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2023, Vol. 19, Number 5

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VIA MEDICA

ORIGINAL ARTICLE

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Effects of the changes between pre- and post-treatment ^{18}F-FDG PET-CT volumetric parameters on overall survival in pleural mesothelioma

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ABSTRACT

Introduction. This study aimed to examine the efficacy of positron emission tomography in fusion with computed tomography (PET-CT) parameters in predicting survival outcomes for patients with malignant pleural mesothelioma.

Material and methods. This study retrospectively evaluated the data of 250 patients who were followed up after a diagnosis of malignant pleural mesothelioma. The relationship of pre-treatment [maximum standardized uptake value (SUV_{max1}), metabolic tumor volume (MTV1), total lesion glycolysis (TLG1), tumor/background (TBR1), pleural thickness1), post-treatment (SUV_{max2}, MTV2, TLG2, TBR2, pleural thickness2], and ΔPET-CT parameters with survival was retrospectively evaluated in 36 patients whose pre- and post-treatment CT scan examinations were complete.

Results. The median age of the patients was 57.5 years, ranging from 35 to 76. Median follow-up time was 16 months, with a range of 7 to 42 months. Median survival was calculated as 18.8 months for all patients. Based on the determined cut-off values, overall survival was determined as 29.9 months in patients with TLG2 ≤ 158 compared to 16 months in patients with TLG2 > 158 ($p = 0.009$) and as 30.9 months in patients with ΔTLG ≤ –62.58 compared to 16 months in patients with ΔTLG > –62.58 ($p = 0.001$). In addition, median overall survival (OS) was determined as 29.9 months in patients with MTV2 ≤ 63.9 compared to 16 months in patients with MTV2 > 63.9 ($p = 0.007$) and as 29.9 months in patients with ΔMTV ≤ –54.03 compared to 16 months in patients with ΔMTV > –54.03 ($p = 0.002$). When evaluated with respect to TBR2; median OS was 29.9 months in patients with TBR2 ≤ 1.84 compared to 16 months in patients with TBR2 > 1.84 ($p = 0.039$).

Conclusions. Our research findings indicate a correlation between OS and volumetric PET-CT measures, specifically TLG and MTV.

Keywords: mesothelioma, ^{18}F-FDG PET-CT, volumetric parameters
Oncol Clin Pract 2023; 19, 5: 309–317

Introduction

Mesothelioma is a primary malignant tumor of the mesothelial lining that originates from pleural, peritoneal, pericardial, and tunica vaginalis mesothelial cells. Pleural mesothelioma accounts for roughly 80% of all cases, and its incidence rises with age, with a median age at diagnosis of 72 years. The five-year survival rate after diagnosis is approximately 10% [1]. Pleural mesothelioma is more common in males and its incidence is increasing globally [2–4].

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It has three subtypes, namely, epithelioid, sarcomatoid, and biphasic, based on the microscopic appearance of the histologically dominant malignant region. The most common histological subtype is the epithelioid type [5]. Asbestos and erionite represent the most important risk factors for the development of malignant pleural mesothelioma [6–8]. Asbestos exists in nature in the form of long fibers and has two main types, namely serpentine, and amphibole. The less carcinogenic serpentine fiber chrysotile constitutes more than 90% of all asbestos produced and used worldwide [9].

In the treatment of mesothelioma, multimodal approaches come to the fore. Unresectable patients and sarcomatoid-type mesotheliomas require chemotherapy treatment. In addition, targeted therapies and immunotherapy have been employed in the treatment in recent years. Although the current treatment approaches have resulted in an improvement in survival, the malignancy is still associated with quite poor 5-year survival.

Imaging techniques such as conventional radiography, computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-FDG positron emission tomography in fusion with computed tomography (PET-CT) scans are employed in diagnosis and treatment.

With the advances in the treatment, imaging methods are gaining more importance and the development of various new response evaluation methods is among the popular topics. ^{18}F-FDG PET-CT is one of the most valuable imaging methods used in the diagnosis and treatment evaluation of patients with mesothelioma. The maximum standardized uptake value (SUV_{max}) on the pre-treatment PET-CT has a prognostic value [10]. The evaluation of post-chemotherapy treatment response is also quite critical in terms of treatment continuation or treatment change. Metabolic tumor parameters measured on PET-CT, such as SUV_{max} and SUV_{mean}, are useful in the evaluation of treatment response [11]. In addition to conventional imaging methods, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) parameters are utilized to assess the efficacy of treatment in tumor response evaluation. Francis and colleagues conducted a study that demonstrated the superiority of metabolic tumor volume parameters, such as MTV and TLG, over SUV_{max} in predicting survival and evaluating treatment response [12].

In this study, we aimed to determine the demographic, clinical, and pathological characteristics of the patients we followed up and treated for pleural mesothelioma, as well as investigate the PET-CT parameters that best predict the treatment response and survival by examining treatment response in these patients.

Material and methods

Selection and evaluation of patients

This study retrospectively evaluated the data of 250 patients diagnosed with pleural mesothelioma in Dicle University, Medical Oncology Clinic between 2017 and 2022. Pre- and post-treatment ^{18}F-FDG PET-CT results could be obtained for 70 of the screened patients. This study analyzed only the results of 36 patients, as the interval between their pre-treatment and post-treatment ^{18}F-FDG PET-CT scans was shorter than 6 months. Patient files were examined to obtain information on age, sex, place of birth, tumor side, date of diagnosis, histological subtype, history of chemotherapy, and survival times.

The study included patients who were 18 years or older, diagnosed with pleural mesothelioma, and had received chemotherapy treatment. The patients had undergone ^{18}F-FDG PET-CT scans both before and after the chemotherapy, which was conducted at either the Nuclear Medicine Department of Dicle University, Faculty of Medicine, or Gazi Yasargil Training and Research Hospital. Patients with a second primary malignancy diagnosis or pleural effusion, patients followed-up or treated at external centers, patients who underwent the two ^{18}F-FDG PET-CT scans with an interval longer than 6 months, and patients whose data could not be obtained were excluded from the study.

Patient files, demographic characteristics, and clinical characteristics were examined; prognostic factors associated with the patients and their treatments were investigated; survival analyses were conducted. The histological type of the tumor was inspected. Overall survival was calculated for the entire population and was analyzed in relation to the semi-quantitative and quantitative parameters from the baseline and interim ^{18}F-FDG PET-CT examinations, which included SUV_{max}, MTV, TLG, percent change in SUV_{max} (ΔSUV_{max}) and TLG (ΔTLG), pleural thickness. Pre-treatment parameters were defined as SUV_{max1}, MTV1, TLG1, tumor/background (TBR1), pleural thickness1; while post-treatment parameters were defined as SUV_{max2}, MTV2, TLG2, TBR2, and pleural thickness2. The differences between the pre-treatment and post-treatment parameters were presented as Δ values.

In this study, OS was defined as the duration from the date of the pre-treatment ^{18}F-FDG PET-CT scan to the date of death or the latest follow-up examination. Progression-free survival (PFS) was defined as the length of time from the start of treatment either to the date of disease progression, the decision to change treatment due to inadequate treatment response, or the last follow-up examination.

Ethical approval was obtained for this study from Dicle University, Faculty of Medicine Non-Invasional Clinical Research Ethics Committee (date: 12.05.2022, approval number: 133).

The ^{18}F-FDG PET-CT imaging protocol for all patients in the study involved a 6-hour fasting period, during which they refrained from consuming food and intravenous glucose. Before FDG injection, a finger stick method was used to confirm that blood glucose levels were ≤ 140 mg/dL. One hour after injection of ^{18}F-FDG at a dose of 3.5–5.5 MBq/kg, scans were obtained from the vertex to mid-thigh while the patients were in a supine position, using either a Discovery IQ 4 ring 20 cm axial FOV PET-CT device (GE Healthcare, Milwaukee, WI, US) or a Siemens Horizon PET-CT device (Siemens Knoxville, TX, US). Non-ionic contrast medium was injected intravenously in all patients who did not have a contraindication.

Evaluation of ^{18}F-FDG PET-CT images

Standardized uptake value is the concentration of radioactivity within the volume of interest (kBq/mL)/ /concentration of injected radioactivity (kBq)/body weight in grams. Among SUV values, SUV_{max} is the one that is used most commonly in clinical practice. The calculation of the SUV_{max} value involves the measurement obtained from the pixel with the highest activity within the region of interest drawn around the lesion. Metabolic tumor volume represents the three-dimensional total volume measured with the region of interest (ROI) drawn around the lesion. In turn, TLG is obtained by the multiplication of the MTV and SUV_{mean} values.

For this study, all ^{18}F-FDG PET-CT images were analyzed using Advantage Workstation software version AW 4.7 (GE Healthcare, Milwaukee, WI, US) by two nuclear medicine specialists, each with a minimum of 10 years of experience in the field. Volumetric regions of interest (VOI) were manually drawn to involve the tumor tissue in all three planes. Metabolic tumor volume and TLG (MTV × SUV_{mean}) values, SUV_{max}, SUV_{peak}, and highest SUV_{peak} values were automatically provided by the device at a 40% SUV threshold. Additionally, a 2-cm VOI was drawn from the liver to obtain SUV_{max} values for the background. TBR values were computed from the ratio of the SUV_{max} values from the tumor to background values. In addition, ΔMTV, ΔTLG, ΔSUV_{max}, ΔHighest SUV_{peak}, and Δthickness values were calculated as below.

The Δparameter was calculated using the formula: [(post-treatment parameter — pre-treatment parameter)/pre-treatment parameter × 100].

Statistical analysis

The statistical analysis of the data was conducted using SPSS 26 (Statistical Package Social Science) software. The Kolmogorov-Smirnov test was used to determine normality for numeric data, which were presented as mean (standard deviation) if normally distributed and as median (min-max) values if not. Categorical data were presented as percentages. Student's t-test was used to analyze normally distributed numeric data, while the Mann-Whitney U test was used for non-normally distributed numeric data. The chi-square test was used for categorical variables. Receiver-operating characteristic (ROC) curve analysis was performed to identify cut-off values, as well as sensitivity and specificity values for statistically significant variables. Survival analysis was conducted using the Kaplan-Meier method, and the log-rank test was used to compare survival rates. A p-value of < 0.05 was considered statistically significant.

Results

Of all the patients included in the study, 19 (52.8%) were male and 17 (47.2%) were female. The median age at diagnosis was 57.5 years (range: 35–76 years), and median follow-up time was 16 months (range: 7–42 months). Median OS was 18.8 months for all patients. Regarding histological subtypes, 31 (86.1%) patients had epithelioid, 2 (5.6%) patients had sarcomatoid, and 2 (5.6%) patients had mixed-type histology. Meanwhile, histological subtype data could not be obtained for one patient. When tumor localizations were evaluated; the tumor was localized within the right hemithorax in 16 (44.4%) patients, within the left hemithorax in 18 (50%) patients, and bilaterally in 2 (5.6%) patients. Tumor localization was costal-mediastinal-diaphragmatic (CMD) in 34 patients and costal in 2 patients. Systemic treatments included either pemetrexed plus platin (PMX + PLT) in 25 patients, or pemetrexed plus platin plus bevacizumab (PMX + PLT + Beva) in 11 patients (Tab. 1). The image of one of the patients included in our study who responded partially to treatment is shown in Figures 1 and 2.

Receiver-operating characteristic analyses performed with the outcome variable taken as death determined SUV_{max1}, TLG2, MTV2, ΔMTV, ΔTLG, ΔHighest SUV_{peak}, and TBR2 as statistically significant. For SUV_{max1}, sensitivity was 63% and specificity 62% at a cut-off value of 7.95. For TLG2, sensitivity was 57% and specificity 56% at a cut-off value of 158. For MTV2, sensitivity was 57% and specificity 62% at a cut-off value of 63.9. For ΔMTV, sensitivity was 68% and specificity 68% at a cut-off value of –54.03. For ΔTLG, sensitivity was 73% and specificity 75% at a cut-off value of –62.58. For ΔHighest SUV_{peak} sensitivity was 63% and specificity 62% at a cut-off value of –7.27. For Highest SUV_{peak2}, sensitivity was 57% and specificity

Table 1. General characteristics and parameter values of the patients

Parameters	n (%)
Age (median range)	57 (35–76)
Sex	
Male	19 (52.8)
Female	17 (47.2)
Histological subtypes	
Epithelioid	31 (86.1)
Sarcomatoid	2 (5.6)
Mixt	2 (5.6)
Hemithorax	
Right	16 (44.4)
Left	18 (50)
Bilateral	2 (5.6)
Localization	
CMD	34 (94.4)
Costal	2 (5.6)
First-line treatment options	
PMX + PLT	25 (69.4)
PMX + PLT + Beva	11 (30.6)
Parameters	**Median (range)**
Pre-treatment values	
MTV1 [cm^3]	113.5 (2.8–863)
TLG1 [mL × cm^3]	400.5 (8.5–5308)
SUV_{max1}	7.95 (2.1–28.9)
Highest SUV_{peak1}	5.2 (1.5–24.9)
TBR1	2.58 (0.55–12.57)
Pleural thickness1	17.5 (5–61)
Post-treatment values	
MTV2 [cm^3]	49.5 (0–980)
TLG2 [mL × cm^3]	158 (0–5447)
SUV_{max2}	6.25 (0–29)
Highest SUV_{peak2}	4.6 (0–25.5)
TBR2	1.84 (0–12)
Pleural thickness2	15.5 (4–64)
Δ Values	
ΔMTV [cm^3]	–54 (–100 to 582)
ΔTLG [mL × cm^3]	–62.58 (–100 to 1132)
ΔSUV_{max}	–22.22 (–100 to 100)
ΔHighest SUV_{peak}	–7.14 (–196 to 52)
ΔTBR	–30.85 (–100 to 105)
ΔPleural thickness	–11.32 (–78 to 260)

Beva — bevacizumab; CMD — costal-mediastinal-diaphragmatic; MTV — metabolic tumor volume; PLT — platin; PMX — pemetrexed; SUV_{max} — maximum standardized uptake value; TBR — tumor/background; TLG — total lesion glycolysis

56% at a cut-off value of 4.6. For TBR2, sensitivity was 63% and specificity 62% at a cut-off value of 1.84. The results of the ROC analyses are presented in Table 2 and Figure 3.

When the patients were evaluated with regard to survival parameters; median OS was calculated as 18.8 months (95% CI 13.9–23.6) for all patients. When the TLG2 value was transformed into a categorical variable by taking 158 as the cut-off value and introduced to survival analysis, median OS was 29.9 (95% CI 15.3––44.4) months in patients with TLG2 ≤ 158 and 16 (95% CI 9–23) months in patients with TLG2 > 158 (p = 0.009). When the patients were categorized into two groups: those with MTV2 values above and below 63.9, median OS was determined as 29.9 (95% CI 15.3–44.4) months in patients with MTV2 ≤ 63.9 and 16 (95% CI 8.9–23) months in patients with MTV2 > 63.9 (p = 0.007). Changes in ^{18}F-FDG PET-CT parameters based on the comparison of the results from post-treatment ^{18}F-FDG PET-CT scan data with pre-treatment ^{18}F-FDG PET-CT were presented in the form of percent change as follows: ΔMTV, ΔTLG, ΔSUV_{max}, ΔHighest SUV_{peak}, ΔTBR ve ΔPleural Thickness. With a threshold of –54.03 for ΔMTV, median OS was 29.9 (95% CI 27.5–32.2) months in patients with ΔMTV ≤ –54.03 and 16 (95% CI 12.4––19.5) months in patients with ΔMTV > –54.03 (p = 0.002) (Fig. 4). When the patients were categorized into two groups: those with ΔTLG below and above –62.58, median OS was 30.9 (95% CI 28–33.7) months in patients with ΔTLG ≤ –62.58 and 16 (95% CI 12.1–19.8) months in patients with ΔTLG > –62.58 (p = 0.001) (Fig. 5). When the patients were analyzed in two groups based on a threshold of 1.84 for TBR2, median OS was 29.9 (95% CI 14–45.7) months in patients with TBR2 ≤ 1.84 and 16 (95% CI 11.2–20.7) months in patients with TBR2 > 1.84 (p = 0.039). Median OS was 29.3 (95% CI 14–44.6) months for patients with SUV_{max1} ≤ 7.95 and 17.1 (95% CI 15.2–19) months for those with SUV_{max} > 7.95 (p = 0.312). Patients with response according to Δpleural thickness had median OS of 29.3 (95% CI 15.6–43) months and those without response had median OS of 17.1 (95% CI 14.8–19.3) months (p = 0.182). Patients' survival analyses are presented in Table 3.

Discussion

Imaging with the use of ^{18}F-FDG PET-CT is a valuable diagnostic modality in patients with mesothelioma and for assessment of treatment response. While SUV_{max} values obtained from ^{18}F-FDG PET-CT have traditionally been used to evaluate treatment response, recently, parameters such as MTV, TLG, highest SUV_{peak}, and pleural thickness have become increasingly important.

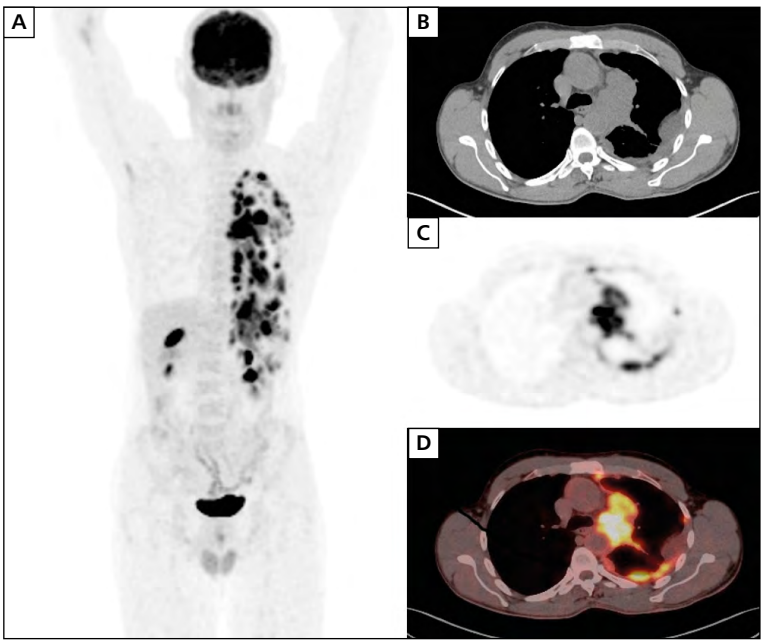

Figure 1. Pre-treatment imaging; **A.** Maximum intensity projection (MIP); **B.** Computed tomography; **C.** Positron emission tomography; **D.** Fusion images

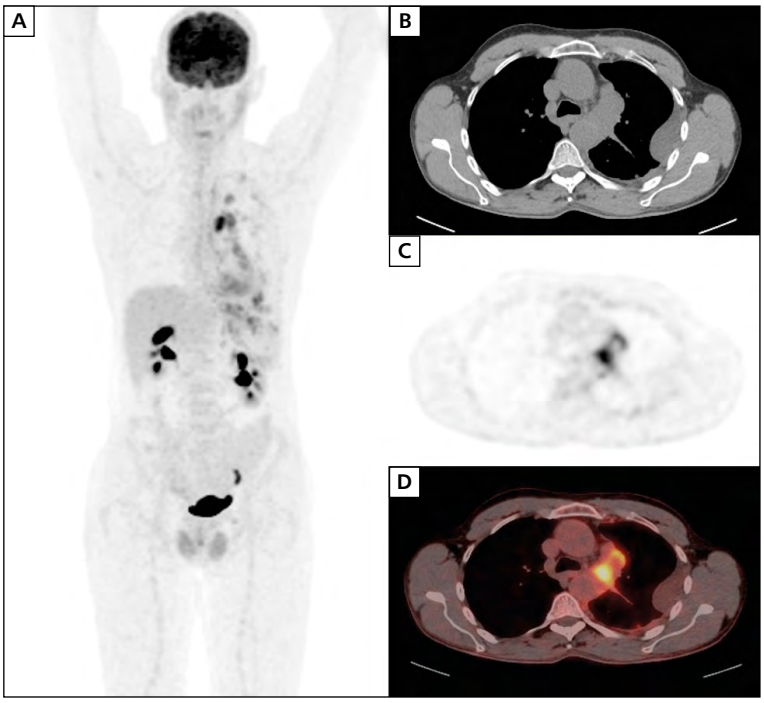

Figure 2. Post-treatment imaging; **A.** Maximum intensity projection (MIP); **B.** Computed tomography; **C.** Positron emission tomography; **D.** Fusion images

In our study, median OS was 29.3 (95% CI 14–44.6) months for patients with $SUV_{max1} \leq 7.95$ and 17.1 (95% CI 15.2–19) months for those with $SUV_{max} > 7.95$ ($p = 0.312$). In line with our results, a study by Schaefer et al. [13] in 2012 including 41 patients did not find a correlation between survival and SUV_{max1} or ΔSUV_{max}. In a 2014 study conducted by Klabatsa et al. [14] in 60 patients, the univariate analysis indicated a hazard ratio of 1.26 (95% CI

Table 2. Sensitivity and specificity ratios and receiver-operating characteristic (ROC) analysis results

Parameters	Cut-off	Sensitivity	Specificity
SUV_{max1}	7.95	63%	62%
TLG2 [mL × cm^3]	158	57%	56%
MTV2 [cm^3]	63.9	57%	62%
ΔMTV [cm^3]	–54.03	68%	68%
ΔTLG [mL × cm^3]	–62.58	73%	75%
ΔHighest SUV_{peak}	–7.27	63%	62%
Highest SUV_{peak2}	4.6	57%	56%
TBR2	1.84	63%	62%
Parameters	**AUC**	**95% CI**	**p-value**
SUV_{max1}	0.69	0.51–0.87	0.049
TLG2 [mL × cm^3]	0.75	0.59–0.91	0.011
MTV2 [cm^3]	0.73	0.56–0.89	0.02
ΔMTV [cm^3]	0.71	0.54–0.88	0.031
ΔTLG [mL × cm^3]	0.76	0.59–0.92	0.009
ΔHighest SUV_{peak}	0.69	0.51–0.88	0.047
Highest SUV_{peak2}	0.71	0.54–0.88	0.03
TBR2	0.72	0.55–0.9	0.022

AUC — area under the curve; CI — confidence interval; MTV — metabolic tumor volume; SUV_{max} — maximum standardized uptake value; TBR — tumor/background; TLG — total lesion glycolysis

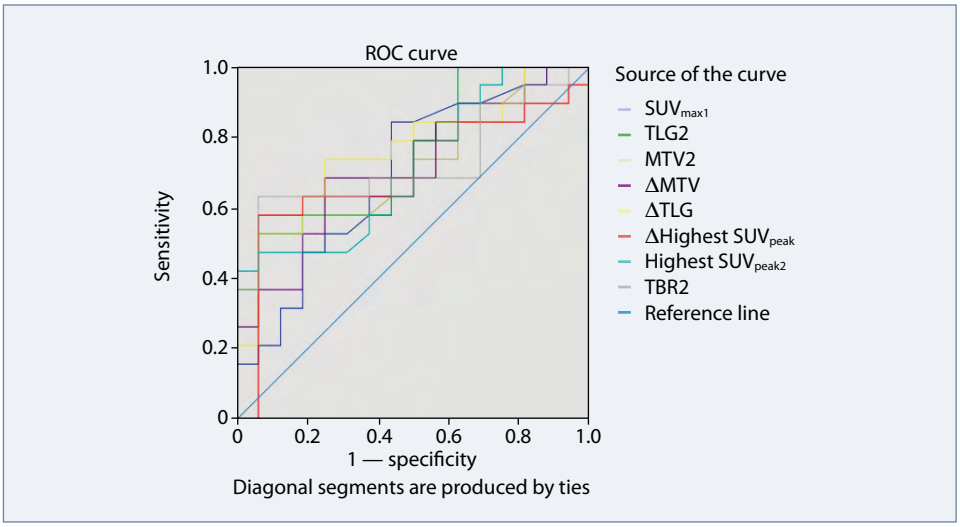

Figure 3. Receiver-operating characteristic (ROC) curve analysis results; MTV — metabolic tumor volume; SUV — standardized uptake value; TBR — tumor/background; TLG — total lesion glycolysis

1.00–1.58) for every 5-unit increase in the SUV_{max1} value ($p = 0.051$). In a 2010 study conducted by Lee et al. [15] in 13 patients, SUV_{max1} was determined as 9.5 ± 4.9 in responsive patients and as 11 ± 6.5 in unresponsive patients ($p = 0.724$). In a 2017 study conducted by Zuccali et al. [16] in 142 patients; the univariate analysis indicated a hazard ratio of 1.1 (95% CI 1.04–1.16) for each unit of increase in the SUV_{max1} value ($p < 0.001$). In the same study, the univariate analysis also determined a hazard ratio of 1.09 (95% CI 1.04–1.15) for every 10-unit increase in ΔSUV_{max} ($p < 0.001$). Moreover, the same study found that higher SUV_{max1} and ΔSUV_{max}

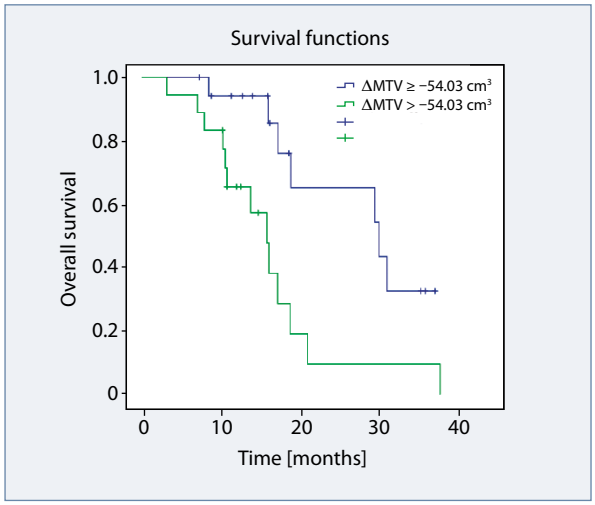

Figure 4. Overall survival results according to Δmetabolic tumor volume (MTV) values; MTV — metabolic tumor volume

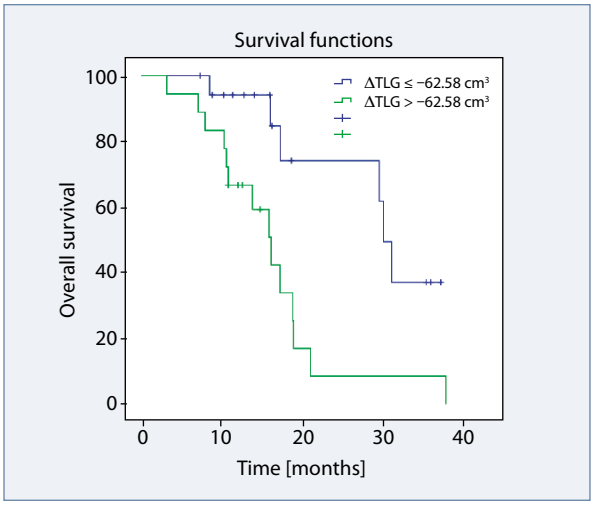

Figure 5. Overall survival results according to Δtotal lesion glycolysis (TLG) values

Table 3. Kaplan-Meier survival analysis results according to parameters

Parameters	mOS [months]	95% CI	p-value
All patients	18.8	13.9–23.6	
TLG2 [mL × cm^3]			0.09
≤ 158	29.9	15.3–44.4	
> 158	16	9.00–23.0	
MTV2 [cm^3]			**0.007**
≤ 63.9	29.9	15.3–44.4	
> 63.9	16	8.9–23	
ΔMTV [cm^3]			**0.002**
< −54.03	29.9	27.5–32.2	
> −54.03	16	12.4–19.5	
ΔTLG [mL × cm^3]			**0.001**
≤ −62.58	30.9	28–33.7	
> −62.58	16	12.1–19.8	
TBR2			**0.039**
≤ 1.84	29.9	14–45.7	
> 1.84	16	11.2–20.7	
SUV_{max1}			0.312
≤ 7.95	29.3	14–44.6	
> 7.95	17.1	15.2–19	
ΔPleural thickness response			0.182
Yes	29.3	15.6–43	
No	17.1	14.8–19.3	

CI — confidence interval; mOS — median overall survival; MTV — metabolic tumor volume; SUV_{max} — maximum standardized uptake value; TBR — tumor/background; TLG — total lesion glycolysis

values were associated with shorter survival times [16]. In a 2013 study conducted by Abakay et al. [10] in 177 patients, median OS was 14 months (95% CI 1.3–16.6) in patients with $SUV_{max1} < 5$ and 10 months (95% CI 8.1–11.8) in patients with $SUV_{max} > 5$ ($p = 0.013$). In a 2006 study conducted by Flores et al. [17] in 137 patients, median OS was 21 months in patients with $SUV_{max} < 10$ and 9.7 months in patients with $SUV_{max} > 10$ ($p = 0.02$). In a 2017 study conducted by Hall et al. [18] in 73 patients, median OS was 17.5 (9–24.5) months in patients with $SUV_{max} < 10.6$ and 8.9 (5.9–16) months in patients with $SUV_{max} > 10.6$ ($p = 0.001$). In the same study, the analysis of 9-week and 9-month PFS revealed higher ΔSUV_{max} values in patients who showed progression than in those who did not [18].

Patients with lower ΔMTV were found to achieve longer survival times in our study. Median OS was 29.9 (95% CI 27.5–32.2) months in patients with $\Delta MTV \leq -54.03$ compared to 16 (95% CI 12.4–19.5) months in patients with $\Delta MTV > -54.03$ ($p = 0.002$). In the study by Hall et al. [18], median OS was 8.8 months (5.9–14.6) in patients with MTV1 > 460 compared to 18.7 months (9.1–24.5) in patients with MTV < 460 ($p < 0.001$). The same study also observed lower ΔMTV values in patients who did not progress compared to those who progressed at the end of a 9-month follow-up period [18]. In the study by Lee et al. [15], patients with lower MTV1 values had longer PFS. The same study found an MTV1 of 70.1 ± 85.4 in responsive patients compared to 676.4 ± 1019.6 in unresponsive patients ($p = 0.045$). In the study by Klabatsa et al. [14], median OS was reported as 6.4 months in patients with MTV > 755 compared to 14.4 months in those with MTV < 755 ($p = 0.001$). Akdeniz et al. [11] also found OS of 24.6 ± 4.1 months in patients with MTV1 < 113 compared to 8.2 ± 1.3 months in those with MTV > 113 ($p = 0.002$).

In our study, we found that higher TLG2 and ΔTLG values were associated with shorter survival times. This is consistent with a study by Zuccali et al. [16], which found median OS of 13.3 months in patients with TLG <534.3 compared to 5.6 months in patients with TLG1 > 534.3 ($p < 0.001$). Median OS was 7.9 months for patients with $\Delta TLG < -30$ compared to 5.6 months in patients with $\Delta TLG > -30$ ($p < 0.001$). In the study by Francis et al. [12], a hazard ratio of 0.7 (95% CI 0.58–0.90) was determined for every 10-unit increase in ΔTLG ($p = 0.008$). In the study by Klabatsa et al. [14], median OS was 6.4 months in patients with TLG1 > 2.914 ml compared to 18.1 months in those with TLG1 < 2.914 ($p < 0.001$). Similarly, the study by Lee et al. [15] also observed shorter survival times in patients with higher TLG1 levels ($p = 0.009$). The same study also determined TLG1 levels of 389.2 ± 492.9 in responsive patients compared to levels of 2666.7 ± 4122.7 in unresponsive patients ($p = 0.093$) [15]. In the study by Akdeniz et al. [11], patients with TLG1 < 419.5 had OS of 22.4 ± 4.2 and patients with TLG > 419.5 had overall survival of 8.5 ± 1.3 ($p = 0.008$).

When evaluated with respect to Δpleural thickness, there was no statistically significant difference between the patients in terms of survival. According to the results of a 2017 study conducted by Kanemura et al. [19] in 82 patients that compared the mRECIST criteria evaluated based ^{18}F-FDG PET-CT on CT results and, ^{18}F-FDG PET-CT was found to be superior in the evaluation of treatment response and prediction of PFS. On the other hand, in the study by Schafer et al. [13], mRECIST evaluation was found to be superior although MTV and TLG obtained by ^{18}F-FDG PET-CT were statistically significant in the prediction of survival.

The limitations of our study include small sample size, heterogeneity of patient groups, and the retrospective nature of the study.

Conclusions

Although there are studies in which metabolic parameters such as SUV_{max1} and ΔSUV_{max} were associated with survival, these parameters were not found to be statistically significant OS predictors. On the other hand, our study and other studies in the literature have determined that volumetric parameters such as ΔMTV and ΔTLG are statistically significant OS predictors. Accordingly, it can be stated that volumetric parameters obtained from ^{18}F-FDG PET-CT are more valuable than metabolic parameters in the prediction of survival. More studies on this matter are needed for this result to receive general acceptance and enter clinical use. In addition, ^{18}F-FDG PET-CT was found to be superior to CT in certain studies that compared the two modalities, and volumetric parameters were found to be superior to pleural thickness in our study. However, more studies on this topic are warranted.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was obtained for this study from Dicle University, Faculty of Medicine Non-Invasional Clinical Research Ethics Committee (date: 12.05.2022, approval number: 133).

All analyses were performed in accordance with the principles of the Declaration of Helsinki.

Author contributions

All authors: consept, design, supervision, fundings, materials, data collection and/or processing, analysis and/or interpretation, literature review, writing, critical review.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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VIA MEDICA

ORIGINAL ARTICLE

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Opinion of representatives of the psycho-oncology community on the lack of coherent systemic solutions on the legal regulation of their profession

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ABSTRACT

Introduction. The profession of psycho-oncologist in Poland is not sufficiently regulated by law. Current solutions in the system involve contradictory regulations on obtaining qualifications to practice, which produces in effect systemic chaos and result in limited availability of services provided to oncology patients and their families by practitioners of this demanding profession.

Material and methods. A survey conducted among psycho-oncologists concerning their professional identity was used in order to examine their opinion on the current legal regulations of this profession and the possible consequences of incoherent law solutions. The study used an original anonymous questionnaire entitled *Survey on selected aspects of the psycho-oncology profession in the context of its scope and method of legal regulation* and the *Job Satisfaction Scale* questionnaire.

Results. The study showed that the inconsistency in legal regulations may result in restricted access to this profession, indicated doubts concerning the legal credentials required to use the professional title of psycho-oncologist and the lack of symmetry in individual competencies of practitioners with different underlying profession.

Conclusions. The research confirmed the organizational chaos which negatively affects the way psycho-oncologists practice their profession. As a consequence the legislator intervention is required in order to modify the legal regulation of this profession.

Keywords: psycho-oncologist, legal regulations, law and medicine, access to guaranteed medical services

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Introduction

The legislator has initiated legislative work on an act, which aims to regulate the conditions and principles of medical practice in professions that have not been covered by statutory regulations so far. The legislative initiative includes issues related to professional development and professional liability of medical professionals [1]. The indicated draft includes professions such as, among others, the orthoptist, podiatrist, preventive medicine specialist, or medical sterilization technician, but not psycho-oncologist. Recognizing the need to raise the profile of other allied medical professions, it was decided to regulate, in the form of the specializationin the fields applicable in healthcare, the profession of addiction psychotherapy specialist [2], and in relation to the profession of a psychotherapist, work in this field is in progress [3]. The profession of psycho-oncologist has not been included in any of the above legislative projects while its current legal regulation is inconsistent,

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as indicated in the doctrine [4]. The survey research, which is the subject of this article, aimed at analyzing whether the *de lege lata* state allows psycho-oncologists to provide highly desirable services in the system of guaranteed services in an uninhibited manner, with appropriate guarantees regarding the legal framework of professional activity or whether the availability of health services of this kind is affected.

Currently, according to the Regulation of the Minister of Health on guaranteed benefits in-hospital treatment, a psycho-oncologist is a person with higher psychological or medical education, who has completed higher education and obtained a master's degree or an equivalent degree and who has completed post-graduate studies in psycho-oncology [5]. A psycho-oncologist participates in the process of providing healthcare services in the general health insurance system and outside it. As part of the guaranteed services, the payer requires the medical institution to have in their personnel a psycho-oncologist in selected types of facilities, including palliative and hospice care (Regulation of the Minister of Health of October 29, 2013, i.e. Journal of Laws of 2022, item 262), outpatient specialist care (Regulation of the Minister of Health of November 6, 2013, i.e. Journal of Laws of 2016, item 357, as amended), or medical rehabilitation (Regulation of the Minister of Health of November 6, 2013, i.e. Journal of Laws of 2021, item 265). The Minister of Health indicated that the presence of a psycho-oncologist is required during the provision of such services as comprehensive oncological care, e.g. for a patient with breast cancer (KON-PIERS) and a patient with colorectal cancer (KON-JG; Regulation of the Minister of Health of 22 November 2013 on guaranteed benefits in the field of hospital treatment, i.e. Journal of Laws of 2021, item 290, as amended). In addition, psycho-oncologists support people with cancer and their families, in particular, in stationary and home hospices, which are run by private entities, and financed outside the guaranteed benefits system.

The legal definition of the profession of psycho-oncologist, which remains in force, is inconsistent with the regulation of this profession, which has been in force since 2018, and results from the announcement of the Minister of Health on the Polish Qualifications Framework (PQF) system [6]. This is because the PQF restricts the group of people who can obtain a qualification in psycho-oncological diagnosis and care to psychologists and psychiatrists only, thus limiting the number of people who are qualified to practice as psycho-oncologists. A third path to acquiring professional qualifications of a psycho-oncologist is through certification in the process of the Polish Psycho-Oncology Society (PPOS). Under this procedure, in addition to psychologists and doctors, representatives of other professions, such as nurses or clergy employed in hospices, would also become certified. In light of the regulations mentioned above, people certified in this way will mostly be unable to formally practice the profession, as the regulations do not allow for the recognition of certificates awarded by PPOS as equivalent to psycho-oncology qualification under PQF. The term 'psycho-oncologist', therefore, currently denotes PPOS-certified psycho-oncologists, not included by the legislator in any of the regulations, psycho-oncologists with postgraduate studies in psycho-oncology as well as psycho-oncologists who will become qualified under the currently implemented market qualification: "Diagnosis and psycho-oncological support for oncological patients, post-cancer patients, and their families and environment".

Material and methods

The study used an original anonymous questionnaire entitled *Survey on selected aspects of the psycho-oncology profession in the context of its scope and method of legal regulation* (hereinafter: POA) and, with the author's consent, the *Job Satisfaction Scale* questionnaire (hereinafter: SSP) [7]. The POA questionnaire contained 12 open-ended and closed-ended questions in which the researchers asked respondents about their educational background, qualifications under which they practice as psycho-oncologists, their intention, if any, to enter the validation and certification process under the Integrated Qualification System (IQS), their perceptions about the nature of the psycho-oncology profession, their preferences regarding access to this profession for different categories of underlying professions, as well as their assessment of the legal status of this profession as per current legislation. In the open-ended questions, the respondents could give free answers to questions about the possible intention to obtain a psycho-oncologist certificate under the Integrated Qualifications System and the reasons why they made this decision or abandoned such an intention, whether they see the profession of psycho-oncologist as strictly medical or in other categories, and whether the current state of legal regulation of this profession in Poland negatively affects the fulfillment of duties of psycho-oncologists or raises concerns about the future of their performance. The respondents were also asked to indicate the three most important, in their opinion, differences in the psycho-oncological practice by representatives of various professions (doctors, psychologists, and psychiatrists) and to specify what their expectations are regarding the legal regulation of the profession in Poland. The SSP questionnaire consisted of 5 questions on job conditions and job satisfaction, rated by the respondents on a scale from 1 to 7, where 1 meant 'strongly disagree' and 7 — 'strongly

agree'. Both questionnaires were available through a free Google tool, and all respondents provided their consent to participate in the study, which was a prerequisite for being able to complete the survey. The tool was made available on various platforms and disseminated to specialized cancer care clinics and other centers providing psycho-oncological care. However, because the professional community is not large, comprising about 1 000 people across the country: 95 people with the Psycho-oncologist Certificate in the Polish Psycho-oncology Association (extraordinary procedure) and about 900 graduates of postgraduate studies in the field of psycho-oncology [8], the survey, conducted in the second half of 2022, was completed by 41 respondents. The data analysis was qualitative.

Results

Of those taking part in the survey, 79.5% declared that they had a degree in psychology, just under 13% had a degree in medicine, and 7.7% were graduates in sociology, nursing, education and counseling, and public health. Most respondents (64.9%) stated that they practice as psycho-oncologists after completing postgraduate studies in psycho-oncology, while 35.1% were certified as psycho-oncologist by PPOS. At this point, it should be emphasized that none of the respondents held the market qualification (Diagnosis and psycho-oncological support for oncological patients, post-cancer patients, and their families and environment) provided under the Integrated Qualifications System in the PQF validation and certification process, which was introduced in December 2018.

Not all respondents declared whether they intended to join the certification process to obtain qualifications under the Integrated Qualifications System. Fewer than 30% declared that they did not intend to due to a lack of financial resources to cover the costs involved; because the certificate would only confirm the status quo (skills); because having postgraduate studies is enough to practice the profession in the light of the Regulation of the Minister of Health on guaranteed inpatient care; because they already held PPOS certification; due to lack of knowledge on how to initiate the procedure; because the course and procedure are below the respondent's qualifications; and also because it is not required by the public payer. The same percentage of respondents who declared their intention to follow this training pathway justified their decision by claiming that a qualification of this kind would confirm their skills in the EU, that it would be part of extrinsic motivation for continuous development or a confirmation of their qualification level, and that by doing so they would improve their knowledge in the field.

While answering open questions, when asked about the nature of their profession as a psycho-oncologist, 47.4% of the respondents said that they saw it as a specialization in psychology, while 42.1% described it as a difficult interdisciplinary field of study, requiring specific know-how and expertise. Only a small proportion of the respondents defined their profession as a typical medical profession (5.3%). The question of whether the current legal status of the psycho-oncology profession in Poland raises anxiety about its prospects within the system of guaranteed healthcare benefits was answered by slightly more than 50% of people, while about 20% indicated that the current legal status has a negative impact on both the way the profession is practiced and their performance.

More than half of the respondents indicated that, in their opinion, only psychologists should have access to the profession, 20% believed that this profession should be open to all medical professions, and the same proportion said that it should also be open to members of professions such as philosophers, theologians, sociologists, occupational therapists, and social workers. The smallest number of respondents considered the profession to be specifically reserved for psychiatrists, i.e. one of the two categories of professions currently eligible for PQF certification. Of all participants, 65.8% provided their psycho-oncologist services based on the requirements of the National Health Fund (NFZ), as part of their contracts for publicly funded healthcare. When asked about job satisfaction level, the majority of the respondents (66%) agreed with the statement that their job was close to ideal, and almost the same number said that their job conditions were excellent (63%). As many as 80% of respondents stated that they were satisfied with their job, and the same number that they so far managed to achieve their goals at work. If the respondents had to choose their job again, as many as 82% would choose the same job.

In their responses to open-ended questions, survey participants emphasized that the lack of legal regulation of the profession of psycho-oncologist is a source of frustration for them and makes them anxious about practicing the profession in an environment where the same services are also provided by insufficiently qualified people. The respondents pointed out that the inconsistency in legal regulations and the long learning path may result in restricted access to the profession, with a consequent reduction in the number of practitioners and thus patients' access to their services. The respondents emphasized their doubts about the legal credentials required to use the professional title of psycho-oncologist and the passive approach of state legislators when it comes to sorting out the existing legal ramifications, as well as the organizational confusion resulting from different educational pathways.

Survey participants pointed out the lack of symmetry in individual competencies of practitioners with

different underlying professions: in the case of doctors, highlighting their lack of psychological training, and in the case of psychologists, the need to acquire knowledge of the diagnosis and treatment of the oncology patient and incorporate it into therapy. Another related problem noted by the respondents is that psychologists are not authorized to prescribe pharmacotherapy and, on the other hand, those psycho-oncologists who are not psychologists do not have the necessary training to provide counseling and are unfamiliar with specific counseling techniques, the use of psychological tools, and lack a certain range of soft skills. As indicated by the respondents, the positioning of psycho-oncologists in the system of guaranteed services may translate into how psycho-oncological help is provided and the time devoted to the recipient of such services, i.e. the frequency and duration of meetings.

The respondents highlighted differences in the approach to the patient: therapeutic (in the case of practitioners with a background in psychology) and medical (in the case of those with a background in psychiatry). The answers provided indicated the important role of knowledge of patients' psychological functioning, understanding the background of different reactions to the illness, and the ability to communicate with the patient and their relatives, as well as different methods of counseling. As a result, a psychologist who uses a subjective and individualized approach, as well as communication skills, conducts their interaction with the client/patient in a different way than a doctor.

When identifying expectations regarding the regulation of the psycho-oncology profession in Poland, the respondents emphasized the need to clarify the current legal situation in the profession, clearly define the scope of responsibilities of practitioners, and the mechanism of building professional and interpersonal qualifications. It was proposed that a specialization in psycho-oncology is created, similar to the specialization in clinical psychology, or that access to the profession be restricted to psychologists only, or that a single, coherent system of awarding qualifications in this area be created. It was noted that it would be desirable to standardize and facilitate access to this profession and legally determine the categories of practitioners who could use this professional title, pointing out the lack of legal transparency in the psycho-oncology profession. Finally, it was advocated that psycho-oncologist should be explicitly included in the category of medical professions and their status upgraded to a specialization in the healthcare system, to provide guarantees for better funding in the system.

Discussion

The literature emphasizes the role of psycho-oncology as a multidisciplinary field on the borderline between medicine and social sciences [9]. The conducted research has shown, however, that the variety of basic professions entitled to practice as psycho-oncologists causes significant differences in professional performance, which means that the standard of practice is not uniform. A psycho-oncologist who is a psychiatrist by education has medical knowledge, while a psycho-oncologist psychologist is competent to provide psychological assistance. In the case of psycho-oncologists with education other than the indicated professions, their qualifications are closely related to the competencies obtained in formal education, i.e. higher psychological or medical studies, defined by the legislator in a very general way, provided that they complete postgraduate studies in psycho-oncology what results in differences in the qualifications held. On the other hand, after obtaining formal qualifications to provide psycho-oncology services, there are no legal instruments to monitor the standard of their performance because the certificate awarded under the IQS is valid indefinitely, and after completing postgraduate studies in psycho-oncology, the practice is unlimited timewise. Meanwhile, the literature indicates the need for developing a useful model of supervision in psycho-oncology [10, 11], as the profession of a psycho-oncologist includes providing therapy for people affected by cancer and their families.

The lack of uniform regulation of the profession results in the impossibility of qualifying it as a medical profession with consequences regarding liability for damage caused in the course of its practice. The lack of professional self-government means that there is nobody that would guard a specific standard of psycho-oncological services within the system of guaranteed benefits and outside it. No entity in the system would be competent to deprive a psycho-oncologist of his/her 'license' in the event of improper performance of services, and there is no procedure applicable in such a situation. Although new challenges for this interdisciplinary activity relate, in particular, to the support of patients and their families in the face of new methods of cancer treatment [12], there is no specific model of continuing education in this field.

Problems related to psycho-oncological care in different countries are closely related to the organization of the healthcare system [13]. In major oncology centers in the world, the inclusion of psychological help in the scope of services is a standard, which results in an improvement in the quality of treatment of patients and an increase in the quality of their lives and dying [14]. As a result of the conducted research, it has been revealed that inconsistent system solutions negatively affect decisions to choose this profession, which in turn may result in a low number of people competent to perform it and thus limit access to these services. A decade ago it was already indicated that not all pediatric onco-hematology centers provide the same satisfactory level of psychosocial care [15].

Conclusions

Taking into account the sample size, the conducted research does not allow for conclusions generalizable to the entire professional environment of psycho-oncologists, however, it seems legitimate to confirm certain assumptions from the data obtained. The way in which the profession of psycho-oncologist is currently regulated in Poland seems insufficient. As this study shows, under the current legislation, there is organizational chaos which negatively affects not only how psycho-oncologists practice their profession but also the accessibility of the services they provide. Legal steps are needed to unify the current system of training which is now split into three non-equivalent paths, as has already been pointed out in the literature [4]. The opinions of our respondents correspond fully with the initiative of the Polish Psycho-Oncology Society, which since 2012 has been requesting that the profession of psycho-oncologist be formally recognized [16]. It seems reasonable for the legislator to intervene to modify the legal regulation of the profession, in particular by unifying the method of obtaining professional qualifications and providing access to the profession. In this regard, it seems desirable to choose one of the modes of access to the profession both by defining the catalog of entry-level professions, which will entitle one to obtain the license to practice as a psycho-oncologist, as well as to define the path of education considering the differences resulting from entry qualifications. Depending on whether a psycho-oncologist will be a doctor, or psychologist, or will represent another profession, the education process should take into account the differences resulting from their education and related system regulations. The legislator should determine the nature of the psycho-oncologist profession as a medical profession, creating legal guarantees of a specific standard of its performance, and consider the postulates of that part of the psycho-oncology community which expresses concerns about the current state of legal regulation of the profession.

Article Information and Declarations

Data availability statement

The data was collected on the basis of voluntary, anonymous surveys.

Ethics statement

Not applicable.

Author contributions

K.K.: conception, design, execution and interpretation of the data.
M.Ch.: execution and interpretation of the data.
M.S.: execution and interpretation of the data.
M.J.J.: conception, design, execution of the data.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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ORIGINAL ARTICLE

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The effect of spirituality-based education on the meaning of life in cancer patients: a quasi-experimental study

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ABSTRACT

Introduction. Patients with cancer face challenges in finding the meaning of life. This study aimed to examine the effect of spirituality-based education on the meaning of life of cancer patients.

Material and methods. This quasi-experimental study was conducted using a pretest and posttest design with two groups. The data were collected by using personal information forms and the meaning-of-life questionnaire. Patients in Iran were selected via convenience sampling and were divided into the experimental (n = 85) and control groups (n = 84) based on nonrandom allocation. The experimental group received six sessions of mobile spirituality-based education in three weeks. One month after the pretest and at the end of the spirituality-based education, the posttest was conducted. The collected data were analyzed using descriptive statistics and inferential statistics with SPSS software.

Results. A comparison of the scores of the patients in the two groups after the intervention suggested a significant increase in the scores for the presence of meaning, search for meaning, and meaning of life for the patients in the experimental group (p = 0.001).

Conclusions. The results of this study indicated that spirituality-based education can be one of the useful, effective, and applicable educational techniques to improve the meaning of life of cancer patients.

Keywords: cancer, education, meaning of life, patient, spirituality

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Introduction

Global cancer statistics indicate that in 2020, 22.8% of all cancers occurred in Europe and 20.9% in the USA. In the same year, 58.3% of cancer deaths occurred in Asia [1]. Cancer is the third leading cause of death in Iran, and it is predicted that 184481 new patients will be diagnosed with cancer in Iran by 2035 [2]. Cancer as a social phenomenon disrupts the daily functioning and social activities of affected patients and influences the individual's ability to perform social roles and take on social responsibility as well as overall meaning of their life [3]. Due to these problems, cancer patients face challenges in finding meaning in their lives, which puts their mental health at risk [4].

As soon as a person is diagnosed with cancer, the meaning of life is threatened and consequently, they are overwhelmed with feelings of powerlessness [5] while having a sense of meaning in life promotes the physical health of cancer patients [6] and contributes to the development of a positive outlook on life [7]. Having a positive sense of meaning in life reduces general anxiety and death anxiety in those patients and, thus, improves their life satisfaction. The meaning of life in cancer patients relieves them of spiritual distress and reduces their fear of death [8]. In fact, cancer patients are less likely to

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experience end-of-life worries by enjoying the meaning of life [9]. Those patients develop firm spiritual beliefs and are empowered to cope with possible death [10]. In other words, when cancer patients understand the meaning of their life, they learn to face death and try harder to fight the disease [11]. On the other hand, cancer patients in Iran have some spiritual problems.

Numerous studies have addressed the meaning of life for cancer patients in the world. A study in Turkey showed that cancer patients with a greater belief in the meaning of life have higher levels of psychological resilience and experience less suffering in life [12]. Another study in Korea suggested that people with cancer seek positive meaning in life by promoting positive emotions and improving their lifestyles, and this gives them hope [13]. The results of a study showed that the meaning of life for cancer patients in Iran induces their personal growth [14]. Another study found that the meaning of life for cancer patients in Portugal improved their relationships with others and their functioning [15]. A study in the United States showed that the meaning of life for cancer patients improved their connection with friends and family members and strengthened their faith in God [16].

Previous studies have highlighted the importance of promoting meaning of life for cancer patients because it is associated with many positive outcomes as detailed above. One of the interventions that can contribute to promoting meaning in life is spirituality-based education. Objectives of spirituality-based education interventions for cancer patients include happiness, hope, and positivity, facilitating and developing coping styles, increased self-motivation and vitality, changing defective motivations, creating a sense of control over the self and environment, creating a sense of being seen by God, reducing emotional problems and stress, and improving resilience to life problems [17]. Thus, the implementation of spirituality-based education for cancer patients, in addition to improving their physical health and reducing the severity of their physical pain [18], also helps to promote their spiritual health [19]. Accordingly, considering the educational role of nurses and a research gap in this field, this study aimed to examine the effect of spirituality-based education on the meaning of life in cancer patients.

Material and methods

This quasi-experimental study was conducted by using a pretest and posttest design with two groups from July to September 2021.

The research population included all outpatient cancer patients who had medical records in Firoozgar and Rasoul Akram hospitals affiliated with the Iran University of Medical Sciences. The sample size was estimated at least 76 persons at the 95% confidence level and test power 80% and assuming that the difference in the effect of spirituality-based education on the meaning in life for the patients in the experimental group compared to the control group must be three points so that this effect is considered statistically significant. However, considering a 10% dropout rate, the sample size was estimated as 85 persons in each group. Then, one patient in the control group left the study. Thus, there were 85 participants in the experimental group from Firoozgar Hospital and 84 participants in the control group from Rasoul Akram Hospital. The study groups were selected from different locations to decrease the risk of information leakage. Patients were referred to the hospital for outpatient chemotherapy and were not hospitalized. The inclusion criteria were having cancer diagnosed by an oncologist. The exclusion criteria were self-reported underlying diseases including heart disease, mental illness, and diabetes. Patients were 18 to 65 years old; they all had smartphones and could easily use the application. The patients in the two groups were selected through convenience sampling and then, were assigned to the experimental and control groups via nonrandom allocation.

The data were collected using personal information forms and the Meaning of Life Questionnaire (MLQ). The personal information form was filled out to record the patients' age, gender, marital status, economic status, level of education, history of cancer surgery, family history of cancer, and type and stage of cancer. The MLQ [20] is a 10-item measure of the Presence of Meaning in Life (items 1, 4, 5, 6, and 9) and the Search for Meaning in Life (items 2, 3, 7, 8, and 10). The items are scored using a seven-point Likert scale ranging from 1 ('absolutely untrue') to 7 ('absolutely true') with item 9 reverse scored. The total score on each dimension varied from 5 to 35, with a higher score for the meaning of life and its dimensions indicating more meaning of life and its dimensions, and vice versa. The validity of the questionnaire was assessed by 5 professors at the Department of Nursing of Iran University of Medical Sciences. To this end, the Persian and English versions were reviewed by the professors, and the content of the Persian version was revised based on their feedback. The developers of the questionnaire assessed its reliability using Cronbach's alpha, and the corresponding values for the presence and search dimensions were 86% and 87%, respectively. The psychometric properties of the questionnaire were assessed for use in Iran and its reliability was evaluated using Cronbach's alpha, and the corresponding values for the presence and search dimensions were 82% and 88%, respectively [21]. In the present study, the questionnaire was administered to a pilot sample of 15 people who matched the participants in

the research sample and the Cronbach's alpha values for the presence and search dimensions were 84% and 86%, respectively, confirming the high reliability of the questionnaire.

Upon receiving the necessary permits to conduct the study, the researcher started the sampling process. Due to concurrence of the study with the COVID-19 pandemic, it was not possible to conduct the spirituality-based education in person, and it was conducted online. To this end, the researcher obtained the patients' phone numbers recorded in their medical records upon making arrangements with the hospitals where the study was to be conducted. The researcher explained the objectives of the study to the patients meeting the inclusion criteria and invited them to participate in the study. Next, an online spirituality-based education group was created on WhatsApp, and the participants were added to the group. The participants had direct access to the researcher. After completing the informed consent form, questionnaires were provided to the patients to be completed for the pretest. One month after the pretest and after the spirituality-based education, the patients completed the questionnaires as the posttest on the WhatsApp social group. The participants in the experimental group received the spirituality-based education online in six 60-minute sessions for three weeks in the form of recorded audio files, PowerPoint, PDF files, and video clips uploaded to the WhatsApp group by the first author. During the spirituality-based education, the patients had access to the members of the research team to ask for help with any ambiguity or problem. Feedback was obtained from the patients after the sessions, and they were asked to do some assignments at the end of each session. The participants also answered questions asked by the researcher online in the interval between the subsequent sessions and provided their opinions and feedback. Feedback was obtained during the presentation of the content and exercises. These exercises were presented at the end of the sessions. They gave and received the necessary feedback from him. In this study, the control group members after the posttest were provided with an electronic booklet containing educational content.

The educational content was prepared following relevant studies published in the literature on spirituality-based education [17, 19, 22–28] and the researcher's personal experiences. The main titles of the educational content can be seen in Table 1. To achieve the validity of the educational content, we had it reviewed by seven faculty members of the Iran University of Medical Sciences who confirmed the content validity. These persons had experience in spirituality-based studies, and their suggestions were applied to the educational content. The collected data were analyzed using descriptive statistics (frequency, percentage, mean, and standard deviation) and inferential statistics (independent samples t-test and paired samples t-test) with SPSS software (version 16) at the significance level of 0.05 ($p < 0.050$).

This study was approved under number IR.IUMS.REC.1399.999 by the ethics committee of Iran University of Medical Sciences. The patients were told that they could leave the study at any time. Furthermore, written consent was obtained from the patients. They were told that the information they provided would remain anonymous and confidential, and there was no compulsion to participate in the study.

Results

According to the Kolmogorov-Smirnov test, quantitative variables had a normal distribution. Table 2

Table 1. Main topics of educational sessions

Session	Content
1	Introduction Providing information about the cancer, prevalence, common symptoms, and causes of cancer Introducing the concept of the meaning of life
2	Introspection and self-awareness as well as the importance of spirituality in self-awareness
3	Sources of fear and anxiety and coping with them, ways to gain peace, the role of trust in gaining peace, achievements, outcomes, and consequences of trusting God
4	Good and bad heritage left by individuals and how to take care of good heritage (A person is remembered by others based on the inheritance he/she leaves behind. So one has to choose whether he/she wants to continue good behavior or bad behavior. For example, we should exhibit behavior such as active listening, support, and respect and avoid bad behavior including insults, punishment, humiliation, blame, aggression, and neglect.)
5	Understanding forgiveness
6	Controlling anger and solving problems using a spiritual approach Conclusion

Table 2. Demographic characteristics of the experimental and control groups

Variable		Experimental group (n = 85)		Control group (n = 84)		p value
		n	[%]	n	[%]	
Age [years]	Less than 40	26	30.9	35	41.2	p = 0.929
	40–49	30	35.7	18	21.2	t* = 0.089
	More than 50	28	33.3	32	37.6	
Gender	Male	47	56	53	62.4	p = 0.397
	Female	37	44	32	37.6	χ^{2**} = 0.716
Marital status	Married	72	9.5	64	75.3	p = 0.346
	Single	8	85.7	14	16.5	χ^2 = 1.275
	Divorced/widow	4	4.8	7	8.3	
Economic situation	Weak	31	36.9	25	29.4	p = 0.098
	Good	49	58.3	48	56.5	χ^2 = 4.647
	Average	4	4.8	12	14.1	
Level of education	Less than diploma	28	33.3	20	23.5	p = 0.36
	Diploma	20	23.8	22	25.9	χ^2 = 2.043
	University	36	42.9	43	50.6	
History of cancer surgery	Yes	30	35.3	24	28.6	p = 0.714
	No	55	64.7	60	71.4	χ^2 = 0.008
Family history of cancer	Yes	49	58.3	49	57.6	p = 0.928
	No	35	41.7	36	42.4	χ^2 = 0.008
Type of cancer	Stomach	22	26.2	23	27.1	p = 0.897
	Colorectal	45	35.6	46	54.1	χ^2 = 1.082
	Breast	13	15.5	10	11.8	
	Liver	14	4.8	6	7.1	
Stage of cancer	First	3	3.6	5	5.9	p = 0.928
	Second	43	51.2	50	58.8	χ^2 = 0.008
	Third	37	44	30	35.3	
	Forth	1	1.2	0	0	

*Independent t-test; **Chi-squared test

shows the participants' demographic characteristics in both groups. As can be seen, the patients in both groups were homogeneous in terms of age (using an independent-samples t-test), gender, marital status, economic status, level of education, history of cancer surgery, family history of cancer, and type and stage of cancer (using a Chi-squared test; $p > 0.05$). A comparison of the pretest scores on the presence of meaning, search for meaning, and meaning in life using the independent samples t-test (Tab. 3) indicated no statistically significant difference between both groups before the spirituality-based education. However, a comparison of the scores of the patients in both groups after the education suggested a significant increase in the scores of the presence of meaning, search for meaning, and meaning in life for the patients in the experimental group ($p = 0.001$). Furthermore, the results of paired samples t-test presented in Table 3 showed no statistically significant difference in the scores for the presence of meaning, search for meaning, and meaning in life for the patients in the control group one month after the education compared to their pre-education scores. In contrast, there were significant differences in the scores for the three variables for the patients in the experimental group one month after the education compared to their pre-education scores ($p = 0.001$).

Discussion

The results of the present study confirmed the hypothesis that the implementation of spirituality-based

Table 3. Comparison of the meaning-of-life scores in the experimental and control groups

Subscales		Pretest		Posttest		p value (paired t-test)
		Mean	Standard Deviation	Mean	Standard Deviation	
Presence	Experimental group	21.73	2.51	28.66	3.86	t = 15.74; df = 83; p = 0.001
	Control group	24.34	3.79	24.35	3.62	t = 0.06; df = 84; p = 0.947
	p value (independent t-test)	t = 5.25; df = 167; p = 0.492		t = 6.02; df = 167; p = 0.001		
Search	Experimental group	23.28	3.9	28.58	3.69	t = 11.69; df = 83; p = 0.001
	Control group	23.14	3.32	23.48	3.17	t = 2.33; df = 84; p = 0.022
	p value (independent t-test)	t = 1.42; df = 167; p = 0.796		t = 4.12; df = 167; p = 0.001		
Total score for meaning in life	Experimental group	45.02	5.56	57.25	7.33	t = 15.49; df = 83; p = 0.001
	Control group	47.48	6.58	47.83	6.1	t = 1.28; df = 84; p = 0.202
	p value (independent t-test)	t = 2.62; df = 167; p = 0.374		t = 6.22; df = 167; p = 0.001		

education for cancer patients leads to improved meaning in their lives. Since cancer is a life-threatening disease, cancer patients have spiritual needs that must be met [29]. Accordingly, a study in Brazil showed that cancer changes the meaning of a person's life, and patients' meaningful values can form the basis for spiritual interventions for them [30].

In this study, spirituality-based education for cancer patients improved the presence of meaning in their lives. The presence of meaning in life for a person is characterized by having a clear and satisfying purpose in life, having a good sense of what makes life meaningful, and understanding the meaning of life for the person. However, the presence of meaning in life for cancer patients can fluctuate for a variety of reasons. For instance, a study in Oman showed that patients experience disrupted meaning in their lives after being diagnosed with cancer, and as a result, the presence of meaning in their lives is impaired [31]. Furthermore, a study in Spain also showed that whenever cancer patients experience a lot of stress, they have trouble finding meaning in their lives [32]. Another study in Turkey showed that when cancer patients have problems with the presence of meaning in life, their psychological capacity decreases [33]. In these circumstances, nurses must perform spirituality-based education. In a similar vein, the results of a systematic review indicated that nursing interventions can reduce the spiritual distress of people with cancer and improve the presence of meaning in their lives [25].

The data in the present study demonstrated that the implementation of a spirituality-based education for cancer patients led to an improvement in their search for meaning in life. In fact, striving to find meaning in life is one of the spiritual needs of cancer patients [34] because it helps them to answer questions about why they live and why they should live happily [35]. Accordingly, research has shown the benefits of seeking meaning in life for cancer patients. The results of a study in Italy showed that cancer patients who sought meaning in their lives experienced lower levels of psychological distress. In fact, they experienced lower levels of anxiety and depression and had better religious orientation [36]. The results of a study in Korea also found that whenever cancer patients searched for the meaning of a better life, their spiritual well-being and coping skills improved accordingly [37]. Thus, as the search for meaning is important for cancer patients, it needs to be promoted through spirituality-based education.

In addition, the results of the present study showed that the implementation of spirituality-based education for cancer patients improves the overall meaning of life for them. It seems that spirituality-based education by emphasizing concepts such as spiritual self-awareness, ways to deal with fear and anxiety, ways to gain peace, trusting God, how to take care of good heritage, forgiveness, and use of problem-solving skills with a spiritual approach, has been able to improve the meaning of life of cancer patients. Given that cancer can affect

the meaning of life in patients [38], the implementation of spirituality-based education to promote the meaning of life in these vulnerable people is necessary because the meaning of life can contribute to enhancing their mental health. Accordingly, a study in Lithuania showed that the meaning of life increases cancer patients' ability to cope with psychological distress [39]. Furthermore, the implementation of spiritual interventions while improving the meaning of life of cancer patients, which was confirmed in this study, can bring other positive effects for these patients. A study in Nigeria indicated that spiritual education could increase the quality of life of cancer patients. The educational content includes the need for spirituality, use of spiritual coping with health challenges, communication and relationships based on trust, spiritual support, and resilience to overcome adversity [22]. In that study, in line with our research, use of spiritual coping with health challenges has led to a positive effect on education. In Indonesia, coping and spiritual well-being of cancer patients increased after receiving spiritual education. The educational content included relaxation for anxiety reduction, the role of God in conflict resolution in life, self-control, and prayer therapy [24]. In that study, in line with what we found, overcoming anxiety through a spiritual approach has led to a positive effect on education. In Iran, spiritual education could promote hope and spiritual well-being of cancer patients. The educational content included the relationship with God, meaning of life, self-actualization, hope, and forgiveness [23]. In the above study, similar to our findings, relationship with God, meaning of life, and forgiveness have led to a positive effect on education. However, the results of some systematic review studies have reported that spirituality-based education has no effect on improving the psychological adjustment of cancer patients [26], and the implementation of spiritual education for people with chronic diseases, including cancer, has little effect on improving their quality of life [27]. Such contradictions warrant the need for further studies in this field.

Given that the spirituality-based education in this study promoted the meaning of life in different dimensions for cancer patients and had other benefits in other mentioned studies, it seems that such education affects participants and is effective.

The cancer patients in the control group participating in this study did not report improvement in their sense of meaning of life due to a lack of spirituality-based education. Similarly, systematic reviews of spiritual interventions for cancer patients showed no improvement in the control groups [17, 25]. Considering the benefits of spirituality-based education, more extensive programs need to be delivered for more cancer patients in this field so that all of them can benefit from this type of education.

This study was conducted with some limitations. For instance, the mental states of individuals could affect their responses to the questionnaire, which was beyond the control of the researcher. In addition, due to the COVID-19 outbreak, it was not possible to conduct the intervention in person for hospitalized patients. In this study, spirituality-based education was conducted online, which was one of the innovations of this study due to the flexibility of this method. However, similar studies need to be performed with the participation of hospitalized cancer patients.

Conclusions

The results of this study indicated that spirituality-based education can be one of useful, effective, and applicable educational techniques to improve the meaning of life in cancer patients. As mentioned, cancer patients have problems finding meaning in their lives and are spiritually harmed. Thus, the findings of this study can be a step towards the implementation of spirituality-based education for people with cancer to improve their sense of meaning in life, their search for meaning in life, and the meaning in life in general. Following these findings, nurses working in oncology wards need to get familiar with the content of spirituality-based education for patients so that they can deliver it to patients in clinical settings if needed.

Article Information and Declarations

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement

The study was conducted according to the criteria set by the declaration of Helsinki.

Author contributions

All authors contributed to this project and article equally.
All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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ORIGINAL ARTICLE

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Survival outcomes of patients diagnosed with muscle-invasive bladder cancer who showed a response after neoadjuvant chemotherapy and refused radical cystectomy, and patients who had radical cystectomy or received chemoradiotherapy

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ABSTRACT

Introduction. We aimed to compare the survival results of patients with muscle-invasive bladder cancer who responded after neoadjuvant chemotherapy (NAC) and did not accept further treatment and those who underwent radical cystectomy or received chemoradiotherapy (CRT).

Material and methods. The study included 53 patients with non-metastatic muscle-invasive bladder cancer who received NAC between 2009 and 2020. Clinical findings and post-NAC survival analysis were evaluated. Survival analyses of patients who underwent radical cystectomy (RC) after NAC, received CRT, and refused treatment were compared.

Results. The median age at diagnosis was 61 (33–80) years. After NAC, 18 patients (34%) received CRT, 9 patients (17%) underwent RC, and 18 patients (34%) refused further treatment. Complete response (CR) was present in 10 (18.4%) patients, partial response (PR) in 35 (66%) patients, stable disease (SD) in 1 (1.9%) patient, and progression in 7 (13.2%) patients. Median overall survival (OS) was 78 months. Median OS was not reached in the RC arm; it was 97 months in the CRT arm and 78 months in the declined-treatment arm. There was no statistical difference between the arms ($p = 0.94$). Median disease-free survival (DFS) was 32 months. Median DFS in the RC arm was 30 months, in the CRT arm — 34 months, and 28 months in the declined-treatment arm after NAC. There was no statistically significant difference between the arms ($p = 0.74$).

Conclusions. We did not find any difference in terms of OS and DFS between patients who after NAC underwent RC, CRT, or refused treatment.

Keywords: chemoradiotherapy, neoadjuvant chemotherapy, muscle-invasive bladder cancer, radical cystectomy, refused treatment

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Introduction

Approximately 20–30% of patients with bladder cancer are diagnosed in the muscle-invasive stage [1]. Even after radical cystectomy (RC), more than 50% of muscle-invasive bladder cancer patients relapse, usually within 2 years [2]. Currently, the standard treatment for muscle-invasive bladder cancer is considered to be RC and bilateral pelvic lymph node dissection (PLND) after cisplatin-based neoadjuvant chemotherapy (NAC), which is specified in most clinical guidelines worldwide [3]. RC after NAC for patients with good performance, and chemoradiotherapy (CRT) after NAC as an alternative for selected, well-informed and compliant patients, especially those for whom radical cystectomy is not an option or is not acceptable, is recommended by the European Association of Urology [4]. Gemcitabine, cisplatin (GC) and methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) are given as NAC regimens [5–7]. Trimodality therapy (TMT) is an organ-sparing method that includes concurrent CRT after transurethral resection of the bladder (TUR-B). NAC is an important part of TMT, which has shown that CRT provides better survival than radiotherapy (RT) alone [8]. Although the effect of NAC on TMT is not fully known, there are increasing reports that adding NAC to TMT may improve survival for these patients [9, 10]. In this study, we aimed to compare the survival outcomes of patients who underwent RC or CRT after NAC and patients who showed a partial response (PR) or complete response (CR) after NAC and were followed up without treatment because they refused it.

Material and methods

The files of 469 patients diagnosed with bladder cancer who applied to the Dicle University Medical Oncology Department between 2009–2020 were scanned. Patients who were metastatic at diagnosis and did not receive NAC and those whose records could not be accessed were excluded from the study. Patients who were eligible for platinum (cisplatin or carboplatin) for neoadjuvant chemotherapy, aged ≥ 18 years, with an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and at least 1 cycle of chemotherapy were included in the study. Fifty-three patients who were diagnosed with non-metastatic muscle-invasive bladder cancer at the time of diagnosis and given NAC were included in the study. Age, sex, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), tumor location in the bladder, additional comorbid disease status, renal failure status, neoadjuvant treatment regimen, type of treatment applied after neoadjuvant chemotherapy, and post-relapse progression treatments were examined. NAC was given as either cisplatin and gemcitabine or carboplatin and gemcitabine. Cisplatin 75 mg/m^2 or carboplatin at an area under the curve (AUC) dose of 4–6 mg/mL per minute on the 1st day; gemcitabine 1000 mg/m^2 was given on the 1st and 8th days at 21-day intervals. After NAC, external radiotherapy (60–66 Gy) to the bladder and pelvic lymph nodes was given for 6 weeks at 25–40 mg/m^2 weekly with concomitant cisplatin or carboplatin (AUC 2). Patients with a diagnosis of low and high-grade urothelial cell carcinoma were included in the study, while patients with a diagnosis of bladder cancer with variant histology were excluded. Pathological T2-4, clinical N0-3, and M0 patients were included in the study. Response status after NAC was evaluated with control TUR-B, chest-whole abdomen computed tomography (CT), and/or FDG positron emission tomography (PET-CT) scans.

Statistics

Statistical analyzes were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, USA). Supplementary statistics were used to evaluate patient characteristics and parameter frequency, and Kaplan-Meier survival analysis was used for survival analysis. Based on the log-rank P value. Cox regression analysis and Enter method were used for univariate analysis in survival analysis. The confidence interval was accepted as 95%, with significance $p < 0.05$.

Results

Fifty-three patients diagnosed with non-metastatic muscle-invasive bladder cancer were included in our study. Forty-eight patients (90.6%) were male and 5 patients (9.4%) were female. The median age was 61 (33–80) years. Twenty-five patients (47.2%) were < 65 years old and 28 patients (52.8%) were ≥ 65 years old. The ECOG performance score of 12 patients (22.6%) was 0 and the ECOG performance score of 41 patients (77.4%) was 1–2. The characteristic features of the patients are presented in Table 1.

Considering the NAC responses; there was CR in 10 (18.4%) patients, PR in 35 (66%) patients, SD in 1 (1.9%) patient, and progression in 7 (13.2%) patients (Tab. 2). After NAC, CR was achieved in 10 patients, RC was performed in 1 of these patients, CRT was given to 2 patients, and 7 patients were followed up because they refused treatment. After NAC, PR was achieved in 32 patients. RC was performed in 8 of the patients who showed PR, CRT was given to the other 14 patients, and the remaining 10 patients were followed up because they refused treatment. While recurrence did not develop in 1 patient who had CR after NAC

Table 1. Baseline characteristics of the patients

Parameters	n (%)
Median age (range)	61 (33–80)
Age [years]	
< 65	25 (47.2)
≥ 65	28 (52.8)
Sex	
Male	48 (90.6)
Female	5 (9.4)
ECOG PS	
0	12 (22.6)
1–2	41 (77.4)
Tumor grade	
Low	6 (11.3)
High	47 (88.7)
Tumor (pT)	
T2	38 (71.7)
T3	8 (15.1)
T4	7 (13.2)
Lymph node (cN)	
N0	20 (37.7)
N1	13 (24.5)
N2	18 (34)
N3	2 (3.8)
Tumor location in the bladder	
Left lateral	13 (24.5)
Anterior	12 (22.6)
Tumor location in the bladder	**n (%)**
Diffuse	11 (20.8)
Posterior	8 (15.1)
Right lateral	7 (13.2)
Trigon	2 (3.8)
Co-morbidities	
No	19 (35.8)
Yes	34 (64.2)
Renal failure	
No	42 (79.2)
Yes	11 (20.8)
Neoadjuvant treatment regimens	
Cisplatin + gemcitabine	45 (84.9)
Carboplatin + gemcitabine	8 (15.1)
Modality after neoadjuvant therapy	
Cystectomy	9 (17)
Chemoradiotherapy	18 (34)
Refused treatment	18 (34)
Chemotherapy	2 (3.7)
Radiotherapy	1 (1.9)
Exitus	5 (9.4)
Metastatic first-line therapy	
Cisplatin and gemcitabine	8 (15.1)
Carboplatin and gemcitabine	1 (1.9)
Carboplatin and paclitaxel	3 (5.7)
Treatment Denied	9 (17)

ECOG — Eastern Cooperative Oncology Group; PS — performance score

Table 2. Response rates after neoadjuvant chemotherapy

Responses	n (%)
Complete response	10 (18.4)
Partial response	35 (66)
Stable disease	1 (1.9)
Progression	7 (13.2)

and underwent RC, progression developed in 4 (50%) of 8 patients who underwent RC after PR was achieved. Since CR was achieved after NAC and the patients did not accept RC, 2 patients who were given CRT did not relapse, but progression developed in 6 (42%) of 14 patients who received CRT after PR was achieved. Recurrence and progression developed in 2 (28%) of 7 patients who showed CR after NAC and were followed up because of treatment refusal. Progression developed in 6 (60%) of the 10 patients who were followed up after NAC with PR because they refused treatment.

In the overall survival (OS) and disease-free survival (DFS) analysis, 5 patients who died during or immediately after NAC, 2 patients who were given chemotherapy due to progression after NAC, and 1 patient who received radiotherapy were not included. Survival analysis was performed for the remaining 45 patients. Median OS was 78 months (Fig. 1). While median OS could not be reached in the RC arm, in the CRT arm, median OS was 97 months [hazard ratio (HR) = 0.88; 95% confidence interval (CI) 0.21–3.8; p = 0.88), and 78 months in the declined-treatment arm of patients who were followed up without treatment because of response after NAC (HR = 1.1; 95% CI 0.27–4.4; p = 0.88). No statistically significant difference was found between the three arms (p = 0.94) (Tab. 3, 4). Median DFS of all patients was 32 months (Fig. 2). In the RC arm, median DFS was 30 months (p = 0.75), in the CRT arm — 34 months (HR = 0.79; 95% CI 0.23–2.7; p = 0.70), and in the declined-treatment arm — 28 months (HR = 1.1; 95% CI 0.35–3.76; p = 0.80).

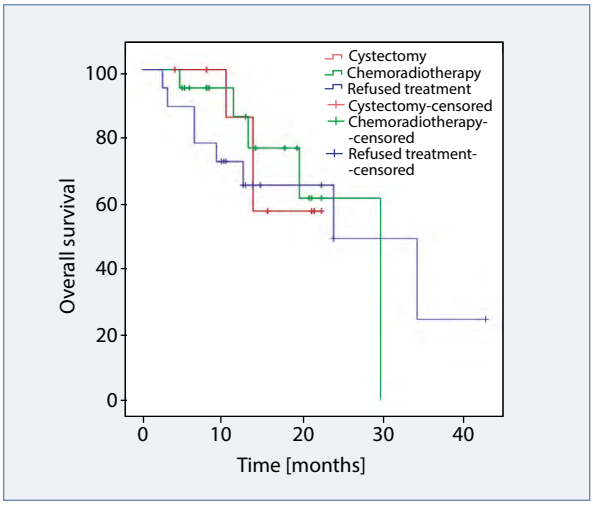

Figure 1. Overall survival of the three groups after neoadjuvant chemotherapy

Table 3. Overall survival according to treatment choice after Neoadjuvant chemotherapy

Variables	HR	95% CI	p value*
Cystectomy	Reference		0.94
Chemoradiotherapy	0.88	0.21–3.8	0.88
Refused treatment	1.1	0.27–4.4	0.88

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio

Table 4. Disease-free survival according to treatment choice after neoadjuvant chemotherapy

Variables	HR	95% CI	p value*
Cystectomy	Reference		0.75
Chemoradiotherapy	0.79	0.23–2.7	0.70
Refused treatment	1.1	0.35–3.7	0.80

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio

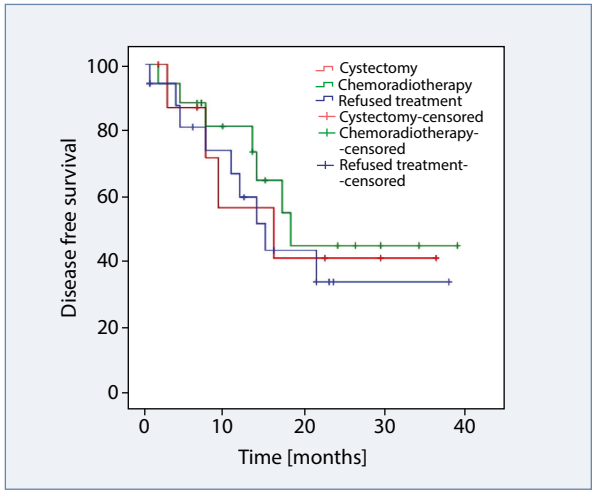

Figure 2. Disease-free survival of the three groups after neoadjuvant chemotherapy

Table 5. Survival outcomes according to treatment choice after neoadjuvant chemotherapy

	Overall survival [months]			Disease-free survival [months]		
	Median	95% CI	p value*	Median	95% CI	p value*
All patients	78		0.94	32		0.74
Cystectomy	NR	NR		30		
Chemoradiotherapy	97	0.21–3.8		34	0.23–2.7	
Refused treatment	78	0.27–4.4		28	0.35–3.7	

*p significance value < 0.05; CI — confidence interval; HR — hazard ratio; NR — not reached

There was no statistically significant difference between the arms (p = 0.74) (Tab. 4, 5).

Median OS was 78 months in patients receiving neoadjuvant cisplatin plus gemcitabine, and 43 months in patients receiving carboplatin plus gemcitabine. Median OS was higher in the cisplatin-treated arm, but no statistically significant difference was found between the two groups (p = 0.82) (Fig. 3). Median DFS was 28 months in 45 patients receiving neoadjuvant cisplatin plus gemcitabine and 14 months in 8 patients receiving carboplatin plus gemcitabine. Median DFS was numerically higher in the cisplatin-treated arm, but there was no statistically significant difference between the two groups (p = 0.31) (Fig. 4).

Parameters that may affect both OS and DFS, such as age (< 65 or ≥ 65), ECOG performance score (0 or 1–2), renal failure status, pT (2 or 3–4), lymph node status, and comorbid diseases evaluated with univariate

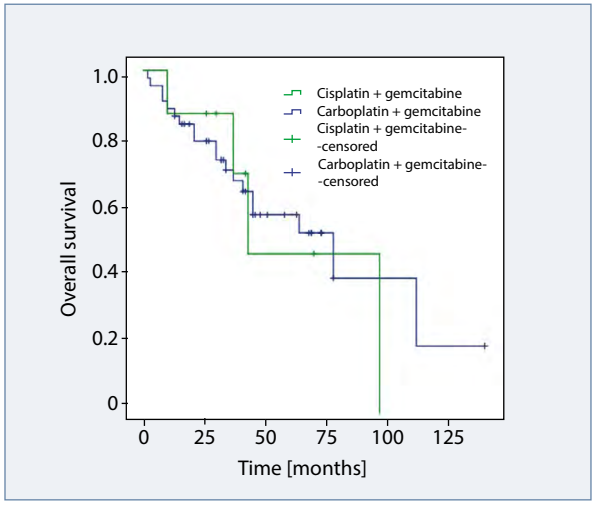

Figure 3. Overall survival with neoadjuvant chemotherapy regimens

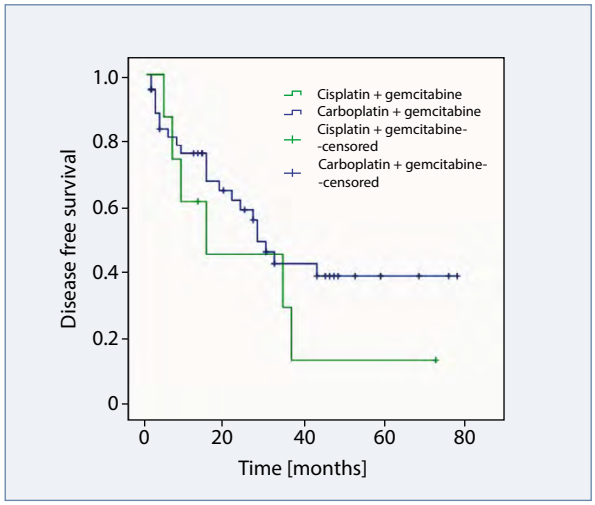

Figure 4. Disease-free survival with neoadjuvant chemotherapy regimens

and multivariate analysis, no statistically significant difference was found.

Discussion

Bladder cancer is the 6th most common cancer in the USA and is usually diagnosed in the elderly. Approximately 20–30% of patients have muscle-invasive bladder cancer at diagnosis. Since most of the pa tients are in the 6th and 7th decades at diagnosis, these patients have additional comorbidities. The general approach accepted worldwide in the treatment of muscle-invasive bladder cancer is RC and PLND after NAC. In patients with muscle-invasive bladder cancer who do not accept RC, TMT is the treatment option recommended by professional community guidelines. In TMT, after TUR-B, definitive CRT is given, and the bladder is thus protected. However, even in the case of a complete response after TMT, recurrences may occur in bladder cancer. There are no prospective randomized studies on active follow-up or CRT in patients who have a complete or partial response after neoadjuvant chemotherapy and do not accept radical cystectomy.

In the past, RC alone was performed by urologists before NAC treatment, and high recurrence rates were encountered. Considering previous studies on this subject; five-year recurrence-free survival (RFS) for pT2, pT3a, pT3b, pT4, and node-positive disease in patients who underwent RC without NAC was found to be 89%, 78%, 62%, 50%, and 35%, respectively [11]. It was assumed that NAC therapy could improve outcomes, and this view was also supported by randomized phase III studies [12–15]. Randomized controlled studies and meta-analyses have shown that administering NAC before RC has an additional 5% OS benefit [13, 15, 16]. In another study, it was shown that RC after platinum-based NAC was associated with a 5% OS and 9% DFS increase compared to pre-determined RC [17]. In a study by Grossman et al., which followed patients for over 11 years, 154 patients were assigned to the RC alone group and 153 to the NAC after RC group. Median OS was 46 months in patients who underwent RC alone, compared to 77 months in patients who underwent RC after NAC ($p = 0.06$). The group of patients who underwent RC after NAC had significantly less residual disease compared to the group of patients who underwent RC alone (38% *vs.* 15%; $p < 0.001$) [13].

In studies, high objective response rates were obtained after NAC. For example, in a study by Nowak-Sadzikowska et al. [18] on muscle-invasive bladder cancer, after NAC CR was obtained in 8 patients (30%), PR was obtained in 13 patients (48%), and SD was obtained in 6 patients (22%). In that study, response assessment after NAC was performed with control TUR-B and pelvic CT [18]. In a study by Hafez et al. on non-metastatic muscle-invasive bladder cancer, the rate of patients who achieved CR after NAC was found to be 60%. In that study, response evaluation was performed 3 weeks after NAC with repeat cystoscopy and, if possible, tumor biopsy, while radiological evaluation (CT and/or MRI) was also performed to support clinical decision-making. The study defined CR as the absence of residual tumor. If no disease was visible on endoscopic biopsy, this was considered a CR. PR was defined as pathologically downstaging to pTa, pT1, pTis, or evidence of radiological response [19]. In another study, CR was achieved in 78% of patients after NAC [20]. In our study, after NAC,

CR was obtained in 10 (18.4%) patients, PR in 35 (66%) patients, and SD in 1 patient (1.9%). We applied control TUR-B to all patients after neoadjuvant chemotherapy. It was accepted that CR was present in 10 patients with no signs of disease on TUR-B, FDG/PET-CT, or CT. Thirty-five patients with < T2 pathology in the control TUR-B and with a response on their imaging were considered as PR.

In previous TMT studies where the benefit of NAC was not clearly defined, NAC was generally not administered before CRT [21–25]. In six Radiation Therapy Oncology Group (RTOG) compilation studies, it was found that 32% of the patients were treated with TMT after NAC [21]. In a review by Giacalone et al. [26], it was found that 25% of patients treated with TMT received NAC. Good evaluation of tumor response after NAC may be an important selection criterion for TMT. The probability of bladder preservation is significantly lower in patients who do not respond to NAC, and direct RC should be considered [13, 19, 27]. In a study in which CRT was given after NAC, CR was obtained in 32 patients (78.04%). RC was performed in 6 (21%) of 9 patients who did not get a CR, and chemotherapy was applied in 3 patients [20]. In the study of Sadzikowska et al. CR was obtained in 18 patients (67%) treated with CRT after NAC [28]. In a review examining the bladder-sparing method, it was shown that TMT had better survival outcomes than RC or RC after NAC [29]. In a study of patients who refused cystectomy after NAC for muscle-invasive bladder cancer, the number and size of invasive tumors were strongly associated with overall survival. In the above study, restaging (second) TUR-B was performed 2–6 weeks after the first TUR-B and was intended to resect all visible or suspected muscle-invasive tumors. Only patients who had muscle-invasive cancer on the second TUR-B had received NAC. In this study, the most important treatment variable predicting better survival was the complete resection of the invasive tumor at restaging TUR-B before starting NAC [30]. In some studies, the bladder-sparing method was found to provide a better quality of life compared to RC without affecting survival [31]. Many studies currently accept the bladder-sparing method in muscle-invasive bladder cancer as an alternative approach. In our study, CR was achieved in 11 (68%) of 18 patients who received CRT after NAC.

A complete response to NAC is the main determinant of survival for patients undergoing cystectomy, but whether the complete response is permanent is unknown if cystectomy is not performed after NAC. In a collaborative study of 118 patients, 5-year cystectomy-free survival, RFS, DFS, and OS after NAC were 76%, 64%, 90%, and 86%, respectively. However, 11% of these patients relapsed with muscle-invasive bladder cancer, and only 4 of 26 patients who underwent rescue RC died due to bladder cancer [32]. It has been stated that chemotherapy alone should not be advocated in the treatment of non-metastatic muscle-invasive bladder cancer because many patients will relapse due to residual disease if RC is not performed, and chemotherapy alone is acceptable in the selected patient group [33]. NAC alone is limited to patients who are scheduled for RC after NAC but achieve a clinical complete response and do not want RC because of this complete response. In our study, recurrence and progression developed in 2 (28%) of 7 patients who had CR after NAC and were followed up because they refused treatment; progression developed in 6 (60%) of 10 patients who had PR after NAC and were followed up because of refusing treatment. Therefore, treatment response after NAC can be used as a predictor of long-term survival.

The limitations of our study were its retrospective character, inadequacy of the patient files related to treatment-related side effects, and the small number of patients.

Conclusions

In conclusion, there was no difference in OS and DFS between patients who underwent RC, received CRT, or refused treatment after NAC. These data need to be confirmed by further studies in a large population to recommend treatment-free follow-up for patients who achieved CR after NAC but refused CRT and RC.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles defined in the Declaration of Helsinki (approval no: 130/2022).

Author contributions

S.T.: conception and design of the study, writing of the article; Z.U.: data analysis and interpretation; S.E.: data analysis and interpretation; S.I.: acquisition of clinical data; Z.K.: acquisition of clinical data; Z.O.: acquisition of clinical data; M.K.: acquisition of clinical data; M.A.K.: data analysis and interpretation; A.I.: data analysis and interpretation.

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Conflict of interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Supplementary material

None.

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ORIGINAL ARTICLE

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EGFR mutation and *ALK* fusion-positive non-small cell lung cancer: a multicenter prospective cohort study in Nagano Prefecture, Japan

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ABSTRACT

Introduction. We prospectively examined current clinical practices in patients with inoperable epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) fusion-positive (*EGFR*$^+$ and *ALK*$^+$, respectively) non-small cell lung cancer (NSCLC) in Nagano Prefecture, Japan.

Material and methods. The study population consisted of newly diagnosed patients with inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in 14 hospitals in Nagano between May 2016 and March 2019. Both initial and subsequent treatment decisions were made at the discretion of the attending physician.

Results. A total of 281 patients with *EGFR*$^+$ NSCLC (mean age, 74 years, 59.1% female) and 26 patients with *ALK*$^+$ NSCLC (mean age, 66 years, 53.8% female) were included in the study. The study population consisted of 148/107/29/20/3 cases with performance status 0/1/2/3/4 and 6/2/31/194/75 cases with clinical stage I/II/III/IV/recurrence, respectively. First-line therapy with tyrosine kinase inhibitors was performed in 259 (92.2%) and 22 (84.6%) patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC, respectively. The median overall survival rate was 41.2 months (95% CI 36.8–45.6 months) with *EGFR*$^+$. It was not reached with *ALK*$^+$.

Conclusions. This observational analysis represents a valuable resource for evaluating the outcomes of treatment in patients with NSCLC.

Keywords: EGFR-TKI, non-small cell lung cancer, ALK inhibitor, cohort study

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Introduction

Lung cancer is the most common malignant disease and the leading cause of death from cancer both worldwide [1] and in Japan [2, 3]. The most common histological type is non-small cell lung cancer (NSCLC), which is predominantly non-squamous NSCLC [3]. Molecular targeted agents, such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and abnormal fusion of anaplastic lymphoma kinase (ALK)-TKIs, have markedly improved overall survival in populations with these targetable genetic alterations [4–12].

The 2016 Japan Lung Cancer Society Guidelines for Treatment of Lung Cancer recommended testing for *EGFR* gene mutation and *ALK* fusion [13], with corresponding TKI treatment as first-line chemotherapy in patients with non-squamous NSCLC whose tumors harbored *EGFR* mutation (*EGFR*$^+$) or *ALK* fusion (*ALK*$^+$). These TKIs have been confirmed to be useful in several clinical studies, especially as first-line therapy [4–11]. In addition, newly developed TKIs targeting *EGFR*$^+$ [10] and *ALK*$^+$ tumors [14, 15] have become available and have been shown to prolong the period of progression-free survival. These new agents could increase the opportunities for choice of first-line or subsequent therapies and may contribute to prolongation of overall survival in *EGFR*$^+$ and *ALK*$^+$ NSCLC. However, real-world data on serial treatment outcomes in patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC are limited [4–8].

This prospective multicenter observational study aimed to evaluate the initial treatment patterns and outcomes in newly diagnosed treatment-naive cases of inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture, Japan. The study evaluated the real-world data of clinical practice and outcomes of patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture.

Material and methods

Patients and data collection

Patients eligible for inclusion in this prospective study were registered at the Cancer Center, Division of Clinical Oncology, Shinshu University School of Medicine, Shinshu University Hospital. The inclusion criteria were newly diagnosed (between May 6, 2016, and March 31, 2019) histologically or cytologically confirmed NSCLC, no prior history of therapy or recurrence following thoracic surgery, or inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC. Patients in whom surgery was inappropriate for medical reasons, such as advanced age, cardiovascular disease, poor pulmonary function, etc., were also enrolled in the study. Consecutive patients were enrolled sequentially in each of the 14 participating hospitals in Nagano prefecture (Tab. S1) to avoid selection bias. Anonymization was performed before registration in each participating hospital, and the anonymized data on baseline demographic and clinical characteristics, including age, sex, smoking history, performance status (PS), histological findings, and clinical stage, were collected from serial case report forms.

The study protocol was approved by the institutional review board of Shinshu University School of Medicine (No. 3407, 10/May/2016, UMIN000003645) and the ethics committee of each participating hospital. Histological diagnosis and NSCLC stage were determined according to the World Health Organization (WHO) classification (version 7 up to 2016, version 8 after 2017), and PS was estimated according to the Eastern Cooperative Oncology Group (ECOG) classification.

EGFR mutations were analyzed using real-time polymerase chain reaction or next-generation sequencing. Patients with any type of *EGFR* mutation were eligible for inclusion in the study; exon 19 deletion and exon 21 L858R susceptibility mutations were classified as common mutations and rare *EGFR* mutations were classified as uncommon. The details of clinical analysis and outcomes in patients with rare *EGFR* mutations were reported previously [16]. ALK fusion was examined by immunohistochemical analysis and/or fluorescence in situ hybridization.

The agents first received after diagnosis were defined as first-line treatments in the present study. Palliative radiotherapy for bone and brain metastases was not included as first-line treatment, but radical radiotherapy, such as stereotactic body radiotherapy (SBRT), was considered first-line treatment. Decisions regarding treatment and choice of TKI were made at the discretion of the attending physician. The types of drugs given as initial treatment were also registered at baseline. We recorded the responses, toxicities, subsequent therapies, and clinical outcomes at 4-monthly intervals. When using individual information, patient privacy was protected in accordance with ethical requirements.

The present study was performed to investigate the real-world first-line treatment practices and survival in patients with inoperable *EGFR*$^+$ and *ALK*$^+$ NSCLC in the Nagano prefecture, Japan. Survival analysis was censored on December 31, 2021. Analysis of overall survival (OS), defined as the interval from the initial date of induction therapy to the date of death or the last follow-up visit, was performed using Kaplan-Meier plots, and the median and 95% confidence interval (CI) was determined. Statistical analyses were performed using NZR Statistics. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

Results

Clinical characteristics

The study population consisted of 281 patients with *EGFR*$^+$ NSCLC [115 men, 40.9% and 166 women, 59.1%; median age, 74 years (range: 34–93 years)]

Table 1. Patient characteristics

Baseline characteristics	*EGFR* n = 281 (%)	*ALK* n = 26 (%)
Median age (range) [years]	74 (34–93)	66 (33–80)
Sex		
Male	115 (40.9%)	12 (46.2%)
Female	166 (59.1%)	14 (53.8%)
Performance status		
0	131 (46.6%)	17 (65.4%)
1	103 (36.7%)	4 (15.4%)
2	24 (8.5%)	5 (19.2%)
3	20 (7.1%)	0
4	3 (1.7%)	0
Smoking history		
Never	172 (61.2%)	13 (50.0%)
Former	92 (32.7%)	11 (42.3%)
Current	17 (6.1%)	2 (7.7%)
Histological type at initial diagnosis		
Adenocarcinoma	273 (97.2%)	26 (100%)
Other	8 (2.8%)	0
Stage		
I	6 (2.1%)	0
II	2 (0.1%)	0
III	27 (9.6%)	4 (15.4%)
IV	176 (62.6%)	18 (69.2%)
Recurrence	70 (24.9%)	4 (15.4%)

Table 2. Initial and second-line therapies in patients with *EGFR*-mutant (A) and *ALK* fusion-positive (B) non-small cell lung cancer

A. *EGFR*

Initial Therapy	n = 281 (%)	Second therapy (n)
TKIs		
Gefitinib	116 (41.3%)	Chemotherapy (26), osimertinib (22), afatinib (9), eroltinib (7), radiation (1), none (38)
Erlotinib (± bevacizumab)	39 (13.9%)	Chemotherpy (12), osimertinib (14), afatinib (3), gefitinib (3), surgery (1), none (3)
Afatinib	60 (21.3%)	Chemotherpy (24), osimertinib (14), erlotinib (1), gefitinib (7), none (7)
Osimertinib	44 (15.6%)	Chemotherpy (14), gefitinib (3), afatinib (2), none (14)
Cytotoxic chemotherapy	11 (3.9%)	Osimertinib (2), afatinib (2), eroltinib (2), gefitinib (5)
Chemoradiation	2 (0.7%)	Chemotherapy (1)
Radiation	4 (1.4%)	None (3)
Best suportive care	5 (1.8%)	

B. *ALK*

Initial therapy	n = 26 (%)	Second therapy (n)
TKIs		
Alectinib	20 (76.9%)	Chemotherapy (5), loratinib (3), certinib (2), none (3)
Crizotinib	2 (7.7%)	Alectinib (2)
Cytotoxic chemotheraphy	2 (7.7%)	Alectinib (2)
Chemoradiation	1 (3.9%)	Chemotherapy (1)
Radiation	1 (3.9%)	Alectinib (1)

TKI — tyrosine kinase inhibitor

and 26 patients with ALK^+ NSCLC [12 men, 46.2% and 14 women, 53.8%; median age, 66 years (range: 33––80 years)]. The median observation period was 31.3 months (range: 0.2–67.6 months]). The clinical characteristics of the study population are summarized in Table 1. In the $EGFR^+$ group, 131 patients were classified as PS 0, 103 as PS 1, 24 as PS 2, 20 as PS 3, and 3 as PS 4. In the ALK^+ group, 17 patients were classified as PS 0, 4 as PS 1, and 5 as PS 2. The histological type was adenocarcinoma in most cases, but the $EGFR^+$ group also included three cases of squamous cell carcinoma, three cases of adenosquamous cell carcinoma, one case of combined small cell carcinoma, and one case classified as not otherwise specified (NOS). Most cases of $EGFR^+$ NSCLC were locally advanced and metastatic (stage III/IV: 203 cases, 72.2%), and 70 patients (24.9%) had recurrence after surgery. In addition, in the $EGFR^+$ group, six were classified as stage I, and two cases were classified as stage II and were considered medically inoperable. Concerning the types of *EGFR* mutation, 136 cases (48.4%) were positive for Del19 and 130 cases (46.3%) had L858R. Fifteen patients had uncommon *EGFR* mutations: G719X in eight cases, L861Q in four cases, S768I in two cases, and exon 19 duplications in one case. ALK^+ NSCLCs included 4 cases of stage III, 18 cases of stage IV, and 5 cases of recurrence after surgery.

Treatment choice

The first- and second-line therapies in $EGFR^+$ and ALK^+ NSCLC groups are summarized in Table 2. The most commonly used agent in the $EGFR^+$ group was gefitinib (116 cases, 41%) followed by erlotinib (39 cases, 14%), afatinib (60 cases, 21%), and osimertinib (44 cases, 16%). Among the cases treated

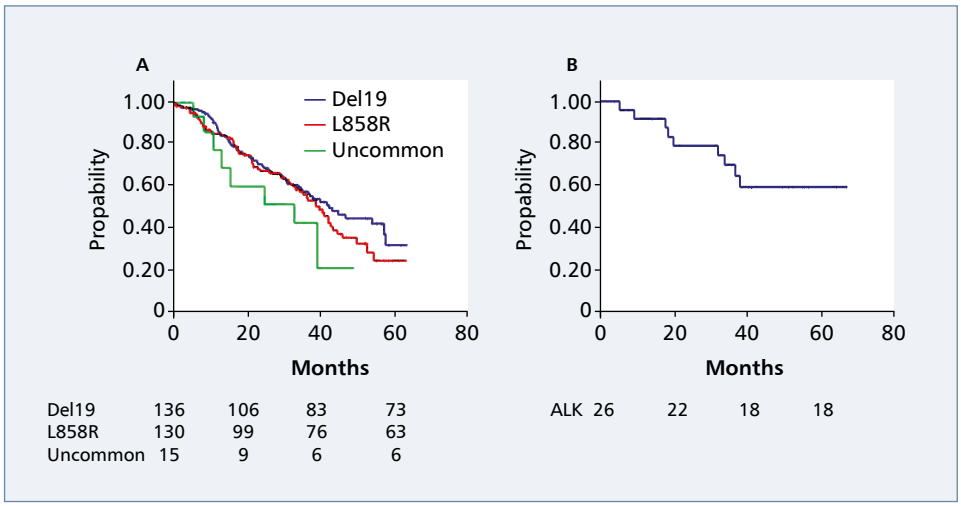

Figure 1. A. Kaplan-Meier plot of overall survival after initial therapy in patients with epidermal growth factor receptor-mutant non-small cell lung cancer; **B.** Kaplan-Meier plot of overall survival after initial therapy in patients with anaplastic lymphoma kinase fusion-positive non-small cell lung cancer

with erlotinib, 12 received bevacizumab combination therapy. Eleven cases (3.9%) were initially treated with cytotoxic chemotherapy. Platinum-doublet chemotherapy was administered in 10 cases, and non-platinum (S-1 monotherapy) was administered in one case. Platinum-based chemoradiotherapy was performed in two cases with clinical stage III. SBRT was performed in four cases classified as stage I (age > 84 years). Best supportive care (BSC), including palliative radiotherapy, was selected in five cases. Therefore, nine patients were not treated with any EGFR-TKIs or cytotoxic chemotherapy. As second-line therapy, chemotherapy was selected in 76 cases (29.3%) initially treated with EGFR-TKIs, and 82 patients (32.8%) were prescribed other TKIs. Osimertinib was used as second-line therapy in 50 cases (19.3%). All patients with *EGFR*$^+$ NSCLC receiving first-line cytotoxic chemotherapy were treated with TKLs as second-line therapy. One patient initially treated with chemoradiotherapy showed no relapse during the follow-up period. Four patients treated with SBRT did not receive further therapy, and three of these patients died.

In the *ALK*$^+$ group, alectinib and crizotinib were administered as first-line therapy in 20 cases (76.9%) and 2 cases (7.7%), respectively. Concurrent chemoradiotherapy was performed in one case classified as stage IIIb, and cisplatin plus pemetrexed chemotherapy was performed in two cases. In addition, one patient received thoracic radiotherapy at a dose of 60 Gy as first-line therapy. Although five cases were treated with chemotherapy as second-line therapy, most patients with *ALK*$^+$ NSCLC were switched to other ALK inhibitors. In one patient treated with chemoradiotherapy as first-line therapy, cytotoxic chemotherapy was selected as second-line therapy followed by ALK inhibitor as third-line chemotherapy.

Survival

The survival curves of the *EGFR*$^+$ and *ALK*$^+$ groups are shown in Figure 1A and 1B, respectively. Median OS in the *EGFR*$^+$ group was 41.3 months (95% CI 36.8–45.7 months) and was similar between the common *EGFR* mutation groups (44.0 months in the Del19 group *vs*. 40.4 months in the L858R group; log-rank test, p = 0.3) (Fig. 1A). However, median OS was significantly lower in patients with uncommon *EGFR* mutations (33.5 months; 95% CI 5.1–61.9 months) than in those with common mutations (log-rank test $p = 2 \times 10^{-5}$) (Fig. 1A). Median OS was not reached in the *ALK*$^+$ group, and the 4-year survival rate was 60.7% (95% CI 40.4–81.1%) (Fig. 1B).

Discussion

This study was performed to determine the current situation in patients with medically treated driver-positive NSCLC in Nagano prefecture, Japan. The analysis included a wide range of criteria for frail NSCLC patients who would likely have been excluded from clinical trials, and so our results reflected daily clinical practice in the treatment and management of driver gene-mutant NSCLC in Japan. We retrospectively examined the number of NSCLC patients treated during the study period in each participating hospital and estimated that 28.8% of NSCLC patients initially received TKIs. This was similar to the proportion obtained by a combined real-world analysis

of hospital-based cancer registries and diagnostic procedure surveys in Japan (33.3%) [17]. Therefore, the data in Nagano prefecture are likely to be close to the daily clinical management of NSCLC in Japan.

We found that non-TKI treatments were applied as initial therapy in 8.0% of *EGFR*$^+$ NSCLC cases and 15.4% of *ALK*$^+$ NSCLC cases, which were slightly higher than the rates of 6.7% and 6.7%, respectively, reported in a previous retrospective observational study of first-line chemotherapy for advanced and metastatic NSCLC (the BRAVE study) conducted at the same time (2017) as our observational study [18]. Non-TKI therapy was applied at high rates in *ALK*$^+$ NSCLC patients in the present study. As newly diagnosed and therapy-naive NSCLC patients were included in the present study and ALK inhibitors were selected as second-line therapy in cases of relapse after first-line chemotherapy, we speculated that the timing of *ALK* testing and/or understanding of *ALK* fusion in certain hospitals may have affected the results. For example, *ALK* testing of samples was performed only after obtaining a negative result for *EFGR* mutation.

In addition, there were nine cases (8.0%) of *EGFR*$^+$ NSCLC with no chance of receiving TKIs in the present study. Our findings in patients with *EGFR*$^+$ NSCLC treated only with BSC were clinically important for understanding the circumstances around lung cancer therapy. The mean age of these patients was 80.8 years and ranged from 68 to 89 years. The youngest patient (68 years old) had stage IV disease and PS 3. Therefore, the selection of BSC was related to advanced age and poor PS. Although EGFR-TKIs were shown to be preferred even in cases of poor PS [19, 20], our experience indicated that this treatment was not applied in some cases in clinical practice. Patients with advanced age and/or poor PS, even with driver gene-mutant NSCLC, must be taken into consideration in daily clinical practice in Nagano prefecture due to the aging of society in this region (https://www.stat.go.jp/data/nihon/02.html).

There have been several observational data studies on the survival of *EGFR*$^+$ NSCLC patients treated with EGFR-TKIs including patients outside of randomized clinical trials [4–8]. Inoue et al. [4] summarized the course of 1660 patients with *EGFR*$^+$ NSCLC treated with TKIs between 2008 and 2012 and reported median OS of 30.8 months. Subsequently, Okamoto et al. [5] reported real-world data for 1656 patients with *EGFR*$^+$ NSCLC treated mainly with first-generation TKIs (99% gefitinib and erlotinib) and reported median OS of 29.5 months. Subgroup analysis of the results of the LUX-Lung 3 phase III trial indicated median OS of 46.9 months in Japanese patients treated with afatinib [6]. Median OS of patients with *EGFR*$^+$ NSCLC in the present study was 41.0 months. As our data included a heterogeneous population of patients, i.e., those receiving only BSC or in the early stages of driver gene-mutant NSCLC, our survival rate was not comparable to those in previous clinical trials and real-world data. However, the survival data in the present study were meaningful to determining the real-world clinical outcomes in patients with *EGFR*$^+$ NSCLC. Further analyses are currently underway to elucidate the differences in survival according to the type of initial EGFR-TKI, TKI treatment sequence pattern, and types of *EGFR* mutations, which will be reported in the near future.

This study had several limitations. First, data on the rates of molecular biomarker testing in participating hospitals were not available. Therefore, our results were unable to reflect daily clinical practice, including the rates of molecular profiling. Second, we could not report a dose reduction and/or suspension of each TKI. Therefore, the clinical outcomes reported here may have been susceptible to physician treatment bias. Finally, the recognition and/or introduction of newly available TKIs may differ between participating hospitals. Nevertheless, a rigorous, and ethical multicenter survey was performed to obtain reference values for clinical practice in patients with inoperable driver-positive NSCLC in Nagano prefecture.

Conclusions

In conclusion, the results of the present study demonstrated real-world clinical outcomes in patients with *EGFR*$^+$ and *ALK*$^+$ NSCLC in Nagano prefecture, Japan. These observational analyses represent a valuable resource for evaluating treatment outcomes in patients with biomarker-positive NSCLC. We are currently planning additional analyses of the treatment sequence in these patients.

Article Information and Declarations

Data availability statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics statement

The study protocol was approved by the Institutional Review Board of Shinshu University School of Medicine (No. 3407, 10/May/2016, UMIN000003645) and the ethics committee approval from each participating hospital was obtained for the collection of anonymized data and creation of the database. The requirement for written informed consent was waived by the Institutional Review Board of Shinshu University School of Medicine.

Author contributions

T. Kobayashi, S.K., K.T., T. Koizumi: conceived and designed the study, supervised the analysis process, interpreted the data, and drafted the manuscript.
All authors contributed to treatment of enrolled patients and data acquisition.
All authors read and approved the final manuscript.

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Conflict of interest

The authors have no conflicts of interest.

Supplementary material

Supplementary Table S1.

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Supplementary material

Table S1. Participating hospitals

Hospital	Department
Nagano Municipal Hospital	Department of Pulmonary Medicine
Nagano Red Cross Hospital	Department of Pulmonary Medicine
Nagano Prefectural Shinshu Medical Center	Department of Thoracic Surgery
Nagano Matsushiro General Hospital	Department of Pulmonary Medicine
Minami Nagano Iryou Center, Shinonoi Hospital	Department of Pulmonary Medicine
Shinshu Ueda Medical Center	Department of Pulmonary Medicine
Saku Central Hospital Advanced Care Center	Department of Pulmonary Medicine
Aizawa Hospital	Department of Pulmonary Medicine
Shinshu University Hospital	First Department of Internal Medicine, Medical Oncology
Suwa Red Cross Hospital	Department of Pulmonary Medicine
Ina Central Hospital	Department of Pulmonary Medicine, Department of Thoracic Surgery
Showa Inan General Hospital	Department of Thoracic Surgery
Iida Municipal Hospital	Department of Pulmonary Medicine
Iida Hospital	Department of Thoracic Surgery

VIA MEDICA

REVIEW ARTICLE

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Selected neurological complications of oncological treatment — literature overview

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ABSTRACT

Treatment in oncology may lead to several adverse side effects, including those affecting the nervous system. These side effects may reduce the quality of life of patients, both during and after treatment, and may necessitate changes in the treatment regimen or reduction of drug doses, thus reducing the effectiveness of therapy. The knowledge of therapy-induced side effects is essential for their early recognition and differentiation from symptoms resulting from the progression of neoplastic disease, metabolic disorders, or infections, requiring prompt initiation of causal treatment. This article presents the current state of knowledge regarding central and peripheral neurotoxicity of treatment in oncology. Adverse effects described after chemo- and radiotherapy are better known but still limit the potential possibilities of the applied treatment. Neurotoxicities of targeted therapy and immunotherapy, which are of increasing importance in the era of personalization of treatment, are presented.
Keywords: neurotoxicity, chemotherapy-induced peripheral polyneuropathy, acute polyneuropathy, chemobrain, ototoxicity, plexopathy

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Introduction

Neurotoxicity of systemic treatment in oncology is the second dose-limiting effect of chemotherapy, after myelotoxicity. Toxicity affects both the central and peripheral nervous systems: it can occur already during treatment and many years after its completion. The probability of its occurrence depends on the dose of the drug, the rhythm of treatment, concomitant use of other drugs and neurotoxic substances, comorbidities of the nervous system, and individual predisposition [1, 2]. Non-selective damage of cellular DNA by chemotherapy, excessive response of the immune system against normal cells induced by immunotherapy, and in the case of radiotherapy, direct or indirect damage of nerve cells, endocrine disorders, or fibrosis of neuronal structures contribute to the development of neurotoxicity [2]. In this article, we present a review of neurological complications of treatment applied in oncology concerning the peripheral and central nervous systems.

Adverse side effects of the peripheral nervous system

Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common nervous adverse system side effects associated with oncological treat-

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ment. It is estimated that this problem affects 30–40% of patients undergoing chemotherapy [3]. It is most commonly induced by platinum derivatives, taxanes, vinca alkaloids, bortezomib, or thalidomide. CIPN can occur after a single dose of a drug or after exceeding a cumulative dose [3, 4]. Chemotherapy-induced peripheral polyneuropathy most often appears in the first two months of treatment and increases in the course of its duration [5]. There is a phenomenon of "the coasting effect" of chemotherapy-induced peripheral polyneuropathy after treatment with platinum derivatives [6, 7]. The predisposing factors of CIPN are older age, pre-existing polyneuropathy, chronic renal failure, current or past smoking, concomitant use of other neurotoxic substances, genetic predisposition [single nucleotide polymorphisms (SNPs) associated with a higher risk of CIPN] [4, 5]. CIPN manifests itself in many ways. Nerve fibers with a small cross-sectional area (C fibers) are mainly damaged, resulting in burning pain, hypersensitivity, and then loss of pain and temperature sensation. Initially, the disorder involves fingers and toes, then spreads proximally and involves larger areas of the extremities (the so-called glove and sock symptom). Patients report numbness, tingling, paresthesia, dysesthesia, and sensory disturbances. These symptoms may be accompanied by pain, lack of deep sensation, balance problems, gait impairment, and loss of ability to perform fine movements. The occurrence of peripheral polyneuropathy during chemotherapy often leads to a reduction of drug doses and sometimes to discontinuation of treatment. Both during and after treatment, peripheral polyneuropathy can significantly reduce quality of life (QoL) and have a negative impact on health status, increasing the risk of falls, inducing sleep disturbances, and contributing to psychiatric disorders (Tab. 1) [3, 6, 8]. The only drug whose efficacy

Table 1. Chemotherapy-induced peripheral polyneuropathy of the most commonly used chemotherapeutics: pathomechanism and clinical presentation [4, 6–8]

Drug group	Mechanism of CIPN	CIPN Symptoms
Platinum derivatives • cisplatin • oxaliplatin • carboplatin	• mitochondrial DNA damage • atrophy of dorsal root ganglion cells • dysfunction of ion channels • impairment of intracellular signaling • increased levels of proinflammatory cytokines	Oxaliplatin is a drug that can induce both chronic peripheral and acute neuropathy Oxaliplatin-induced peripheral polyneuropathy is purely sensory with glove and sock distribution and occurs in 50–70% of those undergoing treatment Cisplatin causes chronic polyneuropathy after 12 months in 5–20% of treated Neurotoxicity resulting mainly from damage to large-diameter fibers is manifested by disturbances of vibration and position sensation Carboplatin has the lowest neurotoxicity in this group. Polyneuropathy is experienced by 13–42% of those treated
Taxanes • paclitaxel • docetaxel • cabasitaxel • nab-paclitaxel	• influence on pore permeability within mitochondria and endoplasmic reticulum • increased synthesis of proinflammatory cytokines (TNF alpha and IL-1 beta), decreased synthesis of anti-inflammatory cytokines (IL-4 and IL-10) • altered expression and function of ion channels leading to morphological and biochemical changes in the dorsal roots of spinal nerves • direct damage to sensory neurons through degeneration of nerve fibers and their demyelination	Taxanes primarily cause damage to small-diameter fibers manifesting as paresthesias, dysesthesias, or numbness in the stocking-and-glove distribution, loss of proprioception, and impairment of fine motor movements Motor neuron function and autonomic nervous system function may be impaired Paclitaxel induces sensory neuropathy of severe severity (G3 and G4) in 20–35% of patients receiving 250 mg/m^2 of chemotherapeutic agent every 3 weeks, and in 5–12% of patients treated with < 200 mg/m^2 administered every 3 weeks
Vinca alkaloids • vincristine • vinorelbine • vindesine • vinblastine	• impaired axonal transport inducing distal axonopathy • changes in axons and dorsal root ganglion neurons leading to primary axonal degeneration called Waller's degeneration • changes in the activity of ion channels and hyperactivity of peripheral nervous system neurons • increased levels of proinflammatory cytokines	Symptoms of polyneuropathy involve both sensory and autonomic nerves. Patients most commonly report numbness, tingling, and neuropathic pain in the extremities. Distribution of glove- and sock-like symptoms in 35–45% of those treated The substance with the highest neuropathic potential in this group of cytostatics is vincristine. Severe polyradiculopathies resembling Guillain-Barré syndrome have been reported. Autonomic nervous system disorders after the use of vinca alkaloids are manifested by constipation, urinary retention, and sometimes orthostatic hypotension

CIPN — chemotherapy-induced peripheral neuropathy

in relieving the symptoms of chemotherapy-induced peripheral polyneuropathy has been confirmed in phase III clinical trials is duloxetine [9, 10]. Last January the results of a prospective study were published to evaluate the efficacy and safety of duloxetine in a group of 100 patients who developed peripheral polyneuropathy during cancer treatment. The response to treatment was evaluated using the PGIC (Patient Global Impression of Change) scale, in which 1 represented no response and 7 represented an excellent response. In this analysis, higher scores, and thus higher treatment efficacy, were obtained in the group of women and those displaying CIPN symptoms for a shorter period. Fifty-seven percent of patients discontinued taking duloxetine early due to adverse effects (37%) and lack of treatment efficacy (20%); men predominated in this subgroup of patients [11].

Plexopathy

Treatments used in oncology can induce plexopathy, i.e. damage to nerve plexuses. It mainly affects the brachial and lumbosacral plexuses. Symptoms are muscle weakness, sensory disturbances, and impaired deep reflexes which may be accompanied by pain [2]. The injury of the plexus is mainly induced by radiotherapy to the thoracic region. The symptoms of plexopathy usually appear with a delay, from 6 months to even 30 years after the end of radiotherapy [2, 12]. In differentiating between plexus cancer infiltration and radiation damage, the etiology secondary to treatment is indicated by mild pain, involvement of the upper part of the plexus, and accompanying lymphedema of the limb. Magnetic resonance imaging and electromyography may be helpful in the diagnosis. Lumbosacral plexopathy is usually associated with radiotherapy to the pelvic region. The predominant symptoms are paresis of the lower extremities, and, less frequently, sensory disturbances [12]. Symptoms of plexus injury, although much less frequent, may occur after treatment with cytarabine, IL-2, or INF-alpha [2].

Acute polyneuropathy

Paclitaxel is a widely used chemotherapeutic agent in oncology that, in addition to causing chronic polyneuropathy, can induce paclitaxel-acute pain syndrome (P-APS). Up to 58% of patients treated with paclitaxel may experience P-APS, and 20% of these patients report pain ranging from 5 to 10 on the 10-point Visual Analogue Scales (VAS) pain scale. The muscle and joint pain experienced by patients most commonly affects the lower extremities, hips, and lower back. Pain experienced after the first infusion does not always correlate with complaints reported with subsequent infusions. The sensory neuropathy accompanying the disorder, including numbness and tingling, is more strongly expressed than autonomic or motor neuropathy [13, 14]. Importantly, patients reporting more severe pain are more likely to develop chronic polyneuropathy. Typically, symptoms appear up to 3 days after drug application and resolve spontaneously within a week. Both the mechanism of onset and prevention are unknown. Treatment is exclusively symptomatic and consists of non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain [3, 13]. Oxaliplatin is another chemotherapeutic agent that can cause acute neuropathy in addition to chronic neuropathy. Symptoms usually appear during the infusion or within hours after its completion and resolve spontaneously within hours or days. It is estimated that up to 96% of patients experience hand dysesthesia provoked by low temperature. Other manifestations of neuropathy include hand and foot paresthesia, cold-induced dysesthesia of the feet, mouth and throat, hand and forearm muscle spasms, trismus, eye pain, and tongue numbness [14, 15]. The incidence of grade 3–4 laryngeal dysesthesia according to the Common Terminology Criteria for Adverse Events (CTCAE) is estimated at 1–2% of patients receiving oxaliplatin for advanced colorectal cancer [15].

Ototoxicity

Cisplatin is the chemotherapeutic agent with the highest ototoxic potential, leading to irreversible bilateral conductive and sensorineural hearing impairment in 20–75% of those treated. Risk factors include younger age, high cumulative dose, duration of treatment, as well as pre-existing hearing loss, noise exposure, intake of other ototoxic substances, malnutrition, renal insufficiency, genetic predisposition, and radiotherapy to the cranial region [5, 16–18]. Initially, hearing impairment involves high-frequency sounds, and once the cumulative dose of cisplatin (100 mg/m^2) is exceeded, it also involves mid-frequency sounds [17]. In addition, most patients report experiencing tinnitus, which can persist after treatment in up to 40% of those treated. This is another complication whose occurrence can reduce QoL by generating anxiety and insomnia, leading to the development of depression [19]. Other less ototoxic substances are carboplatin, vinca alkaloids, and oxaliplatin (Tab. 2) [5].

Peripheral polyneuropathy induced by targeted drugs and immunotherapy

Neurological complications following immune checkpoint inhibitors (ICIs) in the form of anti-CTLA-4, anti-PD1, and anti-PD-L1 antibodies are rare, relatively understudied, but clinically relevant. Severe forms in

Table 2. Selected symptoms of cranial nerve damage along with the factor potentially inducing the disorder [1, 2]

Symptom of cranial nerve damage	Type of treatment used
Loss or deterioration of smell, taste	Radiotherapy Each type of chemotherapy
Eyesight impairment	Cisplatin Oxaliplatin Tamoxifen Bevacizumab Vincristine Radiotherapy
Hearing loss/deterioration	Cisplatin Vincristine Oxaliplatin Radiotherapy
Oculomotor nerve dysfunction	Cytarabine Vincristine Interferon alpha
Ptosis	Vincristine Oxaliplatin

grades 3–4, according to CTCAE v.4.0, affect < 1% of treated patients. Most of these are peripheral nerve dysfunction with clinical features of Guillain-Barré syndrome, peripheral polyneuropathy, meningoradiculitis, or myasthenia gravis. The mean time to onset of immune-related adverse event (irAE) is 6 weeks, except for myasthenia gravis, which may appear as early as after 3 weeks, more often with concomitant myositis and myocarditis, which increases the death rate (~20%) [20–28]. Guillain-Barré syndrome with progressive, symmetric ascending flaccid paresis of the lower limb muscles, weakness or abolition of deep reflexes, hemiparesis of the oculomotor muscles, autonomic disturbances (cardiac arrhythmias, arterial pressure fluctuations), and eventually respiratory failure, is a dose-independent, potentially life-threatening adverse effect of both platinum derivatives and ICIs [20]. These compounds can also cause damage to neuromuscular junctions, manifested by excessive muscle fatigue, drooping eyelids, double vision, slurred speech, impaired chewing and swallowing of food, and, in the end-stage of the disease, dyspnea due to respiratory muscle weakness [2, 3]. Trastuzumab emtansine (T-DM1, trastuzumab emtansine) is an antibody-drug conjugate that contains trastuzumab, a humanized monoclonal antibody bound to a microtubule inhibitor: emtansine (DM1). This drug can lead to clinically significant sensory polyneuropathy [29, 30].

Central nervous system adverse side effects

Headaches

Isolated headaches are a common side effect of oncological treatment and the most common neurologic adverse effect of any pharmacotherapy. Risk factors for headache include a history of headache, blood-brain barrier-penetrating chemotherapy, and intrathecal administration of the drug. Headaches have been reported in 26% of patients receiving cetuximab for advanced colorectal cancer. Other drugs that promote headache include asparaginase, etoposide, fludarabine, methotrexate, rituximab, trastuzumab, tamoxifen, and temozolomide [1–3]. Headache may be a symptom of other neurological complications of systemic treatment, such as aseptic meningitis, posterior reversible leukoencephalopathy syndrome (PRES), idiopathic pseudotumor cerebri, or blood-brain barrier damage induced by radiotherapy [2].

Convulsions

Many drugs lower the seizure threshold, resulting in seizures. These include cisplatin, gemcitabine, 5-fluorouracil, etoposide, paclitaxel, or vincristine [1, 2]. Busulfan is a drug that is associated with a high risk of seizure induction. The risk of seizure occurrence is increased by intrathecal administration of drugs, especially cytarabine or methotrexate. Seizures may be an isolated adverse event or one of the manifestations of other treatment-induced conditions such as encephalopathy or PRES [1, 5].

Chemotherapy-related cognitive impairment

Chemotherapy-related cognitive impairment (CRCI), commonly referred to as 'chemobrain', was first described in 1980. It is estimated to occur in 17% to 75% of patients receiving cancer treatment. Potential mechanisms that may contribute to the development of the disorder include direct neurotoxicity from chemotherapy, decreased levels of neurotransmitters, damage to cellular DNA, and hormonal and immune dysregulation. Cognitive disorders are usually of mild to moderate severity, manifested by deterioration of attention, memory, executive functions, prolonged information processing and reaction time, and limited vocabulary [31–33]. They lead to a reduced QoL; they make it difficult to return to work, reduce self-confidence, and impair social relationships [33, 34]. Subjectively, difficulties are greater than indicated by objective test results. CRCI is reported by more than 50% of patients receiving chemotherapy for breast cancer, which translates into objective test scores in 15–25% of them. The decline in cognitive function in

the study occurred shortly after the start of treatment, with partial return of ability one year after the end of treatment. Observation of patients undergoing hormone therapy alone for breast cancer has shown that the use of anastrozole or tamoxifen may be associated with cognitive decline [33]. Among patients undergoing chemotherapy for colorectal cancer, cognitive impairment after 6 months was reported in 32%, i.e. twice as often as in patients not receiving chemotherapy; at 12 months after the end of treatment the relationship was no longer so clear. No difference in the severity of cognitive impairment has been observed between patients with disseminated and limited forms of colorectal cancer [33, 35]. The use of androgen deprivation therapy (ADT) in patients with prostate cancer may impair cognitive abilities to a small extent, with eye-hand coordination being impaired more frequently [33]. Observation of patients with metastatic renal cell carcinoma undergoing targeted therapy with antiangiogenic drugs confirmed that this type of therapy causes cognitive deterioration in 31% of those treated [36]. Importantly, cognitive impairment is also reported by cancer patients who are not receiving chemotherapy. Thus, the phenomenon of 'chemobrain' is difficult to assess objectively. It should be kept in mind that comorbid metabolic and endocrine disorders, anemia, fatigue, insomnia, or depression are all directly related to cancer, and oncological treatment itself may overlap with the CRCI picture [32].

Neurological complications of immunological treatment

Nervous system side effects occur in 6.1% of patients taking anti-PD-1 antibodies, 3.8% of anti-CTLA-4 antibodies, and 12% of those treated with a combination of both drugs (Tab. 3). The most common manifestation described is headache. Adverse effects induced by immunotherapy may appear already at the beginning of treatment, but also after its completion. The occurrence of pathological symptoms of the central nervous system requires high vigilance and quick differential diagnosis to exclude metabolic disorders, central nervous system metastases, neoplastic invasion of the cerebrospinal meninges or their inflammation and take action appropriate to the diagnosis [37–40]. Other central nervous system side effects induced by immunotherapy include aseptic meningitis, PRES, transverse myelitis, or encephalopathy (Tab. 4) [37, 39].

General principles of treatment of neurological complications induced by immunotherapy

In the case of **mild severity (G1)**, immunotherapy can be continued with the implementation of simultaneous differential diagnosis excluding infectious and metabolic etiology, as well as disease progression [38–40].

In neurological disorders of **moderate severity (G2)**, it is recommended to temporarily hold the treatment with simultaneous implementation of differential diagnostics and consideration of oral steroid therapy, i.e. prednisone 0.5–1 mg/kg body weight. After a reduction in the severity of symptoms, a gradual reduction in the steroid dose over at least 4 weeks to a maximum of 10 mg of prednisone daily is indicated. If the effect does not reappear after the reduction of the steroid dose, treatment can be resumed, but discontinuation of treatment is recommended in case of recurrent side effects of moderate severity [38–40].

In neurological side effects of **high and very high severity (G3 and G4)**, immunotherapy should be discontinued without fail and intravenous steroid therapy should be instituted in the hospital setting, and if ineffective, immunosuppressive treatment should be instituted (Tab. 5) [38–40].

Table 3. The frequency of nervous system adverse side effects induced by antibodies used in systemic cancer treatment [45]

	anti-CTL4	anti-EGFR	anti-HER2	anti-PD1/PDL-1	anti-VEGF
Headache	12%	25%	16%	3%	25%
Neuropathy	1.5%	16%	33%	0.9%	1.3–2.2%
Encephalopathy	5.1%	2–6%	2%	1%	2–4%
Stroke/TIA	2%	< 1%	0.1%	0.9–1.7%	2%
Other	Myasthenia gravis 1% Aseptic meningitis 0.2% Intracerebral hemorrhage: 5% of patients with secondary CNS lesions receiving radiotherapy	Sleep disorders 15%	Convulsions 0.2%	Myasthenia gravis 1% Walking difficulties 1% Sleep disorders 1.2–1.5% Convulsions 0.4%	Sleep disturbance 1.2% Intracranial hemorrhage of at least CTC3 severity < 1% In patients with secondary CNS lesions, seizures were observed in 7–13%, intracerebral hemorrhage in 4%, radionecrosis in 5%

CNS — central nervous system

Table 4. Selected neurological complications induced by oncological treatment

Complication	Manifestation and characteristics
Encephalopathy	Confusion, impaired consciousness, apathy, lethargy, impaired attention, hallucinations, agitation, and seizures [2, 3]
	Acute encephalopathy has been described in 10–25% of patients after ifosfamide treatment. Other substances that may induce encephalopathy include cisplatin, etoposide, mitomycin, fludarabine, and tamoxifen [2]
	Risk factors for encephalopathy include the dose of the drug and its ability to penetrate the blood-brain barrier, concomitant use of CYP2B6 inhibitors, renal failure, and hypoalbuminemia [5]
Cerebellar syndrome	Ataxia, gait disturbances, balance disorders, nystagmus, and scanning speech [2]
	It may occur after molecularly targeted drugs such as trastuzumab or rituximab, as well as after classical chemotherapeutics such as cytarabine [2, 5]
	Risk factors are hepatic and renal failure, age > 40 years, and high doses of drugs used [5]
Aseptic meningitis	Fever, headache, meningeal symptoms, and photophobia [37, 40]
	Symptoms are associated with intrathecal administration of chemotherapeutics and result from irritation of the meninges. They usually appear 2–4 hours after drug application and symptoms resolve by 72 h [5]
	Ipilimumab through abnormal activation of the immune system can induce aseptic meningitis [2]
Posterior reversible leukoencephalopathy syndrome (PRES)	High blood pressure values, headache, dizziness, visual disturbances, disorders of consciousness, and seizures [2, 5]
	The hypertensive crisis that may occur after the use of monoclonal antibodies that bind to vascular endothelial growth factor receptors may lead to the development of PRES. The occurrence of PRES has also been described after cyclosporin, cyclophosphamide, or sunitinib [2]
	The risk factors include pre-treatment hypertension, autoimmune disease, renal failure, high doses of anticancer drugs, organ transplant status, and immunosuppression [5]
Transverse myelitis	Symptoms of sensory and motor nerve damage, back and limb pain, paraplegia, and sphincter dysfunction [5, 40]
	It may occur after intrathecal administration of methotrexate, cytarine, cisplatin, or thiotepa [5]
	Risk factors are concurrent radiotherapy to the craniospinal region, and frequent intrathecal injections [5]
Stroke	Focal neurological symptoms, hemiparesis, speech impairment, facial asymmetry, dizziness, and impaired consciousness [3]
	An increased risk of thromboembolism and thus of ischemic stroke is associated with the use of cisplatin, 5-fluorouracil, gemcitabine, and bleomycin [5]. The use of angiogenesis inhibitors also increases the risk of stroke [2]
	The occurrence of hemorrhagic or ischemic stroke related to the use of chemotherapy is rare. The risk of stroke in the oncology patient population is similar to that in the general population [3]
Major depressive disorders	Anhedonia, apathy, abulia, insomnia, tearfulness, lack of or excessive appetite
	Mood disorders often accompany the diagnosis of cancer. However, there are groups of drugs whose use is associated with an increased risk of depressive disorders. These include procarbazine, carmustine, vinca alkaloids, pemetrexed, fludarabine, taxoids, cetuximab, imatinib, sorafenib, or sunitinib [3]

PRES — posterior reversible leukoencephalopathy syndrome

Central nervous system adverse side effects induced by radiotherapy

Central nervous system (CNS) adverse side effects are divided into early ones, occurring up to 6 months after radiotherapy, and late ones, occurring after 6 months. Early adverse reactions are usually reversible and of low intensity [41, 42]. The most common in this group is fatigue syndrome, which occurs during or shortly after treatment. Other side effects include focal neurological symptoms, cognitive decline, or seizures. PRES induced by systemic therapy may also be a consequence of central nervous system radiotherapy. It appears already after 3 weeks of treatment and is caused by damage to the blood-brain barrier [2, 41, 42]. Leukoencephalopathy, which may manifest as slowly progressing cognitive disorders, personality changes, and even epileptic seizures, usually appears 1–2 years after whole-brain radiotherapy [41]. Another central nervous system side effect after radiotherapy is pseudoprogression of focal lesions, which occurs in 12–64% of patients undergoing radiotherapy. It consists of an increase in the size of focal lesions on magnetic resonance imaging and an increase in central nervous system symptoms. It usually resolves within 6 months after irradiation. It is recognized that up to 30% of early tumor progression on imaging studies is pseudoprogression, and distinguishing between these two clinical situations is essential in

Table 5. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
Myasthenia Gravis	0.12–1.16%	Neurological consultation Laboratory tests: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aldolase, phosphocreatine kinase (CPK), acetylcholine receptor antibodies (AChR-Ab; present in 60% of cases of ICI-induced MG), striated muscle antibodies (i.e. anti-titin, anti-RyR, anti-RAP-SN), tyrosine kinase antibodies (anti-MuSK). Electrophysiological examinations to exclude myositis or neuropathy, i.e. electromyography (EMG), nerve conduction study (NCS) Respiratory function tests Additional tests: • in the case of suspected myocarditis: electrocardiography (ECG), transthoracic ultrasound (TTE), determination of troponins levels • in the case of suspected neoplasm invasion in the central nervous system or other potential causes of symptoms magnetic resonance imaging (MRI)	**Management of symptoms of moderate severity (G2):** **Definitive discontinuation of immunotherapy** Inpatient use of pyridostigmine initially at a dose of 30 mg 3 times daily, with gradual escalation to a maximum of 120 mg up to 4 times daily. Consider inclusion of prednisone initially at a dose of 20 mg daily, with gradual dose escalation to 1 mg/kg per day (do not exceed 100 mg daily) **Management of symptoms of high severity (G3–G4):** **Definitive discontinuation of immunotherapy** Inpatient use of pharmacotherapy: methylprednisolone 1–2 mg/kg. The use of plasmapheresis or intravenous preparations of immunoglobulin, and in the absence of their effectiveness, consider the addition of rituximab Medications that may exacerbate symptoms of myasthenia gravis (i.e. ciprofloxacin, aminoglycosides, or beta-blockers) should be avoided, the respiratory system should be assessed and the patient's neurological status should be monitored
Guillain-Barré Syndrome (GBS)	0.1–0.2%	• Neurological consultation • MRI of the spinal cord • Lumbar puncture (a general examination of the CSF should be performed and potentially infectious agents such as HSV or other viruses should be excluded depending on the clinical picture; CSF pressure should be measured) • Respiratory function tests • Electrophysiological examinations, i.e. electromyography (EMG), electroneurography (NCS) • Additional investigations: determination of specific serum anti-ganglioside antibodies (anti-GQ1b)	**Management of moderate to severe symptoms (G2–G4)** **Definitive discontinuation of immunotherapy.** In-hospital administration of intravenous immunoglobulin or plasmapheresis with pulses of methylprednisolone at a dose of 1 gram daily for 5 days followed by gradual dose reduction over 4 weeks. Steroid therapy is not recommended for idiopathic GBS. The patient should be evaluated neurologically, for respiratory distress and autonomic dysfunction. 15–30% of patients with idiopathic GBS require assisted ventilation. In case of pain, the following are used: gabapentin, pregabalin, and duloxetine
Aseptic meningitis	0.36%	• Neurological consultation should be considered • Lumbar puncture (general examination of cerebrospinal fluid, tests to rule out viral infections including HSV) • MRI of the brain to exclude brain or meningeal metastases	**Management of symptoms of moderate severity (G2):** Hold immunotherapy Until a result is obtained to rule out HSV infection, it is recommended that acyclovir be considered for inclusion After excluding a viral or bacterial etiology, consider starting steroid therapy i.e. prednisone 0.5–1 mg/kg per day or methylprednisolone 1–2 mg/kg per day

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Table 5 cont. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
			Management of symptoms of high severity (G3–G4) **Consider definitive discontinuation of immunotherapy** Hospitalization of the patient Consider inclusion of acyclovir pending PCR result for HSV Once an infectious etiology of the complaint has been ruled out, consider starting steroid therapy i.e. prednisone 0.5–1 mg/kg per day or methylprednisolone 1–2 mg/kg per day
Transverse myelitis	< 0.06%	• Neurological consultation • MRI of the brain and spinal cord • Lumbar puncture (general examination of cerebrospinal fluid, tests to exclude viral infections, onconeuronal antibodies, oligoclonal bands). • Determination of vitamin B12 level, antinuclear antibodies ANA, anti-Ro, anti-La, anti-aquaporin 4 (AQP4-IgG) antibodies, anti-myelin glycoprotein oligodendrocytes antibodies level, paraneoplastic antibodies determination (anti-Hu, anti-CRMP5, anti-CV2), ruling out HIV infection • Evaluation of the presence of constipation and urinary stasis based on bladder imaging	**Definitive discontinuation of immunotherapy.** In-hospital initiation of methylprednisolone 1 g per day for 3–5 days, consideration of plasmapheresis or intravenous immunoglobulin preparations
Encephalitis (often with a limbic encephalitis phenotype, less commonly cerebellitis)	0.84%	• Neurological consultation • MRI of the brain • Lumbar puncture (general examination of cerebrospinal fluid, tests to exclude viral infections, i.e. HSV, paraneoplastic antibodies, oligoclonal bands, antineuronal autoantibodies; assessment of cerebrospinal fluid pressure) • Electroencephalography (EEG) • Laboratory tests: blood count, ESR, glucose, ionogram, total protein, albumin, aminotransferases, alkaline phosphatase, bilirubin, urea, CRP, anti-neutrophil cytoplasmic antibodies (ANCA), TSH, fT3, fT4, TPO, thyroglobulin, paraneoplastic antibodies	**Management of symptoms of moderate severity (G2):** **Definitive discontinuation of immunotherapy** Consider intravenous acyclovir until PCR results are available to rule out HSV 1 and 2 infections Initiate methylprednisolone at 1–2 mg/kg per day. Continue use for up to 4 weeks after resolution of symptoms **Management of symptoms of high severity (G3–G4)** **Definitive discontinuation of immunotherapy** Hospitalization of the patient Methylprednisolone 1g i.v. for 3–5 days in combination with intravenous immunoglobulin preparations or plasmapheresis. This form of steroid therapy should also be considered in patients with observed progression of symptoms within 24 h or with the presence of oligoclonal bands in the CSF In selected cases i.e. autoimmune encephalopathy or no improvement after 7–14 days consider rituximab

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Table 5 cont. Guidelines for diagnostic and therapeutic management of nervous system adverse side effects induced by immunotherapy based on NCCN 01.2022 [37, 44–46]

	Frequency of side effects incidence after administering ICI*	Diagnostics	Management
Peripheral polyneuropathy	1.3%	Factors that may induce polyneuropathy should be excluded, i.e. drugs, infections, metabolic or endocrine disorders, autoimmune diseases, and vascular diseases Consider imaging the cerebrospinal axis In CTCAE grade G2, consider neurological consultation and additional tests such as EMG or NCS Diagnostic procedure for CTCAE grades G3–G4 according to the Guillain-Barré guidelines	For mild symptoms (G1), consider withholding immunotherapy, and evaluate the severity of complaints after one week In the case of moderate symptoms (G2), stop immunotherapy and consider starting prednisone 0.5–1 mg/kg orally. If symptoms progress, include methylprednisolone at 2–4 mg/kg/day Consider including medications to alleviate pain associated with peripheral polyneuropathy such as gabapentin, pregabalin, or duloxetine Treatment of severe cases (G3–G4) is the same as in Guillain-Barré syndrome

*ICI — immune checkpoint inhibitors

making therapeutic decisions regarding the continuation of treatment in patients taking thalidomide [41, 42]. The late and most serious consequence of radiotherapy to the central nervous system area is radiation necrosis. In the literature, its incidence is estimated at up to 24% of patients undergoing radiotherapy, usually 1 to 3 years after the end of treatment, and the most vulnerable areas are the frontal and temporal lobes. The formation of necrosis results from perivascular inflammation, leading to white matter edema. Like in pseudoprogression, one risk factor for occurrence is concurrent chemotherapy. This complication may be asymptomatic or cause drowsiness, headaches, or neurological symptoms, whose picture depends on the location of necrotic lesions [41, 43]. Radiotherapy to the central nervous system and head and neck region increases the risk of stroke through the development of vasculopathy and acceleration of atherosclerosis. Radiotherapy-induced cavernous angiomas develop one to 26 years after irradiation and have a higher risk of bleeding and may cause seizures. Other vascular changes associated with radiation therapy include telangiectasias within the spinal cord vessels, which can be a source of bleeding. SMART (Stroke-like Migraine Attacks after Radiation Therapy) may manifest with episodes of focal neurologic symptoms or seizures and is another late radiation reaction occurring one to 30 years after the end of treatment. It is prevented with medications recommended for migraine prophylaxis [2, 42].

Conclusions

Systemic therapy used in oncology may generate numerous adverse effects on the nervous system. Neurotoxicity is a cause of drug dose reduction and treatment discontinuation; it may also be directly life-threatening. Although the majority of side effects are mild, they may diminish QoL, stigmatize the patient, and make it difficult to return to work or social activity after treatment.

Article Information and Declarations

Conflict of interest

The authors declare no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Implementation of the Polish version of the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11): importance for oncology

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ABSTRACT

Member States of the World Health Organization (WHO), after several years of joint review, approved and implemented the update of the International Statistical Classification of Diseases and Related Health Problems (ICD) in May 2019. Usually, the abbreviated name ICD-11 (International Classification of Diseases, 11th Revision) is used. The new version was created in fully digital form with a search easy-to-use search engine available to every user. Many changes were introduced, and the most important is the redesign of the coding system to adapt it for digital use. ICD-11 codes are divided into main and supplementary codes. Main codes are at least 4 characters long, and 2 levels of extensions, up to 7 characters, are possible. In Poland, the entire process of implementing the ICD-11 is carried out as part of a project coordinated by the Medical Center for Postgraduate Education in cooperation with the Department of Healthcare of the Ministry of Health and the e-Health Center The implementation of the new version and the official introduction of ICD-11 in Poland must be preceded primarily by the amendment of legal acts (laws and regulations) and orders of the President of the National Health Fund, such as those regarding the reimbursement for refunded services and the keeping of medical records.

An important element is the change in the cluster codes in oncology. Selected oncology groups were based on analyses of international reports on morbidity, mortality, cancer registries, and clinical reports. Cluster 02, which deals with cancer, contains 8 subsections detailing disease states associated with abnormal or uncontrolled cell proliferation. This article summarizes and discusses the most important changes in ICD-11, along with providing an introduction to the classification rules in the coding system and individual subsections on cancer.

Keywords: ICD-11, classification, WHO

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Introduction

The International Classification of Diseases (ICD), which was introduced in the mid-nineteenth century as a shortlist for compiling statistical data about causes of death has become, over the years, the dominant classification of diseases, syndromes, and health conditions in people around the world [1]. One of the aims of

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the classification is to collect health data for the assessment of comparable health status at the international level. In addition, 70% of global health spending uses ICD codes for reimbursement and resource allocation. Some 110 countries, representing approximately 60% of the world's population, use ICD death data to organize, fund and monitor the use of health resources.

Despite the dynamic development of all areas of medicine for nearly 100 years, between the initial versions of the International Statistical List and the 10th ICD revision (ICD-10) in 1990, there was virtually no evolution in the structure of the classification, which was a table of terms with associated code values [2]. The basis for the introduction of the ICD-11 was the need to improve the quality of coding and access to its resources, lower costs of its use and update its structure so that it reflects the current state of medicine, which was associated with a properly designed (logical and clear) user interface and better mapping of causes of morbidity and death. Before undertaking work on the new version of the ICD, the WHO reviewed all existing classifications (including categorization and codes) to make the new version reflect medical progress. A team of experts on WHO Classification and Terminology was aware of ICD shortcomings in the era of the IT revolution and the dynamic development of medicine. In 2005, work began on revising the ICD to take advantage of the huge advances made in the early 21st century in computer science, ontology, and medicine. The ICD-11 version was developed by many teams of clinical specialists and experts in particular fields. The teams were divided into 19 thematic advisory groups, the so-called TAGs. Important for this project was the creation of a special "Informatics TAG", which significantly contributed to the development of the new ICD-11 architecture and was elevated to the rank of priority equal to clinical domains. In information systems, a TAG is a keyword or term assigned to information (such as a web bookmark, multimedia, database record, or computer file). This type of metadata helps describe the item and makes it discoverable by browsing or searching. TAGs are usually chosen informally and personally by the creator of the item or by its user, depending on the system although they can also be selected from a controlled vocabulary [3].

World Health Organization member states, after several years of joint review, approved and implemented in May 2019 the International Classification of Diseases ICD-11, which is already in force in 35 countries. It is currently available in English, French, Spanish, Arabic, and Chinese, with translation into further 20 languages in preparation [4].

Since January 1st, 2022, the 11th version of the classification has been officially used in Poland for national and international registration and reporting of the causes of diseases and deaths, reimbursement for health services, statistical analysis, and clinical trials. Poland, like other countries, has at least a 5-year transition period for the implementation and dissemination of the ICD-11. During the transition period, WHO Member States may compile and submit statistical data to the WHO using the previous revision (ICD-10) [5].

Classification structure developed for ICD-11

For the first time, the ICD has been made available not in print but in a digital form (https://icd.who.int/en) and consists of grouping information according to logical rules. The terminology allows healthcare professionals to report information at any level of detail (e.g., body parts, exam results, or other elements that characterize the disease). Only items defined in terminology can be reported. In contrast, the classification contains residual classes ("other specified" and "unspecified"), which ensure that all cases can be classified. In modern classification terminology, a disease can be defined by, for example, establishing a correlation between its components. Terminologies retain information without emphasizing any aspect of the recorded information. Classifications, on the other hand, allow for the identification of "relevant parts" of content (e.g., for public health purposes). An international agreement on these material parts ensures that the aggregated information is comparable in the international context [6].

The ICD-11 architecture includes 3 layers, which are:
— semantic network of biomedical concepts (so-called base);
— traditional table of hierarchical codes that derive from this network (linearization);
— formal ontology that places the meaning of terms in a semantic web. Additionally, each entry in the Semantic Web is associated with an information model with required and optional content (content model) [3].

The new classification allows the encoding of approximately 17 000 unique categories (codes) of diseases and causes of death, while in the previous version of the ICD-10, there were 14 000. There are 80 000 units/elements of the classification; each element has its own number and is grouped into categories. There are over 120 000 concepts and terms and 40 000 synonyms for units/elements and categories with the same number. It should be emphasized that the intelligent coding algorithm currently interprets over 1.6 million terms (including their combinations).

The ICD-11 contains 26 main clusters, including 5 new ones:
— R.03 Diseases of the blood and organs of the human hematopoietic system;

— R.04 Disturbances in the functioning of the immune system;
— R.07 Disturbance of sleep and awakening;
— R.17 Factors determining sexual health;
— R.27 Traditional medicine [7].

In addition to the code classification in the 26 main clusters, there are 2 additional sections (V and X). Section V on the assessment of human functioning enables calculation of the disability score according to the WHO Disability Assessment Schedule (WHODAS 2.0) scale, which allows healthcare professionals to combine the ICD and International Classification of Functioning, Disability and Health (ICF) codes. On the other hand, in section X, the supplementary codes contain additional information (e.g., histological type, active substances, pathogens, medical supplies used, or antibiotic resistance) [8].

The ICD-11 system can be used to code diagnoses in electronic medical records and link them to death records or other data in digital collections. Special tools, such as the ICD-11 Coding Tool, make it easy to find specific ICD-11 codes for any diagnosis from several places that define the unit or category of that classification [9].

Eleventh revision of the International Statistical Classification of Diseases and Related Health Problems codes are divided into main and supplementary codes. Main codes consist of a minimum of 4 characters and have 2 levels of extensions up to 7 characters (including a period, the second character is always a capital letter; no O or L to avoid confusion). All codes in one cluster will always start with the same character. The range of codes is from 1A00.00 to ZZ9Z.ZZ. The letter X describes the extension codes, i.e., additional important information about the disease [8].

A new coding feature introduced in the ICD-11 is post-coordination, which supports combining two or more codes into a cluster describing a clinical concept. Post-coordination enables reporting of coded data with a higher level of detail than in the previous ICD version. One can combine codes consisting, for example, of main codes and supplementary codes in so-called collections/sets of codes. Main codes are combined with a slash "/" and supplementary codes with an "&". The rules for code combinations and the acceptable method of linking main codes and supplementary codes were defined (pathomorphological codes are combined only with codes of neoplastic diseases) [10].

It is possible to combine codes into clusters, e.g.:
— MAINCODE1/MAINCODE2;
— MAINCODE1/MAINCODE2/MAINCODE3;
— E1/MAINCODE2&SUPPLEMENTARYCODE1;
— MAINCODE1 & SUPPLEMENTARYCODE1/ /MAINCODE2/SUPPLEMENTARYCODE2.

The following examples show how clinical situations can be described more accurately by combining main codes with a slash "/" and supplementary codes with an "&" character:

1. Personal history of invasive breast cancer in a patient with contralateral breast cancer
   Cluster: QC40.3/2C61
   Code descriptions:
   QC40.3 Personal history of malignant breast neoplasm (main code)
   2C61 Invasive breast cancer (main code)
2. Personal history of invasive left breast cancer in a patient with right breast cancer
   Cluster: QC40.3&XK8G/2C61&XK8K
   Code descriptions:
   QC40.3 Personal history of malignant breast neoplasm (main code)
   Lateralization: XK8G left side (supplementary code)
   2C61 Invasive ductal carcinoma of the breast (main code)
   Lateralization: XK8K right side (supplementary code)
3. Acute left-sided pyelonephritis caused by *E. coli*
   Cluster: GB51&XK8G&XN6P4
   GB51 Acute pyelonephritis (main code)
   Lateralization: XK8G left side (supplementary code)
   Infectious agent: XN6P4 *Escherichia coli* (supplementary code) [4].

Application of linking the ICD-11, ICF, and ICHI classifications

Historically, the ICD has used certain concepts of disability as common disease entities or disorders (e.g., blindness, deafness, learning disabilities, or paraplegia) and certain concepts of disability for other purposes (e.g., "disability as a consequence of injury", and "limitation of activities due to disability") [6].

The ICD-11, which is based on ontology and the incorporation of its sister classifications, ICF and ICHI (International Classification of Health Interventions), into the same ontological infrastructure enabled full integration of terminology and classifications on a common platform. In this way, it is possible to use the clinical documentation (encoding all the necessary details) for other uses. The ICD-11 ensures consistency with earlier versions of the ICD. Analyses of historical data based on older versions of the ICD can be linked to data analyses based on the ICD-11 [9].

In general, the link between the ICD and ICF classifications found in the ICD-11 can help in the following cases:
— assessments in general medical practice (e.g., in the assessment of working capacity);

— evaluation of social benefits (e.g., invalidity pension);
— payment or reimbursement of benefits — refund;
— needs for assessment (e.g., in the field of rehabilitation, occupational adaptation assistance, long-term care);
— evaluation of intervention results [9].

ICD-11 in the field of cancer — general issues

Rapid progress in oncology has clearly shown that the categorization of malignant and benign tumors based solely on location provides limited information for prevention, treatment, and prognosis. The previous ICD-10 classification system contained a limited number of categories based on pathology (e.g., some cancers of the lymphatic system, melanoma). In the ICD-11, major tumor locations have pathomorphological subcategories first. The selected groups were based on analyzes of international reports on morbidity and mortality, cancer registries, and clinical reports. The redesigned sections have been checked for missing details in relation to ICD use cases. Maintaining the main anatomical axes allows for consistency with previous classifications. However, the structure has been adjusted to anatomical subcategories in several places according to the TNM classification [9].

For tumors of the central nervous system, the distinction between benign and malignant in terms of histological characteristics and clinical course creates a certain uncertainty zone. Therefore, it was decided to move all tumors of the central nervous system beyond the basic framework and group them together.

Progress in the field of molecular biomarkers is dynamic, but it is different in particular groups of cancers. For some cancers, markers with recognized diagnostic and prognostic value have been used for years, but there are areas without biomarkers. Therefore, except for hematopoietic and lymphatic malignancies, molecular markers have not been included in the ICD-11. However, they may be included in Cluster X "Extension Codes" and may be added in the future to more fully describe individual tumor entities as science advances and knowledge of biomarkers deepens [9].

Cancers in the ICD-11 are included in Cluster 02, in which the individual disease entities are cataloged considering the following elements:
— 1st level — type of cancer;
— 2nd level — wide range of sites or systems from which the tumor originates;
— 3rd level — detailed tumor location;
— 4th level — morphological character (histological type) of the tumor.

The exception to the above hierarchy are 3 groups of neoplastic diseases which are:
1. neoplasms of the brain and central nervous system, which include a wide range of sites in the first tier and the combined nature of malignancy and the morphological (histological) type of the tumor in the second tier;
2. neoplasms of hematopoietic or lymphoid tissues, which in the first tier contain a wide range of morphological (histological) types and in the second tier a detailed morphological (histological) type;
3. malignant mesenchymal neoplasms, which in the first tier contain a detailed morphological (histological) type, and in the second tier, its location [9].

Detailed categories for the description of neoplastic diseases

Cluster 02, which deals with cancer, contains 8 subsections detailing disease states associated with abnormal or uncontrolled cell proliferation that is not coordinated with the body's need for normal tissue growth, replacement, or repair. The subsections have been grouped as follows:
— neoplasms of the brain or central nervous system (codes 2A00 to 2A0Z);
— neoplasms of hematopoietic or lymphoid tissues (codes 2A20 to 2B3Z);
— malignant neoplasms, except primary neoplasms of lymphoid, hematopoietic, central nervous systems, or related tissues (codes 2B50 to 2E2Z), including:
  • malignant neoplasms, identified or presumed primary, in specific locations, except for lymphatic, hematopoietic, central nervous systems, or related tissues,
  • malignant neoplasms with ill-defined or unspecified primary foci,
  • malignant tumor metastasis,
— neoplasms *in situ*, except lymphoid, hematopoietic, central nervous systems, or related tissues (codes 2E60 to 2E6Z);
— benign neoplasms other than lymphoid, hematopoietic, central nervous systems, or related tissues (codes 2E80 to 2F5Z);
— neoplasms of uncertain behavior except for lymphoid, hematopoietic, central nervous systems, or related tissues (codes 2F70 to 2F7Z);
— neoplasms of unknown behavior except for lymphoid, hematopoietic, central nervous systems, or related tissues (codes 2F90 to 2F9Z);
— inherited tumor predisposing syndromes (2C65 to LD2F.15) [9].

Implementation of the Polish language version

In Poland, the entire implementation process is carried out as part of the project entitled "Improving the quality of medical information by increasing the competence, knowledge, and skills of employees of healthcare entities in the correct use of the ICD-11 classification" led by the Medical Center for Postgraduate Education in cooperation with the Department of Healthcare at the Ministry of Health and the e-Health Center. The project is financed by the European Social Fund under the Operational Programme Knowledge Education Development 2014–2020.

The stages of the ICD-11 implementation project in Poland, in line with the assumptions, include the development of the Polish version of the ICD-11, then verification of the Polish ICD-11 translation by Postgraduate Medical Education Center (CMKP) subject matter experts and external experts, and in the next stage, assessment and acceptance by national consultants and the development of a set of WHO instruments supporting future users of the classification.

The last stage of the project is the development of programs and the organization of training and workshops for future users of the ICD-11. Improving practical skills in the use of the current classification by healthcare professionals, lecturers at medical universities, death cause coders in the Central Statistical Office and persons conducting epidemiological analyses. According to the project schedule, the expected completion date is 2023.

As stated by the Communication of the Ministry of Health, the final decision on the date of official ICD-11 entry into force will be made after the introduction of legal changes with due consideration for the adequate time needed to prepare for ICD-11 implementation [11].

In the Polish legal system, the rules for reimbursementbetween service providers and the payer, the subject of the procedure for concluding a contract for the provision of healthcare services and the detailed terms and conditions of contracts for the provision of healthcare services — such as hospital treatment — highly specialized services are regulated in the Order of the President of the National Health Fund [12].

The implementation of the new version of the ICD-11 in Poland must be preceded primarily by the amendment of legal acts (acts and regulations) and orders of the President of the National Health Fund, regarding the reimbursement for guaranteed services and keeping medical records. Numerous changes are necessary in the healthcare system (legal and in the field of IT). A very important aspect is the adaptation of the IT systems of both service providers as well as the reporting and reimbursement system of health services of the public payer (KRUS, ZUS, GUS) [13]. The integration of the application with the medical systems of service providers Hospital Information System (HIS) should also be considered, which can be a big call but may also generate additional costs on the part of service providers.

Conclusions

There is no doubt that the introduction of the new version of the ICD should improve the precision of coding medical conditions and causes of death. The ICD-11 has been designed to reflect the state of modern medicine and to implement changes related to its dynamic development. By cataloging known conditions, the ICD-11 can be used for health insurance purposes, for classification and statistical analysis of diseases, and as a global health tracking tool that can be used across countries and languages. The introduction of the ICD-11 should improve the quality of coding by reflecting modern practice and thus generate correct data for the needs of healthcare systems and their regulators.

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REVIEW ARTICLE

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News and updates in the treatment of localized stage triple-negative breast cancer

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ABSTRACT

Compared to other breast cancer subtypes, triple-negative breast cancer presents a worse prognosis and higher mortality. Even in localized stages, the risk of relapse is high, especially in patients with ≥ cT2 and/or ≥ cN1. We know that those patients who achieve a complete pathologic response after neoadjuvant treatment have better disease-free survival. Therefore, many research efforts have been made to try to optimize neoadjuvant chemo/immunotherapy to increase pathologic complete response rates. The available evidence related to that subject matter is summarized in this article. In the field of adjuvant therapy, the challenge of improving disease-free survival in those patients who do not achieve pathologic complete response after neoadjuvant therapy stands out. The second part of this article will deal with the challenges inherent to this issue.

Keywords: adjuvant treatment, disease-free survival, early breast cancer, neoadjuvant treatment, pathological complete response, treatment personalization, triple-negative breast cancer

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Introduction

In the treatment of early-stage triple-negative breast cancer (TNBC), guidelines distinguish between two major therapeutic branches: 1) in those tumors with clinical stage cT1N0, they recommended performing upfront surgery with the possibility of subsequent adjuvant treatment depending on the pathological stage and 2) in those tumors with clinical stage ≥ cT2 and/or ≥ cN1, they recommend neoadjuvant therapy followed by surgery and subsequent adjuvant treatment [1].

Compared to other subtypes of breast cancer, TNBC has a worse prognosis and higher mortality, even when it debuts in a localized form. We know that those patients who achieve a complete pathologic response after neoadjuvant therapy have better disease-free survival. Therefore, research efforts have been oriented towards the optimization of neoadjuvant chemo/immunotherapy to increase pathological complete response (pCR) rates without disregarding the issue of toxicity accumulation that can limit successive lines as well as the selection of patient profiles based on biomarkers that determine their risk of relapse to individualize treatment in terms of adoption of escalation and de-escalation strategies.

We also know that patients who do not achieve pCR have lower disease-free survival (DFS: invasive iDFS or distant DDFS) despite the available adjuvant treatments. In the field of adjuvant therapy, the challenge of improving survival parameters in this subgroup of patients and exploring new drugs as well as escalation strategies stands out.

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Optimizing the search for complete pathologic response in neoadjuvant therapy

Nuances in the management of cT1N0 tumors

In tumors with clinical stage cT1N0, the guidelines initially recommend performing surgery. If the pathologic stage is pT1aN0, follow-up is recommended. However, in all patients whose pathological stage results are ≥ pT2 and/or ≥ pN1 and, generally speaking, also in those with pT1b-c pN0, they recommended performing adjuvant treatment [with chemotherapy (QT) or with targeted therapy (TD) with PARP inhibitors in the case of *BRCA* mutations] [1].

In the case of patients with minimal tumor disease in the pathologic specimen (pT1b-cN0), the question is what parameters are indicative of good prognosis that would allow for individualized management and selection of those patients who may be exempt from the toxicity of adjuvant treatment that can be detrimental to their long-term survival.

The European Society for Medical Oncology (ESMO) 2022 guidelines distinguish four histology types which are associated with good prognosis: apocrine, secretory, medullary, and cystic adenoid. They point out that, within these histology types, follow-up could be considered due to their 5-year overall survival (OS) of more than 92% [1].

However, the frequency of these histologies is low, which has led to the search for other markers that can guide de-escalation, such as the proliferation index (ki67) or tumor-infiltrating lymphocytes (TILs). The prognostic role of TILs is indisputable (level of evidence 1B) and has been demonstrated in several studies [1].

Park et al. [2] reviewed a cohort of 476 patients from 4 centers (1989–2015) with resected TNBC without perioperative QT. Retrospectively, they assessed the percentage of TILs in the surgical specimen, stratifying into two groups: TILs < 30% and TILs ≥ 30%. They concluded that stage I TNBC patients with TILs ≥ 30% form a subgroup with excellent prognosis without adjuvant chemotherapy [at 5 years: DFS 91% (95% CI 84–96), D-DFS 97% (95% CI 93–100), OS 98% (95% CI 95–100)] [2].

Similarly, De Jong et al. [3] retrospectively reviewed a sample of 441 patients from the German registry (1989–2000), younger than 40 years at diagnosis, with pT1-3N0 and without perioperative chemotherapy. They stratified TILs into three groups: < 30%, 30–75%, and ≥ 75%. At 15 years, the cumulative incidence of distant metastases or death was 2.1% for the subgroup with high TILs ≥ 75% (95% CI: 0–5) and 38.4% for the subgroup of low TILs < 30%. Furthermore, each 10% increase in TILs correlated with a 19% decrease in the risk of death [adjusted hazard ratio (HR) = 0.81; 95% CI 0.76–0.87]. They concluded, therefore, that young, QT-naive, N0 TNBC patients with sTILs ≥ 75% have an excellent long-term prognosis, and prospective clinical trials investigating (neo)adjuvant QT de-escalation strategies should be considered in this subgroup [3]. Because of the aforementioned lack of prospective clinical trials, there is still no evidence to make therapeutic decisions based solely on this parameter, and, therefore, it is not currently recommended in the clinical practice guidelines. However, this is an emerging line of research that will provide new developments in the coming years.

Triple-negative breast cancer with ≥ cT2 and/or ≥ cN1: gainig further knowledge of neoadjuvant therapy

For the treatment of TNBC ≥ cT2 and/or ≥ cN1, the NCCN 2022 guidelines issue multiple recommendations regarding options for therapeutic schemes which they classify under three headings: “preferred regimens”, “regimens useful in certain circumstances” “other recommended regimens” [4].

The NCCN 2022 guidelines lay out fundamental concepts according to which: 1) the recommended schedule with the most evidence is AC > T biweekly or weekly (where “A” indicates doxorubicin, “C”, cyclophosphamide, and “T”, paclitaxel) 2) for high-risk TNBC, the guidelines recommend combining QT with pembrolizumab in neoadjuvant treatment according to the KEYNOTE 522 scheme 3) the combination of carboplatin with paclitaxel/docetaxel is mentioned in the preoperative setting but is not routinely recommended for most patients 4) bevacizumab has no place in (neo)adjuvant therapy and is recommended in combination with chemotherapy only for selected patients with recurrent or stage IV disease [4]. The ESMO 2022 guidelines reinforce the same concepts [1].

Neoadjuvant chemotherapy

Classically, three fundamental questions have been considered around the issue of neoadjuvant chemotherapy in TNBC ≥ cT2 and/or ≥ cN1: 1) should carboplatin be added? 2) what is the role of bevacizumab? 3) are anthracyclines necessary? We will try to answer them below.

Should carboplatin be added?

There are subgroups within TNBC (such as those associated with *BRCA* mutations), in which the inherent defect in DNA repair based on homologous recombination increases sensitivity to alkylating agents, such as carboplatin [5]. Table 1 [6–12] summarizes the most important characteristics of the main clinical trials related to the study of the addition of carboplatin to neoadjuvant chemotherapy. Several issues are noteworthy:

1. All trials are phase II except the GeparOcto/GBG84 trial [10] and BrighTNess trial [11, 12], which are phase III;
2. There is great variability in the design of the trials, including combinations and sequencing of different chemotherapy agents, with variability in doses. Some also include targeted therapies (veliparib) or antiangiogenics (bevacizumab). The heterogeneity in the design makes the results difficult to compare;
3. The primary endpoint for all of them was pCR, with significant differences in favor of carboplatin use of around 25% in both BrighTNess [11, 12] and ISPY-2 [9] and around 15% in GeparSixto/GBG66 [8] and CALGB 40603 [7];
4. Regarding survival data, it is remarkable that no trial achieved significant differences in OS. In contrast, in GeparSixto/GBG66 [8] and BrighTNess [11, 12], significant differences in DFS in favor of carboplatin were achieved.

Of all the trials mentioned, BrighTNess [11, 12] is noteworthy for its relevance. It is a three-arm phase III trial that randomized women > 18 years, with ECOG 0–1, with stage II/III TNBC and potential surgical candidates to receive: paclitaxel (first arm), carboplatin (second arm), with the addition of veliparib to the previous combination (third arm), followed by AC and subsequent surgery. It was a positive trial in terms of pCR and DFS (as shown in Tab. 1). Its authors conclude that:

1. adding carboplatin improved pCR ,and this, in turn, translated into improved DFS with no impact on OS;
2. the increase in hematologic toxicity with the addition of carboplatin and the consequent delay in treatment did not worsen end-point outcomes;
3. adding veliparib did not impact pCR, DFS, or OS [11, 12].

What is the role of bevacizumab?

The 2022 NCCN and ESMO guidelines do not consider the use of bevacizumab in the (neo)adjuvant setting [1, 4]. This is because although clinical trials of bevacizumab in the neoadjuvant setting are positive for the primary end-point (pCR), this does not translate into a significant increase in DFS/OS [7, 13–15]. Likewise, in the adjuvant setting, the BEATRICE trial also did not

Table 1. Main trials related to the study of carboplatin in combination in neoadjuvant therapy for the treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
GEICAM 2006/03 [6]	II	94	EC × 4 > T_{100} × 4 T_{75} Cb × 4	30% *vs.* 30%	—
CALGB 40603 [7]	II	443	wP ± Cbq3w > AC × 4 ± Bev	41% *vs.* 54% (increase 13%)*	5 yr DFS: 70.1% *vs.* 70.4% HR = 0.94 (NS) **5 yr OS: 75.6% *vs.* 74.4% HR = 1.12 (NS)**
GeparSixto/ /GBG66 [8]	II	315	wP + wN-PLD ± Bev ± wCb	37% *vs*. 53% (increase 16%)*	3 yr DFS: 86.1% *vs*. 75.8% HR = 0.56* **3 yr OS: 91.9% *vs*. 86% HR = 0.60 (NS)**
ISPY-2 [9]	II	60	wP ± Cb + V > AC × 4	26% *vs*. 51%* (increase 25%)	—
GeparOcto/ /GBG84 [10]	III	403	wP NPLD Cb *vs*. EP q2w × 3 > Cq2w × 3	48,5% *vs*. 51.7%	—
BrighTNess [11, 12]	III	634	wP ± Cb ± V > AC × 4	31% *vs*. 58% (Cb) *vs*. 53% (CbV) (increase 26%)*	**4.5 yr DFS: 68.5% *vs*. 78.2% *vs*. 79.3% 4.5 yr OS: 86.1% *vs*. 88% *vs*. 90% HR = 0.82 (NS) HR = 0.63 (NS) HR = 1.25 (NS)**

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; DFS — disease-free survival; E — epirubicin; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; w — weekly; yr — year

Table 2. Main trials related to the study of bevacizumab in combination with in neoadjuvant therapy for the treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
In the neoadjuvant setting					
CALGB 40603 [7, 14]	II	443	wP ± Cbq3w > AC × 4 ± Beva	41% *vs*. 54% (increase 13%)*	5 yr DFS: 70.1% *vs*. 70.4% HR = 0.94 (NS) **5 yr OS: 75.6% *vs*. 74.4% HR = 1.12 (NS)**
GeparQuinto/ /GBG44 [13]	II	315	ECq3w × 4 > Dq3w × 4 ± Beva	27.9% *vs*. 39.3% (increase 11%)*	3 yr DFS: 75.5% *vs*. 72.9% (NS) **3 yr OS: 85.5% *vs*. 80.9% (NS)**
ARTemis [15]	III	800	T × 3 > CEF × 3 ± Beva	45% *vs*. 31% (increase 14%)*	3.5 yr DFS: 74% *vs*. 78% HR = 1.18 (NS) 3.5 yr OS: 81% *vs*. 84% HR = 1.26 (NS)
In the adjuvant setting					
BEATRIZE [16]	III	2591	AT ± Beva × 4	—	3 yr DFS: 82.7% *vs*. 83.7% HR = 0.87 (NS)

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; DFS — disease-free survival; E — epirubicin; F — fluorouracil; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; yr — year

demonstrate a significant increase in survival parameters [16]. The results of the main trials are summarized in Table 2 [7, 13 –16].

Are anthracyclines necessary?

Anthracyclines are chemotherapeutics with widely demonstrated efficacy in the treatment of TNBC. However, they carry cardiovascular risks and the risk of secondary leukemias in the long term [5]. Especially in localized stages, where the fundamental curative pillar is surgery, it is advisable to try to reduce as much as possible the toxicity derived from neoadjuvant treatment that may be detrimental, in the long term, to the quality of life of the patients and therapeutic possibilities in successive lines. For this reason, de-escalation trials have been designed to try to evaluate the benefit-toxicity balance that anthracyclines bring to perioperative treatment. Some of them include an anthracycline arm in the design. Others, however, omit them and compare them with the results available in the literature. Table 3 [17–21] lists the main trials in this regard.

None of the trials listed in Table 3 conclude in favor of anthracyclines although only two (the NCT01276769 trial [18] and the NeoCART trial [20]) obtain higher pCR rates with the alternative scheme. The remaining trials highlight the non-inferiority of omitting anthracyclines and the resulting benefits in tolerability. The phase II trial NCT01276769 compared paclitaxel plus carboplatin versus epirubicin plus paclitaxel [18]. It concluded the superiority of carboplatin with a significant difference in terms of pCR and DFS at 4 years [18]. However, it should be remembered that the chemotherapy scheme recommended with the most evidence in the 2022 NCCN guidelines is anthracycline plus cyclophosphamide followed by taxane [4]. The design of the study NCT01276769 can, therefore, be questioned for not comparing the taxane-platinum combination with the standard combination. The phase II NeoCART trial, on the other hand, was designed to compare the taxane-platinum combination with AC followed by taxane [20]. A significant pCR benefit in favor of carboplatin was maintained, however, no differences in survival parameters were obtained [20].

Conclusions regarding neoadjuvant chemotherapy

Heterogeneity in the study design makes it difficult to draw clear conclusions. In this regard, Li J. et al. [22] designed a meta-analysis comparing different chemotherapy schedules for the treatment of stage I–III TNBC. They included randomized trials with the control group, published in English. From an initial search of more than 2000 references, they finally selected 35 clinical trials. As the primary objective, they compared pCR, and as the secondary objective they compared the aggregate adverse effects (AEs), defined as total adverse effects grade 3 or higher. They concluded that adding platinum to neoadjuvant TNBC treatment, both in regimens in which it is combined with taxanes alone (TCb; OR = 2.16; 95% CI 1.20–3.91) and in those that also include anthracyclines (ATPt; OR = 2.04; 95% CI 1.69–2.48), significantly increases the pCR rate with respect to AT regimens. Furthermore, without anthracyclines, it improves tolerance without worsening the pCR rate, although no significant differences were obtained in the incidence of severe ALE (OR = 0.66; 95% CI 0.23–1.72) [22].

Table 3. Main trials related to the possibility of omitting anthracyclines in neoadjuvant treatment of early triple-negative breast cancer

Trial	Phase	N	Design	pCR [%]	DFS/OS (HR)
PROGECT (NCT01560663) Compare results with available literature [17]	—	190	TCb q3w × 6	55% Similar rate to ACb but better safety profile.	3 yr DFS: 79% **3 yr OS: 87%**
NCT01276769 [18]	II	91	PCb q3w *vs.* EP q3w × 6	14.0% (EP) *vs.* 38.9% (PCb)*	4 yr DFS: 52.8% (EP) *vs.* 71.1% (PCb)*; p = 0.080 **4 yr OS: 70.1% *vs.* 72.5% (NS); p = 0.980**
TBCRC030 [19]	II	139	wPx12 *vs.* CDDP q3w × 4	11.9% P *vs.* 15.3% CDDP	—
NeoCART [20]	II	93	TCb q3wx6 *vs.* EC × 4 > T × 4	61.4% *vs.* 38.6% *	3 yr DFS: 88.3% *vs.* 90.8% (NS); HR = 0.76 **3 yr OS: 92.8% *vs.* 93.1% (NS); HR = 0.96**
NeoSTOP [21]	II	100	wP ± Cb q3w × 4 > AC × 4 *vs.* TCb q3w × 6	54% *vs.* 54%	3 yr DFS and OS: NS between both arms and significantly higher in those achieving pCR regardless of treatment received pCR 3 yr DFS: 100% *vs.* 81% **pCR 3 yr OS: 100% *vs.* 86%**

*Statistically significant value; > — followed by; A — doxorubicin; Bev — bevacizumab; C — cyclophosphamide; Cb — carboplatin; CDDP — cisplatin; DFS — disease-free survival; E — epirubicin; HR — hazard ratio; NPLD — non-pegylated liposomal doxorubicin; NS — not significant; NS — not significant; OS — overall survival; P — paclitaxel; pCR — pathological complete response; q — dose; T — docetaxel; V — veliparib; w — weekly; yr — year

Neoadjuvant immunotherapy

Figure 1 [23–28] summarizes the current immunotherapy (IT) landscape for neoadjuvant treatment in early-stage TNBC. Atezolizumab gained FDA approval in 2019 and EMA approval in 2020 in combination with paclitaxel-albumin based on the results of the IMPASSION 031 trial [22]. Pembrolizumab was approved in 2021 by the FDA in combination with chemotherapy as neoadjuvant treatment and in adjuvant monotherapy based on the results of the KEYNOTE 522 trial [24, 25]. The EMA also approved it in 2021 but only for CPS ≥10, rectifying the approval in 2022 when it became approved regardless of PDL1 levels. Nivolumab is not tested in early stages, but the phase II TONIC trial was designed for metastatic TNBC [28, 29].

The IMPASSION 031 phase III clinical trial randomized patients with cT2-T4 cN0-N3 cM0 TNBC who had not received prior treatment to receive paclitaxel albumin ± atezolizumab followed by anthracycline + cyclophosphamide ± atezolizumab in the neoadjuvant phase. After surgery, those patients in the IT arm continued with atezolizumab in adjuvant versus placebo in the control arm. It was a positive trial in favor of using atezolizumab in terms of its primary end-point, significantly improving pCR both in the overall sample and when stratifying by PD-L1 (overall: 57.6% *vs.* 41.1%; Δ16.5%; 95% CI 5.9–27.1; PD-L1 positive: 68.8% *vs.* 49.3%, Δ19.5%; 95% CI 4.2–39.8; PD-L1 negative: 47.7% *vs.* 34.4%, Δ13.3%; 95% CI from –0.9 to 27.5). No significant differences were found in survival parameters [23].

The NeoTRIP phase III clinical trial was, in contrast, a pCR-negative trial at its primary endpoint. It randomized patients with previously untreated early-stage TNBC to receive carboplatin + taxane ± atezolizumab. After surgery, adjuvant treatment was performed in both arms with QT (AC/EP/FEC). They concluded that adding atezolizumab to the nab-paclitaxel + carboplatin scheme did not significantly increase the pCR rate [24].

The phase III GEPAR-DUOZE trial is still ongoing. Its design randomizes patients with early TNBC to receive carboplatin + taxane ± atezolizumab followed by epirubicin + cyclophosphamide ± atezolizumab. After surgery, adjuvant will be performed with atezolizumab for the IT arm versus placebo [25].

The phase III KEYNOTE 522 trial, in addition to achieving FDA and EMA approval of pembrolizumab in combination with QT for the perioperative treatment of early TNBC, positioned the scheme at ESMO 2021 as the new standard of care. Patients were randomized to receive carboplatin + taxol ± pembrolizumab sequenced with anthracycline + cyclophosphamide. After surgery, the IT arm maintained pembrolizumab in adjuvant vs. placebo in the control arm. The study concluded in favor of using pembrolizumab in (neo) adjuvant, with a significant increase in pCR rate (66.8% *vs.* 51.2%; p = 0.00055) as well as DFS at 36 months (84.5% *vs.* 76.8%; HR = 0.63; 95% CI 0.43–0.82). The benefit was maintained in all subgroups, being independent of PD-L1 [26, 27].

The results in DFS stratified by pCR of KEYNOTE 522 are interesting. Those patients who achieve

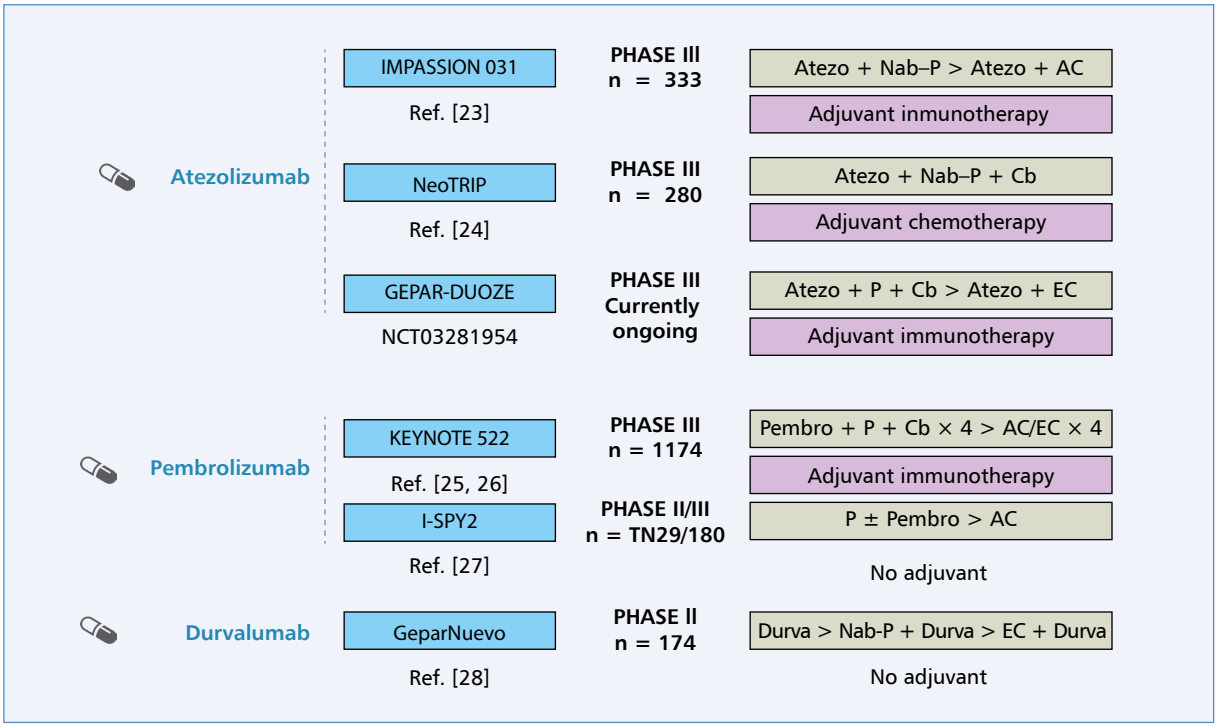

Figure 1. Overview of the main clinical trials on the use of IT in the neoadjuvant treatment of early-stage triple-negative breast cancer [Based on: slide Nº37 SEOM VIRTUAL 2020 "CM TN: Immunotherapy is here to stay" Dr. Elena García-Martínez. Morales Meseguer University Hospital. Murcia]; > — followed by; A — doxorubicin; Atezo — atezolizumab; C — cyclophosphamide; Cb — carboplatin; Durva — durvalumab; E — epirubicin; P — paclitaxel; Pembro — pembrolizumab; T — docetaxel

pCR, regardless of how they achieve it, maintain high DFS 36 months, around 93% (DFS 36 months pCR IT arm 94.4%, DFS 36 months pCR QT arm 92.5%, with no significant difference HR = 0.73; 95% CI 0.39–1.36). However, for those who do not achieve pCR, there is a clear benefit in favor of the use of pembrolizumab (at 36 months, DFS IT *vs.* QT arm 67.4% *vs.* 56.8%; HR = 0.70 95% CI 0.52–0.95). Despite this, it is noteworthy that there continues to be a difference of around 30% in DFS at 36 months between those patients who receive IT and achieve pCR and those who do not. This concept will be important in thinking about the question of adjuvant [26, 27].

The KEYNOTE 522 trial reported no significant difference in terms of OS at 36 months (89.7% *vs.* 86.9%; HR = 0.72; 95% CI 0.51–1.02) [26, 27].

The phase II/III I-SPY2 trial is still ongoing. It has an adaptive design that allows the inclusion of new research arms that are compared in parallel. It is designed for high-risk stage II/III breast tumors, with an interim analysis published on the use of pembrolizumab. Data on 250 patients were analyzed, of which 69 were included in the pembrolizumab arm, with only 20 TNBC. In patients with TNBC, there was a significant increase in the pCR rate (60% *vs.* 12%) in favor of pembrolizumab. Consistent with the results of the KEYNOTE 522 trial, in those patients who did not obtain pCR, the fact of having received pembrolizumab in neoadjuvant therapy improved their DFS with respect to the control [28].

In phase II GeparNuevo trial, which evaluated the combination of durvalumab with QT, was negative in terms of its primary end-point pCR (53.4% *vs.* 44.2%; p = 0.28). However, it is striking that the reported results regarding 3-year survival parameters were all significantly favorable to the durvalumab arm [iDFS 77.2% *vs.* 85.6% (HR = 0.48; 95% CI 0.27–1.09), DDFS 78.4% *vs.* 91.7% (HR = 0.31; 95% CI 0.13–0.74) OS 83.5% *vs.* 95.2% (HR = 0.24; 95% CI 0.08–0.72)] [29].

Issues and challenges in sequential adjuvant

cT2 and/or ≥cN1: the question of adjuvant after neoadjuvant

Figure 2 [26, 27, 30, 31] summarizes adjuvant options after neoadjuvant and surgery in early-stage TNBC.

In patients who achieve pCR

A good starting point to address the question of adjuvant after neoadjuvant treatment in TNBC is to return

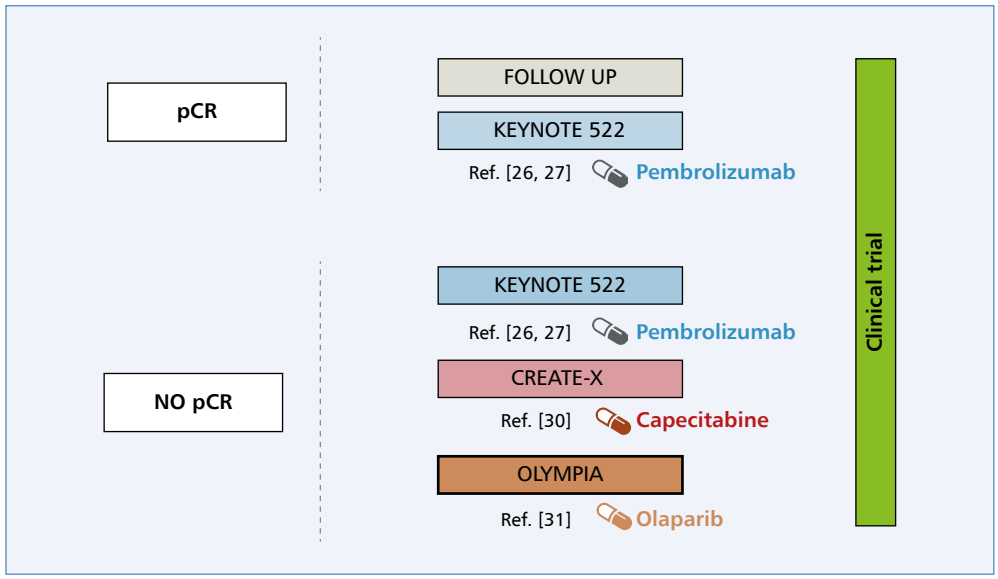

Figure 2. Overview of adjuvant options after neoadjuvant and surgery in early-stage triple-negative breast cancer; pCR — pathological complete response

to the results in pCR-stratified DFS of the KEYNOTE 522 trial, which reinforced the favorable prognosis of patients who achieve pCR, regardless of the treatment with which they achieve it [26, 27].

Within this subgroup of patients, there is the possibility of continuing with pembrolizumab in adjuvant (after performing neoadjuvant with pembrolizumab) based on the KEYNOTE-522 scheme [26, 27].

However, the results of stratification of survival curves by pCR suggest that de-escalation approaches could be explored with a clear clinical impact in terms of toxicity [32, 33]. The OptimICE-PCR trial is designed to randomize patients with TNBC and pCR after neoadjuvant chemoimmunotherapy to adjuvant pembrolizumab for 27 weeks or observation. There are no published results yet [34].

In patients who do not achieve pCR

Given the significant benefit in DFS relative to the use of IT with pembrolizumab according to the KEYNOTE 522 scheme, in those patients who do not achieve pCR it could be concluded that, without a doubt, this subgroup of patients who receive IT in neoadjuvant therapy should continue with pembrolizumab in adjuvant therapy [26, 27]. However, there are several caveats to this categorical statement.

First, the KEYNOTE 522 trial confronted pembrolizumab versus placebo in adjuvant, without including capecitabine in adjuvant as a control group. This is because recruitment for this study began before this drug was positioned in adjuvant as standard of care, following the results of the CREATE-X trial [32, 33]. In the phase III CREATE-X trial capecitabine demonstrated benefit in DFS and OS at 5 years versus placebo (DFS 74.1% *vs.* 67.7%; HR = 0.7; p = 0.005; OS 89.2% *vs.* 83.9%; p < 0.01) [30].

Second, despite continuing with pembrolizumab, DFS remains approximately 30% lower relative to those patients achieving pCR. Bonadio et al. [33] reflected on this point in their article on management of TNBC patients after neoadjuvant pembrolizumab. They pointed out the importance of exploring escalation strategies, such as the possibility of administering concomitant pembrolizumab + capecitabine or designing adjuvant strategies with sequence therapy [33].

In addition, among patients who do not achieve pCR, there is a subgroup with a worse prognosis. Within KEYNOTE-522, a subanalysis of outcomes stratified by residual cancer burden (RCB) was performed. It was observed that patients with higher residual disease burden (defined as RCB-3) had worse survival rates, and it was striking that this subgroup of patients had worse DFS at 3 years in the IT arm compared to the control (DFS 26.2% pembrolizumab; 95% CI 13.5–41 *vs.* 34.6% control; 95% CI 17.5–52.5). In this subgroup, it is urgent to explore escalation strategies [33]. In our center, we tried to include these patients with particularly poor prognoses in a clinical trial.

Third, at the San Antonio Breast Cancer Symposium 2022, a post-hoc analysis exploring the role of adjuvant radiotherapy in the results of the KEYNOTE-522 trial was published as a poster. They classified patients according to whether or not they had received adjuvant radiotherapy and, in those who had received it, distinguished according to whether it was administered concurrently or sequentially. The pCR rate was determined

as the primary endpoint and survival and toxicity data as secondary endpoints. In this post-hoc analysis, the administration of adjuvant RT and how it was administered did not influence the results with respect to pCR and DFS [35].

Fourth, targeted therapy with PARP inhibitors is another possibility in the adjuvant treatment of patients with TNBC and mutated *BRCA*. This mutation is present in about 10–15% of TNBC patients [33]. The phase III OlympiA clinical trial led to the approval of olaparib in an adjuvant setting. They included patients with germline *BRCA1/2* mutation who had received prior perioperative chemotherapy with anthracycline (and/or taxane) based regimens and stratified them into two subgroups: patients with TN tumors on the one hand and patients with HER2-positive/hormone receptor-positive tumors on the other. Within both groups, patients were randomized to receive olaparib versus placebo. The primary endpoint was iDFS, with a statistically significant difference in favor of olaparib at 36 months (85.9% *vs.* 77.1%; HR = 0.58; 95% CI 0.41–0.82), with benefit maintained in all subgroups. It also concluded in favor of olaparib in terms of DDFS at 36 months (87.5% *vs.* 80.4%; HR = 0.57; 95% CI 0.39–0.83). However, no significant difference was found in OS (92% *vs.* 88.3%; HR = 0.68; 95% CI 0.44–1.05) [31].

Bonadio et al. [33] recommend prioritizing olaparib as adjuvant therapy for BRCA-mutated tumors. They point out that, although there are no studies directly comparing olaparib with capecitabine or pembrolizumab, in the case of ovarian cancer (in which the prevalence of *BRCA1/2* germline mutations and homologous recombination deficiency are higher), clinical trials have shown little activity of immunotherapy in monotherapy. By extrapolation, given the pathophysiologic similarity, these authors are betting on olaparib in this particular clinical scenario [33].

Fifth, we should not forget the possibility of including our patients in clinical trials, especially if we can predict, based on the available evidence, a worse prognosis with the treatments approved to date.

Within the broad landscape of clinical trials, the ongoing phase III SASCIA trial is noteworthy. It is designed to compare adjuvant sacitumumab-govitecan *versus* the treating physician's adjuvant treatment of choice. Although they support other patient profiles, patients with TNBC who have not achieved pCR after 16 weeks of neoadjuvant taxane-based QT can be included in this trial [36].

Conclusions

The search for pCR in neoadjuvant therapy and the issues and challenges in sequential adjuvant therapy in localized stages of TNBC are currently two hot topics.

In neoadjuvant, efforts have been directed to optimize the chemotherapy schedule, with the role of platinum-based drugs gaining relevance and the role of anthracyclines being increasingly questioned in relation to their inherent toxicity. The combination with immunotherapy (pembrolizumab) has revolutionized the therapeutic landscape and is currently considered the new standard of care for high-risk patients.

Research on adjuvant therapy after neoadjuvant therapy is at its peak, with numerous investigations open in this field. Although we have tools such as capecitabine, pembrolizumab (in the case of having received neoadjuvant therapy with IT), or olaparib (in the case of germline BRCA-mutated tumors), there is an urgent need to design escalation strategies and investigate new drugs that improve DFS in those patients who do not achieve pCR after neoadjuvant therapy.

Article Information and Declarations

Author contributions

I.S.L.: conceptualization, visualization, methodology, project management, writing: proofreading and editing. J.A.G.M.: proofreading and editing. D.M.G., L.R.L., C.P.G., A.M.M.F. de S., C. de Z. L., B.L.V., N.S.B., F.E.M., E.M.M., D.G.A., I.J.M., B.J.M., B.J.M., J.C.R.: editing.

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Conflict of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE

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Avapritinib in the treatment of gastrointestinal stromal tumors (GIST)

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ABSTRACT

Avapritinib is a highly selective inhibitor of mutated KIT and PDGFRA kinases, approved in 2020 for the treatment of patients with gastrointestinal stromal tumors (GIST). It has particular activity against GIST with the *PDGFRA D842V* mutation associated with imatinib resistance. The safety and efficacy of avapritinib have been evaluated in two clinical trials, NAVIGATOR and VOYAGER, which showed particularly favorable results in patients with the *PDGFRA D842V* mutation. In the NAVIGATOR study, the objective response rate (ORR) in patients with the mutation was 91%. In the VOYAGER study, the ORR was 17.1% in all patients receiving avapritinib and 42.9% in the group of patients with the *PDGFRA D842V* mutation. While the efficacy in the subgroup of patients with the mutation was significantly superior to regorafenib, this benefit was not demonstrated for the overall population. In both studies, adverse events were reported in more than 90% of patients, with more than 50% of patients experiencing Grade 3 or higher reactions. The most commonly reported treatment-related adverse events were nausea, fatigue, anemia, diarrhea, periorbital edema, and cognitive impairment. Based on the preliminary study results, avapritinib was approved in the United States and the European Union for treating patients with metastatic or unresectable GIST with the *PDGRA D842V* mutation. It is the first inhibitor showing activity against this mutation. In this review, we summarize the current data on the efficacy and safety of avapritinib and present its place in the diagnostic and therapeutic guidelines.

Keywords: avapritinib, GIST, *PDGFRA,* tyrosine kinase inhibitor

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal neoplasm of the digestive system. The incidence of GIST is estimated at 10 to 15 cases per million people. It occurs with similar frequency in men and women, and the average age of diagnosis is 65–70 years. GIST originates from interstitial cells of Cajal and can be located in any segment of the gastrointestinal tract, with the most common locations being the stomach (55%) and small intestine (30%) [1].

In most GIST cases, mutations in the *KIT* (75–80%) or *PDGFRA* (10%) genes are found. The region associated with the most frequent mutations in the *KIT* gene is exon 11 (65% of all GISTs), especially codons 557 and 558. In 8–10% of cases, mutations occur in *KIT* exon 9. Primary mutations in other exons of the *KIT* gene, i.e., 13, 17, or 18, are relatively rare [2]. *PDGFRA* mutations are the cause of 10% of all GISTs, with the *D842V* mutation within exon 18 being the most common among them [3]. Other less common *PDGRFA* mutations may be found in exon 12 or 14 [4]. Gastrointestinal stromal tumor with *PDGFRA* mutations is mainly found in the stomach [4].

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The remaining 10–15% of GISTs may be associated with mutations in genes from the *RAS* family (e.g., *BRAF* mutations), *NF1* mutations, or succinate dehydrogenase (SDHA/B/C/D) deficiency. Some GISTs are associated with *NRTK* translocations [2].

Determining the GIST molecular subtype is very important because this information influences further therapeutic decisions. The choice of GIST treatment method depends on the stage and molecular profile of the tumor [5]. GISTs are generally resistant to conventional chemotherapy. The prognosis of GIST has improved since 2002 when the US Food and Drug Administration (FDA) approved imatinib for this indication [6].

The most effective method in the treatment of primary localized GISTs is surgical treatment [7, 8]. In the case of unresectable or metastatic disease, treatment with tyrosine kinase inhibitors (TKIs) is the standard of care. The gold standard in the first line of treatment is imatinib. Sunitinib is used in the second line of treatment, while regorafenib and ripretinib are subsequent-line options [9]. Treatment with imatinib gives the best results in GISTs with mutations in *KIT* exon 11, and it is less effective in *KIT* exon 9 mutations and in some *PDGFRA* mutations [10]. All TKIs used so far are ineffective in the treatment of tumors with the *PDGRFA D842V* mutation [4]. For this reason, this group of patients has a notably poor prognosis.

Due to the resistance to imatinib in GIST patients with the *PDGFRA D842V* mutation, studies on new tyrosine kinase inhibitors are ongoing to find new molecules that could be effective against this mutation. As a result of these studies, avapritinib, a highly selective inhibitor of mutant KIT and PDGFRA kinases, belonging to the type I inhibitors that bind to the KIT and PDGRA proteins in their active conformation, was developed. For GIST with the *PDGFRA D842V* mutation, *in vitro* studies have shown that half of the maximum inhibitory concentration (IC50) of avapritinib is about 3000 times lower than that of imatinib [11]. In addition, avapritinib was selected for its specificity for KIT and PDGFRA activation loop mutations. In 2015, the first clinical trials evaluating the effectiveness and safety of avapritinib were initiated. Based on the preliminary results of the phase I NAVIGATOR study, on January 9, 2020, the FDA approved avapritinib as a first-line drug in patients with metastatic or unresectable GIST with the *PDGRFA* mutation in exon 18, including D842V mutations [12]. This was followed by registration by the European Medicines Agency and the European Commission, which was narrowed down to the treatment of patients with metastatic or unresectable GIST with the *PDGRA D842V* mutation [13].

Pharmacodynamic and pharmacokinetic properties of avapritinib

Avapritinib is a type 1 kinase inhibitor with *in vitro* enzymatic activity against products of mutated *PDGFRA D842V* and *KIT D816V* with IC50 values of 0.24 nM and 0.27 nM. Both of those mutations are generally considered to be resistant to imatinib, sunitinib, and regorafenib. Avapritinib also showed better activity against clinically significant mutation products in exon 11 or 17 of *KIT* than against unmutated *KIT*. Avapritinib inhibits the autophosphorylation of mutant KIT and PDGFRA proteins with IC50 values of 4 nM and 30 nM, respectively. In cell-based assays, avapritinib inhibited proliferation in *KIT*-mutant cell lines, including the mouse mast-cell line and the human mast-cell leukemia cell line. Avapritinib also inhibited the growth of murine mast-cell xenografts with *KIT* exon 17 mutations.

Following single and multiple doses of avapritinib, systemic exposure to avapritinib is dose-dependent, with time to peak concentration (C_{max}) ranging from 2 to 4 hours [13]. Steady-state is reached after approximately 15 days of once-daily dosing. High-fat meals increase C_{max} in healthy subjects compared to C_{max} after overnight fasting. Avapritinib is nearly 99% bound to human plasma proteins, and the estimated mean volume of distribution is 1200 liters. *In vitro*, studies have shown that avapritinib oxidative metabolism is mediated primarily by CYP3A4 and CYP3AP and, to a lesser extent, by CYP2C9. The mean plasma half-life in GIST patients ranges from 32 to 57 hours. Avapritinib is excreted mainly in feces (80%) and, to a lesser extent, in urine (20%) [13].

Efficacy of avapritinib in clinical trials

The safety and efficacy of avapritinib were evaluated in 2 clinical trials: NAVIGATOR (NCT02508532) and VOYAGER (NCT03465722) (Tab. 1).

The NAVIGATOR study was an open-label, non-randomized phase I study in patients with unresectable or metastatic GIST. Two hundred fifty patients were enrolled, 56 of whom had GIST with the *PDGRFRRA D842V* mutation (20 patients in part 1 with dose escalation and 36 patients in part 2). In the first part, the primary endpoints were the maximum tolerated dose, the recommended dose for phase II, and the safety profile of avapritinib. The maximum tolerated dose of avapritinib has been established at 400 mg/day, and the recommended phase II dose at 300 mg/day. In the second part of the study, the primary endpoints were objective response rate (ORR) based on central radiological review by RECIST v1.1 (Response Evaluation Criteria in Solid Tumors) and safety profile.

Table 1. Summary of NAVIGATOR and VOYAGER clinical trial results

Endpoint	NAVIGATOR trial	VOYAGER trial			
	Patients with *PDGFRA D842V* mutation n = 56	All patients receiving avapritinib n = 240	All patients receiving regorafenib n = 236	Patients with *PDGFRA D842V* mutation receiving avapritinib n = 7	Patients with *PDGFRA D842V* mutation receiving regorafenib n = 6
Median PFS	34 months	4.2 months	5.6 months	NR	4.5 months
12-month OS	93%	68.2%	67.4%	–	–
Treatment response according to RECIST 1.1					
ORR	91%	17.1%	7.2%	42.9%	0%
CR	13%	0%	0%	0%	0%
PR	79%	17.1%	7.2%	42.9%	0%
SD	9%	47.1%	67.4%	57.1%	50%

CR — complete response; NR — not reached; ORR — objective response rate; OS — overall survival; PFS — progression-free survival; PR — partial response; RECIST — Response Evaluation Criteria in Solid Tumors; SD — stable disease

In the 56 patients with GIST with the *PDGFRA D842V* mutation, the ORR was 91%, with a complete response (CR) in 7 (13%) and a partial response (PR) in 44 (79%) patients. The median duration of response (DOR) was 27.6 months [95% CI 17.6–not reached (NR)], and median progression-free survival (PFS) was 34 months (95% CI 22.9–NR). The durable clinical benefit translated into an increase in overall survival (OS) although median OS had not been reached at the time of analysis (median follow-up of 27.5 months). The percentage of patients surviving 12, 24, and 36 months was 93%, 75%, and 61%, respectively [14–16].

The VOYAGER study was an open-label, randomized, multicenter phase III study that compared avapritinib with regorafenib in GIST patients previously treated with imatinib and one or two additional TKIs (avapritinib or regorafenib was used as a third or fourth line of treatment). In the study, 476 patients were randomized to one of two groups — 240 patients received avapritinib 300 mg once daily (continuous treatment for 4 weeks), and 236 patients received regorafenib 160 mg once daily (3 weeks of treatment and 1 week off). The primary endpoint of the study was centrally assessed PFS according to mRECIST v1.1 modified for GIST. Baseline circulating DNA (ctDNA) analysis determined the type of mutation in each group. The *PDGFRA* exon 18 mutation was found in 3.8% (18) patients, of whom 13 had the *D842V* mutation [17]. Cross-over was possible in the study, and 41.9% (99/236) of patients receiving regorafenib crossed over to avapritinib after disease progression.

The study did not meet the primary endpoint with no differences in PFS — median PFS for 4.2 months for avapritinib and 5.6 months for regorafenib (HR = 1.25; 95% CI 0.99– 1.57; p = 0.055). In the 13 patients with *PDGFRA D842V* mutated GIST, median PFS was higher for the 7 patients treated with avapritinib (median NR; 95% CI 9.7–NR) than the 6 patients treated with regorafenib (4.5 months; 95% CI 1.7– NR; p = 0.035). When these 13 patients were excluded from the overall study population, median PFS was higher with regorafenib (5.6 months) than avapritinib (3.9 months; HR = 1.34; 95% CI 1.06–1.69; p =0.012).

The OS data were immature at the time of publication, with a median follow-up of 8.5 months for avapritinib and 9.6 months for regorafenib. The OS estimates at 12 months were similar for patients receiving avapritinib and regorafenib (68.2% *vs*. 67.4%). The ORR was higher in patients treated with avapritinib compared to regorafenib — 17.1% *vs*. 7.2%, and the difference persisted even after excluding patients with the *PDGFRA D842V* mutation. In the group of 7 patients with GIST with the *PDGFRA D842V* mutation treated with avapritinib, the ORR was 42.9%, and 57.1% of patients had stable disease. None of the patients experienced disease progression at the first assessment.

Interesting data were provided by the analysis of circulating DNA (ctDNA) in patients treated in the VOYAGER study [18]. When a mutation in the ATP-binding cassette portion of the *KIT* gene was found in the ctDNA, the efficacy of avapritinib was significantly lower than that of regorafenib (median PFS 1.9 *vs*. 5.6 months). In contrast, the response to regorafenib was not dependent on the presence or absence of these alterations. In addition, in the absence of the ATP-binding cassette mutation, median PFS for avapritinib and regorafenib was 5.6 months in both groups. It should be underlined that these are exploratory analyses, and the importance of using ctDNA for inclusion in clinical trials or selection of treatment options in GIST needs to be confirmed in more extensive prospective studies.

The NAVIGATOR and VOYAGER trials showed that avapritinib has anticancer activity in GIST patients with the *PDGFRA D842V* mutation (Tab. 1). The

Table 2. Comparison of the most common adverse reactions to avapritinib in the NAVIGATOR and VOYAGER studies

Adverse event	NAVIGATOR trial (n = 250)		VOYAGER trial (n = 239)	
	All grades	≥ G3	All grades	≥ G3
Total	245 (98%)	147 (72%)	221 (92.5%)	132 (55.2%)
Nausea	161 (64%)	5 (2%)	94 (39.3%)	2 (< 1%)
Fatigue	157 (63%)	15 (7%)	84 (35.1%)	9 (3.8%)
Anemia	136 (54%)	58 (28%)	96 (40.2%)	50 (20.9%)
Cognitive impairment	115 (46%)	8 (4%)	62 (25.9%)	3 (1.3%)
Diarrhea	112 (45%)	10 (5%)	50 (20.9%)	4 (1,7%)
Periorbital edema	110 (44%)	1 (< 1%)	66 (27.6%)	3 (1.3%)
Vomiting	106 (42%)	4 (2%)	44 (18.4%)	0
Decreased appetite	101 (40%)	6 (3%)	42 (17.6%)	2 (< 1%)
Increased lacrimation	88 (35%)	0	42 (17.6%)	0
Memory impairment	81 (32%)	1 (< 1%)	28 (11.7%)	3 (1.3%)
Peripheral edema	80 (32%)	2 (< 1%)	46 (18.8%)	1 (< 1%)
Abdominal pain	64 (26%)	11 (5%)	ND	ND
Constipation	64 (26%)	3 (1%)	ND	ND
Hair discoloration	62 (25%)	1 (1%)	ND	ND
Vertigo	59 (24%)	1 (< 1%)	ND	ND
Face edema	57 (23%)	1 (< 1%)	65 (27.2%)	6 (2.5%)
Increased bilirubin level	54 (22%)	9 (4%)	66 (27.6%)	12 (5%)
Hypokalemia	48 (19%)	6 (3%)	ND	ND
Headache	48 (19%)	1 (< 1%)	ND	ND
Dysgeusia	47 (19%)	0	ND	ND
Body weight loss	46 (18%)	2 (< 1%)	13 (5.4%)	–
Cough	39 (16%)	0	ND	ND
Neutropenia	29 (12%)	4 (2%)	ND	ND
Leukopenia	ND	ND	38 (15.9%)	10 (4.2%)
Treatment discontinuation due to adverse event	54 (22%)	–	20 (8.3%)	–
Death related to adverse evenest	1 (< 1%)	–	0	–

G — grade; ND — no data

VOYAGER study showed that avapritinib was not superior to regorafenib in patients with unresectable or metastatic GIST in the third or later lines of treatment. Patients with various *KIT* and *PDGFRA* exon 18 mutations were included in the study population, and the type of mutation in patients was not determined in some patients. Therefore, the assessment of the effectiveness of these drugs against a specific mutation is not precise, and ctDNA data should be interpreted with caution. Analyzing a small subgroup of patients with the *PDGFRA D842V* mutation (n = 13), it can be concluded that avapritinib is a more effective drug against this mutation than regorafenib.

Avapritinib toxicity

The incidence of adverse events in the phase I NAVIGATOR (NCT02508532) trial in patients with and without the *PDGFRA D842V* mutation was similar and reported by over 99% of patients [16]. Similarly, in the VOYAGER study, in 239 patients treated with avapritinib, at least one adverse event was observed in 92.5%, of which more than 50% were grade 3 or higher (Tab. 2) [17].

Gastrointestinal toxicity — nausea (39–68%), diarrhea (21–66%), and vomiting (18–42%) were common adverse reactions. Fatigue was observed in up to two-thirds of patients, and edema, including periorbital or facial edema, in 20–40% of patients [16, 17]. Cognitive impairment (memory impairment, confusion, encephalopathy) may be an essential issue with avapritinib, reported in 46–57% of patients, of whom approximately 3% had grade 3 or higher. These disorders depend mainly on the drug dose used, as the phase I study demonstrated. Intracranial bleeding occurred in 3–5% of patients [16, 17].

An increased risk of QT prolongation has been observed in clinical trials in patients treated with avapritinib. This has been associated with the risk of ventricular arrhythmias, including *torsade de pointes*. In all grades, the incidence of QT interval prolongation was 2%, while in grade ≥ 3, it was 0.2% [13].

Of the patients treated with avapritinib in the NAVIGATOR study, 22% discontinued treatment due to adverse events, compared to 8.3% in the VOYAGER study [16, 17]. Adverse events leading to treatment discontinuation in NAVIGATOR included: nervous system disorders (14%), psychiatric disorders (7%), and gastrointestinal disorders (2%). Dose modification was required in 73% of patients, and temporary discontinuation of treatment in 89% [16].

Avapritinib in Polish and international guidelines

The 2022 National Comprehensive Cancer Network (NCCN) guidelines recommend using avapritinib therapy in the first line of treatment (recommendation level 2A — an uniform NCCN consensus that the intervention is appropriate) in patients with unresectable or metastatic GIST with the *PDGFRA D842V* mutation. Dasatinib is recommended as a second-line option (2A). Under certain circumstances, for patients with GIST harboring the *PDGFRA D842V* mutation and showing progression despite treatment with avapritinib and dasatinib, ripretinib at a dose of 150 mg daily can be used (2A). Also, the European Society of Clinical Oncology (ESMO) guidelines indicate avapritinib as the basis for treating advanced GISTs with the *PDGFRA D842V* mutation (III, A: ESMO-MCBS v1.1. score: 3; ESCAT score: I–B) [19]. These recommendations are also reflected in the recommendations of the Polish Society of Clinical Oncology (PTOK) [20].

In the case of localized GISTs with the *PDGRA D842V* mutation, adjuvant imatinib therapy should not be used (IV, D). If radical surgery is unfeasible or is associated with severe consequences and the tumor contains the *PDGFRA D842V* mutation, neoadjuvant therapy with avapritinib may be considered (III, A: ESMO-MCBS v1.1 score: 3; ESCAT score: I–B) although reports on preoperative treatment are very scarce [19].

Practical information

When treating patients with GIST, the recommended starting dose of avapritinib is 300 mg. The tablet is administered orally daily on an empty stomach [13]. Treatment is continued until disease progresses or severe side effects occur. It is not recommended to use avapritinib concomitantly with moderate or potent CYP3A inhibitors (these include some macrolides: erythromycin, clarithromycin, telithromycin, antifungals — itraconazole, ketoconazole, voriconazole, drugs used to treat HIV/AIDS — cobicistat, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, conivaptan used to treat hyponatremia, and boceprevir used to treat hepatitis, and grapefruit juice). If discontinuation of the CYP3A inhibitor is not possible, the daily dose of avapritinib should be reduced from 300 mg to 100 mg [13].

No dose adjustment of avapritinib is required in patients 65 years of age and older. No dose adjustment is recommended in patients with mild hepatic impairment [total bilirubin < upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin 1–1.5 × ULN and any AST level], moderate impairment (total bilirubin 1.5–3.0 × ULN and any AST level), and mild-to-moderate renal impairment (creatinine clearance 30–59 mL/min). Avapritinib has not been studied in patients with severe hepatic (Child-Pugh class C) and renal (creatinine clearance 15–29 mL/min) impairment or end-stage renal disease and, therefore, is not recommended in these groups of patients [13].

Avapritinib may increase the risk of bleeding, and complete blood counts (including platelet counts) and coagulation parameters should be monitored during treatment. Monitoring is particularly important in patients with conditions predisposing to bleeding and in patients receiving anticoagulant therapy. Another important complication of avapritinib is intracranial bleeding. If the patient develops neurological symptoms of intracranial bleeding (vision problems, severe headache, drowsiness, or weakness), treatment should be discontinued immediately, and diagnostics should be performed through magnetic resonance imaging or computed tomography. If the diagnosis of intracranial hemorrhage is confirmed, treatment should be permanently discontinued [13].

Article Information and Declarations

Author contributions

B.K.: literature review, preparation of the original version of the manuscript, preparation of figures; N.W.: literature review, preparation of the original version of the manuscript, preparation of figures; P.S.: preparation of the work concept, literature review; preparation of the final version of the manuscript, supervision of the team; P.R.: preparation of the final version of the manuscript, supervision of the team.

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Conflict of interest

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Trastuzumab deruxtecan in the treatment of adult patients with HER2-positive breast cancer

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ABSTRACT

In 2020, approximately 18,000 women in Poland were diagnosed with breast cancer, and 6,000 of them died. In recent years, we have witnessed significant progress in the diagnosis and treatment of breast cancer patients. When detected early and treated appropriately, the prognosis is very good, and even some patients with distant metastases have experienced long-term survival. The most common biological subtype is hormone receptor-positive breast cancer, accounting for about 70% of diagnoses, showing expression of estrogen and progesterone receptors. Triple-negative breast cancer and HER2-positive breast cancer each make up approximately 15% of all cases. In the treatment of advanced HER2-positive breast cancer, a combination of docetaxel with pertuzumab and trastuzumab is used in the first line. In subsequent lines of treatment, options include trastuzumab deruxtecan (T-DXd), trastuzumab emtansine, lapatinib, tucatinib, margetuximab, and trastuzumab.

Trastuzumab derukstekan is an immunoconjugate that, upon entering the cell, releases a cytostatic agent that destroys its genetic material and neighboring cells (the "bystander effect"). It significantly prolongs the time to disease progression and overall survival compared to standard treatments used in the second and subsequent lines of treatment. It represents an effective and valuable therapeutic option for patients with early-stage HER2-positive metastatic breast cancer.

Keywords: breast cancer, HER-positive breast cancer, trastuzumab deruxtecan

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Introduction

Breast cancer (BC) is the most common malignancy diagnosed in women in Poland and worldwide, and second, after lung cancer, cancer-related cause of death. In 2020, approximately 18,000 women in Poland were diagnosed with breast cancer and 6,000 died from it. The incidence of breast cancer is increasing in all age groups, which is primarily related to changes in women's lifestyles [1]. Postponing the first birth, childlessness, sedentary lifestyle, obesity, smoking, drinking alcohol, and prolonged hormone replacement therapy (HRT) are just some of the modifiable factors that contribute to the increased incidence of breast cancer [2].

Enormous progress in the diagnosis and treatment of breast cancer has been observed in recent years. If this disease is detected early and treated appropriately, the prognosis is very good, and long-term survival is observed even in some patients with distant metastases. There are several specific biological subtypes of BC distinguished in daily clinical practice, based on the status of estrogen, progesterone, and HER2 receptors, as well as Ki-67 proliferation index value.

The most common biological subtype is hormone-dependent BC, with positive expression of estrogen (ER) and progesterone receptors (PR), accounting for approximately 70% of cases. Both triple-negative (TNBC) and HER2-positive BC account for approximately 15%

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of all cases. They are characterized by an aggressive course, rapid cell proliferation, increased risk of disease recurrence, metastasizing to parenchymal organs, and development of treatment resistance [3].

HER2 receptor

The *HER2* gene is located on chromosome 17, and its amplification leads to overexpression of the HER2 receptor. There are various interchangeable terms in the literature, which describe this receptor. The name of HER2 results from its similarity to the human epidermal growth factor receptor (HER1). The HER2 receptor was derived from glioblastoma multiforme cell lines, one of the neuronal tumors, hence the name Neu. In turn, the name ErbB-2 is related to *HER2* gene similarity to the avian erythroblastosis oncogene B, encoding epidermal growth factor receptor (EGFR). Gene cloning showed that HER2, Neu, and ErbB-2 are encoded by the same ortholog.

The epidermal growth factor receptor family includes 4 receptors: HER1/EGFR, HER2, HER3, and HER4. The receptor is composed of an extramembrane part that binds to the ligand, a lipophilic transmembrane part, and an intramembrane part with tyrosine kinase activity. HER2 overexpression leads to its dimerization and activation of proliferation and repair pathways, including PI3K-AKT-mTOR, mainly in a ligand--dependent or independent manner. Activation of HER2-dependent mechanisms is one of the most important factors leading to growth and regeneration of breast cancer cells and apoptosis inhibition [4].

The *HER2* gene was discovered in 1984 by Weinberg's group. Subsequently, Dennis Slamon described the overexpression of the *HER2* gene protein product on the surface of aggressive BC subtype cells. In the mid-1990s, clinical trials were initiated with use of trastuzumab, a human monoclonal antibody that inhibits the dimerization of the HER2 receptor with other EGFR family receptors in patients with advanced HER-positive breast cancer [5]. In 2005, the results of a study involving approximately 10,000 patients with early breast cancer were published, showing that the use of trastuzumab in adjuvant treatment reduced the risk of recurrence by half and risk of death by approximately 30%. In addition to inhibiting signal transduction, trastuzumab stimulates antibody-dependent cytotoxicity and the immune system to destroy cancer cells; it also has anti-angiogenic effects and shows additive or synergistic activity with chemotherapy [6–8].

There are ongoing studies on new drugs that inhibit HER2 receptor: monoclonal antibodies (pertuzumab) and tyrosine kinase inhibitors (lapatinib, tucatinib, neratinib), which will significantly improve the prognosis of patients with early and advanced breast cancer [9–12]. Recently, immunoconjugates, i.e. a combination of an antibody with a cytostatic drug, which is called a "Trojan horse", are gaining more and more importance. After binding to the cellular surface receptor, the molecule penetrates the cell, releases a cytostatic agent that damages the genetic material and leads to cell apoptosis. In the next step, it leads to damage to neighboring cells, which is called the "bystander effect".

Advanced HER2-positive breast cancer

Based on the results of the Cleopatra study, chemotherapy combined with dual HER2 blockade with pertuzumab and trastuzumab is the standard of care in the treatment of patients with metastatic HER2-positive breast cancer. In patients with newly diagnosed metastatic or recurrent breast cancer, docetaxel was used in combination with two antibodies at least 12 months after completion of definitive treatment. After 6 courses of combination therapy, treatment with pertuzumab and trastuzumab was continued until disease progression or unacceptable side effects prevented further therapy. Among 808 enrolled patients, 402 patients were randomly assigned to triple therapy, and 406 patients received docetaxel in combination with trastuzumab and placebo. After a median follow-up of approximately 99 months, median overall survival (OS) in the experimental arm was 57.1 months and in the control arm 40.8 months [hazard ratio (HR) = 0.69; 95% confidence interval (CI) 0.58–0.82], and the risk of death was reduced by approximately 30% [10].

Until recently, the standard of care in the next treatment line was the use of trastuzumab emtansine. According to the results of the EMILIA study, which enrolled 991 patients, therapy with trastuzumab emtansine was associated with prolonged progression-free survival (PFS) compared to lapatinib and capecitabine (9.6 *vs.* 6.4 months; HR = 0.65; 95% CI 0.55–0.77; $p < 0.001$), as well as prolonged OS (30.9 *vs.* 25.1 months; HR = 0.68; 95% CI 0.55–0.85; $p < 0.001$) and a better objective response rate (43.6%, *vs.* 30.8%; $p < 0.001$). Trastuzumab emtansine showed not only greater effectiveness but also a more favorable safety profile and better tolerability in patients previously treated with taxanes and trastuzumab [13].

In patients previously treated with pertuzumab and trastuzumab in combination with docetaxel and trastuzumab emtansine, the use of tucatinib in subsequent line prolonged PFS (7.8 *vs.* 5.6 months, HR = 0.54; 95% CI 0.42–0.71; p < 0.001) and OS (21.9 *vs.* 17.4 months; HR = 0.66; 95% CI 0.50–0.88; p = 0.005) as compared with placebo with trastuzumab and capecitabine. Previous studies indicated the activity of tyrosine kinase inhibitors in combination with capecitabine in patients with central nervous system (CNS) metastases; however, adverse events limited treatment initiations. Blockade of the extramembrane and intramembrane domains in the experimental arm improved the prognosis of patients with stable and progressive brain metastases, with acceptable tolerance [12].

Subsequent treatment lines include a combination of lapatinib with capecitabine, trastuzumab with capecitabine, or another cytostatic. Due to the low objective response rate (9–27%) and short PFS (3.3–6.1 months), the search for a therapy with higher effectiveness was extremely important [11, 14–16].

Trastuzumab deruxtecan

Trastuzumab deruxtecan (T-DXd) is an immunoconjugate, a combination of trastuzumab with a cytostatic agent — a topoisomerase I inhibitor. The effectiveness of T-DXd was established in the phase II DESTINY-Breast01 study, which enrolled patients with advanced HER2-positive breast cancer after progression on trastuzumab emtansine therapy. The study showed an objective response rate of 61% and a benefit in terms of PFS prolongation [17].

Phase III DESTINY-Breast02 study was designed to confirm the effectiveness of T-DXd in patients previously treated with trastuzumab emtansine compared to the investigator's choice therapy. It enrolled 608 patients, of whom 406 were randomly assigned to the experimental arm and 202 to the lapatinib or trastuzumab with capecitabine arm. The median patient age was 54 years, and ER expression was detected in approximately 60% of patients in both arms. Fewer than 80% of patients had previously received pertuzumab-based therapy, almost 80% had metastases to parenchymal organs, and almost 20% had CNS metastases. The median of prior treatment lines, excluding hormone therapy, was 2 in both groups. Median PFS was in favor of T-DXd (17.8 *vs.* 6.9 months; HR = 0.36; p < 0.0001). Clinical benefits were observed in all subgroups, regardless of ER status, prior pertuzumab therapy, as well as parenchymal organ and CNS metastases. Median OS in the experimental arm was significantly longer than in the control arm (39.2 *vs.* 26.5 months; HR = 0.66; p = 0.0021). Objective responses were observed in 70% of patients treated with T-DXd and in 29% of patients in the investigator's choice therapy arm. Notably, 6% of patients in the T-DXd arm and 27% in the control arm received T-DXd after progression.

In the subgroup of patients with stable CNS metastases (18% in each arm), prolonged PFS was observed, and further analysis will help to precisely determine the effectiveness of T-DXd in this special patient population.

In total 14% of patients receiving T-DXd therapy and 5% of patients receiving therapy of the investigator's choice required treatment discontinuation due to adverse events. In the T-DXd arm, the predominant symptoms were pneumonia (6%) and interstitial lung disease (4%), while in the control arm, it was hand-foot syndrome (2%). There were 4 treatment-related deaths in patients receiving T-DXd: pulmonary complications occurred in 3 patients and acute myeloid leukemia in 1 patient. The most common adverse events were: nausea, vomiting, fatigue, alopecia, and hand–foot syndrome.

Interstitial lung disease (ILD) occurred in 42 (10%) patients in the T-DXd group and 1 (< 1%) patient in the control arm. The median time to ILD onset was 29.9 and 2.9 months, respectively.

Left ventricular dysfunction was observed in 18 (4%) patients treated with T-DXd and in 3 (2%) patients receiving therapy of the investigator's choice. Treatment was discontinued for this reason in 2 (< 1%) and 1 (< 1%) patients, respectively [18].

Median PFS in the DESTINY-Breast02 study was significantly longer than median PFS achieved in other studies using new therapies in previously treated patients with advanced HER2-positive breast cancer. In studies with trastuzumab emtansine, margetuximab, neratinib, and tucatinib, median PFS was 5.6 to 7.8 months. Obviously, it is important to remember that this is only a numerical comparison of the duration of response (DoR), and not a head-to-head comparison [12–15].

Encouraging results of T-DXd use after trastuzumab emtansine therapy in previously treated patients prompted researchers to evaluate the effectiveness and safety of this drug in earlier stages of BC. The DESTINY-Breast03 study compared the effectiveness of two immunoconjugates: trastuzumab emtansine and T-DXd. Trastuzumab emtansine consists of an antibody and a cytostatic agent — a microtubule inhibitor, while T-DXd contains a topoisomerase I inhibitor. The number of cytostatic molecules in relation to the antibody is more than twice as high in the case of T-DXd than in the case of trastuzumab emtansine (8 *vs.* 3.5).

Patients were qualified for the study after progression on trastuzumab and taxanes perioperative therapy due to advanced or recurrent disease during or up to 6 months after its completion. In total 261 patients were qualified for the experimental arm and 263 for the trastuzumab emtansine arm. The median age was approximately 54 years in both arms. Median PFS was over 4-fold longer in the T-DXd arm (28.8 months *vs.* 6.8 months; HR = 0.33; 95% CI 0.26–0.43). Median OS was not reached in the experimental arm, and the risk of death was reduced by approximately 35% (HR = 0.64; 95% CI 0.47–0.87; p = 0.0037). Objective responses were observed much more often in the experimental arm (79% *vs.* 35%). Complete responses were observed in 21% of patients treated with T-DXd and in 10% of patients receiving trastuzumab emtansine. The effectiveness of therapy was observed in all analyzed subgroups, regardless of ER status, use of pertuzumab, metastases in parenchymal organs, and CNS.

In 20% of patients in the T-DXd group and 7% of patients in the trastuzumab emtansine group, treatment was discontinued due to adverse events: pneumonia and interstitial lung disease, and thrombocytopenia and pneumonia, respectively. Pulmonary complications occurred in 15% of patients receiving the experimental drug and in 3% of patients receiving standard therapy, and no death due to these AEs was observed in either group. The median time to complication was 8.1 months for T-DXd and 11.7 months for trastuzumab emtansine. The remaining AEs were consistent with the drug's safety profile. Trastuzumab deruxtecan was used in subsequent treatment lines in 2% of patients in the experimental arm and 7% of patients in the control arm [19].

In the EMILIA study, the median follow-up was 19.1 months, and median OS was 30.9 months, while after 2 years of follow-up in the DESTINY-Breast03 study, median OS for the experimental arm was not achieved, and PFS achieved in this study was the longest achieved so far in patients with HER2-positive advanced breast cancer [13]. The results of previous studies have varied, with median PFS of approximately 10 months, and even the results of the CLEOPATRA study, using dual HER2 blockade combined with chemotherapy in the first treatment line were not so encouraging (PFS 18.7 months) [10].

The exceptional effectiveness of T-DXd in the treatment of patients with advanced breast cancer makes it revert to earlier stages of the disease. Currently, the DESTINY-Breast09 study is ongoing, with previously untreated patients with advanced HER2-positive breast cancer randomly assigned to 3 arms: docetaxel in combination with pertuzumab and trastuzumab, T-DXd in combination with pertuzumab, and T-DXd. The results of this study may be very interesting, especially considering safety profile and tolerability, with expected extraordinary effectiveness [20].

Conclusions

Trastuzumab deruxtecan is an effective and valuable therapeutic option for patients with advanced HER2-positive breast cancer at an early stage of treatment. In addition to the well-known gastrointestinal and hematological side effects, which are manageable in daily clinical practice, pulmonary complications constitute a new challenge and will require good cooperation of an interdisciplinary team including an oncologist, a radiologist, and a pulmonologist. The benefits resulting from previous experience encourage attempts to introduce the drug at an early stage of therapy, including perioperative treatment.

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Commentary

on *Trastuzumab deruxtecan in the treatment of adult patients with HER-positive breast cancer*

Breast cancer is a diverse malignancy in terms of molecular characteristics. Approximately 15% of breast cancers are characterized by expression of human epidermal receptor type 2 (HER2) or amplification of the *HER2* gene [1]. HER2-positive cancers have a more aggressive course than HER2-negative cancers; however, the introduction of anti-HER2 drugs (trastuzumab, pertuzumab, lapatinib, tucatinib, and neratinib) significantly improved prognosis in this population. Further progress in the treatment of patients with HER2-positive breast cancer is associated with the introduction of conjugates composed of trastuzumab and cytotoxic drugs, for example, the combination of trastuzumab and emtansine (T-DM1) and trastuzumab and deruxtecan (T-DXd).

The current classification of HER2-positive or HER2-negative breast cancers has changed due to identification of cancers with low HER2 expression (HER2-low category), e.g. with immunohistochemical (IHC) score of 1+ or 2+ without in situ hybridization (ISH) amplification. HER2-low breast cancers may include some triple-negative and luminal cancers [2].

In 2022, the results of the phase III DESTINY-Breast04 study were published, which assessed the value of T-DXd compared to chemotherapy of the investigator's choice (paclitaxel, nab-paclitaxel, gemcitabine, capecitabine or eribulin) in breast cancer patients with low HER2 expression and with or without expression of hormone receptors (HRs). Qualified patients had previously failed chemotherapy and hormone therapy. A significant prolongation of progression-free survival and overall survival was observed, mainly driven by patients with hormone-dependent cancer (10 *vs*. 5 months and 24 *vs*. 17.5 months, respectively). Clinical benefits in patients with HR-negative breast cancer were also significant, but numerically slightly smaller than in patients with hormone-dependent cancer (progression-free survival and overall survival were 8.5 and 3 months and 18 *vs*. 8 months, respectively). Treatment with T-DXd was generally slightly better tolerated, but interstitial lung disease and reduced left ventricular ejection fraction were more common in patients receiving conjugate [3]. Patients receiving T-DXd in the future should be carefully monitored for the risk of both of these complications.

The results of the DESTINY-Breast04 study justified the registration of T-DXd in the treatment of patients with advanced breast cancer with low HER2 expression after previous chemotherapy. The drug is not currently reimbursed in Poland for this indication although the results of this pivotal study provide a convincing justification for the use of T-DXd in another indication in BC patients, apart from those discussed in this publication.

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VIA MEDICA

CASE REPORT

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Individualized surgical treatment in patients with advanced gastrointestinal stromal tumor — a case series

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ABSTRACT

In this case series we present the cases of two patients at a metastatic stage of stomach gastrointestinal stromal tumor, who received treatment with imatinib. After a period of disease stability patients showed signs of resistance to the first-line therapy and despite the promising switch to sunitinib, developed life-threatening complications. Salvage surgeries were performed, aimed at preserving patients life and simultaneously reducing the tumor mass. Operation greatly improved patients condition and allowed for successful continuation of tyrosine kinase inhibitor treatment, showing that surgery should be considered a viable complement to the chemotherapeutical treatment.

Keywords: gastrointestinal stromal tumors, neoplasm metastasis, salvage therapy, imatinib mesylate, fistula

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Introduction

Gastrointestinal stromal tumors (GIST) are considered the most common mesenchymal neoplasms of the gastrointestinal tract [1]. Their overall incidence is estimated to be between 10 and 20 cases per million, occurring predominantly in patients above 50 years old, with equal distribution between men and women [2, 3]. Typically, GIST is located in the stomach or the small intestine, originating from the interstitial cells of Cajal, which act as pacemaker cells regulating peristalsis in the gastrointestinal tract [4]. Most commonly GIST arises as an effect of gain of function mutation in the KIT proto-oncogene or less predominantly in the *PDGFRA* gene [2, 5, 6].

The diagnosis of GIST comprises recognizing its clinical and molecular features, as wella s a characteristic anatomic location of the tumor. The majority of GISTs show a positive expression of characteristic KIT (CD117), DOG-1, and CD34 markers in the immunohistochemical analysis [7].

Gastrointestinal stromal tumors range in size and aggressiveness, but all of them can eventually give metastases. Patients may present with symptoms such as gastrointestinal bleeding, abdominal pain, and dysphagia, but are often fully asymptomatic. Due to a lack of specific symptoms, patients frequently seek medical advice when the disease is already in its advanced stage, with 20% to 30% of presenting patients having metastases at the point of the initial diagnosis [8].

Here we present two cases of patients at a metastatic stage of stomach GIST.

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Case report

Case 1

A 55-year-old woman was referred by her general practitioner to the Department of Gastrointestinal Cancer with a 3-month history of discomfort in the abdominal region as the only symptom. On physical examination, the patient had a mildly enlarged liver, with a palpable, uneven border.

The patient was immediately taken for a computed tomography (CT) scan of the abdomen, revealing a growth in the left epigastrium measuring 106 × 76 mm and multiple metastases in the liver. Gastroscopy was performed, displaying a massive, ulcerated infiltration on the posterior wall of the stomach. Additional peritoneal metastases were shown in the following positron emission tomography-computed tomography (PET-CT) scan. A liver metastasis biopsy was performed. Tissues were analyzed with immunohistochemical staining, which revealed a set of markers characteristic for GIST: CD 117 (+), DOG-1 (+), and CD 34 (+), confirming the diagnosis. Due to the diffuse metastases, a radical operation was not possible, thus systemic therapy with imatinib was administered.

A follow-up CT scan after 5 months revealed an area of elevated radiodensity in the tumor on the gastric wall (from 27 HU to 48 HU). The patient was taken for gastroscopy, which showed a spot of changed tissue on the inner surface of the stomach, associated with the large, submucosal tumor. The observed symptoms of tumor progression resulted in the introduction of second-line treatment with sunitinib. The new treatment caused a moderate regression, as the tumor measured consecutively: 90 × 70 mm, 82 × 65 mm, and finally 76 × 60 mm (the best response) in the successive follow-up CT scans. Despite a good response to the treatment, the disease remained in the dissemination phase (metastases to the liver and peritoneum).

After 3 years of treatment, the patient presented to the clinic again, with signs of esophageal erosion and esophagitis [endoscopically classified as grade B in the Los Angeles (LA) classification], as well as anemia. The patient was promptly taken for a CT scan, which revealed development of a fistula in the gastric wall damaged by the neoplastic process (Fig. 1).

To combat the swift decline in the patient's overall condition, it was decided that a salvage surgery is necessary. A wedge resection of the stomach with the primary tumor was performed, with tumor tissues submitted for a histopathological examination. The tumor showed histopathological signs of regression, probably responsible for the formation of the fistula. The patient's condition substantially improved after surgery although the disease was still in the stage of dissemination (metastases to the liver and peritoneum).

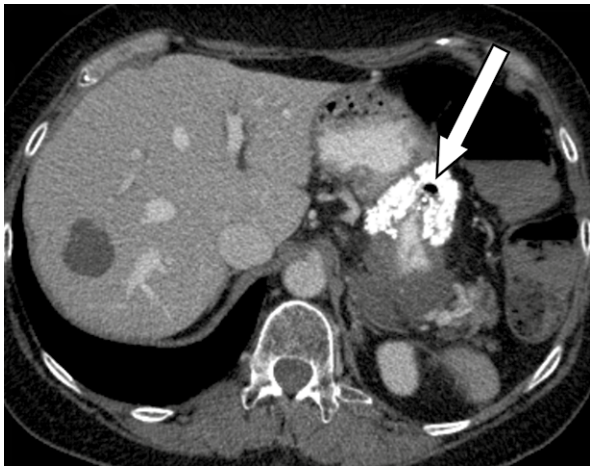

Figure 1. Computed tomography image of the abdomen showing a partially calcified tumor, with signs of decay in the central section. Visible fistula canal to the gastric lumen (arrow)

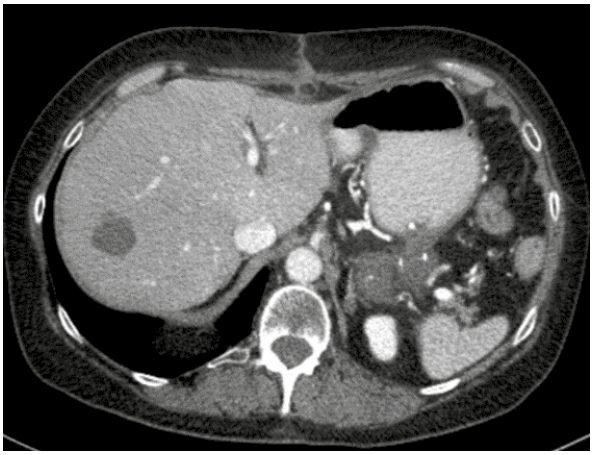

Figure 2. Computed tomography image of the abdomen 3 months after surgery. Status after partial resection of the tumor

A follow-up CT scan with contrast, performed 3 months later, confirmed a successful closure of the fistula (Fig. 2). The tumor measured 42 × 30 mm, which demonstrated a further shrinking of the tumor in the postoperative period. In the 40-month course of follow-up examinations after surgery, the patient's condition remains stable despite the diffuse neoplastic process. The patient continues the treatment with sunitinib.

Case 2

A 49-year-old man was admitted to the Department of Gastrointestinal Cancer with a suspicion of a neoplastic process of unknown character recognized by a primary care practitioner. On a physical examination,

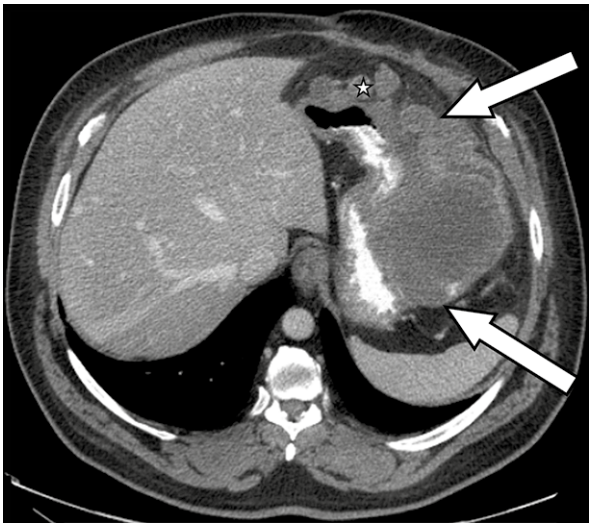

Figure 3. Computed tomography image of an exophytic tumor in the gastric wall (arrows). Visible metastasis in the peritoneum (*)

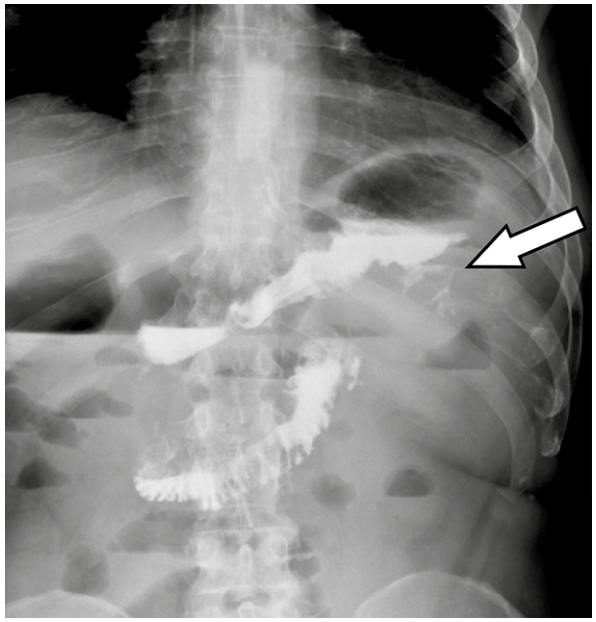

Figure 4. Computed tomography image of the abdomen, revealing the presence of a fistula to the tumor mass (arrow)

an atypical mass in the patient's left epigastrium with a diameter of around 20 cm was detected.

In order to remove the abnormality, laparotomy was performed; however, it revealed a diffuse neoplastic process affecting the stomach, as well as segment VI of the liver, the pancreas, distal part of the duodenum, spleen, the greater omentum, and the peritoneum (Fig. 3). A radical operation was not possible, thus treatment with imatinib was introduced instead.

A month later the patient presented again with signs of significant anemia and melena. Emergency gastroscopy was performed, showing stomach contents resembling "ground coffee" and a clotted ulceration on the greater curvature of the stomach. A following CT scan revealed an underlying nodular tumor, measuring 150 × 120 mm. The biopsied mass was analyzed with immunohistochemical staining, which unveiled the presence of characteristic markers such as CD 117 (+), DOG-1 (+), and CD 34 (+), confirming the diagnosis of GIST. Additionally, a genetic test showed a deletion affecting exon 11 of the KIT gene, further reinforcing the diagnosis.

In the follow-up CT scans, the tumor was gradually shrinking (104 × 92 mm), unfortunately, two years later, the patient presented with a fever and lack of bowel movement. Another CT scan revealed a sudden growth of the tumor (144 × 107 mm) as well as visible bubbles of gas within the tumor, suggesting a formation of a fistula between the tumor and the splenic flexure of the colon (Fig. 4). That progression prompted the introduction of second-line treatment with sunitinib, but despite the change in medication and extensive ambulatory care, the patient's condition deteriorated. A loss of over 30 kg of weight in two months was reported as well as a development of life-threatening anemia, with signs of upper gastrointestinal bleeding.

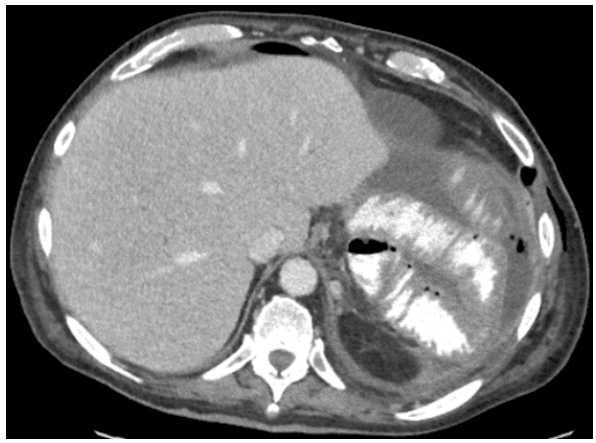

Figure 5. Computed tomography image of the abdomen after surgery. Status post total gastrectomy

In order to improve the patient's quality of life, palliative surgery was performed, consisting of transverse colectomy, gastrectomy, splenectomy, and partial pancreatectomy with a reconstruction of the gastrointestinal tract by a roux-en-Y gastric by-pass (Fig. 5). Following surgery, the patient's condition was gradually improving. After the withdrawal of life-threatening symptoms, the patient was referred to the Department of General Surgery and Clinical Nutrition for further treatment. The patient died 19 months after surgery due to disease progression.

Discussion

Before the application of specific tyrosine kinase inhibitor (TKI) — imatinib, GIST was considered resistant to any form of conventional chemotherapy or radiotherapy [9]. The standard therapy for a patient with GIST diagnosis was limited to surgery, with no established method of complex treatment for advanced tumors. The introduction of Imatinib mesylate in the treatment of GIST has changed treatment capabilities, allowing for clinically validated suppression of tumor growth, thus making GIST treatment a paradigm in the treatment of solid tumors with molecularly targeted therapy. Imatinib is an inhibitor targeting multiple receptor tyrosine kinases which are responsible for carcinogenesis of most GIST [2]. It blocks the signaling *via* KIT, the pathway which malfunctions. Imatinib's affinity to the etiology of GIST resulted in a global change in the therapeutic approach, as it allows approximately 65–80% of patients to achieve a partial response, with another 15–20% having a stable disease [2, 10].

Unfortunately, 40 to 50% of patients show signs of disease progression after 2–3 years of therapy. Complete responses are also quite rare (5–7%) [4]. This is likely caused by the tumor forming resistance to Imatinib, probably via the mechanism of additional mutations in the KIT gene limiting the effectiveness of the medication [11]. Patients who do not respond to Imatinib or do not tolerate it are administered a second-line treatment with sunitinib, which is a similar inhibitor of tyrosine kinase. Unfortunately, the tumor tends to form a resistance to it as well. As the quality of response in clinical trials is still far below the intended, we are eager to search for improvements in our methods.

Surgery in GIST therapy remains an important part of the therapeutic process. For all non-metastatic tumors of diameter above 2 cm, a surgical approach is preferred, curing about 60% of patients [12]. The optimal outcome of the operation is a total gross resection of the tumor, with safety margins and no ruptures, which would significantly increase the risk of peritoneal spread. Neoadjuvant treatment is typically administered when the tumor cannot be removed in a radical operation or a size reduction of a potentially resectable tumor is likely to cause life-threatening complications.

Surgery is also considered, after a maximal response to Imatinib, if the tumor masses are fully resectable, as it could decrease the risk of developing resistance to the medication. Crucially, in cases where the tumor masses are not fully resectable after a maximal response to TKI, surgical treatment is neither recommended nor discouraged. There have been reports of successful resections of metastatic lesions with no evidence of disease in long-term follow-up [13]. It remains unknown whether cytoreduction (i.e. conscious partial resection) for patients with stable disease on Imatinib reduces the chance of tumor developing resistance. Similarly, the benefits of the surgical approach in cases with resistance to Imatinib are yet to be estimated [8].

As TKI treatment can result in massive degeneration of tissues, and life-threatening complications such as tumor ruptures, perforations, hemorrhages, and bowel or bronchus obstructions. In such situations, rescue surgery is a viable method of managing those emergencies and should be performed in cases of an apparent threat to the patient's life [14].

The two cases of patients with advanced GIST of the stomach presented here are precedents in which life-threatening conditions of the patients forced surgeons to perform salvage surgeries on the tumors. Partial resection of GIST (primary tumors in the presence of metastatic lesions) was primarily meant to stop the deterioration of the patient's health, but it also significantly decreased the tumor mass. The striking observation in both of these cases is that the operation proved to be a viable form of cytoreduction. The imatinib and the sunitinib treatments allowed for moderate regression, but eventually proved unable to save the patients from severe complications in the long term. The cases described were different in terms of response to the therapy: in the first case, the patient developed a fistula as a consequence of a good response to the second-line treatment, in the second case, the patient had clinical progression during therapy.

For those patients, performed cytoreduction surgeries enabled the chemotherapeutic agents to function effectively again, resulting in an improvement in their condition. Therefore, cytoreduction should be carefully considered in patients treated for GIST with the TKI, optimally when the maximum effect of the therapy has been achieved [15]. That usually corresponds to the interval between the 6th and the 18th month of TKI therapy [16]. A surgical intervention, preferably through function-sparing surgery, is thus a viable complement to TKI therapy. Our patients in both cases did not fulfill the criteria for maximum effect of TKI therapy because they were in the dissemination phase of GIST from the very beginning of the therapy.

Conclusions

The palliative treatment of GIST with tyrosine kinase inhibitors has major limitations, likely diminished with an introduction of surgical intervention into the therapeutic process. Effective therapy of GIST requires a balance between surgical and chemotherapeutic treatments. Surgery is likely to improve the outcome for patients who respond to TKI treatment and should be considered when the maximum effect of the therapy

has been achieved. Salvage surgery should be considered whenever the patient's condition precludes continuation of TKI and surgery may lead to a reintroduction of the therapy; however, all treatment decisions should be undertaken after individualized assessment by a multidisciplinary team.

Article Information and Declarations

Ethics statement

The retrospective study of all data was conducted in accordance with the Declaration of Helsinki.

Author contributions

The authors confirm contribution to the paper as follows: J. Pałucki, M.L., I.P., A.K., T.O.: clinical investigation; J. Pytlos, T.O.: writing — original draft; all authors: writing — review and editing.

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None to be declared.

Conflict of interest

The authors declare no conflict of interest.

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VIA MEDICA

CLINICAL VIGNETTE

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SARS-CoV-2 recurrent infections in a patient with metastatic colon cancer during chemotherapy

Keywords: SARS-CoV-2, chemotherapy, colon cancer, recurrent infections

A 72-year-old man with a metastatic *KRAS* gene mutated colon adenocarcinoma was admitted to the hospital for effort dyspnea and subfebrile body temperature. He was after transversostomy in 2019 and in the course of a palliative chemotherapy FOLFIRI regimen (irinotecan, calcium folinate, 5-fluorouracil) with secondary prophylaxis with filgrastim. On admission (August 2020), his general condition was quite good — Eastern Cooperative Oncology Group Performance Scale 1 (ECOG PS 1). He reported fatigue, dyspnea, partial loss of taste, and cold sweat. A polymerase chain reaction test (RT-PCR; KIT LabSystem) was positive for SARS-CoV-2 (RdRP, E, and N gene positive). In this period, the variant of the concern (VC) was primarily Wuhan SARS-CoV-2. Non-contrast computed tomography (NCCT) of the chest showed ground glass opacifications in the subpleural region, focal consolidations, and moderate pleural effusion, mostly in the lower field of the right lung (Fig. 1A, B). The patient was admitted to a single-ward hospital for the treatment of pneumonia. He received oxygen therapy, a prophylactic dose of low molecular weight heparin, ceftriaxone, and 1 unit of convalescent plasma. He finished the treatment after 13 days, obtaining the elimination of the virus confirmed by the RT-PCR test and resolution of inflammatory changes in the control NCCT (Fig. 2A, B). Due to treatment with convalescent plasma, he was not qualified for direct vaccination against SARS-CoV-2. Then, from 09/2020, due to colon cancer progression, he received the second-line palliative chemotherapy FOLFOX4 (oxaliplatin, calcium folinate, 5-fluorouracil). In April 2021, he was hospitalized in the Surgery Department to restore the continuity of the digestive tract. After the operation, the SARS-CoV-2 RT-PCR test was positive again. In this period, the British variant (Alpha) was dominant

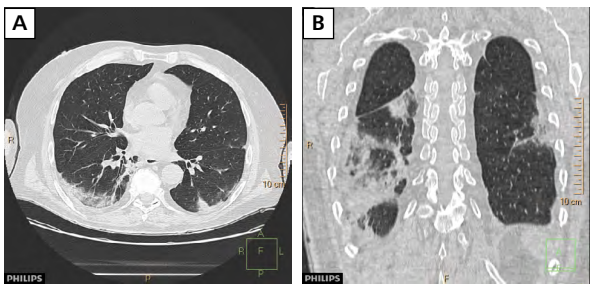

Figure 1. Non-contrast computed tomography of the chest lung window was performed on the day of admission. The pulmonary changes in keeping with SARS-CoV-2 infection are visible — ground glass opacifications in the subpleural region, focal consolidations, and moderate pleural effusion; **A.** Axial scan; **B.** Coronal scan

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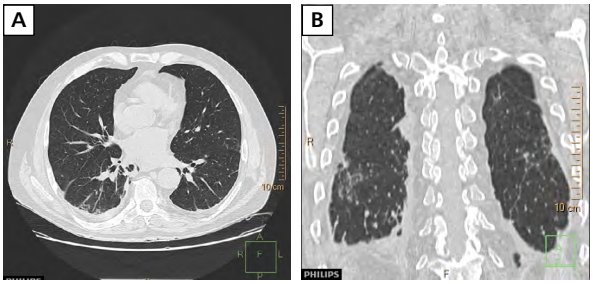

Figure 2. Non-contrast computed tomography of the chest lung window was performed on the 9th day of treatment. The partial regression of pulmonary changes in keeping with COVID-19 infection are visible — subpleural fibrotic changes and moderate pleural effusion; **A.** Axial scan; **B.** Coronal scan

(who.int/activities). Chest NCCT showed patchy interstitial densities in the lower and middle fields of both lungs. He was in good general condition (ECOG 1), without symptoms of respiratory failure or fever, but he had a purulent discharge from the postoperative wound. He was admitted to the isolation ward and initially treated with cefuroxime and metronidazole, and then according to the antibiogram for *Morganella morgani* with piperacillin-tazobactam, and ciprofloxacin. During hospitalization, he developed shortness of breath and severe respiratory symptoms (saturation when breathing room air < 90%) with increasing inflammatory parameters. We administered oxygen therapy, steroid therapy, transfusion of 1 unit of convalescent plasma, and remdesivir in a loading dose of 200 mg intravenously followed by 100 mg daily for 5 days in total. Respiratory efficiency improved and saturation normalized (≥ 95%). One month later, he was admitted in emergency mode and operated on due to an entero-cutaneous fistula and wound infection. He died in June 2021 due to postoperative complications.

Patients with colorectal cancer are in the group with increased risk of severe complications during SARS-CoV-2 infection [1]. This group includes all immunocompromised patients, regardless of their vaccination status, as well as people aged > 70 years who have received the last dose of the primary series of vaccination > 6 months and have an additional risk factor, e.g. active cancer [2]. The several key complications of SARS-CoV-2 infection in this group is COVID-19-disease pneumonia that can lead to acute respiratory distress syndrome. The course of SARS-CoV-2 infection and COVID-19 disease in immunocompromised patients depends on the immune system efficiency and probably on the virus variant. SARS-CoV-2 vaccines reduce the risk of developing a severe infection and improve the prognosis of patients with COVID-19 disease. According to recent studies, patients with gastrointestinal cancer undergoing systemic therapy have a good immune response to vaccination [3]. Lau et al. showed that the anti-spike antibody level significantly increased after the first dose of the vaccine, and one month after the second dose, 90% of patients have seropositivity [3]. However, the pseudoviral neutralization (pVNT80) decreased after 20–39 days after the second dose [3]. According to the recommendations, the SARS-CoV-2 vaccine should be given before the start of the chemotherapy or before the next cycle to avoid the nadir phase [4]. Due to the waning of vaccine immunity booster doses are now widely recommended [2].

Article Information and Declarations

Author contributions

F.Z., R.D.: conception and design.
All authors: provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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