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Address for correspondence:
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Original article

Malnutrition in cancer patients

Frequency of malnutrition in older adults according to different types of cancer

Teodoro J. Oscanoa[1, 2, 3], Edwin C. Cieza[1, 2, 3], Maryam Pourhassan[4], Roman Romero-Ortuno[5, 6]

[1] Universidad Nacional Mayor de San Marcos, Facultad de Medicina, Lima, Peru
[2] Universidad de San Martín de Porres, Facultad de Medicina Humana, Lima, Peru
[3] Geriatric Department, Almenara Hospital, ESSALUD, Lima, Peru
[4] Department of Geriatric Medicine, Marien Hospital Herne, Ruhr-Universität Bochum, Herne, Germany
[5] Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland
[6] Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland

Introduction. The severity and prevalence of cancer-related malnutrition vary among different cancer types. This study assessed malnutrition frequency in older adults (≥60 years) based on specific cancer types.

Material and methods. An observational, retrospective, case-control study reviewed electronic reports, with (cases) and without cancer (control) patients. Malnutrition was defined using the Mini Nutritional Assessment Short Form (MNA-SF).

Results. Malnutrition prevalence was 31.5% in cases and 13.2% in controls ($p < 0.001$), with an odds ratio (OR) of 3.0; 95% CI: 2.0–4.5; $p < 0.001$. The highest malnutrition risk was associated with pancreatic cancer (OR: 47.2), followed by head and neck (OR: 18.2), esophagus and stomach (OR: 15.9), lung (OR: 13.3), bile ducts (OR: 18.2), and colorectal (OR: 4.2) cancers ($p < 0.001$).

Conclusions. The prevalence of malnutrition varies by cancer type, with pancreatic, head and neck, esophagus, stomach, and lung cancers showing the highest risk.

Key words: malnutrition, neoplasms, geriatric oncology, aged patients, elderly patients, cancer

Introduction

Malnutrition, a state arising from disruptions in nutrient balance and inflammatory activity, can manifest acutely, subacutely, or chronically. Such imbalances lead to changes in body composition and an overall functional decline [1]. Malnutrition can be categorized into three types based on its etiology: starvation-related malnutrition (as seen in conditions like anorexia nervosa), chronic disease-related malnutrition (commonly associated with conditions such as cancer and rheumatoid arthritis), and acute disease or injury-related malnutrition (often observed in severe infections and burns) [2]. In recent European research, it was highlighted that older adults, specifically those over 65, face concerning rates of malnutrition: 28% in hospital settings, 17.5% in residential care, and 8.5% in community settings are at high risk [3]. In contrast, a Peruvian study demonstrated even more alarming rates, indicating that up to 60% of hospitalized older adults (aged over 60) were malnourished [4].

For cancer patients, the battle against malnutrition is particularly challenging. Disease-related shifts in nutritional

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and metabolic statuses often give rise to malnutrition, as well as conditions like sarcopenia and cachexia, both of which can significantly impact survival [5]. Cancer-related malnutrition is a progressive process often leading to sarcopenia, which involves the loss of skeletal muscle mass, often accompanied by a reduction in adipose tissue. Sarcopenia is characterized by low muscle strength and reduced muscle mass, resulting in decreased physical strength and function, ultimately affecting the patient's overall quality of life [6]. Cancer cachexia is currently understood as a multifactorial host-phagocytic syndrome, marked by a continuous decline in skeletal muscle mass, sometimes accompanied by loss of fat tissue [7]. Between 15% to 45% of patients exhibit involuntary weight loss at the time of cancer diagnosis, with an estimated 40% to 80% at risk of developing malnutrition as their illness progresses [8]. On the other hand, a recent meta-analytic study in older adults with cancer found that malnutrition is associated with an increased risk of mortality from all causes [9].

The prevalence of malnutrition in older adult patients with cancer has been calculated to be 41.9% [10]. Key risk factors contributing to malnutrition in this population include the type of tumor, adverse reactions linked to cancer treatments, cachexia, and age-related anorexia [10]. Despite the various factors associated with malnutrition in cancer patients, it has been observed that specific cancer types carry a higher risk of malnutrition and cachexia compared to others [11]. For instance, lung and pancreatic neoplasms are more frequently associated with wasting syndrome [12]. Recognizing this differential risk, our research aims to provide a comparative analysis, exploring the relationship between various cancer types and their associated malnutrition risks in older adults.

Material and methods

Setting

The present study employed a retrospective, observational, case-control design and was conducted at the Day Hospital of the Geriatric Department at Almenara Hospital, a reference hospital in Lima, Peru. The study involved a review of Comprehensive Geriatric Assessment (CGA) reports of older patients (≥60 years), both outpatient and hospitalized, conducted from January 2018 to April 2022. Patients diagnosed with cancer were categorized as cases, while those without cancer were referred to as controls. The inclusion criteria for the review of electronic medical records were as follows: participants had to have a diagnosis of cancer (except for controls) and complete CGA reports, which included a nutritional evaluation using the Mini Nutritional Assessment short version (MNA-SF). Patients in both the case and control groups were excluded if their nutritional evaluation did not use MNA-SF (e.g., relying solely on body mass index).

Comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA) was conducted by two trained geriatricians who assessed various domains, including function and mobility, nutritional status, cognition, mood, social environment, and comorbidities. Evaluation of basic activities of daily living (ADL) and instrumental activities of daily living (IADL) was performed using the Barthel index [13] and the Lawton index [14], respectively. Comorbidity evaluation utilized the Charlson index [15]. In defining depressive syndrome, DSM IV criteria were applied [16]. Cognitive assessment was carried out with the Mini-Mental State Examination (MMSE) Spanish version [17], and social assessment was conducted using the Gijon social family assessment scale [18].

Clinical identification of malnutrition

The Mini Nutritional Assessment Short Form (MNA-SF) was employed for nutritional risk identification. MNA-SF comprises six questions with a maximum score of 14, classifying patients as normal (12–14 points), at risk of malnutrition (8–11), or malnourished (<8). The latter category was used in the present study for malnutrition identification. MNA-SF has demonstrated good inter-observer reliability, with sensitivity and specificity values of 89% and 82%, respectively [19].

Statistical analysis

In both cases and controls, the distribution of patients was determined based on demographic factors (age and sex) and clinical data (nutritional status, cognitive impairment, comorbidity, frailty, and function status). Comparative descriptive statistical analysis was performed between the case and control groups, including variables such as median, mean (when normally distributed), standard deviation, median and range for continuous variables, and relative frequency for categorical variables. To compare cases and controls, we utilized the difference in means or frequencies, as appropriate.

To calculate the risk (odds ratio) of malnutrition associated with specific cancer types, cases with a particular cancer type were compared with the risk in the control group without cancer. The chi-square association test was employed to analyze the data. For tabular comparisons, 2 x 2 tables were constructed, comparing patients with or without malnutrition to those with a specific type of cancer (e.g., pancreatic cancer) and patients without cancer. Statistically significant differences were considered when $p < 0.001$.

Ethical considerations

This study received approval from the Research Ethics Committee of Hospital Nacional Guillermo Almenara Irigoyen in Lima, Peru (letter 80-CIEI-OIyD-GRPA-ESSALUD-2023, March 27, 2023). Stringent measures were implemented to safeguard patient information and ensure their privacy. Informed consent was obtained from all subjects.

Results

During the study period a total of 1,224 comprehensive geriatric assessments (CGAs) were conducted at the Day Hospital

of the Geriatrics Department at Almenara Hospital in Lima, Peru. Of these, 643 patients were considered for our analysis based on the presence of complete data, primarily the application of MNA-SF for malnutrition classification. Patients utilizing other metrics like body mass index (BMI) for malnutrition were excluded, leading to the omission of 581 patients.

The age distribution was 77.5 ± 7.5 years for cases and 79.8 ± 7.4 years for controls ($p < 0.001$). Malnutrition was significantly more prevalent among cases at 31.4% compared to 13.2% in controls ($p < 0.001$). Other significant variances between cases and controls encompassed factors such as BMI, age, the Charlson Comorbidity Index, and the frequency of depression (all $p < 0.001$). Comprehensive data comparisons are detailed in table I and figure 1. The ten most frequent neoplasms included colorectal (20.3%), esophagus and stomach (18.4%), prostate (9.6%), hematologic malignancies (lymphoma and leukemia) (10.5%), prostate (9.6%), breast (7.1%), skin (7.1%), gynecologic cancers (cervix, endometrium, ovary) (6.8%), lung (5.9%), pancreas (5.1%), and bile duct (4.2%) – see table II. Malnutrition frequency in older adults according to different cancer types are presented in table II. Our review identified the ten most prevalent neoplasms as follows:

- colorectal (20.3%),
- esophagus and stomach (18.4%),
- prostate (9.6%),

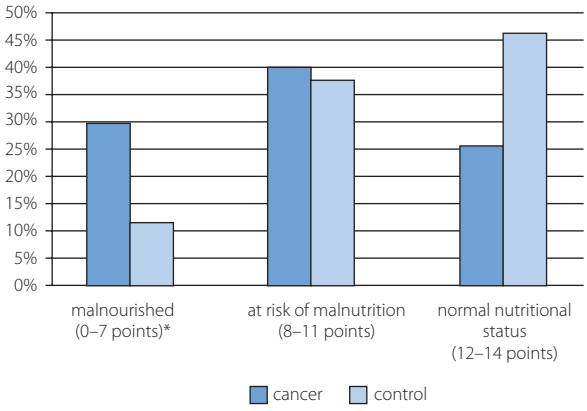

Figure 1. Frequency of malnutrition in older patients with or without cancer

* – according to the Mini Nutritional Assessment Short Form (MNA-SF)

- hematologic malignancies encompassing lymphoma and leukemia (10.5%),
- breast (7.1%),
- skin (7.1%),
- gynecologic cancers which include cervix, endometrium, and ovary (6.8%),
- lung (5.9%),
- pancreas (5.1%),
- bile duct (4.2%).

Table I. Patient characteristics

Variables	Cases (patients with cancer (n = 354)	Controls (patients without cancer) (n = 289)	p value
age, years (SD)	77.5 (7.5)	79.8 (7.4)	<0.001
male sex (%)	185 (52.3%)	130 (45.0%)	NS
female sex (%)	169 (47.7%)	159 (55.0%)	NS
Mini Nutritional Assessment Short Form (MNA-SF)			
total MNA-SF (SD)	9.2 (3.1)	10.8 (2.8)	<0.001
MNA-SF: 12–14 points – normal (%)	96 (27.1%)	138 (47.8%)	<0.001
MNA-SF: 8–11 points – at risk (%)	147 (41.5%)	113 (39.0%)	NS
MNA-SF: 0–7 points – malnourished (%)	111 (31.4%)	38 (13.2%)	<0.001
BMI: kg/m² – (SD – mean)	24.5 (4.2)	25.5 (5.1)	<0.001
Charlson Comorbidity Index, points – (SD – mean)	3.2 (1.9)	1.9 (1.2)	<0.001
Barthel Index for Activities of Daily Living points (SD)	88.2 (20.2)	86.4 (19.7)	NS
Lawton Instrumental Activities of Daily Living Scale score, points (SD – mean)	5.1 (2.3)	4.6 (2.5)	NS
percent of patients with depression (DSM IV criteria)	64	81	<0.001
percent of patients with social problem (Gijon Social Family Assessment Scale: >14 points)	5	10	NS
MMSE score (SD)	23.7 (5.5)	22.7 (6.3)	NS

NS – not significant; SD – standard deviation; MNA-SF – Mini Nutritional Assessment Short Form; BMI – body mass index; MMSE – Mini Mental State Examination

Table II. Malnutrition frequency in older adults according to different cancer types

Tumor site	Total number of cancer patients (n = 354)		Mini Nutritional Assessment Short Form (MNA-SF)						Odds ratio (95% CI) (MNA-SF: <8 cancer *vs.* control <8)	p value
			Normal nutritional status (12–14 points), n = 96 (27%)		At risk of malnutrition (8–11 points), n = 147 (42%)		Malnourished (<8 points), n = 111 (31%)			
	n	%	n	%	n	%	n	%		
colorectal	72	20.3	19	26.4	31	43.1	22	30.6	4.21 (2.07–8.56)	0.0001
esophagus and stomach	65	18.4	8	12.3	29	44.6	28	43.1	15.89 (6.81–37.09)	< 0.0001
hematological (non-Hodgkin lymphoma, leukemia)	37	10.5	11	29.7	16	43.2	10	27.1	3.30 (1.30–8.36)	0.0117
prostate	34	9.6	15	44.1	12	35.3	7	20.6	1.70 (0.65–4.45)	0.2846
breast	25	7.1	11	44.0	13	52.0	1	4.0	0.33 (0.04–2.64)	0.2960
skin	17	4.8	12	70.6	5	29.4	0	4.0	0.14 (0.01–2.49)	0.1993
gynecologic cancer (cervix, endometrium, ovary)	24	6.8	11	45.8	9	37.5	4	16.7	1.32 (0.40–4.38)	0.6495
lung	21	5.9	3	14.3	7	33.3	11	52.4	13.32 (3.54–50.16)	0.0001
pancreas	18	5.1	1	5.6	4	22.2	13	72.2	47.21 (5.99–372.43)	0.0003
bile ducts	15	4.2	1	6.7	9	60	5	33.3	18.16 (2.06–160.13)	0.0090
urologic (kidney, bladder)	10	2.8	2	20.0	4	40.0	4	40.0	7.26 (1.28–41.17)	0.0251
head and neck	8	2.3	1	12.5	2	25.0	5	33.3	18.16 (2.06–160.13)	0.0090
liver	3	0.8	1	33.3	1	33.3	1	33.3	3.63 (0.22–59.42)	0.3658
other/unknown primary sites	5	1.4	0	0	5	100	0	0	–	–
two tumor sites	8	2.3	4	50.0	1	12.5	3	37.5	2.72 (0.58–12.70)	0.2021
metastatic tumor	63	17.8	17	27.0	25	39.7	21	33.3	4.49 (2.16–9.34)	0.0001

In patients with two types of cancer, only one was taken into account, which could potentially affect nutritional status

Notably, certain types of neoplasms were especially associated with malnutrition, including pancreas (OR: 47.2; 95% CI: 6.0–372.4; p < 0.001), head and neck (OR: 18.2; 95% CI: 2.1–160.1; p < 0.001), esophagus and stomach (OR: 15.9; 95% CI: 6.8–37.1; p < 0.001), lung (OR: 13.3; 95% CI: 3.5–50.2; p < 0.001), bile duct (OR: 18.2; 95% CI: 2.1–160.1, p < 0.001), and colorectal (OR: 4.2; 95% CI: 2.1–8.6, p < 0.001) – see table II and figure 2.

Discussion

The findings of our study underscore the diverse risk of malnutrition in older adults depending on the specific neoplasia. Notably, certain neoplasms, including pancreatic, head and neck, esophagus and stomach, lung, bile duct, and colorectal cancers, were predominantly linked with malnutrition. In contrast, the frequency of malnutrition was relatively low in cases of prostate, breast, and skin neoplasms. Muscaritoli et al. conducted a study to assess the prevalence of malnutrition in outpatient cancer patients during their initial medical oncology visit. They utilized the Mini Nutritional Assessment (MNA), and the mean age of the patients was 62.7 years [20]. Their findings revealed the order of malnutrition frequency in cancer patients as follows:

- gastroesophageal (40.2%),
- pancreatic (33.7%),
- head and neck (23.8%),
- respiratory (20.9%),
- genitourinary (15.8%),
- unknown primary (14.3%),

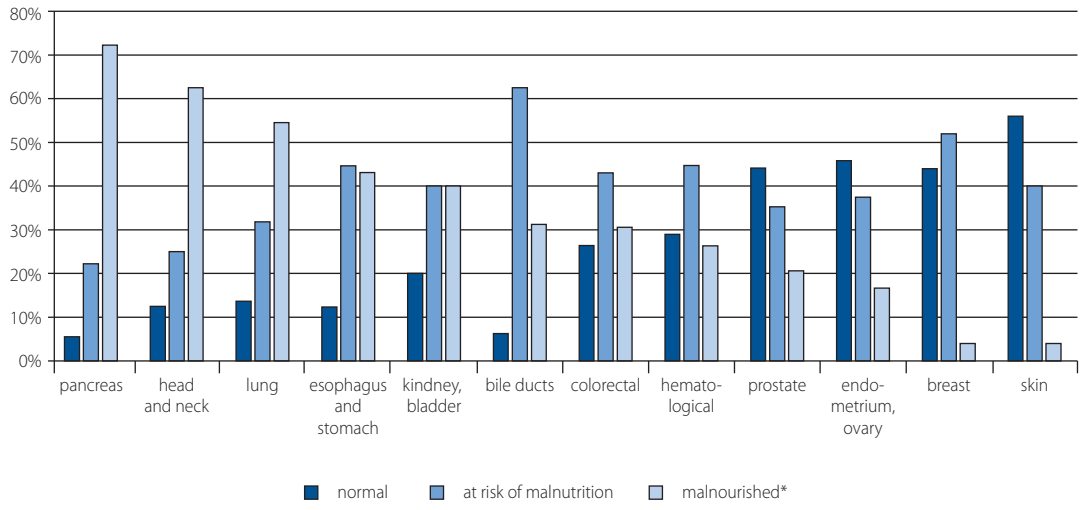

Figure 2. Malnutrition frequency in older adults according to different cancer types

* – according to the Mini Nutritional Assessment Short Form (MNA-SF)

- colorectal (13.4%) [20].

Other studies have been conducted on older adults to explore the relationship between types of cancer and malnutrition. However, these studies did not use the MNA as the operational definition of malnutrition. Nonetheless, their results align with our study, indicating that pancreatic, head and neck, and lung cancers are most frequently associated with malnutrition [21–23]. In line with our findings, Muscaritoli et al. highlighted a similar trend in the prevalence of malnutrition among outpatient cancer patients (mean age 62.7 years), using the Mini Nutritional Assessment (MNA) for evaluation. Their analysis pinpointed varying frequencies of malnutrition across cancer types, with gastroesophageal cancers leading at 40.2%, followed by pancreatic (33.7%), head and neck (23.8%), respiratory (20.9%), genitourinary (15.8%), cancers of unknown origin (14.3%), and colorectal (13.4%). Other research, although not exclusively employing MNA, have mirrored our observations, consistently indicating that pancreatic, head and neck, and lung cancers are intrinsically associated with malnutrition.

Nicholson et al. investigated the association between unexpected weight loss and cancer. They identified that the most closely associated neoplasms were pancreatic cancer, cancer of unknown primary, gastroesophageal cancer, lymphoma, hepatobiliary cancer, lung cancer, bowel cancer, and renal-tract cancer [24]. Similarly, our findings resonate with the low prevalence of malnutrition in certain cancers – specifically prostate and breast – echoing established research outcomes.

One of the key factors contributing to variations in the risk of malnutrition among different types of cancer may be linked to the varying likelihood of developing cachexia. Cachexia emerges as a consequence of tumor-induced activation of inflammatory pathways, which subsequently initiates a wasting response characterized by symptoms such as anorexia, disrupted metabolism, and involuntary loss of both lean muscle and fat mass [11]. Presently, there is an ongoing debate regarding whether cancer cachexia should be classified as a nutritional disorder or as a systemic inflammatory syndrome. The available evidence lends support to the idea of cachexia as a "disease-related inflammation accompanied by malnutrition" [25].

Pancreatic cancer is notably linked with involuntary weight loss and malnutrition, with around 71% of patients presenting with cachexia upon diagnosis. [26]. Cachexia in pancreatic cancer is driven by an inflammatory process with significant catabolic effects. Studies indicate that pancreatic tumors secrete an array of cytokines, such as interleukin-1 (IL-1), IL-6, IL-8 and tumor necrosis factor alpha (TNF-α). Notably, TNF-α stands out for its robust role in advancing cachexia, spurring processes like lipolysis, proteolysis, insulin resistance, and muscular deterioration [27]. In pancreatic cancer, another contributing factor to malnutrition is anorexia and decreased appetite, which is mediated by IL-1. This interleukin triggers the release of serotonin, which, in turn, contributes to the constant activation of POMC/CART (cocaine- and amphetamine-regulated transcript) neurons [27]. Additionally, malnutrition in pancreatic cancer can be attributed to mechanical factors that disrupt nutrient absorption. These factors include external compression caused by the tumor or its surgical removal, resulting in anatomical changes that lead to pain and symptoms affecting eating and nutrient absorption (such as fatigue, dysphagia, gastroparesis, constipation, and pancreatic insufficiency). Tumor growth can also cause intestinal obstruction by infiltrating or compressing the duodenum or stomach, which clinically manifests as nausea and vomiting [28]. Adverse reactions to chemotherapy and radiotherapy further contribute to malnutrition, presenting as symptoms like nausea, vomiting, anorexia, and abdominal pain.

Another cancer type that frequently leads to significant malnutrition is lung cancer. The mechanisms of cachexia in lung cancer appear to be similar to those in pancreatic cancer, particularly involving an inflammatory process and its catabolic effects. However, in lung cancer, the inflammatory process intensifies and may be exacerbated by comorbidities associated with lung cancer, such as chronic obstructive pulmonary disease (COPD) and idiopathic interstitial pneumonia, which can also contribute to cachexia [29].

Some limitations to the present study should be discussed. We employed a retrospective case-control design, focusing on CGA reports. The inclusion criteria were restricted to patients with comprehensive reports, particularly those assessed using the MNA-SF, irrespective of their cancer status. A significant gap in our data was the absence of details about the cancer stage, even though the study included patients across various metastatic stages. Information about ongoing chemotherapy or surgical procedures at the time of the CGA was also missing. Nevertheless, our research sheds light on the varying prevalence of malnutrition among different cancer types in comparison to control subjects.

Furthermore, the adoption of the MNA-SF for nutritional evaluation poses an additional limitation, potentially making our findings less aligned with studies employing alternative assessment methods. To illustrate, a recent meta-analysis delving into the heightened mortality risk associated with malnutrition in cancer patients covered ten studies; only one utilized the MNA-SF, while five leveraged the MNA. This underscores the diverse methodologies present in current research literature.

Conclusions

In conclusion, the prevalence of malnutrition in older adults with cancer varied depending on the specific type of cancer. Neoplasms most strongly associated with malnutrition included pancreatic, head and neck, esophagus and stomach, lung, bile duct, and colorectal cancers. In contrast, prostate, breast, and skin neoplasms exhibited a lower frequency of malnutrition. These findings underscore the importance of tailored nutritional assessment and support strategies for older cancer patients, taking into account the specific cancer type and its associated risk factors.

Article information and declarations

Author contributions

Teodoro J. Oscanoa – conceptualization, writing – original draft preparation, writing – review and editing.

Edwin C. Cieza – data curation, formal analysis, writing – review and editing.

Maryam Pourhassan – data curation, formal analysis.

Roman Romero-Ortuno – writing – original draft preparation, writing – review and editing.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restriction.

Ethics statement

This study was approved by the Research Ethics Committee of Almenara Hospital in Lima, Peru (letter 80-CIEI-OIyD-GRPA--ESSALUD-2023, March 27, 2023). The necessary strategies were implemented to maintain the privacy of patient information.

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Conflict of interest

None declared

Teodoro J. Oscanoa PhdD
Universidad de San Martín de Porres
Facultad de Medicina Humana
Av. Alameda del Corregidor 1502
La Molina 15024 Lima, Perú
e-mail: tjoscanoae@gmail.com

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Original article

Lung cancer

Predicting overall survival in non-small cell lung cancer patients receiving concurrent radiochemotherapy and adjuvant durvalumab – a Polish real-world single-center experience

Barbara A. Łochowska[1, 2], Konrad Stawiski[2, 3], Kasper Kuna[3], Zuzanna Nowicka[3], Mariusz Łochowski[4], Jacek Fijuth[2]

[1]*Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, Lodz, Poland*
[2]*Department of Radiotherapy and General Oncology, Copernicus Memorial Hospital, Lodz, Poland*
[3]*Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland*
[4]*Clinic of Thoracic Surgery and Respiratory Rehabilitation, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland*

Introduction. Adjuvant durvalumab has become a standard treatment protocol for patients with locally advanced non-small cell lung cancer (LA-NSCLC). However, there is still limited knowledge about prognostic factors in a real-world setting across this specific patient group.

Materials and methods. In our single-center retrospective study, we evaluated 45 patients to identify predictors of overall survival (OS) in LA-NSCLC. We utilized the univariable Cox proportional hazards models, and we developed multivariable Cox models after adjusting for the known clinical predictors.

Results. In univariable analysis nodal status, the percentage of basophils in peripheral blood before treatment and D--dimers were associated with OS. Multivariable analysis, adjusted for age, sex, T characteristics, and nodal status revealed that the percentage of basophils is a significant predictor of OS. A higher percentage of basophils was associated with improved OS (HR = 0.077, 95% CI: 0.007–0.853, p = 0.037).

Conclusions. Our study indicates that a lower serum percentage of basophils may be associated with better OS in patients with LA-NSCLC. These findings should be validated in larger cohorts.

Key words: lung cancer, immunotherapy, durvalumab, prognostic biomarkers

Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death worldwide [1], with locally advanced (LA)-NSCLC accounting for a significant portion of diagnoses [2]. Concurrent chemoradiation therapy (CCRT) has long been the standard of care for these patients, offering locoregional control and improved survival [3]. However, the emergence of immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape. The original PACIFIC trial [4] published in 2017, established durvalumab – a monoclonal antibody targeting the PD-L1 receptor – as a new standard of care by demonstrating a significant improvement in overall survival (OS)

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compared to placebo in patients with unresectable stage III NSCLC receiving concurrent platinum-based chemotherapy and radiation therapy [5]. This landmark study paved the way for the widespread adoption of durvalumab consolidation therapy in clinical practice.

Investigations into biomarkers associated with a response to durvalumab are ongoing. Tumor PD-L1 expression has been shown to be a predictive factor in some studies, although its role remains controversial due to variations in testing methods and interpretation [5]. Other biomarkers, such as tumor mutational burden [6] and immune gene signatures [7], are also being investigated and may provide valuable insights into patient selection and treatment response. Additionally, emerging research suggests that genetic alterations, such as *KRAS* mutations, may hold promise for identifying patients who are less likely to benefit from durvalumab therapy [8].

Recent studies have explored the potential of various clinical and biological factors to predict survival in durvalumab-treated NSCLC patients. For instance, a study by Liu et al. identified the baseline neutrophils-to-lymphocytes ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as promising predictors of OS, highlighting the potential role of systemic immune status in treatment response [9]. Similarly, another study published in 2021 found that patients with low infiltration of CD8 + PD-L1 + T-cells and M2 macrophages achieved better progression-free survival (PFS) following durvalumab consolidation, suggesting the importance of pre-existing antitumor immunity [10]. In patients diagnosed with squamous cell carcinoma the higher percentage of basophils in tumor microenvironment (TME) was associated with longer OS [11]. The higher basophil counts were also demonstrated as significant predictors for a higher probability of tumor size reduction within three months, with an increased risk of immune-related adverse events [12]. In a study by Wang et al. the basophil-to-lymphocyte ratio was associated with a shorter OS [13]. Durvalumab has been available to the general patient population in Poland since 2021 via a government-controlled program.

In this single-center study, we aimed to contribute to the growing body of knowledge on predictive factors for OS in LA-NSCLC patients treated with CCRT and adjuvant durvalumab.

Material and methods

Population

In this retrospective cohort analysis, we examined cases of inoperable NSCLC that were treated with CCRT and with adjuvant durvalumab during the years 2021–2022 at our institution (Copernicus Memorial Hospital, Lodz, Poland). Since 2021, the cost of adjuvant durvalumab has been covered by the public healthcare system in Poland, thereby making it accessible to all patients in this cohort. The patients were followed up until December 31, 2023. Our group consisted of 16 (35.6%) women and the median age of participants was 70 years old (65–75). The majority of patients received cisplatin as a chemotherapeutic agent (62.2%), and the median radiation dose was 60 Gy.

All the participants who received durvalumab were enrolled in a strictly government-regulated program for the adjuvant treatment of histopathologically diagnosed NSCLC in Poland. To qualify for the durvalumab consolidation therapy, patients must be diagnosed with stage III NSCLC and demonstrate no disease progression following concurrent chemoradiotherapy. The absence of disease progression must be confirmed through a computed tomography (CT) scan, conducted within a six-week window following the completion of the radiotherapy. Moreover, the patients must have completed a course of CCRT involving platinum derivatives. The patient's overall health and wellness are also considered, with only those having a good performance status (Eastern Cooperative Oncology Group Performance Status, ECOG PS, 0 or 1) being deemed fit for the treatment. Furthermore, patients must not have any uncontrolled coexisting diseases or active autoimmune diseases, with the exception of diabetes, hypothyroidism, psoriasis, or vitiligo (which are manageable and do not interfere with the durvalumab treatment).

Additionally, before the treatment, the patients' bone marrow, kidney, and liver functions must be also assessed to ensure they are within the normal range and suitable for treatment. Pregnant women were not enrolled to study, and women of a maternal age were obliged to use appropriate contraception methods. Any contraindications to durvalumab or the presence of other uncontrolled malignancies disqualify a patient from the program. However, patients who have previously undergone durvalumab therapy may be considered for continued treatment, provided they met all the aforementioned criteria and showed no signs of disease progression.

Statistical analysis

Statistical analyses were performed using R software v4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). P values < 0.05 were considered significant. Nominal variables are shown as numbers with percentages and continuous variables are shown as medians with the interquartile range. We used the Cox proportional hazards model to evaluate the prognostic value of clinical and laboratory results in univariable and multivariable analysis after adjusting for patient sex, age, T-characteristics, and nodal status. OS curves were analyzed using the Kaplan–Meier method; to calculate differences between groups a log-rank test was used.

Results

In the period spanning 2021–2022, CCRT and adjuvant durvalumab were administered to a cohort of 45 patients. The clinical characteristics of the study group are presented in table I. During the follow-up period, which extended to 42 months (with a median follow-up time of 14 months), 10 patients experienced fatal events (fig. 1A).

Table I. Study group description

Parameter	n (% or median – IQR)
female	16 (35.56%)
male	29 (64.44%)
age – years	70.0 (65.0–75.0)
smoking during RCHT – yes	12 (29.27%)
pack years	50 (40.0–70.0)
T characteristic	
1	9 (20.0%)
2	10 (22.22%)
3	20 (44.44%)
4	5 (11.11%)
x	1 (2.22%)
N characteristic	
1	6 (13.33%)
2	35 (77.78%)
3	4 (8.89%)
PTV volume – cm^3	321.1 (231.1–480.8)
treatment time – days	44.0 (41.0–46.0)
cisplatin *vs.* carboplatin	28 (62.22%)
histology	
adenocarcinoma	18 (40.0%)
squamous-cell carcinoma	20 (44.44%)
large cell neuroendocrine carcinoma	3 (6.67%)
not otherwise specified	4 (8.89%)
second agent	
etoposide	11 (24.44%)
paclitaxel	9 (20.0%)
vinorelibine	25 (55.56%)
time from end of RT to durvalumab administration – days	71.0 (60.5–79.0)
time from lab test to RT start	1.0 (0.0–3.0)
laboratory parameters	
white blood cell count – 10^3/µl	7.18 (6.20–8.72)
red blood cell count – 10^6/µl	4.26 (3.79–4.57)
hemoglobin – g/dl	12.60 (11.60–13.80)
hematocrit – %	37.60 (34.50–41.00)
PLT – 10^3/µl	254.0 (204.00–301.00)
PCT – %	0.27 (0.21–0.31)
neutrophils – %	60.10 (51.10–66.30)
lymphocytes – %	26.10 (20.60–34.30)
monocytes – %	9.40 (8.20–11.90)
eosinophils – %	1.60 (0.70–3.20)
basophils – %	0.70 (0.40–0.90)
neutrophil count – 10^3/µl	4.14 (3.30–5.09)
lymphocyte count – 10^3/µl	1.88 (1.55–2.40)
monocyte count – 10^3/µl	0.72 (0.56–0.93)
eosinophil count – 10^3/µl	0.12 (0.06–0.22)
basophil count – 10^3/µl	0.04 (0.03–0.06)
glucose – mg/dl	106.00 (96.00–130.00)
sodium – mmol/l	139.00 (137.00–142.00)
potassium – mmol/l	4.50 (4.20–4.90)
urea – mg/dl	38.30 (30.10–49.10)
creatinine – mg/dl	0.84 (0.72–1.10)
eGFR – ml/min/1,73 m^2	60.00 (60.00–60.00)
CRP – mg/l	4.65 (1.84–11.90)
D dimers	0.74 (0.55–1.29)
prothrombin time – seconds	12.20 (11.35–13.50)
INR	1.05 (0.97–1.17)
APTT – seconds	25.60 (25.25–28.60)
fibrinogen – mg/dl	401.00 (344.00–565.25)
procalcitonine – ng/ml	0.12 (0.06–0.25)
NLR	2.31 (1.51–3.08)
LMR	2.82 (1.98–3.34)
PLR	132.45 (103.64–184.71)
SII	571.67 (368.81–962.29)

EGFR – estimated glomerular filtration rate; INR – international normalized ratio; APTT – activated partial thromboplastin time; NLR – neutrophil to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index

As shown in table II, the univariable analysis revealed that nodal status (p = 0.015), (fig. 1C), a higher initial percentage of basophils (p = 0.020), though not their absolute number (p = 0.109), and d-dimers (p = 0.048) were significant predictors of OS in this group of patients. The smoking pack years did not demonstrate statistical significance in predicting overall survival (p = 0.731). In a multivariable analysis adjusted for patient age and sex, T characteristic, and nodal status, the percentage of basophils was a significant predictor of OS (p = 0.037) (tab. IV). After adjusting

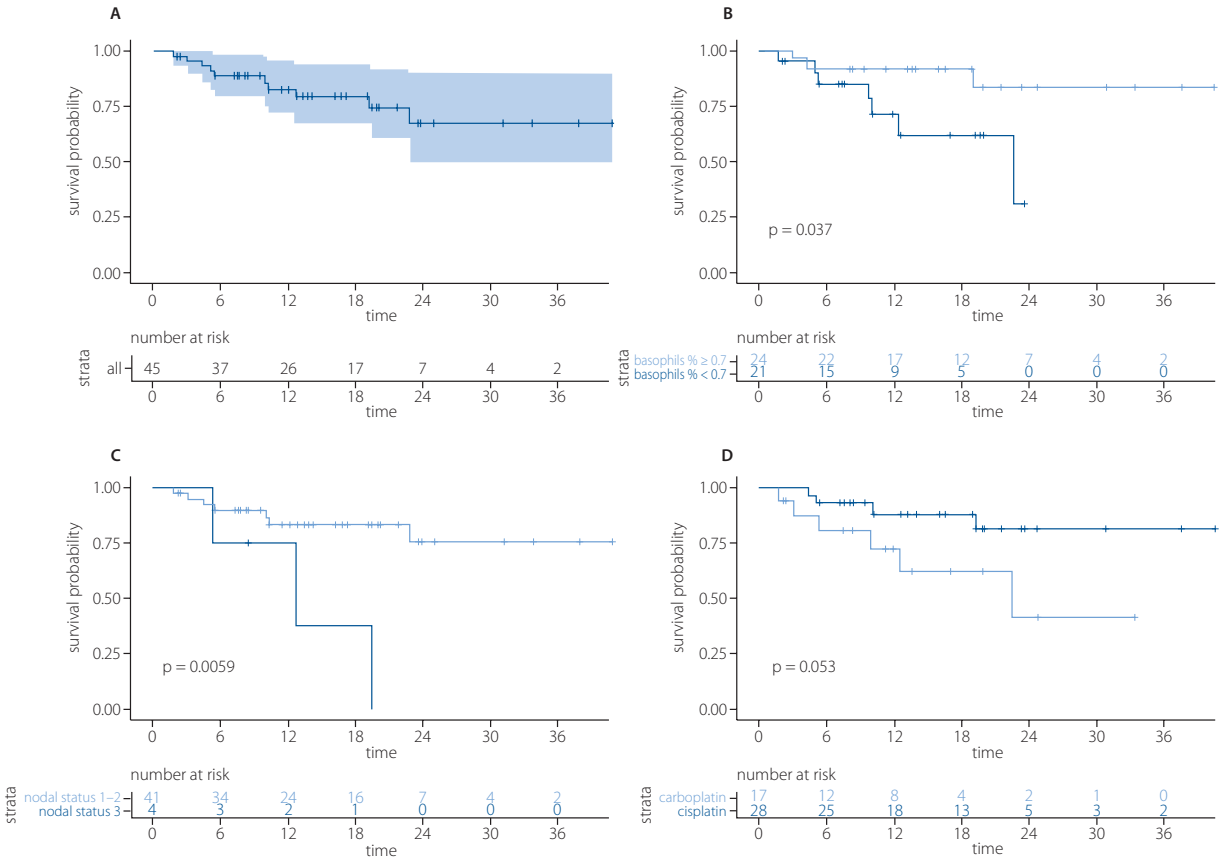

Figure 1. Panel A presents overall survival for the whole study group. Panel B represents a KM plot for groups with higher and lower percentages of basophils. Panel C presents a KM plot for groups divided according to their nodal status. Panel D presents a KM plot for groups treated with carboplatin or cisplatin

Table II. Univariable analysis with the Cox model based on clinical variables for OS

Characteristic	HR (95% CI)	p value
female	–	–
male	1.447 (0.374–5.602)	0.592
age – years	1.094 (0.985–1.210)	0.092
smoking during RCHT – yes	0.749 (0.144–3.90)	0.731
pack years	0.995 (0.970–1.020)	0.731
T characteristic		
1	–	–
2	4.126 (0.459–37.060)	
3	2.307 (0.269–19.750)	0.206
4	–	–
x	–	–
N characteristic		
1–2	–	–
3	5.653 (1.407–22.720)	0.015
PTV volume	2.718 (2.716–2.718)	0.195
treatment time	2.858 (2.557–3.287)	0.369
platin		
carboplatin	–	–
cisplatin	0.306 (0.086–1.088)	0.067
second agent		
etoposide	–	–
paclitaxel	0.989 (0.1650–5.927)	>0.9
vinorelibine	1.033 (0.242–4.417)	>0.9
durvalumab to RT time	1.020 (0.965–1.080)	0.485
time from lab test to RT start		
white blood cell count – 10^3/µl	0.973 (0.843–1.120)	0.704
red blood cell count – 10^6/µl	0.555 (0.156–1.980)	0.365
hemoglobin – g/dl	0.850 (0.562–1.290)	0.443
hematocrit – %	0.974 (0.848–1.120)	0.707
PLT – 10^3/µl	0.993 (0.982–1.000)	0.194

Table II cont. Univariable analysis with the Cox model based on clinical variables for OS

Characteristic	HR (95% CI)	p value
PCT – %	0.000 (3.04 x 10^{-9}–10.1)	0.122
neutrophils – %	1.020 (0.973–1.060)	0.453
lymphocytes – %	0.983 (0.926–1.040)	0.575
monocytes – %	0.982 (0.849–1.140)	0.812
eosinophils – %	0.905 (0.67–1.220)	0.516
basophils – %	0.063 (0.006–0.642)	0.020
neutrophil count – 10^3/µl	0.989 (0.858–1.140)	0.88
lymphocyte count – 10^3/µl	0.865 (0.414–1.810)	0.699
monocyte count – 10^3/µl	0.840 (0.149–4.730)	0.843
eosinophil count – 10^3/µl	0.325 (0.007–14.700)	0.563
basophil count – 10^3/µl	1.26 x 10^{12} (3.37 x 10^{-27}–469.0)	0.109
glucose – mg/dl	1.010 (0.997–1.030)	0.125
sodium – mmol/l	0.960 (0.804–1.150)	0.648
potassium – mmol/l	0.942 (0.305–2.910)	0.918
urea – mg/dl	1.010 (0.981–1.030)	0.592
creatinine – mg/dl	2.930 (0.709–12.100)	0.137
eGFR – ml/min/1.73 m^2	0.966 (0.892–1.050)	0.406
CRP – mg/l	1.030 (0.980–1.070)	0.268
D dimers	1.240 (1.000–1.540)	0.048
prothrombin time – seconds	2.170 (0.877–5.340)	0.094
APTT – seconds	0.928 (0.601–1.430)	0.734
fibrinogen – mg/dl	1.000 (0.999–1.010)	0.165
procalcitonine – ng/ml	4.490 (0.994–20.300)	0.051
NLR	1.050 (0.808–1.370)	0.699
LMR	0.893 (0.600–1.330)	0.578
PLR	0.998 (0.990–1.010)	0.574
SII	1.000 (0.999–1.000)	0.705

HR – hazard ratio, CI – confidence interval; EGFR – estimated glomerular filtration rate; INR – international normalized ratio; APTT– activated partial thromboplastin time; NLR – neutrophil to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PLR – platelet to lymphocyte ratio; SII – systemic immune-inflammation index

Table III. Multivariable Cox model of clinical factors and pack years on overall survival (OS)

Characteristic	HR (95% CI)	p value
female	–	–
male	0.800 (0.078–8.162)	0.851
age – years	1.316 (1.066–1.618)	0.010
T characteristic	0.820 (0.150–4.495)	0.819
nodal status	10.026 (1.017–98.846)	0.048
pack years	1.003 (0.969–1.039)	0.845

HR – hazard ratio, CI – confidence interval

Table IV. Multivariable Cox model of clinical factors and percentage of basophils on overall survival (OS)

Characteristic	HR (95% CI)	p value
female	–	–
male	2.728 (0.476–15.620)	0.257
age – years	1.080 (0.987–1.182)	0.093
T characteristic	0.996 (0.265–3.741)	0.995
nodal status	11.20 (1.746–71.827)	0.011
basophils – %	0.077 (0.007–0.853)	0.037

HR – hazard ratio, CI – confidence interval

for the same clinical prognostic factors, d-dimers were not associated significantly with OS (p = 0.115).

The best cutoff value for the percentage of basophils was 0.7% (fig. 1B). In the univariable Cox model, the group with a percentage of basophils below this value demonstrated a trend toward significantly shorter OS (HR = 3.917, CI: 0.991–15.480, p = 0.052).

Discussion

In this study, we conducted a comprehensive single-center analysis of lung cancer patients who were treated with concurrent radiochemotherapy and adjuvant durvalumab. We sought associations between pre-treatment clinical and laboratory variables with overall survival in a real-world setting. Ongoing studies are currently focused on exploring various factors associated with the benefits of durvalumab [14–17]. While the neutrophil-to-lymphocyte ratio (NLR) has previously been identified as a predictor of OS in lung cancer patients [18], in our cohort, NLR did not show any significance in predicting OS in both univariate and multivariable models. However, in the multivariable model adjusted for age, sex, T characteristic, and nodal status, the percentage of basophils was significantly associated with OS; while the mechanism behind this association is presently unclear, it may be validated in bigger cohorts. In a study by Krizova et al., higher baseline basophils were demonstrated as a significant predictor of longer PFS in NSCLC patients treated with ICIs [19]. The absolute count of basophils was also demonstrated as a potential biomarker

of ICI in advanced gastric cancer patients [20]. Another report by Liu et al. associated lower baseline basophil count with shorter disease-free survival [21].

In NSCLC patients, the main clinical predictors of survival are staging, ECOG status, weight loss, and serum albumin levels [22]. With the emergence of ICIs in the treatment of NSCLC, the PD-L1 expression was analyzed as a predictive factor. In a report by Bryant et al. [15], the group treated with durvalumab and with higher expression of PD-L1 had a longer PFS compared to the group that was not treated with ICI. Unfortunately, due to missing PD-L1 expression status in our cohort, we were not able to analyze its predictive value.

The tumor microenvironment is composed of various immune cells, and alterations in the composition of this infiltration have garnered significant interest in recent years [11, 25–27]. A study by Lavin et al. utilizing single-cell analysis to inspect the TME found fewer basophils in the TME of stage I adenocarcinoma compared to normal lung tissue [28]. Interestingly, a small proportion of basophils found in TME and non-involved lung parenchyma expressed PD-L1. The basophil levels in tumor-draining lymph nodes has been shown to be a useful predictor in pancreatic ductal adenocarcinoma, where, contrary to our results, higher levels were associated with poorer survival [29]. Additionally, a low percentage of basophils was found by Stankovic et al. in the immune infiltrate of NSCLC patients [30]. Future studies should explore the exact molecular alterations in basophils found in the TME.

One major limitation of our study is the small sample size. Additionally, our observation period was limited to two years, which may be considered relatively short. Furthermore, patients in our study received various chemotherapy regimens (carboplatin *vs.* cisplatin) (fig. 1D). To fully evaluate the significance of survival predictors in LA-NSCLC patients, more extensive studies with larger cohorts are needed.

Conclusions

In our univariate analysis significant predictors of OS in this group of patients were: nodal status, higher percentage of basophils, and D-dimer levels prior to the CCRT. In the multivariable Cox model, the percentage of basophils was associated with OS. The findings from this study could potentially contribute to the existing body of knowledge, influencing future studies search for predictors of OS, and illustrating the benefits of treatment with durvalumab in NSCLC.

Article information and declarations

Author contributions

Barbara A. Łochowska – conceptualization, investigation.
Konrad Stawiski – formal analysis, methodology, writing – review and editing.
Kasper Kuna – project administration, validation, writing – original draft preparation.
Zuzanna Nowicka – visualization, data curation, writing – review and editing.
Mariusz Łochowski – resources.
Jacek Fijuth – supervision.

Data availability

Datasets used for analysis for this study are available from the corresponding author upon reasonable request.

Ethics statement

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

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Conflict of interest

None declared

Barbara A. Łochowska
Copernicus Memorial Hospital in Lodz
Department of Radiotherapy and General Oncology
ul. Pabianicka 62
93-513 Łódź, Poland
e-mail: blochowska@op.pl

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Original article

Skin cancers

Melanoma incidence in 17,252 organ transplant recipients in Poland between 2010 and 2022

Aleksandra Kulbat[1, 2], Karolina Richter[2, 3], Marta Krzysztofik[4], Krzysztof Batko[5], Aleksandra Karwańska[6], Marta Kołodziej-Rzepa[1, 2, 3], Tomasz Wojewoda[2, 3], Wojciech M. Wysocki[1, 2, 3]

[1]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Oncological Surgery, 5th Military Clinical Hospital in Krakow, Krakow, Poland*
[3]*Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[4]*Department of Dermatology and Venerology, Stefan Zeromski Municipal Hospital, Krakow, Poland*
[5]*Department of Dermatology, Jagiellonian University Medical College, Krakow, Poland*
[6]*Department of Dermatology and Venerology, National Medical Institute MSWiA, Warsaw, Poland*

Introduction. Numerous studies indicate an increased incidence of skin malignancies among organ transplant recipients. Melanoma pose a significant threat to post-transplant recipients, leading to considerable mortality. This study explores the incidence of melanoma after 17,252 organ transplantations in Poland over the past 13 years.

Materials and methods. The data on the occurrence of melanoma in patients after renal, heart, or liver transplantation were obtained from the National Health Fund, encompassing individuals who underwent kidney, heart, or liver transplantation between 2010 and 2022. The analysis focused on skin melanoma (C43).

Results. The study examined skin melanoma in renal (12,250 cases), liver (3,584 cases), and heart (1,418 cases) transplant recipients over a period of thirteen years. Melanoma incidence slightly increased in renal recipients (1-year cumulative incidence 0.016% *vs.* 0.007%, $p = 0.024$; 5-year cumulative incidence 0.131% *vs.* 0.040% $p < 0.001$; the 10-year cumulative incidence 0.213% *vs.* 0,09, $p < 0.001$). In liver transplant recipients there is a non-significant difference 1-year after transplantation (cumulative incidence 0.03% *vs.* 0.01%, $p = 0.337$) but after 5 and 10 years the difference between the two groups remains statistically significant (5-year cumulative incidence 0.14% *vs.* 0.04%, $p < 0.014$; the 10-year cumulative incidence 0.14% *vs.* 0.09%, $p < 0.001$). In heart transplant recipients, a paradoxical reduction in incidence was observed compared to the general population (1-year cumulative incidence 0% *vs.* 0.01%, $p = 0.317$; 5-year cumulative incidence 0.07% *vs.* 0.04%, $p = 0.049$; the 10-year cumulative incidence 0.07% *vs.* 0.09, $p < 0.001$).

Conclusions. The incidence of melanoma increases in kidney transplant recipients over the first 10 years post-transplant, with a peak between 4 to 7 years. For heart and liver transplant recipients, melanoma cases occur within the initial 5 years post-transplant, and no new cases were recorded afterward. The long-term surviving kidney, heart, and liver transplant recipients show a steady rise in new cases over time. Our study, based on a thorough analysis of data from the National Health Fund, confirms the link between an elevated risk of melanoma in organ transplant recipients.

Key words: skin cancer, melanoma, transplant recipients, transplantation

How to cite:

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Introduction

In 2023, according to the National Health Fund, a total 1,910 organ transplants were performed in Poland, including 1,055 kidney transplants, 550 liver transplants, and 178 heart transplants, marking an unprecedented achievement in the country's medical history [1]. This notable increase surpassed previous numbers, such as 1,608 organ transplants in 2012 [2]. The global prevalence of organ transplants has been steadily rising, reaching hundreds of thousands annually.

Organ transplantation, hailed as the sole long-term curative treatment for end-stage renal, heart, or liver disease, introduces complex lifelong therapy for recipients. The lifelong immunosuppressive treatment necessary for adequate graft function makes recipients susceptible to various diseases, prominently increasing the risk of cancer. Melanoma, though comprising only 4% of cutaneous malignancies, contributes to 80% of skin cancer deaths in the general population, underscoring its significance among both transplant and non-transplant individuals [3].

The results of available studies show that transplant recipients face a 1,5- to 8-fold increased risk of melanoma compared to the general population, depending on the studied population [4–6], but the risk of developing melanoma consistently increases in all presented data over the time since transplantation.

Data from different European studies also show significant diversity in the risk of neoplasia despite a similar geographical latitude, indicating additional risk factors for the occurrence of cancer, such as genetic predispositions, the influence of applied treatment, or the frequency of human papillomavirus (HPV) infection [7, 8]. Unfortunately, despite numerous works, there is a lack of epidemiological studies based on a large number of patients, especially regarding the frequency of melanoma, which would help in a precise assessment of the real risk of skin cancer in the transplant recipient group.

This report explores the incidence of melanoma after organ transplantation in Poland over the past 13 years (2010–2022), providing insights into the challenges and risks encountered by transplant recipients. This is the largest analysis performed on that particular subject in Poland so far. The study is based on a National Health Fund dataset (public health insurance governmental agency), which provides the most accurate information on actual health incidents for all Polish citizens.

Materials and methods

The data on the occurrence of melanoma in patients after renal, heart, or liver transplantation were obtained from the National Health Fund. The dataset includes patients who underwent renal, heart, or liver transplantation between 2010 and 2022, and it was used to identify a cohort of patients with a diagnosis of melanoma based on any inpatient or outpatient claim associated with an International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code for melanoma (C43.0–C43.9).

The information is presented through distinct sets of diagrams, illustrating melanoma (C43) in recipients of the most commonly transplanted organs in Poland – specifically, in renal transplant recipients, liver transplant recipients, and heart transplant recipients. Exclusion criteria included a history of previous organ transplantation and transplantation of more than one of the mentioned organs. Differences in the occurrence of melanoma skin cancer are presented in the diagrams. It is important to note that diagrams related to each specific patient group use a consistent percentage scale for uniform data presentation. To investigate the association between two categorical variables, analytical methods, including Fisher's exact test and the two-sample test for equality of proportions (applied without a continuity correction) were employed. An alpha level ($\alpha = 0.05$) was chosen as the criterion for determining statistical significance. Analyses were conducted using the R Statistical language (version 4.3.1; R Core Team, 2023) on Windows 10 Pro 64 (build 19045).

Based on data obtained from the National Health Fund, we calculated the cumulative incidence rate of melanoma, coded as C43, among organ transplant (Tx) recipients compared to a control population over a 1-, 5-, and 10-year follow-up period. The dataset for this time frame (between 2010 and 2020) was created using information acquired from the National Cancer Registry [9].

Results

The cumulative incidence rate of melanoma, coded as C43, among renal transplant (Tx) recipients compared to a control population over a 1-, 5-, and 10-year follow-up period provided an insightful perspective into the risk stratification associated with this malignancy post-transplantation.

Renal Tx recipients vs. *control population*

The analysis covered 12,250 renal transplant recipients (2010–2022), examining the risk of melanoma skin cancer. The histogram (fig. 1) displays the percentage of melanoma cases among living renal transplant recipients. A slight increase is observed in the fourth to seventh years (0.04% and 0.07%, respectively), followed by a decrease in subsequent years. No cases are reported after the tenth year.

Table I presented the cumulative incidence rates of melanoma (C43) in patients post renal Tx as opposed to a control population over 1-, 5-, and 10-year intervals, allowing for a comparative oncological risk assessment. The observed trend in table I suggests that renal transplant recipients exhibited a higher cumulative incidence of melanoma skin cancer over time when compared to the general population. This elevated risk could be attributed to the immunosuppressive regimens required to maintain graft function, which can reduce the efficacy of the immune system to detect and eliminate malignant

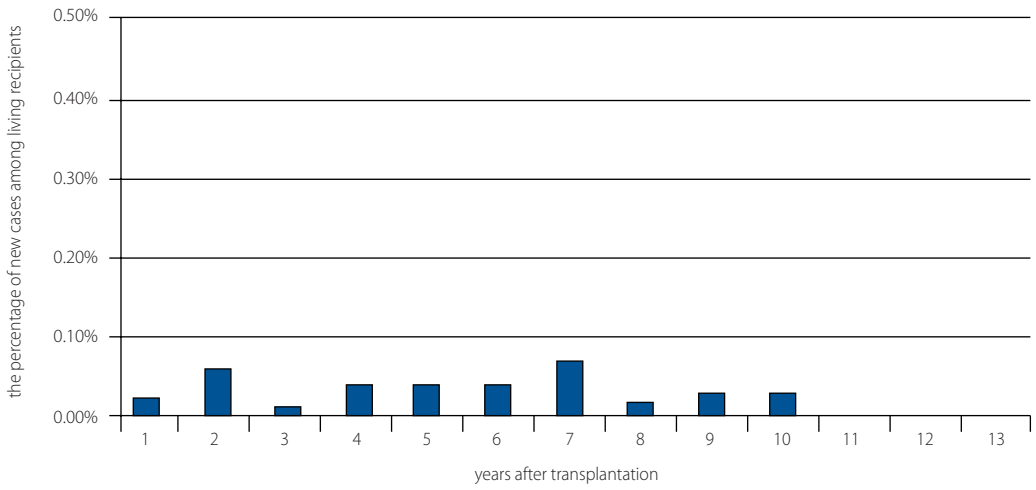

Figure 1. Melanoma in renal transplant recipients

Table I. Cumulative incidence rate of melanoma (C43) over time in patients with renal Tx and control population

Follow-up	Stratification by Tx		p value[b]
	yes[a] N_1 = 12,205	no[a] N_2 = 37.75 mln	
1 yr.	2 (0.02%)	2,660 (0.01%)	0.024
5 yr.	16 (0.13%)	15,092 (0.04%)	<0.001
10 yr.	26 (0.21%)	34,313 (0.09%)	<0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions

cells. The significantly higher incidence rates in the renal transplant recipients highlighted the interplay between immunosuppression and carcinogenesis.

In the immediate 1-year follow-up, the incidence of melanoma in the renal transplant cohort was 0.016% (2 cases *per* 12,205 patients), which was statistically higher (p = 0.024) than the 0.007% (2,660 cases *per* 37.75 million) observed in the general population. The 5-year cumulative incidence notably increased in the transplant recipients to 0.131% (16 cases *per* 12,205 patients), with a further amplified contrast to the control population's 0.040% (1,592 cases *per* 37.75 million), a difference that was highly significant (p < 0.001). At 10-year, the incidence in the transplant group further escalated to 0.213% (26 cases *per* 12,205 patients), while the control population incidence was 0.091% (34,313 cases *per* 37.75 million), again with a statistically significant difference (p < 0.001).

Liver Tx recipients vs. *control population*

The analysis encompassed 3,584 liver transplant recipients, investigating the risk of melanoma skin cancer. The histogram (fig. 2) illustrates the percentage of melanoma cases among living liver transplant recipients at different intervals post-transplant. The data reveals fluctuations, reaching a peak of 0.12% in the third year, while the other years have either minimal or zero reported cases. Notably, no cases are documented

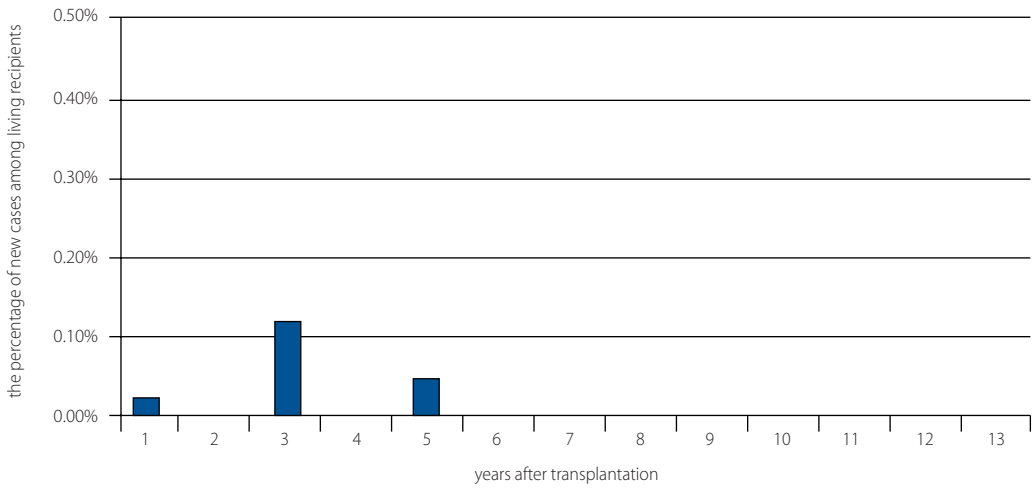

Figure 2. Melanoma in liver transplant recipients

Table II. Cumulative incidence rate of melanoma (C43) over time in patients with liver Tx and control population

Follow-up	Stratification by Tx		p value[b]
	yes[a], N_1 = 3,584	no[a], N_2 = 37.75 mln	
1 yr.	1 (0.03%)	2,660 (0.01%)	0.337[c]
5 yr.	5 (0.14%)	15,092 (0.04%)	0.014
10 yr.	5 (0.14%)	34,313 (0.09%)	<0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions; [c] – Fisher's exact test

from the fourth to the thirteenth-year post-transplant. This data effectively portrays the patterns in melanoma incidence among liver transplant recipients over a thirteen-year period.

Table II presented the cumulative incidence rates of melanoma (C43) in patients post liver Tx as opposed to a control population over 1-, 5-, and 10-year intervals, allowing for a comparative oncological risk assessment.

In the 1-year follow-up, there was a single case of melanoma (0.028%) among the 12,205 liver Tx patients, compared to a 0.007% incidence (2,660 cases) within the control population of 37.75 million. The p value of 0.337 indicated no significant difference in the melanoma incidence rate between the liver Tx cohort and the general population at this interval. At the 5-year milestone, the cumulative incidence in liver Tx patients slightly increased to 0.140% (5 cases out of 12,205 patients), which was statistically higher than the control group's 0.040% incidence (1,592 cases out of 37.75 million), with a p-value of 0.014. By the 10-year follow-up, the incidence rate remained at 0.140% (5 cases *per* 12,205 patients) in the liver Tx group, which is intriguing as it did not increase from the 5-year mark. In contrast, the control group's incidence raised to 0.091% (34,313 cases *per* 37.75 million), with the difference between the two groups remaining statistically significant ($p < 0.001$).

Heart Tx recipients vs. *control population*

The assessment of non-melanoma skin cancer risk involved 1,418 heart transplant recipients. During the initial three years post-transplant, no new cases of melanoma were reported. However, in the fourth year post-transplant, a slight increase in the percentage of cases was observed, reaching 0.16%. From the fifth to the thirteenth year, no new cases were recorded. This histogram (fig. 3) depicts a minimal percentage of melanoma cases among the population of heart transplant recipients in the years following the procedure. Table III delineated the cumulative incidence rate of melanoma (C43) in heart Tx recipients compared with a control population over a 1-, 5-, and 10-year follow-up period.

At 1-year, there were no reported cases of melanoma (0%) among the 1,408 heart Tx recipients, in contrast to the control population's 0.007% incidence (2,660 cases out of 37.75 million). The $p = 0.317$ indicated no statistically significant difference between the groups, which could be due to the relatively short period post-transplantation, not allowing sufficient time for melanoma development or detection. By the 5-year follow-up, the cumulative incidence of melanoma in heart Tx patients was recorded at 0.071% (1 case out of 1,408 patients), which was statistically higher than the control group's incidence of 0.040% (1,592 cases out of 37.75 million), with a p-value of 0.049. The 10-year data revealed the incidence in the heart Tx cohort remained at 0.071% (1 case *per* 1,408 patients), without an increase from the 5-year incidence. This was in contrast to the control population's incidence, which rose to 0.091% (34,313 cases per 37.75 million), with the difference between the groups remaining statistically significant ($p = 0.001$), this time higher in the control group.

Discussion

Melanoma after organ transplantation results in substantial mortality [10, 11]. Several studies have examined the risk of skin melanoma after transplantation, demonstrating

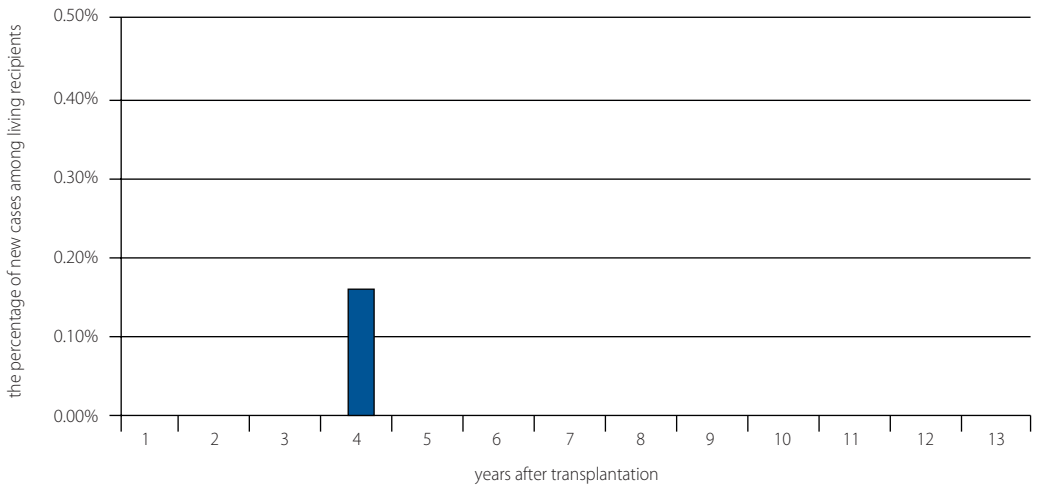

Figure 3. Melanoma in heart transplant recipients

Table III. Cumulative incidence rate of melanoma (C43) over time in patients with heart Tx and control population

Follow-up	Stratification by Tx		p value[b]
	yes[a], N_1 = 1408	no[a], N_2 = 37.75 mln	
1 yr.	0 (0%)	2,660 (0.01%)	0.317[c]
5 yr.	1 (0.07%)	15,092 (0.040%)	0.049
10 yr.	1 (0.07%)	34,313 (0.09%)	0.001

N – population size; n – incidence rate of melanoma; [a] – n (%); [b] – two-sample test for equality of proportions; [c] – Fisher's exact test

a broad and diversified range of the presented increase in the risk of incidence. This raises many questions regarding the scale of this phenomenon in Poland. Studies available for the Polish population describe individual cases conducted on a small group of individuals, or pertain to past times when immunosuppressive treatment often differed from the currently used protocols [4, 12–15].

Our study aimed to reanalyze the potential connection between organ transplant recipients in Poland and the prevalence of melanoma. The authors conducted an analysis of data from the National Health Fund, revealing the occurrence of melanoma in the three most common groups on life-long immunosuppressive therapy:

- renal transplant recipients,
- liver transplant recipients, and
- heart transplant recipients.

Cases of melanoma were recorded only within the first 10 years after renal transplantation, and the cumulative risk of developing melanoma in this period was 0.21%, while the population incidence in this range of time, according to data from the National Cancer Registry, was 0.09%. This suggested a sustained and growing divergence in the risk profile for melanoma between the two groups, possibly attributable to chronic immunosuppressive therapy, which although facilitating survival may contribute to the accumulation of oncogenic mutations and the growth of malignant cells by limiting the body's natural antitumor immune responses.

Melanoma cases in liver transplant recipients were reported only in the first 5 years (cumulative risk 0.14%). This statistically significant difference suggests the potential impact of the post-transplant condition, including the immunosuppressive therapy necessary to prevent liver graft rejection, on the risk of developing melanoma. By the 10-year follow-up, the incidence rate remained at the same level, which is intriguing as it did not increase from the 5-year mark. The stable incidence rate in the liver Tx cohort over the 5 to 10-year period might suggest a plateau effect in the risk of melanoma post-transplant, indicating that the highest risk period may be within the first five years post-transplant. These findings suggest that liver Tx patients have an increased cumulative incidence of melanoma when compared to the general population, particularly evident beyond the 1-year post-transplant period, likely influenced by immunomodulatory effects of long-term immunosuppression, which may reduce immunosurveillance, and allow for the development and progression of melanoma.

Heart transplant recipients in Poland also received a melanoma diagnosis only within 5 years of organ transplantation, but not significantly (cumulative risk 0.07% *vs.* 0.04% in the control group). At 1-year, there were no reported cases of melanoma which could be due to the relatively short period post-transplantation, not allowing sufficient time for melanoma development or detection. The stabilization of melanoma incidence in the heart Tx group from 5 to 10 years might suggest that the period of highest vulnerability to melanoma in heart transplant recipients was within the first five years following transplantation. The analytical interpretation of this data suggests an epidemiological anomaly where the expected increased risk of melanoma in an immunocompromised cohort, such as heart Tx recipients, was not observed over the long term. Instead, a paradoxical reduction in incidence was noted when compared to the general population.

Our study has several important limitations. Firstly, the detailed data of our interest in the National Health Fund database are only available from 2010 on. Moreover, there is a potential for overdiagnosis (i.e. "overreporting" C43 by general practitioners at referral without proper histopathological diagnosis), which we attempted to mitigate by considering only hospital and clinical data concerning the diagnoses (i.e. we excluded ICD codes entered at primary care units). To further clarify the available dataset, we also compared the obtained number of patients with those in the PolTransplant database. Datasets largely overlap (between 2010 and 2020, 42,756 diagnoses of C43 were established based on National Health Fund data, and respectively, 37,585 based on the National Cancer Registry report [15]). Despite the above, the strength of our report lies in its scrupulous analysis of available data, strict inclusion criteria, and integrating them to create a clinically important consensus.

To the best of our knowledge, the study is the first analysis of such a large population of organ transplant recipients in our country and in Europe, with data sourced from one of the most reliable medical information repositories run by a public governmental agency concerning transplant recipients in Poland.

As the data elucidates, organ transplantation and the associated life-long changes for the patient (like immunosuppression) bring not only benefits, but is also associated with a greater risk of melanoma prevalence, however, it is not as high as previously believed. In our opinion it is obligatory to inform patients and educate them in self-examination techniques, while also encouraging them to undergo frequent follow-up visits for skin lesion control within the first few years post-transplant. Guidelines recommend that transplant recipients should

be screened for skin cancer at least twice a year from five years post-transplantation [16–18]. We hope that the presented results will allow for a real assessment of the risk of developing melanoma in our country, and contribute to standardizing screening practices in this group of patients, offering valuable insights for medical professionals and researchers.

Conclusions

The incidence of melanoma has been observed to increase among renal transplant recipients over the first 10 years post-transplant, with a peak in cases occurring between 4 and 7 years after transplantation. In heart and liver transplant recipients, cases of melanoma are reported within the first 5 years post-transplant, and no new cases have been recorded after this period. The 10-year cumulative melanoma incidence slightly increased in renal recipients (0.213% *vs*. 0.09, $p < 0.001$) and in liver transplant recipients (0.14% *vs*. 0.09%, $p < 0.001$) as opposed to the general population of Poland.

After a thorough analysis of data obtained from the National Health Fund in Poland, our study confirms that melanoma risk increased in the group of renal and liver recipients, but there is no association between melanoma occurrence and heart transplantation. The melanoma risk increase in renal, liver, and heart transplant recipients, although statistically significant, is lower than was believed before the study. The authors particularly emphasize the value of monitoring transplant recipients for skin melanoma, with special attention paid to patients living over 5 years with a transplanted organ.

Article information and declarations

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Ethics statement

No ethical issues or concerns were applicable to this research.

Author contributions

Aleksandra Kulbat – conceptualization, data curation, project administration, resources, software, validation, visualization, writing – original draft preparation, writing – review and editing.

Karolina Richter – visualization, writing – original draft preparation.

Marta Krzysztofik – writing – original draft preparation.

Krzysztof Batko – writing – original draft preparation, formal analysis, validation.

Aleksandra Karwańska – writing – original draft preparation.

Marta Kołodziej-Rzepa – writing – review and editing, supervision.

Tomasz Wojewoda – writing – review and editing, supervision.

Wojciech M. Wysocki – conceptualization, writing – funding acquisition, original draft preparation, writing – review and editing, supervision.

Conflict of interest

None declared

Aleksandra Kulbat
Maria Sklodowska-Curie National Research Institute of Oncology
ul. Roentgen 5
02-781 Warszawa, Poland
e-mail: alexandra.kulbat@gmail.com

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Original article

Cancer prevention and public health

Linking payment to volume – does it work in oncological surgery in Poland?

Monika Raulinajtys-Grzybek[1, 2], Barbara Więckowska[3]

[1]Department of Management Accounting, Warsaw School of Economics, Warsaw, Poland
[2]Collegium of Business Administration, Warsaw School of Economics, Warsaw, Poland
[3]Department of Innovation in Health Care, Warsaw School of Economics, Warsaw, Poland

Introduction. This study aims to evaluate the impact of a new financing policy (25% bonus) on the centralization of radical surgical procedures for cancer treatment in high-volume hospitals in Poland. It builds on existing research that demonstrates a positive correlation between treatment outcomes and the volume of patients managed at a center, extending to various cancer types and treatment modalities including both surgical and non-surgical approaches.

Material and methods. Reimbursement data was collected about all radical surgery procedures related to cancer treatment funded from public sources in Poland in 2019–2022. Hospitals were clustered in three groups: 1) high-volume, 2) "close to" high-volume, and 3) low-volume hospitals. To assess the maximum number of providers in each type of cancer surgery, the volume procedures for low-volume hospitals was recalculated.

Results. In the years 2018–2022, over 450 hospitals provided radical surgery services in the 13 cancer groups studied. This value changed slightly during the period under study. In almost half of the analyzed cancer groups, the number of low-volume hospitals is increasing. An increasing number of hospitals are providing services below the thresholds. At the same time, across almost all studied groups, the number of high-volume hospitals also increased. Analysis of the distribution of services by clusters proves the gradual concentration of the market. The share of radical surgery services provided by low-volume hospitals decreased from 39% in 2019 to 35% in 2022. The share of services provided in high-volume hospitals increased gradually from 49% to 57% (highest for prostate, kidney and thyroid cancers).

Conclusions. The financial model providing additional revenue for high-volume hospitals with additional requirements regarding the treatment process, as well as having no required minimal volume of procedures, induced the centralization of radical oncology surgery only insignificantly.

Key words: financial incentives, high volume hospitals, cancer surgery, reimbursement

Introduction

For many cancer types, survival as well as outcomes are improved when patients receive management at treatment centers that encounter high numbers of patients annually. Studies have researched and confirmed a relationship between surgeon volume and improved health outcomes for high-risk surgical procedures in oncology. Other studies show that higher hospital surgery volumes are also associated with better outcomes compared to low-volume hospitals [1]. Some research even shows that greater hospital volume can be a substitute for surgeon's individual experience, by transferring the organizational learning curve [2]. This correlation is specifically important for

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less common diseases and tumors when patients benefit from being treated in high-volume centers [3].

The research on volume-outcome associations have been held on numerous types of cancer procedures, both resections as well as reconstructions: colon cancer [4, 5], colorectal surgery [6], rectal surgery [7–9], pancreatic or esophageal cancer resections or free tissue transfer [10], breast cancer surgery [9], lung cancer [11]. Also research on nonsurgical treatment of oncology patients has shown improved survival for treatment in high-volume hospitals [12, 13].

Improved outcomes are associated with clinical outcomes such as mortality, short-term and medium-term survival, in-hospital death, complications, or length of stay. This is confirmed for different types of oncological surgery, including laparoscopy [5, 6] and robotic surgery [14]. Other research shows that lower number of complications is positively associated with lower costs of cancer nonsurgical treatment [15, 16].

As a consequence of the evidence on volume-outcome associations, efforts have been made in several countries and areas to introduce regulation on minimum volume or other means to promote centralization [17]. Such a policy has also been introduced in Poland in oncological surgery – it differentiates prices for treatment, with higher prices granted to high-volume hospitals. The research on the effects of such policies is still relatively limited and new. Hospitals' reaction can differ depending on factors such as the distance that the patient has to the nearest high-volume hospital as well as the hospital's capacity.

The aim of the study was to analyze the impact of the new financing policy on the centralization of the procedures of radical surgery in cancer treatment to high-volume hospitals in Poland. This analysis focuses on the primary outcome of whether the radical surgery was concentrated at high-volume hospitals compared to the situation before the financial mechanism was introduced.

Material and methods

Overview of oncological package and selection of primary outcome

The oncology package was the first approach in Poland to coordinated care of cancer patients. The primary goal of this reform was to improve treatment results by shortening the time from suspicion of cancer to the initiation of treatment, and to provide comprehensive care at every stage of the disease (using the Diagnostics and Oncological Treatment Card, hereinafter: DiLO).

The oncology package introduced maximum deadlines for oncological diagnostics, and defined requirements for healthcare providers to ensure a quick and comprehensive service of a specific standard. Healthcare providers were obliged to provide access to several diagnostic tests as part of oncological diagnostics at the level of outpatient specialist care within a specified period (28 days to conduct preliminary diagnostics in order to confirm or exclude cancer; another 21 days to conduct comprehensive diagnostics in order to determine the type, stage and location of the cancer). During hospital treatment (which should be commenced within 14 days), it was necessary to conduct a medical consultation panel and provide access to all cancer treatment methods, i.e. surgical treatment, chemical treatment and radiotherapy [18]. Economic incentives were also used to increase the efficiency of the diagnostic and treatment process.

The concept of a "leading center" was also introduced. One of the conditions for such a center was to have a surgical ward (this condition does not apply to malignant tumors of the hematopoietic or lymphatic system) [19]. The aim was to induce centralization of dispersed surgical practice. Access to radiotherapy and chemotherapy could be guaranteed through a cooperation agreement or subcontracting.

In 2018, the National Health Fund introduced financial mechanisms. The goal was to strengthen the concentration of providers. Hospitals specializing in performing specific surgical procedures to oncology patients (with a DiLO card) were granted higher prices for their services. The 25% bonus was granted to hospitals that exceeded the threshold for the volume of procedures in a given cancer group (tab. I) and provided these services within DiLO conditions.

Study period

We used NFZ reimbursement data from January 1, 2019, through December 31, 2022. We defined the starting point as

Table I. Volumes of radical surgery procedures that entitle higher prices – 2018 year

Cancer type	Volumes of radical surgery procedures
lung cancer	70
urinary bladder cancer	30
ovarian cancer	30
colorectal cancer	75
uterine cancer	60
kidney cancer	50
breast cancer	250
prostate cancer	75
pancreatic cancer	30
stomach cancer	30
thyroid cancer	75
central nervous system cancer	150
throat cancer	50

Source: Ordinance No. 87/2018/DSOZ of the President of the National Health Fund of August 23, 2018, amending the order on determining the conditions for concluding and implementing contracts such as hospital treatment and hospital treatment – highly specialized services

the first year after the "25% plus for high-volume hospitals" financial mechanism was introduced. The intervention was introduced on July 1, 2018, for all hospitals. Recognizing that it takes time to redesign clinical care and optimize performance in a new payment model, we have analyzed the data starting from the first full year after the new model was introduced to the last available period, which was 2022.

Radical surgery in cancer treatment

We included all radical surgery procedures related to the cancer treatment for which the "25% plus for high-volume hospitals" mechanism was introduced. We included only hospitals which provided treatment funded by the NFZ, the only public payer. These are almost all the procedures provided in Poland, as hospital treatment is hardly ever funded from private sources [20]. NFZ reimbursement data was obtained for each provider and contained information about principal discharge diagnoses (ICD-10), provided procedures (ICD-9 CM) and financing type (oncological package/not oncological package).

Hospitals were clustered in three groups: 1) hospitals granted a 25% high-volume benefit, 2) "close to" high-volume hospitals i.e. hospitals providing sufficient volume of procedures to be granted the benefit but not fulfilling the other criteria for the oncological package, and 3) low-volume hospitals.

To assess the maximum number of providers in each type of cancer surgery, we recalculated the number of procedures provided by providers in low-volume hospitals and divided them by surgery threshold value for defined cancer type.

Results

Change in the number of hospitals

In the years 2018–2022, over 450 hospitals provided radical surgery services in the 13 cancer groups studied (tab. II). This value changed slightly during the period under study. The largest number of providers were observed in procedures involving colorectal cancer (416 in 2019). At the same time, the largest decrease in their number was observed within this treatment group (a drop of 24 centers in 2022). A similar decline (22 centers) was observed in the case of radical surgery for stomach cancer. However, the highest relative decrease (by 11%) was recorded for breast cancer – out of 176 hospitals reporting services in 2019, 156 were recorded in 2022. A reduction in the number of hospitals (by 2) was also observed in kidney cancer. In the remaining locations, there were no changes (ovarian cancer, lung cancer) or an increase in the number of hospitals (throat cancer, prostate cancer, uterine cancer, central nervous system cancer, urinary bladder cancer, thyroid cancer and pancreatic cancer).

In the case of almost half of the analyzed cancer groups (i.e. throat cancer, kidney cancer, central nervous system cancer, urinary bladder cancer, thyroid cancer and pancreatic cancer), an increasing number of hospitals are providing services below the thresholds (fig. 1). At the same time, in almost all studied groups (except for pancreatic cancer), the number of hospitals providing services above the required threshold increased. This is not the result of the emergence of new service providers but the reorganization of service providers who were previously in the "potentially above the threshold" category, i.e. providing services in a volume exceeding the required threshold but not meeting the conditions of the DiLO card (probably due to the inability to provide consultation or meet the deadlines for diagnosis and initiation of treatment).

Table II. Number of hospitals by cancer type

Cancer type	Year and number of hospitals			
	2019	2020	2021	2022
throat	88	92	93	95
prostate	132	135	137	135
ovarian	178	183	175	178
colorectal	416	418	394	392
uterine	245	249	248	248
kidney	179	186	183	177
central nervous system	78	79	81	82
urinary bladder	133	140	137	139
breast	176	167	155	156
lung	36	41	40	36
thyroid	172	162	176	191
pancreatic	117	127	122	119
stomach	272	261	250	250
total	471	475	456	455

Source: "Healthy Data" website, published by eHealth Center

The degree of concentration of the market for radical surgery procedures

Analysis of the distribution of the number of services by category of hospitals proves the gradual concentration of the market (tab. III). The share of radical surgery services provided by hospitals not meeting the threshold decreased from 39% in 2019 to 35% in 2022. During the period under review, the share of services provided by hospitals in the "potentially above the threshold" category also decreased by 3 percentage points. In turn, the share of services provided in hospitals above the threshold increased gradually from 49% to 57%. On the other hand, it can be stated that more than 40% of services are still provided by hospitals below the threshold.

Concentration of procedures in large centers is observed in all (except for pancreatic cancer) examined cancer groups (fig. 2). In the case of radical surgery for prostate, kidney and thyroid cancers, the increase in the share of services provided by high-volume hospitals was 15 percentage points, 14 percentage points and 12 percentage points, respectively.

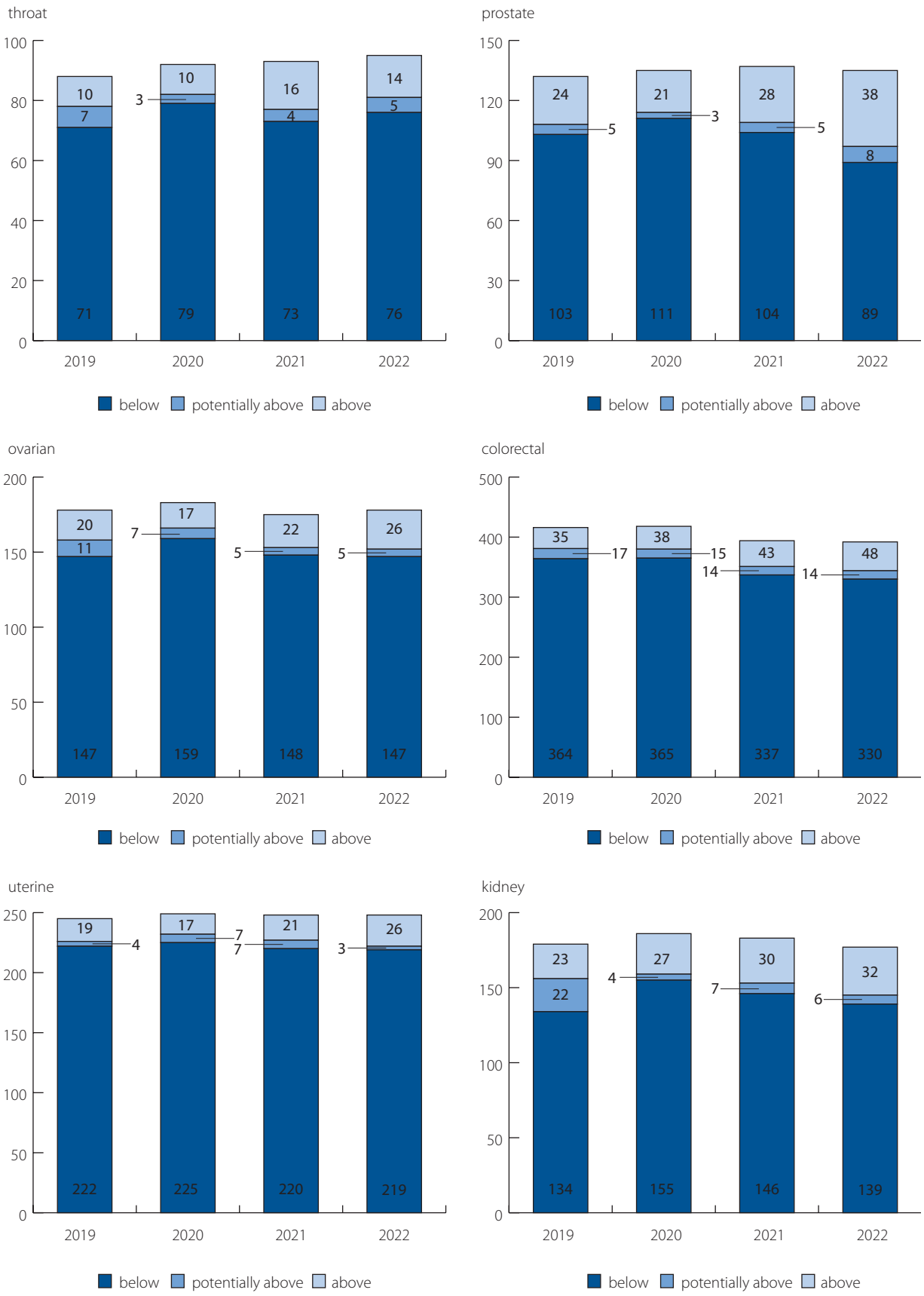

Figure 1. Number of hospitals by cancer group and category

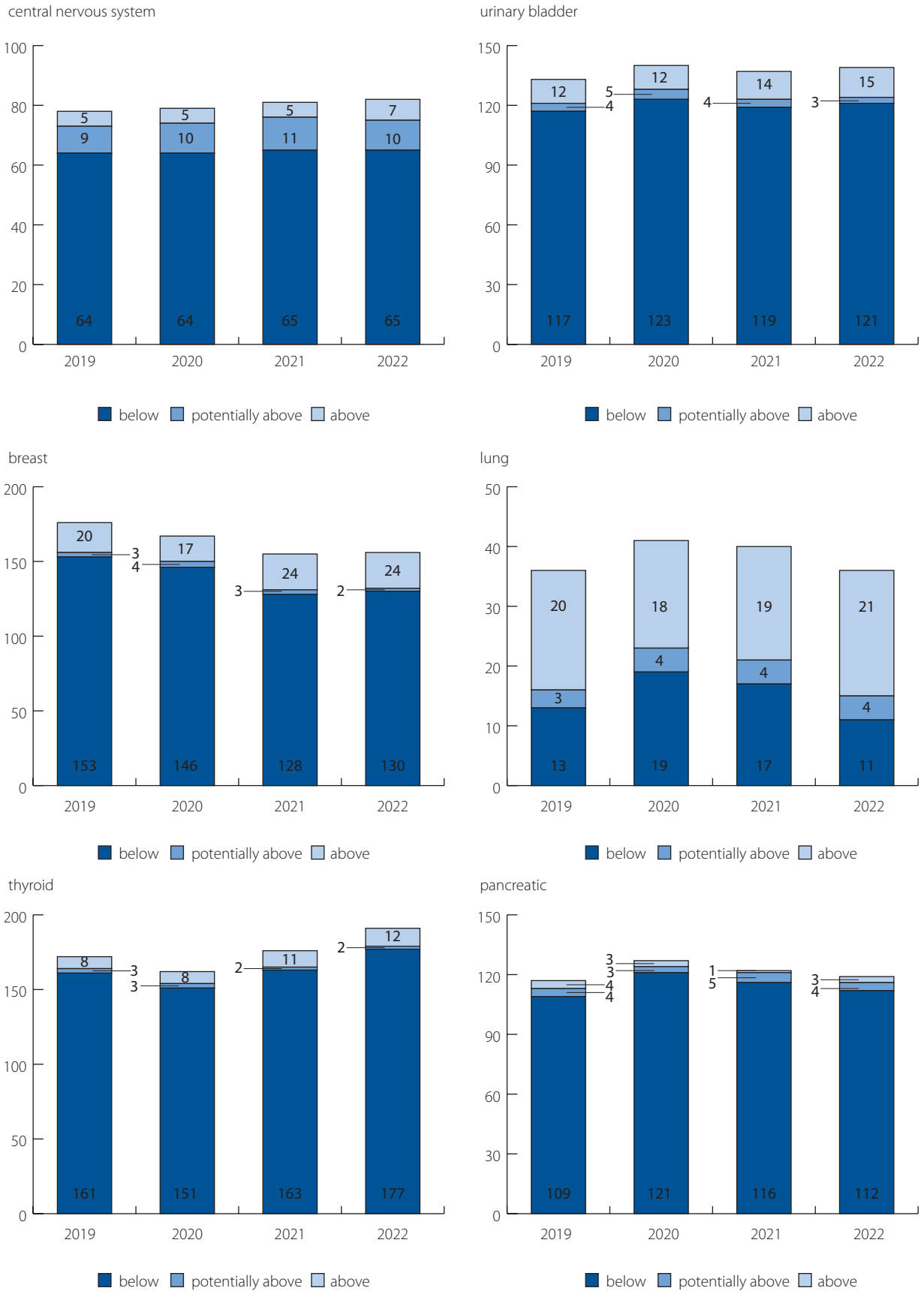

Figure 1 cont. Number of hospitals by cancer group and category

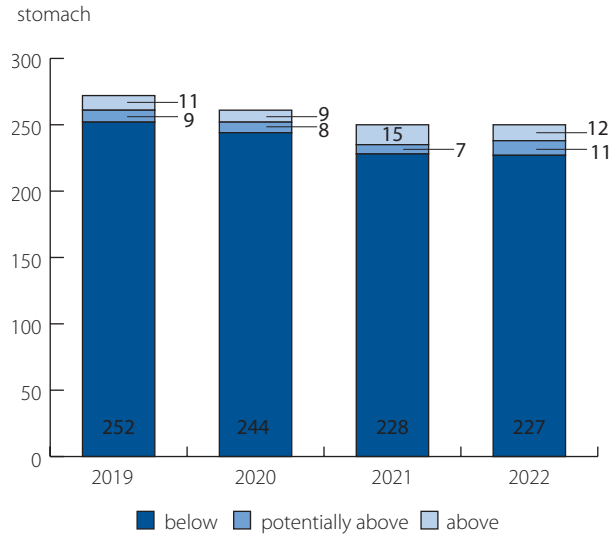

Figure 1 cont. Number of hospitals by cancer group and category

*above the threshold – the volume of procedures performed as part of the oncological package or comprehensive oncological care was at least equal to the threshold value; potentially above the threshold – the volume of procedures was at least equal to the threshold value, regardless of the scope of services in which it was reported; below threshold – the volume of treatments below the threshold value. Source: own calculation based on "Healthy Data" website, published by eHealth Center

Table III. Number of radical surgeries by hospital category

Year	Total	Below the threshold		Potentially above the threshold		Above the threshold	
2019	76,884	30,303	39%	9,271	12%	37,310	49%
2020	69,074	28,820	42%	7,308	11%	32,946	48%
2021	75,098	26,832	36%	7,516	10%	40,750	54%
2022	82,975	28,714	35%	7,229	9%	47,032	57%

Source: own calculation based on "Healthy data" website, published by eHealth Center.

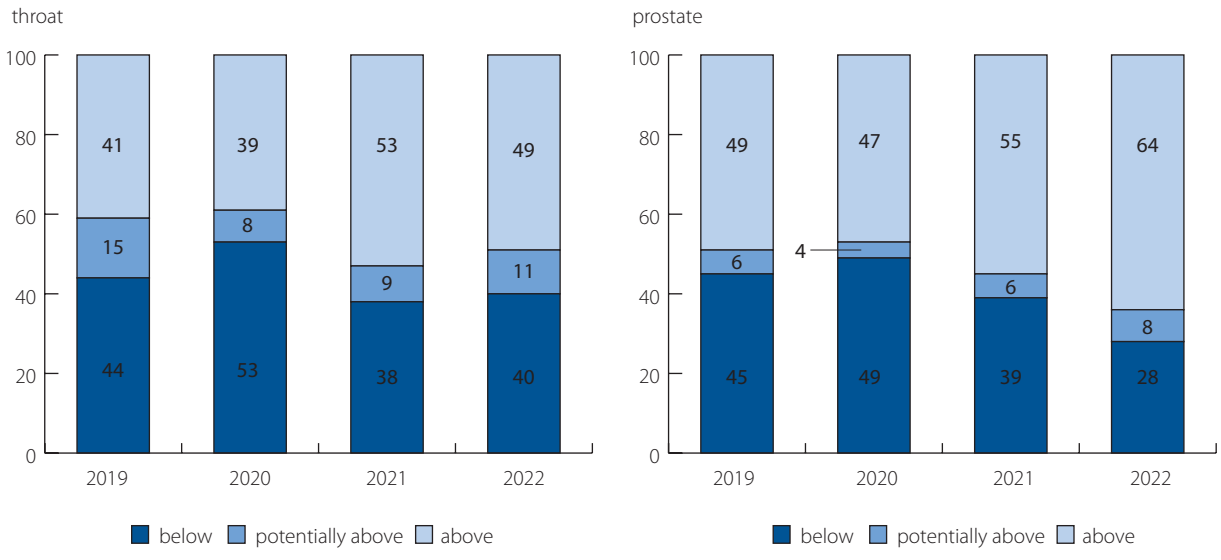

Figure 2. Structure of surgeries by cancer group and hospital category

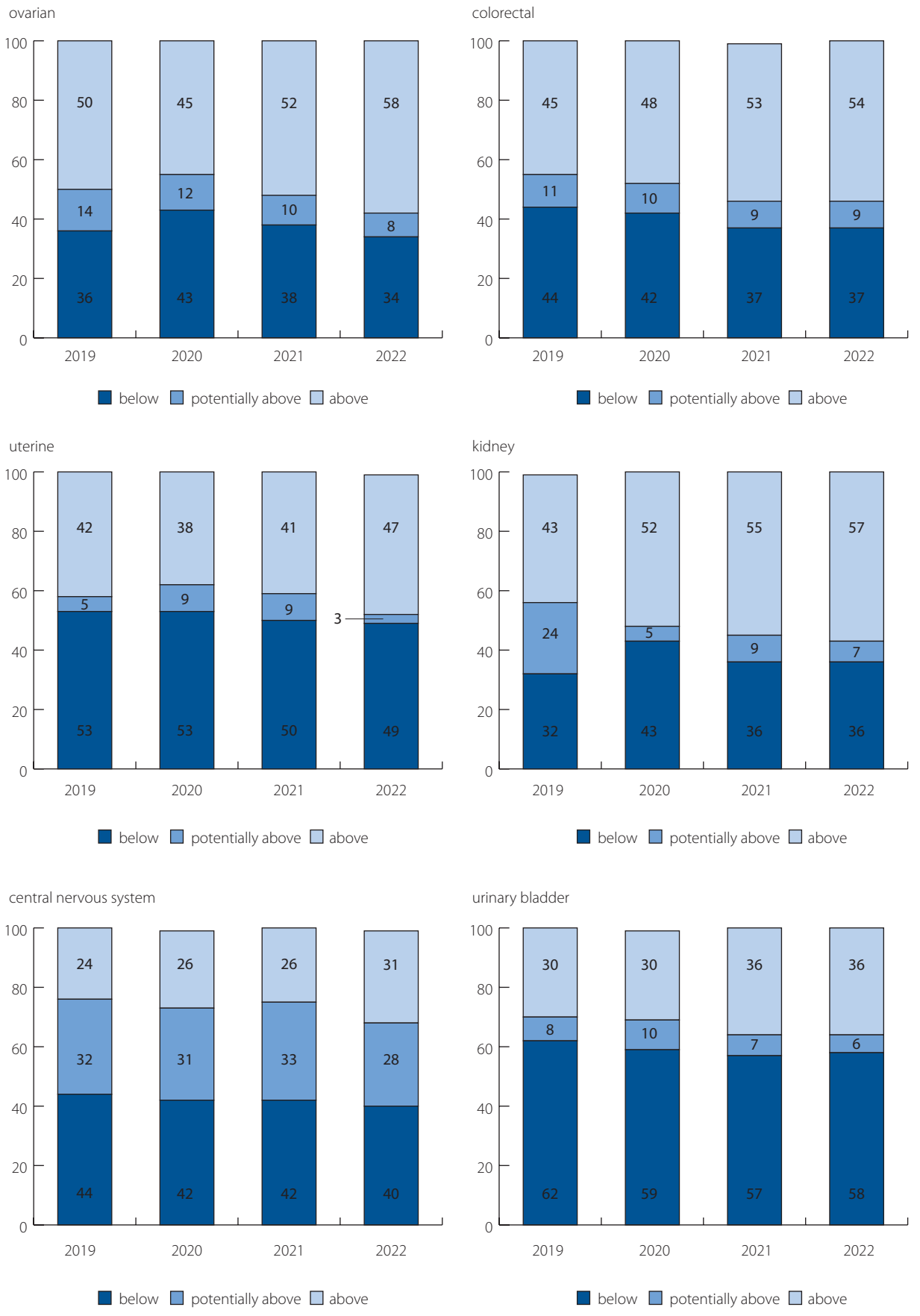

Figure 2 cont. Structure of surgeries by cancer group and hospital category

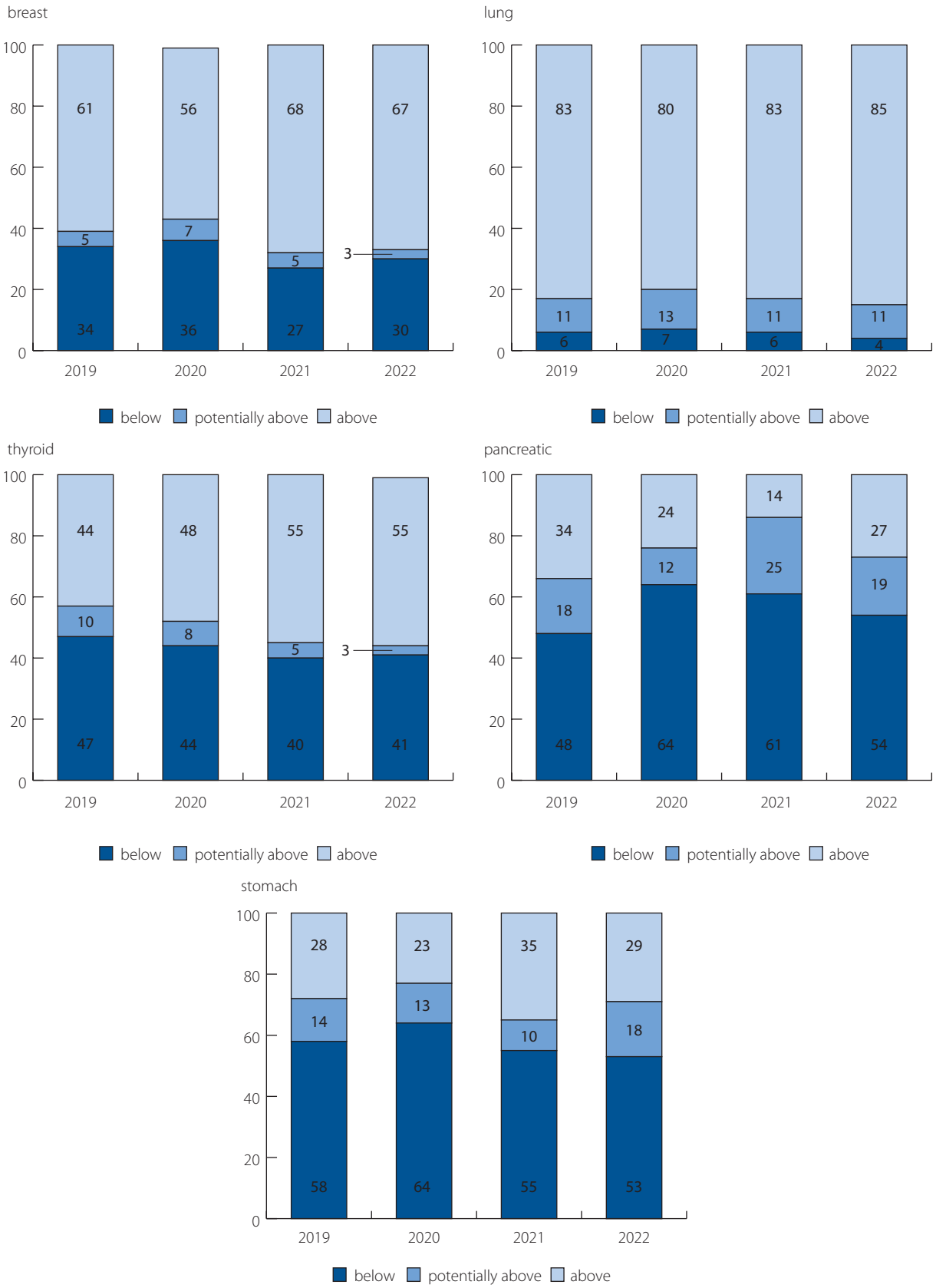

Figure 2 cont. Structure of surgeries by cancer group and hospital category

Source: own calculation based on "Healthyd" website, published by eHealth Center

Table IV. Number of hospitals providing radical surgeries and projection* by cancer type (2022 year)

Cancer type	2022	2022*	Difference
throat	95	38	–57
prostate	135	80	–55
ovarian	178	62	–116
colorectal	392	133	–259
uterine	248	81	–167
kidney	177	80	–97
central nervous system	82	37	–45
urinary bladder	139	56	–83
breast	156	48	–108
lung	36	28	–8
thyroid	191	40	–151
pancreatic	119	27	–92
stomach	250	66	–184

*max number of hospitals i.e. assuming that hospitals below threshold provide number of services accounted to threshold (ceteris paribus). Source: own calculation based on "Healthy data" website, published by eHealth Center

In turn, small increases (at the level of 1 pp or 2 pp) were observed among procedures performed in lung cancers and stomach cancers. In the remaining groups the increase was 6 pp–9 pp.

Considering the number of services provided in hospitals that do not meet the volume threshold, it should be concluded that across all cancer groups the number of healthcare providers providing radical surgery should be limited (tab. IV). The biggest changes should concern healthcare providers performing procedures in colorectal cancer surgery – a reduction to 133 healthcare providers in the country instead of the current number of 392.

Discussion

The implemented solution of determining the threshold above which a hospital qualifies as high-volume is a solution used in some countries, since several studies show positive clinical outcomes related to cancer treatment in high-volume hospitals – emphasising it especially for the most complicated, rare procedures. Individual countries differ in how they implement this solution, which largely depends on the type of healthcare system. Some countries, especially those dominated by publicly financed health care, have introduced more strict regulatory procedures [21]. For example, researchers in the German sector have determined minimum thresholds for treatment procedures that ensure better outcomes [22]. However, solutions defining volume thresholds also exist in the United States [23].

The example of Johns Hopkins Hospital or the Leapfrog Group have illustrated effective actions toward increasing the share of individual hospitals in the total number of procedures. The analysis conducted for Poland did not show such strong effects in the examined period (four consecutive years after the implementation of the change). The reason for the weak consolidation effect may be an insufficiently large financial incentive that constitutes a real incentive for hospitals to increase the volume of activities. The reasons may also be organizational – large hospitals may not have sufficiently large resources to be able to consume a significant increase in the number of services. Additionally, some hospitals may fail to meet the organizational conditions for the DILO card. The additional financing may not cover the costs related to the reorganization of the treatment process to meet the deadlines for starting treatment or implementing counseling.

On the other hand, the solution used in Poland introduces an incentive for high-volume hospitals, while at the same time there are no entry barriers for hospitals performing fewer procedures, preventing them from entering the market. What is important is that oncology had no budget cap before – all services provided were financed. The solution of excluding from the market providers with fewer than the required number of procedures is used in Poland, for example, in relation to arthroplasty procedures; it is justified by the learning curve and the need to continuously provide services to maintain high quality.

Additionally, it is the patients and their referring doctors who decide on where the surgery is performed. Educating and informing patients and referring doctors on hospital volumes and outcomes for different procedures would be useful. Public dissemination of performance data is already under way in some countries [21]. In Poland, data on the number of services is available in the payer's information system as well as on the "Healthy data" website, but they do not constitute a source of information for patients or doctors considered when choosing the hospital performing the procedure.

In healthcare systems in which patients are free to choose where to be treated, understanding patients' behavior and what drives them towards the most effective choice is of paramount importance. As Italian research shows, the distance to hospitals is among the most significant factors that play a role in the patient decision process. The same research has shown, however, that patients affected by comorbidities are more responsive to hospital quality and less to distance [24].

A policy of centralization of the most complex cancer surgery may lead to improved outcomes, and therefore, the introduction of financial or institutional incentives is justified. As shown by Ciesielski et al., the specialization of the surgical department on surgical oncology improves the outcomes [25]. Efforts should focus on optimizing the balance between patient access to specialty care and the experience of the treating center [12]. Perhaps improving the care coordination (e.g. providing post-hospitalization care closer to home) would be an important facilitator of the surgery centralization process.

The dispersion of radical oncological surgery procedures in Poland may be partly because doctors work in more than

one hospital and perform surgical procedures in each facility. According to the "Maps of health needs", the average number of jobs for doctors specializing in oncological surgery in 2019 was 1.78, for thoracic surgeons – 2.08, and for general surgeons – 1.61 [26]. This means that the surgeon's experience often goes beyond the experience acquired in each hospital. At the same time, however, research on the importance of volume of procedures performed in a given hospital indicates that this relationship is complex. A study by Harmon et al. [2] indicated that medium-volume surgeons achieved excellent outcomes similar to high-volume surgeons when operating in medium--volume or high-volume hospitals, but not in low-volume hospitals. As shown by Huo et al., [27] the doctor's experience is crucial, but it is strengthened by the experience of the hospital, which translates into the experience of the entire team. This justifies centralization, not only in terms of the number of hospitals, but also of the surgeons who carry out the most complex treatments within them [28]. In Poland, such a solution is used for robotic treatments.

The analysis of quantitative data indicates that to effectively achieve the goal of consolidating radical oncological surgery procedures, it is necessary to strengthen the mechanisms used or tweak them. A possible direction is to implement more rigid regulations specifying hospitals authorized to perform these procedures or specifying a minimum threshold for the volume of services below which the most complex procedures will not be financed by the payer.

The presented data also provoke consideration of a more thorough restructuring of the mechanism used. The incentives of provider payment systems are known to have an impact on the volume and quality of care. Research conducted by Link et al. [29] showed that the implementation of a minimum threshold for colon or rectal resections would exclude a lot of hospitals in the Netherlands that provide high quality treatment and include hospitals with lower-than-expected quality.

The number of procedures is an imperfect parameter of treatment quality. Surgical quality is influenced by case mix, surgical technique, diagnosis, process designs, organizational structures and volume. High volume has a positive impact on several of those factors, but only to some extent leads to quality improvement. Some authors write about a quality plateau [30] or a surrogate parameter that should be supplemented with other quality measurements – structural, process and result [29, 31, 32]. In Poland, such an opportunity is provided by regulations on the oncology network and the adopted Quality Act, which supports the implementation of quality parameters in the system and relates them to the level of hospital revenue.

A limitation of the study is that it does not account for the impact of the COVID-19 pandemic, which could have influenced the number of procedures conducted in hospitals. Although all hospitals operated under challenging conditions during the pandemic, the degree to which individual facilities were affected varied significantly. Additionally, the authors analyzed the values documenting the changes but have not further analyzed the causes of this situation. A further area that could be explored is the influence of other factors on the use of health services, and the subsequent volume of provision in a given hospital. These factors could include political or social factors, for example. Further qualitative research is needed.

Conclusions

The financial model introduced for radical oncology surgery was aimed to induce centralization of services. It is based on the additional revenue for high-volume hospitals with additional requirements regarding the treatment process. Its desired impact was insignificant, as the share of services performed in high-volume hospitals increased in a very slow peace and at the same time there were new providers entering the market with low number of surgical procedures.

Article information and declarations

Data availability statement

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

Authors contributions

Monika Raulinajtys-Grzybek – conceptualization, writing – original draft preparation, writing – review and editing.
Barbara Więckowska – conceptualization, data curation, writing – original draft preparation, writing – review and editing.

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Conflict of interest

None declared

Monika Raulinajtys-Grzybek
Warsaw School of Economics
Department of Management Accounting
al. Niepodległości 162
02-554 Warszawa, Poland
e-mail: mrauli@sgh.waw.pl

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Original article

Cancer epidemiology

HPV vaccination coverage in the European Region

Mariola Borowska, Paweł Koczkodaj, Marta Mańczuk

Cancer Epidemiology and Primary Prevention Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Introduction. The human papillomavirus (HPV) is an established cause of cervical cancer and other HPV-related diseases. This study aims to analyze the variation in coverage by HPV vaccination programs – particularly within European Region countries – and explore possible health outcomes.

Material and methods. A comprehensive literature review and analysis of epidemiological data were conducted, focusing on HPV vaccination coverage rates, the implementation of vaccination programs, and their outcomes across the EU/EEA. The study examined various vaccination models, including school-based and health center-based programs, to understand their effectiveness in achieving high vaccination coverage and the associated reduction in HPV-related disease burden.

Results. The study's analysis identified significant variations in HPV vaccination coverage across the EU/EEA. School-based vaccination programs, particularly, were highly effective in reaching the target population, achieving coverage rates significantly higher than those observed in countries relying on health center-based or mixed-model vaccination strategies.

Conclusions. HPV vaccination programs have played a crucial role in reducing the burden of HPV-related diseases. These programs' success largely depends on achieving high vaccination coverage, which is more effectively realized through school-based vaccination strategies.

Key words: human papillomavirus, HPV vaccination, cancer prevention, cervical cancer, school-based intervention, coverage

Introduction

HPV is a human papillomavirus [1]. There are over 180 types of HPV, including low-risk types that cause benign genital warts (condylomas) and papillomas and high-risk types with a high oncogenic potential, which are responsible for precancerous lesions, cervical cancer, and other types of cancer. An HPV infection occurs sexually, most frequently shortly after the initiation of one's sexual activity. In the course of their lives, 80% of sexually active men and women have been or will be infected with HPV [2, 3]. HPV infections are the direct cause of nearly 99.7% of cervical cancer cases. The virus is transmitted sexually. Virus transmission is also possible through contact with an infected person's mucous membranes or skin. According to the World Health Organization, cervical cancer is the 4th most common type of cancer worldwide. It is detected in over half a million women every year. It has led to the death of 250,000 women [4].

The introduction of HPV vaccinations has led to a reduction in the number of HPV 6/11/16/18 infections, genital warts, low-grade cervical cytological abnormalities, and histologically confirmed cervical abnormalities [5, 6]. The results of randomized trials have demonstrated the high safety profile of HPV vaccines [7]. The most significant benefits are observed in the population of girls vaccinated before exposure to HPV

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in countries that have achieved high vaccination coverage rates (VCR) [5, 7]. HPV remains a significant source of cervical cancer morbidity and mortality worldwide. In light of this, implementing universal vaccination programs against HPV is vital for improving cancer prevention [5]. In 2018, the WHO paid particular attention to cervical cancer and set a target of 90% HPV vaccination coverage for the population by 2030 [8].

According to the World Health Organization's global strategy, every country should achieve the 90–70–90 targets by 2030 to eliminate cervical cancer in the next century:

- 90% of girls fully vaccinated with the HPV vaccine before the age of 15,
- 70% of women after screening tests before the age of 35 (and again before the age of 45), and
- 90% of diagnosed women on treatment (those with precancerous changes and those with advanced course of disease).

WHO mathematical models show that implementing the abovementioned activities in the coming years may lead to a global decline of cervical cancer incidence by 42% by 2045 and 97% by 2120 [9].

The first country worldwide to introduce a national, universal HPV vaccination program was Australia. The program was launched in 2007, and the first population group to be vaccinated against HPV was girls. In 2013, boys were also vaccinated. In the European region, Great Britain was the first to launch a universal HPV vaccination program for girls in 2008 [10]. By 2019, almost all EU/EEA countries had introduced the HPV vaccination into their national vaccination programs. 30 out of 31 countries have universal vaccination programs for girls, and 11 also have catch-up vaccination programs for older age groups [11].

In most countries, universal HPV vaccination programs are fully financed from public funds. In a few countries, the patient covers a part of the costs (this concerns mainly catch-up vaccinations). According to the current data (as of May 2023), 125 countries worldwide have universal vaccinations against HPV (data from the Our World in Data platform) [10, 12].

The study aimed to analyze data on vaccination in the population eligible for the HPV vaccination as part of free national vaccinations in individual European Union/European Economic Area countries.

Material and methods

The material consists of epidemiological data on vaccinations against human papillomavirus in girls and boys under universal preventive programs in individual countries. The data come from collective information on vaccination coverage in eligible populations across various countries. A focused literature review was conducted using the National Ministry of Health websites, the WHO database, and the Our World in Data database. The data were collected for the following aspects: vaccination rate in the population per country, date of launching the vaccination per country, and vaccination model, i.e., vaccinations in schools, health centers, pharmacies, or under a mixed model.

Results

Australia was the first country to introduce a universal HPV vaccination program, where girls were vaccinated in 2007 and boys in 2013.

Due to the HPV vaccine's excellent safety profile, efficacy, and population effectiveness, in 2017, the World Health Organization (WHO) published an updated position on HPV vaccinations with a recommendation on HPV vaccinations for persons aged 9–14 years (and, if funds are available, catch-up vaccinations for persons up to 18 years of age) in all countries of the world.

By 2019, almost all EU/EEA countries had introduced HPV vaccinations into the national universal vaccination programs. 30 out of 31 countries (except Poland) have universal vaccination programs for girls, and 11 have also implemented catch-up vaccination programs in older age groups. Universal immunization programs have been extended to the male population in 14 of 30 countries (Austria, Belgium, Croatia, The Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Netherlands, Norway, Sweden, and The United Kingdom), and many other countries plan to extend their programs shortly. In one country (Liechtenstein), catch-up vaccinations are also performed among older boys. In most countries, vaccinations are fully financed from public funds, and in a few countries, it is the patient who covers a part of the costs (this concerns mainly catch-up vaccinations). Differences between countries are mostly related to the age of the target populations, which is 9–14 years for girls and boys, 10–26 years for girls, and 10–18 years for boys under the catch-up vaccination programs. Poland introduced the HPV vaccination into the national vaccination program in June 2023 as part of the National Public HPV Vaccination Program (tab. I).

The vaccination model in European countries is based on vaccinations in schools, health centers, pharmacies, and the mixed model. Population vaccination models include vaccinations in schools. For example, in Belgium, vaccinations in children are scheduled automatically, and only if the guardian declares no consent the child is not vaccinated (opt-out manner). Another model includes vaccinations in medical centers or other places, e.g., pharmacies. The mixed model includes vaccination both in health centers and schools (fig. 1).

Since 2014, the HPV vaccination has been introduced in schools in Hungary, where vaccination coverage is almost 80%. In Belgium, the vaccination rate is 90%. In Spain, a reimbursed HPV vaccination program for girls has been operating since 2018. Currently, the vaccination rate is 80%. Subject to reimbursement are vaccinations for girls and vaccinations for high-risk groups: persons with primary immune disorders, HIV carriers, and homosexual men. In Romania, the vaccination

Table I. HPV vaccination coverage in the target populations in Europe

Country	Implementation	Vaccination model	Vaccination coverage
Austria	2014	mixed	53%
Belgium	2008	schools	90%
Bulgaria	2013	health centers	no data
Croatia	2016	schools	no data
The Czech Republic	2012	health centers	29%
Denmark	2008	health centers	80%
Finland	2013	schools	68%
France	2007	health centers	19%
Greece	2008	health centers	no data
The Netherlands	2010	mixed	53%
Spain	2007	mixed	82%
Iceland	2010	schools	88%
Ireland	2010	schools	72%
Lichtenstein	no data	mixed	no data
Luxembourg	2008	health centers	no data
Lithuania	2016	no data	no data
Latvia	2010	mixed	33%
Macedonia	2009	schools	54%
Malta	2012	PHCs	79%
Monaco	2006	no data	no data
Germany	2007	health centers	31%
Norway	2009	schools	79%
Poland	2023	health centers	18%
Portugal	2008	mixed	84%
Russia	2014	no data	<30%
Romania	2008	mixed	no data
Slovakia	no data	schools	no data
Slovenia	2009	schools	46%
Switzerland	2008	mixed	56%
Sweden	2011	schools	80%
The United Kingdom	2008	schools	85%
Hungary	2014	no data	76%
Italy	2008	health centers	42%

Based on data from the OECD iLibrary: https://www.oecd-ilibrary.org/social-issues-migration-health/eu-country-cancer-profiles_55f07000-en [13] and Our World in Data https://ourworldindata.org/grapher/human-papillomavirus-vaccine-immunization-schedule?tab=table [12]

program was introduced relatively early, i.e., in 2008, but it was suspended and resumed many times, which has resulted in poor vaccination rates. The mixed model is used in Romania, i.e., health centers and schools participate in the program.

In Poland, from June 1 to December 29, 2023, 152,000 teenagers aged 12 and 13 (63% girls and 37% boys) were vaccinated under the National Public HPV Vaccination Program, representing approximately 18.3% of the eligible population. The vaccinations are part of recommended protective measures, with vaccine purchases funded by the Ministry of Health starting from June 1, 2023, as per announcements made on February 23, 2023 (Official Gazette of the Ministry of Health, item 16) and September 29, 2023 (Official Gazette of the Ministry of Health, item 88). The Transparency Council of the Agency for Health Technology Assessment and Tariff System (AOTMiT) evaluated the effectiveness of HPV vaccines in preventing cervical cancer, according to which the two vaccines available in Poland – Cervarix, 0.5 ml dose (GlaxoSmithKline Biologicals S.A.) and Gardasil 9, 0.5 ml dose (Merck Sharp & Dohme B.V.) – are effective in preventing cervical cancer. There is no reliable evidence to suggest the clinical superiority of either vaccine in terms of clinically significant endpoints.

Discussion

The most common and dangerous disease caused by the HPV infection is cervical cancer. According to WHO data, cervical cancer is the fourth most common cancer among women worldwide; in 2020, it caused the death of over 324,000 women. [2] In Poland, cervical cancer incidence and mortality rates are 12.2/100,000 and 5.4/100,000, respectively, and the incidence of head and neck cancer is 1.27/100,000 (data from 2018). [14] While infection with HPV types 16 and 18 is associated with approximately 70% of cervical cancer cases, HPV infection is etiologically associated with the development of other diseases [15]. It is estimated that worldwide nine out of ten cases of anal cancer, seven out of ten cases of vaginal cancer, one out of two cases of penile cancer, and four out of ten cases of vulvar cancer are caused by the HPV infection [16, 17].

The estimated effectiveness of vaccinations at the population level has been confirmed for HPV infections, genital warts, and advanced precancerous conditions of the cervix. These changes appear relatively quickly after contact with the HPV (the incubation period for genital warts and precancerous conditions of the cervix ranges from a few to several months) [18, 19].

In 2015, a meta-analysis of 20 studies covering 140 million person-years in countries where >50% of girls were vaccinated was published. The results showed that the incidence of HPV infections types 16 and 18 was reduced by 68% (relative risk [RR]: 0.32 [95% CI: 0.19–0.52]). The risk of HPV infections type 31, 33, and 45 was also reduced (RR: 0.72 [95% CI: 0.54–0.96]), which suggests cross-protection. The incidence of genital warts in girls aged 13–19 decreased by 61%

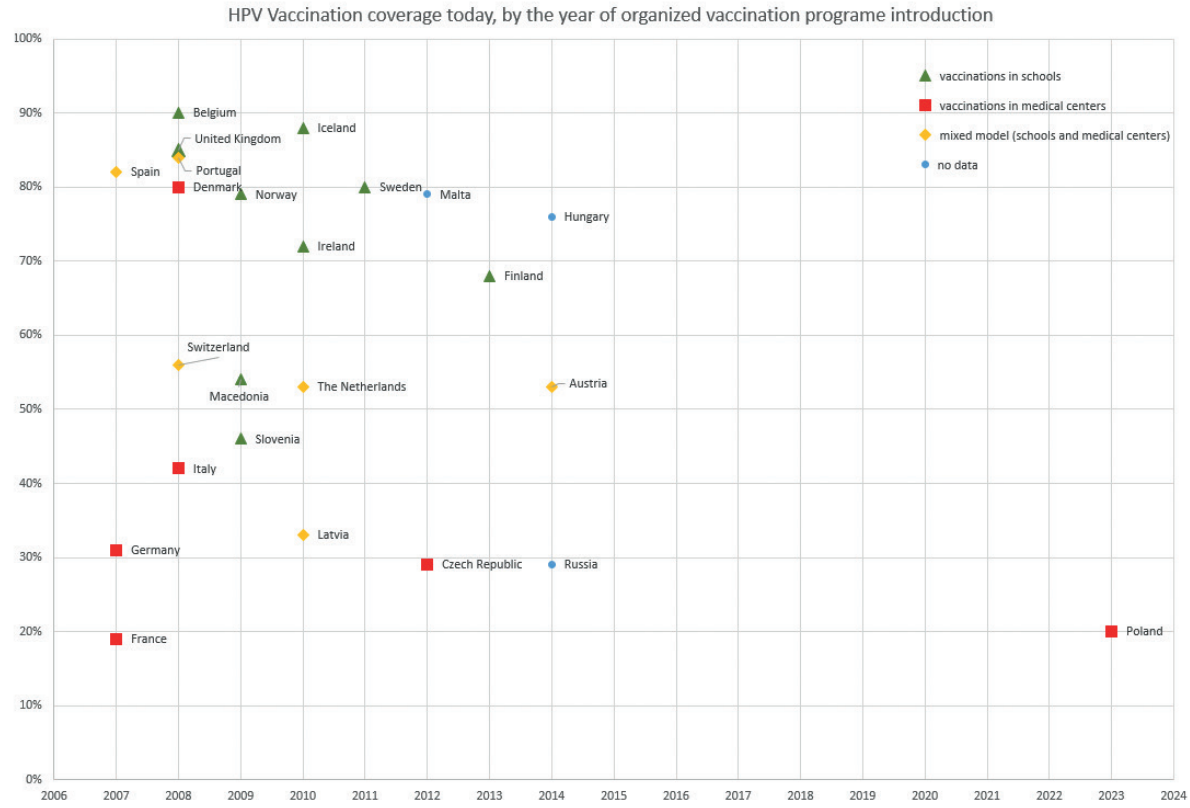

Figure 1. HPV vaccination coverage by the year of introduction of the organized vaccination program

Based on data from the OECD iLibrary: https://www.oecd-ilibrary.org/social-issues-migration-health/eu-country-cancer-profiles_55f07000-en [13] and Our World in Data https://ourworldindata.org/grapher/human-papillomavirus-vaccine-immunization-schedule?tab=table [12]

(RR: 0.39 [95% CI: 0.22–0.71]). Reduction in the incidence of genital warts was observed in men <20 years of age (RR: 0.66 [95% CI: 0.47–0.91]) and in women aged 20–39 (RR: 0.68 [95% CI: 0.51–0.89]), which indicates the development of population (herd) immunity [19]. These results have been confirmed in recent publications, constituting new evidence of the population effect of the HPV vaccination. The results of a meta-analysis conducted in 2019 by Drolet et al. indicated that after several years of widespread, routine vaccinations among girls aged 13–19 in developed countries, the incidence of HPV 16 and 18 decreased by 83%, and HPV 31, 33, and 45 fell by 54%. The incidence of anogenital warts among boys aged 15–19 decreased by 48% [5]. In Australia, a reduction in the frequency of carrying vaccine HPV types was observed in unvaccinated men [20, 21]. A decrease in the incidence of genital warts was also observed in Italy, Canada, Denmark, Israel, Spain, the United States, and Sweden [22–28]. A reduction in the frequency of HPV infections was observed in population-based studies of men and young women in the United States and young women in the United Kingdom [29–31]. Another significant piece of evidence supporting the effectiveness of HPV vaccinations in the population for the prevention of cervical cancer, several decades before the anticipated reduction in the incidence of invasive cancer, is data indicating a decrease in the incidence of cervical intraepithelial neoplasia. This data has been collected in Australia, Denmark, Sweden, and the United States [32].

Implementing a structured HPV vaccination program is much more common in countries with a high vaccination rate. Importantly, in areas with high HPV vaccination rates, vaccinations took place mainly in schools, the HPV vaccine was always administered on-site, and the reminder communications were sent to children's parents. In areas with meager vaccination rates, the HPV vaccine was administered mainly in health centers or private doctors' offices. Access to HPV vaccinations can be facilitated by increasing the availability of on-site vaccines, sending reminders to parents, and administering vaccines in schools, which results in high vaccination coverage [33–35].

In Poland, the percentage of children vaccinated under the National Public HPV Vaccination Program should be compared with the number of vaccinations carried out as part of health policy programs, including those implemented by local government units. Only then can the total number of girls and boys vaccinated against HPV – both under the National Public HPV Vaccination Program and through health policy programs – be estimated. The estimate should also include children whose parents funded vaccinations privately.

However, local government programs are not available in every city, especially in rural areas. Hence, the National Public HPV Vaccination Program increases the coverage of the eligible population for vaccination.

Among the factors contributing to the low vaccination rate are registration in the central system, which may pose a barrier for parents and providers alike, anti-vaccine propaganda, the presence of fake news related to vaccination, and anti-vaccine movements. Responding to these challenges includes accurate education, promotion, and intersectoral cooperation. The Polish Ministry of National Education website features a message regarding HPV vaccinations, and this information should be disseminated to schools. However, no other actions have been identified to date regarding promoting HPV vaccinations in educational facilities. The experience of countries where vaccinations are administered in schools suggests high effectiveness, as these countries report high HP vaccination take-up rates among children and adolescents. Children and adolescents spend a significant portion of their time in school. In contrast, contact with primary healthcare facilities is less frequent at 12 and 13, as health assessments are not commonly conducted at this age. An interesting initiative appears to be an SMS campaign developed based on experiences from COVID-19 vaccinations.

The literature review on interventions aimed at improving HPV vaccination coverage, which was conducted by Walling et al., stressed community-based interventions as effective in promoting and implementing HPV vaccinations. Community-based interventions, primarily vaccinations in schools, are often associated with high vaccination coverage since they increase access to vaccinations. For example, in Switzerland, where the practical implementation of vaccinations varied depending on location, implementing the mixed vaccination model showed that the vaccination rate was higher in the areas where vaccinations were performed in schools. School-based vaccination programs have also been particularly effective in achieving high HPV vaccination rates in Australia [33–36].

Conclusions

The effectiveness of population-based HPV vaccination programs has been confirmed in many scientific studies. Monitoring of HPV vaccinations is crucial to ensure vaccination sustainability and, consequently, to ensure population effects related to the prevention of cervical cancer and other cancer sites. Countries that offer reimbursed national vaccinations in the school-based vaccination model achieve the highest vaccination rates. Countries that offer reimbursed national vaccinations in the medical center-based vaccination model achieve significantly lower vaccination rates. A vaccination model based on primary schools should be considered to increase vaccination take-up within the public HPV vaccination program in Poland.

Article information and declarations

Author contributions

Mariola Borowska – conceptualization, data curation, writing – original draft preparation.

Paweł Koczkodaj – conceptualization, writing – review and editing.

Marta Mańczuk – conceptualization, formal analysis, supervision, writing – review and editing.

Data availability statement

Publicly available data. All sources are indicated in the manuscript.

Conflict of interest

None declared

Marta Mańczuk
Maria Sklodowska-Curie National Research Institute of Oncology
Cancer Epidemiology and Primary Prevention Department
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: Marta.Manczuk@nio.gov.pl

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Post-treatment surveillance principles for selected skin cancers – recommendations of the Surveillance Standardization Section of the Polish Oncology Society

Wojciech M. Wysocki[1, 2, 3], Aleksandra Kulbat[2, 4], Marta Krzysztofik[5], Karolina Richter[1, 2], Elżbieta Wójtowicz[6], Joanna B. Wysocka[7], Paweł Brzewski[5, 8], Grażyna Kamińska-Winciorek[9], Hanna Koseła-Paterczyk[10], Jacek Mackiewicz[11, 12], Witold Owczarek[13], Piotr Rutkowski[10], Marcin Ziętek[14, 15]

[1]*Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[2]*Department of Oncological Surgery, 5th Military Clinical Hospital in Krakow, Krakow, Poland*
[3]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[4]*Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Poland*
[5]*Department of Dermatology and Venereology, Stefan Zeromski Municipal Hospital, Krakow, Poland*
[6]*Skin Cancer Unit, 5th Military Clinical Hospital in Krakow, Poland*
[7]*Department of Pathology, National Institute of Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland*
[8]*Chair of Dermatology, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[9]*Department of Bone Marrow Transplantation and Hematology-Oncology, Skin Cancer and Melanoma Team, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Poland*
[10]*Departament of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[11]*Department of Medical and Experimental Oncology, Institute of Oncology, Poznan University of Medical Sciences, Poznan, Poland*
[12]*Department of Diagnostics and Cancer Immunology, Greater Poland Cancer Center, Poznan, Poland*
[13]*Dermatology Clinic, Military Institute of Medicine - National Research Institute, Warsaw, Poland*
[14]*Department of Surgical Oncology, Lower Silesian Oncology, Pulmonology and Hematology Center, Wroclaw, Poland*
[15]*Department of Oncology, Wroclaw Medical University, Wroclaw, Poland*

The paper presents recommendations concerning the surveillance of patients after the treatment of squamous-cell carcinoma (SCC), basal-cell carcinoma (BCC) and Merkel-cell carcinoma (MCC) based on the current European and American recommendations. This overview discusses the methodology and detailed recommendations concerning the post-treatment surveillance, with special attention to the clinical examination, dermatoscopy, imaging diagnostics and patient education. The recommendations emphasise the significance of early monitoring for recurrences, and early detection of new skin cancers, adapted to individual risk factors in a patient and the characteristics of primary cancer. Also the significance of patient education, with regards to the protection against sun radiation and the role of skin self-examination are stressed.

Key words: skin cancer, carcinoma, squamous cell, basal cell, Merkel cell, skin neoplasms, follow-up, survivorship, skin self-examination

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Introduction

Squamous-cell carcinoma (SCC) and basal-cell carcinoma (BCC) are the most frequently occurring malignant tumours in Caucasians [1–3]. Merkel-cell carcinoma (MCC) is a cancer that occurs many times less frequently than the two previous types of the skin cancer, yet with respect to the aggressive course and a relatively significant incidence in the population characteristic of the residents of Poland, it also came under the spotlight of the Surveillance Standardization Section of the Polish Oncology (https://www.pto.med.pl/sekcja-standaryzacji-nadzoru-po-leczeniu-onkologicznym) [4].

In spite of the large prevalence of the above cancers in people, the existing recommendations concerning the principles of surveillance after the treatment, published so far, were significantly diversified and were based, to a large degree, on consensus conferences and opinions of expert groups appointed on an *ad hoc* basis by various organisations. However, within the two recent years, updated agreed European recommendations concerning the clinical management in SCC, BCC and MCC were published under the common banner of the European Association of Dermato-Oncology (EADO), European Dermatology Forum (EDF), European Society for Radiotherapy and Oncology (ESTRO), European Union of Medical Specialists (UEMS), European Academy of Dermatology and Venereology (EADV) and European Organization for Research and Treatment of Cancer (EORTC) and European Society for Medical Oncology (ESMO) [1–5].

The objective of this study was to work out uniform recommendations concerning the surveillance after the completion of the treatment of the patients with SCC, BCC and MCC designed for doctors of numerous specialisations, including family doctors, taking into consideration the manner of operation of the national healthcare system in Poland.

Material and methods

A critical overview of some selected guidelines for clinical management with regards to their fragments referring to the surveillance of convalescents who completed the treatment of SCC, BCC and MCC [1–8] was made. The overview did not include the skin melanoma, because, for this cancer, specific national guidelines concerning the surveillance after the treatment have recently been published [9–10].

Recommendations

The surveillance of the patients after the treatment of skin basal-cell cancer

The objective of the surveillance after the treatment of BCC is the following: local recurrence; another primary BCC, and other skin cancers with similar risk factors for development (squamous-cell carcinoma, melanoma).

The first follow-up visit after the treatment should include detailed information for the patient on the following: diagnosis and prognosis; risk factors of skin cancers; methods of protection against sun radiation; clinical signs of local recurrence which can be detected by the patients themselves;

Table I. The principles of surveillance of the patients with basal cell carcinoma of the skin without signs of an active disease [1, 5]

Intervention	Recommendation
medical examination, involving, in particular in the scar, its area and the entire skin	every 6–12 months in the first 5 years, and then at least every 12 months[#]
dermatological assessment (with dermatoscopy) of the skin in the patients with at least 1 of the additional recurrence risk factors listed below: • a planned solid organ, bone marrow or hematopoietic cells transplantation or a history of it; • the occurrence of at least 1 skin melanoma within the last 5 years; • the occurrence of at least 4 non-melanocytic skin cancers within the last 5 years	every 4–6 months for the first 5 years, then every 6–12 months (lifetime) [#]
patient self-examination of the scar and the entire skin once a month	the patients should be appropriately trained (in particular those with recurring lesions) and an immediate medical visit must be recommended in case of noticing any lesion in the place of a previous surgical intervention
skin protection against UV	sun exposure should be limited during the midday (between 10 a.m. and 4 p.m.), protective clothing must be worn, including headgear and sunglasses; regular use of broad-spectrum sunscreens is recommended on the exposed skin (especially for people with light complexion)
imaging diagnostics if, on account of initial stage/ location, physical examination might not be efficient to diagnose recurrence	imaging technique (ultrasound, CT, MRI), the target area and frequency should be defined by a multispecialist team upon the completion of the treatment, on the basis of the suspicion of the type of recurrence (i.e. local, regional, metastatic)

Note! During the first follow-up visit detailed information concerning the risk of recurrence must be communicated to the patient, which will facilitate self-diagnosis; there are data available showing that in patients with non-advanced form of BCC and whose personal characteristics make self-surveillance possible, only one follow-up visit is possible when all the information concerning the skin protection and self-examination is communicated.

[#] – the definite frequency of the interventions undertaken within the surveillance process depends first of all, on individual characteristics of the disease and treatment response; more intensive schedule of visits should apply to convalescents after treatment with primarily local advancement of BCC or BCC with regional/systemic dissemination

Table II. Recommended surveillance principles after the treatment of patients with squamous-cell carcinoma of the skin without the signs of an active disease [2, 3, 6]

Disease stage upon diagnosis	Medical examination of the skin and regional lymph nodes	Regional lymph nodes ultrasound	Other imaging procedures (CT, MRI, PET-CT)	Other interventions
low risk	every 12 months for the first 2 years	not necessary if the lymph nodes are not palpable during physical examination	not necessary without clinical indications	• patient self-examination of the regional lymph nodes and the entire skin to be made once per month[a] • skin protection against sun (SPF 30–50)[b]
high risk*	every 3–6 months for the first 2 years, then every 12 months	every 3–6 months for the first 2 years	not necessary without clinical indications	
very high risk**	every 3 months for the first 5 years and then every 6–12 months	every 3–6 for the first 5 years and then every 6–12 months	every 3–6 for the first 3 years and then depending on the clinical situation	
all convalescents after SCC, who are at the same time transplant recipients or have a chronic lymphatic leukaemia	every 3–6 months for a lifetime	in accordance with the classification to the risk group	in accordance with the classification to the risk group	

Note! The definite frequency of the interventions undertaken within the surveillance process depends first of all, on individual characteristics of the disease and treatment response.

[a] – the patients should be appropriately trained (in particular those with recurring lesions) and an immediate medical visit must be recommended in case of noticing any lesion in the place of a previous surgical intervention; [b] – sun exposure should be limited between 10 a.m. and 4 p.m., protective clothing, including headgear and sunglasses, should be worn. Regular use of broad-spectrum sunscreens is recommended on the exposed skin (especially for people with light complexion); * – squamous-cell carcinoma without *in-transit*, regional or distant metastases (i.e. N0 M0) with accompanying high risk factors of local or distant recurrence (see table IV); ** – squamous-cell carcinoma with regional (i.e. N+) or systemic (i.e. M1) dissemination

the necessity of self-examination of the patient's skin on connection with an increased risk of developing new primary cancer [1].

Overall cumulative risk of BCC recurrence is low, yet the risk of developing a subsequent basal-cell carcinoma is approx. 30–50% within 5 years [9]. On account of the BCC prevalence and a large number of convalescents, the manner of surveillance must be adapted to the risk of recurrence. A large BCC recurrence risk group is made up by the patients with a history of a previous BCC recurrence and patients with a history of numerous BCCs. BCC tumors with a high risk of recurrence are most often located on the face and characterized by an aggressive course with perineural and perivascular infiltration [1]. Moreover, the process of individualisation of the surveillance must include the histopathological variants of BCC burdened with a high risk of recurrence. The recent WHO classification of skin tumors introduced the distinction into BCC subtypes connected with a low risk (superficial, nodular, with adnexal differentiation and fibroepithelial) and with a high risk (micronodular, infiltrating, sclerosing, basosquamous carcinoma and BCC with sarcomatoid differentiation) of recurrence [10]. In the case of patients with a history of irradiation (especially with the use of older techniques) in the therapy of BCC or other cancers, the surveillance must also include the risk of development of post-irradiation cancer within the irradiated field. On the basis of the collected date, the guidelines were formulated, as presented in table I.

The surveillance of patients after the completion of treatment of skin squamous-cell carcinoma

The objective of the surveillance after the treatment of BCC is the following: local, regional and distant recurrence; another SCC; diagnosis of other skin cancers with similar risk factors for development (basal-cell carcinoma, melanoma); clinical and radiological assessment of the treatment efficiency and adverse effects; education of the patient and their carers about the risk of recurrence [2, 6]. Additionally, follow-up visits allow to treat the precancerous skin lesions, which is especially important

Table III. High risk factors of local or distant recurrence in skin squamous-cell carcinoma [2, 3]

Risk factor	Characteristic
diameter	>20 mm
location	lips, ears, temples
thickness	>6 mm or infiltration outside subcutaneous adipose tissue
histological differentiation	low (poorly differentiated)
desmoplasia	present
infiltration of peripheral nerve fibres	present (microscopic, symptomatic or radiological)
bone infiltration	present
immunosuppression	present
surgical margin	positive

in the case of the patients with an increased field of carcinogenesis, patients with immunosuppression and numerous primary SCCs [3].

Squamous-cell carcinoma of the skin occurs primarily in elderly persons with numerous comorbidities. This leads to the necessity of adaptation of the surveillance principles to an individual situation of the patient and involvement of the closest caring persons to the surveillance process (e.g. family members of the nursing facility staff) [2, 3].

In the case of patients with a history of SCC therapy involving irradiation, the surveillance should include the risk of development of post-irradiation cancers within the irradiation field. The recommendations, based on the collected data, are summarized in tables II and III.

The surveillance of patients after the treatment of Merkel-cell carcinoma of the skin

The objective of the surveillance after the treatment of MCC includes the following: diagnosing the recurrence at an early stage; diagnosis of other skin cancers with similar risk factors for development (SCC, BCC, skin melanoma); clinical and radiological assessment of the treatment efficiency and adverse effects; increasing the awareness of the risk of recurrence in the patient and their carers [2, 4].

The website of an international organisation dedicated to patients with MCC presents a Recurrence Risk Calculator, which might be helpful to individualise the surveillance program after the treatment (https://merkelcell.org/prognosis/recur/) (fig. 1). Based on the collected data, the recommendations were formulated as presented in the table IV.

Conclusions

Based on the overview of the European and American recommendations concerning the principles of patient surveillance after the treatment of skin cancers, some cardinal rules may be defined in this respect:

1. The fundamental method of patient surveillance after the treatment of these skin cancers involves regular clinical assessment (initially every 3–6 months, then every 6–12 months), possibly supplemented by dermatoscopic assessment of the entire skin. Special attention should be given to the area of the scar, regional lymph nodes and the skin areas exposed to the same risk factors.
2. The selection of imaging diagnostic procedures within the surveillance process should be based on the initial stage of the skin cancer, its location and the presence of additional risk factors (first of all chronic immunosuppression) and the findings of an interdisciplinary team after the treatment is completed; the selection of imaging diagnostic procedures should follow the principle of using the basic and easily accessible procedures first (such as ultrasound), followed by other imaging methods (i.e. CT, MRI or PET) as needed.

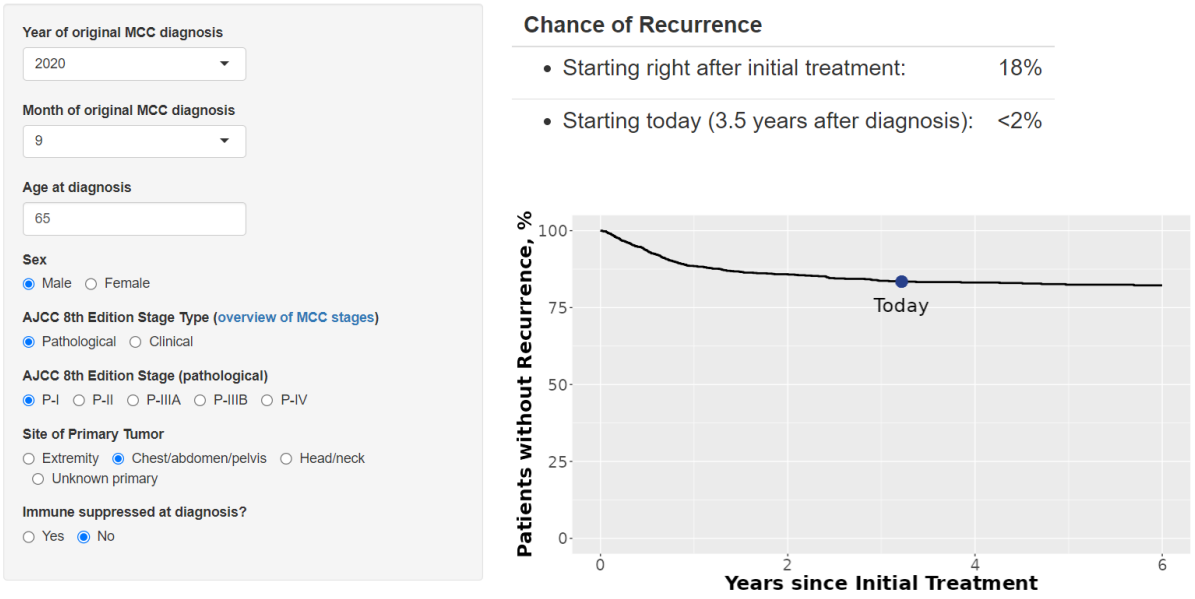

Figure 1. MCC Recurrence Risk Calculator available at: https://merkelcell.org/

Table IV. Recommended surveillance principles after the treatment of patients with Merkel-cell carcinoma of the skin without the signs of an active disease [4, 7]

Disease stage upon diagnosis	Interventions undertaken in patients without the signs of active disease	Frequency of interventions	Additional remarks
stage 0–II without high risk factors*	physical examination and interview with dermatoscopic assessment of the whole body, palpation of the scar and surrounding skin and lymph nodes	every 3–6 months for the first 3 years, then every 12 months up to 5 years	in the case of primary location of the tumour within the head or neck: the recommended imaging diagnostics as in the case of patients with higher disease stages (i.e. ^{18}F-FDG PET/CT of the whole body or contrast enhanced neck/chest/ abdominal/ pelvis CT and head MRI or CT)
	ultrasound assessment of the scar, lymph nodes and lymphatic drainage	every 3–6 months for the first 3 years, then every 12 months up to 5 years	
stage III, in good clinical condition and not in immunosuppression	physical examination and interview with dermatoscopic assessment of the whole body, palpation of the scar and surrounding skin and lymph nodes	every 3 months for the first 3 years, then every 6 months up to 5 years, then once per year	
	ultrasound assessment of the scar, lymphatic drainage or the area and lymph nodes	every 3 months for the first 3 years, then every 6 months up to 5 years	
	^{18}F-FDG PET/CT of the whole body (if accessible) or contrast enhanced neck/chest/ abdominal/ pelvis CT and head MRI or CT	every 3–6 months for the first 3 years, then every 6–12 months up to 5 years	
stage IV and lower stages with a bad clinical condition	individual follow-up program for a specific patient		
patients in immunosuppression, irrespectively of the MCC stage	physical examination and interview with dermatoscopic assessment of the whole body, palpation of the scar and surrounding skin and lymph nodes	every 3 months for the first 3 years, then every 6 months	in the case of lack of recurrence or any other primary tumour, after 5 years, follow-up visits can be made once per year
	ultrasound assessment of the scar, lymphatic drainage or the area and lymph nodes	every 3 months for the first 3 years, then every 6 months up to 5 years	
	^{18}F-FDG PET/CT of the whole body (if accessible) or contrast enhanced neck/chest/ abdominal/ pelvis CT and head MRI or CT	Every 3–6 months for the first 3 years, then every 6–12 months up to 5 years	

* – high risk factors in Merkel-cell carcinoma: tumour diameter ⩾2 cm, chronic immunosuppression, primary location of the tumour within the head or neck, lymph nodes involvement or the lack of correct specification of the condition of the lymph nodes (Nx), infiltration of the lymphatic or blood vessels; ^{18}F-FDG PET – positron emission tomography with the use of ^{18}F-fluorodeoxyglucose; CT – computed tomography; MR – magnetic resonance

3. On account of the easiness of identification of the majority of recurrences by the patient themselves as well as continual impact of the main factors of risk of recurrence, a significant role in the surveillance process is played by the education of a patient (or their carers) concerning clinical signs of skin cancer recurrences and protection UV radiation (i.e. avoiding sun exposure between 10 a.m. and 4 p.m.; wearing protective clothing, including headgear and sunglasses; regularly using of broad-spectrum sunscreens on the exposed skin (especially for people with light complexion) and self-examination of the skin.

Article information and declarations

Author contributions

Wojciech M. Wysocki – conceptualization, writing – review and editing.
Aleksandra Kulbat – writing – original draft preparation.
Marta Krzysztofik – writing – original draft preparation.
Karolina Richter – writing – original draft preparation.
Elżbieta Wójtowicz – writing – original draft preparation.
Joanna B. Wysocka – writing – original draft preparation.
Paweł Brzewski – writing – original draft preparation.
Grażyna Kamińska-Winciorek – revision and editing.
Hanna Koseła-Paterczyk – revision and editing.
Jacek Mackiewicz – revision and editing.
Witold Owczarek – revision and editing.
Piotr Rutkowski – revision and editing.
Marcin Ziętek – writing – original draft preparation.

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Ethics statement

No ethical issues or concerns were applicable to this research.

Conflict of interest

Piotr Rutkowski has received honoraria for lectures and advisory boards from MSD, BMS, Novartis, Pierre Fabre, Sanofi, Madison Pharma, Genesis, Astra Zeneca outside of the scope of this paper.

Wojciech M. Wysocki
5th Military Clinical Hospital in Krakow
Department of Oncological Surgery
ul. Wrocławska 1–3
30-901 Kraków, Poland
e-mail: wwysocki@nowotwory.edu.pl

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Guidelines and recommendations

Public health

Infectious disease prophylaxis and treatment in cancer patients, with particular emphasis on COVID-19. Interdisciplinary position statement of Polish experts

Piotr Rutkowski[1], Bożena Cybulska-Stopa[2, 3], Jacek Jassem[4], Adam Płużański[1], Krzysztof Tomasiewicz[5], Lucjan Wyrwicz[1], Piotr Wysocki[6], Jacek Wysocki[7], Robert Flisiak[8]

[1]*Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Lower Silesian Oncology Center, Pulmonology and Hematology, Wroclaw, Poland*
[3]*Department of Hematology and Oncology, Faculty of Medicine, Wroclaw University of Science and Technology, Wroclaw, Poland*
[4]*Medical University of Gdansk, Gdansk, Poland*
[5]*Medical University of Lublin, Lublin, Poland*
[6]*Jagiellonian University, Collegium Medicum Hospital, Krakow, Poland*
[7]*Poznan University of Medical Sciences, Poznan, Poland*
[8]*Medical University of Bialystok, Bialystok, Poland*

Infectious diseases constitute a significant burden for cancer patients. This became particularly evident during the COVID-19 pandemic. Due to cancer itself and its treatment, the course of infectious diseases in oncology patients is often unpredictable and may negatively affect them. Preventing infectious diseases through a wide range of vaccinations may help maintain the continuity of treatment and constitute an element of holistic patient care. Testing patients with symptoms or suspected infections allows proper treatment and may avoid unfavorable consequences. More education on preventing and treating infectious diseases is necessary to improve the standard of cancer care.

Key words: infectious diseases, cancer, vaccines, COVID-19

Introduction

Cancer patients present an increased risk of severe infections. However, their awareness of the need for preventive measures is low. In the United States of America, the number of cancer-related deaths among cancer patients increased slightly between 2018 and 2021 [1]. In parallel, a significant increase in other death causes was observed, mainly due to the COVID-19 pandemic. The number of deaths in cancer patients caused by non-cancer causes was highest in the winter months of 2021 and 2022, corresponding to subsequent waves of COVID-19 [1]. In Poland, a significant increase in the mortality of cancer patients was also observed during the COVID-19 pandemic, although some deaths may be attributed to delayed diagnosis and poorer access to health care. The highest 30-day mortality was noted in patients with lung cancer. Mortality rates due to vaccine-preventable infections (including influenza, COVID-19 and pneumococcal diseases) in cancer patients are higher than 10%, reaching up to 50% in cases of invasive pneumococcal disease [2–4].

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Taking into account Polish cancer patients' insufficient awareness of the burden of infectious diseases, their prevention, testing and treatment, we present herewith the interdisciplinary expert position statement on these aspects from the perspective of infectious diseases, vaccinology and oncology. Considering the significant impact of the COVID-19 pandemic on cancer patients, this article focuses mainly on this infectious disease. We aim to facilitate actions to implement the prevention of infectious diseases in cancer patients, focusing on COVID-19 [1].

Infectious diseases burden in cancer patients, focusing on COVID-19

Infectious diseases have a significant impact on cancer patients. Vaccinations can effectively protect against the consequences of infectious diseases, allow the continuity of anticancer therapy, and a decrease in mortality [1, 5]. This impact is apparent for COVID-19, where subsequent infection waves were accompanied by peaks of excess deaths [1]. Indeed, people with a history or current cancer are at high risk of severe disease and death from this infection [6–8]. In the case of seasonal influenza, hospitalized cancer patients were shown to have higher mortality, longer hospital stays and a greater risk of health-related complications, including pneumonia, neutropenia and sepsis [9]. Importantly, viral infections pave the way for bacterial infections. Therefore, *Streptococcus pneumoniae* infections are secondary infections or co-infections, which in immunosuppressed cancer patients may be particularly harmful [10–12].

Typically, hematologic malignancies carry an increased risk of severe infections compared to solid tumors, as shown for COVID-19 [13, 14]. At the same time, however, solid malignancies are more common than hematologic malignancies [15]. Importantly, cancer patients are not a homogeneous group. The main risk factors for severe COVID-19 in cancer patients are:

- multiple comorbidities [6, 16–18],
- type of cancer (including acute leukemia, lung cancer, genital cancer, thyroid cancer) [6, 17, 19, 20],
- cytotoxic treatment (including time elapsed since therapy) [18],
- bone marrow transplants,
- advanced age [6, 16–18],
- male gender [6, 16, 17, 19],
- ethnicity [6, 16, 17, 19],
- multi-neoplastic syndromes [17],
- smoking [16],
- average or poor Eastern Cooperative Oncology Group performance status [16],
- history of active cancer versus cancer in remission [16].

Due to impaired immune system and treatment-related immunosuppression, cancer patients are more susceptible to unpredictable courses of infections and post-infectious complications [21]. Numerous factors related to cancer influence the course of infectious diseases:

- corticosteroids and other immunosuppressive drugs reduce the immune response,
- cytotoxic drugs may cause bone marrow suppression, which may lead to thrombocytopenia and neutropenia, thus prompting bacterial infections [22],
- radiotherapy-related lymphopenia increases the risk of severe viral infections [22],
- inhibiting the activity of immune checkpoints may result in excessive cytokine production and may contribute to the development of a cytokine storm.

Multiple factors increase the risk of severe COVID-19 infections in cancer patients. These include impaired immune system function, synergistic inflammatory reaction, chronic inflammation, increased expression of the ACE2 receptor (in some cancer types) and TMPRSS2 (prostate cancer), and increased procoagulant activity. The SARS-CoV-2 virus is evolving, which changes the burden of COVID-19. During the dominance of the BA.1 and BA.2 subvariants (early Omicron phase), the mortality among hospitalized patients was 12–14%. During the dominance of BA.5, BA.2.75, BQ.1 and XBB.1.5 subvariants (late Omicron phase), the overall burden of COVID-19 was lower in the general population but persisted in hospitalized patients at the alarming level of 9% [23]. The number of deaths among cancer patients was the highest during the COVID-19 wave in early 2022 and was disproportionately higher than that in the general population [24]. Unvaccinated individuals are much more susceptible to COVID-19 sequelae; therefore, vaccination appears to be the most effective prevention of severe COVID-19 infection [25].

Complications of infectious diseases in cancer patients

Recently, much attention has been paid to complications following infection with the SARS-CoV-2 virus called long-COVID syndrome [26, 27]. It is estimated that this syndrome may affect as many as ⅓ of patients [27]. It manifests as persistent impaired functioning of the respiratory and cardiovascular systems, fatigue and cognitive disorder [28], which may last several weeks or months after the infection [29]. An analysis of the OnCovid registry showed that complications persisted after COVID-19 for 6 and 12 months in 9.8% and 8.0% of patients, respectively. Factors associated with a higher complication risk included male gender, age ≥65 years, ≥2 comorbidities, history of smoking and a severe course of COVID-19 [29].

The time of virus elimination (identified as a positive PCR test) is longer in cancer patients than in patients with an effective immune system [30–33]. Such situations may affect the continuity of anticancer treatment. Indeed, the data from the OnCovid registry showed that anticancer treatment was modified or discontinued in 14.6% and 22.9% of patients, respectively, and treatment termination due to COVID-19 complications was associated with a significantly reduced survival compared to that among patients who continued treatment

(hazard ratio [HR]: 6.75; 95% confidence interval [CI]: 2.37–19.9) [34]. Current recommendations advise treatment continuation in the case of asymptomatic chronic viremia.

The vaccination benefits for cancer patients include preventing severe disease, hospitalization and death. Still, vaccinations may also shorten possible infection duration, limit potential therapeutic breaks, or avoid deferring the antitumor treatment. Interruption of the ongoing treatment due to any infection is a significant problem that intensifies during seasonal infection peaks, mainly considering COVID-19 and influenza. The general public underestimates infections as a medical problem, and this also applies to cancer patients. Often, patients who require anticancer treatment, including surgery, show up with an active infection and rarely use vaccination. The COVID-19 pandemic caused a significant increase in the number of excess cancer deaths resulting from delayed cancer diagnosis [35]. The spread of the SARS-CoV-2 virus affected cancer screening, health problems reporting, diagnosis, access to treatment and clinical research. Consequently, preventive vaccinations are gaining new importance as a basis for maintaining the continuity of the diagnostics and therapy of cancer patients [36].

Vaccinations in cancer patients

Cancer itself and immunosuppressive anticancer treatment hinder the protective effects of some vaccinations by reducing seroconversion and accelerating the waning of immunity over time [37, 38]. For these reasons, cancer patient vaccination schedules may differ from those used in the general population (e.g., the number of doses and revaccination frequency), therefore the vaccination history should be in particular documented (e.g. centralized electronic vaccination system) [39]. Unfortunately, knowledge of this topic is scarce. Of note, the example of vaccination against COVID-19 shows that despite a significantly weakened humoral response, the cellular response often remains satisfactory [37].

A comprehensive approach to vaccinations for cancer patients is often presented in a graphic form as the so-called vaccination calendar. Developing such calendars for the general cancer population is difficult due to limited knowledge. However, vaccination schedules exist for some risk groups, including patients with hematologic malignancies or asplenia [40] and rheumatic diseases [41]. Table I shows the recommended seasonal and year-round vaccinations for cancer patients [21].

In Poland, detailed data on vaccination rates in particular risk groups are lacking; thus, assessing cancer patients' vaccination willingness is difficult. Available data indicate that overall influenza vaccination coverage in Poland is low (around 5% each year in the general population and around 20% among people aged ≥65 years) [42]. The primary COVID-19 vaccination rate is about 60%, and the first and second booster doses were taken by 30% and 7.7% of Poles, respectively. According to the American Society of Clinical Oncology (ASCO) data, the COVID-19 vaccination rate is about 20% lower than in the general population, which may also apply to other vaccinations [43, 44].

Table I. Recommended seasonal and year-round vaccinations for cancer patients [21]

Vaccination type	Infectious disease	Optimal vaccination time	Practical remarks
seasonal	COVID-19	vaccination against COVID-19 should be performed in line with the latest national or international recommendations for a given season once the adapted vaccine becomes available. However, the vaccination should not be delayed, awaiting the availability of the adapted vaccine [70]. Revaccination should take place every 6–12 months in consultation with a health care provider, and at least 3 months after COVID-19 recovery [71]	for detailed vaccination schedules, refer to current vaccination calendars recommended by the Polish Vaccinology Society [72] for brand names of specific vaccines, see table II. The non-seasonal infections may overlap with seasonal infections during the autumnal-winter period, presenting more severe clinical outcomes, such as influenza and pneumococcal disease [73]. Vaccination against seasonal and non-seasonal infections may be administered during a single visit or at separate visits, provided they contain non-live antigens [74]. Considering seasonal infections, it is important to protect patients before the fall-winter period. It is also worth getting vaccinated during the season. For best protection time see the "Optimal vaccination time" column [75]
	influenza	in Poland, the influenza epidemic season lasts from October to May and peaks from January to March [76]. Considering it takes about 2 weeks to develop protective antibodies, the best time to get vaccinated is in September. However, if this optimal vaccination period is missed, vaccination is indicated till the circulation of given viral strains [77]	
	RSV	RSV vaccine is currently a single-dose vaccine with no need for revaccination. This vaccination should be provided before RSV infections peak, which typically starts in October, meaning in late summer or early fall [78–80]	
non-seasonal	pneumococcal disease, meningococcal disease, HBV, HiB, HPV, VZV, Tdap	no specific vaccination time throughout the year is indicated. Therefore, a year-round vaccination is possible; however, the faster vaccination is administered, the better for patient protection	

COVID-19 – coronavirus disease; HBV – hepatitis B virus; HiB – *Haemophilus influenzae* type B; HPV – human papillomavirus; RSV – respiratory syncytial virus; VZV – varicella zoster virus; Tdap – tetanus, diphtheria, pertussis vaccine

Table II. Indications, vaccines, dosage regimens and patient payment levels of vaccines available in Poland (46, 80–87)

Vaccination	Indication	Trade name*	Dosage schedule	Reimbursement charge
influenza	vaccination once a year before the infectious season with an inactivated vaccine	Influvac Tetra[1] Vaxigrip Tetra	1 dose during the infectious season	18–64 years – 50% payment (refund)[1] 65+ – free of charge
COVID-19	all cancer patients or those previously treated for cancer should be vaccinated against COVID-19	Comirnaty – mRNA vaccine Nuvaxovid – protein vaccine Spikevax – mRNA vaccine	1 dose during the infectious season**	free of charge (National COVID-19 Vaccination Program)
pneumococcal diseases	Pneumococcal conjugate vaccine should be administered to adult cancer patients who have not been vaccinated against pneumococci	Prevenar 20 Prevenar 13 (PCV13) – 13-valent conjugate vaccine Pneumovax 23 (PPV23) – 23-valent polysaccharide vaccine	PCV13 + PPV23** after min. 8 weeks or PVC20; people who previously received PPV23 should receive PCV13 or PCV20 after ≥1 year	Prevenar 13 is free of charge for people 65+ with increased risk of pneumococcal disease development. The Protective Vaccination Program for 2024 provides free pneumococcal vaccinations for all people before or after immunosuppressive or biological treatment. Currently, there is no information about which vaccine will be reimbursed under the National Immunization Program (NIP)
meningococcal diseases	patients at increased risk of meningococcal infection: with functional or anatomical asplenia, complement deficiencies, taking a C5 complement inhibitor (e.g., eculizumab, ravulizumab) should receive a quadrivalent vaccine against meningococci of serogroup ACWY and a monovalent vaccine against meningococci of serogroup B	NeisVac-C – conjugate vaccine against serogroup C Nimenrix – conjugate vaccine against the ACWY serogroup Bexsero – protein vaccine against serogroup B Trumenba – recombinant vaccine against serogroup B	1 dose 1 dose 2 doses at an interval of not less than 1 month 2 doses 6 months apart	fully paid
human papillomavirus (HPV)	the recombinant 3-dose HPV vaccine should be administered to men and women ≤26 years and may be considered for patients ≤45 years	Cervarix – bivalent vaccine Gardasil 9 – 9-valent vaccine	3 doses administered at 0, 2 and 6 months	Cervarix vaccine – 50% payment – refund; the universal free-of-charge HPV vaccination program using the Cervarix and Gardasil 9 vaccines is aimed at girls and boys aged 12 and 13; Cervarix is free-of-charge for people under 18 years of age (list 18–).
shingles (VZV)	administration of recombinant herpes zoster vaccine (VZV) is recommended for adult patients ≥50 years and for persons ≥18 years at risk for herpes zoster	Shingrix	2 doses 2–6 months apart in immunocompromised individuals who would benefit from achieving optimal immunization in a shorter period; alternatively, an abbreviated regimen of 2 doses administered ≥1 month apart	Shingrix is 50% reimbursed in people ≥65 years and elderly people from risk groups, including generalized malignancy

Table II cont. Indications, vaccines, dosage regimens and patient payment levels of vaccines available in Poland (46, 80–87)

Vaccination	Indication	Trade name*	Dosage schedule	Reimbursement charge
respiratory syncytial virus (RSV)	passive protection against lower respiratory tract diseases caused by respiratory syncytial virus (RSV) in infants from birth to 6 months of age after maternal vaccination during pregnancy	Abrysvo – bivalent vaccine	1 dose	fully paid
	active immunization of people ≥60 years against lower respiratory tract diseases caused by RSV. The effectiveness of the vaccine in cancer patients is unknown	Arexvy – monovalent vaccine	1 dose	fully paid
diphtheria/tetanus/whooping cough (Tdap)	administered every 10 years	Adacel Boostrix	1 dose	The National Immunization Program for 2024 provides free-of-charge Tdap vaccinations for all people who are before or after transplantation of hematopoietic cells, internal organs, splenectomy, with asplenia, or splenic dysfunctions

[1] Influvac Tetra is reimbursed for the entire group aged 18–64, and Vaxigrip Tetra for people aged 18–64 with additional risk factors; * – vaccines available in Poland as of January 3, 2024; ** – additional doses may be administered to people with severe immune disorders by national recommendations. As of January 3, 2024, no published recommendations exist for this patient population

The implementation of vaccination depends on the patient's attitude and individual understanding of the importance of the recommendation. Therefore, there is an apparent need for educational activities to address both patients and their immediate environment [36]. One such element is the vaccination advice based on current recommendations given by an oncologist. Issuing a vaccine prescription against, e.g., pneumococci, RSV, or shingles may motivate the patient. The patient should be informed that several preventive vaccinations, except those using live microorganisms, can be administered during one visit. Within the scope of permissions, primary care physicians and pharmacists may implement oncologists' recommendations. Additionally, an important issue is the implementation of the cocoon strategy, which includes, among others, vaccination of household members, close relatives and healthcare workers [36, 45].

Vaccination recommendations for adult patients with hematological malignancies are available in Polish, implemented into clinical practice and updated [40]. However, there are no similar national recommendations for patients with solid tumors. In 2018, joint recommendations for preventing infectious diseases were developed by ASCO and the Infectious Diseases Society of America (IDSA) [46]. That said, they do not respond to all current medical needs. In turn, the latest National Comprehensive Cancer Network (NCCN) guidelines cover the prevention and treatment of infectious diseases in a more up-to-date and comprehensive way, taking into account influenza, COVID-19, pneumococcal and meningococcal infections, HPV, RSV, VZV, Tdap and other infections (47). Table II summarizes these recommendations, pointing out the vaccines available in Poland, their standard dosages and reimbursement status.

Diagnosis of cancer is a rough emotional experience and may distract patients from the implementation of prophylactic measures, including vaccinations [48, 49]. Additionally, the COVID-19 pandemic hampered cancer treatment and appropriate prevention implementation [50]. The patient should be clearly informed that infection may affect anticancer treatment. The vaccination should ideally be performed at cancer diagnosis and before anticancer treatment, as this may lower vaccine effectiveness. Inactivated vaccines should be administered at least two weeks (vaccines containing live microorganisms at least four weeks) before starting treatment. Due to the risk of infection induction, vaccinations containing live microorganisms are contraindicated during chemotherapy and in immunocompromised patients [51]. In turn, vaccinations without live microorganisms can be safely used in these populations [21]. If vaccination is substantiated after anticancer therapy, the optimal time is from three to 12 months after its completion, depending on the vaccine and oncological treatment [51].

The vaccinations indicated in table II are safe for cancer patients. The contraindications to vaccination are limited and include, among others:

- active infection,
- active cancer during intensive chemotherapy and/or radiotherapy (however, there are no clear contraindications to the administration of influenza and COVID-19 vaccines),
- intensive immunosuppression, i.e., corticosteroid therapy (calculated for prednisone >0.5 mg/kg/day for over 14 days), rituximab, or other anti-CD20 monoclonal antibodies,
- allergic reactions to a given vaccine [51].

Notably, influenza vaccinations were shown to prolong overall survival (OS) in cancer patients administered immune checkpoint inhibitors (ICI) [52]. Given influenza's relatively low mortality, vaccination against more deadly infections (e.g., COVID-19) may carry even greater OS benefit [53].

Vaccination access for cancer patients in Poland

Cancer patients should be among the vaccination priority groups due to their high risk of severe infections and complications [21, 36, 47]. Access to vaccinations in Poland has been recently significantly improved (tab. II), due the extension of reimbursement of pneumococcal and influenza vaccines and local vaccination prevention programs [54, 55].

An essential step in improving the protection of cancer patients by vaccination should be the development of national practice guidelines addressed to medical oncologists, surgeons and radiation oncologists. Currently, the reimbursement system for medicinal products is dispersed between pharmacies and primary care facilities, and in the case of vaccinations, it does not cover specialist treatment. Hence, although oncologists know the importance of vaccinations, they are not implemented in clinical practice. To facilitate this process, vaccination points should be located in cancer centers. A good example is the Świętokrzyskie Oncology Center, where vaccinations against pneumococci are carried out in patients with most common solid and hematological malignancies [56]. It is postulated that all vaccines necessary for comprehensive primary prevention should be available in hospitals and administered within the facility. All of the above ventures should increase vaccination rates in a population that is particularly sensitive to the severe course of infections, and these actions may also include other groups of patients.

The National Oncology Strategy provides an opportunity to popularize vaccination prevention [57]. So far, the popularization of vaccinations in Poland has been limited, illustrated by low HPV vaccination rates [58]. Therefore, broad educational activities in the field of vaccinations in Poland are still needed.

Testing and treatment of COVID-19 in cancer patients

Despite preventive measures, infectious diseases in cancer patients remain a significant challenge. The American Covid Data Tracker data for 2018–2021 clearly shows increased mortality due to cancer as an underlying cause and a significant increase in the number of deaths due to infectious diseases, particularly COVID-19 [1].

Despite the accessibility of combo antigen tests (including COVID-19, RSV, influenza A and B) as part of primary health care services in Poland, they are not performed sufficiently frequently. This situation hinders causal treatment implementation, e.g., influenza (oseltamivir) and COVID-19 [59, 60]. Subsequently, the number of these infections and the overall data for the Polish population are blurred. Considering these facts, the WHO focuses on testing all symptomatic and high-risk asymptomatic patients [61]. According to the current IDSA diagnostic algorithm, testing for COVID-19 should only be performed in symptomatic patients [62]. It is recommended to use antigen tests with a diagnostic sensitivity and specificity of at least 90% and 97%, respectively. If symptoms suggestive of COVID-19 persist and the first test is negative, it should be repeated after 3–4 days, when the highest concentration of antigens is recorded [63].

According to the recently updated WHO COVID-19 treatment guidelines, depending on the clinical condition of cancer patients, the risk of severe COVID-19 may be classified as high or moderate, corresponding to a hospitalization risk of 6% and 3%, respectively [64]. The current guidelines are similar to those in the general population [64]. These recommendations are in line with those of the Polish Society of Epidemiologists and Infectious Disease Physicians from 2022 because inhaled budesonide and the use of monoclonal antibodies against the S protein of the SARS-CoV-2 virus are principally no longer relevant for clinical practice [64, 65].

According to Polish guidelines, antiviral treatment can be used in the first and second COVID-19 stages, i.e., in the mild and full-symptomatic phases, before the development of respiratory failure [65]. According to the latest WHO recommendations, the only strongly recommended therapy in the early phase of COVID-19 in patients at high risk of hospitalization is a short-term oral course of nirmatrelvir/ritonavir (NIR/RIT). The use of NIR/RIT may be considered in patients with a moderate risk of hospitalization [61]. In contrast, the indications for molnupiravir and remdesivir in patients at high risk of hospitalization are weak or conditional.

According to NCCN guidelines for cancer-related infections, NIR/RIT or remdesivir may be used in patients with acute illness, recent onset of symptoms and high risk of COVID-19 progression (prolonged neutropenia, lymphopenia, or T-cell dysfunction accompanying hematologic malignancies and lung cancer). During hospitalization, treatment with remdesivir is recommended. NIR/RIT and/or remdesivir may be used in patients with persistent SARS-CoV-2 infection, typically in patients with B-cell hematologic malignancies [47].

The authorization of molnupiravir in the European Union was withdrawn in June 2023 [66]. So far, remdesivir and NIR/RIT are not reimbursed in Poland, although the reimbursement process for NIR/RIT is ongoing [67]. Given the burden of COVID-19

and the high mortality of cancer patients, access to effective treatment of this infection in Poland remains an unmet medical need [61].

NIR/RIT may interact with anticancer drugs; it is therefore recommended that potential interactions be checked using a simple online tool on the University of Liverpool website [68]. Since NIR/RIT therapy is short-term (up to 5 days from COVID-19 symptoms' onset), in most cases, drug interactions can be prevented by modifying treatment doses or changing some active substances [64]. Of great importance is that drug--drug interactions for NIR/RIT are based on data obtained from ritonavir studies in HIV, where these compounds were used at a higher dose and in a chronic manner [61, 64]. Ritonavir, being an inhibitor of some cytochrome P450 isoenzymes (mainly CYP3A4, CYP2D6) and having a high affinity for P-glycoprotein (P-gp), may affect the concentration of other concomitantly administered drugs [64]. Hence, when implementing the NIR/RIT, a risk-benefit ratio should always be considered.

Many patients are not aware of the risk of severe COVID-19 and neglect antigen testing after viral exposure or symptoms emergence. Likewise, few at-risk people know that appropriate treatment may reduce their risk of hospitalization and death due to COVID-19. Further, patients must realize that delayed intervention may substantially reduce treatment efficacy. Patients must be educated about the risk of progression to severe COVID-19 and know what to do once they develop symptoms and test positive for COVID-19. The post-vaccination immunity weakens over time, whereas the willingness to receive subsequent booster doses decreases, allowing for SARS-CoV-2 immune escape. It is expected, therefore, that the number of hospitalizations among vaccinated people, especially among high-risk groups, will increase [61]. A cross-sectional study in the US showed that hospitalizations due to breakthrough infection were reported in up to 25% of vaccinated patients during the dominance of the Omicron variant. Therefore, owing to the low rate of booster vaccinations, the proportion of patients hospitalized with COVID-19 is expected to increase [69]. For this reason, providing effective COVID-19 treatment for cancer patients and other high-risk patients remains an important issue.

Conclusions

Infections pose a significant threat to cancer patients. The COVID-19 pandemic caused a significant disruption in cancer management, worsened treatment outcomes and significantly increased cancer mortality – directly and indirectly. Vaccinations remain the cornerstone of preventing the consequences of infections. However, the COVID-19 booster and influenza vaccination rates remain low in Poland.

A vital issue hindering the implementation of recommended vaccinations in cancer patients is a concern of primary care physicians and patients about vaccination safety after cancer diagnosis. Therefore, the development of Polish vaccination recommendations for patients with solid malignancies is an urgent medical need. Cancer patients themselves are often unaware of the risk of severe infections, especially COVID-19, which reduces their willingness to vaccination, testing and implementing casual treatment. A limited number of cancer patients are aware of outpatient COVID-19 treatment options. Therefore, education on this matter is essential. The health care system should shorten the patient clinical path and enable the co-administration of necessary vaccinations during a single visit. The organization and financing of the health care system should also support rapid diagnosis and treatment of infections in cancer patients. Organizational, logistic and reimbursement changes are warranted to improve patients' safety in all cancer care institutions.

Article information and declarations

Author contributions

Piotr Rutkowski – conceptualization, supervision, writing – original draft preparation, writing – review and editing.
Bożena Cybulska-Stopa – conceptualization, writing – original draft preparation, writing – review and editing.
Jacek Jassem – conceptualization, writing – original draft preparation, writing – review and editing.
Adam Płużański – conceptualization, writing – original draft preparation, writing – review and editing.
Krzysztof Tomasiewicz – conceptualization, writing – original draft preparation, writing – review and editing.
Lucjan Wyrwicz – conceptualization, writing – original draft preparation, writing – review and editing.
Piotr Wysocki – conceptualization, writing – original draft preparation, writing – review and editing.
Jacek Wysocki – conceptualization, writing – original draft preparation, writing – review and editing.
Robert Flisiak – conceptualization, writing – original draft preparation, writing – review and editing.

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Conflicts of Interest

Piotr Rutkowski – consulting fees (Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Philogen, Pfizer), honoraria (Bristol Myers Squibb, MSD, Novartis, Pfizer, Pierre Fabre, Sanofi, Merck, Astra Zeneca), Speakers' Bureau (Pfizer, Novartis, Pierre Fabre,

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Marcin Balcerzak
Medink
ul. Ogrodowa 11d/1
05-500 Mysiadło, Poland
e-mail: marcin.balcerzak@medink.eu

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Review article

Head and neck cancers

The management of oral cancer – current standards and future perspectives. A review of the literature

Natalia Amrogowicz[1], Tomasz Rutkowski[2]

[1] 1st Radiation and Clinical Oncology Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Department of Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice Branch, Gliwice, Poland

Oral cancer (OC) is one of the most common cancers of the head and neck region, with approximately 1,950 new cases reported in Poland in 2019. The main factors contributing to the development of OC are cigarette smoking and excessive alcohol consumption. Squamous cell carcinoma accounts for more than 90% of all OCs. In patients with OC, surgery is the treatment of choice, but there is a high number of patients who require complementary treatment – radiotherapy or radiochemotherapy. The treatment of these tumours should be comprehensive and multidisciplinary. Due to suboptimal treatment outcomes in this patient group, numerous clinical trials are being conducted to search for new, more effective treatments. The aim of this study was to review the literature on current and new methods of diagnosis and treatment of OC, and to analyse the clinical trials currently available for OC patients in Poland. Despite the use of modern drugs, only modest progress has been made in terms of treatment efficacy.

Key words: oral cancer treatment, clinical trials

Introduction

Oral cancer (OC) is one of the most common cancers in the head and neck region. In 2020, there were 377,713 new cases worldwide, with the highest incidence found in the Asian countries of Pakistan, Sri Lanka and India [1]. According to the American Joint Committee on Cancer (AJCC) classification, OC is a squamous cell carcinoma (SCC) originating in the mucosa of the upper and lower lip, cheek, retromolar trigone, vestibule of oral cavity, alveolar process and upper and lower gingiva, hard palate, movable part of the tongue and the floor of the mouth. Treatment of tumours located in this area should be comprehensive and multidisciplinary. The aim of this study was to review the literature on current and new methods for diagnosing and treating oral cancer, and to analyse the clinical trials currently available for oral cancer patients in Poland.

Epidemiology

Epidemiological data show that in 2019, approximately 1,950 new cases (accounting for approximately 1.13% of all malignancies) and 1,234 deaths from OC were reported in Poland [2]. According to World Health Organization (WHO) data, Poland ranked 5th in Europe in the number of new cases (after Ukraine, Belarus, Hungary and Latvia) and 6th in Europe in the number of deaths (after Ukraine, Romania, Lithuania, Malta and Moldova) due to OC [1–2]. According to a report by the National Cancer Registry, since 2001, there has been a clear upwards trend in both incidence and mortality from OC for all possible locations with the exception of lip cancer in men, where there has been a gradual decline in incidence. Men are more frequently affected by OC. The movable part of the tongue (data for 2019) is the most common oral location of OC

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in the Polish population at present. The peak incidence of OC occurs after the age of 50 years [1].

Ethiology

The main factors influencing the development of OC in Poland include cigarette smoking and excessive alcohol consumption. Tobacco use in any form (chewing, smoking) can lead to the development of cancer in the oral cavity and pharynx [3–5]. Smoking is estimated to be associated with a 7-fold increased relative risk of developing OC, and alcohol consumption >50 g/day is associated with a 6-fold increased risk of developing OC [3]. Both stimulant users had a significantly increased risk of developing OC. The additive effect associated with alcohol consumption potentates the activation of procarcinogens present in tobacco. Alcohol abusers who are heavy smokers have a 38-fold greater risk of developing OC than non-users of either stimulant [6].

Another stimulant popular in Asian countries, used by about 20% of the world's population, that increases the risk of OC is betel (areca nut) chewing. According to a study, betel chewing increases the risk of OC mortality by approximately 12.5 times [7].

The risk of developing OC increases with age, and only about 6% of all OCs develop in patients younger than 45 or even 40 years of age. This approach applies mainly to patients with cancer of the mobile part of the tongue. Among these patients, approximately ¼ had not been exposed to any of the currently known risk factors. It is thought that in these people, the development of cancer may be caused by other yet unknown factors or have a viral basis, e.g. in the course of the human papillomavirus (HPV) infection.

The human papillomavirus is a known aetiological factor in the development of oropharyngeal cancer [8]. Its role in the development of OC is controversial, but it is also thought to cause this type of cancer in younger subgroups of patients [9–10]. The most common virus types identified in OC were HPV-16 and HPV-18 [11–14]. The occurrence of HPV-associated cancers is associated with better prognosis [8].

Other viruses that may underlie cancer in the head and neck region are the herpes virus (HSV) and the Epstein–Barr virus (EBV). Lip cancers may be related to HSV infection. Its nucleic acids have been shown to be present in lip cancers, while antibody levels for HSV-1 and HSV-2 are greater in patients with lip cancer than in controls [15]. Furthermore, the presence of HSV in smokers is associated with an increased risk of cancer [16]. The Epstein–Barr virus may also be associated with the development of OC, but at this point, its role remains controversial [17–22].

Poor oral hygiene, bacterial and fungal infections causing periodontal disease are documented irritants in the oral cavity, which consequently constitute risk factors for the development of cancer in this area [23]. In the elderly, ill-fitting dentures that cause chronic irritation of the mucosa are an additional factor influencing the development of cancer, especially of the gums and tongue shafts [24].

Dietary factors also influence the development of OC. Freedman et al. showed that low fruit and vegetable intake was associated with an increased risk of head and neck cancer [25]. A Mediterranean diet has been shown to have a beneficial effect on reducing the risk of oral and oropharyngeal cancers [26].

Other aetiological factors include UV radiation (lip cancer), low socioeconomic status, ionising radiation and genetic syndromes associated with the impairment of genes responsible for DNA repair and induced cell death (e.g., Li–Fraumeni syndrome, Fanconi anaemia), riboflavin and iron deficiency (Plummer–Vinson syndrome) and lupus and syphilis-like lesions [6, 27–28].

Histology

The oral cavity is highly exposed to external factors that can cause pre-cancerous lesions on mucous membranes that, over time, may develop into malignant tumours. These conditions include whitish (leukoplakia) and red patches (erythroplasia, erythroplakia), lichen planus and rhomboid tongue inflammation. Conditions directly leading to the development of malignancy include small-, medium- and high-grade squamous metaplasia or dysplasia and carcinoma in situ [27, 29–30]. SCC accounts for more than 90% of all OCs [31–32]. Other histopathological diagnoses, such as basaloid carcinoma and papillary carcinoma, are rare [33].

The lymphatic system that drains the oral cavity is extremely extensive. The presence of cervical lymph node metastases is an important prognostic factor [34–36]. Although macroscopic cervical lymph node metastases can be predicted to some extent by clinical staging, the probability of hidden neck lymph node metastases is high, ranging from 20% to 45% [37–40]. The submental and submandibular lymph nodes are the first stations of lymphatic metastasis, followed by group II and III neck lymph nodes. Because of the crossed lymphatic drainage through the anterior group of submandibular nodes, OCs can metastasise bilaterally and even contralaterally [38]. Tumour cells originating from the OC may bypass the first or even second metastatic station, and move to more distant levels according to the so-called skip pattern of metastasis [41]. There is an internationally accepted consensus that removal of neck lymph nodes is generally recommended, especially if the risk of hidden metastases exceeds 15–20% [42–43]. Several studies have shown that the depth of primary tumour infiltration (DOI) proportionally influences the risk of cervical lymph node metastasis [37, 44].

A complete histopathological report after OC resection should, as a standard, include the histological type of tumour and its grade of differentiation, tumour dimensions, DOI, description of removed bony structures infiltration, assessment of neuroinvasion and angioinvasion, width of the surgical

margins, number of lymph nodes removed, number of involved lymph nodes, presence of extranodal extension with the designation of nodal groups, and the stage of pTN according to the current TNM classification (currently TNM 8th edition according to the AJCC) [45–47]. For the reliability of complete histopathological reports, adequately labelled preparations by the operating team are essential.

In modern histopathological diagnoses, which involves combining classical risk factors with molecular biology, new scales are being sought to assess personalised risk for patients. Such scales and new prognostic factors may include the type of infiltration (pattern of infiltration – POI) [48–49], assessment of the lymphocytic response (LHR) [50], assessment of the aggressive risk scale, tumour budding [51] and HPV status determination, especially in tumours also involving the oropharynx [52]. For immunotherapy, it is also necessary to determine the status of PD1 and PD-L1 in histopathological material [53–54] or its equivalent. The combined positive score (CPS), which is defined as the sum of PD-L1-stained tumour cells and surrounding lymphocytes and macrophages divided by the total number of viable tumour cells multiplied by 100 [55], seems to be a standard procedure.

In recent years, there have also been a number of studies tested which investigate the role of various genetic and molecular factors in postoperative material and surgical margins – including *PTEN* [56], *TIMP3*, *SFRP1*, *SFRP2*, *CDH1*, *RASSF1*, *RORA*, *DAPK1* [57], TIL – tumour-infiltrating lymphocytes [58] and many others [59–61]. However, a clear statement of their clinical utility requires further research.

Diagnostic and treatment

Diagnostic imaging – a computed tomography (CT) scan of the head and neck with contrast to assess bone infiltration seems to be crucial prior to treatment decision-making. For the assessment of soft tissue infiltration and donor vessels for reconstructive surgery, contrast-enhanced magnetic resonance imaging (MRI) is indicated as the sole diagnostic tool or supplementation of CT scans. A chest X-ray or chest CT scan and abdominal ultrasound are also indicated to exclude the possibility of distant spread of disease. In patients with a higher risk of distant metastases, positron emission tomography (PET) examination could also be considered. Careful laryngological examination of the oral cavity should not be omitted.

Surgery is the treatment of choice for patients with OC. Surgery involves resection of the primary tumour within the margins of healthy tissue with histopathological examination of the margins (intraoperative) and cervical lymphadenectomy to an extent appropriate for the disease stage (with an intraoperative histopathological evaluation of the adjacent lymph node groups). Depending on the extent of resection, concomitant reconstructive surgery of the tissue defect should be considered – locoregional or free flap reconstruction [33].

Prehabilitation to prepare patients for aggressive treatment, often followed by a significant functional, energetic and metabolic burden, should always be considered. Prehabilitation includes assessment of nutritional status and prevention of malnutrition; psychological support and education about the disease; treatment methods; preoperative pharmaceutical care; and information about the patient's social benefits after treatment. After surgery, early rehabilitation of speech, swallowing and consumption of fluids and meals of different consistencies is crucial for further outcomes.

The indications for postoperative radiotherapy (pRT) include stage of the primary tumour (T3 or T4), regional lymph node involvement, nerve infiltration, blood vessel congestion and lymphatic vessel infiltration. Positive postoperative margins and extracapsular extension (ECE) for lymph nodes are indications for postoperative concurrent radiochemotherapy fractionated conventionally with platinum compounds [62–65].

Despite the above, clinical practice shows that, according to histopathological findings, almost all patients with OC after surgery require at least complementary RT. In selected cases with a "save" postsurgical histopathological report, abandoning of complementary treatment could be considered. The patient's age, general performance status and additional medical conditions have to be assumed. On the one hand, age may be an indication to abandon RT, taking into account the side effects and the risk of a second cancer; on the other hand, our clinical experience shows that OC in younger patients can be extremely aggressive.

According to the National Comprehensive Cancer Network (NCCN) guidelines 2.2023, pRT should be started no later than 6 weeks after surgery. Conventional fractionated radiotherapy (RT) (2 Gy/fx), 5 days a week (Monday to Friday) over 6–6.5 weeks to a total dose of 60–66 Gy for areas at high risk of recurrence and to a dose of 44–50 Gy for elective areas is preferred. Intensity-modulated radiation therapy (IMRT) or 3-dimensional conformal radiation therapy (3D-CRT) is currently the technique of choice [66].

In advanced cases, despite pRT, the risk of locoregional recurrence and distant metastases is relatively high (5-year PFS 36%, 5-year OS 40% and 5-year LRC 69% [65]; incidence rate of DM, median 6.0% [67]). The risk increases with adverse prognostic factors according to the postoperative histopathological examination. Risk factors include positive surgical margins [65, 68–71], lymph node metastases with ECE [62–63, 68–74], perineural infiltration [62, 75], and cancer cell emboli in blood vessels [75]. To reduce the risk of failure in this group of patients, postoperative chemoradiotherapy (CHRT) should always be considered.

Cooper et al. (2004) showed that the addition of chemotherapy (CHT) to pRT significantly prolonged DFS (HR for disease or death 0.78; $p = 0.04$) but had no effect on OS (HR for death 0.84, $p = 0.19$) [65]. Similarly, Bernier et al. (2005) showed that

the addition of CHT to high-risk groups at the 5-year follow-up significantly prolonged PFS (47 *vs*. 36%) and OS (53 *vs*. 40%) without significantly increasing late adverse effects [64].

Definitive RT or brachytherapy (BT) (when anatomically feasible and at a low stage – T1, possibly T2, without lymph node spread) could be considered as a less effective primary treatment alternative to surgery when surgery is not feasible or the patient does not consent. For definitive RT, the NCCN guidelines 2.2023 outline three possible fractionation modalities – standard RT fractionation to a total dose of 66–70 Gy (2 Gy/fraction), 5 days a week to the primary tumour area and metastatic lymph nodes; RT with concomitant boost – 72 Gy in 6 weeks – 1.8 Gy per fraction to large fields and a 1.5 Gy boost as a second daily fraction during the last 12 days of treatment or RT 66–70 Gy for 6 days a week or hyperfractionated RT – 81.6 Gy over 7 weeks (1.2 Gy/fraction, twice daily). For radical BT, the NCCN suggests LDR brachytherapy (0.4–0.5 Gy/h) as a boost to external-field RT to a total dose of 50 Gy or alone to a total dose of 60–70 Gy or HDR BT – a 21 Gy boost in 3 fractions combined with external-field RT to a dose of 50 Gy or as a single treatment – 45–60 Gy in 3–6 Gy fractions [66]. However, RT to high, curative doses only in selected cases is applicable due to the proximity of the maxilla and the high risk of bone necrosis.

As an alternative method for external beam boost in patients with early-stage disease, the use of intraoperative radiotherapy (IORT) at a single dose of 5–7.5 Gy, followed by external beam radiotherapy up to 50 Gy could be considered [76].

In the literature, 5-year OS for patients with OC after pRT ranges from 59% to 70%. Survival rates may vary depending on the anatomical location of the various subsites, stage, grade of OC, age at diagnosis, treatment and comorbidities [77].

In patients with initially unresectable tumours, induction chemotherapy (indCHT) could be an option. Despite the often observed clinical benefit, the efficacy of such treatment has not been proven in randomised clinical trials [78–80]. In general, the results of treatment in this group of patients are suboptimal, and clinical trials to search for new, more effective treatments are needed.

Examples of such trials are described below. The most promising clinical trials available for patients with operable OC include GORTEC 2018-01 (NIVOPOSTOP), the MK-3475-689 trial and the MS202359-0002 trial.

GORTEC 2018-01 (NIVOPOSTOP) is a randomised phase III clinical trial evaluating postoperative adjuvant therapy with nivolumab concomitantly with CHRT in high-risk patients following radical surgery. Nivolumab starts 3 weeks before CHRT and is continuing in the dose of 360 mg on days 1, 22 and 43 of CHRT. After completion of CHRT, nivolumab alone is administered as maintenance treatment. In the control arm, patients receive standard CHRT with 100 mg/m^2 cisplatin on days 1, 22 and 43 of RT [81].

In another phase III study, pembrolizumab is given twice every 3 weeks prior to surgery, and is continuing in combination with RT or CHRT after surgery (MK-3475-689). In another randomised double-blind phase III clinical trial after surgery, patients receive xevinapant and RT when the platinum-derived compound is contraindicated. In this study, in the experimental arm, patients receive 3 cycles of xevinapant at a dose of 200 mg/day once daily from day 1 to day 14 in a 3-week cycle in combination with RT followed by 3 cycles of xevinapant (1 to day 14) in a 3-week cycle (each cycle lasts 3 weeks). In the control arm, a placebo is used in the same way [82]. In patients who have relapsed after radical treatment, salvage surgery is the treatment of choice. The 5-year OS rate after salvage surgery ranges from 10–74% and depends largely on risk factors, mainly the presence of nodal recurrence and prior treatment. Better results are observed in younger patients without nodal recurrence and those who did not received RT as primary treatment [83–84]. When surgery is not possible, stereotactic RT is attempted, limited by the radiation dose previously received. Vargo et al., in a multicentre study of SBRT for recurrent or second primary head and neck cancer, showed a 2-year patient survival rate of 16.3% [85].

There are two studies summarising the clinical outcomes of repeat salvage irradiation with curative intent for unresectable recurrent squamous cell carcinoma of the head and neck – the RTOG 96-10 and RTOG 99-11 trials, which investigated reirradiation with concurrent chemotherapy [86–87]. Previous RT in eligible patients should be terminated at least 6-months earlier. The results of these studies highlight the uncertain prognosis for patients with recurrent disease treated with re-irradiation with 2-year OS rates of 15.2% in RTOG 96–10 patients and 25.9% in RTOG 99-11 patients. Unfortunately, only 20–30% of patients with primary treatment failure are candidates for salvage surgery or RT [88]. For these patients, palliative systemic treatment or best supportive care is the only option. An approximately 30% response rate and median progression-free survival (PFS) of 3 to 4 months and a median overall survival (OS) of 6 to 8 months could be obtained with platinum combined with fluorouracil or a taxans [89–90]. An EXTREME trial with cetuximab, an inhibitor of epidermal growth factor receptor (EGFR) added to a platinum-based chemotherapy with fluorouracil, significantly increased PFS from 3.3 to 5.6 months and median OS from 7.4 months to 10.1 months compared to chemotherapy alone [91]. A KEYNOTE-048 trial showed that patients with metastatic H&N cancer or recurrent H&N may benefit from pembrolizumab given alone (when slow progression without clinical symptoms is observed) or when it is combined with platinum and fluorouracil (for quick progression and/or aggravated clinical symptoms of this tumour) when the combined positive score (CPS) ≥1 has been found [92]. The results of this trial showed a statistically significant increase in 2-year overall survival (OS) to 31% for patients treated with the combination of pembrolizumab with chemotherapy versus 17% for patients treated with standard treatment (cetuximab with chemotherapy) [92]. Monotherapy with docetaxel,

methotrexate or cetuximab for several years was the only therapeutic option for those who failed first-line palliative chemotherapy. Currently, for second-line treatment, nivolumab could be used according to the results of the CheckMate study 141. This study showed a statistically significant improvement in OS (1-yr 36.0% *vs.* 16.6% in favour of nivolumab compared with standard treatment) in patients randomised to the nivolumab group compared with the investigator-selected treatment group, as well as a significant increase in response time (median 9.7 months *vs*. 4.0 months) [93].

For recurrent or untreated OC and primary disseminated cancers, various clinical trials are also being conducted to improve the results. [94–100]. Current trials evaluate the efficacy of other drugs, such as lenvatinib in combination with pembrolizumab versus pembrolizumab monotherapy, GSK3359609 or placebo in combination with pembrolizumab or a comparison of BNT113 in combination with pembrolizumab versus pembrolizumab monotherapy [94–96].

For distant dissemination in oligometastatic disease, the treatment of choice is also primary surgery or, if ineligible, stereotactic radiotherapy. Preliminary results from the SABR-COMET trial of ablative stereotactic radiotherapy in patients with up to five metastatic sites from any primary tumour site showed improved progression-free survival (12 *vs*. 6 months, $p < 0.01$) and overall survival (41 *vs*. 28 months, $p = 0.09$) when metastatic sites were treated with irradiation [97]. Sun et al. simulated 5-year survival rates of 20% in selected patients with head and neck cancer who underwent oligometastasis surgery with stereotactic irradiation of metastases [98].

In symptomatic patients with poor performance status who are not eligible for surgery, palliative radiotherapy remains the treatment of choice. Mohanti et al. described similar weekly treatment in a large retrospective study involving 505 patients. Patients were treated with a dose of 20 Gy in five fractions. Symptom relief was obtained in 47–59% of the patients following palliative RT [99]. Compared to the Fortin et al. study, in which patients were treated with a dose of 25 Gy in 5 fractions, this regimen showed a lower objective response rate of 50% [100]. Furthermore, all patients in this cohort developed patchy mucositis at follow-up, 1 month after treatment.

Conclusions

There is an urgent need to develop new, more effective treatment methods for oral cancer patients. In this context, the role of immunotherapy as well as targeted therapies should be more extensively investigated. Several ongoing clinical trials evaluate novel therapeutic approaches, such as immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab), monoclonal antibodies (cetuximab), small molecule inhibitors (lenvatinib) or cancer vaccines (BNT113).

Moreover, further research is warranted to establish new prognostic and predictive factors, as well as disease and patient stratification models. These could enable personalized therapy tailored to the biological characteristics of the tumour and the patient. Genetic and molecular analyses seem especially interesting in this matter.

Special attention should also be paid to gaining a better understanding the etiopathogenesis of oral cancer. The role of HPV infection, but also other potential viral factors, requires further elucidation. Additionally, promotion of healthy lifestyles and reduction of risk factor exposure in the general population could contribute to oral cancer prevention at the public health level.

In summary, advancing the diagnostics and treatment of oral cancer calls for a coordinated effort from various fields of clinical medicine and basic science. Only multidirectional research and multidisciplinary collaboration can bring a significant improvement in the outcomes of patients affected by this disease.

Article information and declarations

Author contributions

Natalia Amrogowicz – concept, literature review, writing – original draft preparation.
Tomasz Rutkowski – concept, writing – review and editing.

Conflict of interest

None declared

Natalia Amrogowicz
Maria Sklodowska-Curie National Research Institute of Oncology
Gliwice Branch
1st Radiation and Clinical Oncology Department
Wybrzeże Armii Krajowej 15
44-102 Gliwice, Poland
e-mail: Natalia.Amrogowicz@gliwice.nio.gov.pl

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Review article

Colorectal cancer

The connection between *Fusobacterium nucleatum* levels and chemoresistance in colorectal cancer – a systematic review

Datis Kalali[1], Vasiliki Tzalili[1], Doxakis Anestakis[1, 2]

[1]*Medical School, University of Cyprus, Nicosia, Cyprus*
[2]*Laboratory of Autopsy Pathology, Forensic Service of Thessaloniki, Ministry of Justice, Thessaloniki, Greece*

Introduction. The lack of response to chemotherapeutic drugs is one of the major challenges faced in the treatment of colorectal cancer. Several studies have indicated that the microbiome of the bowel affects the treatment response and specifically, certain bacterial species contribute to the development of chemoresistance. With *Fusobacterium nucleatum* being one of the bacterial species frequently found in the bowel of colorectal cancer patients, the present systematic review was undertaken to gather the existing literature on the relationship of *Fusobacterium nucleatum* with chemotherapy response.

Material and methods. Major online academic databases were searched using a combination of keywords and Boolean operators, in order to retrieve literature on the topic from inception until February 2023. Observational studies with relevant information were included in the present systematic review and their quality was assessed.

Results. A total of 7 studies with 2,280 colorectal cancer patients who underwent adjuvant or palliative chemotherapy were included in the qualitative synthesis. No study with a major risk of bias was found after a quality assessment. The majority of studies observed poorer prognosis in patients who had high levels of *Fusobacterium nucleatum* in their bowel, although, due to the small number of studies, a meta-analysis could not be performed.

Conclusions. High levels of *Fusobacterium nucleatum* result in a poorer response to chemotherapy in colorectal cancer. Nevertheless, to further verify this assertation, more observational and experimental studies must be undertaken in the clinical field.

Key words: colorectal cancer, colon cancer, *Fusobacterium nucleatum,* chemoresistance

Introduction

Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality globally, with its incidence rate predicted to be doubled in the upcoming decade [1]. One of the underlying reasons for its high mortality in some patients is the lack of response to chemotherapy, also known as chemoresistance, since adjuvant and palliative chemotherapy remain one of the main therapeutic strategies in the therapy of CRC [2–4]. There are many possible molecular mechanisms that can affect the response to chemotherapy in cancer cells, usually involving genetic mutations that occur during the tumor's progression [5]. Nevertheless, other factors may also result in the development of resistance, especially those which trigger genetic mutations. The bowel's microbial composition, typically known as the microbiome, has recently been found to be related to the formation of drug resistance

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in CRC and indeed increase the risk of occurrence of certain related mutations [6, 7].

One of the most commonly found bacteria in the microbiome of CRC patients is the anaerobic gram-negative species *Fusobacterium nucleatum* (*Fn*); it has been shown that the latter species affects the formation and progression of tumors [8]. For this reason, CRC patients are sometimes screened for *Fn* levels in the bowel and are classified as *Fn*-positive or *Fn*--negative based on the concentration of the species in biopsy or stool samples [9, 10]. More specifically, research has indicated that *Fn* is related to poor prognosis in CRC, suggesting that the bacterium may perhaps be an underlying cause of drug resistance [11, 12]. Hence, in this study, a systematic review was performed on all existing literature that relate levels of *Fn* with chemotherapy outcomes in colorectal malignancies, so as to assess whether there is a relation between chemoresistance and *Fn*-positivity. Such an association would certainly provide new insights for medical oncologists and researchers on how to combat drug resistance and improves the outcomes of chemotherapy in CRC.

Material and methods

The present systematic review has been registered in the OSF Registries platform on 16 January 2024, after the completion of the study.

Search strategy

A systematic literature search was performed in the electronic databases PubMed, SCOPUS and Embase from inception until January 2023, using a combination of keywords and Boolean operators. The keywords used were: "*F. nucleatum*", "*Fusobacterium nucleatum*", "colorectal", "colon", "bowel", "cancer", "carcinoma", "tumor", "chemoresistance" and "chemotherapy resistance". The search was limited to citations written in English.

After the retrieval of the literature, duplicate citations were removed by using the citation manger EndNote and subsequently, all remaining citations were assessed for eligibility by screening their titles and abstracts. The inclusion criteria for this systematic review were observational studies which compared outcomes between *Fn*-positive and *Fn*-negative bowel cancer patients who received chemotherapy. In turn, full-text versions of citations were assessed and studies which met the inclusion criteria were included in this review. The search and screening process was performed by two independent reviewers (DK and VT).

Data extraction and quality assessment

Data regarding the design of the studies, the number of participants, the stage and position of the tumors, the chemotherapy regimens used and the treatment outcomes were extracted from the eligible studies by two independent reviewers (DK and VT). In turn, the reviewers assessed the quality of the included studies using the Newcastle-Ottawa scale which evaluates the quality of the inclusion process of each study, the comparability between the cohorts and their respective outcomes [13]. Disagreements did not arise between the two reviewers during the whole selection and assessment process.

Results

Included studies

The electronic database search retrieved a total of 111 articles, out of which only a total of 63 articles remained after removal of duplicates. After screening the abstracts and titles of each citation, a total of 24 citations were deemed irrelevant and hence excluded from the study. From the remaining 39 citations, which were assessed based on the content of their full texts, a total of 12 citations did not contain relevant information on chemotherapy outcomes, 9 citations were review articles, 8 citations were animal studies and 3 citations were *in vitro* studies. Since the included studies were very heterogenous in their design and method of conduction, the presentation of the results varied and our review only contained a small number of studies, a meta-analysis was not conducted. Figure 1 presents a PRISMA diagram of the search strategy and inclusion process. The characteristics of the included studies are summarized in table I.

In general, the studies involved in this systematic review included a total of 2,280 patients with tumors in the colon or the rectum who underwent adjuvant or palliative chemotherapy. All studies, except one, found that *Fn*-positivity was associated with a higher risk of mortality and a lower survival expectancy in patients taking chemotherapeutic drugs, indicating that *Fn* colonies in the bowel are associated with a lower response to chemotherapy [14, 15, 17–20]. The study

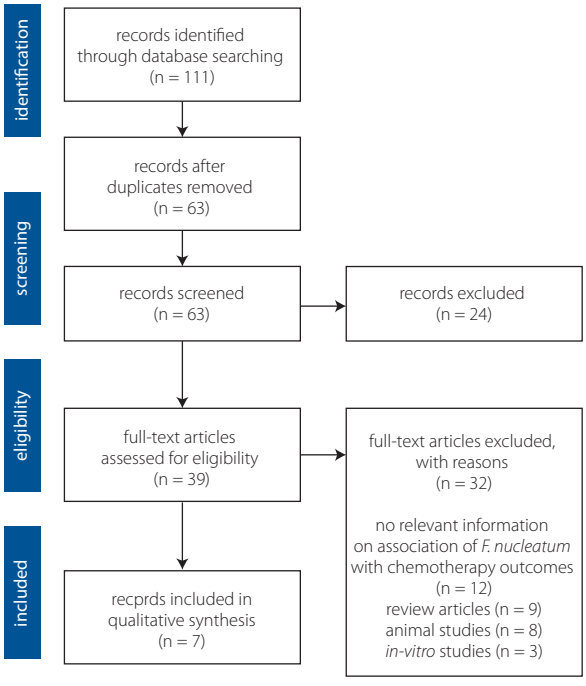

Figure 1. PRISMA diagram of the search strategy and inclusion process

Table I. Characteristics of the studies included in the qualitative synthesis

Study (author, year)	Type of study	Participants (n)	Tumor stage	Tumor location	Chemotherapy regimen	Association of *Fn*-levels and outcomes	p value
Borozan et al., 2022 [14]	retrospective cohort	total: 736 *Fn*-positive: 83 *Fn*-negative: 653	stage I, II, III and IV (distribution unknown)	colon and rectum	unknown	HR = 1.92 (CSM of *Fn*-positive *vs.* *Fn*-negative)	0.029
Chen et al., 2019 [15]	retrospective cohort	total: 91 *Fn*-positive: 25 *Fn*-negative: 66	stage II: 51 stage III: 40	colon: 77 rectum: 14	adjuvant FOLFOX or XELOX	HR = 2.09 (CSM of *Fn*-positive *vs.* *Fn*-negative)	0.032
Hanna et al., 2022 [16]	retrospective cohort	total: 38 *Fn*-positive: 12 *Fn*-negative: 26	stage II: 9 stage III: 29	rectum	unknown	no association found	–
Kim et al., 2018 [17]	retrospective cohort	total: 424 *Fn*-positive: 272 *Fn*-negative: 152	stage II and III (distribution unknown)	colon and rectum	adjuvant FOLFOX	association of high *Fn* levels with lower overall survival (only in right-sided colon cancers)	–
Lee et al., 2018 [18]	retrospective cohort	total: 118 (distribution unknown)	stage IV	colon and rectum	palliative FOLFOX, XELOX, SOX, FOLFIRI or capecitabine monotherapy	HR = 1.69 (CSM of *Fn*-positive *vs.* *Fn*-negative)	0.034
Oh et al., 2019 [19]	retrospective cohort	total: 593 *Fn*-positive: 204 *Fn*-negative: 389	stage II: 90 stage III: 503	colon and rectum	adjuvant FOLFOX or XELOX	HR = 0.4 (DFS of *Fn*-positive *vs.* *Fn*-negative)	0.043
Yan et al., 2017 [20]	retrospective cohort	total: 280 *Fn*-positive: 187 *Fn*-negative: 93	stage III: 218 stage IV: 62	colon: 150 rectum:130	adjuvant FOLFOX	HR = 2.13 (CSM of *Fn*-positive *vs.* *Fn*-negative)	<0.001

Fn – *Fusobacterium nucleatum*; HR – hazard ratio; CSM – cancer-specific mortality; DFS – disease-free survival; FOLFOX – folinic acid, fluorouracil, and oxaliplatin; XELOX – capecitabine and oxaliplatin; SOX – S-1 and oxaliplatin; FOLFIRI – folinic acid, fluorouracil, and irinotecan

which found no statistically significant difference, included patients with rectal cancer only [16]. One study by Kim et. al limited the results only to patients with right-sided carcinomas, in other words, carcinomas found within the cecum, the ascending or the transverse colon [17]. In all studies, a regimen of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (XELOX) was used for adjuvant post-surgery chemotherapy. However, in the case of palliative chemotherapy, the S-1 and oxaliplatin (SOX) or folinic acid, fluorouracil, and irinotecan (FOLFIRI) regimens were also used in some patients [18]. Overall, most studies found an approximately twofold hazard ratio of cancer-specific mortality (CSM) in patients who were *Fn*-positive [14, 15, 18, 20].

Quality assessment

The Newcastle-Ottawa scale was used by two reviewers (DK and VT) to evaluate the quality of each individual study included in this systematic review and the results have been recorded in table II. In general, the studies were classified as good quality in accordance with the Agency for Healthcare Research and Quality (AHRQ) standards, since for all studies, 3 or 4 stars were given in the selection domain, 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome domain [13]. This confirms that the conclusions of this systematic review are not highly affected by bias.

Discussion

The present systematic review evaluated all existing literature relating levels of *Fn* to the efficacy of chemotherapy in patients with CRC. As seen through the results, the existence of high levels of *Fn* lower the response to chemotherapy in CRC patients and are associated with poorer prognosis. Indeed, *in-vitro* studies have managed to discover that *Fn* can promote chemoresistance by triggering signaling pathways which result in the expression of drug efflux pumps, deactivation of apoptotic mechanisms and modulation of cellular autophagy [21, 22]. The results of this review verify the latter assertations in clinical studies since patients with *Fn* in their bowel have a poorer response to chemotherapy.

Nonetheless, as mentioned previously, one study did not find statistically significant results in the case of rectal cancer and another study only found significant results in right-sided carcinomas [16, 17]. This finding brings up the topic of tumor sidedness in CRC, which has been of great interest in recent years. In fact, a meta-analysis in 2017 concluded that tumors found in the right colon are associated with poorer prognosis results [23]. Therefore, it is rational for studies involving right-sided tumors to show poorer prognosis than left-sided tumors, which also include rectal tumors. On the other hand, researchers have discovered that *Fn*-positive cancers are much more frequent in right-sided carcinomas and quite rare in rectal tumors; therefore a lack of relationship between *Fn*-positivity and chemoresistance in rectal tumors does not significantly affect the conclusions of this review [24, 25].

It is also worth mentioning that some limitations exist in this systematic review, although it was performed in complete accordance with the Cochrane guidelines, and no potential bias was found in the quality assessment using the Newcastle-Ottawa scale [26]. Foremost, all included studies had a retrospective design, making them more prone to bias and therefore lowering the quality of the evidence [27]. Moreover, the whole review included only a few number of patients, lowering the statistical reliability of the results [28]. Simultaneously, the fact that the qualitative synthesis only included seven studies reporting their outcomes in different ways, made it difficult for a formal meta-analysis to be conducted.

Table II. Quality assessment of studies included in the review

Study (author, year)	Newcastle-Ottawa scale scores			
	Selection	Comparability	Outcome	Total
Borozan et al., 2022 [14]	4	2	3	9
Chen et al., 2019 [15]	3	2	1	6
Hanna et al., 2022[16]	3	1	2	6
Kim et al., 2018 [17]	3	2	2	7
Lee et al., 2018 [18]	3	2	2	7
Oh et al., 2019 [19]	3	2	2	7
Yan et al., 2017 [20]	3	2	2	7

Conclusions

The present study managed to collect evidence indicating that *Fn*-positivity is directly related to the development of chemoresistance. Hence, one of the novel strategies for better CRC chemotherapy outcomes would be to adjust the colorectal microbiome and eradicate the existence of the species *Fusobacterium nucleatum* within the bowel. There are several ways of achieving the latter, including the adjuvant administration of antibiotics such as metronidazole to eradicate anaerobes [29, 30]. Other methods of regulating the microbiome and eradicating such bacteria is through the use of probiotics and including specific foods to the patient's diet, such as yogurt, kefir and sourdough bread alongside anticancer treatments [31–33]. Indeed, a patient's diet has been found to be correlated with chemotherapy outcomes [34]. Nevertheless, there is an urgent need for more studies and clinical trials to be conducted in this field in order to evaluate the effectiveness of the forementioned methods and their results on chemotherapy response. More prospective studies should also be undertaken in order to collect stronger evidence that *Fn*-positivity contributes to

the development of chemoresistance in CRC, allowing researchers to conduct a meta-analysis confirming the assertation.

Article information and declarations

Author contributions

Datis Kalali – conceptualisation, methodology, investigation, project administration, supervision, formal analysis, manuscript draft.

Vasiliki Tzalili – methodology, investigation, formal analysis.

Doxakis Anestakis – manuscript revision and editing.

Conflict of interest

None declared

Datis Kalali
University of Cyprus
Medical School
1 Panepistimiou Avenue
2109 Aglantzia, Nicosia
P.O. Box 20537, 1678 Nicosia, Cyprus
e-mail: kalali.datis@ucy.ac.cy

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Review article

Clinical nutrition in oncology

Nutritional problems of patients after gastrectomy and the risk of malnutrition

Ewelina Grochowska[1], Aleksandra Gazi[1], Agnieszka Surwiłło-Snarska[1], Aleksandra Kapała[1, 2]

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

The radical treatment for advanced gastric cancer is gastrectomy. This procedure disrupts the anatomy and physiology of the gastrointestinal tract. After surgery, nausea, heartburn, biliary regurgitation, feeling early satiety, belching, lack of appetite and swallowing problems are reported to affect food intake. Decreased absorption, loss of nutrients and increased energy requirements of cancer patients lead to weight loss and the development of malnutrition. After gastrectomy, the composition of the intestinal microbiome changes, the exocrine activity of the pancreas decreases and deficiency-metabolic disorders (including iron, vitamin B_{12}, zinc, and vitamin D) develop. Approximately 60–70% of gastrectomy patients experience a clinically significant deterioration in their quality of life. Nutritional management should include dietary modification, appropriate nutritional supplementation and close monitoring of the nutritional status of these patients.

Key words: gastric cancer, gastrectomy, malnutrition, vitamins, trace elements

Introduction

Gastric cancer is one of the most frequently diagnosed cancers in the world. More than 1.1 million new cases and approximately 800,000 deaths are reported annually. Over 85% of gastric cancer cases are registered in countries with a high and very high Human Developing Index, mainly in Asia (China) [1].

Primary risk factors for gastric cancer include infection with *Helicobacter pylori* – chronic infection leads to a cascade of changes in the structure of the gastric mucosa – inadequate diet (rich in salt and canned and smoked foods, poor in fresh fruits and vegetables), smoking, alcohol consumption, obesity, gastroesophageal reflux, age, male gender and genetic predisposition [1, 2].

Adenocarcinomas account for 90% of all gastric cancers. Other malignancies occurring in the gastric tract include gastrointestinal stromal tumors (GIST), lymphomas, sarcomas and neuroendocrine tumors (NET). According to Lauren's classification, there are intestinal, diffuse and mixed types of gastric cancer, and according to the location, tumors of the distal and proximal parts of the gastric tract are distinguished [1].

Gastric cancer treatment

Radical treatment is the surgical removal of the tumor. Depending on the stage and location of the cancer, surgical treatment may consist of subtotal gastrectomy (excision of ¾ of the stomach, radical removal without removing the stomach in its entirety) and total gastrectomy (complete removal of the stomach). The standard of treatment for patients with locally advanced gastric cancer is perioperative chemotherapy administered before and after total gastrectomy with

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D_2 lymphadenectomy (stations 1–12) with Roux-en-Y reconstruction of the gastrointestinal tract. The operation involves suturing the oesophagus with a loop of the small intestine. This loop is connected to a part of the intestine that guides bile and pancreatic juice from the duodenum [3, 4]. This procedure disrupts the anatomy and physiology of the gastrointestinal tract, interferes with the digestion and absorption of nutrients and leads to problems with the digestive tract [5].

Nutritional problems of patients after gastrectomy

Gastrectomy results in a risk of chronic nausea, heartburn, dumping of food content into the mouth, the feeling of early satiety, belching, lack of appetite, dysphagia, abdominal pain and diarrhea. The greatest intensity of symptoms was observed in the first months after surgery before the digestive tract adapts to the new conditions. Their intensity decreases with time. Deficiency-metabolic disorders accompany patients for the rest of their lives. Each of the ailments affects the food intake quantity of patients, which causes weight loss and deterioration of the their quality of life [5, 6].

One of the early consequences of gastrectomy is dumping syndrome. The leading cause of dumping syndrome is the sudden passage of high-osmolarity food into the small intestine, which provokes the accumulation of excessive fluid in the intestines and increased secretion of intestinal hormones. Approximately 15–30 minutes after eating an overly large meal, there is fullness in the epigastrium, bloating, abdominal pain, nausea, sometimes diarrhea, palpitations, the urge to lie down or sit up, sweating, pale or flushed skin, dizziness, fainting [4, 7, 8]. In Esther Una Cidon's study, dumping syndrome symptoms occurred in 27% of patients after gastrectomy [9]. In preventing dumping syndrome, it is essential to eat small, frequent meals (even 6–8 meals a day), eat slowly, limit fluids during meals and compose meals so that each contains a source of protein and fat [4]. Postprandial hypoglycemia (late postprandial syndrome) is a sharp drop in blood glucose levels combined with feelings of hunger, sweating and even impaired consciousness. It occurs 1–3 hours after a meal and is caused by a rapid insulin response to hyperglycemia resulting from the rapid absorption of simple sugars in the early small intestine. A low glycemic index diet containing complex carbohydrates and fibre is recommended to prevent future hypoglycemia. A low glycemic index diet prevents a sudden glycemic peak and insulin release [10].

Loss of appetite is the most common problem after gastrectomy. It may be influenced by the secretion of cholecystokinin after surgery, which precludes satiety and causes a feeling of satiety. Concentrations of the hormones GLP-1 (glucagon-like peptide 1), PYY (intestinal hormone peptide) and ghrelin are altered. Ghrelin is referred to as the hunger hormone, after surgery, its concentration decreases by 65% [11–13]. Loss of appetite after gastrectomy is reported by about 80% of patients [9]. One year after surgery, it is still reported by more than 30% of patients [14].

About 80% of patients after gastrectomy present symptoms such as epigastric pain, heartburn, biliary regurgitation and occasionally vomiting. The described complaints lead to reflux esophagitis which occurs when the intestinal loop separating the oesophagus from the duodenum or inter-intestinal anastomosis is too short, and no replacement valve mechanism has been created [4]. Preservation of the lower oesophagal sphincter may protect against reflux esophagitis. In a study by Tomit et al., reflux symptoms were present in 30.8% of patients without a lower oesophagal sphincter and only among 8% of patients in whom the sphincter remained. Symptoms of reflux esophagitis are usually more severe in the early postoperative period but can occur chronically, more than a year after surgery. Symptoms of dysphagia and odynophagia accompany post-gastrectomy patients due to altered oesophagal biomechanics (changes in oesophagal muscle tone), alkaline reflux esophagitis, vagus nerve damage and anastomotic stenosis [15]. In a study by Karanicolas et al., dysphagia, loss of appetite and eating restrictions were the most common symptoms. They occurred in 45-55% of patients in the immediate post-gastrectomy period. Among the surveyed people, 40% reported reflux symptoms, and 30% reported nausea/vomiting. Total gastrectomy patients are more likely to report diarrhea than subtotal gastrectomy patients [16].

Biliary diversion after gastrectomy, changes in the pH of the gastrointestinal tract and loss of the gastric barrier affect the composition of the gut microbiome. Gastrectomy-induced dysbiosis is characterized by an increased abundance of typical oral cavity bacteria, an increase in aero-tolerant bacteria and an increased abundance of bile acid-transforming bacteria. Increased amounts of *Streptococcus*, *Veillonella*, *Prevotella*, *Oribacterium*, *Mogibacterium* were observed in the gut microbiome of patients after gastrectomy [17, 18]. Liang and colleagues observed a higher abundance of *Veillonella* bacteria, as well as *Escherichia/Shigella* and *Clostridium*, and a lower abundance of *Bacteroides* in the intestinal microflora of gastrectomy patients. The abundance of genera *Akkermansia*, *Lactobacillus* and *Dialister* significantly changed in the perioperative period [19]. Changing the composition of the intestinal microbiome affects the induction of chronic inflammation, resulting in damage to the intestinal mucosa, disruption of intestinal ion transport and increased permeability of the mucosa to pathogens, resulting in diarrhea. Patients are often accompanied by symptoms such as diarrhea, bloating, abdominal discomfort and abdominal pain, referred to as SIBO (small intestinal bacterial overgrowth) [17]. In a Pérez Aisa et al. study, SIBO was found in 61.6% of patients after gastrectomy [20].

Altered bile acid flow and pancreatic insufficiency due to disturbances in hormonal regulation of gastrointestinal secretory function, lack of synchronization between food intake including pancreatic secretion, and rapid intestinal transit

can lead to steatorrhea [4]. Significant reduction in exocrine pancreatic activity and continuous decrease in pancreatic volume over five years post-operation were observed after total gastrectomy [21]. Pancreatic insufficiency is one of the causes of malabsorption. However, routine use of pancreatic enzymes is not justified. Existing studies on pancreatic enzyme supplementation after gastrectomy show inconsistent results. A study by Catarci et al. assessed that pancreatic enzyme supplementation improves nutritional status and quality of life after gastrectomy, particularly within 3 months post-operation [22].

Felice van Erning and colleagues assessed the occurrence of nutritional problems after gastrectomy up to one-year post-surgery between 2015 and 2021. Patients after gastric resection most commonly reported loss of appetite (22.2%), taste disturbances (15.8%) and dry mouth (14.4%). The occurrence of symptoms was evaluated before and after the operation. Before the surgery, 26.4% of the participants reported experiencing 2 or more nutritional problems; after the surgery, it was 42.4%. Among the participants, 53.6% reported no discomfort before the operation, whereas after the surgery, it was 43.7% [7]. Surgery and adjuvant chemotherapy exacerbate discomfort and worsen the quality of life. Patients undergoing chemotherapy experience its toxicity. Loss of appetite, dry mouth, weight loss and nausea were more common in the group of patients after gastrectomy with chemotherapy than after surgery alone [23].

Among approximately 60-70% of patients, there is clinically significant deterioration in quality of life shortly after gastrectomy. In about ⅓ of patients, symptoms persist for longer than 6 months post-surgery [16]. Total gastric resection results in weight loss, on average 15% of preoperative weight [24]. Over 50% of patients after gastrectomy are malnourished or at risk of malnutrition [5, 25]. In the context of preventing and treating malnutrition, cooperation between a doctor and a dietitian is crucial. Appropriate management aims to limit excessive weight loss and help patients alleviate post-operative discomfort [26].

Gastrectomy leads to the occurrence of nutritional deficiencies. The frequency of diagnosing zinc deficiencies in patients after gastrectomy varies from 10 to 75% [27]. Gastric resection with Roux-en-Y reconstruction may increase the risk of fat-soluble vitamin deficiencies – A, D, E, K [28]. Vitamin D deficiency contributes to decreased bone mineral density and disturbances in mass and structure (osteoporosis). The level of vitamin D may drop post-surgery by up to 36% [29]. The development of osteomalacia and osteoporosis is also influenced by calcium deficiency, which results from the duodenum being bypassed by the ingested food, changes in pH in the upper gastrointestinal tract and insufficient dietary intake due to a common problem with lactose tolerance and cow's milk protein [28]. Incidence of osteoporosis after gastrectomy can affect about 40% of patients; older patients, women and people with diabetes are more at risk [30].

Iron deficiency anaemia is also a common sequela of total gastrectomy. It is diagnosed in 40–70% of patients after gastrectomy [28, 29]. It is caused by perioperative blood loss and a change in the pH of the upper gastrointestinal tract. Increased pH in this region impairs the reduction of trivalent iron to the better-absorbed divalent iron. The way the gastrointestinal tract is reconstructed after gastrectomy causes the digestive contents to bypass the duodenum and upper part of the small intestine. The lower consumption of iron-rich foods is another cause of iron deficiency [4, 28, 29]. Folic acid and vitamin B_{12} deficiency is a leading cause of megaloblastic anaemia. Vitamin B_{12} deficiency is significantly more common due to the lack of the Castle's factor, which enables the absorption of this vitamin. The onset time of disease symptoms depends on the condition of the gastric mucosa before treatment and the body's vitamin reserves. Lifelong supplementation of vitamin B_{12} through intramuscular injections is recommended [28, 29]. During the five years after gastrectomy, the incidence of anaemia increases; the risk of anaemia is higher in women, patients after total gastrectomy, diabetics and patients with low body mass index (BMI) [31]. Anaemia is also significantly more common in patients with advanced T-stage and lymph node metastasis. Patients with anaemia have lower concentrations of nutritional markers (albumin, prealbumin) and overall survival rates [32].

Conclusions

The increased energy demands of oncological patients, inadequate intake, reduced absorption and loss of nutrients can lead to weight loss and malnutrition. Nutritional management should include dietary modification, appropriate nutritional supplementation and careful monitoring of these patients' nutritional status (fig. 1, 2).

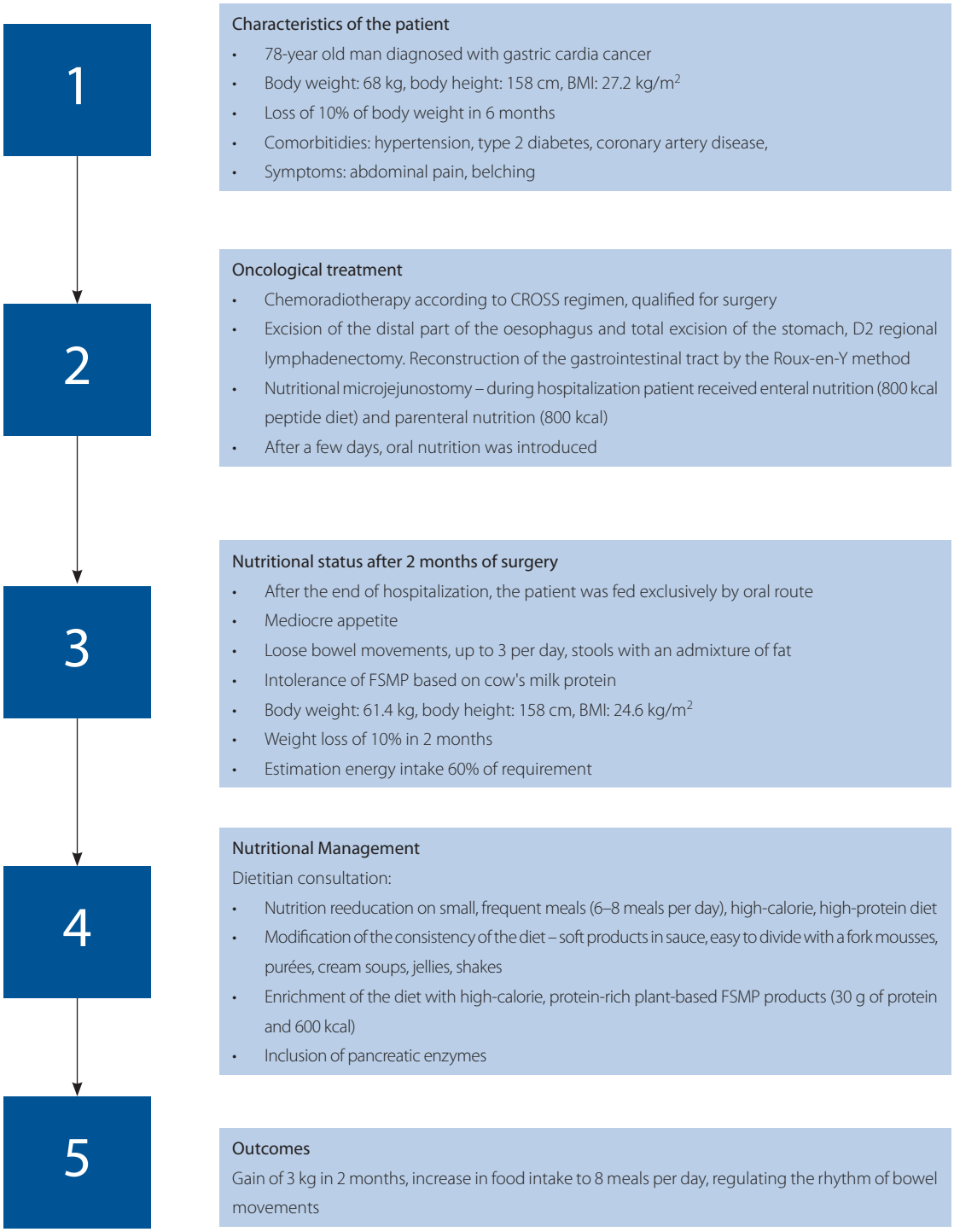

Figure 1. Case study 1

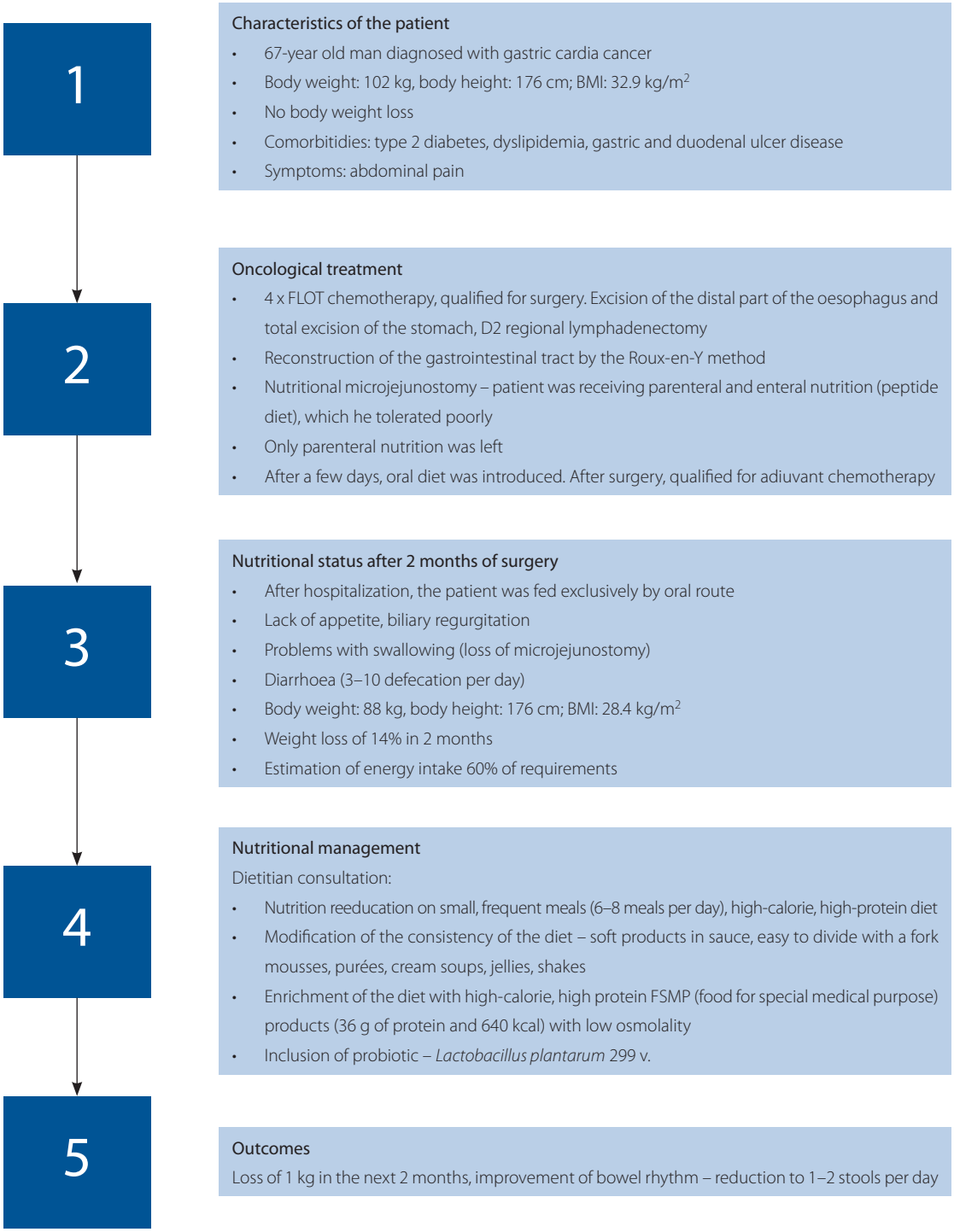

Figure 2. Case study 2

Article information and declarations

Author contributions

Ewelina Grochowska – conceptualization, project administration, writing – original draft preparation.
Aleksandra Gazi – visualization.
Agnieszka Surwiłło-Snarska – visualization.
Aleksandra Kapała – writing – review and editing.

Conflict of interest

None declared

Ewelina Grochowska
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Clinical Nutrition
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: ewelina.grochowska@nio.gov.pl

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Review article

Tumor pathology

The Paris System for Reporting Urinary Cytology – a critical review of its role in advancing precision diagnostics with insights into artificial intelligence integration

Irmina M. Michałek[1], Monika Durzyńska[1], Florentino L. Caetano dos Santos[2]

[1]*Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Harvard Business School, Harvard University, Boston, MA, USA*

Urinary cytology serves as a vital diagnostic tool for urothelial carcinoma, offering a non-invasive screening method and guiding treatment decisions. The Paris System for Reporting Urinary Cytology (TPS) addresses historical challenges, providing a structured framework and enhancing diagnostic precision. The review explores the integration of artificial intelligence (AI) into urinary cytology, emphasizing its collaborative potential with TPS. A systematic literature review analyzes AI applications, revealing promising advancements but highlighting concerns about generalizability and over-reliance on deep learning. The study underscores the importance of collaborative efforts for successful AI implementation, addressing challenges and ensuring seamless integration into clinical practice. While the synergy between TPS and AI shows promise, cautious consideration is necessary for widespread and reliable adoption, emphasizing ongoing refinement and validation.

Key words: urinary cytology, urothelial carcinoma, The Paris System for Reporting Urinary Cytology, precision diagnostics, standardized reporting, diagnostic challenges, clinical implications

Introduction

Urinary cytology plays an important role in the diagnosis of urothelial carcinoma, a type of cancer that primarily affects the urinary tract, including the bladder, ureters, and renal pelvis [1]. The significance of urinary cytology lies in its ability to detect abnormal cells shed from the lining of the urinary tract into the urine. These cells, when carefully examined under a microscope, can provide valuable information about the presence of urothelial carcinoma and its potential aggressiveness.

Urinary cytology emerges as a pivotal diagnostic modality in urothelial carcinoma, providing a multifaceted approach to enhance patient care. The non-invasive screening capability of urinary cytology offers a straightforward and repeatable method, making it an invaluable tool for routine monitoring, especially in high-risk populations with a history of bladder cancer. Complementary to advanced imaging studies such as cystoscopy, urinary cytology contributes unique insights at the cellular level, confirming the presence of cancerous cells and guiding subsequent diagnostic and treatment decisions [1].

One of the distinctive strengths of urinary cytology lies in its capacity to reduce the necessity for invasive procedures. The non-invasive nature of urine sample collection minimizes patient discomfort and contributes to a more patient-friendly

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diagnostic approach. In cases where urinary cytology indicates a low likelihood of urothelial carcinoma, unnecessary invasive interventions may be avoided, aligning with the principles of personalized and targeted medicine.

The Paris System for Reporting Urinary Cytology (TPS) is a standardized classification system designed to improve the consistency and precision of reporting urinary cytology, providing distinct categories with defined clinical implications [2, 3]. Before TPS, interpreting results faced challenges, including subjective interpretations, lack of standardized criteria, and inconsistencies [2, 4]. Pathologists used varied terminology, leading to confusion, while different classification systems hindered result comparison. Limited interobserver agreement and unclear clinical implications posed further issues, risking overdiagnosis or underdiagnosis. TPS addressed these challenges, offering a structured framework, improving consistency, and enhancing clinical utility in urinary cytology reporting [5].

This review aims to analyze TPS's effectiveness in overcoming historical challenges. Additionally, the research explores artificial intelligence (AI) and image processing integration in urinary cytology, emphasizing image analysis, pattern recognition, and potential contributions to personalized treatment strategies. Anticipated findings aim to enhance understanding of the synergistic relationship between TPS and AI, illuminating their potential to revolutionize urinary cytology reporting for improved diagnostic precision in oncology.

Overview of TPS

The TPS introduces a structured classification system comprising categories with distinct clinical implications [2, 3]. TPS categorizes specimens as non-diagnostic, negative for high-grade urothelial carcinoma, atypical urothelial cells, suspicious for high-grade urothelial carcinoma, high-grade urothelial carcinoma, and other malignancies. This standardized approach addresses the historical lack of uniformity, providing clear criteria for each category. TPS significantly improves communication between pathologists and clinicians, ensuring a consistent understanding of findings, and facilitating informed decision-making in patient management.

The TPS demonstrates notable strengths in enhancing diagnostic precision. Its standardized categories provide a clear and consistent framework, reducing the subjectivity that previously characterized urinary cytology reporting. The structured approach, including categories like "atypical urothelial cells" and "suspicious for high-grade urothelial carcinoma," facilitates more accurate and reliable interpretations [6]. By offering well-defined criteria for each category, TPS minimizes variability among pathologists, resulting in improved diagnostic precision [7, 8]. This standardization is particularly crucial in the context of urothelial carcinoma, where early and precise diagnosis is paramount for effective clinical management.

Several studies and real-world examples have highlighted the effectiveness of TPS in providing a standardized and comprehensive system for urinary cytology reporting [9]. However, like any diagnostic system, TPS has areas for improvement. Challenges may arise in cases with borderline or atypical features, where the interpretation may still rely on the pathologist's expertise. Ongoing research and feedback from clinical practice are essential for refining TPS and addressing any limitations, ensuring its continuous evolution to meet the dynamic demands of urinary cytology diagnostics.

Despite its strengths, the implementation of TPS in clinical practice is not without challenges. One notable controversy surrounds the concern of potential over-reliance on urinary cytology alone for the diagnosis of urothelial carcinoma, highlighting the need for a multimodal approach. Additionally, challenges persist in standardizing reporting across diverse clinical settings, laboratories, and pathologists. Ensuring consistent adherence to TPS criteria and overcoming interobserver variability remain ongoing challenges. Ongoing efforts are directed toward addressing these controversies and challenges, with a focus on refining TPS guidelines and fostering broader acceptance within the medical community [3].

The role of AI in urinary cytology

Currently, urine cytology is assessed through manual examination by skilled cytopathologists, who visually identify and interpret cellular abnormalities. However, the increasing volume of samples and the need for precision make automated analysis crucial. Automation ensures consistent and efficient evaluation, reducing the potential for human error and enabling faster turnaround times. Implementing automated tools, especially with the integration of AI, not only enhances diagnostic accuracy but also addresses the growing demand for streamlined and standardized urinary cytology reporting in clinical settings.

In medical diagnostics, AI emerges as a transformative force, promising heightened precision and efficiency [10]. Within urinary cytology, its applications, notably in image analysis and pattern recognition, offer enhanced capabilities for accurate diagnosis. Recent studies showcase the integration of AI tools with the TPS, underscoring their collaborative potential to refine diagnostic accuracy [11]. This synergy between AI and TPS represents a significant stride towards advancing urinary cytology as a more effective and reliable diagnostic tool.

AI advancements in urinary cytology

In this study, a systematic literature review was performed by searching PubMed until January 8, 2024, utilizing the query ("Urine"[Mesh]) AND (("Artificial Intelligence"[Mesh]) OR ("Diagnosis, Computer-Assisted"[Mesh])). While the study protocol was not registered, deviating from the PRISMA guidelines, it was a deliberate choice as the systematic review served as a supportive tool rather than the primary focus. The aim was to offer insights into the current landscape of artificial intelligence applications in automated urine cytology analysis, providing

a comprehensive understanding of the state of the field as of the specified date.

The inclusion criteria for the literature review were meticulously defined: eligible papers had to focus on urine cytology testing for potential urothelial diagnosis, employ artificial intelligence or image processing for automated image analysis, involve human materials, be published in English, and have a publication date of 2014 or later. Conversely, exclusion criteria were clearly outlined, excluding papers on urine testing for non-oncological purposes, those not assessing image analysis method performance, studies where the model only described cellular features without offering a provisional diagnosis, and those based on animal studies. This stringent criteria framework ensured a focused and relevant selection of literature aligning with the study's objectives.

The search process in PubMed initially yielded 81 titles, which were subjected to title screening, resulting in the selection of 12 abstracts for further evaluation (fig. 1). After thorough abstract screening, 7 articles were chosen for full-text reading. To ensure a comprehensive review, 4 additional references were manually added. In total, 11 articles underwent full-text examination. Following a meticulous review, 8 articles were deemed relevant and included in the comprehensive analysis, ensuring the synthesis of the most pertinent information for the study's objectives (tab. I).

The studies included in the review exhibited diverse aims and employed varied study designs. Dataset sizes ranged widely, from 49 to 2405 cytology slides, with some studies adopting the conventional division into subsets for model development, validation, and testing. Notably, the imaging methods used varied, with one study utilizing digital still camera images and others employing whole-slide images obtained through digital pathology scanners. Despite these differences, a consistent benchmark for evaluating model performance across the majority of the studies was maintained; the comparison to previous assessments conducted by experienced cytopathologists served as the universally recognized golden standard in all instances.

Among the eight studies included, three specifically focused on AI-assisted methods for the detection of high-grade urothelial carcinoma cells or atypical cells. The predominant trend observed in most of the published research involved the utilization of deep learning models to automate predicted diagnoses. Notably, only one of the studies employed classical image processing methods, indicating a prevalent reliance on advanced deep learning approaches for the development and implementation of AI in automated urine cytology analysis.

The evaluation of model performance in the study encompassed various metrics, with most studies reporting the area under the curve (AUC). The AUC is a metric used in binary classification models, representing the ability of the model to distinguish between positive and negative instances. It ranges from 0 to 1, with a higher AUC indicating better discriminatory

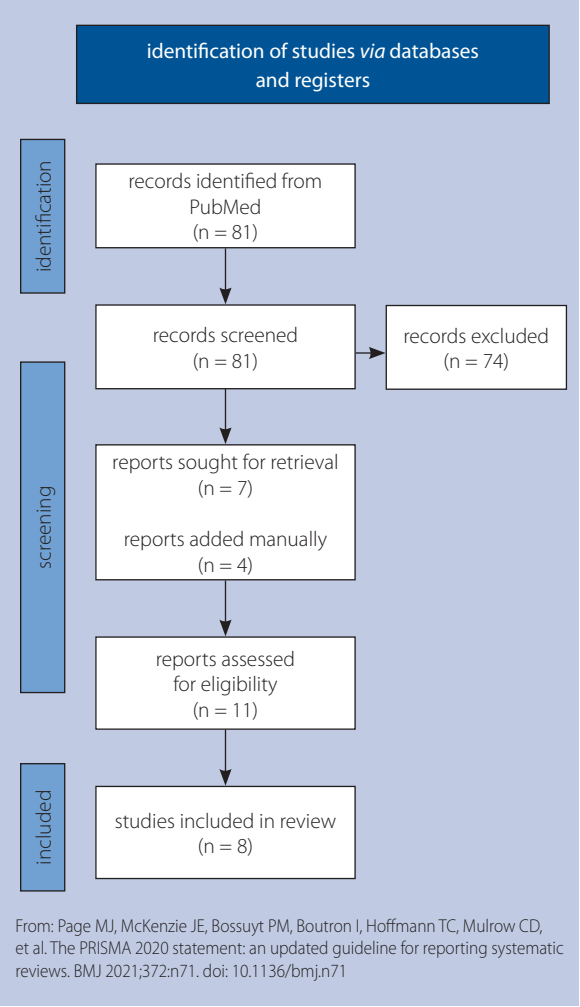

Figure 1. PRISMA 2020 flow diagram

power. In the presented studies, the AUC values of the developed models ranged from 0.78 to 0.99, suggesting a high level of accuracy. Additionally, specificity, indicating the model's ability to correctly identify negative instances, varied between 83% and 85%, while sensitivity, reflecting the model's capability to identify positive instances, ranged from 63% to 97%. These metrics collectively provided a comprehensive assessment of the models' discriminatory performance and diagnostic accuracy in automated urine cytology analysis.

While AI advancements in urinary cytology exhibit promise, the heterogeneity in study methodologies and dataset sizes raises concerns about generalizability. The reliance on deep learning without classical image processing warrants scrutiny, as the field may benefit from a more balanced exploration of diverse methodologies. Additionally, the high AUC values suggest robust discriminatory power, yet skepticism lingers over potential overfitting to specific datasets. Despite these reservations, the transformative potential of AI in urothelial carcinoma diagnostics is evident, but careful consideration and validation are crucial in ensuring the reliability and applicability of these models in diverse clinical scenarios.

Table I. Overview of AI-/image-processing-assisted diagnostic approaches in urinary cytology: a comparative analysis of image analysis methods and model performance

Reference	Year	Country	Cytology / cytoblock	Automation of diagnosis	Image analysis method	Size of dataset	Golden standard	Time required for analysis	Performance of the model (best model if multiple models)
Gelwan E. et al. [12]	2019	USA	cytology slides scanned (whole-slide images)	AI-assisted	image processing (SurePath and BCCS software)	53 slides	–	–	–
Lebret T. et al. [13]	2022	France	cytology slides scanned (whole-slide images)	automated	machine learning (VisioCyt software)	1,360 slides: 598 training 762 validation	cytology result by pathologist	–	sensitivity – 85% specificity – 81%
Lilli L. et al. [14]	2021	Italy	cytology slides images made using digital still camera	automated	deep learning	60 slides (690 images performed, and data augmentation procedure conducted to multiply the dataset): 2,616 training 872 validation 872 testing	–	–	–
Nojima S. et al. [15]	2021	Japan	cytology slides scanned (whole-slide images)	automated	deep learning	232 slides (divided into 61,512 images): 64% training 16% validation 20% testing	cytology result by pathologist	–	AUC – 0.99 F1 score – 0.90 sensitivity AI – 91% specificity AI – 97% accuracy AI – 95% precision AI – 90%
Ou Y.C. et al. [16]	2022	Taiwan	cytology slides scanned (whole-slide images)	AI-assisted	deep learning	150 slides: 7 training 12 validation 131 testing	–	–	–
Sanghvi A.B. et al. [17]	2019	USA	cytology slides scanned (whole-slide images)	automated	deep learning	2,405 cytology slides: 1615 training 790 validation	cytology result by pathologist	–	AUC – 0.88 sensitivity – 80% specificity – 85%
Tsuji K. et al. [11]	2023	Japan	cytology slides scanned (whole-slide images)	AI-assisted	deep learning	535 slides: 181 development 39 testing cell level 315 testing slide level 117 histological slides from the same patients	cytology result by pathologist + comparison with subsequent histopathology results	139 s	AUC – 0.78 accuracy – 86% prediction of HGUC in histopathology based on cytology analysis: sensitivity: model – 63% pathologist – 46% p = 0.0037 specificity: AI – 83% pathologist – 89% p = 0.13

Table I cont. Overview of AI-/image-processing-assisted diagnostic approaches in urinary cytology: a comparative analysis of image analysis methods and model performance

Reference	Year	Country	Cytology / cytoblock	Automation of diagnosis	Image analysis method	Size of dataset	Golden standard	Time required for analysis	Performance of the model (best model if multiple models)
									accuracy: AI – 74% pathologist – 68% p = 0.08
Zhang Z. et al. [18]	2020	China	cytology slides scanned (whole-slide images)	automated	deep learning	49 slides: 37 training 12 testing	cytology result by pathologist	–	–

Challenges, considerations, and future directions

The integration of AI tools in urinary cytology reporting brings forth potential challenges. One significant hurdle is the need for robust datasets that encompass the diverse spectrum of urinary cytology specimens. Limited datasets may hinder the AI's ability to accurately identify nuanced patterns or rare abnormalities. Additionally, the interpretability of AI-generated results poses a challenge, as understanding the underlying decision-making process of complex algorithms is crucial to gain trust in their clinical application. Ensuring the seamless integration of AI into existing laboratory workflows and addressing issues related to standardization and validation are key challenges that must be overcome to realize the full potential of AI in urinary cytology reporting.

Successful implementation of AI tools in urinary cytology reporting hinges on collaborative efforts between pathologists, clinicians, and AI developers. Establishing a strong synergy among these stakeholders is essential for tailoring AI algorithms to meet the specific needs of urinary cytology diagnostics. Collaborative endeavors foster a mutual understanding of the clinical context and intricacies of pathology, enabling AI developers to design algorithms that align with the nuanced decision-making processes of pathologists. Continuous communication and feedback loops ensure that AI tools are refined based on real-world clinical experiences, optimizing their performance over time. This collaborative approach not only accelerates the development and validation of AI algorithms but also enhances their acceptance and integration into routine clinical practice, ultimately improving diagnostic accuracy and patient outcomes.

Conclusions

In summary, the critical review underscores the transformative impact of the TPS in addressing historical challenges and providing a standardized framework. TPS enhances diagnostic precision, reduces subjectivity, and improves communication between pathologists and clinicians [19]. The integration of AI introduces exciting prospects, but the prevailing reliance on advanced algorithms raises concerns about potential overfitting and limited exploration of alternative methodologies. The collaboration between TPS and AI shows promise, but a cautious approach is essential to ensure the reliability and applicability of these advancements across diverse clinical scenarios.

Article information and declarations

Author contributions

Irmina M. Michałek – conceptualization, literature analysis, writing – original draft, writing – review and editing.
Monika Durzyńska – writing – review and editing.
Florentino L. Caetano dos Santos – literature analysis, writing – review and editing.

Conflict of interest

None declared

Irmina M. Michałek
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Pathology
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: irmina.michalek@nio.gov.pl

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High CA 19.9 concentration as a diagnostic dilemma in gastrointestinal cancer survivors

Aleksandra Grela-Wojewoda[1], Mirosława Puskulluoglu[1], Joanna Anioł[2], Marek Ziobro[1]

[1]*Department of Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland*
[2]*Department of Radiology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland*

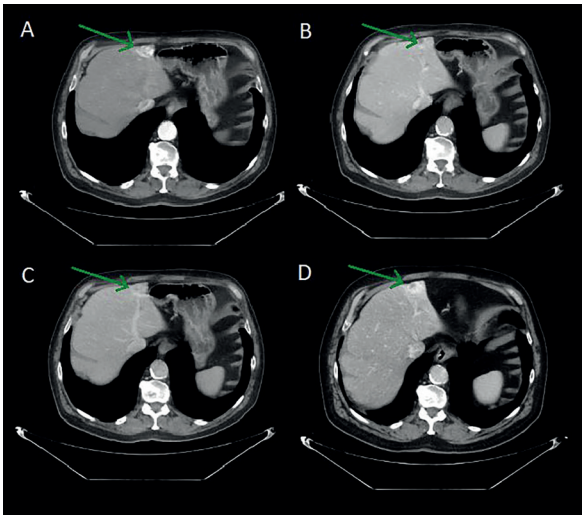

Figure 1. Abdominal contrast-enhanced computed tomography. In the liver, beneath the frontal capsule, there is an oval lesion that enhances after the administration of contrast medium intravenously. This enhancement is observed in the arterial phase (**A**), followed by a "wash out" in the portal (**B**) and venous phases (**C**). The lesion should be differentiated between a metastatic or primary liver tumor and an atypical hemangioma. A follow-up abdominal computed tomography (**D**) performed after 22 months revealed an oval lesion of the same size and enhancement pattern

In March 2021, an elevated concentration of CA 19.9 (1177.95 U/ml) was detected in a 71-year-old patient during a routine check-up. The remaining biochemical parameters, including the CEA marker, and the blood count, were within normal limits. The patient remained asymptomatic. In the previous year (January 2020), the patient underwent a right-sided hemicolectomy as a curative treatment for partially mucinous G2 adenocarcinoma (pT4bN0R0LV0). Based on an elevated concentration of CA 19.9, suspicion was raised regarding primary biliary carcinoma or dissemination of CRC. An abdominal and pelvic computed tomography (CT) in May 2021 revealed a hepatic lesion, necessitating differentiation between cholangiocarcinoma and atypical hemangioma (fig. 1 A–C). After 22 months, a follow-up CT did not confirm the presence of malignancy and stable CT picture (fig. 1 D). Concurrently, CA 19.9 concentrations, initially elevated in multiple measurements, exhibited a decrease, returning to normal levels by June 2021. At present, the patient remains asymptomatic, with imaging and biochemical test results within the normal range. This clinical case shows that a CA 19.9 marker concentration test is not intended for screening purposes, but is useful for monitoring the treatment and follow-up of patients with gastrointestinal malignancies who demonstrated elevated levels prior to initiating therapy. In addition, a high concentration of Ca 19.9 is not a pathognomonic symptom of gastrointestinal cancers. Numerous non-neoplastic conditions may manifest with elevated levels of CA 19.9 [1, 2].

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Combined immunotherapy for renal-cell carcinoma (RCC) in geriatric patients

Artur Drobniak[1], Łukasz Stokłosa[1, 2, 3], Renata Pacholczak-Madej[1, 4, 5]

[1]Department of Chemotherapy, The District Hospital, Sucha Beskidzka, Poland
[2]Department of Chemotherapy, The Specialistic Hospital, Nowy Targ, Poland
[3]Department of the Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland
[4]Department of Gynecological Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland
[5]Department of Anatomy, Jagiellonian University, Medical College, Krakow, Poland

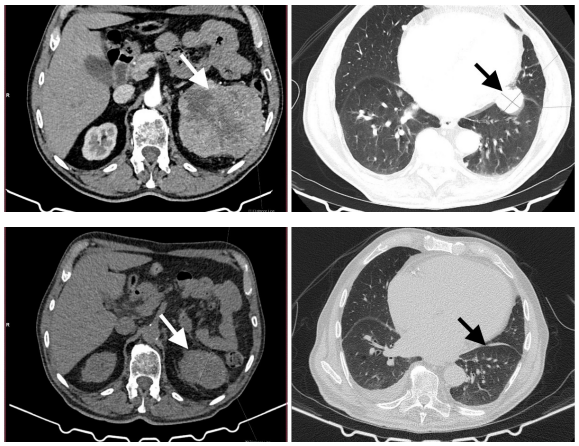

Figure 1 . A baseline CT revealed a 96-mm-sized primary tumor in the left kidney and a metastatic tumor in the left lung (**A**, **B**). The best overall response with reduction in diameter in both target lesions (**C**, **D**)

Combined immunotherapy with nivolumab and ipilimumab has become the standard first-line therapy for intermediate and poor--risk patients with RCC specifically those with clear cell (ccRCC) and sarcomatous components. However, in a pivotal CheckMate 214 trial [1], the median age was 62, and patients 65 years did not benefit. An octogenarian patient with ccRCC presented to our Unit. A CT confirmed the disease stage as cT3aN1M1 (fig. 1 A, B). The patient was unsuitable for nephrectomy due to biological age and advancement of the disease. According to the prognostic criteria of the IMDC [2], the patient fell into the intermediate-risk group (time from diagnosis to treatment <1 year and KS <80%). He was qualified for combined immunotherapy, adhering to the criteria of the National Drug Program (NDP). The initial treatment cycles were well-tolerated, with no significant treatment-related adverse events (trAEs). The CT scan performed after 4 cycles of nivolumab (3 mg/kg every 3 weeks) and ipilimumab (1 mg/kg every 3 weeks), revealed PR per the iRECIST criteria. Subsequently, the patient experienced general malaise (G1 CTCAE), kidney injury (G2), and hepatotoxicity (G2), which did not preclude the continuation of maintenance monotherapy with nivolumab (480 mg every 4 weeks per protocol). These trAEs were successfully managed with treatment interruption. In summary, the patient received 11 cycles (4 in combination and 6 in monotherapy) with stable disease per iRECIST in the last CT scan (fig. 1 C, D). This case highlights that chronological age alone should not be a direct contraindication for combined immunotherapy, as it may offer improved outcomes with manageable trAEs also in the elderly population.

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