivariable analysis was also performed in the logistic regression model, differentiating the constructive style from the destructive style. The results are presented in table V.

As a result of the logistic regression analysis differentiating the constructive style from the destructive style (in accordance with the record: mental adaptation style to cancer – constructive style / destructive style), the following variables were reported as statistically significant: educational level (p = 0.01) and alcohol consumption before cancer diagnosis (p = 0.02). Done stepwise procedure. Final predictors of the dependent variable were identified, such as:

- educational (below high school *vs.* high school and master's degree) – OR = 5.33 (95% CI: 1.85–15.20),
- circumstances of suspicion of cancer diagnosis (by a patient *vs.* by a doctor) – OR = 0.40 (95% CI: 0.14–0.98),
- family history of colorectal cancer (yes *vs.* no) – OR = 0.24 (95% CI: 0.11–0.78),
- alcohol consumption before cancer diagnosis (no *vs.* yes) – OR = 0.21 (95% CI: 0.03–0.82).

Discussion

The aim of this study was to assess the prevalence and elucidate determinants influencing mental adjustment in patients with colorectal cancer.

Table IV. The results of the analysis of a logistic regression from full model (fully adjusted) for the circumstances accompanying the presence of a destructive style of mental adjustment to cancer

Variable	Regression coefficient	p value
sex (female *vs.* male)	0.24	0.30
place of residence (city *vs.* country)	0.25	0.48
education level (lower than secondary level *vs.* secondary and higher education)	0.36	0.07
marital status (in a relationship *vs.* single)	0.78	0.21
employment (working person *vs.* unemployed person)	0.21	0.32
belief (believer *vs.* non-believer)	–0.04	0.85
housing conditions (alone *vs.* with a family member)	0.65	0.29
support from family (no *vs.* yes)	0.16	0.65
financial status (satisfactory *vs.* non-satisfactory)	0.18	0.66
circumstances of cancer diagnosis (by a patient *vs.* by a doctor)	–0.24	0.20
a family history of colorectal cancer (yes *vs.* no)	0.44	0.36
satisfaction with medical care (yes *vs.* no)	0.18	0.64
occurrence of chronic disease – without mental disease (yes *vs.* no)	–0.05	0.83
occurrence of other cancers diseases (yes *vs.* no)	0.39	0.35
fitness status (unchanged *vs.* worse)	0.25	0.28
nutritional status (unchanged *vs.* worse)	0.08	0.67
smoking status before being diagnosed with cancer (no *vs.* yes)	–0.34	0.14
consuming alcohol before being diagnosed with cancer (no *vs.* yes)	–0.46	0.22

Table V. The results of the analysis of a logistic regression from full model (fully adjusted) differentiating the constructive style from the destructive style

Variable	Regression coefficient	p value
sex (female *vs.* male)	0.72	0.06
place of residence (city *vs.* country)	0.61	0.20
education level (lower than secondary level *vs.* secondary and higher education)	0.89	0.01
marital status (in a relationship *vs.* single)	5.91	0.88
employment (working person *vs.* unemployed person)	–0.20	0.50
belief (believer *vs.* non-believer)	–0.51	0.32
housing conditions (alone *vs.* with a family member)	5.54	0.90
support from family (no *vs.* yes)	5.23	0.89
financial status (satisfactory *vs.* non-satisfactory)	1.50	0.07
circumstances of cancer diagnosis (by a patient *vs.* by a doctor)	–0.39	0.11
a family history of colorectal cancer (yes *vs.* no)	–0.61	0.08
satisfaction with medical care (yes *vs.* no)	–1.20	0.23
occurrence of chronic disease (without mental disease) (yes *vs.* no)	–0.33	0.41
occurrence of other cancers diseases (yes *vs.* no)	1.49	0.19
fitness status (unchanged *vs.* worse)	–0.44	0.54
nutritional status (unchanged *vs.* worse)	0.20	0.61
smoking status before being diagnosed with cancer (no *vs.* yes)	–0.41	0.22
consuming alcohol before being diagnosed with cancer (no *vs.* yes)	–1.51	0.02

The results suggest that 26.5% of participants of the study express the destructive style of mental adjustment to cancer. Among the participants who had a lower educational level, the mean risk of qualification above-mentioned style was two times higher (OR = 1.85). The constructive style of mental adjustment to cancer disease is expressed among 22.5% of participants. This style occurred 3 times more in participants with a family history of colorectal cancer (OR = 3.33), almost 5 times more often in participants who declared a non-worsening condition (OR = 4.94) and 2.4 more often in respondents with a non-smoking history. Female sex, lower educational levels and the declaration of a satisfactory financial status were factors which decreased the chance of occurrence of the constructive style (OR = 0.40, OR = 0.25, and OR = 0.22, respectively).

The study by I. Kapela [11] presents significantly different results. The authors of the study observed among 34.5% of the respondents features indicating the presence of a destructive style, while the features of the constructive style were noted among 77.2% of the respondents. The differences in the percentage values presented in the author's own work and in the work by I. Kapela may be related to a longer time period since the diagnosis of cancer in the group of patients participating in the cited study. Most of the patients participating in the above-mentioned study were individuals diagnosed with the disease up to 4 years prior, while the group of patients in our study are exclusively individuals with a newly diagnosed cancer who qualified for surgical treatment.

In this study, people with lower than high school education presented less often with a constructive style than people with a master's degree. This relationship was also confirmed in the study by J. A. Glińska et al. from 2020 [12], where the constructive style was expressed more often in the group of respondents with a higher educational level.

A limitation of this study is the number of participants who were not representative of patients with colorectal cancer. Primarily, this is because the enrolment for the study took place only in one hospital and implemented randomly. Only patients who were awaiting surgery to remove their cancer and gave informed consent to participate in the study were included in the study. Consequently, the study did not include people living outside the Silesian Voivodship, or outside the Upper Silesian-Zagłębie Metropolis, who were being treated in other hospital centers.

The advantage of this study is the complete response rate to the questionnaires. This was the result of direct contact between the respondent and the interviewer that took place in the treatment hospital. During the interview the patients were separated, focusing only on the questionnaire and interviewer. Potentially, this could decrease the risk of disruption during the interview by external sources. Additionally, it could decrease the chance of misunderstanding questions included in the questionnaire. Finally, the study used a validated questionnaire commonly used in research in Poland, in this case, the questionnaire is the only research tool that can be used in this type of research.

Another advantage of the study was the comparable number of men and women (89 and 111, respectively), with a non-statistically significant difference in age. Importantly, the author's own study uses a multivariable analysis, which enables the control of confounding factors. This procedure is sometimes omitted in the works of other authors. Cogently, there are reasons to assume that the conducted study has a significant impact for the current knowledge about the frequency and conditions of disease acceptance among patients with colorectal cancer.

The results may be used in planning and conducting psychological care in patients with colorectal cancer qualified for surgery.

Conclusions

1. Among the patients with colorectal cancer in the period immediately preceding surgical intervention, the destructive and constructive style of mental adaptation to colorectal cancer occurs with a similar frequency, in 26.5% and in 22.5% of patients respectively.
2. Frequent presentation for the constructive style of behavior is observed in the case of patients with a family history of colorectal cancer, as well as in patients declaring unchanged fitness status. The destructive style of behavior qualification is more frequent among patients with lower educational levels (lower than secondary level).

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Angelina P. Kaleta-Pilarska
Medical University of Silesia in Katowice
Faculty of Medical Sciences
Department of Epidemiology
ul. Medyków 18
40-752 Katowice, Poland
e-mail: akaleta@sum.edu.pl

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Predicting neutropenia dynamics after radiation therapy in multiple myeloma patients receiving first-line bortezomib-based chemotherapy – a pilot study

Michał Masłowski[1], Konrad Stawiski[1, 2], Adam Zięba[1], Damian Mikulski[2, 3], Julia Bednarek[4], Jacek Fijuth[1, 5]

[1]*Department of Radiotherapy, Copernicus Memorial Hospital in Lodz, Lodz, Poland*
[2]*Department of Biostatistics and Translational Research, Medical University of Lodz, Lodz, Poland*
[3]*Department of Hematology, Copernicus Memorial Hospital in Lodz, Lodz, Poland*
[4]*Faculty of Medicine, Medical University of Lodz, Lodz, Poland*
[5]*Department of Radiation Oncology, Medical University of Lodz, Lodz, Poland*

Introduction. Radiation therapy (RT) is a useful modality for achieving local control and symptom relief in patients with multiple myeloma (MM), but its use can result in adverse effects such as neutropenia, which may be aggravated by prior chemotherapy.

Material and methods. In this retrospective study, we analyzed 530 complete blood count results of 32 MM patients who underwent RT for symptomatic bone pain between cycles or after completing first-line bortezomib-based chemotherapy (VCD). To evaluate the dynamics of neutrophil count (ANC) changes, we developed a generalized additive model (GAM) using initial ANC, dosage (BED10), and treatment volume (PTV) as predictors.

Results. Our GAM model demonstrated that ANC nadir after RT can be expected approximately 16 days after treatment initiation. The delivery of 8 Gy in 1 fraction resulted in the lowest ANC nadir, while a dose of 30 Gy in 10–15 fractions was deemed the safest. For PTV = 1000 cm^3, an initial ANC level of at least 1.42 × 10^3/μl was associated with no incidence of severe neutropenia irrespective of the fractionation scheme. Longer courses allowed for treatment delivery without significant neutropenia even with an initial ANC of 1.23 × 10^3/μl on the day of RT initiation.

Conclusions. Our model could aid in optimizing treatment strategies for MM patients receiving RT and chemotherapy. Further research is needed to validate our findings and evaluate the feasibility of implementing this model in clinical practice.

Key words: multiple myeloma, radiotherapy, neutropenia

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Introduction

Multiple myeloma (MM) remains an incurable plasma cell malignancy that tends to affect older adults. Although the mainstay treatment for MM is systemic chemotherapy, even 70–80% of patients with MM have osteolytic lesions at diagnosis [1].

Over the last decade, multiple myeloma patients have experienced several breakthroughs leading to prolonged survival. This is mostly attributed to novel effective systemic therapies [2]. Additional radiation therapy (RT) is considered rather supportive, offering very effective symptom relief for tumor deposits (plasmacytomas) in bone or soft tissues [3]. Nevertheless, as plasma cell neoplasms are radiosensitive tumors [4], RT can provide durable local control of symptomatic lesions. In a recent analysis of patients with spinal cord compression caused by myeloma, after RT, 64% of non-ambulatory patients regained their ability to walk again. RT provided excellent 1-year local control of 93% [5].

While high treatment efficacy is desirable, it is important to consider that it may not be achievable without incurring certain adverse effects. High dose irradiation to the larger volume of bone marrow prevents compensatory hyperplasia, which leads to hematological complications like neutropenia [6]. However, in the last decade, we have also experienced the development of modern radiation therapy techniques. These developments result in better conformity of the treatment and fewer adverse effects [7]. Introduction of high-dose treatments like stereotactic body radiation therapy (SBRT) [8] raises the important questions about the updated role of RT in MM management. Although increasingly effective [9], some reports highlight that modern radiation techniques, like VMAT (volumetric modulated arc therapy), can increase the risk of lymphopenia by irradiating large volumes of tissue with low doses of radiation [10]. Cytopenias, including neutropenia, have been associated with worse outcomes in MM [11].

VCD (bortezomib, cyclophosphamide, and dexamethasone) is a chemotherapy regimen commonly used as first line treatment for multiple myeloma. Neutrophils, like other rapidly dividing cells, are sensitive to bortezomib's action on the proteasome, leading to a decrease in their number. After VCD, neutropenia typically occurs around 7–10 days after the start of treatment. The nadir is usually reached 10–14 days after the start of treatment. The duration of neutropenia depends on the individual and the severity of the neutropenia, but it typically resolves within a week or two after the nadir is reached [12]. Although this three-drug combination shows significant efficacy and manageable toxicity as a treatment for MM, its association with significant risk of pneumonia and neutropenia [13] can cause prolongation of RT initiation. Due to the overlap in toxicities, combination treatment is often discouraged.

Postponing the start of radiation treatment due to the risk of exacerbating complications from chemotherapy may, however, be associated with a deterioration in quality of life. Additionally, although interplay between RT and novel drug combinations has not been thoroughly studied, preliminary results suggest that ionizing radiation combined with bortezomib enhances NK cell-mediated anticancer immune responses [14], and bortezomib could promote radiosensitivity [15].

Here, we have developed an advanced preliminary statistical model to predict the expected severity and dynamics of neutropenia after radiation therapy in patients receiving VCD as a first-line treatment. The model utilizes the radiation planning target volume (PTV), biologically effective dose with an alfa/beta value of 10 (BED10), and the initial absolute neutrophil count (ANC) to estimate the rate of ANC decrease and subsequent increase in the days following the start of radiotherapy.

Material and methods

In this pilot study, we conducted a retrospective analysis of 34 patients with multiple myeloma who received radiation therapy at the Department of Radiotherapy, Copernicus Memorial Hospital in Lodz between 2018 and 2020. We included symptomatic patients (with pain) who received radiation therapy between cycles or after completing first-line bortezomib-based chemotherapy (VCD). As per institutional protocol, radiation and systemic treatments were not overlapped, and all the included patients received their last dose of systemic treatment more than 14 days before starting radiation therapy. All patients received photon-based radiation therapy targeted at the affected bony area. Clinical target volume (CTV) was identified using CT, MRI, or PET-CT scans and was contoured according to guidelines [16]. The planning target volume (PTV) was defined as the geometric extension of the CTV by 7 mm, according to institutional recommendations.

For the selected patients, we identified and collected 534 absolute neutrophil count (ANC) results from complete blood counts with differential (CBC) performed up to 30 days before and up to 90 days after radiotherapy. We excluded patients who had less than five CBC blood tests during this period. The gaps between daily studies were imputed using an exponentially-weighted moving average, with a moving window of 30 days.

We developed a generalized additive model using LOESS (GAM) for log-transformed neutrophil count. Logarithmic transformation ensured a normal distribution. Based on clinical knowledge and expectations, the model included a starting neutrophil count (on the day the radiation therapy started), a biologically effective dose with an alfa/beta value of 10 (BED10), and planning target volume (PTV) as predictors. We used hyperparameter optimization with a 10-fold cross-validation to select optimal degrees of freedom for all terms, and the model with the maximum R-squared was chosen as the final model. We used ANOVA for nonparametric effects to assess the association of predictors with the model output. Neutropenia of grade 2 or higher, according to the CTCAE version 5.0, was defined as an ANC lower than 1500/microliter.

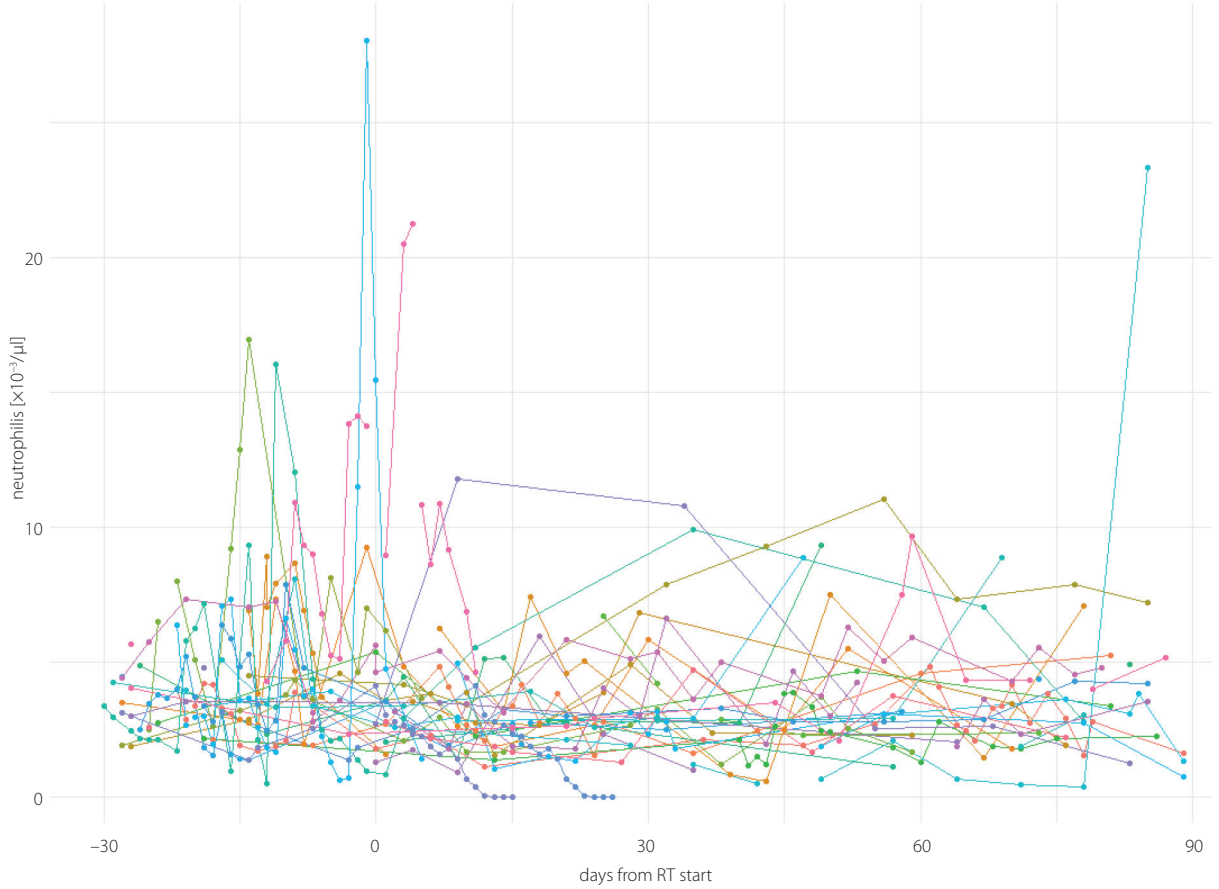

Figure 1. Measurements of neutrophils in particular patients up to 30 days before and 90 days after radiation initiation. Zero indicates the start of radiation treatment

All analyses were performed in R (version 4.1.2). Neutropenia was defined according to CTCAE version 5.0. All analyses were performed in R (version 4.1.2).

Results

The final study material consisted of 530 ANC measurements of 32 patients who experienced various changes in ANC levels after radiotherapy (fig. 1). Two patients had to be excluded due to a lack of sufficient CBC measurements (<5 per patient). Profiles showing the interpolated changes in ANC levels in selected patients are shown in figure 2.

The mean age of the study group at the start of radiation therapy was 64.03 years (range 43 to 84 years, median 61.5 years). The median BED10 of the applied fractionation schemes was 36 Gy (range 14.4 to 55.1 Gy; interquartile range (IQR) = 11), which corresponds to a median EQD2 of 23.5 Gy. The most commonly used fractionation schemes were 30 Gy in 10 fractions (31.2%) and 20 Gy in 5 fractions (25%). The dose was delivered to various volumes (PTV) of bony tissue, with a median volume of 754.5 cm³ (IQR = 726.6 cm³) (fig. 2). The majority of patients were treated with intensity-modulated radiation therapy (IMRT) (68.8%), while the remaining patients were treated with VMAT.

Spline models developed for high and low BED10 and PTV volumes (median split) didn't present significantly different dynamics of normalized ANC change (fig. 2). Developed GAM model showed that decrease in ANC follows initiation of RT and reaches a nadir around 16 days after RT starts (fig. 3). The root mean squared error of the developed model was 589 neutrophils per microliter. ANOVA for nonparametric effects showed that both BED10 and PTV volume, as well as starting ANC, have a significant effect on model outcomes ($p < 0.001$). As seen in figure 3, generally decrease in ANC increased with PTV volume, although the effect was not pronounced in volumes lower than 1000 cm³. Interestingly, delivery of 8 Gy in 1 fraction (BED10 = 14.4 Gy) was associated with the lowest ANC nadir. A dose of 30 Gy in 10 or 15 fractions was associated with the lowest change in ANC levels. The application of 20 Gy in 5 fractions (BED10 = 28 Gy) showed moderately low ANC nadir.

Figure 4 shows the relationships estimated by the GAM model between the starting ANC, nadir, and expected days of grade 3 or higher neutropenia, compared between different fractionation schemes and calculated for a PTV volume of 1000 cm³. Notably, the expected ANC nadir was lowest for 8 Gy in 1 fraction, regardless of the starting ANC level. According to the developed model, a starting level of ANC = 1.42×10^3/µl was associated with no occurrence of severe neutropenia

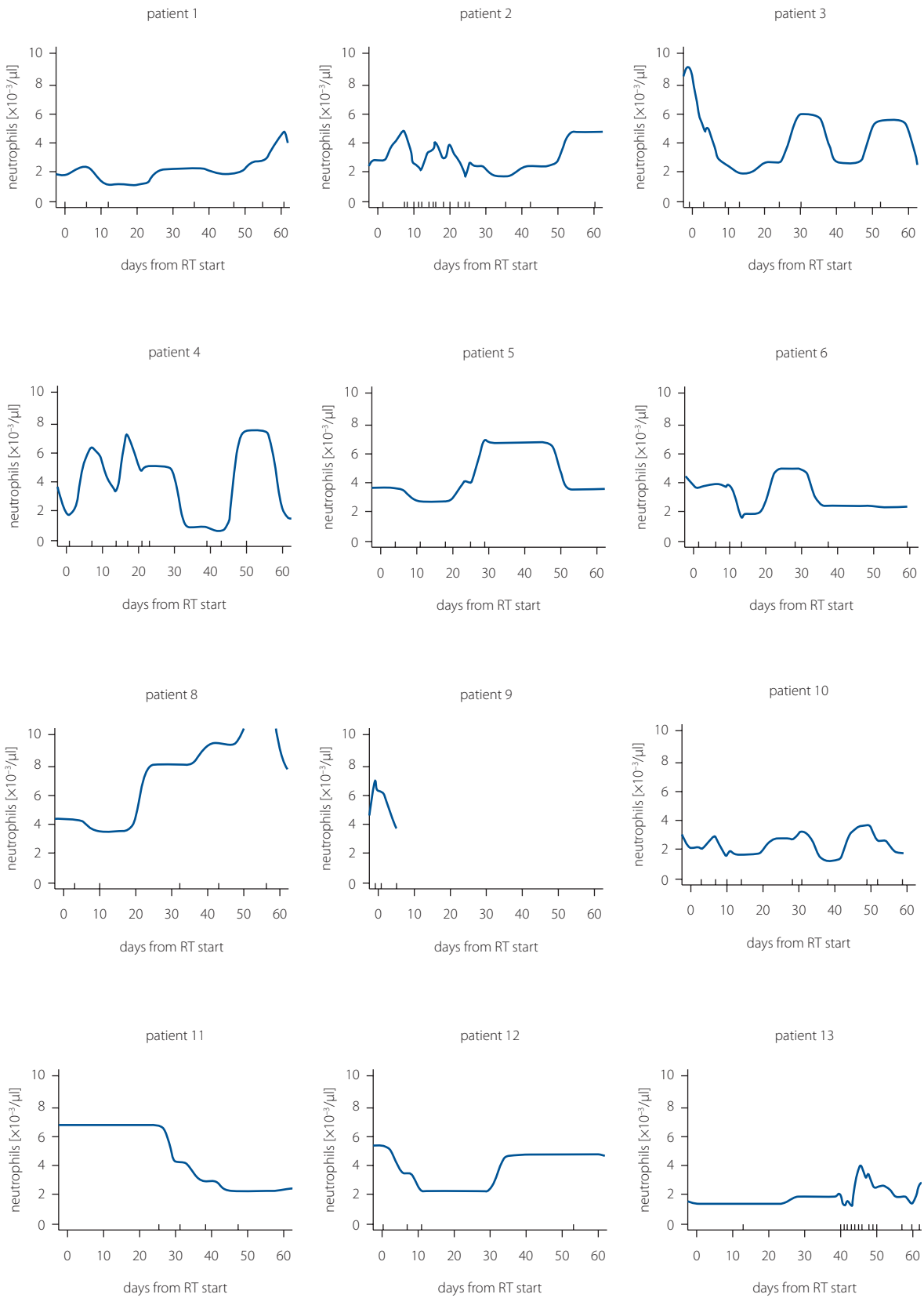

Figure 2. Profiles showing the interpolated changes in ANC levels in selected patients

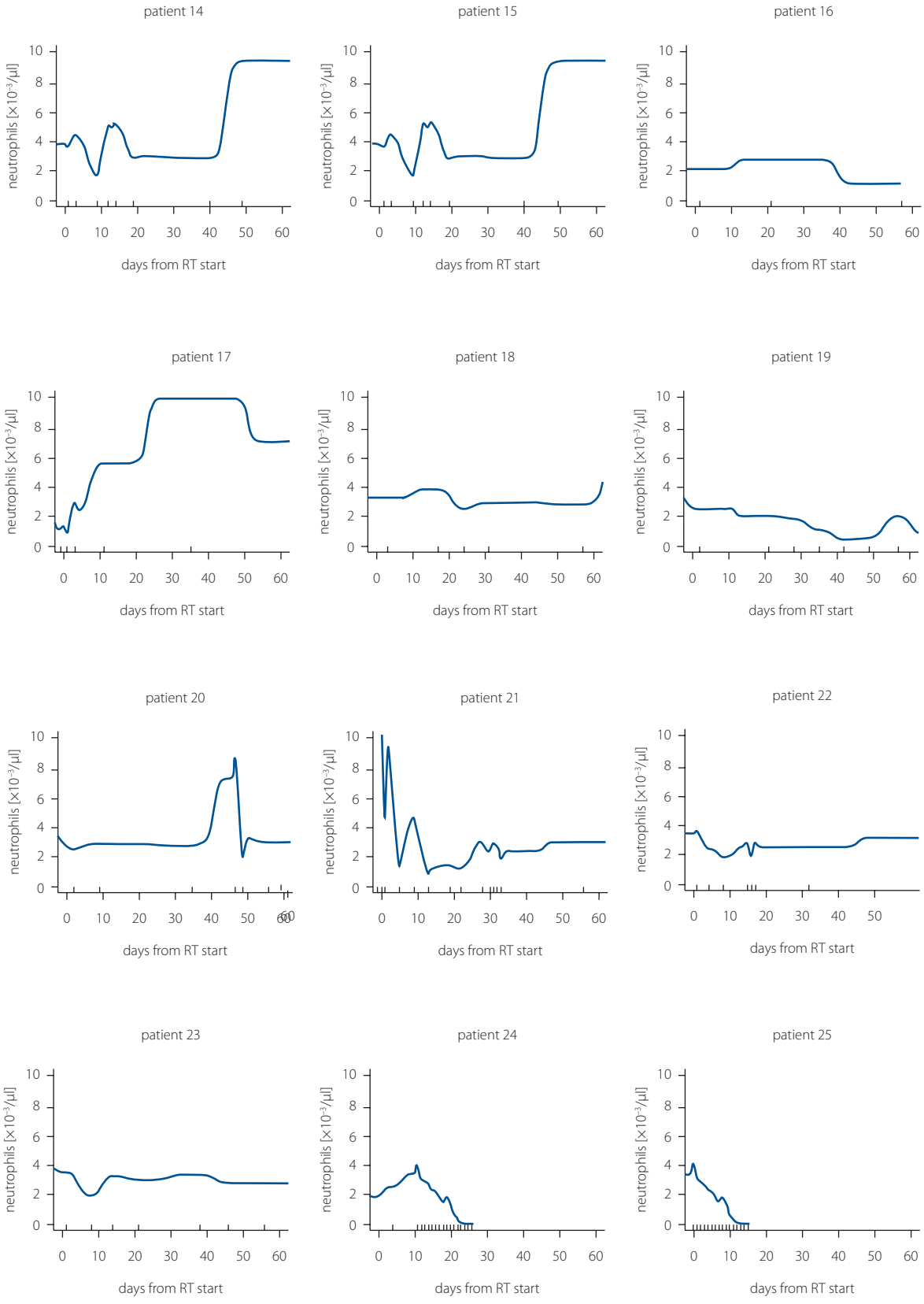

Figure 2. cont. Profiles showing the interpolated changes in ANC levels in selected patients

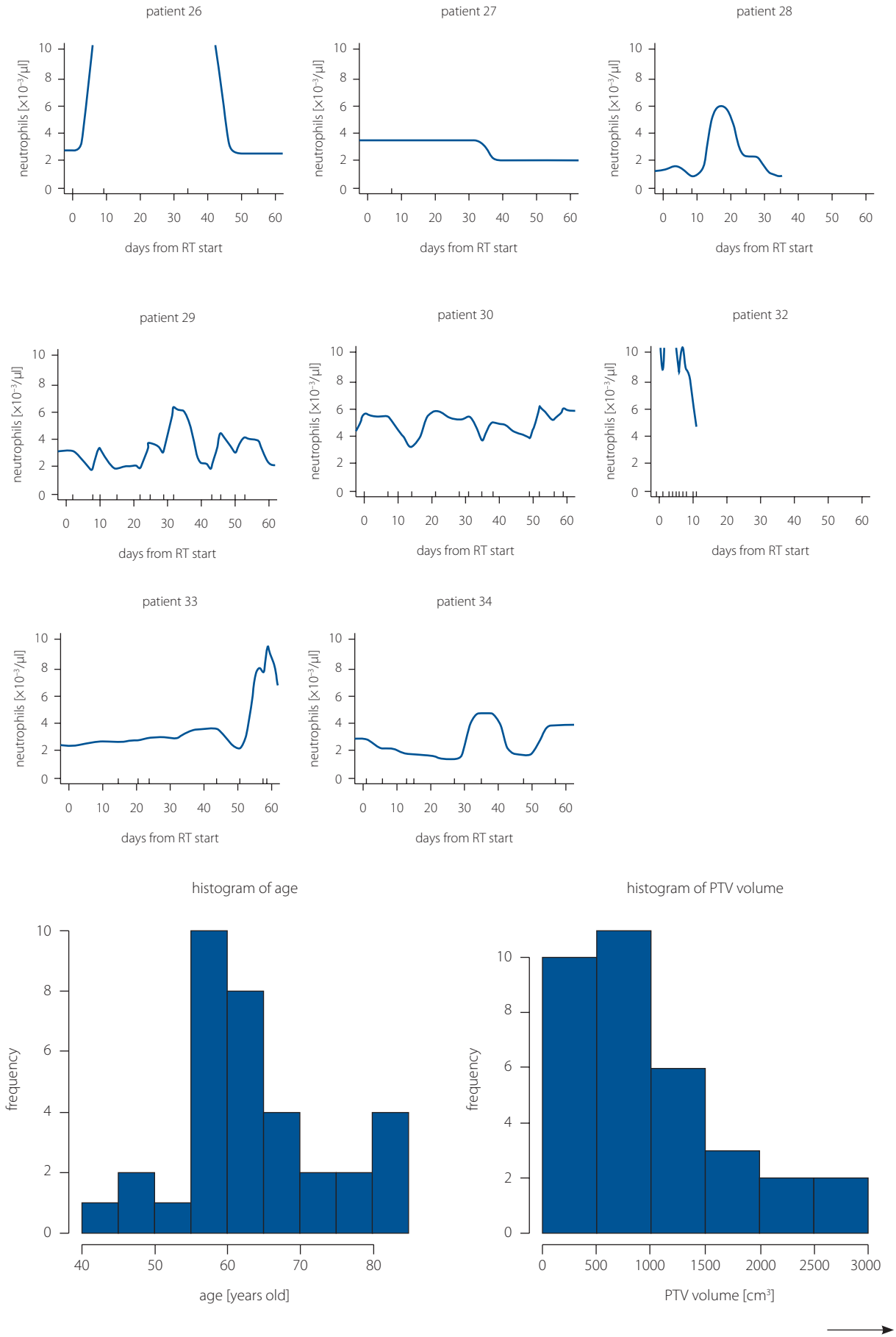

Figure 2. cont. Profiles showing the interpolated changes in ANC levels in selected patients

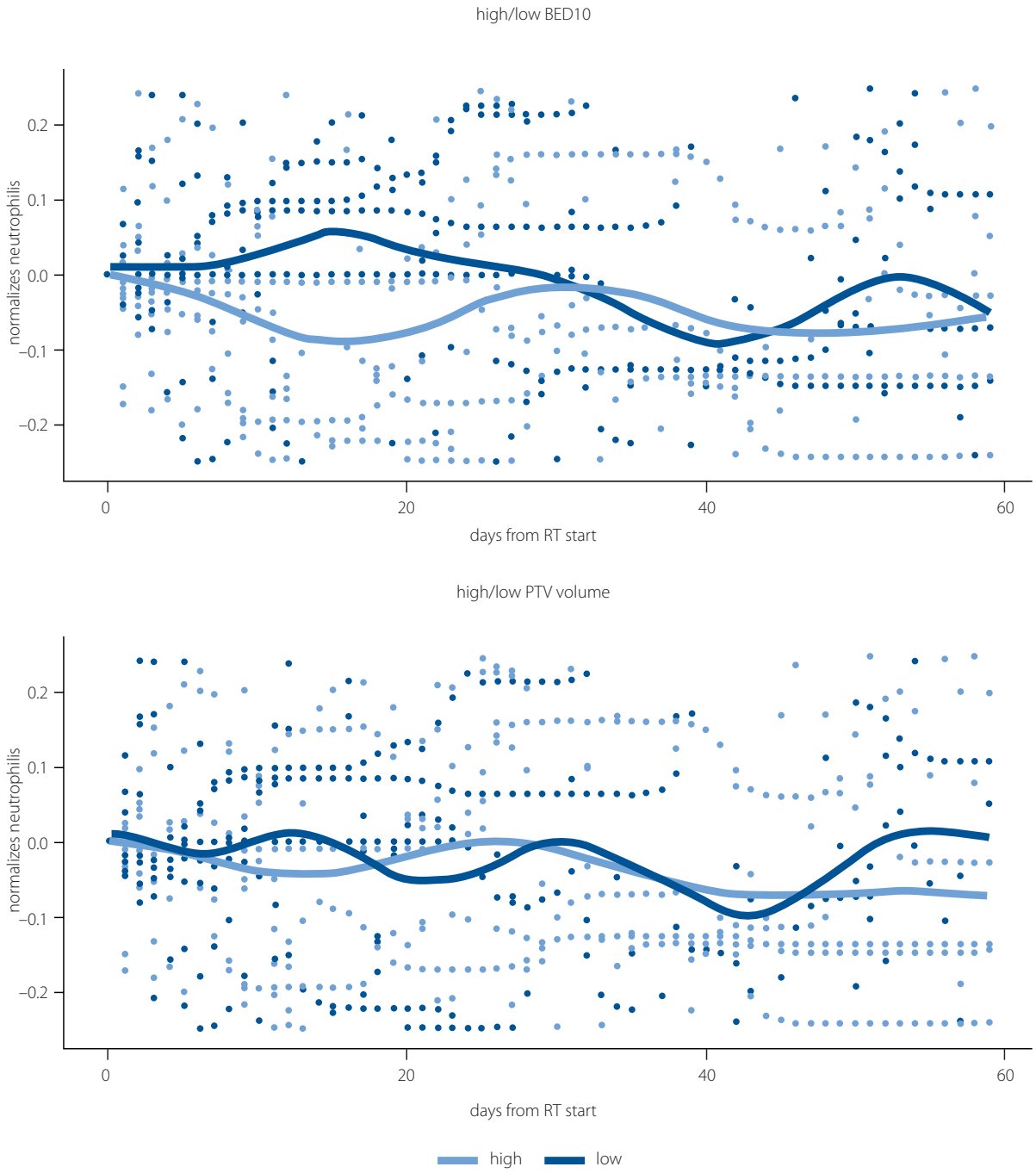

Figure 2. cont. Profiles showing the interpolated changes in ANC levels in selected patients

(grade 3 or 4 according to CTCAE), regardless of the fractionation scheme. The safest fraction was 30 Gy in 15 fractions. As shown by the model, the use of this dosing could provide treatment without severe neutropenia even with ANC = 1.23×10^3/μl on the day of RT start.

Discussion

In this pilot study we developed a statistical model explaining neutropenia severity and dynamics after radiation therapy in patients treated with bortezomib-based first-line systemic treatment. The model utilized PTV, BED10 and initial ANC to estimate how ANC will change in the days following the start of RT. Although the model metrics could be for sure improved if additional predictors were included, by enforcing low complexity we derived potentially clinically useful observations. All included predictors had significant effect on model outcomes.

The studied group was slightly younger than expected, as the average age at diagnosis with multiple myeloma is 69 years, compared to the observed average age of 64 years in our study [16]. Most often applied fractionation schemes were consistent with guidelines for palliative care of multiple myeloma patients

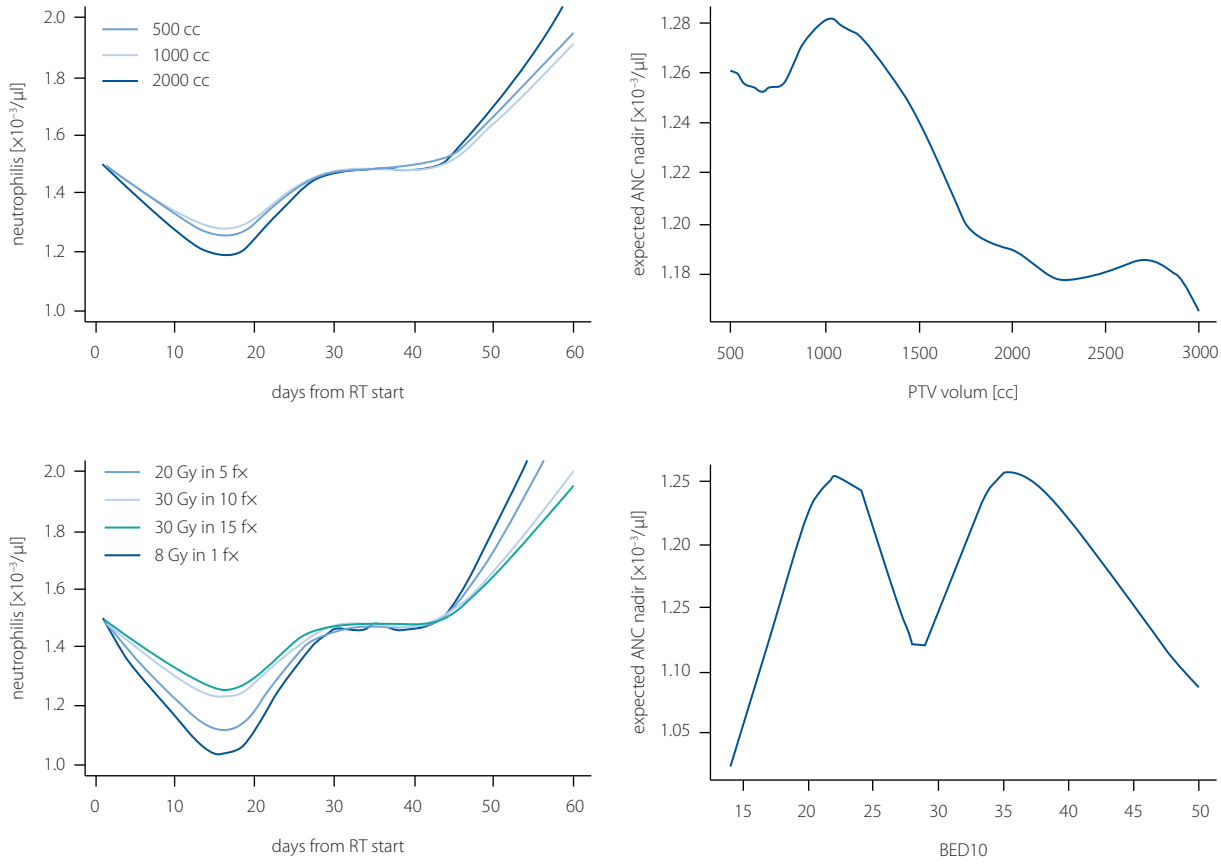

Figure 3. Effect of fractionation scheme (BED10) and PTV volume on neutrophil count estimated by GAM model and relationship of ANC nadir and changes in BED10 and PTV volume [cc; cm^3]. Median values were considered for non-modified variables. Initial ANC of 1.5 × 103/µl was used for calculations

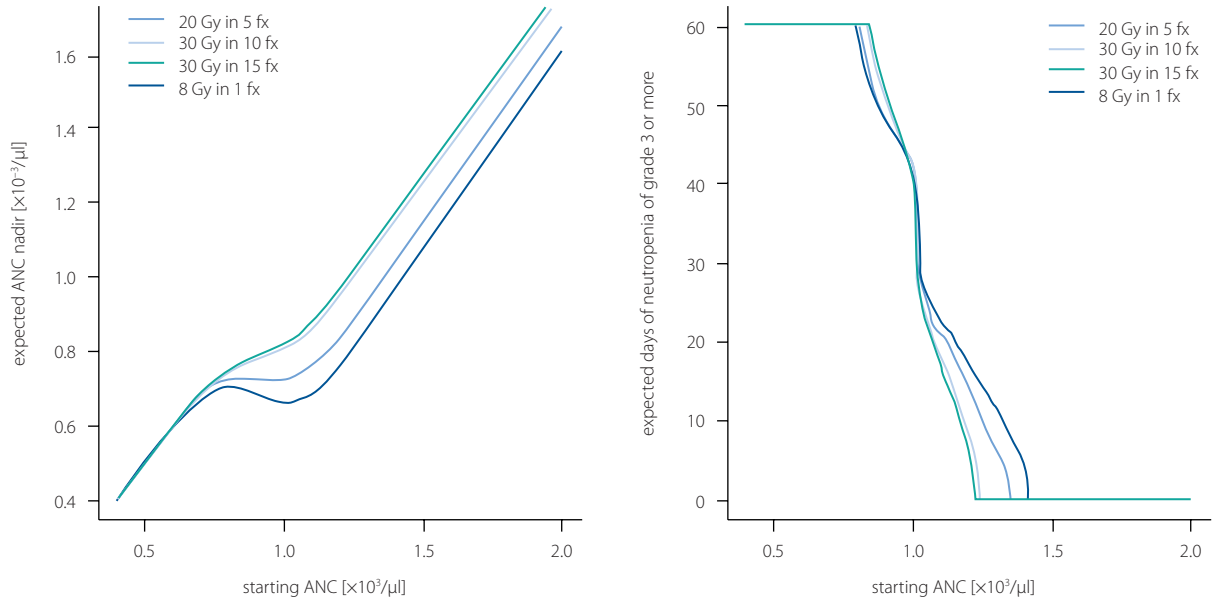

Figure 4. Relationship between starting ANC, nadir and expected days of neutropenia of grade 2 or more compared between different fractionation schemes. Calculations were performed for a PTV volume of 1000 cm^3

[17]. Each patient 17 CBC results per patient in studied timeframe aligns with the intent of radical systemic treatment.

The developed model provided significant clinically valuable insights. We observed that the ANC nadir after radiotherapy of bony lesions in MM can be expected around 16 days after RT initiation. This is an interesting observation, as most cytotoxic regimens cause neutropenic nadirs between days 10 and 14 [18]. The decrease of ANC seems, however, to be

dependent on BED10 (fractionation scheme), PTV volume and initial ANC level. As expected, in our data, a greater irradiated volume was associated with a more intense ANC nadir. We noticed, however, that the nadir was lowest for 8 Gy in 1 fraction regardless of starting ANC level. This observation should be treated with caution, considering that radiation oncologists tend to use 8 Gy in 1 fraction as a scheme for fragile patients with poor prognosis [19]. Considering that MM is frequently associated with severe pancytopenia in advanced stages, we might expect low bone marrow tolerability in these patients. Nevertheless, it is essential to emphasize that patients in our study were treated with bortezomib-based systemic treatment, which requires a good initial performance status.

In our study, the application of a radiation dose of 30 Gy in 15 fractions (2.0 Gy fraction dose) was found to be associated with the smallest decline in absolute neutrophil count (ANC) and was therefore identified as the safest option. Our model indicates that utilization of this treatment schema remains safe even when ANC levels are as low as 1.23 × 103/μl for PTV volumes of 1000 cm³, in contrast to the 1.42 × 103/μl threshold required when 8 Gy in 1 fraction is employed. This observation is interesting in the context of a retrospective review of 172 patients conducted by Rades et al. [20]. In this study, the authors compared shorter courses (8 Gy in 1 fraction, 20 Gy in 5 fractions) with longer courses of RT (30 Gy in 10 fractions, 37.5 Gy in 15 fractions, or 40 Gy in 20 fractions) for spinal cord compression caused by myeloma and concluded that longer courses are associated with improved motor function. Comparable functional outcomes were noted for longer course regimens. Additionally, in a randomized prospective clinical trial by Rudzianskiene et al. [21], a dose of 30 Gy in 10 fractions achieved better quality of life than 8 Gy in 1 fraction. Thus, in the context of our results, 30 Gy in 10 or 15 fractions seems to be not only safer, but also more effective.

Longer survival of multiple myeloma patients promotes the idea of RT dose reduction to reduce long-term toxicity, especially as long-term survivors tend to have multiple courses of RT. A recent retrospective review of 772 patients with the administration of lower dose of 20 Gy in fractions of 2 Gy (BED10 = 24 Gy) per day offers long-lasting pain relief, reduces the occurrence of bone marrow fibrosis, and allows for subsequent effective reirradiation [22]. In this review, a plurality of patients were treated with schemes with BED10 between 20 and 25 Gy (43%). Our model (as illustrated in figure 2) suggests that such regimens are associated with the lowest decrease in absolute neutrophil count (ANC). It is important to note, however, that the authors observed a small but statistically significant increase in reirradiation rates for BED10 ≤ 28 Gy.

This study had several limitations associated with its retrospective design. Firstly, the study did not assess the potential benefit of radiation treatment, such as pain relief or effects on survival. As low doses seem to be effective in MM [22], in the context of important preclinical evidence [14], future work will have to assess if an increased dose is associated with additional benefits beyond quality of life.

In many cases, more intensive treatments are associated with more adverse events but better clinical outcomes [23]. Secondly, the use of G-CSF and steroids prescribed by radiation oncologists and hematologists may have influenced the results. The effects of these drugs can be seen in some patients in this study, as G-CSF shortens the neutropenia period in responsive patients and can greatly impact the model. The cytotoxicity of radiotherapy and chemotherapy leads to a deficiency in all hematopoietic cell lines, but an increase in ANC could also be seen in patients who develop infections [24]. To address these complexities, a 30-day pre-treatment period was included in the analysis so that the dynamics of ANC changes before the start of RT could influence the model parameters. However, future studies should consider these factors in their analysis.

Conclusions

In the context of systemic therapy for multiple myeloma (MM), the role of radiation therapy (RT) is evolving, and its potential benefits at all stages of treatment are being investigated. However, concerns about the possible addition of toxicities may limit its current application.

In this paper we developed a preliminary model to estimate the dynamics of radiation-induced neutropenia in MM patients who had already undergone bortezomib-based chemotherapy. Our model determined the safety of radiation therapy in this patient population by analyzing the effects of different radiation schemes on absolute neutrophil count (ANC) levels. Our findings indicated that longer radiation schemes, such as 30 Gy in 10–15 fractions, can be safely administered to a volume of PTV = 1000 cm^3 – even if the ANC level is as low as 1.23 × 103/μl on the day of RT initiation. These results have the potential to guide clinical decision-making regarding the overlap of radiation and chemotherapy toxicities.

Overall, our study highlights the importance of developing predictive models to optimize treatment strategies in patients with MM undergoing RT and chemotherapy. Further research is needed to validate these findings and determine the feasibility of implementing this model in clinical practice.

Conflict of interest: none declared

Michał Masłowski
Copernicus Memorial Hospital in Lodz
Department of Radiotherapy
ul. Pabianicka 62
93-513 Łódź, Poland
e-mail: maslowskimichal@gmail.com

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Editorial

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The Nutrition in oncology section

I am proud to invite you to follow a new series of articles on clinical nutrition in oncology in *Nowotwory. Journal of Oncology*. Modern oncology is a field of continuous progress in surgery, radiotherapy and systemic treatment. However, the last decades have clearly shown that the use of clinical nutrition can significantly improve the results of oncological treatment.

Nutritional support extends the overall survival rate, disease progression-free time, the frequency of complications, particularly infectious ones, the length of hospital stay and treatment costs. Even in the advanced stage of the disease, parenteral nutrition contributed to the extension of survival time by an average of 70 days, and in pancreatic and gastric cancer, even by 3–4 months. It is known that malnutrition is a phenomenon that often accompanies cancer. Depending on its type, it occurs in 30–80% of patients at diagnosis. ⅓ of patients worsen nutritional status in the hospital, and 10–20% of oncological patients die of malnutrition and not disease progression.

Hoping for your interest in this subject, I encourage you to read the first article in the series *Glucose metabolism disorders in cancer patients* by Katarzyna Różycka and me. I am convinced that adding nutritional support to the routine practice of an oncologist will support your therapeutic success.

Aleksandra Kapała
Section Editor
Nutrition in oncology

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Glucose metabolism disorders in cancer patients

Katarzyna Różycka[1], Aleksandra Kapała[1, 2]

[1]Department of Clinical Nutrition, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Diabetes and cancer are among the most frequently cited causes of disability worldwide. The pathomechanism of glycemia disorders and carcinogenesis have common features that drive each other. Diabetes is estimated to be present in 8–18% of cancer patients. Hyperglycemia and its consequences are associated with an increased risk of cancer development, disease progression, and an increased risk of death. Treatment of glucose metabolism disorders requires an individual approach regarding nutrition and lifestyle.

Key words: hyperglycemia, hyperinsulinemia, nutritional therapy, malignancy

Introduction

Cancer and diabetes share common risk factors, such as obesity, smoking, age, physical inactivity, and poor diet. From year to year, they are becoming an increasing public health problem worldwide. Chronic diseases such as heart disease, cancer, and diabetes are significant causes of death and disability, requiring constant medical care, contributing to a poor quality of life. Cancer and diabetes generate approximately 500 billion USD in healthcare costs annually [1, 2]. Being diagnosed with cancer increases the risk of chronic diseases such as hypertension, diabetes, ischemic heart disease and arrhythmias, and depression. The coexistence of chronic diseases is noted in about seven out of ten cancer patients. Conducted in 2010–2015, US medical costs analysis of 3,657 adult cancer patients showed that 83.9% of this group had at least one chronic disease, and 29.7% reported four or more diseases. Total health expenditures were $6,388 higher for those with comorbidities than those without multiple conditions. In addition, cancer with comorbidities was associated with a 34% increase in healthcare expenditure compared to people without cancer [3].

According to the report of the International Agency for Research on Cancer, in 2020 there were 19.3 million cases of cancer and 10 million deaths. Today, one in five people will develop cancer in their lifetime, and one in eight men and one in 11 women will die from it. It is estimated that by 2040, cancer incidence will increase by 47% compared to 2020 and will reach 28.4 million cases [4]. The number of cancer cases in Poland has almost tripled over the last four decades – in 2018, 185,630 cases in total were recorded. Data from the National Cancer Registry suggest that by 2025 the number of cases will increase by 25.1% (up to 99.5 thousand) in women and by 13.9% (up to 90.4 thousand) in men [5].

In the case of diabetes, it is concluded that in 2021 approximately 537 million adults aged 20 to 79 suffered from it, i.e., 10.5% of the world's population. This number is estimated to reach 643 million in 2030 and 783 million by 2045. One person

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dies every 5 seconds due to diabetes, resulting in 6.7 million deaths in 2021. In addition, 541 million adults worldwide have impaired glucose tolerance, putting them at high risk of developing type 2 diabetes [6]. Looking at data from Poland, in 2018 every eleventh adult had diabetes, which means 2.9 million people were diagnosed with the disease.

Overall, 8–18% of patients with cancer have diabetes coexisting, and this percentage depends on the location of the tumor. In the case of pancreatic cancer, it is suggested that the onset of diabetes may be an early sign of pancreatic cancer, especially in patients with average or low body weight. Interesting conclusions are provided by a meta-analysis of 36 studies assessing the risk of pancreatic cancer in diabetic patients. Diabetes increased the risk of pancreatic cancer, but the risk was about 50% higher in people with a history of diabetes <4 years compared to those with diabetes 5–9 or >10 years [7].

Diagnostic of glucose metabolism disorders

Patients with cancer and comorbidities like obesity, dyslipidemia or cardiovascular disease are at high risk of glucose metabolism disorders. Therefore they should undergo thorough diagnostics. According to the World Health Organization (WHO) [6], hyperglycemic states are defined as:

- normal fasting blood glucose: 70–99 mg/dl (3.9–5.5 mmol/l),
- impaired fasting glucose (IFG): 100–125 mg/dl (5.6–6.9 mmol/l),
- impaired glucose tolerance (IGT): at 120 minutes of the oral glucose tolerance test (OGTT), blood glucose 140–199 mg/dl (7.8–11 mmol/l),
- prediabetes – IFG and/or IGT,
- diabetes – one of the following criteria:
  - casual glucose ≥200 mg/dl (11.1 mmol/dl) and symptoms of hyperglycaemia such as increased thirst, weakness, and polyuria,
  - twice (each measurement on a different day) fasting blood glucose in the morning, and the result was ≥126 mg/dl (≥7.0 mmol/l),
  - one-time HbA1c – value ≥ 6.5% (≥ 48 mmol/mol),
  - blood glucose at 120 minutes OGTT ≥ 200 mg/dl (≥11.1 mmol/l).

Insulin resistance can be identified by:

- HOMA index (Homeostatic Model Assessment) – cut-off value >1.0–1.5 [8, 9],
- QUICKI index (quantitative insulin sensitivity check index) – cut-off value: <0.34 [10, 11],
- insulin values during the glucose tolerance test (OGTT):
  - fasting insulin >15 mIU/l,
  - insulinemia in the 120th minute of the test >75 mIU/l,
  - insulinemia at any test point >150 mIU/l [12].

Different cut-off points for the diagnosis of insulin resistance appear in the literature. Unfortunately, no standardized laboratory standards indicate insulin resistance after performing a glucose tolerance test, which is a problem in the diagnostic process. The gold standard for assessing insulin sensitivity is the euglycemic insulin clamp. However, this method is technically challenging, labor-intensive and expensive. Subsequently it is not used in routine patient care [13].

Malignant tumors and diabetes

The incidence of malignant neoplasms in diabetic patients is significantly higher than in the general population, especially for breast, ovarian, endometrial, prostate, pancreatic and colorectal cancer [14]. The results of 40 studies involving 56,111 women with diabetes showed an increased risk of breast cancer by 16%. Still, no increased risk of cancer was observed in premenopausal women and women with type 1 diabetes [15]. A recently updated meta-analysis of 22 studies [16] showed that women with diabetes had a 72% higher risk of developing endometrial cancer than women without diabetes, consistent with the results of a previous meta-analysis by E. Friberg et al. in 2007 [17]. A meta-analysis of 10 prospective cohort studies showed a relationship between diabetes and an increased risk of colorectal cancer [18].

Diabetes is associated with an increased risk of malignancy and disease progression and an increased risk of death. The results of four extensive analyses of the risk of cancer death in different locations are consistent and indicate an increased risk of death in colon, rectal, brest, ovarian and pancreatic cancer in the presence of diabetes. Data comes from a Spanish FRESCO analysis of 10 years of follow-up in 55,292 subjects (15.6% with diabetes), 97 prospective studies with 820,900 patients, including 6% with diabetes, analyses of more than 20 cohorts representative of the Asian population (771,297 people, 4.7% with diabetes) and the National Health Research Institute in Hong Kong, which involved 895,434 people with diabetes and the same number of people without diabetes [19–22].

The common pathophysiological basis for malignant tumors and diabetes

Many biological mechanisms may explain the link between diabetes and cancer development. Metabolic disorders observed in the course of diabetes may contribute to the initiation and progression of carcinogenesis (fig. 1) [23].

Hyperglycemia induces oxidative stress and DNA damage. It can also contribute to the formation of advanced glycation end products (AGEs), which cause inflammation and may promote neoplastic transformation [24–26]. In addition, cancer cells switch their metabolism to the glycolytic pathway, which results in increased glucose uptake. This phenomenon is known as the Warburg effect and has been recognized as a characteristic of almost all cancer cells [27–29].

Under conditions of hyperinsulinemia observed in patients with type 2 diabetes, activation of pathways leading to carcinogenesis was noted in response to reduced sensitivity of peripheral tissues to insulin. Under conditions of increased

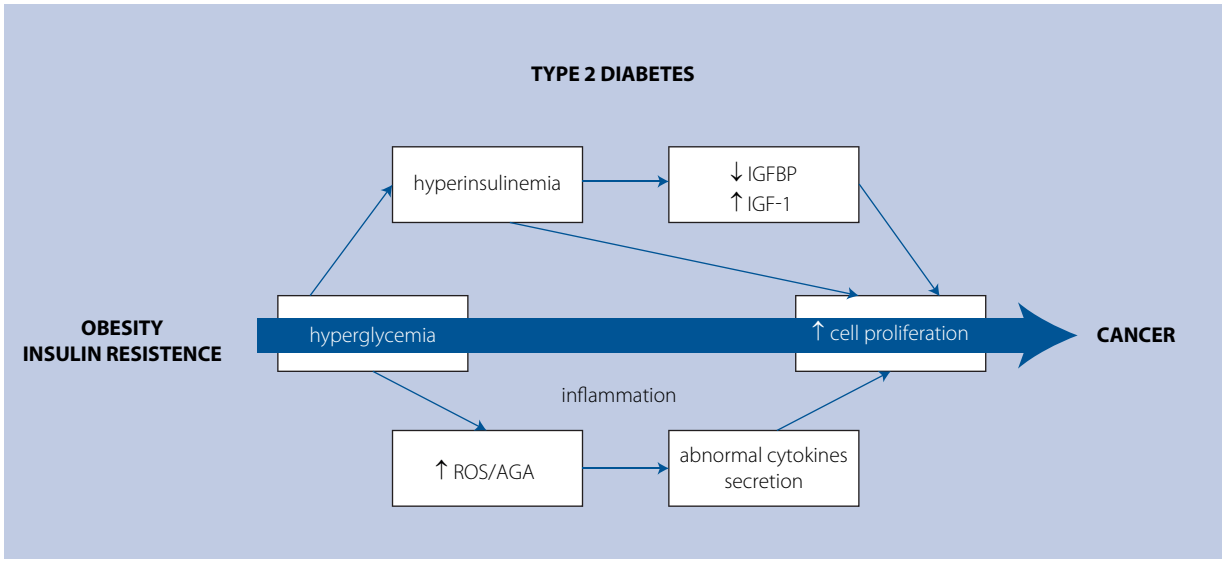

Figure 1. Pathophysiological links between obesity, insulin resistance, type 2 diabetes, inflammation, and cancer. Figure adapted from Cignarelli et al. [23]

insulin concentration, it may bind to receptors for insulin-like growth factors (IGF-1 and IGF-2), which, in contrast to insulin receptors, show mainly mitogenic and transformative activity. Insulin and insulin-like growth factors bind to the receptors (IR/IGF-1R), which leads to the activation of the tyrosine kinase and subsequent activation of the PI3K/AKT pathway. Activation of the IR/PI3K/AKT signaling pathway as a result of phosphorylation activates mTOR kinase, which is involved in angiogenesis, and the proliferation and migration of cancer cells. The insulin-like growth factor receptor activates the MAPK pathway, resulting in cell growth and differentiation [30–32].

Chronic inflammation that develops in both diabetes and obesity may promote the development of cancer cells. Most reports concern the acceleration of the carcinogenesis process due to the activation of pro-inflammatory cytokines. They encourage the growth of cancer cells (tumor necrosis factor – TNF-α, interleukin-6 -Il-6), promote angiogenesis (TNF-α, IL-17, TGF-β), impair the function of macrophages and NK cells, and facilitate metastasis (TGF-β transforming growth factor, TNF-α, IL-6) [23, 33].

Adipose tissue, considered an active organ that secretes adipokines, also participates in carcinogenesis. Leptin, adiponectin, and resistin regulate hunger and satiety, insulin sensitivity, hematopoiesis, inflammation, and angiogenesis. In obesity, there is an imbalance in the secretion of adipokines and an increased risk of developing a chronic inflammatory process, insulin resistance or excessive and uncontrolled cell proliferation. Under normal conditions, leptin is responsible for satiety and maintaining a healthy body weight. The concentration of leptin increases in proportion to the mass of adipose tissue. An elevated concentration of leptin is a typical finding for obesity. Excessive leptin secretion is observed in breast, lung, colon, uterus, thyroid, and pancreatic ancers. It affects proliferative activity, stimulates transcription activator 3 (STAT3) of an oncoprotein activated in many cancers, and promotes angiogenesis [34]. In turn, adiponectin is a peptide that has a protective effect against the development of chronic inflammation, obesity, and type 2 diabetes and is inversely correlated with adipose tissue content in the body. Under physiological conditions, it participates in the metabolism of glucose and fats. Low serum adiponectin levels are associated with an increased risk of malignant tumors: gastric, breast, prostate, colorectal, endometrial, renal cell carcinoma, and leukemia [34, 35]. Resistin is a pro-inflammatory cytokine associated with obesity, diabetes, and insulin resistance. Studies show elevated serum resistin levels in breast, colon, lung or kidney cancer patients. Resistin has been associated with an increased risk of progression, angiogenesis, and metastasis [36].

Anticancer treatment and glucose metabolism disorders

Patients treated for cancer are at risk of hyperglycaemia, which may contribute to adverse events such as increased risk of infection or all-cause mortality. Diabetic patients are more exposed to chemotherapy toxicity manifested by fever, neutropenia or anemia [36–38]. Many cytostatic drugs have been associated with developing hyperglycemia in non-diabetic patients. Docetaxel, everolimus, and temsirolimus alone or combined with other agents can promote hyperglycemia. Androgen deprivation therapy, commonly used in prostate cancer, increases the risk of developing hyperglycemia and diabetes [39]. As a result of combining chemotherapy with widely used corticosteroids, insulin resistance and related hyperglycaemia may be expected, which may lead to the need to reduce the dose of cytostatics or postpone treatment [40, 41].

Currently, Immune checkpoint inhibitor (ICI) therapy, a breakthrough in cancer therapy, is widely used. However, it may lead to an increased risk of side effects of immune origin.

Immunotherapy plays an essential role in the treatment of advanced cancers for example, lung, kidney, head and neck, GI tract, ovarian, urothelial and melanoma, and can also induce disorders of glucose metabolism. Inhibition of immunological endpoints may induce adverse effects directed against host tissues and cause type 1 diabetes. It is estimated that diabetes related to immunotherapy affects about 1–2% of patients, and its symptoms are severe and manifest as ketoacidosis or acute pancreatitis. The determination of C-peptide is helpful in the diagnosis, and its low concentration in case of hyperglycaemia may suggest diabetes induced by immunotherapy. Diabetes in subjects treated with ICI may develop immediately after starting therapy and after a few months or even a year. Therefore, it is crucial to monitor glycemia with each drug administration [42].

Many factors can induce and exacerbate hyperglycemia in cancer patients, including poor diet, lack of physical activity, high BMI, severe stress or infections. A meta-analysis of 23 studies (various cancer types) showed an association of diabetes detected before cancer diagnosis with a 41% increase in mortality compared to subjects without diabetes before cancer onset [43]. Studies involving 5,922 patients with stage II and III colon cancer have shown that diabetes is associated with shorter overall survival and shorter progression-free survival [44]. Similar observations have been made for other cancers, including gallbladder, ovarian, breast and pancreatic cancer [45–48]. Cancer patients with diabetes may develop complications during treatment, such as kidney function impairment, heart disorders, neuropathy, and severe diarrhea [1]. The occurrence of complications may contribute to providing the patient with suboptimal care. A Dutch study showed that patients with diabetes and esophageal, colon, breast and ovarian cancer received anticancer treatment in reduced doses, unlike those without diabetes [41].

Nutritional treatment of glucose metabolism disorders in cancer patients

Diet and healthy lifestyle

Nutritional recommendations for patients with hyperglycemia during cancer treatment should be tailored individually. Nutritional management will be different for obese patients than for those who are malnourished or at risk of malnutrition. The leading ailments, the type of oncological therapy used, and the type of cancer and comorbidities should also be considered.

Depending on the tumor's location, we distinguish cancers with different degrees of malnutrition risk. The highest percentage of malnutrition is observed in cancers of the pancreas, esophagus, stomach, and head and neck organs, where the risk reaches as much as 70% and usually worsens during oncological treatment. The group with an intermediate risk of developing malnutrition (approx. 50%) are patients with cancers of the lungs, colon, ovaries and lymphomas. On the other hand, breast and prostate cancer – occurring most often in the population – is associated with the lowest risk of malnutrition, 10–20% of cases. In this group of patients, we focus primarily on introducing proper nutrition and preventing or treating those who are overweight and suffering from obesity [31]. Studies suggest that approximately 30–50% of women with breast cancer increase their body weight by more than 5% during and after chemotherapy [49]. For prostate cancer, every 5 kg/m^2 increase in BMI is associated with a 21% increase in the risk of recurrence. An analysis of 59 studies involving 280,199 patients showed that obesity increases the risk of prostate cancer-related death by 19% and the risk of death from any cause by 9% [49]. The WCRF (World Cancer Research Fund) and AICR (American Institute for Cancer Research) report suggest that approximately 21% of all obesity-related cancers could be avoided if the adult population had a BMI <25 kg/m^2 [50].

Assessment of nutritional status and nutritional support

The essential element of assessing the patient's nutritional status is an interview conducted by a physician and a clinical dietician, during which information is collected about weight loss, gastrointestinal symptoms, and the severity of the disease (cancer type, stage, and treatment plan).

The first element of nutritional intervention is a dietary consultation and modification of the diet. If the ordinary oral diet is not enough, we supplement it with food for special medical purposes (FSMP), which can supplement the oral diet. Many preparations are available on the market, both in powder and liquid form, with a sweet or dry taste. When choosing a preparation for patients with glucose metabolism disorders, attention should be paid to the composition – a good choice will be a high-protein product (20–25% protein of the formula content; 8–10 g of protein per 100 ml), with the content of MUFA fatty acids, limited supply of carbohydrates and with the content of numerous fractions of fibre. When choosing medical food, an important feature is osmolarity, which should be close to the physiological osmolarity in the gastrointestinal tract on an empty stomach – approx. 280–380 mOsm/l. High-osmolarity formulas may affect the tolerance of the product and, in consequence, the compliance and effectiveness of the nutritional treatment.

If oral nutrition is insufficient, artificial nutrition should be introduced, depending on the indications, intravenous or parenteral. An option for patients with glycaemic disorders with indications for enteral nutrition is using formulas dedicated to diabetics. Those formulas are characterized by a higher proportion of polysaccharides and, on average, the total amount of carbohydrates is 35%. The glycaemic index is low <50. Commonly used sucrose has been replaced with sweeteners. Preparations for diabetics contain several types of dietary fibre. Fats are mainly in the form of monounsaturated fatty acids.

Selected preparations also contain EFAs from the omega-3 group (essential unsaturated fatty acids from the omega-3 family). Enteral formulas have a similar composition to oral food supplements, but most of them do not contain flavourings and contain more water. Preparations for diabetics are beneficial in patients with uncontrolled glycaemia and the case of complicated diabetes. According to the current recommendations, patients with diabetes may receive standard preparations. Still, in the case of complications with uncontrolled glycemia or complications of the disease, a dedicated formula should be introduced [59]. In patients requiring parenteral nutrition, up to 50% of energy from fat may be considered. Artificial nutrition usually requires simultaneous use of hypoglycaemic drugs, in the case of TPN (total parenteral nutrition), intensive insulin therapy [60].

Protein

The diet of an oncological patient should contain increased protein content – it is recommended to have at least 1.2–1.5 g of protein/kg of body weight/day, in the case of malnourished patients undergoing surgical procedures, even 2 g/kg of body weight/day. Good protein sources include eggs, milk and dairy products, fish, steamed/boiled or roast meat, and tofu. It is not recommended to eat fried and grilled products.

The diet should also include naturally occurring antioxidant and anti-inflammatory compounds – quercetin (apples, onions), sulforaphane (broccoli, broccoli sprouts, brussels sprouts), resveratrol (dark grape, cranberry, blackberry). In conclusion, the diet should be based on the principles of the Mediterranean diet with appropriate modifications tailored to the individual patient.

Carbohydrates

The principles of nutrition in patients with glucose metabolism disorders are based mainly on limiting simple carbohydrates in the diet, the source of which is predominantly white and brown sugar, sweets and sweet drinks. Products containing glucose-fructose syrup should be avoided, as well as fructose itself as a sugar substitute. Honey, fruit juices, and fruit drinks should be limited. Natural sweeteners can be used, e.g., stevia and xylitol. Homemade low-sugar cakes, oat bars, fresh fruits, dark chocolate, min. 70% cocoa may be used as a dessert. The main source of carbohydrates should be products with a low glycemic index of <50.

Dietary fiber plays an essential role in the diet. According to the WCRF/AICR recommendations, at least 30 grams should be consumed daily [51]. A meta-analysis of 10 prospective studies shows that every additional 10g of dietary fiber is associated with a 9% reduction in colorectal cancer risk. The authors suggest that while all sources of fiber may be beneficial in preventing colorectal cancer, the most robust evidence favors cereal-derived fiber [52]. The main sources of dietary fiber are unprocessed cereal products, legumes, vegetables and fruits. Depending on the dietary function of fiber in the human body, a fraction of water-soluble and insoluble fiber is distinguished.

Good sources of soluble fibre are fruits (apples, citrus fruits), vegetables (parsley, carrots, eggplant), legumes (peas, beans), cereals (oats, barley), linseed, psyllium and nuts. Insoluble fibre is found mainly in whole grain cereal products (bread, cereals, wholegrain flours, bran, coarse groats, brown rice), fruit and vegetable skins, some fruits (blackcurrant) and vegetables (green peas) [53]. From the point of view of glucose metabolism disorders, water-soluble fibre is essential. The properties of soluble fibre contribute to improving glycaemic control – reducing fasting glucose and insulin levels and HbA1c. Adding soluble fibre may delay gastric emptying and slow down glucose absorption in the small intestine. Glucagon-like peptide (GLP-1) is released into the bloodstream, as a result of which the beta cells of the pancreas are stimulated, and an improvement in the sensitivity of the cells to insulin is observed. In addition, due to the fermentation of dietary fibre by the microbiome, short-chain fatty acids such as butyric and propionic acids are formed, affecting various metabolic pathways, including the glucose metabolism. Even a few weeks of using a diet rich in fibre cause an increased concentration of butyric acid, which is associated with an improvement in postprandial glycemia and insulin concentration [54, 55].

Studies show that dietary fibre, like many other nutritional components, can stimulate the growth of beneficial bacteria in the large intestine and thus modify the microbiome, which plays a key role in the occurrence and course of diet-related diseases such as diabetes, obesity, and cardiovascular disease. Probiotic strains such as *Lactobacillus salivarius* UBLS22, *L. casei* UBLC 42, *L. plantarum* UBLP 40, *L. acidophilus* UBLA 34, *Bifidobacterium breve* UBBR 01, *Bacillus coagulans Unique-IS2* (daily dosage 3 x 108 / x 109 CFU) support the economy carbohydrate, among others, by increasing insulin sensitivity, regulating the secretion of intestinal hormones or antioxidant activity [56–58].

Fats

The proportion of fat in the diet should be 30–40%, corresponding to the fat content of the Mediterranean diet. In the case of malnourished patients with poor appetite and concomitant diabetes, they are recommended easily digestible fats that are a source of MCT (medium chain triglycerides): butter, coconut fat (milk, oil, cream, yoghurt). They are an essential energy donor for a malnourished patient, and their metabolism differs from that of long-chain fatty acids. The diet should also include vegetable fats that are a source of monounsaturated fatty acids (MUFA), which stabilize postprandial glycemia and the need for insulin (rapeseed oil, avocado). As a source of polyunsaturated fatty acids (PUFA) – olive oil, linseed oil, and some nuts such as walnuts, hazelnuts, and pecans are recommended. In the case of overweight and obese patients, the share of MCT fats should not exceed 10% of the daily requirement for fats, and the supply of fats should be based mainly on sources of MUFA and PUFA. In all patients, sunflower oil, peanut oil, palm oil, processed

cheese, blue cheese, mayonnaise, pâté, lard, pork fat, and fatty and processed meat products should be limited.

Physical activity

Physical activity is tolerated and safe at various stages of cancer, even in patients with advanced disease. Moderate-intensity activity (50–75% of maximum baseline heart rate or aerobic capacity) is recommended for 10–60 minutes per session three times a week. Physical activity in cancer patients is associated with maintaining or improving muscle strength and aerobic capacity, as well as health-related quality of life, self-esteem, and reducing fatigue and anxiety. At the same time, exercise improves insulin sensitivity, which is the basis of the non-pharmacological treatment of diabetes. The approach to physical activity should be individualized, as some patients require training in walking or bedside exercises.

In contrast, other groups of patients will require more advanced resistance or aerobic exercise. Studies suggest the advantage of resistance exercises over aerobic exercises and show positive effects on increases in muscle strength. For cancer survivors, it is recommended to maintain a healthy lifestyle, including a balanced, healthy diet, regular physical activity, and a BMI in the range of 18.5 to 25 kg/m^2 [60].

Conflict of interest: none declared

Aleksandra Kapała
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Clinical Nutrition
ul. Roentgena 5
02-781 Warsaw, Poland
e-mail: aleksandra.kapala@pib-nio.pl

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Expert consensus statement on tobacco control sustainability in Poland

Łukasz Balwicki[1], Marta Miller[2], Magdalena Cedzyńska[3], Irena Przepiórka[3], Jarosław Pinkas[4], Wioleta Tomczak[1], Tomasz Zdrojewski[5]

[1]*Department of Public Health and Social Medicine, Medical University of Gdansk, Gdansk, Poland*
[2]*Medical University of Gdansk, Gdansk, Poland*
[3]*The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[4]*Centre of Postgraduate Medical Education in Warsaw, Warsaw, Poland*
[5]*Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland*

Introduction. Tobacco use poses a significant public health threat in Poland, with high rates of consumption and detrimental effects on individuals. Tobacco is responsible for one-third of all cancer deaths in Poland. This study aimed to develop an expert consensus statement on tobacco control sustainability in Poland.

Material and methods. An expert consensus hybrid meeting was conducted, gathering national tobacco control experts from various fields. The meeting utilized the Index of Tobacco Control Sustainability (ITCS) to identify critical indicators for a sustainable national tobacco control program.

Results. Key recommendations include developing a comprehensive tobacco control strategy and program, establishing inter-governmental coordination, strengthening civil society involvement, creating a dedicated Tobacco Control Unit, allocating government annual funding for tobacco control operations, and strengthening organizational resistance to tobacco industry interference.

Conclusions. Poland needs to build the institutional capacity and address sustainable financial resources on an annual basis to effectively organize sustainable tobacco control.

Key words: tobacco control, cancer prevention, consensus, expert

Introduction

Globally, tobacco use remains a major public health issue, impacting both individuals and societies in harmful ways. Poland is currently facing a crucial challenge due to the high level of tobacco consumption. Available data recently indicate an upward trajectory in the prevalence of smoking in the country [1]. As many as 28.8% of adult Poles (30.8% of men and 27.1% of women) admitted to smoking daily in 2022 [2]. Moreover, 26.2% of Polish youth admitted to smoking at least once in the previous 30 days [3].

Smoking negatively affects all organs of the human body, including the heart and circulatory system by increasing the risk of ischemic heart disease, among other conditions. It can cause incurable respiratory diseases such as chronic obstructive pulmonary disease (COPD), emphysema, asthma,

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or increase the risk of several cancers. It has been shown that smoking can cause the development of at least twelve different malignancies including lung cancer, laryngeal cancer, bladder cancer, and stomach cancer [4].

Insights from the Global Burden of Disease (GDB) study have unveiled the profound impact of tobacco-induced cancers on the Polish population. In 2019, tobacco-related neoplasms caused the deaths of about 39,816.79 people and accounted for 32.6% of all deaths from malignant neoplasms. Tobacco dependence caused 26.6% of all deaths among Polish men and 13.8% of all deaths among Polish women in 2019. It is also among the main factors responsible for lost healthy life years for Poles (17.2% of total disability-adjusted life years [DALYs] in 2019) [5]. The health status of the Polish population is profoundly affected by tobacco-related diseases, underscoring the need for proactive tobacco control measures which should be an indispensable part of cancer prevention strategies.

The urgency as regards comprehensive tobacco control in Poland is further compounded by the persistent activities of the tobacco industry. Despite the ban on advertising and promoting tobacco products in Poland, tobacco companies exploit legal loopholes and the weak enforcement of existing laws to carry out their marketing activities [6]. The industry continues to employ marketing tactics that target vulnerable populations. In order to target young adults, they strategically place advertisements in locations associated with social gatherings and entertainment [7]. What is more, the tobacco industry possesses the capacity to exert influence over tobacco control policies in Poland. This influence is achieved through a range of strategies, such as cultivating a positive image, demonstrating a willingness to engage in policy-making procedures, and employing various forms of pressure to exert influence and lobby those in power [8].

Even so, Poland has not yet established effective countermeasures. Besides the implementation of European directives and, to some extent, the World Health Organization's Framework Convention on Tobacco Control [9], prevention efforts have been very scattered. A study by Balwicki et al. showed both inadequate planning of and funding for Polish the Tobacco Control Program in the years 2000–2018 [10].

The study aimed to develop an expert consensus statement on tobacco control sustainability in Poland. Expert opinions were sought from diverse fields encompassing public health, medicine, research, and policies to ensure a multidisciplinary approach that incorporates various perspectives.

Material and methods

An expert consensus hybrid meeting was held on November 4, 2022, in Warsaw in the Ministry of Health. Polish national tobacco control experts representing public institutions, academia, and civil society organizations were invited to participate in the meeting to discuss the sustainability of national tobacco control in Poland. The discussion was a part of global initiative of The International Union Against Tuberculosis and Lung Disease called The Index of Tobacco Control Sustainability (ITCS). ITCS is a tool to assess and guide national tobacco control programs to become more sustainable [11]. The open discussion was structured by 31 indicators that have a critical influence on the national capacity to deliver effective and sustainable tobacco control into the future. The ITCS identifies the structures, policies, and resources that a country already has in place, and thus its progress towards establishing a sustainable national tobacco control program. After the meeting, a first draft including a statement was circulated to the panelists, discussed and edited. The present document was formulated and agreed on by all attending experts in this field.

Results

Tobacco control strategy: the program and inter-governmental coordination

Poland lacks a tobacco control strategy and a comprehensive program. A tobacco control strategy should provide a roadmap for addressing smoking prevalence and nicotine addiction effectively. It enables the government to implement evidence-based policies and interventions, allocate resources efficiently, and monitor progress in reducing tobacco use. Without a clear strategy, efforts to control tobacco may lack direction and coordination, leading to suboptimal outcomes. A tobacco control program should be based on the above mentioned strategy, describing in detail the activities that lead to achievement of the goals. The program should be comprehensive, covering all aspects of tobacco control expressed in the World Health Organization Framework Convention on Tobacco Control (WHO FCTC) and its guidelines [12] as well as aspects expressed in WHO MPOWER package [13]. Additionally, establishing a functioning inter-governmental coordination mechanism is vital for effective collaboration and cooperation among different government agencies and public institutions involved in tobacco control. This mechanism can facilitate the exchange of information, coordination of efforts, and alignment of strategies, thereby ensuring a cohesive and unified approach to reducing tobacco use. It is critical for the country to allocate designated government funding annually to support tobacco control strategies and activities, including capacity building.

Consensus statement

It is crucial for Poland to develop a comprehensive tobacco control strategy and a program in line with the WHO FCTC guidelines. The realization of the strategy and program should be warranted by a functioning inter-governmental coordination mechanism.

Funding of tobacco control

Currently, no specific, annual funding is allocated for tobacco control activities, highlighting the need for sustainable financial

support. The Polish government should allocate specific funding on an annual basis to support the implementation of tobacco control strategies and activities. These finances should encompass capacity-building activities, both at governmental and civil society levels, necessary for effective tobacco control. Money could come from the deduction of excise tax on tobacco products as recommended by the World Health Organization [14].

Consensus statement

Poland should allocate designated, annual government funding for tobacco control operations and capacity building for tobacco control personnel and organizations.

Coordination of tobacco control

Poland does not have a properly functioning Tobacco Control Unit nor coordination mechanism for tobacco control activities. As a result campaigns and activities are scattered with no long-term plan or evaluation. It is also not clear who oversees the implementation of tobacco control law, tobacco industry activities, as well as tobacco and new nicotine product use. Establishing a Tobacco Control Unit in Poland is crucial to coordinate national tobacco control activities. It facilitates collaboration, strategic planning, data analysis, advocacy, and public awareness. By coordination of efforts and utilizing evidence-based approaches, the unit could enhance the effectiveness of tobacco control measures and contribute to reducing smoking prevalence and related harms.

Consensus statement

It is crucial for Poland to establish a Tobacco Control Unit and coordinating mechanism to manage tobacco control activities nationally.

Civil society in tobacco control

A civil society tobacco control network does not exist in Poland. Strengthening the civil society community and forming a national advisory committee with civil society representatives is crucial for supporting the implementation of tobacco control strategies and programs across Poland. This approach ensures inclusivity, taps into specialized knowledge, mobilizes grassroots support, and enables independent monitoring and evaluation, leading to more effective and accountable tobacco control efforts. Civil society is also needed for communication and advocacy efforts for stronger tobacco control.

Consensus statement

Poland should strengthen its civil society community and form a national advisory committee with civil society representatives to support strategy and program implementation.

Monitoring and evaluation of tobacco control

Monitoring and evaluation play a vital role in effective tobacco control programs. While Poland lacks a comprehensive mortality and morbidity recording system, the incidence of lung cancer serves as a vital indicator of the actual and prevailing tobacco-related situation. Poland's involvement in the GDB initiative allows for the provision of data that helps assess the extent of DALYs lost due to tobacco use. Nevertheless, it is noteworthy that Poland currently lacks a national evaluation framework, and the integration of evaluation practices into major policy implementation plans remains limited. Data on economic and social tobacco costs are not calculated regularly for Poland. Establishing a robust monitoring and evaluation system is imperative in tracking the impact of tobacco control efforts accurately, guiding evidence-based policymaking, and effectively addressing the challenges posed by tobacco-related mortality and morbidity in the country.

Consensus statement

Monitoring and evaluation should be a part of Polish tobacco control.

Resistance to tobacco industry interference

Poland has a weak organizational resistance to tobacco industry interference. A report of the Global Tobacco Industry Interference Index 2021 shows many examples of unnecessary interaction and collaboration between the Polish government and the tobacco industry [15]. Tobacco industry Interference results in insufficient legal regulations, lowering the quality of decisions made and reducing the effectiveness of tobacco control. The Act of 16 September on government employees establishes general policies governing the duties and performance of government officials and staff. It explicitly prohibits officials from engaging in activities that could be perceived as conflicting with their duties or raising suspicions of partiality or self-interest. However, the Ministry of Health has yet to adopt a specific policy aligned with Article 5.3 of the World Health Organization Framework Convention on Tobacco Control. Moreover, there is currently no comprehensive adoption of the WHO FCTC Article 5.3 policy across all other ministries in Poland. Further progress is still needed to ensure robust measures are in place to counteract the influence of the tobacco industry at both the ministry level and throughout various government bodies in the country.

Consensus statement

Poland should strengthen organizational resistance to tobacco industry interference implementing WHO FCTC Art 5.3 provisions.

Conclusions

In order to effectively push out tobacco control in Poland, the country needs to build institutional capacity and address sustainable financial resources on an annual basis. A Polish tobacco control program should address all aspects of preventive measures described in the WHO FCTC which Poland is a party

to. Lack of organized efforts can worsen the epidemiological situation and have a profound impact on tobacco related diseases, including cancer.

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Marta Miller
Medical University of Gdansk
ul. Marii Skłodowskiej-Curie 3a
80-210 Gdańsk, Poland
e-mail: mmiller@gumed.edu.pl

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Alcohol availability, consumption, and knowledge of alcohol-related cancer risk among citizens of Warsaw

Elwira Gliwska[1, 2], Anna M. Badowska-Kozakiewicz[1]

[1]*Department of Cancer Prevention, Faculty of Health Sciences, Medical University of Warsaw, Poland*
[2]*Cancer Epidemiology and Primary Prevention Department, The Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction. The high availability of alcohol products and low awareness of their harmful effects appear to influence individual health conditions and cancer risk.

Material and methods. We used publicly available data on alcohol retailers in Warsaw to assess the availability of alcohol products for each district of the city and the AUDIT C questionnaire to assess drinking behavior.

Results. Alcohol outlets were located within 500 meters of residence for most of the study group. We found risky alcohol consumption in about 15% of respondents. Knowledge about the harmfulness of excessive alcohol consumption had a statistically significant effect on the number of drinks consumed ($p < 0.05$).

Conclusions. The study confirmed the high availability and affordability of alcoholic products and the high percentage of risky alcohol behaviors among Warsaw's citizens. In addition, low awareness of the harmful effects of alcohol was associated with higher consumption, which emphasizes the need to improve educational strategies.

Key words: cancer prevention, alcohol, non-communicable diseases, alcohol retailers, primary prevention

Introduction

Alcohols are a class of organic compounds characterized by one or more hydroxyl groups (-OH) attached to a carbon atom of an alkyl group. The commonly used term "alcohol" refers to ethanol (also known as ethyl alcohol), which contains two carbon atoms. Ethanol is the form of alcohol found in beverages such as beer, wine, and liquor [1].

Alcohol is a known psychoactive substance that affects all systems in the human body and is addictive. Alcohol consumption is a contributory factor of many different health conditions, such as cardiovascular disease, cirrhosis of the liver, and some cancers. The short-term effects of alcohol consumption are usually caused by binge drinking and can lead to severe health disorders such as injuries, violence, alcohol poisoning, risky sexual behavior, or miscarriages [2]. However, occasional alcohol consumption is also associated with numerous health complications. Moderate alcohol consumption is generally considered one drink per day for women and two for men. This model of alcohol consumption is thought to reduce alcohol-related harms [3]. The harmfulness of alcohol, its influence on various systems in the body, and its overall impact on health should be considered. Although some studies have shown that moderate alcohol consumption can positively impact human health or life expectancy [4], its negative impact on cancer risk should guide societal recommendations. According to the WHO, there is no safe limit for alcohol consumption, given

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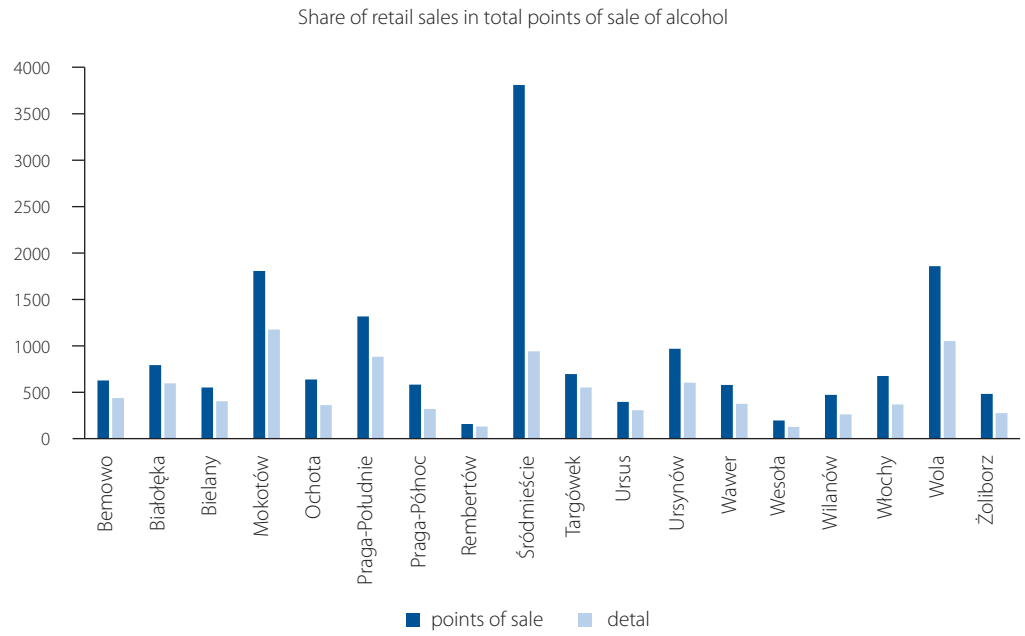

Figure 1. Number of alcohol sales points in Warsaw for individual districts

the increased risk of cancer [5]. So far, four main pathways for the carcinogenic effect of alcohol have been discovered. The first is related to acetaldehyde, the breakdown product of alcohol known to cause DNA damage.

Alcohol consumption is also linked to hormone imbalance, particularly harmful to women. The other mechanisms of carcinogenicity are related to alcohol-induced oxidative stress and folic acid deficiency. Of note, an association between alcohol consumption and increased risk of cancers of the gastrointestinal tract, as well as the liver, pancreas, and breast cancers, has been demonstrated. Moreover, this association appears to be dose-dependent [6]. Global alcohol consumption remains alarmingly high.

Furthermore, it is estimated that over 4% of all cancers are attributable to alcohol. Appropriate measures to reduce alcohol consumption would, therefore, likely significantly reduce the burden of cancer [7]. Given the demonstrated association between alcohol consumption and increased cancer risk, it seems warranted to examine the factors influencing alcohol consumption in larger populations and society's knowledge of the harmfulness of alcohol so as to reduce the number of preventable cancers.

Materials and methods

The study used a validated questionnaire on alcohol consumption called AUDIT C combined with original questions on awareness of the harmfulness of alcohol and its effects on cancer risk. The survey was conducted through online forums involving residents of different districts of Warsaw, Poland. In addition, the availability of alcohol outlets for each district was analyzed using publicly available information from Warsaw City Hall. We performed statistical analyses using the IBM SPSS Statistics 27 package to test the research hypotheses. The significance level in this chapter was assumed to be $\alpha = 0.05$.

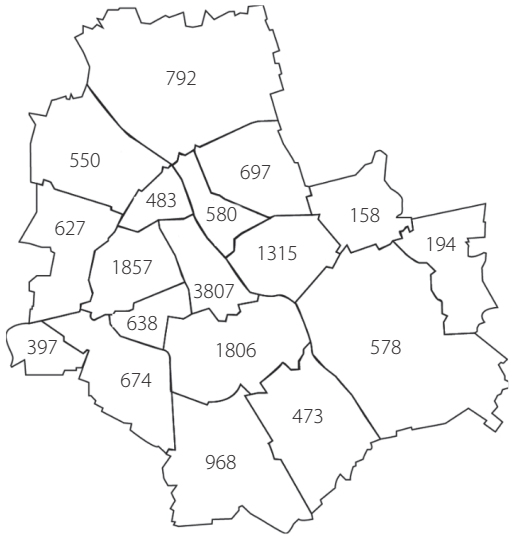

Figure 2. The share of retail sales in total points of sale of alcohol in Warsaw

Results

According to the data of the public information bulletin of Warsaw City Hall, in 2021 there were 16,594 alcohol outlets. The distribution of outlets by district is shown in figure 1. Retail licenses accounted for the largest share of permits issued for the sale of alcohol; the percentage of retail sales in the total number of alcohol outlets is shown in figure 2.

The study group consisted of 682 residents of Warsaw (524 F, 76.9%; 136 M, 20%). Most respondents were between 24 and 54 years old, had higher education, and described their financial situation as somewhat favorable. Respondents lived in the following districts:

- Bemowo – 2.8%,
- Białołęka – 4.4%,
- Bielany – 9.5%,
- Mokotów – 2.3%,
- Ochota – 0.9%,
- Praga-Południe – 31.7%,
- Praga-Północ – 1.5%,
- Rembertów – 0.9%,
- Śródmieście – 2.1%,
- Targówek – 9.7%,
- Ursus – 4.3%,
- Ursynów – 9%,
- Wawer – 1.9%,
- Wesoła – 0.1%,
- Wilanów – 0.3%,
- Włochy – 0.6%,
- Wola – 2.8%,
- Żoliborz – 12.8%

32.2% of respondents stated that the nearest alcohol outlet was located at a distance of less than 100 m from their place of residence, 48.2% of respondents said that it was located at a distance of 100 to 500 m, 11.6% of respondents answered that it was located at a distance of 501 to 1000 m, and 1.8% of respondents believed that it was located at a distance of more than 1000 m. The density of places where alcohol is sold in Warsaw is shown for each district in table I.

The relationship between the frequency of alcohol consumption and the distance of the liquor store from the place of residence was analyzed. We performed a chi-square analysis for cross-tabulation to test the hypothesis that the frequency of alcohol consumption depends on the distance of the liquor store from the place of residence (H1). The results are shown in table II.

The analysis revealed an insignificant relationship between the frequency of alcohol consumption and the distance of the liquor store from the place of residence.

The next step was to analyze the association between the availability of 24-hour liquor stores and the degree of alcohol use disorder using the chi-square analysis for the cross-tabulations. The study was conducted to test the hypothesis that greater availability of alcohol stores near a residence is

Table I. Density of points of sale (POS) per km^2 for districts of Warsaw

District	Area (km^2)	Number of residents	Population density (per km^2)	Number of POS	Number of POS – detal	Density (POS/km^2)
Bemowo	24.95	125,270	5021	627	437	25.13026
Białołęka	73.04	132,281	1811	792	597	10.84337
Bielany	32.34	130,848	4046	550	403	17.0068
Mokotów	35.42	217,424	6138	1806	1175	50.98814
Ochota	9.72	82,018	8438	638	360	65.63786
Praga-Południe	22.38	180,066	8046	1315	881	58.75782
Praga-Północ	11.42	63,442	5609	580	321	50.78809
Rembertów	19.3	24,679	1279	158	130	8.186528
Śródmieście	15.57	111,338	7151	3807	940	244.5087
Targówek	24.22	124,742	5127	697	550	28.77787
Ursus	9.36	62,399	6667	397	306	42.41453
Ursynów	43.79	151,288	3455	968	603	22.1055
Wawer	79.7	79,078	992	578	375	7.252196
Wesoła	22.94	25,926	1130	194	127	8.456844
Wilanów	36.73	43,423	1182	473	261	12.87776
Włochy	28.63	44,343	1549	674	368	23.54174
Wola	19.26	142,694	7409	1857	1052	96.41745
Żoliborz	8.47	52,907	6246	483	276	57.02479

Table II. The relationship between the frequency of alcohol consumption and the distance of the liquor store from the place of residence

How often do you drink alcohol-containing beverages?	How far is the nearest alcohol sales outlet from your residence?								overall		χ^2	p	V_c
	below 100 m		between 100–500 m		between 501–1000 m		above 1000 m						
	N	%	N	%	N	%	N	%	N	%			
never	2	1.0	4	1.6	1	1.6	0	0.0	7	1.4	8.62	0.735	0.08
once a month	58	29.9	68	28.0	20	31.7	5	50.0	151	29.6			
2–3 a month	82	42.3	108	44.4	30	47.6	5	50.0	225	44.1			
2–3 a week	35	18.0	50	20.6	9	14.3	0	0.0	94	18.4			
4 or more per week	17	8.8	13	5.3	3	4.8	0	0.0	33	6.5			
overall	194	100.0	243	100.0	63	100.0	10	100.0	510	100.0			

N – number of subjects; χ^2 – chi-square; p – value; V Cramera – effect size

Table III. Relationship between the availability of alcohol stores and the degree of alcohol use disorder

Are there any alcohol points of sale in your area open around the clock?	Risk levels associated with alcohol consumption								overall		χ^2	p	V_c
	low-risk drinking		risky drinking		harmful drinking		suspicion of alcohol addiction						
	N	%	N	%	N	%	N	%	N	%			
no	130_a	28.7	18_b	18.2	$4_{a.b}$	25.0	$2_{a.b}$	11.8	154	26.3	17.98	0.035	0.10
yes, one	147_a	32.5	32_a	32.3	4_a	25.0	6_a	35.3	189	32.3			
yes, a few	162_a	35.8	42_a	42.4	5_a	31.3	8_a	47.1	217	37.1			
yes, many	14_a	3.1	$7_{a.b}$	7.1	3_b	18.8	$1_{a.b}$	5.9	25	4.3			
overall	453	100.0	99	100.0	16	100.0	17	100.0	585	100.0			

N – number of subjects; χ^2 – chi-square; p-value; V Cramera – effect size; each subscript letter represents a subset of the severity of alcohol use disorder with column ratios that do not differ significantly by a level of 0.05

associated with a higher percentage of risky alcohol use. The results are presented in table III.

There was a significant association between the availability of alcohol stores and the extent of alcohol use disorder. However, the strength of this effect was weak. We performed additional post hoc analyzes to examine the exact differences (results are shown in the captions of table III). It was found that most individuals who did not have access to alcohol stores that were open around the clock were at low risk of suffering from alcohol use disorder. However, of those individuals with access to many alcohol stores around the clock, most were also at low risk of alcohol use disorder.

We performed a chi-square analysis for the cross-tabulation to test the hypothesis that awareness of the harmfulness of alcohol reduces alcohol use. The results are shown in table IV.

A significant relationship was found between the awareness of the harmfulness of alcohol and the frequency of alcohol consumption ($p < 0.05$). The strength of this effect is weak. We performed additional post hoc analyses to check the exact differences (the results are presented in the captions of table IV). It found that most people who said that any amount of alcohol was harmful to the body drank once a month or less than two or three times a week. Additionally, most people who believed it possible to take four standard servings a day without health risks, regardless of gender, drank two or more times a week or two or three times a month.

In the next step, we checked if the availability of 24-hour alcoholic stores causes higher monthly expenses on alcohol among the inhabitants of Warsaw. The results are presented in table V.

The relationship between the availability of alcohol stores and the amount of money spent on buying alcohol was insignificant.

Discussion

The availability of alcohol significantly impacts alcohol consumption, and many policies aim to reduce access to alcoholic products [8]. According to Shrek A. et al., reduced availability of alcohol leads to lower per capita consumption, with a focus on takeaway alcohol products [9]. In addition, data from the International Alcohol Control Study by Grey-Philip et al. have shown that most alcohol consumed in Europe is essentially takeaway products [10].

Table IV. The relationship between the awareness of the harmfulness of alcohol and the frequency of alcohol consumption

How much alcohol do you think can be consumed without health risks?	How often do you drink alcoholic beverages?										overall		χ^2	p	V_c
	never		once a month or less		2–3 per month		2–3 per week		4 or more per week						
	N	%	N	%	N	%	N	%	N	%	N	%			
any amount of alcohol is harmful to the body	$4_{a,b}$	57.1	107_{b}	69.9	$135_{a.b}$	58.4	48_{a}	51.1	$15_{a.b}$	45.5	309	0.597	28.68	0.004	0.14
one portion per day	3_{a}	42.9	32_{a}	20.9	65_{a}	28.1	28_{a}	29.8	8_{a}	24.2	136	0.263			
two portions per day for females and 4 for male	0_{a}	0.0	10_{a}	6.5	30_{a}	13.0	13_{a}	13.8	7_{a}	21.2	60	0.116			
four portions per day	$0_{a,b}$	0.0	$4_{a.b}$	2.6	1_{b}	0.4	5_{a}	5.3	3_{a}	9.1	13	0.025			
overall	7	100.0	153	100.0	231	100.0	94	100.0	33	100.0	518	1.000			

N – number of subjects; χ^2 – chi-square; p – value; V Cramera – effect size; each subscript letter represents a subset of the question: How often do you drink alcoholic drinks, the proportions of which do not differ significantly from each other at the level of 0.05

Table V. The relationship between the availability of alcohol stores and the amount of money spent on buying alcohol

Are there any 24-hour alcohol points of sale in your area open around the clock?	How much money do you spend on alcohol monthly?								overall		χ^2	p	V_c
	up to 20 PLN		between 21 –50 PLN		between 51–100 PLN		above 100 PLN						
	N	%	N	%	N	%	N	%	N	%			
no	47	27.3	41	27.5	23	23.2	24	26.7	135	26.5	9.38	0.403	0.08
yes, one	60	34.9	49	32.9	33	33.3	27	30.0	169	33.1			
yes, a few	63	36.6	53	35.6	35	35.4	33	36.7	184	36.1			
yes, many	2	1.2	6	4.0	8	8.1	6	6.7	22	4.3			
overall	172	100	149	100.0	99	100.0	90	100.0	510	100.0			

N – number of subjects; χ^2 – chi-square; p – value; V Cramera – effect size

At the same time, the COVID-19 pandemic showed that the reduced availability of alcohol products in bars or restaurants had no effect on alcohol consumption, which was increasing in most European countries at that time. This finding suggests that takeaway alcohol products and 24-hour alcohol stores may have a more significant share of alcohol consumption than places usually associated with alcohol consumption [11–14].

However, according to our data, neither the frequency nor the total amount of alcohol consumed depended on the availability of alcohol stores near the residence. This finding probably suggests that the frequency of alcohol consumption is more likely to be influenced by other individual, environmental, or social factors, such as personal vulnerability to addiction or stress coping strategies [15–17]. It has also been suggested that shortening the hours of alcohol sales may reduce alcohol consumption [18–20]. In the study by Hahn R.A. et al., it was recommended that prohibiting the extension of alcohol sales hours by 2 hours or more prevents alcohol-related harms, while interventions that reduce sales hours in local alcohol outlets by 2 hours or more may be an effective alcohol prevention strategy [21]. This statement contrasts with the results of our study, which found that the availability of 24-hour alcohol outlets close to home did not affect the frequency and quantity of alcohol consumption.

Similarly, the presence of these outlets was found not to affect the amount of money spent on alcohol. According to our data, a factor that probably influences the amount of alcohol consumption is awareness of its adverse effects on health and cancer risk. In general, understanding the potential carcinogenic effects of alcohol is insufficient in European countries, and according to Scheideler et al., alcohol consumption is too rarely associated with a significant risk factor of cancer, and more decisive measures are needed to increase awareness [22]. As confirmed by the results of our study, individuals who were informed that each dose of alcohol increases the risk of disease statistically drank less alcohol than individuals who were unaware. Social awareness of the increased risk of cancer is expected to lead to lower alcohol consumption, justifying educational and information campaigns on this topic.

These findings are consistent with the conclusions of the Weerasinghe et al. study, which found that understanding the link between alcohol and cancer risk would improve public support for alcohol policies such as higher prices [23].

Considering that cancer is a significant public health threat and alcohol is a recognized carcinogen, alcohol advertising bans and improving health literacy regarding alcohol's harmfulness seem necessary [24]. However, implementing

harm-reduction strategies may be currently more complicated due to new sources of exposure to alcohol advertising (social media), the attitudes of adolescents and young adults toward alcohol, and post-pandemic changes in stress-coping strategies among society.

There is also a problem of underestimating alcohol consumption that is frequently highlighted in the literature. According to Boniface S. et al., the underestimation of alcohol consumption is widespread among groups of heavy drinkers [25], which means that data from studies on alcohol consumption may be seriously distorted. Therefore we may conclude that alcohol consumption is an avoidable cancer risk factor that requires intensified action by policymakers, including increasing awareness and limiting exposure to alcohol advertisements and availability so as to protect future generations.

Conclusions

Awareness that alcohol is a defined carcinogen is insufficient among the citizens of Warsaw, Poland. In addition, health literacy regarding the harm caused by alcohol may influence alcohol consumption. Therefore, educational campaigns and other policy interventions must be emphasized to improve individuals' knowledge of alcohol-related harm, significantly decreasing cancer risk.

Conflict of interest: none declared

Elwira Gliwska
Maria Sklodowska-Curie National Research Institute of Oncology
Cancer Epidemiology and Primary Prevention Department
ul. Wawelska 15/B
02-034 Warszawa, Poland
e-mail: elwira.gliwska@pib-nio.pl

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Liver tumors

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Liver transplantation in primary liver tumors

Piotr Smoter[1], Marcin Kotulski[1], Katarzyna Smoter[2], Tadeusz Wróblewski[1], Michał Grąt[1]

[1]*Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland*
[2]*Department of Obstetrics, Perinatology and Gynecology, Medical University of Warsaw, Warsaw, Poland*

As transplant medicine has evolved in recent decades so too have the indications for liver transplantation (LT). Active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, and nowadays LT plays a major role in the treatment strategies of liver tumors. It offers excellent long-term outcomes for certain patients with hepatocellular carcinoma (HCC) and carefully selected patients with cholangiocarcinoma (CCA), who undergo neoadjuvant chemoradiatotherapy. In certain clinical courses of rare primary liver tumors, hepatic epithelioid haemangio-endothelioma (HEHE) and hepatic adenoma (HA), liver transplantation is also considered the best treatment option. Optimal patient selection has become the key issue to achieve the best possible outcomes and to deal with the alleviating shortage of organs. The recent tendency to incorporate markers of tumor biology into selection criteria, rather than simply focusing on tumor size and number, has led to further extension of indications for LT in patients with liver malignancy. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with primary liver tumors, mainly primary liver cancers.

Key words: orthotopic liver transplantation, primary liver tumor, hepatocellular carcinoma, cholangiocarcinoma, hepatic epithelioid haemangio-endothelioma

Introduction

Liver transplantation (LT) with its more than 60-year-history is widely recognized as a treatment of choice of both acute and end-stage chronic liver failure. Immunosuppressive therapy, routinely administered after LT, plays an essential role in overcoming immune-related allograft rejection, at the same time it has the potential to promote neoplastic transformations in graft recipients. At the early stage of the development of transplant programs, both the history of oncological treatment as well as active malignancy were considered as contraindications for organ transplantation. Over the years, together with the great progress in transplant medicine, we have witnessed the milestone extension of indications for liver transplantation. Transplant centers have started to register patients with primary or metastatic liver tumors on the transplant waiting lists and liver transplantation has been established as a standard treatment of liver tumors in carefully selected patients. As a result of the significant discrepancy between graft demand and supply, optimal patient selection has become the key issue and the most challenging element of organ allocation. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with primary liver tumors, most of all primary liver cancers.

Liver cancer

Liver cancer is one of the leading malignancies responsible for the global cancer burden. According to current statistics, primary liver cancer is the sixth most commonly diagnosed cancer and the third most common reason for cancer-related

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death worldwide. In 2020 approximately 906,000 new cases and 830,000 deaths for primary liver cancer were reported. Incidence and mortality rates are 2 to 3 times greater among men than among women [1].

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the principal histologic type of liver cancer, accounting for 75–85% of all primary liver tumors worldwide [2]. Well-established risk factors of HCC comprise chronic liver disease and cirrhosis due to hepatitis B virus and/or hepatitis C virus, excessive alcohol intake, aflatoxin contamination of crops, type II diabetes, obesity, metabolic syndrome and non-alcoholic fatty liver disease (NAFLD). The most important global risk factors for HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. HBV is a DNA virus that commonly integrates into the host genome and directly promotes mutations in liver cells, while HCV is an RNA virus that can cause liver cirrhotic changes and promotes tumorigenesis through repetitive damage, regeneration and fibrosis. Introduction of HBV universal vaccination as well as effective therapies against chronic HBV and HCV infections gradually lessen the role of those risk factors and contribute to the decreasing prevalence of HCC in most high-risk countries in Eastern and South-Eastern Asia. On the other hand, however, due to the increasing prevalence of metabolic risk factors, the global incidence of HCC has tended to increase in recent decades. The upward trend has been observed in most European countries, Americas, Australia and in India [2–4].

Hepatocellular carcinoma is known to be associated with poor prognosis. The overall survival in untreated patients with HCC does not exceed 10 months [5]. Only approximately 50% of cases are detected in the early stages when radical treatment is still possible to achieve [6]. For decades the mainstay of curative treatment for HCC has been hepatectomy. Despite the progress in surgical techniques and perioperative care, the high incidence of intrahepatic recurrence has been observed contributing to unsatisfactory long-term survival. Moreover, considering that the majority of HCC occurs in cirrhotic livers, the use of hepatectomy has often been limited by the presence of portal hypertension and poor hepatic function. That has led to the introduction of liver transplantation, performed instead of resection. The above issues have led to the introduction of liver transplantation, performed instead of resection, to treatment methods in HCC as well as to the prompt development of a number of forms of locoregional therapy that have been used with curative intent in irresectable and/or recurrent HCC. Those are radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection (PEI) together referred to as "curative locoregional therapy (CLRT)" [7–10].

Primary liver transplantation (PLT) for HCC represents the ideal treatment because it targets both the neoplastic tumor and the underlying liver disease. Since the turn of the 20th and 21st centuries, PLT has been established as a standard treatment of HCC, but only in carefully selected patients. Early PLTs performed for HCC had been associated with unsatisfactory outcomes mainly because of poor patient selection. In 1996, based on the results of the observational study, Mazzaferro et al. defined the criteria, widely known as Milan criteria (MC), to select HCC patients for PLT [11]. In accordance with MC, primary liver transplantation was performed only in HCC patients with single lesion ≤5 cm, or up to 3 lesions ≤3 cm each in the absence of tumor vascular invasion or evidence of extra-hepatic metastases. That approach resulted in outcomes of HCC patients comparable to patients without HCC (75% 4-year survival rate and 83% recurrence-free survival rate). The Milan criteria have been successfully adopted worldwide and incorporated into the United Network for Organ Sharing (UNOS) criteria since 2002, for listing patients with HCC for liver transplant [12].

The growing experience over the last two decades has shown, however, that adherence to MC could be too strict and patients beyond MC may also benefit from LT. Consequently, a number of expanded criteria have been developed based both on tumor morphometry as well as on biomarkers and tumor response to locoregional therapy, parameters that are likely to reflect the real tumor biology and aggressiveness. Further investigations have proven that expanded criteria are still associated with favorable 5-year survival rates up to 64–79% [13, 14]. Among LT-HCC criteria based on tumor morphometry, University of California, San Francisco (UCSF), and among expanded criteria based on tumor morphometry, the criteria of University of California, San Francisco (UCSF) and the up-to-seven criteria have become most popular and widely used. The University of California, San Francisco (UCSF) criteria, established in 2001 by Yao et al. [15] considered a single lesion ≤6.5 cm, or 2–3 lesions ≤4.5 cm each, with total tumor diameter ≤8 cm. The 5 year post-LT survival was estimated to be 72.4% with tumor recurrence up to 11.4%. Initially the criteria had been based on explant pathology, but subsequently were validated with the use of pre-LT imaging. In the prospective study from 2007 by Yao et al. [16], patients who fell within the UCSF criteria demonstrated 80% 5 year post-LT recurrence-free survival (RFS). In 2009, another extended criteria were proposed by Mazzaferro et al. [17] based on a cohort of 1556 patients undergoing cadaveric LT and LDLT for HCC from 36 transplant centers. The criteria were defined as hepatocellular carcinomas with seven as the sum of the size of the largest tumor (in cm) and the number of tumors and named Up-to-seven criteria. The 283 patients without microvascular invasion from the investigate cohort, who fell within the Up-to-seven criteria achieved a 5-year overall survival of 71.2%. The limitation of the above criteria was that they utilized data from postoperative histology concerning microvascular invasion. Among other extended morphometric-based criteria, Toronto criteria from 2016 [18]

are worth mentioning. With the implementation of the Toronto criteria, the 5-year overall survival rate was 68% and did not differ significantly from survival in patients within Milan criteria. The main limitation was the need for a preoperative biopsy, what is not routinely recommended.

In order to avoid pretransplant invasive methods and to achieve an adequate prognosis of tumor recurrence, the investigators searched for the best prognostic serologic biomarkers for HCC. AFP has been the biomarker most commonly investigated in relation to HCC and has been recently adopted by UNOS as a marker to exclude or include patients from transplant listing [12]. However, the optimal cutoff AFP value clearly indicating higher risk for HCC recurrence has not been found. One of the most popular HCC-LT extended criteria including AFP level are the Hangzhou criteria from 2008 (absence of macrovascular invasion and total tumor diameter ≤ 8 cm; in case of tumor diameter >8 cm, non--poorly differentiated HCC and AFP level ≤400 ng/ml) [19]. With the use of those criteria an additional 37.5% of patients who would have been beyond Milan criteria were able to be transplanted. However, once again a pretransplant biopsy was needed in greater lesions, limiting the clinical application of the Hangzhou criteria.

A significant association between AFP levels and vascular invasion has been reported [20]. AFP greater than 1000 ng/ml was observed to be the strongest pretransplant predictor of vascular invasion and consequently tumor recurrence. In the model of Duvoux et al., an AFP level ≤100 ng/ml in the setting of patients with 1-3 lesions with a maximum tumor diameter of 6 cm was associated with 5-year survival near 70% [21]. Grąt et al. [22] reported a nearly linear association between AFP and the risk of HCC recurrence. In the retrospective cohort study based on 121 HCC patients after LT, the AFP cutoff level <100 ng/ml in combination with either UCSF or Up-to-seven criteria was associated with superior (100%) 5-year recurrence-free survival. Several molecular signatures have also been investigated as potential biomarkers of HCC. In the study of Dwornik et al. [23] a higher rate of mutations in 9 suppressor genes was associated with a poorer outcome independently of tumor mass or the presence of vascular invasion. German investigators analyzed specific microRNA expression patterns in tumor samples and observed more accurate prediction of HCC recurrence with the use of Milan criteria along with a predictive score based on the miR-214 and miR-3187 expression levels compared to prediction based on MC alone. [24].

The idea to down-stage the tumor by applying LRT has arisen with the aim to initially reduce tumor burden and subsequently meet transplant criteria. Many studies have reported favorable long-term outcomes for transplant patients with HCC beyond Milan criteria which were successfully downstaged to within Milan criteria by applying LRT [25, 26]. Moreover, the response of HCC to different types of locoregional therapy has been shown to be an important marker for patient survival [27]. Interestingly, the wait times after locoregional therapy prior to transplant can also serve as surrogate markers of tumor biology. Shorter wait times have been associated with higher posttransplant mortality [28]. The most current UNOS policy requires a 6-month waiting period for patients listed with HCC prior to receiving MELD exception points in order to accurately assess tumor biology over time [12].

Owing to the increasing shortage of organs, the limited availability of appropriate living donors and the associated risk of drop-out from the transplant waiting list, mainly attributed to tumor progression, another surgical strategy has been introduced to clinical practice. Patients with resectable and transplantable HCC are offered primary liver resection that can be followed by so called "salvage liver transplantation" (SLT) in case of transplantable tumor recurrence. Nowadays SLT is proposed as a curative option for the intrahepatic recurrence of HCC, but it is still not widely used because of insufficient number of organs. A systematic review of treatment strategies for recurrent HCC published in 2019 evaluated SLT to be superior to curative locoregional therapy in terms of the 5-year overall survival and 1-, 3-, 5-year disease-free survival. Patients after SLT had a significantly higher 3- and 5-years disease-free survival compared to those who underwent the repeated hepatectomy (RH) [7, 29]. However, in an intention-to-treat analysis from 2018, the SLT strategy was revealed to be curative in only 56% of patients with cirrhosis and CC. Lower MELD score, transarterial chemoembolization (TACE) performed prior to resection, postoperative complications after initial resection, and higher T-stage in the resected specimen were shown to diminish the chance for successful SLT [29]. The largest current meta-analysis concerning STL strategy had been published in 2022 [30]. SLT and PLT were shown to have comparable surgical outcomes. The 1-year overall survival rate presented no significant difference between SLT and PLT, whereas 3- and 5-year overall survival rates were slightly, but significantly lower in SLT compared to the PLT group.

Current guidelines, published in 2020 (31), focus mainly on the optimal selection of patients with HCC for both deceased donor LT (DDLT) and living donor LT (LDLT). LT is recommended as a first-line option for HCC within Milan criteria, unsuitable for low-morbidity resection and ablation. In patients beyond Milan criteria, qualification for LT should be based on measurable pre-LT conditions including tumor size and number, tumor biology (including alpha-fetoprotein), probability of survival, transplant benefit, organ availability, waitlist composition and allocation priorities. In the case of LDLT, a combination of morphological and biological criteria should be employed to attempt to maximize recipient benefit while minimizing donor risk. The minimum acceptable recipient overall survival should be 60% at 5 years after LDLT, while estimated donor risk should be low aiming for zero donor mortality.

Interestingly, in the last decade recipients over 70 years with end-stage liver disease and HCC have become one of the fastest growing subgroup of patients undergoing liver transplantation [32]. It clearly highlights the progress transplant medicine has made over the years and the role it plays nowadays in cancer treatment.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most commonly reported primary liver tumor that accounts for 10–15% of all liver cancers. In general, CCA is the primary malignancy of the biliary tract. Based on its localization it is classified as either intrahepatic (IH CCA) or extrahepatic, with the second-order bile ducts serving as the separation point. Furthermore, extrahepatic cholangiocarcinoma has been divided into perihilar (pCCA) and distal extrahepatic cholangiocarcinoma at the level of the cystic duct [33].

Perihilar cholangiocarcinoma is the most common type of cholangiocarcinoma accounting for 50–67% of all cases [34]. The IH CCA incidence has increased over the past three decades while the incidence of perihilar and distal extrahepatic CCA has remained stable. The reasons for the observed trend remain unclear. There are several recognized risk factors of cholangiocarcinoma, including primary sclerosing cholangitis, liver fluke infection, hepatolithiasis, biliary malformation and, what is less obvious, cirrhosis and hepatitis C. Primary sclerosing cholangitis (PSC) is believed to be the most important risk factor, associated with a prevalence of cholangiocarcinoma of 5–15% [35, 36]. The lack of early symptoms of CCA and low specificity of diagnostic modalities are associated with extremely unfavorable prognosis in this primary liver tumor.

The treatment strategy of CCA is strongly associated with the primary localization of the tumor. Perihilar localization is observed to have slightly better prognosis compared to primary intrahepatic CCA, and in recent decades has been first introduced to indications for LT. In addition to LT, other new methods of management have been adopted to pCCA patients, including preoperative portal vein embolisation and biliary drainage, neoadjuvant chemotherapy and chemoradiation therapy [37]. The best long-term survival is observed in cases of surgical resection with negative surgical margins, but many patients are unresectable due to locally advanced or metastatic disease at diagnosis. Unresectable disease had earlier been approached only with non-curative treatment options with a zero 5-year survival rate. Since the late 1990s, pioneering liver transplantation (LT) had been performed as an option in patients with pCCA, with the aim of achieving negative resection margins. The initial results in unselected patients were disappointing [38]. Further attempts at Mayo Clinic led to the development of a protocol consisting of strict selection of patients and pretransplant multimodal chemoradiotherapy; this was associated with a great improvement in survivals (5-year OS greater than 80%) [39]. Mayo Clinic criteria for inclusion in the transplantation protocol were: pathologically confirmed hilar cholangiocarcinoma or CA19-9 >100 ng/ml in the presence of a radiographically malignant structure, tumor size <3 cm, absence of distant metastases on CT (and/or MRI) and isotope bone scan and no evidence of lymph node metastases. Neoadjuvant chemoradiatotherapy consisted of external beam radiation therapy together with intravenous fluorouracil, followed by intraluminal brachytherapy and oral Capecitabine while awaiting liver transplantation. Patients with a good response to neoadjuvant therapy were subsequently transplanted.

Since that time the Mayo Clinic Protocol has been adopted by other transplant centers worldwide, and nowadays relatively good outcomes are reported in LT for pCCA in highly selected patients, who all should undergo intensive pretransplant chemoradiotherapy. Compared with LT for other indications, however, an increased risk of late arterial and portal vein complications has been reported, most probably due to former radiation. In those cases graft loss can be avoided with close follow-up and prompt intervention for vascular complications [40]. Excellent long-term survival is achieved in patients with early-stage unresectable pCCA and patients with primary sclerosing cholangitis (PSC)-associated pCCA. Patient outcomes after LT for PSC-associated pCCA are superior to de novo pCCA. Thus, in a recent report from 2021, authors claim that liver transplantation together with aggressive neoadjuvant chemotherapy should be the treatment of choice for patients with pCCA arising in the setting of PSC [40, 41]. Current studies focus on the role of either strict selection of patients or the need for neoadjuvant chemoradiotherapy in treatment strategy of pCCA [41, 42]. In a recent report from an international, multicenter, retrospective cohort study, adjustments in neoadjuvant chemoradiotherapy, such as omitting radiotherapy, have been advocated [42]. Such changes may reduce the risk of hepatic vascular complications and further improve the outcome in patients with pCCA undergoing liver transplantation [43].

For years intrahepatic cholangiocellular carcinoma has been associated with extremely poor outcomes and considered as a contraindication for LT. Progress in chemotherapy and observational data of incidental transplantations in patients with IH CCA have recently intrahepatic HCC to another indications for LT. However, based on the first metaanalysis from 2021, the indications for LT in IH CCA are limited to a single tumor sized <2 cm and carefully selected patients with advanced IH CCA after neoadjuvant therapy [44, 45].

Hepatic epithelioid haemangio-endothelioma

Hepatic epithelioid haemangio-endothelioma (HEHE) is a very rare malignant tumor of vascular origin and uncertain biological behavior, predominantly effecting females. The degree of malignancy of HEHE is considered to be between that of hemangioma and that of hemangiosarcoma of the liver. Regar-

ding the multifocal growth, HEHE can often be misdiagnosed as a metastatic disease or multifocal HCC. Due to the rarity of the disease and unpredictable tumor behavior, optimal treatment has not been fully established. Treatment strategies are dependent on the clinical course of HEHE and include observation, anti-angiogenic drugs, radiotherapy/chemotherapy and surgical approach with hepatectomy in solitary lesions and liver transplantation (LT) in multifocal, diffuse, unresectable or recurrent tumors. Nowadays, in the case of unresectable intrahepatic disease, LT is regarded as a treatment of choice. Interestingly, the presence of metastasis is not a contraindication for LT since it has been observed not to influence survival [46, 47].

In a series of 110 patients with HEHE, who underwent LT between 1987 and 2005, reported by Rodriguez et al., the 5-year survival rate was 64% [48]. In 2006 Mehrabi et al. [49] reviewed 434 cases of HEHE. Liver transplantation was the most common treatment method in that group of patients (44.8%) and the reported 1-year and 5-year survival rates were 96% and 54.5% respectively. Favorable outcomes of LT performed in a series of 18 patients with HEHE were also reported in the report of Krasnodębski et al. [50]. Two of the 18 recipients had concomitant extrahepatic tumors. No disease recurrence was observed during a median follow-up of 65.9 months. The survival probability calculated using the Kaplan-Meier estimator after 1, 5, and 15 years was 94.0%, 82.6%, and 41.3%, respectively Fukuhara et al. suggested that adjuvant therapy performed in aggressive cases with vascular infiltration before disease recurrence might be beneficial and reported the use of the mTOR inhibitor everolimus in combination with tacrolimus to achieve not only immunosuppression, but also an antitumor effect after LT in the case of HEHE with massive vascular infiltration [51].

Hepatic adenoma

Hepatic adenoma (HA) is a benign liver tumor that most commonly occurs in women of reproductive age. The risk factors of HA development are oral contraceptives and some underlying liver diseases, including glycogen storage disease (GSD) and Abernethy malformation (absence of the portal vein). The clinical manifestation of HA varies from asymptomatic cases, through lesions accompanied with abdominal pain up to tumors leading to hepatomegaly or liver rupture with intraperitoneal bleeding. HA is associated with increased risk of HCC development, particularly in patients with glycogen storage disease. Treatment options depend on clinical presentation and range from regular follow-up imaging, withdrawal of hormone-containing pills to liver resection or, ultimately, liver transplantation. In patients with multiple HA and GDS the risk of HCC significantly increases. LT provides definitive prevention against HCC, corrects primary hepatic enzyme defect and most metabolic abnormalities observed in GSD patients [52].

Apart from single case reports, there are only two larger studies on liver transplantation for HA in literature. A European report from 2016, based on data from the European Liver Transplant Registry, identified 49 patients who underwent LT for adenomatosis in the years 1986–2013 [53]. The main indications for LT in this cohort of patients were suspicion or histologically proven HCC. A recent American report from 2022 analyzed data from the United Network for Organ Sharing (UNOS) database and identified 142 HA patients who underwent LT in years 1987–2022 in the United States. The most common indications for LT were suspected malignancy (39.7%), unresectable HA (31.7%), and increasing size of HA lesions (27.0%). Glicogen storage disease (GSD) was present in 53.1% of patients. LT in HA patients was associated with excellent long-term outcomes. The 1-, 3-, and 5-year patient survival rates were 94.2% , 89.7% and 86.3% respectively [54].

Conclusions

Since active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, liver transplantation has gradually started playing a role in the treatment strategies of liver tumors. Nowadays LT is one of the major therapeutic approaches in primary liver cancers and in rare liver tumors. The majority of HCC cases, the leading histologic type of liver cancer, occur in cirrhotic liver and primary liver transplantation for HCC constitutes the leading histologic type of liver cancer and in most cases occurs in cirrhotic liver. Primary liver transplantation for HCC represents the ideal treatment because it targets both the tumor and the underlying liver disease. The outcomes of selected HCC patients treated with LT are comparable to patients without HCC, even when gradually expanded criteria are implemented. Unresectable pCCA, that had earlier been fatal in 100% of cases, is now associated with relatively good outcomes in carefully selected transplant patients, who undergo neoadjuvant chemoradiatotherapy. In particular, excellent long-term survival is achieved in patients with early-stage unresectable pCCA and patients with primary sclerosing cholangitis (PSC)-associated pCCA. Even IH CCA, associated with an extremely poor outcome and for years considered a strong contraindication for LT, has recently been introduced for LT in carefully selected patients after neoadjuvant therapy. Rare primary liver tumors, HEHE and AH, are also successfully treated with liver transplantation in unresectable intrahepatic lesions (HEHE) or suspected malignancy (AH). Due to the gradual progress in transplant medicine, further extension of indications for LT in primary liver tumors will certainly be observed.

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Piotr Smoter
Medical University of Warsaw
Department of General, Transplant and Liver Surgery
ul. Banacha 1a
02-097 Warszawa, Poland
e-mail: piotr.smoter@wum.edu.pl

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Uterine leiomyosarcoma metastatic to the pancreas

Anna Rygula[1], Michał Kowalski[1], Marcin Ziętek[2, 3]

[1]Student Research Group of Oncology, Department of Oncology, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Oncology, Wroclaw Medical University, Wroclaw, Poland
[3]2nd Department of Surgical Oncology, Lower Silesian Oncology, Pulmonology and Haematology Centre, Wroclaw, Poland

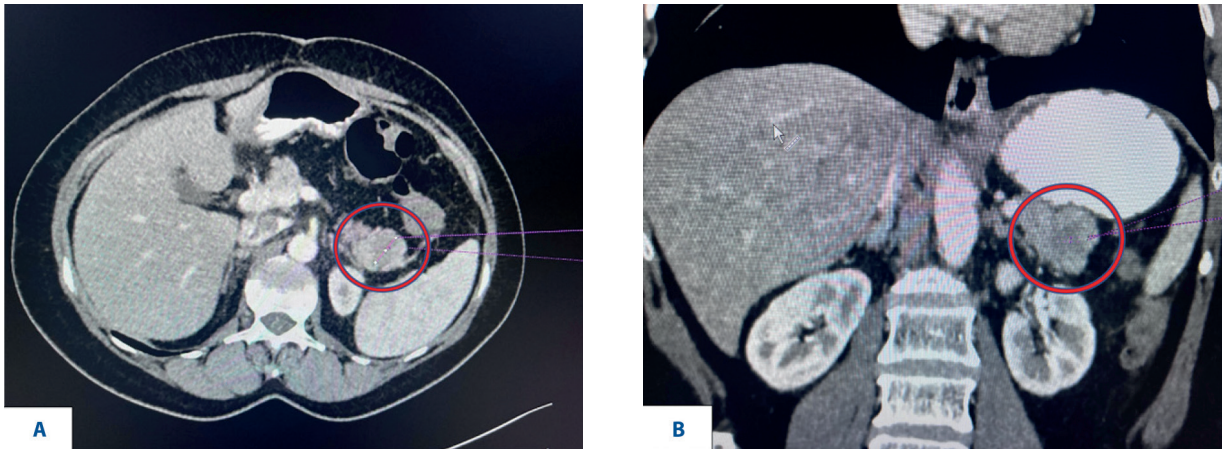

Figure 1. Computed tomography images of the metastatic pancreatic tumor before excision. **A** – image of a 5 cm tumor in the tail of the pancreas – transverse view; **B** – image of a 5 cm tumor in the tail of the pancreas – coronal view

In July 2021, a 57-year-old woman with a medical history of uterine leiomyosarcoma, diagnosed and excised in 2016, was referred to the Lower Silesian Oncology Center. PET-CT results revealed a nodular lesion of 6.7x5.8x7 cm in the pelvis and a focal lesion in the tail of the pancreas. In August 2021, the patient underwent a laparotomy to remove a retroperitoneal tumor and the vaginal stump. The pancreatic tail tumor was not excised due to the repeated laparotomy and the local advancement of the pelvic tumor. The histopathological examination revealed leiomyosarcoma G2 and infiltration of leiomyosarcoma in the sigmoid colon. Subsequently, a median relaparotomy was performed to excise the tail tumor, and an examination of the postoperative material revealed metastatic leiomyosarcoma (fig. 1). The patient was offered adjuvant doxorubicin chemotherapy but refused treatment. Radical surgery is recommended to treat retroperitoneal sarcomas, and complete cross resection is associated with improved survival [1, 2]. Adjuvant therapy typically involves doxorubicin or ifosfamide chemotherapy [2]. Incomplete mass removal should not be performed if the tumor is unresectable, as it worsens the patient's prognosis.

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Rare skin tumor – primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder

Damian W. Trzos[1], Wojciech M. Wysocki[1, 2, 3]

[1]Department of General and Oncological Surgery, 5th Military Clinical Hospital in Krakow, Krakow, Poland
[2]Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland
[3]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

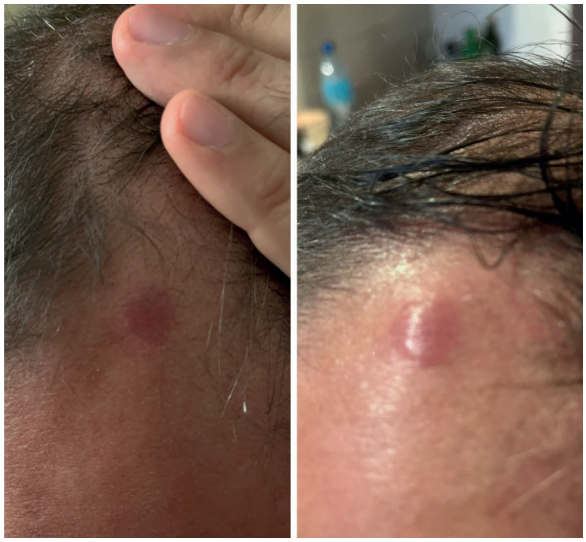

Figure 1. Patient's nodular lesion on the forehead

Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCS-TCLPD) is a rare disease with no clear diagnostic and treatment guidelines [1]. According to the WHO classification of hematopoietic neoplasms, this is an indolent T-cell lymphoproliferative disorder confined to the skin, with a characteristic population of T cells with a follicular T-helper phenotype [2]. So far, this poorly defined disease has an undetermined malignant potential [3].

We present a case report of a 46-years-old Caucasian male who presented with a flat circular erythematous skin lesion on his forehead (fig. 1). The lesion was excised and histopathology revealed a skin covered with epithelium without atypia, massive lymphocytic infiltration extending into the subcutaneous tissue. There was perivascular infiltration and infiltration of skin appendages; CD3+ T cells predominate the lesion; CD4+ significantly predominate over CD8–/+, CD30–. The image most closely matched PCS-TCLPD.

PCS-TCLPD has no long-term risk of secondary lymphomas and an excellent prognosis. It has an indolent clinical behavior with a 5-year survival rate of 100% [1, 2]. Imaging modalities and bone marrow evaluations are of a relatively low diagnostic value and are not mandatory [1]. Local surgical treatment can be used with a high degree of success and should be considered before other options [1]. In summary, PCS-TCLPD is a rare disease, usually presenting as a plaque or nodule in the head and neck region and can be treated successfully by simple surgical excision with clear margins [3].

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