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Original article

Cancer genetics

Retrospective analysis of the treatment of *BRCA1* and *BRCA2* mutation carriers – the experience of a single-center tertiary institution

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Introduction. Breast cancer gene 1 and 2 (*BRCA1/2*) mutation carriers are at a higher risk of developing breast cancer. There are several established risk-reducing therapies. Our study aimed to characterize the *BRCA1/2* mutation carriers, and to evaluate the implemented treatment methods.

Material and methods. A retrospective analysis of clinical records of 96 female patients hospitalized from October 2019 to December 2022 in the Breast Cancer Unit in Lodz, Poland.

Results. Out of 85 *BRCA1* and 11 *BRCA2* mutation carriers, 96.88% received nipple-sparing or skin-sparing, unilateral or bilateral risk-reducing mastectomies. Out of all the patients, 36 developed 38 breast cancers. One patient was diagnosed with breast cancer 2 years after a bilateral risk-reducing mastectomy. The most common breast cancer subtype was triple-negative breast cancer (73.68%). The patients could receive surgery, chemotherapy, endocrine therapy and radiotherapy. 18 patients had neoadjuvant chemotherapy, in 6 of these patients a complete pathological response (ypT0N0) was achieved.

Conclusions. Oncoplastic bilateral risk-reducing mastectomies are effective and safe procedures.

Key words: breast cancer gene 1/2, breast cancer, risk-reducing mastectomy, hereditary breast cancer, breast cancer unit

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in the world. It accounted for 24.5% of new oncological cases and 15.5% of cancer-associated deaths in the female population worldwide in 2020 [1]. Several conditions increase the risk of developing BC, they can be divided into modifiable and unmodifiable risk factors. One of the most important genetic factors associated with familial susceptibility is a mutation in the genes: breast cancer gene 1 (*BRCA1*) or breast cancer gene 2 (*BRCA2*) [2, 3]. Women that carry mutations have a lifetime risk of breast cancer development up to 87% for *BRCA1*, and up to 69% for *BRCA2* [4–6].

Early detection of mutations in the above genes enables patients to reduce the incidence of breast malignancies by risk-reducing therapies like risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO), or early detection by means of regular MRI and mammography screening, or chemoprevention with tamoxifen [7–10].

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The aim of our study was to characterize and describe the population of female *BRCA1* or *BRCA2* mutation carriers admitted to the Breast Cancer Unit in Lodz, Poland, and to evaluate treatment methods for breast cancer and susceptibility due to *BRCA1/2* mutations.

Material and methods

The Medical University of Lodz Ethics Committee stated that this study is not a medical experiment and does not require the opinion of the Bioethical Commission (RNN/29/23/KE; 14 February 2023). We retrospectively identified 96 female patients who tested positive for a mutation in the *BRCA1* or *BRCA2* genes. We included women hospitalized from October 2019 to December 2022 in the Breast Cancer Unit, Lodz, Poland. The clinical and histopathological data were obtained from the hospital records. Statistical analysis was performed using Microsoft Excel.

Results

Out of the included patients, 85 (88.54%) were *BRCA1* mutation carriers, and 11 (11.46%) were *BRCA2* mutation carriers. 93 (96.88%) of the patients underwent a risk-reducing mastectomy (n = 82 in *BRCA1*, n = 11 in *BRCA2*). Three women did not receive risk-reducing procedures and at the time of data collection, they were treated due to breast cancer. The median age on the day of the RRM procedure was 40 (25–65) in the *BRCA1* group and 42 (33–48) in the *BRCA2* group. The patients in our study underwent bilateral (mutation carriers) or unilateral risk-reducing procedures (mutation carriers who developed breast cancer in one breast). All these women received oncoplastic and reconstructive techniques – NSM (nipple-sparing mastectomy) or SSM (skin-sparing mastectomy) or SRM (skin-reducing mastectomy). The characteristics of patients in view of the above procedures are shown in table I.

36 (37.5%) women developed 38 breast cancers. 34 patients developed one cancer in one breast (left n = 13, right n = 21), one patient had two independent, non-simultaneous cancers in the left breast and one woman developed bilateral breast cancer. In one patient, a 9 mm cancer of the breast was incidentally found in the left breast specimen after risk-reducing mastectomy, not visualized on preoperative breast MRI. One patient developed breast cancer 2 years after a bilateral risk-reducing mastectomy performed in another institution.

In the group of *BRCA1* mutation carriers (fig. 1), 52 (61.18%) did not develop breast cancer, 31 (36.47%) developed one cancer in one breast, one (1.18%) developed 2 cancers in one breast (left breast), and one (1.18%) developed bilateral breast cancer. In the *BRCA2* group, 8 (72.73%) patients did not develop breast cancer, 3 (27.27%) developed breast cancer in one breast (all cancers in the right breast).

The most common molecular subtype of breast cancer in the described group of patients was triple negative; it accounted for 28 (73.68%) cases. Other subtypes included: luminal A (n = 5) and luminal B (HER2-negative) (n = 5). The only histopathological subtype was no special type (NST) (38; 100%). We found grade 3 (G3) in 26 cases (68.42%), G2 in 9, G1 in 1 and GX in 2 tumors. We stated Ki-67 expression ≤20–29% as low and >30% as high. High Ki-67 expression was found in 28 cancers, and in 10 tumor samples it was identified as low. A description of the histological and molecular features of the cancers is shown in table II.

Table I. Risk-reducing mastectomies (RRM) in the described groups of mutation carriers

Procedure	Mutation	
	BRCA1 (n = 82)	*BRCA2* (n = 11)
left RRM	14	3
right RRM	12	0
bilateral RRM	56	8

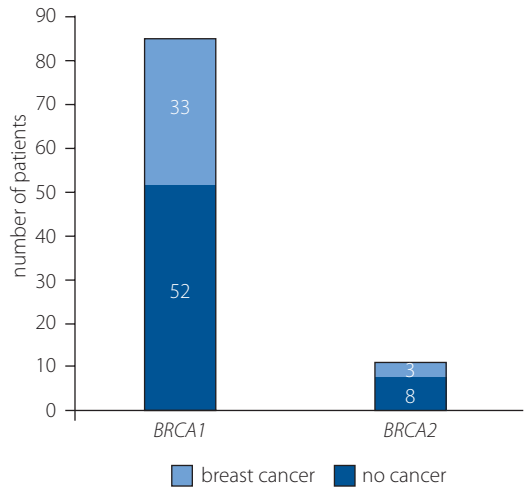

Figure 1. Patients who tested positive for the *BRCA1* or *BRCA2* mutation

Among the patients, tumor sizes T1 (n = 15) and T2 (n = 15) were predominant. Most commonly, in 16 patients, there was no axillary lymph node involvement (N0). Only one woman (*BRCA1*+) developed bone metastases (stage IV), this patient received a mastectomy with delayed breast reconstruction, and postoperative radiotherapy + hormone therapy. The staging of tumors in the characterized group can be seen in table III.

Patients who developed breast cancer could undergo surgery, chemotherapy (neoadjuvant and adjuvant), adjuvant endocrine therapy and postoperative radiotherapy. In relation to surgical cancer treatment, patients received such techniques (n = 37):

- nipple-sparing mastectomy with immediate prepectoral breast reconstruction (n = 13),
- skin-sparing mastectomy with immediate prepectoral breast reconstruction (n = 6),

Table II. Histopathological characteristics of the tumors

Histopathological subtype	Mutation	
	BRCA1 (n = 35)	*BRCA2* (n = 3)
no special type (NST)	35	3
grading		
GX	2	0
G1	0	1
G2	9	0
G3	24	2
Ki-67 expression		
low (≤20–29%)	8	2
high (>30%)	27	1
molecular subtype		
triple-negative (basal-like)	27	1
luminal A	3	2
luminal B (HER2–)	5	0

Table III. Breast cancer staging in the described patients

TNM classification	Mutation	
	BRCA1 (n = 34)	*BRCA2* (n = 3)
primary tumor (T)		
yT0	5	1
T1	14	1
T2	15	0
T3	0	1
regional lymph nodes (N)		
yN0	10	1
N0	15	1
N1	9	1
distant metastases (M)		
M0	33	3
M1	1	0

- breast-conserving therapy (n = 6),
- mastectomy with delayed reconstruction (n = 8),
- mastectomy (n = 4).

Breast-conserving therapy (BCT) was offered to patients who met the criteria to receive this treatment and they were not stated as *BRCA1/2* mutation carriers at the time of breast cancer diagnosis. Because of a strong family history of breast cancer, after the surgery, women consulted with geneticists, and all

Table IV. Treatment (other than surgical excision) received by the patients

Treatment	Mutation	
	BRCA1 (n = 33)	*BRCA2* (n = 3)
HT	4	0
RTH + HT	1	2
preop CHT	10	1
preop CHT + RTH	5	0
preop CHT + RTH + HT	1	0
preop CHT + CHT + RTH	1	0
CHT	8	0
CHT + RTH	2	0
CHT + RTH + HT	1	0

preop CHT – preoperative chemotherapy; CHT – adjuvant chemotherapy; RTH – radiotherapy; HT – hormone therapy

of these patients were proven to carry mutations. 26 patients underwent a sentinel lymph node biopsy, the rest received an axillary lymph node dissection. 18 patients had neoadjuvant chemotherapy, in 6 of these patients (33.33%) a complete pathological response (ypT0N0) was achieved. The description of treatment methods is shown in table IV.

Discussion

With over 2.2 million newly diagnosed cases and over 680,000 deaths recorded in 2020, female breast cancer is considered the most common cancer and the fifth cause of cancer mortality worldwide [1]. Breast cancer may manifest as sporadic (90–95% of all BCs) or hereditary (5–10%) disease [5, 11, 12]. Cases of multiple breast and/or ovarian cancer incidents in families and individuals, those diagnosed at a young age, and male breast cancers may suggest hereditary syndromes [3]. Studies have shown that mutations in several genes can be associated with familial susceptibility to breast cancer development. Commonly mentioned genes include *BRCA1/BRCA2*, *TP53*, *PALB2*, *PTEN*, *CHEK2*, and *ATM* [6, 11–13].

The *BRCA1* (17q21) and *BRCA2* (13q12-q13) genes are tumor suppressors whose main functions are the maintenance of genomic stability and negative regulation of tumor growth. Mutation-carrying individuals, whose gene functions are lost or reduced, are at higher risk of developing breast and ovarian cancer [5, 6, 14]. What is more, abnormal functions of the *BRCA2* gene lead to increased susceptibility to cancers of organs such as the pancreas and prostate [11, 12].

Concerning BC, individuals with a mutation in the *BRCA1* gene most commonly develop TNBC (triple negative breast cancer), where there is no expression of estrogen-receptors, progesterone-receptors, and no overexpression of HER2/*neu* [11, 12]. In our study, the triple-negative subtype was also

the most common molecular type in the *BRCA1* group (n = 27; 77.14%). Due to the lack of drug targets, chemotherapy plays a crucial role in the treatment of TNBC [15]. In the context of the histologic grade of tumors, *BRCA1+* breast cancers are rather considered to be poorly differentiated (G3) [12]. In the described group of patients, out of 35 *BRCA1+* tumors, 24 (68.57%) were stated as high-grade (G3) cancers.

Surgical oncologists' approach to breast cancer surgery and risk-reducing procedures has been transformed from radical mastectomy to conservative mastectomy with immediate reconstruction. Present oncoplastic surgery focuses on providing oncologically safe procedures with possibly the best aesthetic outcomes. Techniques such as NSM, concentrated on preserving the NAC (nipple-areolar complex), and SSM, where NAC is excised with glandular tissue (but may be reconstructed in a subsequent procedure), are considered to achieve the above-mentioned goals [16, 17]. As was reported, the patients involved in our study received various types of surgical operations for breast cancer, including NSM, SSM, BCT, and radical mastectomy with or without delayed reconstruction. Novel surgical techniques, NSM and SSM with immediate prepectoral breast reconstruction, were provided in 19 cases of breast cancer. 8 women received delayed reconstruction after mastectomy.

As regards the risk-reducing mastectomy, studies have proven that it offers >90% breast cancer risk reduction [18, 19]. Several research papers, regarding the effects of RRM, described such positive outcomes as a gain in life expectancy, decreased all-cause and breast cancer-specific mortality rates, and decreased breast cancer incidence rate, compared to surveillance [8, 20, 21]. In the study of Heemskerk-Gerritsen et al., BRRM (bilateral risk-reducing mastectomy), compared with surveillance (mammography + clinical-and self-examination), was proven to have higher ten-year breast cancer-free survival (100% *vs.* 74%) and higher ten-year overall survival (99% *vs.* 96%) [8]. Besides, the proactive surgical approach can ensure psychological well-being by mitigating cancer-related anxiety [19]. Like any other surgical procedure, oncoplastic risk-reducing mastectomies with immediate reconstruction entail the risk of complications. These include nipple-areola or mastectomy skin flap necrosis, wound infection, breast asymmetry, BIA-ALCL (breast implant-associated anaplastic large cell lymphoma), and unsatisfying aesthetic results [17, 22, 23]. There is also a chance after RRM that a patient might have to undergo revisional surgery [19]. Even after the NSM procedure there still remains a low risk of cancer development, due to the possibility of remaining a portion of glandular tissue in the NAC. In our analyzed group, we documented a case of a woman who was treated for breast cancer that developed after bilateral RRM. In contraposition to our evaluation, in the study of Jakub et al., after 548 risk-reducing NSMs in 346 *BRCA1/2* mutation carriers, there was no case of primary breast cancer on both sides after the bilateral procedure, or ipsilateral side after the unilateral risk-reducing procedure [24]. Surgeons' doubts about glandular breast tissue that can be left in the NAC after NSM and the associated risk of cancer were partly resolved. Baltzer et al., in a study of 105 female patients, found that NAC represents a tiny fraction (1.3%) of the entire breast tissue. With an extremely small chance of breast cancer development, this study supports the safety of the described procedure [25].

Women carrying *BRCA1/2* mutations, who were diagnosed with a primary cancer of one of the breasts, are still vulnerable to the next malignancy incidence. They have a higher risk of contralateral breast cancer compared to the general population [22, 26].

In the study of Kuchenbaecker et al., the cumulative risk for ovarian cancer development in *BRCA1* and *BRCA2* patients was estimated at 44% (95% confidence interval [CI], 36–53%) and 17% (95% CI, 11–25%) respectively [4]. There is scientific evidence that risk-reducing salpingo-oophorectomy is effective in decreasing ovarian cancer incidence and mortality [27]. In regard to breast cancer, besides RRM, the mutation carriers may also opt for RRSO. In patients without previous breast cancer diagnosis, it was shown that risk-reducing salpingo-oophorectomy can reduce all-cause mortality, breast cancer-specific mortality, ovarian cancer-specific mortality, and risk of breast cancer development [9].

For the good of women, it seems important to spread public awareness of hereditary syndromes related to breast and ovarian cancer, and ways to handle them. Evans, D Gareth et al., showed increased genetic consultations uptake in the United Kingdom after the famous decision of the actress Angelina Jolie who, in May 2013, chose to undergo BRRM because of being a *BRCA1* mutation carrier [28].

It is believed that the best quality of care for breast cancer patients can be accessible in breast cancer units (BCU). These centers, organized in one location, provide highly qualified specialists and services that focus particularly on breast cancer detection and its treatment. Units consist of a multidisciplinary team involving geneticists, radiologists, pathologists, surgeons, oncologists, radiation oncologists and psychologists [29, 30].

There are limitations to our study. A relatively small number of mutation carriers were involved in the analysis. There is a need for further research in the field of *BRCA*-mutation carriers treatment and its associated outcomes.

Conclusions

The *BRCA1* and *BRCA2* mutations are related to a higher risk of breast cancer development, especially triple-negative subtypes. Knowledge of being a mutation carrier enables the patients to take steps to minimize the risk of malignancy occurrence. A bilateral risk-reducing mastectomy, performed with oncoplastic techniques, remains an effective oncological procedure for women who test positive for *BRCA1* or *BRCA2* mutations. Due to the possibility of finding malignant tissue not visualized on preoperative imaging

scans, a proper histological examination of post-RRM specimens is essential.

Surgical oncologists must clearly inform the patients about various risk-reducing approaches and potential post-surgical complications, changes in body image and self-perception after the surgery.

Article information and declarations

Data availability statement

The data presented in this study are available on request from the corresponding author.

Ethics statement

The Medical University of Lodz Ethics Committee stated that this study is not a medical experiment and does not require the opinion of the Bioethical Commission (RNN/29/23/KE; 14 February 2023).

Author contributions

Grzegorz Stępień – writing, original draft preparation, data collection.

Thomas Wow – supervision, review.

Agnieszka Kołacińska-Wow – data collection, supervision, conceptualization, review.

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Conflict of interest

None declared

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Original article

Cancer epidemiology

Socioeconomic factors and suicide risk in Polish cancer patients – a population-based cohort study exploring associations and implications

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Introduction. This study aimed to explore socioeconomic factors influencing the suicide rate in Polish cancer patients.
Material and methods. Data on cancer cases and socioeconomic covariates were obtained from the Polish National Cancer Registry and Statistics Poland. Suicide rates were calculated for each year. Multivariable linear regression analyses explored associations between unemployment, income, university education, access to physicians overall and to psychiatry hospitals, and suicide incidence.
Results. The study included 1.43 million cancer patients diagnosed between 2009 and 2019. Among them, 830 suicides were identified, with higher rates among men. Income *per capita* and higher education degrees were significant predictors of suicide among male cancer patients ($p = 0.05$ and 0.01, respectively). However, no significant associations were found for female cancer patients. The regression models explained 13% of the variation in male suicide incidence.
Conclusions. Lower income and higher education levels increase suicide risk in male cancer patients, highlighting the need for targeted interventions.

Key words: cancer, suicide, risk, epidemiology, cohort study

Introduction

Extensive evidence suggests that various socioeconomic factors significantly influence suicide rates in the general population. Protective factors such as marriage, parenting, and religiousness play a role in preventing suicides, although their impact varies by gender. Economic factors, including unemployment and low socioeconomic status, strongly predict suicide risk at an individual level [1].

A study examining gender-specific suicide rates across 35 countries found that higher suicide rates among both males and females were associated with increased female labor force participation, unemployment, and a larger proportion of elderly individuals. However, increased health spending *per capita* was linked to lower suicide rates for both genders. The study highlighted the influence of labor market and economic factors on suicide rates, surpassing the significance

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of population-level indicators of interpersonal relationships. Additionally, males exhibited greater sensitivity to changes in the social environment compared to females [2, 3].

Furthermore, evidence indicates that environmental factors can impact suicide rates among cancer patients. A study utilizing the American Surveillance, Epidemiology, and End Results Program (SEER) database investigated sociological risk factors for suicide death in leukemia patients and revealed a significantly higher death rate in areas with a high proportion of individuals holding at least a bachelor's degree [4].

However, there remains a gap in our knowledge regarding the socioeconomic factors associated with suicide incidence among cancer patients in the Polish population. Thus, this study aims to fill this gap and provide insights into the specific factors influencing suicide risk in this population.

Material and methods

Data source for cancer patient suicides

The data for this study were derived from the Polish Suicidality in Cancer Patients study (PolSCa), which is a cohort study previously described in the literature [5, 6]. Information on cancer cases was obtained from the Polish National Cancer Registry (PLCR), a non-profit national institution responsible for statistical and epidemiological cancer research in Poland. The PLCR encompasses all newly diagnosed cancer cases in the country and requires mandatory reporting. Rigorous validation processes, including verification by trained PLCR coders and adherence to recommendations from the European Network of Cancer Registries, ensure data accuracy. The unique Polish personal identification number (PESEL) is utilized within the PLCR system to prevent duplicate coding for the same patient. Detailed information regarding the operational principles of the PLCR can be found elsewhere [7].

The study population comprised individuals aged 15 years or older diagnosed with primary malignant neoplasms, excluding non-melanoma skin cancers (ICD-10 codes: C00–C43, C45–C76, C80–C96). In cases where patients had multiple independent coexisting neoplasms, only the most recent diagnosis was considered. All eligible cases diagnosed between January 1, 2009, and December 31, 2019, were included in the study. The follow-up period extended until the occurrence of suicide (ICD-10 codes: X60–X84), death from other causes, or December 31, 2019, whichever came first.

Data source for covariates

Based on existing literature [2, 3], several variables were identified as potential covariates influencing the suicide rate among patients diagnosed with cancer. These covariates included the unemployment rate, income *per capita*, the proportion of individuals holding at least a bachelor's degree (referred to as the higher education degree rate), overall access to physicians (referred to as the physician access index), and access to psychiatric services (referred to as the psychiatry access index). Data for all these variables were obtained from Statistics Poland, spanning the years 2009 to 2019 and encompassing 16 of the highest level administrative regions (voivodships).

The unemployment rate was defined as the registered unemployment rate, representing the ratio of registered unemployed individuals to the active civilian population. This rate includes individuals employed in individual farming households, considered as part of the active civilian workforce.

Income *per capita* was defined as the average monthly gross remuneration, including income tax advances and mandatory social security contributions (pension, disability, and sickness) paid by the insured employee. The data pertained to entities within the national economy with a workforce of 10 or more individuals, as well as budgetary entities regardless of the workforce size.

The higher education degree rate was defined as the number of university graduates with at least a bachelor's degree per 10,000 population. The physician access index was defined as the number of physicians working at their primary workplace per 10,000 population. The psychiatry access index was defined as the number of psychiatric hospital beds per 10,000 population.

Statistical analysis

Initially, we calculated the suicide rate per 1,000 previously diagnosed cancer patients. The numerator consisted of the number of suicides that occurred within a given year among patients previously diagnosed with cancer. The denominator included the mid-year population of cancer patients, representing the number of individuals living with a malignant tumor diagnosis on June 30th of the respective year. We calculated this rate for each calendar year, stratified by patient gender and region (voivodship).

To explore the association between suicide incidence (dependent variable) in patients with cancer and several independent variables (unemployment rate, income *per capita*, higher education degree rate, the physician access index, and psychiatry access index), separate multivariable linear regression analyses were conducted for males and females.

To examine the correlation between the physician access index and psychiatry access index, we calculated the correlation coefficient, which measures the strength and direction of the linear relationship between the two variables. The resulting correlation coefficient was 0.30, indicating a positive but weak correlation. Considering the comprehensive evaluation of healthcare resource impact on suicide incidence among patients with cancer, we decided to include both variables in the analysis.

The regression model was constructed using the formula "suicide incidence ~ unemployment rate + income *per capita* + education degree rate + physician access index + psychiatry access index". The model was summarized by presenting coefficient estimates, standard errors, t-values, and associated

p-values for each independent variable. All statistical analyses were conducted using R software (version 2023.06.0+421).

Compliance with ethical standards

The utilization of individual-level data from the Polish National Cancer Registry (PLCR) for statistical and scientific purposes complies with Polish legislation. The PLCR adheres to stringent regulations to ensure the confidentiality and protection of individuals. This study was conducted in accordance with the guidelines provided by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [8].

Results

Study population characteristics

The study encompassed a total of 1.43 million individuals (717,144 man and 709,517 women) who were diagnosed with cancer between January 1, 2009, and December 31, 2019. Over the course of the follow-up period, a total of 830 suicide cases were identified among the patients diagnosed with primary cancer, with 683 cases occurring in men and 147 cases in women. Throughout the study period spanning from 2009 to 2019, the incidence rate of suicide per 1,000 patients with cancer ranged from 0.0 to 2.9, depending on voivodship, gender, and year.

Socioeconomic factors and risk of suicide in patients with cancer

A multiple linear regression analysis was performed to investigate the association between socioeconomic factors and suicide incidence among cancer patients in the Polish population (tab. I).

Among male cancer patients, the regression analysis revealed that income *per capita* ($p = 0.05$) and the rate of higher education degrees ($p = 0.01$) were statistically significant predictors of suicide incidence (tab. I). The results indicated that a decrease in income and an increase in educational attainment were associated with a higher incidence of suicide. Additionally, the psychiatry access index ($p = 0.03$) demonstrated a statistically significant positive association with suicide incidence among male cancer patients. However, the unemployment rate ($p = 0.44$) and the physician access index ($p = 0.34$) did not exhibit statistically significant associations with suicide incidence among male cancer patients. The multiple R-squared value for the model was 0.13, suggesting that approximately 13% of the variability in suicide incidence among male cancer patients was explained by the included independent variables. The adjusted R-squared value, accounting for predictors and degrees of freedom, was 0.10. The F-statistic (4.516) with a p-value of <0.01 indicated that the overall regression model was statistically significant, demonstrating a significant combined effect of the independent variables on suicide incidence among male cancer patients.

In contrast, none of the independent variables reached statistical significance in predicting suicide incidence among female cancer patients (tab. I). The estimates for unemployment rate ($p = 0.60$), income *per capita* ($p = 0.08$), educational attainment ($p = 0.15$), psychiatry access index ($p = 0.80$), and physician access index ($p = 0.13$) did not show statistically significant associations with suicide incidence among female cancer patients.

The multiple R-squared value for the model was 0.06, and the adjusted R-squared value was 0.03. The F-statistic (1.958) with a p-value of 0.09 indicated that the overall regression model did not reach statistical significance, suggesting that the combined effect of the independent variables did not significantly impact suicide incidence among female cancer patients in the Polish population.

Discussion

Added value of the study in the context of the literature

The literature on population-based studies examining the association between socioeconomic factors and the risk of suicide in cancer patients is limited. To date, only two relevant studies have been conducted, both in the United States, and focused on factors such as urbanization, financial status, and university education [4, 9]. However, there is a lack of research exploring the impact of access to healthcare resources on suicide risk in the oncological patient population. To the best of our knowledge, our study is

Table I. Linear regression results for suicide incidence among male and female cancer patients

Variable	Men †				Women ‡			
	estimate	std. error	t-value	p-value	estimate	std. error	t-value	p-value
(intercept)	0.47	0.30	1.55	0.12	0.11	0.11	1.02	0.31
unemployment rate	–0.01	0.01	–0.77	0.44	–0.00	0.00	–0.53	0.60
income *per capita*	–0.00	0.00	–2.02	0.05	–0.00	0.00	–1.79	0.08
the higher education degree rate	0.00	0.00	2.60	0.01	0.00	0.00	1.46	0.15
the physician access index	0.01	0.01	0.96	0.34	0.00	0.00	1.51	0.13
the psychiatry access index	0.08	0.03	2.22	0.03	–0.00	0.01	–0.25	0.80

† – multiple R-squared: 0.13, adjusted R-squared: 0.10, F-statistic: 4.52, p-value: <0.01; ‡ – multiple R-squared: 0.06, adjusted R-squared: 0.03, F-statistic: 1.96, p-value: 0.09; intercept – a mathematical constant, no clinical interpretation

the first to comprehensively analyze the influence of healthcare resource access, including physicians and psychiatry services, on the risk of suicide among cancer patients.

This study adds to the growing body of evidence on the association between socioeconomic factors and suicide incidence in cancer patients. By specifically examining variables such as income *per capita* and the higher education degree rate, the study identifies these factors as significant predictors of suicide incidence among male cancer patients. These findings align with a study conducted in the United States, which also highlights the importance of addressing economic disparities and educational attainment in understanding suicide risk among individuals with cancer [9].

Moreover, this study explores the impact of healthcare resource access on suicide risk in cancer patients. The inclusion of the physician access index and psychiatry access index provides insights into the relationship between the availability of medical professionals and suicide incidence. The finding of a positive association between the number of psychiatric beds and suicide incidence among male cancer patients may initially seem counterintuitive. Several potential explanations can shed light on this result. Reverse causality suggests that areas with higher suicide rates allocate more resources, including psychiatric beds, to address increased mental health needs. Improved accessibility and identification may lead to higher detection rates in areas with more psychiatric beds. The complexity of cases or regional differences in mental health infrastructure, policies, or cultural factors could also play a role. The multifactorial nature of suicide and potential confounding variables should be considered.

Furthermore, this study adds value by considering gender-specific differences in the associations between socioeconomic factors and suicide incidence. While the study identifies significant predictors of suicide among male cancer patients, none of the independent variables reached statistical significance for female cancer patients. This finding highlights the need for further investigation into gender-specific factors and the complex interplay between socioeconomic variables and suicide risk in female cancer patients.

Overall, this study's added value lies in its comprehensive examination of socioeconomic factors and healthcare resource access as potential determinants of suicide incidence in cancer patients. By identifying significant predictors and exploring gender differences, the study contributes to a deeper understanding of the complex relationships between these factors and suicide risk, which can inform targeted interventions and support strategies to mitigate suicide risk in this vulnerable population.

Implications for the field of the study

The findings of this study have important implications for the field of suicide prevention and cancer care. The identification of socioeconomic factors associated with suicide risk in cancer patients provides valuable insights for targeted interventions and support programs. Specifically, the significant associations observed between income *per capita* and higher education degree rate with suicide incidence among male cancer patients highlight the importance of addressing economic disparities and promoting educational opportunities to mitigate suicide risk. These findings emphasize the importance of implementing comprehensive and tailored strategies to address the multifaceted challenges faced by cancer patients at risk of suicide, ultimately improving their overall well-being and quality of life.

Strengths and limitations of the study

The present study has several strengths. First, the data were derived from the PolSCa, a cohort study with a comprehensive design that provides a reliable and representative sample of cancer patients in Poland. The use of the PLCR data ensured the inclusion of all newly diagnosed cancer cases in the country, while strict validation processes guaranteed data accuracy. Furthermore, the study considered a wide range of potential covariates, including socioeconomic factors and access to healthcare resources, to explore their association with suicide incidence among cancer patients.

However, certain limitations must be acknowledged. Firstly, although the study covered a substantial period from 2009 to 2019, the follow-up period was limited, and longer-term outcomes could not be assessed. Moreover, the study focused on the Polish population, which may limit the generalizability of the findings to other populations or settings. Lastly, while multiple socioeconomic factors were considered, the inclusion of additional variables, such as social support or mental health status, could have provided a more comprehensive understanding of the factors influencing suicide incidence among cancer patients.

Conclusions

In this study examining the association between socioeconomic factors and suicide incidence among cancer patients in the Polish population, several key findings emerged. Among male cancer patients, income *per capita* and a higher education degree rate were significant predictors of suicide incidence, indicating that lower income and higher university-level education rate were associated with an increased risk of suicide. However, the unemployment rate and the physician access index did not show significant associations. In contrast, none of the independent variables reached statistical significance in predicting suicide incidence among female cancer patients. These findings emphasize the need for targeted interventions and support for at-risk subgroups in cancer patients to mitigate the risk of suicide.

Article information and declarations

Data availability

We complied with all relevant ethical regulations. The data analyzed in this study were obtained from the PLCR and are

available upon reasonable request by contacting the PLCR at krn@nio.gov.pl and subject to ethical approvals in place and material transfer agreements. Following national regulations, these data were exempt from institutional review board reviews. There were no participants in the study; thus, there was no consent form. Detailed legislative aspects of the National Polish Cancer Registry are regulated by Polish Law (Dz.U. 2018 poz. 1197). Waiver of ethics approval was deemed unnecessary according to national legislation (reference to the relevant legislation https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20180001197).

Ethics statement

The utilization of individual-level data from the Polish National Cancer Registry (PLCR) for statistical and scientific purposes complies with Polish legislation. The PLCR adheres to stringent regulations to ensure the confidentiality and protection of individuals. This study was conducted in accordance with the guidelines provided by Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Author contributions

All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Irmina M. Michalek – study concept and design, acquisition, analysis, and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding.

Florentino L. Caetano dos Santos – acquisition, analysis, and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding

Urszula Wojciechowska – acquisition, analysis, and interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding

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Conflict of interest

None declared

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Review article

Cardiooncology

Pharmacological prevention methods in patients with cardiovascular disease with breast cancer – when, how, and for whom?

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Breast cancer is the leading cause of cancer-related deaths in women worldwide. Patients with breast cancer are at an increased risk of cardiovascular toxicity, presently defined as cancer therapy-related cardiovascular toxicity (CTR-CVT). This article provides a summary of the current knowledge on pharmacological cardiovascular prevention in breast cancer patients. The European Society of Cardiology (ESC) guidelines on cardio-oncology have defined CTR-CVT. Baseline risk stratification with widely accepted risk scores is essential to identify patients at higher risk of CTR-CVT. The guidelines recommend the use of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and β-blockers as preventive medications in high-risk patients. Clinical trials have shown ambiguous results for ACE-I/ARBs and β-blockers in reducing cardiotoxicity, while co-administration of ACE-I/ARBs and β-blockers did not show additional benefits in preventing cardiac dysfunction. Further research is needed to verify the efficacy of novel cardioprotective medication and optimize pharmacological strategies for cardiovascular prevention in breast cancer patients.

Key words: cardio-toxicity, cardiovascular prevention

Introduction

Breast cancer is the most diagnosed cancer and the leading cause of deaths due to cancer among women worldwide. In the United States, it is the second most common cancer among female patients and is the second leading cause of cancer deaths with incidence being relatively stable over the past two decades [1, 2]. As well as in the US, in Europe breast cancer is the most common cancer among female patients, with an estimated 522,000 new cases and 137,000 deaths in 2020 [3, 4]. It should be noted that both in Europe and the USA, the mortality rates of breast cancer have been declining likely due to advances in its successful detection and introduction of more efficacious therapeutic protocols.

Nonetheless, breast cancer patients are often at an increased risk of developing cardiovascular disease, due to a wide variety of factors, including baseline disease, cancer treatment strategies, as well as lifestyle changes associated with cancer [5, 6]. In the recent years, attempts have been made to stratify the risk of development of cardiovascular disease, especially a rather acutely developing cardiac dysfunction, labelled as "cancer therapy-related cardiovascular toxicity (CTR-CVT)" [7]. In patients at risk of CTR-CVT development, the introduction

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of preventive methods prior to cancer treatment might reduce the risk of the development of such conditions. Among those, pharmacological strategies can play a critical role in reducing this risk of cardio-toxicity, with a possible influence on a patient's quality of life, the efficacy of cancer treatment, and long-term outcomes. The aim of the manuscript is to briefly summarize the current knowledge on pharmacological cardiovascular prevention in patients with breast cancer.

Definition and clinical significance of cancer treatment-related cardiovascular toxicity

The definition of cardiotoxicity, or as it should be named at present, CTR-CVT, has been established in the recent European Society of Cardiology (ESC) guidelines on cardio-oncology [7]. The guidelines have divided the broad spectrum of CTR-CVT on the basis of the pathomechanism and clinical manifestation, including the development of heart failure (HF), myocarditis, toxicity to the vascular structures, or the presence of hypertension, or rhythm disorders. Most notable is the definition of cancer therapy-related cardiac dysfunction (CTRCD), which encompasses the wide spectrum of myocardial damage associated with anticancer therapy. The definition of CTRCD according to the ESC guidelines is presented in table I. It should be noted that the definition allows to diagnose CTRCD solely on the basis of echocardiography, even in the absence of any clinical signs or symptoms of HF, although the guidelines recommend other imaging modalities, including magnetic resonance imaging in certain clinical situations [8]. The other important definitions, including the specific criteria for diagnosing myocarditis, defining vascular complications and arterial hypertension or arrhythmias were also thoroughly defined in the guidelines. The unification of those definitions is crucial, since it will allow to more cautiously monitor their real prevalence, as in the past the frequencies reported in the literature could have varied significantly due to differences in diagnostic criteria for each condition [9].

Similar to patients with other types of cancer, patients with breast cancer who receive treatment are at risk of developing CTRCD, which can lead to serious complications and may significantly impact the quality of life. The most prevalent types of cardiovascular adverse effects are presented in table II. Moreover, cardiac failure can interfere with assumed cancer treatment protocol, and result in a necessity to either reduce the dosing or the frequency of administered therapies, thus affecting the effectiveness of the cancer treatment, and affecting outcomes [10–12]. Finally, it has been demonstrated that the development

Table I. Definitions of cancer therapy-related cardiac dysfunction (CTRCD) on the basis of the 2022 ESC guidelines on cardio-oncology [7]

Cardiac dysfunction		Recommendations
symptomatic	very severe	HF requiring support with inotropic drugs, mechanical circulatory support or consideration of heart transplantation
	severe	HF requiring hospitalization
	moderate	need for intensification of diuretic therapy or escalation of HF treatment in the outpatient setting
	mild	mild HF symptoms without necessity to modify the therapy
asymptomatic	severe	new reduction in LVEF to <40%
	moderate	new reduction in LVEF by ≥10% to LVEF of 40–49% or new reduction in LVEF of <10% to LVEF of 40–49% and new relative decrease in GLS of ≥15% or new increase in cardiac biomarkers[a]
	mild	LVEF of ≥50% and new relative decrease in GLS of >15% from baseline and/or new increase in cardiac biomarkers

LVEF – left ventricle ejection fraction; GLS – global longitudinal strain; BNP – B-type natriuretic peptide; HF – heart failure; NT-proBNP – N-terminal pro-B-type natriuretic peptide; [a] – cTnI/cTnT ≥ 99th percentile; BNP ≥ 35 pg/ml; NT-proBNP ≥ 125 pg/ml or a new significant increase from baseline beyond the biological and analytical variability of the test used

Table II. The most common adverse cardiovascular events associated with anti-cancer drugs

Anti-cancer drug group	Cardiovascular adverse events reported most frequently
anthracyclines	heart failure, arrhythmias, pericarditis
HER2-targeted therapies	heart failure, arrhythmias, hypertension
tyrosine kinase inhibitors	QT interval prolongation, hypertension, arrhythmias
aromatase Inhibitors	low risk of cardiotoxicity, potentially: dyslipidemia, atherosclerosis progression, arrhythmias

of CTRCD is associated with an increased long-term risk of HF in patients who experienced CTRCD [13, 14].

The years of experience with treatment of patients with cancer have demonstrated how to – at the present stage of knowledge – stratify patients according to their baseline risk for development of CTRCD. As a rule of thumb, an early identification of patients at higher risk of medical procedures has been widely proven to improve prognosis and is therefore recommended. Similarly, the ESC guidelines on cardio-oncology specify that it's best to define the baseline risk right at the time of cancer diagnosis, even before initiation and planning of treatment. Although there is no single, established pathway on how to optimally screen and then risk-stratify patients according to their baseline CV risk, the parameters which according to the ESC should be taken into consideration before initiation of anti-cancer treatment are listed in table III, while the detailed guidelines on cardiovascular prevention in patients with cancer are presented in table IV.

After thorough assessment of patients' baseline cardiovascular risk, the physicians should stratify the patient's therapeutic toxicity risk. In recent years, multiple risk scores for identification of CV toxicity were analyzed, although the detailed risk score, would be recommended to remain as it is. Heart Failure Association–International Cardio-Oncology Society (HFA-ICOS) provides the most comprehensive data and thus has been included in the recent ESC guidelines as the preferred one, with a class IIa recommendation [15–17]. The HFA-ICOS classification is based on almost every factor assessed at baseline and defines the risk with regards to the strategy of anti-cancer treatment, depending on the possible influence of every individual drug group on every risk factor. For instance, the very high risk of cardiotoxicity in patients with cardiac amyloidosis has been highly documented only for multiple myeloma therapies. With regard to chemotherapy schemes utilized in the treatment of breast cancer, most often anthracyclines and/or anti-HER2 drugs, the risk of CTR-CVT is very high only if the patients have had HF or CTR-CVT in the past, or if the patient scheduled for trastuzumab had received trastuzumab before. With regard to other chemotherapeutic groups used in the treatment of breast cancer, such as VEGF inhibitors, there are plenty of factors associated with a very high risk of CTR-CVT, including any history of HF or even asymptomatic left ventricular contractile dysfunction, as well as a history of any significant atherosclerotic cardiovascular disease. Any other factors of known significance, including the history of MI/PCI, decreased LVEF or advanced age should be noted, and, based on their calculable association with CTR-CVT, the total risk score could be then evaluated and subsequently divided into low-, moderate- or high-risk.

The stratification of CV toxicity risk at baseline is important, because on the basis of the initial assessment, all further surveillance should be performed. Those could include routine follow-up

Table III. Parameters requiring verification at baseline in order to define CV risk prior to cancer treatment initiation according to the 2022 ESC guidelines on cardio-oncology [7]

Parameters requiring verification at baseline in order to define CV risk prior to cancer treatment initiation
CV risk factors (with emphasis on the modifiable risk factors)
CVD history
cancer history
cancer treatment history
physical examination (including vital parameters)
baseline ECG (including QTc analysis)
transthoracic echocardiography (including GLS, and 3D echocardiography if possible)
laboratory parameters: BNP/NT-proBNP, cTn, FPG/HbA1c, creatinine/eGFR, lipid profile

BNP – B-type natriuretic peptide; cTn – cardiac troponin; CV – cardiovascular; CVD – cardiovascular disease; ECG – electrocardiography; eGFR – estimated glomerular filtration rate; FPG – fasting plasma glucose; GLS – global longitudinal strain; HbA1c – glycated hemoglobin; NT-proBNP – N-terminal pro-B-type natriuretic peptide; QTc – corrected QT interval

Table IV. Recommendations on the appropriate primary prevention of cancer therapy-related cardiovascular toxicity according to the 2022 ESC guidelines on cardio-oncology [7]

Recommendations	Class of recommendation, level of evidence
management of CVRF according to the 2021 ESC guidelines on CVD prevention in clinical practice is recommended before, during, and after cancer therapy	I, C
dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
ACE-I or ARB and β-blockers recommended for HF should be considered for primary prevention in high- and very high--risk patients receiving anthracyclines and/or anti-HER2 therapies	IIa, B
ACE-I or ARB and β-blockers recommended for HF should be considered for primary prevention in high- and very high--risk patients receiving targeted cancer therapies that may cause HF	IIa, C
statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk	IIa, B

ACE-I – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CV – cardiovascular; CVD – CV disease; CVRF – CV risk factors; ESC – European Society of Cardiology; HER2 – human epidermal receptor 2; HF – heart failure

visits in the oncology clinic if the patient is at low-risk of CTR-CVT, or a more detailed follow-up if the patient is in the moderate risk group. However, the general rule should be that patients with low- and moderate risk of CTR-CVT should not have the anti-cancer therapy delayed and should initiate treatment at the earliest possible stage. In those categories, a referral to a cardiology clinic or at least to an experienced cardiologist is necessary only if the CTR-CVT develops; an exception being that a treating oncologist might consider referral to the cardiology department regardless of the development of CTR-CVT in patients at moderate risk.

If the patient is considered as high- or very-high risk of CTR--CVT, after a baseline assessment, a referral to a cardio-oncology clinic is mandatory, and cardioprotective medication should be considered at baseline to mitigate that risk during cancer treatment. Moreover, for those patients, the guidelines recommend discussing all the risks and benefits associated with potentially cardiotoxic treatment in a multidisciplinary team to establish the most optimal strategy going forward.

Cardiovascular prevention

In the general population, the present ESC guidelines on cardiovascular prevention specify non-pharmacological, and pharmacological interventions which should be initiated to reduce the cardiovascular risk [18]. However, many of the suggested preventive strategies were deemed ineffective in patients with cancer. Although a straightforward answer to such discrepancy in outcomes is difficult to be presented, it could be speculated that among patients with cancer, it is the baseline disease, and often the presence of various CV risk factors, that in combination increase the baseline CV risk and thus reduce the reckoned efficacy of preventive strategies.

The ESC guidelines on cardio-oncology recommend initiation of "cardio-preventive" medication in patients with high- or very-high risk of CTR-CVT, stratified according to the initial baseline risk assessment. In those patients, an anti-cancer drug with the lowest possible cardiotoxicity risk should be selected. Moreover, the guidelines recommend consideration of administration of specific cardioprotective drugs in those patients. Those, apart from implementation of strategies mitigating the risk of anthracycline-induced cardiotoxicity, including treatment with dexrazoxane or liposomal anthracyclines, refer to the introduction of neurohormonal therapies, including angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs), β-blockers, and preventive treatment with statins [19]. ACE-I/ARBs and β-blockers are the groups of drugs commonly used as a first-line therapy in patients with heart failure, or hypertension, and have been also shown to improve cardiovascular outcomes in patients with cancer [20].

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers

Two large, randomized trials – Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) and Cardiotoxicity Prevention in Breast Cancer Patients Treated With Anthracyclines and/or Trastuzumab (SAFE) investigated the role of primary prevention of CTR-CVT with the use of ACE-I or ARBs specifically in patients with breast cancer. In PRADA, 130 patients with early breast cancer, treated with anthracyclines, underwent randomization to either candesartan (member of ARBs) or metoprolol (a β-blocker). Prevention with candesartan but not with metoprolol was associated with a statistically significantly lower LVEF reduction (candesartan *vs.* non-candesartan: 0.8% *vs.* 2.6%, $p = 0.026$). On the contrary, treatment with metoprolol was associated with smaller increases in levels of cardiac troponins [21]. However, in the long-term analysis, no differences in LVEF were observed in any of the studied groups [22].

In the SAFE trial, which was performed in a 4-arm design, an interim analysis performed after 12 months of follow-up revealed that in patients with no prior cardiovascular disease, cardioprotective therapy with ramipril (an ACE-I) or bisoprolol (a β-blocker), was associated with improved echocardiography outcomes than in patients treated with a placebo [23]. In detail, patients treated preventively with both drugs demonstrated a slight (0.1%) improvement in left ventricular global longitudinal strain (GLS), while GLS was reduced in the placebo arm (by 6.0%) as well as in patients treated with ramipril or bisoprolol monotherapy (respectively by 1.5% and 0.6%, $p < 0.001$). Moreover, the number of patients experiencing a major reduction of LVEF (by ≥10% in the 3D-echocardiography) was lower in the group treated with ramipril and/or bisoprolol, with 6.8%, 11.5%, and 11.4% of patients experiencing such an endpoint when treated with respectively combined therapy, ramipril or bisoprolol monotherapy. In patients administered with placebo, 19% experienced a major LVEF reduction [23].

The molecular rationale for prevention of CTRCD with either ACE-I or ARB is broad, although it is speculated that it is mostly based on preclinical studies in which mice with knockout of angiotensin II type 1a receptor gene, are at a significantly reduced risk of anthracycline-induced cardiotoxicity [24]. Moreover, in the general population, administration of ACE-I or ARBs was associated with improvements on both macroscopic and microscopic levels. Inhibition of RAA resulted in a reduction of myocardial fibrosis, while intracellularly, in an improvement of mitochondrial function, reduction of oxidative stress, and positive alterations in the calcium homeostasis [25, 26], all mechanisms which might explain the benefits associated with ACE-I/ARBs in patients with cancer.

β-blockers

The efficacy of β-adrenolytics in the prevention of CTR-CVT has already been discussed in the two aforementioned trials, which evaluated metoprolol and bisoprolol, two of four β-blockers recommended in the treatment of heart failure in the overall population. The efficacy of the third was evaluated in the Carvedilol for Prevention of Chemotherapy-Related

Cardiotoxicity (CECCY) trial [27]. In this placebo-controlled trial performed on 200 patients with HER2-negative breast cancer, chemotherapy and parallel treatment with carvedilol, a non-cardioselective β-blocker did not reduce the occurrence of cardiotoxicity (defined as the proportion of patients with a ≥10% reduction in LVEF, carvedilol vs placebo: 14.5% *vs.* 13.5%; p = 0.99) and did not influence the LVEF assessed as a continuous variable at 6-month follow-up when compared with the placebo. However, the trial did provide results analogous to those from the PRADA trial, as the use of carvedilol was associated with a lower increase in cardiac troponin I during anthracycline treatment. Thus, it may be speculated that there might be a class-effect of β-blockers in reducing the risk of myocardial injury associated with anthracycline treatment. Among the potential mechanisms of such cardioprotective activity, the anti-oxidative effect exhibited by β-blockers has been proposed, which is demonstrated e.g. in a lower risk of intracellular lipid peroxidation and mitochondrial dysfunction [28].

In general, both ACE-I, ARBs, and β-adrenolytics have constituted the cornerstone of modern treatment of heart failure, as they significantly attenuate the pathophysiological neurohormonal pathways in patients with HF. In patients with a decreased cardiac contractile function, a pathological cascade based on the sustained activation of neurohormonal responses develops. The elements of the cascade include the hyperactivity of the adrenergic system, and activation of the renin-angiotensin-aldosterone pathway. All the aforementioned drug groups act as inhibitors of those pathways, and by stabilizing the cardiac homeostasis they were proved to reduce morbidity and mortality in patients with chronic heart failure [29].

Finally, based solely on the data presented above, it could be speculated that if both preventive strategies (ACE-I/ARB and β-blockers) were proved effective, their co-administration might further increase the efficacy of prevention of CTR-CVT. However, in the previously mentioned PRADA trial, one arm of patients were randomized to a parallel preventive strategy with candesartan and metoprolol, and, in comparison with the monotherapy groups, no significant differences were observed with regard to LVEF reduction. Then, on the other hand, there is the important OVERCOME trial, in which 90 patients with malignant hemopathies treated with intensive chemotherapy were randomized to either preventive administration of enalapril and carvedilol, or matching placebo. During a 6-month follow-up, a significantly lower reduction of LVEF was noted in the arm taking ACEI and β-blockers than the placebo (a statistically significant difference of 3.1% in echocardiography and a difference of 3.4% on the verge of significance in magnetic resonance imaging), with a lower risk of combined clinical endpoint demonstrated in the intervention arm [30]. Thus, it appears that by recommending a simultaneous introduction of preventive ACE-I/ARB and β-blockers in patients with high or very high risk of CTR-CVT, the ESC guidelines on cardio-oncology, at least partially follow the newly introduced strategy of an early introduction of all four major "game-changing" drugs for treatment of chronic HF advocated in the ESC guidelines on HF. Nonetheless, at present, the evidence supporting preventive co-administration of ACE-I/ARB + β-blocker is rather scarce.

Statins

Statins are cholesterol-lowering drugs that in patients with high or very high cardiovascular risk have been shown to reduce the risk of myocardial infarction, stroke, and mortality [31]. Research has shown that patients with breast cancer treated with statins might have a lower risk of cardiovascular events compared to those who do not receive this treatment. Moreover, some retrospective data report that a chronic treatment with statins might even increase the LVEF [32]. The postulated molecular mechanisms included pleiotropic effects of statins, including their anti-inflammatory, anti-apoptotic, and even anti-proliferative effect on the tumor cells [33, 34]. Moreover, as cholesterol is a biochemical precursor molecule for estrogens, the modifications to the lipid metabolism equilibrium caused by statins might in result indirectly modulate the response to estrogens at a cellular level [35].

However, data on the efficacy of statins in prevention of CTR-CVT are based mostly on retrospective, observational studies. A recently published PREVENT trial, which included patients with early breast cancer or lymphoma, did not confirm the cardioprotective effect of statins, as the mean (±SD) LVEF values were 61.7 ± 5.5% before treatment and 57.4 ± 6.8% at 24 months in the placebo group and 62.6 ± 6.4% before treatment and 57.7 ± 5.6% at 24 months in patients treated with 40 mg of one of the most potent statins – atorvastatin [36]. Moreover, no difference in the percentages of patients with a major (defined as by ≥10%) reduction of LVEF, or changes in LV strain, LV mass, cognitive function, or levels of inflammation biomarkers were noted between patients treated with atorvastatin and placebo. The results of the Statins to Prevent the Cardiotoxicity From Anthracyclines (STOP-CA) and Statins for the Primary Prevention of Heart Failure in Patients Receiving Anthracyclines Pilot Study (SPARE-HF) are eagerly anticipated in either confirming, or repudiating the cardioprotective effect of statins in patients with cancer [37, 38].

Spironolactone, flozins, ARNI

The ESC guidelines on cardio-oncology do not specifically address the subject of the introduction of preventive treatment with other groups which are at present considered the golden standard in patients with chronic HF. It should be noted that all of them might potentially be beneficial in preventing CTR-CVT in patients with breast cancer who are beginning oncological treatment. Spironolactone, the mineralocorticoid receptor antagonist (MRA), has been proven to reduce morbidity and mortality in patients with HF [39–41]. Its major mechanism

of action lies in the inhibition of aldosterone receptors. In patients with HF, when the activity of the RAA axis is pathologically increased, and subsequently so is the concentration of aldosterone, the end-product of this axis, the hyperactivity of aldosterone increases the myocardial fibrosis developing in response to the myocardial injury. Thus, there might be a pathophysiological rationale for preventive treatment with MRA in patients treated with potentially cardio-toxic drugs.

However, the evidence supporting MRA in such a setting is rather scarce, as to date there has only been one randomized trial, which included only 83 patients with breast cancer treated with either doxorubicin or epirubicin. Those were randomized to preventive therapy with 25 mg daily of spironolactone or placebo. After the completion of a follow-up of approximately 24 weeks, preventive therapy with spironolactone resulted in a lower reduction of LVEF assessed echocardiographically (LVEF decrease from 67.0 ± 6.1 to 65.7 ± 7.4 in the spironolactone group, and from 67.7 ± 6.3 to 53.6 ± 6.8 in the control group between-group $p < 0.001$) [42]. Moreover, similar to the findings from the studies with β-adrenolytic drugs, the trial showed that spironolactone resulted in an attenuated increase in cardiac troponin I elevation, and while in the control group, levels of all serum biomarkers were altered by chemotherapy, no significant difference in any of the measured parameters (including NT-proBNP, troponin, creatinine kinase – myocardial) was observed in patients taking spironolactone. Finally, the authors point a remark that the left ventricular diastolic function was maintained in patients from the spironolactone group, while a progression of diastolic dysfunction was observed in the group administered with a placebo, which further confirms that the mechanism of action of spironolactone might lay in reduced fibrosis caused by excessive aldosterone levels.

The results of the CECCY, PRADA, SAFE, and aforementioned spironolactone trial clearly indicate the possible benefit of RAA axis inhibitors on cardiac contractile function. Moreover, in the preclinical studies it was demonstrated that apart from the RAA axis, an increased activation of natriuretic peptide cellular pathways decreases the risk of anthracycline-induced cardiomyopathy. Another rather novel drug in the treatment of HF is sacubitril-valsartan. Its mechanism of action lays on the inhibition of the RAA axis, owing to the activity of valsartan – an ARB – and activation of the natriuretic peptide pathway mediated by sacubitril – an inhibitor of neprylisin, an enzyme responsible for the degradation of many important molecules, including natriuretic peptides. Thus, the use of a cardioprotective strategy with sacubitril-valsartan in patients treated with potentially cardiotoxic drugs has a strong pathophysiological rationale.

The data on the administration of sacubitril/valsartan in patients with cardiac damage caused by cancer therapy come mostly from retrospective analyses. A Spanish registry investigated 67 patients (of whom 45% were patients with breast cancer) with symptomatic HF caused by cancer therapy, in whom sacubitril/valsartan was introduced. In those subjects, significant increases in LVEF and reductions in NT-proBNP levels, and left ventricular dimensions were noted, followed by a clinically meaningful improvement in patients' HF symptoms [43]. In another single-center analysis, echocardiographically determined cardiotoxicity developed in 28 of 635 patients, most of whom were treated with anthracyclines, and approximately a quarter with anti-HER2 therapy. Treatment with sacubitril/valsartan reduced NT-proBNP and increased patients' exertional capacity and left ventricular ejection fraction (32.3 ± 5.5% *vs.* 26.7 ± 5.4%; $p < 0.001$) [44].

At present, there are data from only one randomized trial investigating the use of sacubitril-valsartan in patients with cancer. The study has been performed in Russia and was restricted to 112 subjects with cancer and a preexisting HF who were administered a preventive treatment with nebivolol and eplerenone, and randomized to either sacubitril-valsartan or candesartan. After 6 months, there was a benefit of smaller LVEF reduction and improvement of quality of life with the former [45].

It should be noted that a multi-center, double-blinded trial evaluating the efficacy and safety of sacubitril/valsartan in the prevention of CTR-CVT in patients with cancer will shortly be starting recruitment [46]. The study, which will be performed in three tertiary oncological centers in Poland will randomize a total of 480 patients with early breast cancer undergoing treatment with anthracyclines and/or anti-HER2 drugs to the highest-tolerated dose of sacubitril/valsartan or placebo in 1:1 ratio. The patients will be monitored, including a routine transthoracic echocardiography (TTE) for 24 months, and the primary endpoint of the trial will be the occurrence of a decrease in LVEF by ≥5% in TTE within 24 months. The first results are expected at the beginning of 2028, pending recruitment of participants.

Finally, the last group of drugs recommended in HF are SGLT-2 inhibitors. In the last years, several clinical trials have demonstrated their beneficial effects on heart failure outcomes, with a reduction in the risk of cardiovascular death and hospitalization for heart failure, regardless of the presence of diabetes [47, 48]. The mechanism of action of SGLT2 inhibitors, which involves blocking glucose reabsorption in the SGLT-2 sodium-glucose co-transporters in kidneys, also leads to other effects that are beneficial in HF. By reducing sodium and water reuptake in the kidneys, SGLT-2 inhibitors increase diuresis and thus decrease blood volume, which can improve cardiac contractility. Additionally, SGLT-2 inhibitors have been shown to improve endothelial function, reduce oxidative stress, and improve myocardial cellular metabolic pathways [49]. To date, no randomized study investigated the efficacy of SGLT-2 inhibitors in the prevention of CTR-CVT, and the sole evidence for their potential benefit is derived from a recent retrospective analysis, which included diabetic patients with cancer treated with SGLT-2 inhibitors; they

Table V. Recommendations for baseline risk assessment and monitoring during endocrine therapy for patients with breast cancer, according to the 2022 ESC guidelines on cardio-oncology [7]

Recommendations	Class of recommendation, level of evidence
baseline CV risk assessment and estimation of 10-year fatal and non-fatal CVD risk with SCORE2 or SCORE2-OP is recommended in BC patients receiving endocrine therapies without pre-existing CVD	I, C
dexrazoxane should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B
liposomal anthracyclines should be considered in adult patients with cancer at high and very high CV toxicity risk when anthracycline chemotherapy is indicated	IIa, B

BC – breast cancer; CV – cardiovascular; CVD – cardiovascular disease; ECG – electrocardiogram; SCORE2 – systematic coronary risk estimation 2; SCORE2-OP – systematic coronary risk estimation 2 – older persons

were compared in a 1:3 ratio to control subjects not being administered SGLT-2 inhibitors. When compared to the control group, patients pretreated with SGLT-2 inhibitors were at a significantly reduced risk of a composite endpoint of cardiac events, including the incidence of HF, admissions due to HF, the development of new cardiomyopathy, or clinically significant arrhythmias (3% *vs.* 20%; $p = 0.025$) [50]. Moreover, the risk of all-cause death was significantly lower (9% *vs.* 43%; $p < 0.001$), albeit such a strong effect on mortality is hardly attributable solely to the action of SGLT-2 inhibitors. Nonetheless, a randomized trial evaluating the efficacy of one of the SGLT-2 inhibitors, empagliflozin (Empagliflozin in the Prevention of Cardiotoxicity in Cancer Patients Undergoing Chemotherapy Based on Anthracyclines – EMPACT) will soon start recruitment in Polish centers, and the first results are expected in 2028 [51].

Non-pharmacological preventive measures

In addition to medication, lifestyle modifications such as exercise, a healthy diet, and smoking cessation are essential for reducing cardiovascular disease risk in breast cancer patients. Prior studies have shown that due to various factors, patients after diagnosis of cancer tend to reduce physical activity and gain weight by an average of 2.7 kg [52, 53]. Physical activity has been shown to reduce the intracellular oxidative stress, and improve exertional capacity in patients with breast cancer. This might suggest a rationale for improvement in prognosis and reduction of the risk of development of CTR-CVT [54, 55]. However, to date, no clear guidelines defining the optimal exertion thresholds for groups at risk of cardiotoxicity were presented. Nonetheless, the guidelines of the American College of Sports Medicine specify the optimal physical exercise type and intensiveness for cancer survivors [56].

Endocrine treatment and its clinical implications

Approximately 65–70% of patients with breast cancer might have a hormone receptor-positive tumor, and in some of those patients therapy with either selective estrogen receptor modulators (SERM) or aromatase inhibitors (AI) might be initiated [57]. Although treatment with SERM or AI does not lead to the development of CTRCD to a degree similar to the one observed in anthracyclines or anti-HER2 treatment, therapy with those two groups of drugs confers an increased risk of dyslipidemia, metabolic syndrome, hypertension, and thus major cardiovascular events such as myocardial infarction [58–60]. Moreover, tamoxifen has consistently been demonstrated to increase the risk of venous thromboembolism (VTE) and therefore therapy based on tamoxifen should not be recommended for patients with an increased risk of thrombotic events [61]. The ESC guidelines on cardio-oncology specify that prior to the introduction of the endocrine therapies in patients with breast cancer, a 10-year risk of fatal and non-fatal cardiovascular events should be assessed, and in those perceived as high risk, such risk should be re-evaluated every year. The detailed recommendations on baseline risk assessment and monitoring during endocrine therapy for breast cancer are listed in table V. The risk scores recommended in the guidelines are either SCORE2 or SCORE2-OP, however other validated risk scores can also be accepted [62, 63]. After risk assessment, it is of the utmost importance to discuss the risks of VTE, and major vascular events with patients at risk, while recognizing that the benefits of breast cancer treatment usually outweigh the cardiovascular risks. However, an emphasis should be placed on the optimal control of CV risk factors, including optimal lipid-lowering therapy, control of blood pressure, with exercise and a healthy diet encouraged.

Article information and declarations

Author contributions

Maciej Dyrbuś – conception and design, analysis and interpretation of data, drafting of the manuscript.
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Review article

Biomarkers

The importance of selected biomarkers in the clinical practice of breast cancer patients

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Breast cancer is considered the most commonly diagnosed tumors. Biomarkers used for the diagnosis and treatment of breast cancer are: tissue biomarkers (PR, ER, HER2, Ki-67) and serum biomarkers (CA-15-3, CA-125, CA-27-29, CEA, cytokeratins). ECD HER2, metalloproteinases and leptin are emerging as promising biomarkers for breast cancer. There is a growing need for personalized diagnostics based on tumour genome characterization, relying on a liquid biopsy containing components such as CTC and ctDNA, cell-free RNA. Biomarkers can also be used use as a target for anti-breast cancer treatment (PGRN and sortilin, AR, PD-1/PD-L1). Another potential field of application of breast cancer biomarkers is monitoring treatment side effects, such us inflammatory biomarkers causing cardiotoxicity, thyroiditis biomarkers (TSH, FT4, TPOab TgAb) in IrAE, NF-L and MCP-1 in ICI-associated neurotoxity. It is expected that new prognostic and predictive biomarkers will be developed that can provide accurate and reliable information for clinical application. Through the recognition of emerging biomarkers, it is possible to identify subgroups of patients who benefit from targeted therapies and managing treatment by monitoring side effects. However, these new biomarkers need to be validated and tested for their suitability before entering clinical use.

Key words: breast cancer, biomarkers, personalized diagnostics, anti-cancer therapy, adverse events

Introduction

According to Global Cancer Statistics 2020, breast cancer is considered the most commonly diagnosed tumor with 2.3 million new cases of breast cancer reported in 2020. It is the fifth leading cause of cancer mortality globally, whereas in women it is the leading cause of cancer death [1]. The highest incidence rates of breast cancer in 2020 were reported in Belgium and the Netherlands with the highest mortality in Barbados and Fiji [2]. In Poland in 2020, the most common cancer in women was breast (23.8%), and it is the second (15%) leading cause of death after lung cancer (18%) [3]. The risk factors for breast cancer are gender, age, genetic factors, ethnicity, early menstruation, late menopause and shorter periods of breastfeeding. The increased incidence rate is associated with lifestyle such as alcohol consumption, obesity, use of hormonal therapy and contraceptives [4].

Treatment of breast cancer depends on its clinical stage, the histological type and its accompanying biomarkers. Nowadays there are many available methods for molecular profiling, hormone indications etc. The general classification of breast cancer is based on the division into sarcomas and carcinomas [5]. Carcinomas are divided into two histopathological types: pre-invasive *in situ* cancer and invasive cancer. Pre-invasive *in situ* carcinomas are further divided into ductal *in situ* carcinomas (DCIS) and lobular *in situ* carcinomas (LCIS).

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Independently from histological subtypes, breast cancers have been classified by molecular examination: luminal A and B subtypes, epidermal growth factor receptor 2 (HER2)-positive breast cancer and triple negative breast cancer (TNBC). The luminal A type of breast cancer is characterized by the presence of an estrogen-receptor (ER) and/or progesterone-receptor (PR), the absence of *HER2* and low expression of genes associated with proliferation (Ki-67). The luminal B subtype includes either HER-positive or HER--negative tumors. Progesterone and estrogen receptors are also found here. In contrast to luminal A, luminal B tumors have higher expression of proliferation-related genes assessed by the Ki-67 designation [6]. Luminal A tumors grow slowly and have a better prognosis, while luminal B tumors are higher grade and have a poorer prognosis. ER is similarly expressed in both A and B subtypes and is used to distinguish luminal from non-luminal disease. Triple-negative breast cancer (TNBC) is a type of breast cancer that lacks the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). It is characterized by an unfavorable prognosis and aggressive biology since patients with TNBC do not benefit from endocrine or anti-HER2 therapy [7].

The presence of proteins or other substances in the serum, body fluids and tissues allow for an early diagnosis of cancer and recurrence of the disease. A biomarker is a substance (nucleic acids, proteins, carbohydrates, lipids) which is either qualitatively or quantitatively abnormally expressed by the tumor tissue or released after cell death by apoptosis, necrosis or destruction by immune cells in biological fluids such as blood serum, urine, saliva or the cerebrospinal fluid. A biomarker can be measured as an indicator of normal biological or pathogenic processes. Some of these biomarkers can be used by physicians to identify the type of cancer and stages of progression, as well as determining a specific treatment and further monitoring response to treatment. However, a lack of specificity is observed for some biomarkers, which is a barrier for their use in cancer screening. As a non-specific tool they complement imaging tests.

Based on their clinical use, two major types of biomarkers can be distinguished: prognostic and predictive. Prognostic markers predict the natural course of a cancer and differentiate good-outcome tumors from poor-outcome tumors. However, no prognostic marker can exactly predict an outcome for a particular patient. It informs about the outcome for a heterogeneous patient population. A predictive marker delivers in advance information on whether the patient is or is not likely to benefit from a particular therapy. The absence of a given marker or a decrease in its concentration during therapy is also of prognostic importance. Therefore, the use of predictive markers enables reducing the overtreatment of patients with benign malignancy and avoiding undertreatment of patients with aggressive tumors [8, 9].

This review covers information about biomarkers currently available for breast cancer management, as well as new promising biomarkers and their potential use in the future.

Biomarkers for the diagnosis and treatment of breast cancer

Biomarkers used in clinical practice are helpful in:

- risk assessment for patients who are unaffected and considering preventive strategies,
- screening for detection of early-stage cancer,
- diagnosis in staging, grading and choice of therapy,
- for prognostic purposes, predicting and monitoring treatment response,
- detecting recurrence after therapy.

Some biomarkers are only used for specific purposes, whereas another can serve in more than one type of application.

Tissue biomarkers

Biomarkers in the biopsy material play an important role in the diagnosis of breast cancer and the choice of treatment.

Determination of various subtypes of breast cancer based on diagnostic evaluation of hormone receptors (ER and PR), HER2 is recommended to be assessed by American Society of Clinical Oncology (ASCO) guidelines due to their prognostic and predictive relevance [10]. These markers are highly specific, and nowadays are routinely used for the diagnostic of breast cancer. Additionally, Ki-67 proliferation index is helpful in differentiating luminal A and luminal B molecular subtypes. The detection of ER, PR, HER2 and Ki-67 affects decisions on the type of undertaken therapy. They are tissue biomarkers, their disadvantage is that an invasive surgical biopsy is required.

At present, the most important predictive biomarker for breast cancer is the estrogen receptor (ER). The measurement of ER is mandatory in all newly diagnosed cases of breast cancer. Its main application is as a predictive marker for endocrine therapy, since ER levels may be correlated with the beneficial effects of antiestrogen therapy. The occurrence of ER helps to identify patients with early breast cancer for adjuvant treatment with drugs such as estrogen receptor modulators (tamoxifen) or aromatase inhibitors (AI), preventing the stimulation of breast cancer proliferation [11]. Two izoforms of estrogen receptor have been identified ER-α, and -β [12]. They have different effects on cancer cells. ER-α stimulates transcription while ER-β inhibits it. The proportions of ER-α and ER-β in the cell determine cell division or inhibition and resistance to hormonal treatment. ER-β is a negative regulator of ER-α [13]. ER-α plays a crucial role in the progression and proliferation of breast cancer. There are some inconsistencies about the role of the ER-β, since there are studies indicating its anticancer and carcinogenic role in breast cancer [14]. The progesterone receptor (PR) is routinely examined together with ER in breast cancer as an important biomarker. PR is involved in molecular

subtyping and plays a substantial role in treatment decisions. It is thought that the absence of PR reflected a nonfunctional ER pathway and was less responsive to tamoxifen [15]. ER+/PR+ breast cancers respond better to hormone therapy than ER+/PR– breast cancers and have a better breast cancer-specific survival rate [16, 17]. The tumors that are ER– and PR+ demonstrate an intermediate response to endocrine therapy [18]. The expression of ER and PR receptors is not permanent and may change spontaneously during the course of the disease or as a result of therapy. The complete loss of ER during endocrine therapy is rare, whereas about half of tumors lose PR completely becoming resistant to therapy. Metastatic tumors have a much more aggressive course after the loss of PR in comparison with tumors with PR expression [19].

Hormonal resistance of breast cancer can be primary or acquired. Primary resistance occurs from the beginning of treatment. It may result from an inappropriate proportion between the level of ER-α and ER-β receptors. This results in the transcription of estrogen-dependent genes and the synthesis of proteins leading to breast progression of tamoxifen resistance. Primary resistance to tamoxifen occurs in breast cancers with high overexpression of the HER2 receptor. Acquired resistance develops as a response to a long-term block or impairment in DNA transcription and protein synthesis responsible for tumor progression. The cancer cell bypasses the tamoxifen-induced blockade and becomes hypersensitive to estrogens and tamoxifen. This causes even small doses of estrogen or tamoxifen to lead to transcription and tumor progression [13].

HER2 is a glycoprotein tyrosine kinase receptor belonging to the EGFR family. HER2 consists of three parts: an intracellular tyrosine kinase domain, a transmembrane lipophilic segment and an extracellular domain (ECD). According to the ASCO testing guideline, breast cancer is considered HER2 positive if the presence of transmembrane HER2 overexpression in the tumor tissue is confirmed by an immunohistochemistry assay or fluorescence in situ hybridization (FISH) [10]. HER2 is overexpressed in approximately 20% of breast cancers and it correlates with a poor clinical prognosis [17, 20, 21]. HER2 is important in choosing the right management in breast cancer patients. An overexpression of HER2 in breast cancer is a strong predictor of benefitting from treatment with trastuzumab (Herceptin) [22]. Trastuzumab is a monoclonal antibody against the extracellular domain of *HER2*, which, when used in adjuvant therapy, significantly extends overall survival in early breast cancer patients [23]. Except for breast cancer, *HER2* overexpression has been recognized in several different solid tumors such as lung, head and neck.

KI-67 is an index providing the information about the proliferation of malignant tumors. High levels of Ki-67 are associated with poorer outcomes. According to St. Gallen's recommendation from 2015, a cut-off point of Ki-67 ≥ 20% could be used to differentiate between low and high values [24]. Ki-67 has been shown to be prognostic of clinical outcomes in breast cancer as well as a predictor of response to neoadjuvant chemotherapy or endocrine treatment. Expression of Ki-67 is often used to identify patients with a high risk of relapse.

Serum biomarkers

Serum biomarkers (so-called "wet biomarkers") are easily accessible at any time and through any blood collection. They are minimally invasive, and therefore can be detected more often than tissue indicators [25]. Biomarkers can quickly provide additional information on patient prognosis and response to treatment. For breast cancer patients' prognosis and response to treatment, serum biomarkers are more convenient and cost-effective compared to mammograms and frequent tissue biopsies.

Among the standard serum tumor markers, CA-15-3 is dedicated to breast cancer. Due to the low diagnostic sensitivity, it is not used in the diagnosis of cancer, but may be important in monitoring treatment. Other recognized serum markers, such as CEA, CA-125 or CA-27-29, may be elevated in metastatic disease.

Increased expression of CA-15-3 in breast tumors is related to invasiveness and metastatic potential [26]. The main utility of CA-15-3 as a biomarker is monitoring therapy in patients with advanced breast cancer, because a relationship between in CA-15-3 levels and the response to chemotherapy has been observed [27]. CA-27-29 is clinically comparable to CA-15-3 due to lack of specificity. Higher serum levels of CA-27-29 may reflect an increased tumor burden [28, 29]. Persistently elevated CA-27-29 levels may indicate treatment failure or the progression of disease [30]. Increased levels of CA-125 have been observed in the majority of metastatic breast cancer patients [31]. The limitations of serum biomarkers such as CA-15-3 and CA-125 are that their temporary elevated levels in serum may occur after starting therapy, due to tumor lysis caused by chemotherapy. High levels of CEA in the blood are usually related to metastasis of breast cancer [32]. A combination of CA-15-3 and CEA is used as a diagnostic tool for relapse of breast cancer [33]. High levels of CA-15-3 together with CEA are associated with worse clinical outcomes since they indicate high tumor burden [34, 35].

In breast cancer, cytokeratins are applicable as serum biomarkers. The complex of cytokeratin fragments 8, 18 and 19 constitute a circulating polypeptide TPA (tissue polypeptide antigen). TPA indicates ongoing cell death and lysis [36]. TPS (tissue polypeptide specific antigen), an antigenic determinant associated with human cytokeratin 18, is released from proliferating cells during tumor development, when intensive multiplication-and disintegration of cells may take place. The rate of concentration increase of TPS is correlated with the rate of progression of the neoplastic process. This increase provides information about the growth of the tumor before the clinical manifestations of the cancer. The level of TPS indicates the proliferative activity of neoplastic tissue regardless

of tumor size, and it is an independent prognostic factor for disease-free survival and overall survival [37, 38].

The use of the biomarkers listed above has some limitations in their use in diagnostic tests for breast cancer. Their main disadvantage is the lack of sensitivity and specificity, which makes them useless for screening purposes. At low stages of cancer, serum biomarkers have low diagnostic sensitivity [39]. The conventional serum biomarker testing is recommended but not mandatory. Their application plays an auxiliary role in the clinical management of breast cancer. Therefore, it is important to continue to search for new factors involved in tumor progression which can help to identify the risk groups, detect the disease at early stages and assess the risk of future relapse.

New biomarkers with a potential application in breast cancer

An example of a promising biomarker in breast cancer can be the extracellular domain (ECD) of *HER2*. The ECD HER2 is released into the blood by means of proteolytic enzymes (shedding). The remaining shortened peptide in the cell membrane is more oncogenic than the full length receptor. The release of the extracellular domain into the serum is increased in metastases compared to primary breast cancer [40]. HER2 is a risk factor of relapse, high-grade malignancy index and metastasis. Some studies suggest that the soluble HER2 ECD is a better prognostic tool than tissue HER2 and its prognostic value is independent of the *HER2* status of the tumor [41, 42].

Metalloproteinases are proteolytic enzymes that digest basement membrane and extracellular matrix (ECM) components, enabling metastasis and angiogenesis in breast cancer [43]. Some studies suggest the potential to use MMP-9 as a predictor of breast cancer progression, since there is a relationship between high MMP-9 expression and the occurrence of distant metastases in breast cancer patients and poor prognosis [44].

Another potential biomarker for breast cancer risk is leptin. Leptin is produced mainly by fat cells and is overexpressed in obese individuals. It is known as the "obesity hormone", the blood level of which increases in proportion to the amount of body fat. In physiological conditions, leptin plays a crucial role in the regulation of energy balance by reducing appetite and increasing metabolism. Leptin has also been shown to promote cell proliferation and the development of breast cancer. Leptin and its receptors regulate progression, angiogenesis, metastasis and immunosuppression. Elevated serum leptin levels are associated with poor cancer prognosis, therefore it may be a potential biomarker of breast cancer risk, especially in overweight women or postmenopausal women [44, 45].

Biomarkers in liquid biopsy

Tumor biopsy is still the gold standard for diagnosis and classification of breast cancer, however, there is a growing need for personalized diagnostics based on tumor genome characterization, relying on blood samples known as liquid biopsy. The liquid biopsy, similar to serum biomarkers, is non-invasive, enables frequent sampling and following patients over time. It can deliver information for understanding tumor characteristics and cell dissemination. Various components of tumor cells are released into the bloodstream: circulating tumor cells (CTC) and circulating DNA (ctDNA), cell-free RNA and exosomes. These elements can be used as potential biomarkers personalizing cancer treatment based on these real-time results.

Circulating tumor cells (CTCs) are malignant cells that following apoptosis, necrosis or active release are shed into the lymphatic or vascular system. CTCs in the bloodstream could be responsible for metastatic progression of breast cancer. The presence of CTCs indicates residual disease, increased risk of metastasis and poorer results for CTC-positive patients. Tracking the presence of ctDNA in serial postoperative serum samples may be used as a predictor of early relapse in ctDNA-positive patients [46]. Some researchers observed that breast cancer patients with levels of CTCs lower than 5 per 7.5 ml had a higher progression-free survival and overall survival in comparison with patients with higher levels of CTCs [47]. The strong correlation between CTCs results and radiographically confirmed progression of metastatic breast cancer indicates that CTCs numeration is useful in assessing the effectiveness of therapy [48]. Although it can be difficult to isolate CTCs from blood due to their short half-life, they have proven to be beneficial as a prognostic tool for cancer patients. CTCs circulating in the bloodstream can also be analyzed for their contents such as protein, DNA, messenger/matrix RNA (mRNA), mitochondrial RNA (miRNA). One of the protein biomarkers contained in CTCs is for example CA-15-3 [49]. CTCs markers often reflect the genetic profile of tumors because they represent a part of the patient's tumor that could be assessed for target antigens. However, some difficulties have been observed in differentiating between primary and metastatic tumors with CTC origin. Researchers found that CTCs represented metastatic tumors rather than primary tumors. There is some evidence that primary ER+/PR+ breast tumors have spread CTCs that are ER–/ PR–, which have a significant importance in decisions regarding the choice of treatment [50]. Additionally, discrepancies between HER2 level of expression in ductal breast tumors and plasma CTCs have been observed, confirming the difference in expression profiling between CTCs and primary tumors [51].

Circulating tumor DNA (ctDNA) is fragmented DNA derived directly from tumor cells or circulating tumor cells (CTC). Cell-free DNA can be detected in free form in sera or plasma [52]. In healthy individuals, ctDNA is present at low levels, whereas higher levels of ctDNA in cancer patients reflect progressive tumor sizes, nodal involvement and metastasis.

Determination of circulating tumor DNA may serve as a marker for the presence of disease and a tool for molecular tumor assessment at different time points in the disease.

It has been proven that analyses of mutations in ctDNA could detect tumors at early stages [53]. CtDNA compared with DNA isolated from primary tumors shows the presence of identical genetic changes that are specific to the tumor type. At present, the diagnosis and selection of breast cancer treatment is based on the analysis of tumor biopsy, but the information from the biopsy is not permanent due to changes in the tumor and its resistance to treatment. Examination of ctDNA overcomes tumor heterogeneity. Some researchers report on ctDNA's platform detecting genomic changes in breast cancer patients, showing its clinical utility for monitoring of disease [54]. In breast cancer, ctDNA enables monitoring the response to treatment and clinical prognosis. In tumors responding to treatment, a sharp decrease in ctDNA levels is observed [55, 56]. The levels of ctDNA are very high in advanced cancer, therefore it is possible to perform a liquid biopsy for molecular testing of ctDNA which may serve as a non-invasive tool for real-time monitoring of disease development [57].

Tumorgenesis is accompanied by high gene expression which leads to synthesis of large amounts of RNA shed from the tumor cells into the blood. The released RNA particles are called cell-free mRNA (cfRNA), and consist of mRNA and miRNA. In cancer patients the amount and composition of miRNA is modified. CfRNA analysis is useful due to its higher concentration in the blood compared to ctDNA in patients at an early stage of cancer. Analysis of cfRNA provides valuable information about tumor gene expression that could be used to monitor treatment and drug resistance of the tumor. For instance, miRNA was used to predict resistance to trastuzumab in HER2+ metastatic breast cancer patients. A several type of miRNA with distinct expression of HER2+ metastatic breast cancer patients with different sensitivities to trastuzumab have been found [58]. The prognostic and predictive value of a real-time PCR assay for cytokeratin-19 (CK-19) mRNA isolated from CTCs has been evaluated. The study suggested that detection of CK-19 mRNA expression may have a clinical impact on overall survival in patients with breast cancer, since they showed poor overall survival [59].

Despite numerous reports on the benefits of liquid biopsy, it has not yet been standardized as a routine diagnostic method in clinical settings of breast cancer. It is expected that the sequencing of the genetic material contained in ctDNA and cfRNA obtained from liquid biopsy will lead to the implementation of this diagnostic tool for routine diagnosis, early detection and follow-up of breast cancer patients.

Biomarkers as a target for anticancer therapy

An important potential application of biomarkers in breast cancer management is their use as a target for anticancer treatment.

Progranulin (PGRN) promotes tumorigenesis as a growth factor since it stimulates the proliferation and survival of several cancer cell types [60]. Progranulin and its receptor sortilin are highly expressed in breast cancer and are associated with various clinical properties. PGRN is considered a poor prognostic factor because it inhibits tamoxifen-induced apoptosis [61]. The expression of progranulin in tumor and serum samples correlates with pathological grading, lymph node metastasis and angiogenesis [62]. Sortilin is linked to breast cancer progression and recurrence in advanced diseases [63]. High co-expression of progranulin and sortilin is associated with decreased breast cancer specific survival [64].

PGRN and sortilin targeting has potentials of application in novel targeted therapy of breast cancer consisting of blocking their tumor-promoting interplay. This offers a unique cancer treatment principle based on selectively targeting the microenvironment of the communication system. In vitro studies indicate that the use of PGRN-neutralizing antibodies and their receptors cause decreased expression of tyrosine-protein kinase and the tyrosine-protein kinase receptor involved in the metastasis of breast cancer [65]. Another in vitro study showed that inhibiting progranulin with the anti-progranulin antibody caused an inhibition of survival and a reduction in migration of TNBC cell lines. The decrease in Ki-67 expression and reduction in the expression of angiogenic proteins VEGF and HIF-1α was also observed [66]. Blocking PGRN with antibody treatment may provide novel-targeted solutions in TNBC treatment resulting in the inhibition of breast cell tumor proliferation. An *in vivo* study proved that sortilin inhibition decreases progranulin-dependent breast cancer progression and the expansion of cancer stem cells [67]. These results suggest that targeting PGRN may be involved in optimizing treatment protocols for breast cancer patients, however further *in vivo* studies regarding serum PGRN should be conducted.

Another emerging potential therapeutic target for breast cancer treatment is the androgen receptor (AR). AR been detected in around 70–90% of breast cancers [68]. AR is considered as a good prognostic factor in ER-α positive breast cancer, since it interferes with the function of ER-α and suppresses tumor growth. However, in the case of ER-α negative breast cancer patients such as HER2+ and TNBC, the AR exhibits oncogenic properties contributing to cancer development. Androgen receptor–targeted therapies have demonstrated promising results in clinical trials in patients with breast cancer. A potential treatment for breast cancer cells is a selective AR modulator such as enobosarm. In vitro studies in the cell line of TMBC indicate that enobosarm inhibits the metastasis promoting factors (IL-6, MPO-13) and therefore blocks migration and invasion. Several AR antagonists have been examined as well. Bicalutamide interrupts the DNA-binding domain binding to the androgen related element. The outcome of the application of bicalutamide has achieved a 19% clinical benefit rate at 6 months and 12 weeks median progression-free survival (PFS) in patients with AR-negative and AR-positive advanced breast cancer. Other biomarkers of response to AR inhibitors should be established in the future [69].

Immune checkpoints play a very important role in the regulation of immune responses involved in cancer elimination. One of them is the programmed cell death-1 receptor (PD-1). PD-1 is expressed in immune effector system cells such as T cells, B cells, natural killer cells and dendritic cells. It is activated by PD-L1, expressed by the majority of human cells. The PD-1/PD-L1 pathway is crucial in maintaining immune tolerance, thus creating a mechanism of immune escape in response to cancer. Cancer cells are capable of activating PD-1 on T cells specific for the cancer antigen by abnormally expressing programmed death-ligand 1 (PD-L1) on their surface. The PD-1/PD-L1 inhibitory pathway is used by solid tumors to silence the immune system [70]. PD-L1 expression is correlated with large tumor size, high grade and high proliferation rate, as well as being inversely related to the survival of breast cancer patients [71]. It has been proven that the blockade of immune checkpoints anti-PD-1/PD-L1 using appropriate monoclonal antibodies triggers effective anticancer responses in many types of solid tumors, such as breast cancers. The inhibitors against PD-1/PD-L1 prevent the suppression of anti-cancer immune responses, allowing the immune system to attack and eliminate tumor cells by modulation T-cell activation and suppressing tumor growth. Immune checkpoint inhibitors (ICIs) are new immunotherapeutic agents that interrupt the interaction between PD-1 and PD-L1.

The application of ICIs against PD-1/PD-L1 is emerging as a new treatment option in breast cancer [72]. The expression of PD-L1 is higher in TNBC than in other molecular subtypes of breast cancer. There are 2 monoclonal antibodies approved by the FDA to treat breast cancer: pembrolizumab and atezolizumab [73]. It was shown *in vivo* that responses to antibody therapy were greater in tumors with high PD-L1 expression. The presence of PD-1 and PD-L1 have been proposed as biomarkers predictive of a response to PD-1/PD-L1 inhibition. The antagonists of the PD-1/PD-L1 pathway induce clinical responses in some patients with metastatic TNBC [74]. However, there are some patients positive for PD-L1 who do not respond to the treatment, while some patients negative for PD-L1 may respond [75]. This makes PD-L1 an imperfect predictive biomarker. Tumor responses with anti-PD-1 and PD-L1 antibodies are mediated by tumor antigen-specific T cells that were previously blocked by the PD-1/PD-L1 pathway.

Awareness of the presence or absence of T cells in breast cancer is crucial in understanding the mechanisms of cancer escape from immune surveillance and for response to anti-PD-1 and PD-L1 antibody therapy. Decisions on the use of anti-PD-1/L1 antibody therapy should be based on the assessment of the presence or absence of T cells specific for the tumor antigen, which are inhibited by PD-L1 expression by tumor cells [76]. Tumor infiltrating lymphocytes (TILs) are an important biomarker in immunotherapy of breast cancer. The presence of tumor-infiltrating lymphocytes (TILs) is a favorable prognostic factor in breast cancer, since they interact with ICI therapy to improve the clinical response. A higher density of TILs has been associated with favorable clinical outcomes in breast cancer: a significantly lower risk of relapse or death, metastasis and overall mortality. To date, the strongest relationship between TILs and treatment outcomes has been demonstrated for the TNBC type of breast cancer [77]. Another study in HER2+ breast cancer patients treated with adjuvant trastuzumab found that increased levels of TILs were correlated with decreased distant recurrence [78].

Biomarkers in adverse events in anti-cancer therapy

Another potential field of application of breast cancer biomarkers is their application in monitoring the side effects of treatment.

The most serious toxic effect of chemotherapy in breast cancer treatment is heart muscle failure, known as so-called "cardiotoxicity". The role of anti-breast cancer drugs such as trastuzumab and anthracyclines in determining cardiotoxicity has been demonstrated in numerous studies [79, 80]. It has been proven that tumor-related inflammation is an important factor in the development and progression of heart failure. Many studies point to biomarkers of inflammation for the risk assessment of breast cancer patients treated for cancer in early detection of cardiotoxicity.

These inflammatory biomarkers are high-sensitivity C-reactive protein (hsCRP), myeloperoxidase (MPO), soluble growth stimulation expressed gene 2 (sST2), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), growth differentiation factor-15 (GDF-15), endothelin-1 (ET-1) and galectin-3. Two of these factors, sST2 and galectin-3, were recommended in the latest ACC/AHA HF (American College of Cardiology and American Heart Association, guideline for management of heart failure) guidelines to be used as useful in risk of heart failure stratification in clinical settings, since they are able to track treatment responses [81]. Additionally, troponins and creatinine kinase have been identified as the serum cardiac biomarkers of choice for assessing myocardial injury. Various studies have evaluated the role of natriuretic peptides (NPs) in the diagnosis and prediction of anticancer drug-induced cardiotoxicity [82].

Immunotherapy has significantly improved the prognosis for many breast cancer patients, but it can also generate a wide range of serious immune-related adverse events (irAEs) which can be serious and even fatal. IrAEs are autoimmune conditions that can affect any organ. The most common are dermatitis, diarrhea/colitis and endocrinopathies such as thyroid disorders. IrAEs appear later and have a longer duration compared to chemotherapy-related adverse events. Since IrAEs can interfere with treatment management, it would be helpful to determine IrAE-related biomarkers.

In monitoring the ICI treatment of breast cancer thyroiditis, biomarker levels are useful. Thyroiditis following ICIs in breast cancer patients should be detected by routine blood tests

of TSH and FT4 and morning cortisol levels for concurrent adrenal insufficiency. Baseline TSH levels were observed to be significantly higher in patients who developed hypothyroidism as the initial thyroid irAE. The association of hypothyroidism with baseline TSH levels may suggest progression of pre-existing Hashimoto's subclinical thyroiditis accelerated by ICI treatment rather than ICI-induced thyroiditis [83]. ICI treatment may be continued if patients with asymptomatic and subclinical hypothyroidism have elevated TSH but normal T4 levels [84]. Moreover, additional testing for thyroid peroxidase antibodies (TPOab) and thyroglobulin antibody (TgAb) is recommended. Some studies show an association between TPOAb and TgAb positivity at baseline and the incidence of thyroid irAE associated with ICI. The presence of TPOAb and TgAb was evident in patients who developed thyroid dysfunction. The titers of these antibodies were higher in patients with overt thyroid irAEs than in patients with or without subclinical thyroid irAEs. These results suggest that pre-existing thyroid autoimmunity may be a strong risk factor for the future development of ICI-associated thyroid toxicity [83].

Neurological adverse events associated with ICI and chemotherapy are of particular interest. One of them is chemotherapy-induced peripheral neuropathy (CIPN). The occurrence of CIPN often forces clinicians to change the course of therapy which is associated with a decrease in anti-cancer effectiveness. Therefore, it is necessary to determine the biomarkers of neurotoxicity.

In the blood serum of patients with severe CIPN, researchers observed significantly higher concentrations of neurofilament light chains (NF-L). NF-Ls are part of the cytoskeleton of peripheral and central nervous system neurons. Due to the damage to the peripheral nervous system in chemotherapy-induced peripheral neuropathy, NF-L is released to the cerebrospinal fluid. Very low concentration of NF-Ls are also detected in serum of treated patients. Previous studies have confirmed the relationship between the degree of CIPN and the increase in NF-L concentration, underlining NF-L's potential as a translational biomarker [84, 85].

A potential biomarker for ICI-associated neurotoxicity is the monocyte chemotactic protein 1 (MCP-1). MCP-1 is a chemoattractant and activator of monocytes, promoting their infiltration into the tumor, it also causes the production of angiogenesis factors that promote angiogenesis and stimulate cell proliferation. MCP-1 is one of the chemokines with the highest expression during inflammation. There are studies indicating that patients with higher-grade neurotoxicity had significantly elevated serum MCP-1 levels at baseline compared to patients without neurological adverse events [86].

Conclusions

Since breast cancer is one of the most prevalent diagnosed cancers among women, there is an expectation for developing new prognostic and predictive biomarkers that would provide accurate and reliable information for clinical applications. In recent years, particular emphasis has been placed on the development of personalized breast cancer diagnosis with the use of the liquid biopsy, enabling accurate characterization of the tumor. Through the recognition of emerging biomarkers, it is possible to identify subgroups of patients who benefit from targeted therapies and manage treatment by monitoring side effects. There is still a huge clinical need for new objective prognostic biomarkers for adverse events in breast cancer therapies**.** However, these new biomarkers need to be validated and tested for their suitability before entering clinical use.

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Author contributions

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Conflict of interest

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Review article

Radiotherapy

Have innovations in radiotherapy for head and neck cancer improved the curability of the disease?

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In an era of distinct technological innovations in radiotherapy, a clinically important question has arisen: can the increase of radiotherapy (RT) effectiveness be attributed to these innovations, at least in the case of head and neck (H&N) cancers? In order to answer this question, 133 studies were published, including 21,058 patients who were selected for the present survey with H&N cancer treated within the period of 1970–2010. Three end-points, e.g. 5-year local tumor control (LTC), disease-free survival (DFS) and overall survival (OS) and their average values were evaluated over the consecutive decades. For cancer in the early stage, both LTC and DFS were constantly high (80–90%) through the analyzed decades. For locally advanced cancer, average rates of LTC and an DFS were also constant, but much lower than expected (40–45%). The OS had an increasing tendency: from 45–50% in 1980 to more than 70% in 2010. It may suggest that during the 5-year follow-up period, some proportion (~20%) of advanced tumors gradually progressed from local to chronic disease. Various technical and clinical problems influencing the results of the present review are discussed in detail. Some uncertainties and doubts regarding the RT trials may suggest that "evidence based" recommendations might not be satisfactory, as in the era of combined treatment modalities; it may seem reasonable to replace them with "individually personalized combined therapy". However, nowadays the only plausible solution to improve H&N cancer curability is to intensify all efforts to detect it in the very early stages of the disease and to increase various activities to convince people to participate in regular prophylactic examinations.

Key words: head and neck cancers, local tumor control, disease-free survival, overall survival end-points, early cancer diagnosis, permanent curability

Technological revolution and innovations

The era of orthovoltage radiotherapy (RT) and the Ralston Paterson "school of radiation dose delivery" [1] lasted for over 60 years. During these years radiotherapy planning was relatively simple: based on X-ray radiographs and 2D-coplanar, geometrically regular, well-shaped 2–6 beams focused on the tumor (fig. 1), whilst dose distribution was calculated based on diagrams of the percentage depth isodoses.

During the 1970s, cobalt units were gradually replaced by high-tech linear accelerators (Linacs), offering a wide range of MV

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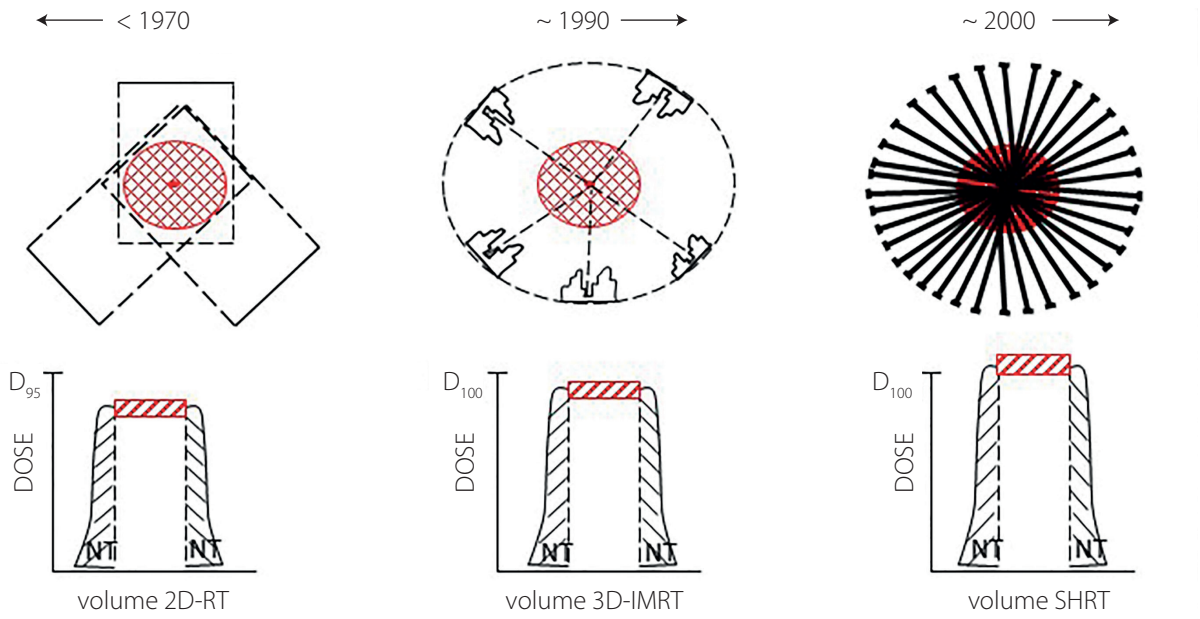

Figure 1. Schemes of three different techniques used in radiotherapy during <1970 and >2000 year with respective dose distribution within the tumor (T) and in the surrounding normal tissues (NT). 2D-RT – two dimensional nonconformal RT; 3D-IMRT – three dimensional dose intensity modulated conformal RT; SHRT – stereotactic hypofractionated multidimensional, conformal RT

energy (5–>20 MV) photon and electron beams. As opposed to Paterson's principles, Fletcher's rules were based on radiobiological principles, and have been universally accepted [2]. Linacs were gradually enriched with multileaf collimators (MLC), cone-beam CTs, real-time tumor tracking, fusion of the CT and Linacs (tomotherapy). Corollary to these technological innovations, RT planning has begun to use precise 3D-conformal IMRT, IGRT, IART, respiratory gating RT, biologically targeted IMRT [3–14], defined by Coleman et al. [12] as SMART radiotherapy. Irregular beam shapes made it possible to tailor the radiation dose which was focused both on the tumor and its margins, with a sharp decrease of radiation beyond this area (fig. 1). However, clinical practice has shown that this comprehensive and powerful solution is in fact a sword of Damocles. On the one hand, conformal techniques offer a substantial decrease in the dose deposited in the surrounding healthy tissues, and therefore reduce the risk of serious late complications., whilst on the other hand there is a risk of cold spot(s), even small ones, in the tumor volume, due to the dose within the tumor; this is likely to lower the preliminary predicted probability of local tumor control [14].

Such technological and systemic innovations [3–14] in three-dimensional RT has opened the possibility for various altered dose fractionation schedules used either alone or combined with other therapeutic modalities like surgery or chemotherapy [12, 15–17]. Moreover, proton and boron therapy have appeared, yet their set up is extremely expensive so the practical use is still somewhat limited. The next interesting option, increasingly growing in popularity, is stereotactic hypofractionated radiotherapy (radiosurgery, SHRT, SHRS) [18–20]. Although its principles were already defined in 1948 by Takahaschi [8], SHRT has been widely used only since 2000, mainly due to special modifications of the Linacs (VMAT) and the new robotic CyberKnife. A key-principle of this method is the use of many (even more than 100) pencil beams focused on the tumor, with a sharp down dose gradient beyond its bounds (fig. 1). SHRT is an example of a "round game" in radiotherapy, meaning the return of RT to its roots, when in the 1900s, single or a very few large dose fractions were being used. This method was, however, quickly abandoned because of the very high incidence of lethal late complications. After more than 100 years, it came back to the RT arena, offering many pencil beams and robotic computerized 3D-dose planning systems instead of geometrically shaped single or two-dimensional field techniques and a low energy X-ray beam. Moreover, SHRT can be used as radical therapy or as a palliative treatment in the case of single or multiple distant metastases irradiated during a single set-up session. However, SHRT has one important limitation – it can only be used in the case of small and well-defined lesions.

This impressive progress in the use of radiation as one of the cancer treatment modalities provokes another important question: did all these achievements result in an increase of permanent curability of cancer patients, at least those with head and neck malignant tumors?

End-points of RT effectiveness

Since radiotherapy has been also used as a local treatment of malignant or some benign tumors or localized distant metastases, local tumor control (LTC) has been widely accepted.

That is why it is used as an appropriate end-point with a 5-year follow-up, at least for head and neck cancer, because about 80% of local recurrences occur within the first 3 years of completing the irradiation. However, when some cases are lost from observation and their follow-up is shorter than 5-years, then the actuarial LTC is limited, assuming the risk of recurrence which may occur if the follow-up lasts 5 years. The estimated date of an average limited LTC should therefore be interpreted with great caution because such averages might be underestimated.

Sometimes, LTC is erroneously identified with tumor cure probability (TCP), so it is misinterpreted as an indicator of tumor or even a patient's curability, which in fact is not. The TCP is only a preliminary predictor of local eradiation of the tumor by the RT and individually estimated based on the tumor origin, type, stage (in fact a tumor volume rather than a stage), and the planned dose fractionation. The TCP is estimated based on radiobiological principles, but it is very often untrue and thus disappointing. If the dose is heterogeneously distributed within the tumor volume, and, for example, 50% of the planned dose is delivered to only 1% of the tumor (usually invisible on a tumor volume histogram [DVH]), then it completely ruins the predicted TCP, and its real value decreases close to zero. Therefore, the TCP has nothing to do with a patient's curability by RT.

Complete tumor regression (CR) is definitely unsuitable for an evaluation of RT effectiveness, although there are some suggestions that the CR might be a prerequisite for the LTC, but it rarely happens. One may believe that the CR is the clinical effect of radiation cell kill, but it is not, because it only indicates how fast and effectively dead cancer cells are removed out of the tumor mass by immunological and cellular homeostatic defensive processes.

Disease-free-survival (DFS) is a proper and representative end-point which is close to the chance of the permanent patient's curability, because it represents the LTC without local recurrence and/or distant metastases. However, real DFS which is the absolute number of patients who survived the outlined follow-up, must be distinguished from the censored DFS, for the same reasons as a real *vs.* actuarial LTC. The more cases are censored the lower reliability of the estimates. The 5-year DFS seems a reasonable time-limit for the H&N cancer, but for some other tumors (e.g. breast, lung cancers), this period is too short, and sometimes even 10 years are not enough.

Overall survival (OS) is usually reported as an additional end-point, however its validity in relation to permanent patient's curability remains uncertain since it does not inform how many patients are permanently cured and how many live with local recurrence and/or distant metastases.

LTC, DFS, OS results in the last four decades of RT

The present survey is the review of a large variety of retrospective prospective studies and clinical randomized trials, whose results were published in the literature between 1970 and 2010. Many studies reported incomplete results. The present review includes only complete rates of well documented three end-points, which are the LTC, DFS and the OS, although not all three end-points were reported in each study [10, 17, 23–35]. Furthermore, only studies on radiotherapy alone or as a primary treatment or sometimes combined with sequential or concurrent chemotherapy were selected. Four decades of treatment have been analyzed, and therefore the respective number of end-points differ. Altogether, 341 rates of the LTC, DFS and OS have been selected for the present analyses (tab. I). The rate of LTCs reported up to 1970 are lower than LTC rates in the following decades. In the remaining three decades, the LTC, DFS and OS rates did not differ very much. The LTC, DFS and OS were estimated for an overall number of 21,058 patients treated by RT using one of the four different dose fractionation schedules (tab. II). All the data are subdivided into two groups, i.e. tumors in the early stage T1–2N0M0 and advanced tumors in stage T2–4N+M0. Altered *vs.* conventional dose fractionations were used in the randomized trials and the number of patients recruited to each arm of these studies was more or less the same. Therefore, the overall number of patients treated with conventional fractionation was the largest and it includes 10,209 cases (48%).

Figure 2 illustrates the distribution of dots representing the LTC, DFS and OS rates documented in the studies selected for the present review. This figure shows a wide spread of black dots representing the 5-year LTC and DFS of patients with locally advanced head and neck cancer reported during 1980–2010, although its ranges were relatively narrow, not substantially changed over the last 30–40 years. It should be emphasized that during that extended period, tremendous high-tech progress in linacs and its tools and computerized 3D--dose planning systems have taken place; yet it has not really

Table I. Number of studies analyzing three RT end-points recruited to the present survey

End point	1970–1975	1980–1985	1990–1995	≥2010	Overall
local tumor control		32	40	36	108
disease-free-survival	6	37	35	37	115
overall survival	8	35	37	38	118
total	14	104	112	111	

Table II. Number of patients included in the selected studies presented in table I

Radiotherapy schedules	Number of patients	Percentage of patients
conventional	2638	12
altered *vs.* conventional	15,142	72
SHRT	1863	9
chemoradiation	1415	7
total	21,058	100

SHRT – stereotactic hypofractionated multidimensional

improved LTC and DFS results, with average rates invariably oscillating around 40–45%. Even the use of altered dose fractionation did not change these highly unsatisfactory, average rates of LTC and DFS [24, 25]. Promising results have been offered by concurrent chemoradiation which increased average LTC and DFS by 10–15%. There is a marked increase in LTC and DFS for patients with early stages (T1–2N0M0) of head and neck cancer to an average level of 80–≥90%, and also when the SHRS has been used. By contrast to the LTC and DFS end-points, OS significantly increased from about 40–45% in the 80s to >70% in the 2000s. The higher rates and prolonged OS over these 30 years do not necessarily suggest a benefit of RT but rather a gradual progression of the disease from local to chronic.

Comments

The curability of cancer patients means that an appropriate therapy (radiotherapy alone or combined modalities) will permanently and irreversibly eradicate all clonogenic cancer cells. Theoretically it should result in a 100% permanent cure rate. For radiotherapy (also for other therapeutic modalities in oncology) this might be an illusion because of the random nature of radiation cell killing. Tumor stem cells are defined as clonogenic or colony forming cells, which may constitute only a small proportion of all tumor cells [36]. If only one stem cell survives irradiation, then it will be able to reconstruct the primary tumor as a local recurrence, although their genotype and phenotype may substantially differ from that in the primary tumor. Therefore, the key point of radiotherapy is to eradicate the last cancer stem cell, to ensure the tumor never regrows, but this is a theory only, and, moreover, it is impossible to recognize tumor stem cells in situ, and to establish their number and localization. Therefore, regarding a patient's curability, when estimating the LTC and DFS, the word "probability" instead of "certainty" is used.

Analyzing the results presented in the figure 2, two major questions arise. First, what is the reason for the small wide spread of dots representing the LTC, DFS and the OS, despite the outstanding technological and computerized 3D-RT planning advances during the last three decades; secondly, why during that period, did the RT efficacy represented by the LTC and DFS rates not increase? It seems that there are at least three important reasons. First of all, in clinical radiotherapy for H&N cancer clinical data, not only that recruited the present study, look like a "fruit basket". To a single study or two-three arms of the randomized trials were usually recruited H&N tumors with various sites and wide range stages (T2–4N+M0) [25, 26, 37]. Therefore, the range of initial tumor volumes (and respective initial number of cancer cells as well) was even wider. For such a diversity of parameters, a single and same 3D-dose fractionation was used within each arm of the study. The main aim was to estimate the most effective dose which would produce a significant increase in LTC and DFS. The use of the same dose fractionation for T2N0M0 as for T4N0M0 to achieve the highest therapeutic benefit is in fact ridiculous in the light of all radiobiological principles. Some years ago, L. Peters suggested that it is like searching for a single "Holy Grail", which could be

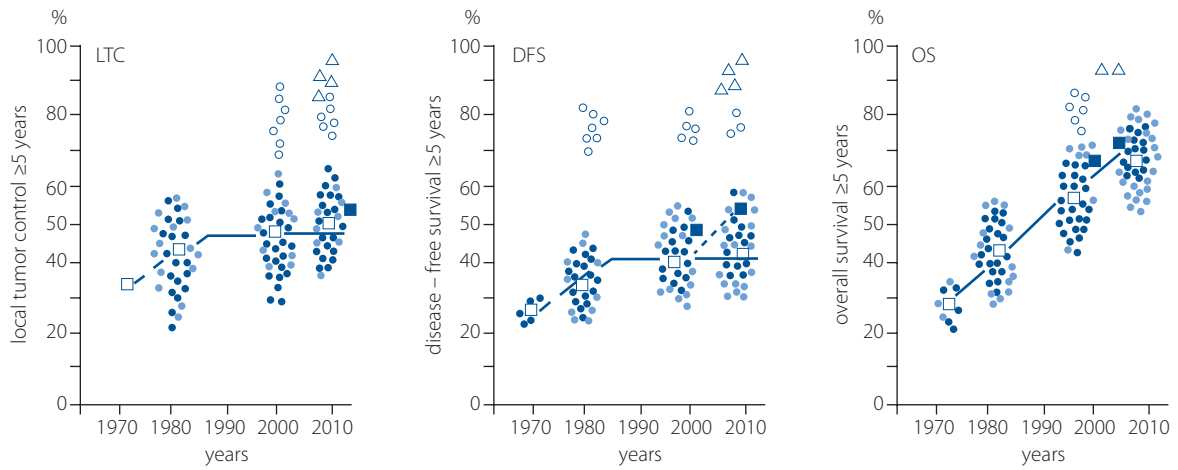

Figure 2. Distribution of the 5-year LTC, DFS and OS rates of (dost) during four decades of radiotherapy documented by the results of studical recruited to the present survey □ – average rates of the respective end-points for advanced H&N cancers; ■ – average rates representing concurrent chemo-radiation; open circles – early staged H&N cancers; △ – results of the SHRS

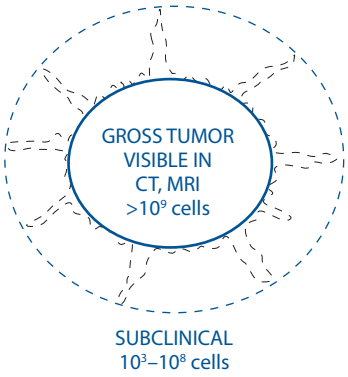

Figure 3. Schematic tumor volume (gross mass) with subclinical microscopic irregular cancer cell deposits

compared with a blind man looking for a needle in a haystack. The effect of the mixture of tumors in early and advanced stages is shown as a theoretical example in figure 3.

From a practical point of view, if the total dose of 70 Gy in 35 fractions is used to irradiate T1N0M0 H&N cancer, which contains about 10^9 clonogenic cancer cells then on average 0.1 cell/tumor should theoretically survive. It means that in a group of 100 such tumors, in 90 of them all the cells will die and in the remaining 10 tumors, 2, 4, 8 or more cells will survive, which gives on average 0.1 cell/tumors. Therefore, tumor cure probability (TCP = $e^{-0.1}$) will reach a level of 90%, which usually happens in RT practice. However, if the same dose is used to irradiate T3N0M0 tumor with 10^{11} clonogenic cells, then an average survival would be 1 cell/tumor, which as a consequence gives TCP of e^{-1} = 37%, what also happens? This is not a theory but a real every day situation in radiotherapy.

One important point of view articulated 75 years ago in 1949 by Paterson [1], and 50 years later by Suit [38], is that a local success, important for patients, is to be free of local problems, but it does not affect the likelihood of the patient's curability.

An increase in the DFS seems to be realistic by effectively augmenting the LTC. Already Paterson in his textbook of radiotherapy published in 1949 (the first textbook in the world) strongly emphasized that "optimal tumor dose (TCD is actual term) must be assessed in terms of dose related to time, not as a dose alone. The dose/day of treatment is important from the beginning, because a low initial rate cannot be compensate by a high rate later, or vice versa. A most often forgotten corollary is that the treatment planned must be completed in the shortest time possible". It should lower a risk of local recurrences and/or distant metastases (the last failure type is not a key-problem in the case of the H&N squamous cell carcinomas, may be except nasopharyngeal cancer). It may seem surprising (fig. 2) that average rates of the LTC and DFS for advanced tumors have remained at a similar level during the last 30 years. One plausible explanation could be that LTC rates shortly after completing RT were much higher, and they decreased during the follow-up, as the result of local recurrences. Finally, averages of both end-points reached similar levels at the 5-year follow-up. At first glance, a relatively wide spread of data dots representing the LTC and DFS rates may suggest differences in tumor radiosensitivity, but it is unrealistic to accept such wide variations in squamous cell carcinomas which are the subject of the present review. It could rather be the results of the pronounced variability in the initial tumor volume and the respective number of cancer cells (not TNM), which received a suboptimal radiation dosage. Falling into two major categories of H&N cancers, the LTC for tumors in the early stage treated adequately is very high, whereas for advanced tumors the LTC is usually low, and therefore the average rate is unexpectedly more or less moderate. In the present analysis we decided to separate these two categories.

High curability is a fundamental goal of radical RT, which can be attempted when the whole area containing cancer cells is covered homogenously by respectively optimal dose delivered in the shortest overall time possible. Moreover, an important point is that cancer should be effectively controlled at the first attempt, because there is seldom a second chance. And this is the next important problem.

Generally, cancers usually have an irregular shape (except capsular or cystic tumors, very rare in the H&N) with the spread of subclinical cellular deposits beyond the bounds of the gross tumor mass (fig. 3). Gross mass is the only visible part of the tumor on the CT, MRI scans, and therefore the real tumor bounds cannot be precisely defined, since subclinical spread of tumor cell deposits are beyond the resolution of the CT or MRI and it is unable to determine the exact extent of the growing tumor. Spread of cellular deposits beyond the gross tumor mass is a major attribute of advanced rather than "early" tumors.

Currently, the aim of 3D conformal RT planning is to tailor irregularly shaped radiation beams within the CTV and PTV margins, and focus on the gross tumor mass, and with the dose gradient beyond, to spare the surrounding [fig. 3] normal tissue. Therefore, there is a risk of missing microscopic deposits of cancer cells aside individual volume. Regardless of that risk, collimator leaf(s) may sometimes cover even a very small part of the tumor volume (overconformality). Both events are a potential source of local recurrence of the tumor. If 10^3–10^6 clonogenic cancer cells were missed (even 1 stem cell is enough) beyond the irradiated volume, then local recurrence will likely occur clinically during 6–12 months after completing the treatment. To minimize that risk, the planned dose-volume-histograms (DVH) must be very carefully analyzed. It has to be emphasized that purely physical dose distributions might be misleading, and therefore the physical DVH should be converted into biologically normalized DVHs, where each pixel of dose becomes equivalent if it would be given in 2.0 Gy/fractions. Such a simple procedure discloses overdosage or underdosage

subregions of the whole tumor volume. It is a pity that such checking is often ignored in daily RT practice, and therefore, it could partially contribute in some way to the unsatisfactory average rates of LTC and DFS, shown in figure 2.

Dose cold and hot spots (the second one in the gross tumor volume can be ignored) are the third major problem, especially for heterogeneous dose distribution within the irradiated area. The UICC recommends using the D_{95} as a reference parameter and it was acceptable for 2D dose planning homogenously distributed within the irradiated volume. When the 2D procedure was replaced by precise and highly sophisticated 3D–4D dose planning techniques, already more than 10 years ago, Jack Fowler strongly emphasized that D_{95} should, without doubt, be replaced by D_{100} as a reference factor, however the D_{95} still remains in daily practice. If preliminarily predicted TCP is 90% and dose planning is tailored to such prediction, that if even a small tumor subvolume will receive a few percent lower dose (cold spot), then in such an underdosed subvolume on average 1.0 instead of 0.1 cancer cell will survive, and therefore the TCP for that subvolume will be substantially lowered (TCP = e^{-1} = 0.37), and collorary overall LTC will lower to only 33% (0.90 x 0.37).

Withers [22] and Suit [38] pointed out that "the essential art of treatment planning is choosing where and how much of extra-tumoural radiation shall go". However, this does not necessarily seem to be true after all, since once a tumor cold spot is underdosed, it will definitely ruin the expected high LTC, and any extra boost dose delivered thereafter will not neutralize such negative effect. Therefore this moves us to the beginning, that precise 3D-dose planning with the removal of any existing dose cold spots is a key point in achieving the LTC and DFS as high as predicted.

A final comment as regards overall survival (OS) in the present review shows an increasing tendency through the last 30 year period. The OS is not a proper and adequate end-point for an assessment of the patient's permanent curability, although it is often used as an argument to express improvements of the efficacy of oncologic therapy as a whole. In the present review relatively moderate 5-year LTC and DFS of 45–50% compared with much higher average the OS may likely be interpreted as the gradual progress of a local cancer disease into its chronic phase (in about 20–25% in the present review), and the higher OS with prolonged survival can be a result of effective palliative therapy. SHRS has been found as a highly effective RT, not only radical but also local palliative therapy as well [19, 20]. Analyzing the OS as an end-point for prolonged survival, there is relatively small number of studies focused on the quality of life and what kind of price is paid for prolonged life. It does not look very optimistic. According to List and Bilir [39], about more than 50% of patients have difficulties in eating and swallowing, a decreased sense of taste, dry mouth (95%) and 30–35% reported sticky saliva, pain, unsatisfied appearance, which may recover is less than 35% of patients. This is the price which patients with a chronic phase of H&N cancer may pay for prolonged survival, in other tumor types and origins as well.

To sum up, it is a pity that RT efficacy for locally advanced H&N cancer has not changed a lot during the last 3 decades and it still does not look overly optimistic, but it is not all bad news. Tumors in the early stage usually have well defined bounds as microscopic deposits of cancer cells have not had enough time to develop yet and therefore have not spread out of the tumor bounds. Radiation beams are precisely tailored to cover homogenously whole PTV to eliminate overconformality, or dose cold spots. Therefore, the likelihood of a high LTC and DFS (~80–90%) by RT alone is not surprising. On the contrary, many studies including trials on various 3D-techniques and altered dose fractionation [15, 21, 23, 26, 28, 29] have convincingly shown that the effectiveness of RT alone for advanced H&N cancers is limited and generally disappointing. Ultimate proof of that comes from the four-arm RTOG-9003 trial [24]. Delivery of a total dose in the range of 67.2–81.6 Gy using altered fractionation to irradiate advanced H&N cancers resulted in similar LTC of 40–45%, in each arm of this trial. This became a strong argument for replacing RT alone by combined therapeutic strategy, which includes RT. Concurrent chemoradiation has been an attractive solution, although meta-analysis [26] showed a rather low (4%) average benefit of local tumor control. Combined therapy including various sequences of surgery, radiation and chemotherapy has been enriched by genomic, proteomic-molecular identifiers and modifiers (fig. 4), becoming promising options to improve cancer patient's permanent curability. The point to be emphasized is the advertisement of a "quantum leap" in the improvement of the efficacy using 3D-IMRT in the local treatment of various tumor sites including the use of respiratory gating in the case of lung cancer. Glatstein [40, 41] pointed out that many investigators admit they are still uncertain, but suspect that some improvement could be expected. An objective evaluation of the benefits of IMRT has never been done and it still remains an open question. It is often suggested that high-tech RT has a high success rate but it is unclear as to what that success refers to, i.e., a permanent cure or local control only. Moreover about 80% patients are treated using RT beyond clinical trials.

Irrespective, of many uncertainties [44, 45], the "evidence based" RT is strongly forced and recommended as an obligatory guide and instruction for the RT planning and delivery based on the trial's results. However, throughout all these efforts, spanning 30 years, of trying to improve RT efficacy, the recruitment of various, different tumor sites and sizes (although all being squamous cell cancers) to each arm of the trials to test one or two different RT schedules is an antimony of individual therapy, and in fact it fails. Some trials evaluating molecular agents combined with RT are restricted to the conclusion that the tested regimens are safe

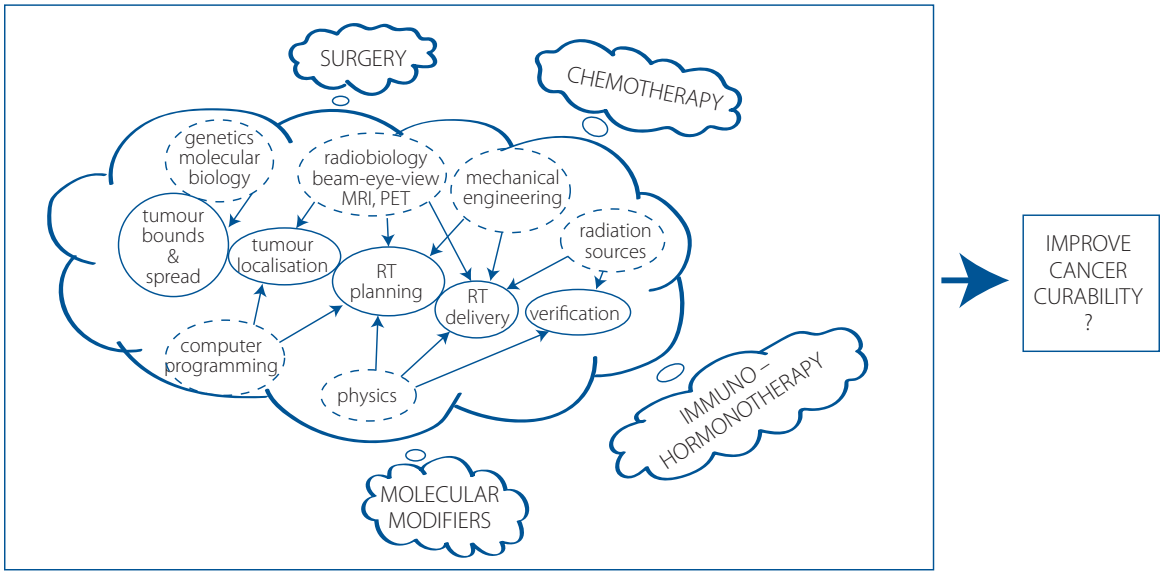

Figure 4. Scheme of the elements of multimodality combined treatment: strategy as an instrument for improvement cancer curability

Table III. Local tumor control depending on ratio of early *vs.* advanced stage cancer treated by RT

Current and expected rate of early *vs.* advanced cases		Early	Advanced	Early and advanced
current rate	no. cases	40	60	100
	average LTC	80%	20%	44%
	no. with LTC	32	12	44
expected rate	no. cases	70	30	100
	average LTC	80%	20%	62%
	no. with LTC	56	6	62

LTC – local tumor control

and feasible – not one word regarding its efficacy is mentioned. Thus, it seems reasonable and reliable that "evidence based" cancer therapy (results are often biased and are not reliable facts) might be replaced in favor of "personalized combined therapy", individually tailored to each single cancer patient. But this seems to be a promising future only, which we believe in or not. In conclusion, the only reasonable solution at the present moment, is to intensify all efforts to change the unsatisfactory ratio of early versus advanced tumors from 4:6 to 7:3, in favor of early stage tumors (tab. III B). Detection of cancers in the early stage of disease needs intensive and convincing efforts to increase access to early and fast diagnostics to effectively increase public awareness that till now early detection of cancer is reasonable solution to achieve the highest permanent curability for the patient.

Article information and declarations

Conflict of interest

None declared

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Review article

Leukemia

Methotrexate-associated oral mucositis in children with acute lymphoblastic leukemia

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Methotrexate is an antifolate widely used in oncology and rheumatology that plays an important role in the treatment of acute lymphoblastic leukemia in children. One of its most common side effects is oral mucositis, which is a general term for ulceration and inflammation of the mucous membrane of the mouth. It can severely affect a patient's quality of life, causes poor nutrition, and may lead to discontinuation of the next course of chemotherapy. Oral mucositis typically develops a few days after chemotherapy infusion. Due to this risk, it appears reasonable to use preventive agents against oral mucositis before the inclusion of methotrexate in therapy. To date, clinical trials have examined the effectiveness of medications such as glutamine, palifermin, chlorhexidine, amifostine, cyclooxygenase-1 inhibitor, leucovorin or other methods including laser therapy and oral cryotherapy. There are also several methods used to control already established inflammation and reduce pain more effectively: laser therapy, platelet-rich plasma and platelet gel, taxifolin, film-forming and coating agents. A crucial role is played by supportive interventions involving analgesic treatment, including topical morphine and benzydamine and a modern approach to pain management – for example, the use of virtual reality.

Key words: leukemia, methotrexate, chemotherapy, oral mucositis

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignant tumor in the pediatric population while it accounts for only 2% in adults [1]. Of all childhood cancers, leukemia accounts for about 26%, and ALL is the most common (about 85% of all leukemias) [2]. Intensive chemotherapy still regimens the first line of treatment of acute leukemia. However, it is not without adverse effects. The most frequent are pancytopenia, infectious disease and organ toxicity. Table I presents the side effects of frequently-used chemotherapy.

Methotrexate (MTX), an antifolate agent, is one of the most widely used and frequently studied drugs in various malignancies including leukemia and plays a crucial role in treating ALL in children. According to protocol AIEOP-BFM-2017, children in low-risk and intermediate-risk groups receive four 24 h infusions of high-dose methotrexate (HD-MTX) during Protocole M. Children in the high-risk group receive HD-MTX during the first and second HR block. All of the children receive methotrexate at a dose 20 mg/m² once a week during maintenance therapy [11].

Pathogenesis of methotrexate toxicity

Methotrexate is a folate antagonist – it inhibits dihydrofolate reductase (DHFR). This enzyme reduces folic acid to

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Table I. Common side effects of widely used chemotherapeutic drugs

Medication	Adverse effect
vinca alkaloids (e.g. vincristine) [3]	neurotoxicity (peripheral neuropathy), constipation
cyclophosphamide [4, 5]	hemorrhagic cystitis, early-onset pneumonitis, pulmonary pneumonitis
methotrexate [6, 7]	hepatic toxicity, gastrointestinal toxicity, skin and mucosa toxicity, nephrotoxicity
cytarabine [8]	ocular toxicity (corneal pain, keratoconjunctivitis, blurred vision), maculopapular rash, bone pain
PEG-asparaginase [9]	thrombosis, pancreatitis, hyperglycemia, and hepatotoxicity
anthracyclines (e.g. doxorubicin, daunorubicin) [10]	cardiomyopathy

tetrahydrofolic acid. Tetrahydrofolate has to be built up by a DHFR-catalyzed reaction. Inhibition of DHFR by methotrexate results in a deficiency of thymidylate and purines and then a decrease in nucleic acid synthesis, which leads to inhibited cells division. Methotrexate acts mainly in the "S" phase in a cell cycle, and is therefore appropriate for leukemias and lymphomas. Cytotoxic MTX occurs mainly in rapidly multiplying cells such as epithelial. These cells are susceptible to the effects of cytotoxic therapy because they undergo rapid turnover, usually every 7 to 14 days [13]. In addition, this effect can be exacerbated by bacterial or fungal infections, especially during neutropenia, which is relatively common in children with ALL.

For MTX, transport is essential to generate a sufficient quantity of intracellular drug to maximally inhibit DHFR and to provide a substrate for the synthesis of MTX polyglutamyl derivatives required for cellular drug retention as well as sustaining antitumor effects [14]. MTX enters cells through an active transporter called reduced folate carrier (RFC), a gene located on chromosome 21q22 [15]. In Down syndrome (DS), each somatic cell has an extra copy of this chromosome, resulting in an accumulation of MTX in the form of MTX polyglutamate [16]. This explains the severe toxicity of MTX in patients with DS, especially in the gastro-intestinal tract. After receiving a high-dose of 5 g/m² of MTX (HD-MTX), patients with DS showed significantly higher rates of severe leukopenia, thrombocytopenia, infections and oral mucositis compared to patients without DS, who received the same dose [17]. Knowing how the metabolism of MTX differs in children with DS, HD-MTX is administered differently in DS. According to the AIEOP-BFM-2017 protocol, children with DS receive a reduced dose of 0.5 g/m² of MTX, and then, if there is no severe toxicity, the dose is increased to 2 g/m² and finally 5 g/m² [10]. It is important to emphasize that children with DS who receive lower doses of MTX do not have a higher risk of relapse than children without DS who receive high-dose MTX. Moreover, among children with DS, there is no significant difference in the risk of relapse between children who received a first dose of MTX 0.5 g/m² and children who received MTX at a dose of 5 g/m² [18].

Methods of prevention

As mentioned, the use of methotrexate in treating ALL can cause a number of side effects, including oral mucositis with varying degrees of severity. This is a frequent complication, often contributing to a significant decrease in the patient's quality of life due to pain and difficulties with oral intake of solid foods and liquids [19]. Considering the risk of its occurrence, it is already advisable to use preventive agents against stomatitis before including methotrexate in therapy. It is not possible to achieve one-hundred percent efficacy in preventing oral mucositis (OM), but there is a chance of decreasing its occurrence and alleviating its course in ALL patients.

Glutamine

Glutamine is one of a group of conditionally essential amino acids, especially under conditions of catabolic stress, when glutamine consumption by the kidney, gastrointestinal tract and immune system compartment increases rapidly. These observations reflect the dependence of growing cancer cells on glutamine, with some cancer cells dying promptly while being deprived of glutamine [20]. On the other hand, glutamine can regulate the inflammatory response and immune balance, reduce intestinal damage, maintain the intestinal mucosal barrier and reduce the translocation of the microbiota of the intestine [21]. From an analysis of the available literature, it was concluded that oral glutamine supplementation may be reasonable for the prevention of OM.

Gaurav et al. summarized the metabolism and therapeutic applicability of glutamine on animal models. They reported that this substance reduces the immunosuppressive effect of MTX, reducing the incidence of side effects including the inflammation of mucous membranes, especially the intestinal epithelium, as well as the oral cavity [22]. Another study compared the effectiveness of parenteral glutamine in patients with ALL receiving HD-MTX in consolidation therapy. In the study group, glutamine administration was initiated within 48 h of the start of chemotherapy and continued for 3 days. It was found that the incidence of OM was considerably lower in this group than in the control group, in which patients did not

receive glutamine. There was no severe oral mucositis in any patient in the study group. Moreover, no severe adverse reactions related to glutamine administration were reported [23]. Widjaja et al. conducted a similar study, but in the study group, they included oral glutamine 24 h before HD-MTX administration and continued its administration for 14 days. As a result, oral mucositis occurred in 4.2% in the glutamine group and 62.5% in the group receiving the placebo. Additionally, the duration of hospitalization of children taking glutamine was significantly shorter. That leads to the conclusion that glutamine may be an effective and safe adjunct in the future for preventing mucositis during MTX chemotherapy [24].

Palifermin

Palifermin is a recombinant human keratinocyte growth factor (KGF) with cytoprotective effects. It has been shown to stimulate epithelial cell proliferation in many tissues of the organism. It binds to specific receptors on the surface of cells that line the mouth, stomach and intestines. This potentially may help protect healthy tissues from certain side effects caused by certain types of cancer treatment [25].

One research study from 2016 investigated the efficacy of palifermin in preventing oral mucositis in children with ALL by intravenous administration 3 days before and 3 days after chemotherapy. Children in the study group had significantly less frequent and less severe mucositis (none had WHO grade III or IV mucositis) [26]. The clinical study by Schmidt et al. examined pediatric patients with ALL who developed severe oral mucositis (WHO grade III–IV) at the first stage of therapy. They were then administered palifermin with subsequent similar cycles of chemotherapy. The incidence of mucositis decreased significantly, and its duration shortened. This confirmed the hypothesis that palifermin could reduce the incidence, severity and duration of OM in HD-MTX-based chemotherapy and have a beneficial effect on patients' quality of life [27].

Laser therapy

Low-level laser therapy (LLLT), also known as photobiomodulation therapy (PBMT), is a non-invasive method of preventing and treating mucositis by applying a high-density monochromatic narrow-band light source of varying wavelengths (630–830 nm) to the mucosa. The proven clinical efficacy of PBMT in preventing mucositis has led to its increasing use in pediatric oncology [28]. Several studies have been published demonstrating the effectiveness of prophylactic laser therapy in children with ALL undergoing MTX treatment. One of them retrospectively examined the association of OM with PBMT in several pediatric oncology disease entities. MTX was the second most frequent cause of OM. PBMT significantly reduced the severity and incidence of OM in patients with ALL [29]. A study by de Castro et al. compared the course of chemotherapy treatment in patients using prophylactic oral laser therapy and laser therapy included only after the onset of OM symptoms. Summarizing the results, laser therapy has been proven effective in the treatment and prevention of OM, but prophylactic treatment resulted in better clinical outcomes at the end of treatment [30].

In contrast, another study compared the clinical outcomes of pediatric oncology patients receiving or not receiving prophylactic lasotherapy. Tests on a group of 60 patients indicated no evidence of benefit from such treatment in children with chemotherapy-treated malignancy, especially when optimal dental and oral care was ensured [31].

Chlorhexidine

Chlorhexidine is an antiseptic solution used topically for various purposes, such as preoperative skin preparation, hand washing, vaginal antisepsis or treatment of gingivitis. It has broad spectrum activity against gram-positive and gram-negative bacteria, facultative anaerobes and aerobes, yeasts and certain lipid-bound viruses [32]. In view of this microbial-destroying effect, an attempt was made to implement chlorhexidine in the prevention of oral mucositis in oncology patients.

In the first trial, 0.12% chlorhexidine gluconate was administered to a study group of children with ALL for 10 days after each MTX infusion. Among these patients, a quarter developed grade I OM. In the control group, signs of inflammation appeared in 80% and were more severe [33]. A similar study was conducted among patients at a Brazilian Medical Center, with comparable results – a significant reduction in the incidence of OM was noted in children who received 0.12% chlorhexidine mouthwash during intensive chemotherapy [34]. Soares et al. conducted a study evaluating clinical and microbiological changes in the oral mucosa of children with ALL during chemotherapy and after prophylactic use of chlorhexidine. Only five children developed features of OM, and microbiological tests resulted in a reduced number of pathogenic microorganisms, including coagulase-negative staphylococci, *Candida albicans*, E. coli and Stenotrophomonas maltophilia. No control group was formed in the study [35]. The results presented above suggest that systematic prophylactic treatment with the chlorhexidine compound and careful attention to oral hygiene reduce the incidence of oral complications in children with ALL undergoing antineoplastic chemotherapy.

Other

A few single reports on other medical agents were also found, which may in future provide a basis for expanding research on their effectiveness in preventing OM.

Leucovorin is a derivative of folic acid used in the treatment of methotrexate toxicity and chemotherapy regimens [36]. The administration of leucovorin during MTX treatment increases cellular folate levels, so it has been hypothesized that this may further contribute to the reduced incidence of OM after subsequent courses of MTX [37].

In pathogenesis, methotrexate-induced oral mucositis is thought to develop through epithelial damage by reactive

oxygen species, disruption of cell growth and apoptosis or necrosis. This exposes the mucous membranes to oral infections caused by bacteria and fungi. The administration of MTX leads to an increase in oxidative stress and, consequently, cytotoxicity [38]. A study by Maiguma et al. examined the prophylactic use of a free radical scavenger (amifostine) and a cyclooxygenase-1 inhibitor as a disruptor of hydroxyl radical production. From an electron spin resonance study, it was found that methotrexate-induced cell damage was restored by amifostine and cyclooxygenase-1 inhibitor, and it was suggested that they may be useful protective agents against the chemotherapeutic toxicity of this drug [39].

The last preventive method suggested will be cryotherapy, which involves patients holding ice-chips in their mouths continuously during chemotherapy. No scientific studies have been found proving the efficacy of this method for MTX treatment, but several research papers have demonstrated its effectiveness against other chemotherapeutics, such as 5-FU or mephalan, and during conditioning before HSCT. It is assumed that ice causes local vasoconstriction, which reduces drug delivery to the oral mucosa tissues and therefore reduces the risk of OM. In the cited studies, patients in the study group developed severe OM less often, required less intensive and shorter analgesic treatment, and avoided the need for TPN. This leads to the hypothesis that it is advisable to conduct further randomized studies examining the beneficial effects of cryotherapy on OM caused also by other medications, including MTX [40–43].

Clinical picture

MTX-associated oral mucositis typically develops a few days after chemotherapy. Symptoms are varied, ranging from mild soreness in the mouth to severe symptoms requiring total parenteral nutrition. The most common symptom is pain requiring analgesics. Other symptoms include: burning sensation in the mouth, difficulty swallowing leading to cessation of water and food intake. Changes in the oral mucosa develop from redness to ulcers. Due to pancytopenia after chemotherapy, bleeding from the ulcers may occur [44]. According to the WHO toxicity grading scale there are four grades of presence of oral mucositis:

I. oral soreness, erythema,
II. oral erythema, ulcers,
III. oral ulcers, only liquids intake (due to the mucositis),
IV. oral ulcers, oral alimentation impossible (due to the mucositis) [45].

In the next figures (fig. 1–8) four grades of MTX-oral mucositis in children with ALL are presented. The source of all the photographs is the authors

Treatment of oral mucositis

A completely effective method of treating OM after chemotherapy has not been developed to date. There are several medications used to manage inflammation and reduce pain more quickly, as further described below. However, none provide certain efficacy and they are not widely published in treatment protocols. Therapeutic management is therefore based on agents that regenerate the oral mucosa and reduce inflammation. In addition, supportive treatment in the form of analgesics, antibacterials, antifungals, dietary modification, including total parenteral nutrition, and changes in oral hygiene are practiced.

Laser therapy

Different biological effects have been described to explain the mechanism of laser therapeutic efficacy: increased collagen production, the activation of energy production in the mitochondria, the detoxification of free radicals, the proliferation of fibroblast cells and stimulation of angiogenesis [28]. The literature examining the efficacy of LLLT in treating OM in a population of children with ALL was analyzed by the authors.

The first cited randomized clinical trial was conducted by Reyad et al. on a group of 14 patients. The study group was undergoing treatment with PBMT in addition to standard symptomatic therapy. There was a significant reduction in the severity

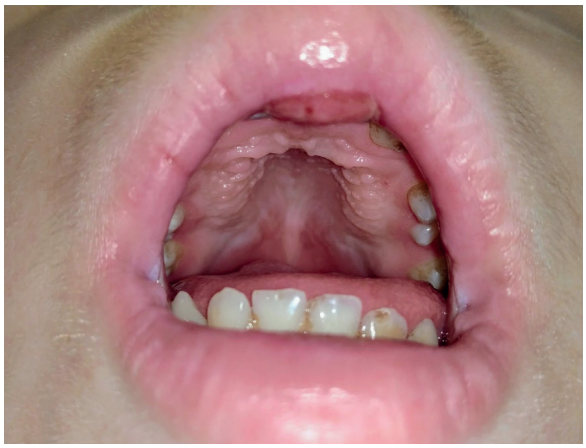

Figure 1. Oral mucositis grade I: erythema can be seen on the soft palate and upper labia; the patient complained of soreness on swallowing

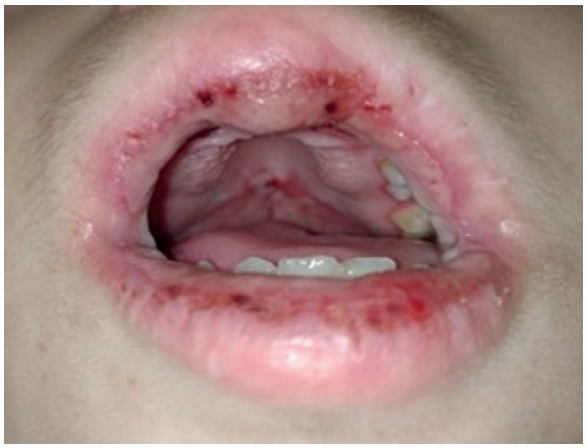

Figure 2. Oral mucositis grade II: erythema and ulcers can be seen in the labias

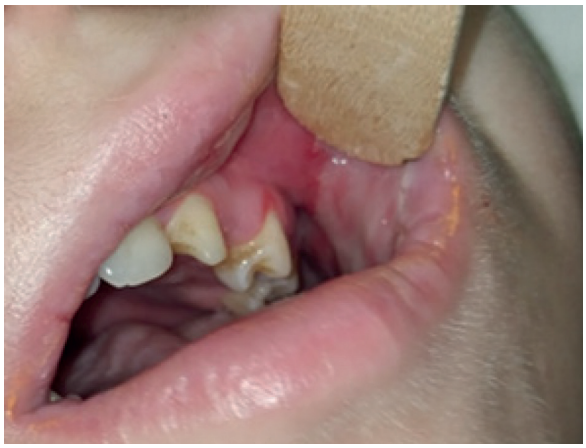

Figure 3. Oral mucositis grade II: erythema and ulcers can be seen in the buccal mucosa

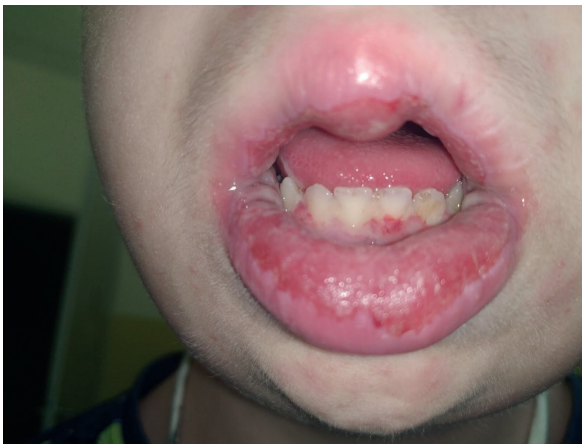

Figure 4. Oral mucositis grade III: ulcers with extensive erythema can be seen

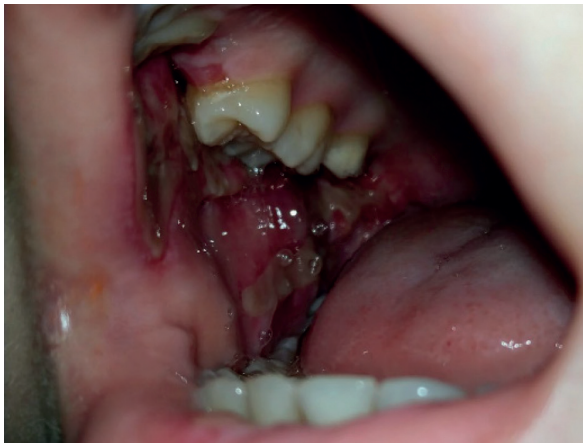

Figure 5. Oral mucositis grade III: ulcers with extensive erythema can be seen. Only liquid food intake

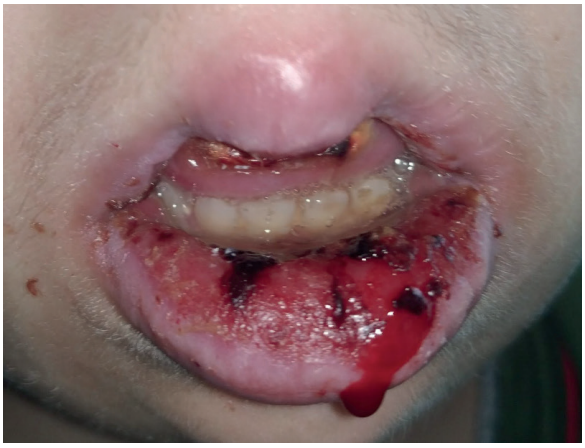

Figure 6. Oral mucositis grade IV: generalized ulcers, erythema. Bleeding from the labias. Nourishing was no longer possible for this patient. Total parenteral nutrition was started

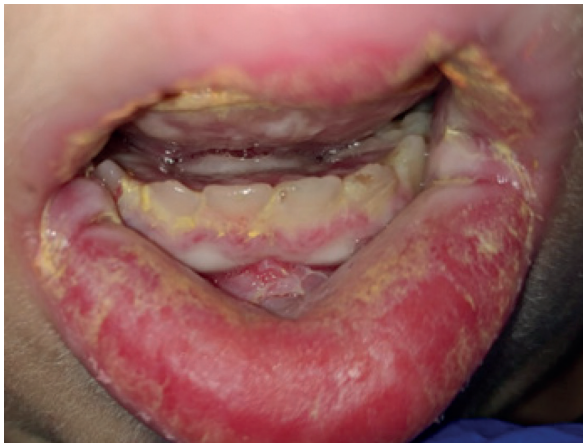

Figure 7. Oral mucositis grade IV: generalized ulcers, erythema, leukemia

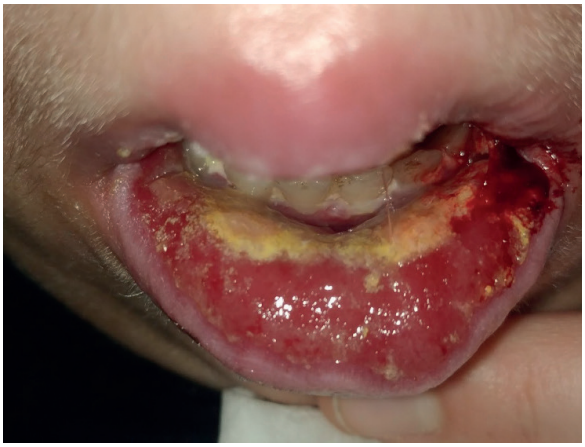

Figure 8. Oral mucositis grade IV: generalized ulcers, erythema, leukemia. yellow coating after antifungals

of pain on the 10th day of treatment and a reduction in the degree of OM on the 14th day of treatment compared to the control group [46]. Another trial compared the use of LLLT or placebo in cancer patients receiving chemotherapy or hematopoietic stem cell transplantation; 86% of the participants were leukemia patients. In the laser-treated group, the average duration of OM to resolution of clinical symptoms was significantly shorter [47]. Other clinical studies by Cauwels et al., Karaman et al. and Fiwek et al. conducted similar clinical proceedings to those presented earlier. All obtained results confirmed that the use of PBMT reduces pain and discomfort in patients and has a positive effect on the severity and duration of OM [48–50].

Platelet-rich plasma and platelet gel

Platelet-rich plasma (PRP) contains a platelet concentration five times higher than the baseline, cytokines, growth factors, adhesion molecules, a certain amount of red blood cells (RBCs) and white blood cells (WBCs) depending on the preparation method. It is obtained from fresh peripheral blood with a platelet concentration above the baseline value [51]. Platelet gel (PG) is derived from PRP and consists of platelet concentrate (PC) deposited in a semisolid network of polymerized fibrin. The biological reasoning behind the use of PRP and PG in regenerative medicine is related to the degranulation of platelets, allowing the release of growth factors, reducing the inflammatory response and promoting cell proliferation and differentiation in the targeted tissue. Use of PRP has broadened considerably to encompass many fields of medicine, including dermatology, orthopedics, surgery, sports medicine, aesthetic medicine and dentistry [52]. Some reports have also been published about the efficacy of these agents in reducing neuropathic and neurological pain associated with injuries. The use of platelet concentrates accelerates the healing of surgical wounds, skin ulcers, lesions typical of diabetic foot and chronic mucositis, as well as muscle and tendon repair [53].

Within the last few years, there has also been an attempt to use this agent in the field of oncology, including pediatrics. Piccin et al. examined the effectiveness of PG in treatment of severe oral and esophageal mucositis in an adult patient undergoing auto-HSCT for non-Hodgkin lymphoma. The patient self-administered the preparation in her oral cavity. A significant improvement in mucositis and pain was noted after only 3 days of consecutive use. On day 8, the inflammation was found to have regressed. No side effects of the preparation were observed [54]. Another study described a five-year-old girl with rhabdomyosarcoma undergoing intensive chemotherapy who developed stage IV OM with severe pain and fever during the second course of treatment. She was treated with antimicrobial drugs, analgesics, chlorhexidine and oral rinses, but no improvement was observed after three days of therapy. The decision was made to start a thrice-daily oral application of platelet gel. After just 12 h, significant improvement in mucosal condition was observed, and two days later the patient did not require analgesic treatment, was able to receive oral nutrition, continue chemotherapy treatment, and the oral ulcers were progressively improving [55].

Picardi et al. conducted a study on an Italian group of patients affected by hematologic malignancies and who after allo-HSCT developed cGvHD with oral involvement in the form of painful ulcers and impaired oral nutrition. Limited oral ulceration cGvHD was treated with PG alone, while the most extensive cGvHD received PG in combination with steroids. The results indicated that all patients treated with PG achieved rapid improvement in oral pain and food intake after just 2 applications of the gel. The absence of ulcer recurrence at the site of previous platelet gel application proves that its growth factor-rich content makes it a viable tool for maintaining long-term tissue repair [56]. The 2021 clinical trial studied the effectiveness of platelet gel in children with stage II and III OM during chemotherapy. In the study group, PG was applied to mucosal lesions four times a day in addition to standard treatment including analgesics, antimicrobials, and oral rinses. In almost all patients, the application of PG provided relief, reduced pain and decreased any burning sensation after the first day of application. In addition, there was a significant improvement in the appearance of the mucous membranes and regression of the inflammatory lesions within 4–5 days [57].

Other

There are several other individual, insufficiently researched ideas and treatments for OM. Additional scientific studies reporting innovative treatment attempts are presented and summarized hereafter.

Taxifolin is a bioactive flavonoid found commonly in grapes or olive oil, among others, with well-established pharmacological effects, including having anti-inflammatory, antioxidant properties, and also antimicrobial and anticancer potential. It reduces oxidative stress, modulates signaling pathways to prevent apoptosis and decreases the expression of pro-inflammatory cytokines [58, 59]. Bayramoglu et al. conducted a study on MTX-treated rats, administering taxifolin by gavage. The oral mucosa was subsequently analyzed macroscopically, histopathologically and biochemically. It was found that taxifolin antagonized the MTX-induced increase in oxidative and pro-inflammatory factors and decrease in antioxidant properties in the internal tissues of the cheek and tongue. Taxifolin also significantly reduced histopathological damage induced by MTX administration. The results suggest that taxifolin may be useful in the treatment of MTX-induced oral mucositis [60].

Film-forming or coating agents might also be useful for the treatment of established mucositis. These include sucralfate and hydroxypropyl cellulose, whose efficacy in reducing OM has been clinically studied. An initial randomized clinical trial reported good outcomes in reducing the severity of OM in a patient population treated with chemotherapy (5-fluorouracil) after treatment with sucralfate. However, a subsequent double-blind phase III study did not support the hypothesis from the initial study, as there were no differences in the severity or duration of inflammation between the study and placebo group [61]. Hydroxypropyl cellulose is a bioadhesive substance that can function as a protective barrier over mucosal ulceration enabling pain relief and improved healing. The study group included chemotherapy-treated patients with symptoms of OM. After application of the gel with hydroxypropyl cellulose and benzocaine hydrochloride, oral pain and discomfort were assessed using a visual analog scale (VAS) and visual assessments of the amount of drug that remained on the mucosal lesions. Benzocaine hydrochloride, combined with a protective, mucoadhesive film coating, alleviated discomfort even with

exposure to an irritating beverage. This indicates that the administered treatment may enable patients with OM to drink and eat with significantly reduced or no pain. However, the results are difficult to interpret due to the use of a gel combining two active substances in the study group [13, 62].

Pain management

Pain may be the only symptom of OM, although it is usually the first of many. The crucial issue remains to control it effectively, as severe pain impairs food and drink intake, which may result in malnutrition and mineral deficiencies. In addition to the classic analgesic ladder approach in children, additional less-known pain management methods are presented, including topical analgesics and the use of virtual reality.

Topical morphine

The use of non-opioid topical analgesics can reduce the dose of systemic opioids. Compared to their administration, topical morphine has been shown to have even more beneficial effects. These include simplicity of use, low cost and minimal systemic side effects. The benefits are not only related to pain relief. There is also some evidence that opioid receptors are expressed on oral epithelial cells and morphine may accelerate cell migration, which in turn can enhance the wound healing process. Topical morphine is applied as a solution to swish and spit. There have been studies on the selection of the most effective percentage solution. Sarvizadeh et al. reported that 2% morphine was effective in reducing the severity of OM. However, its use with a pediatric population suffering from ALL is unknown. MASCC/ISOO suggest 0.2% topical morphine mouthwash for the treatment of OM-associated pain in head and neck cancer patients treated with RTX/CTX [63, 64].

Benzydamine

Benzydamine is a local anti-inflammatory drug that also has analgesic properties. It is an inhibitor of leukocyte-endothelial interactions, neutrophil degranulation, vasodilation and vascular permeability. It also reduces the synthesis of TNF-α, IL-1β and prostaglandins [65]. Although it is widely used in radiotherapy-induced OM, there is still no strong evidence for its use in hematologic malignancies. However, given that it is feasible, inexpensive and frequently administered in pediatrics, more studies are needed in children with ALL [66].

Virtual reality

Virtual reality (VR) is a feasible, non-pharmacological method of distraction and adjustment to conventional pain management. VR is a digital simulation. It can be either immersive (IVR) or non-immersive, depending on the patient's point of view and the experience created during use. Non-immersive VR allows content to be viewed through traditional graphical displays, such as a TV or smartphone, while IVR includes head-mounted glasses and motion tracking systems. This allows full immersion to be attained. VR distraction has the potential to manage pain and anxiety in children with hematological cancers [67].

Virtual reality can be used for more than just the management of chronicling pain associated with malignant disease. It has been tested in patients undergoing painful procedures, such as burn wound care, with the following results: reduced pain scores and decreased use of opioids [68]. The aforementioned results indicate that this use of virtual reality may prove helpful during the treatment of children with oral mucositis. This distraction and diversion may be particularly important during procedures that increase a child's pain sensation associated with oral interventions, which include physical examination, mouth rinsing or application of topical medications.

Conclusions

Methotrexate, an antifolate agent, is one of the most widely used drugs in various malignancies and plays a crucial role in treating ALL in children. Patients with Down syndrome have an extra copy of the gene responsible for encoding the transporter for methotrexate, resulting in a significant increase in the toxicity of the drug in this group. One of the most frequent side effects following its administration is inflammation of the mucosa, including the oral cavity. Clinical trials have evaluated the effectiveness of medications such as glutamine, palifermin, chlorhexidine, amifostine, cyclooxygenase-1 inhibitors, leucovorin, or other methods including laser therapy and oral cryotherapy in preventing OM. Typically, oral mucositis develops a few days after chemotherapy. Symptoms are varied, ranging from mild soreness in the mouth to erythema, ulcers and severe pain. There are several methods used to control established inflammation and reduce pain more effectively: laser therapy, platelet-rich plasma and platelet gel, taxifolin, film-forming and coating agents. Crucial support is offered by interventions involving analgesic treatment, including topical morphine and benzydamine and a more recent approach based on virtual reality, for example.

Article information and declarations

Author contributions

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Review article

Liver tumors

The influence of fluid therapy on short- and long-term outcomes in patients undergoing liver resection for malignant indications

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Although fluid therapy in hepatic surgery affects the postoperative course and morbidity, there is a paucity of unequivocal guidelines in the literature as to which of three fluid strategies to use: liberal, restrictive or goal-directed. We performed a review of literature regarding fluid management strategies in major abdominal procedures, focusing on hepatic surgery. The quantity and quality of fluids infused perioperatively is often dependent on the preference of the physician, institutional experience and practices. A liberal fluid regimen carries the risk of impaired wound healing and prolonged ileus, furthermore in liver surgery it may increase blood loss. Restrictive fluid therapy is the mainstay of the anesthetic management in hepatic resections, keeping the central venous pressure low controls outflow from the liver and results in a decrease in intraoperative blood loss. In recent years, goal-directed fluid therapy (GDFT), as a component of enhanced recovery pathways after surgery (ERAS) programs, has gained in popularity. It is based on the concept of hemodynamic optimization in order to ensure optimal tissue perfusion and oxygen delivery. Furthermore, a fluid infusion strategy should be individualized in terms of the unique pathophysiology of the patient (e.g. cirrhosis) and the specific requirements of the surgical technique (laparoscopic procedures). Controversy regarding often contradictory data, leaves the clinician at a loss as to which fluid strategy will best serve the patient. Therefore, it is imperative to design and conduct clinical trials in a homogenous group of patients to define the optimal type and amount of fluid for patients undergoing hepatic surgery.

Key words: liver resection, fluid management, goal-directed therapy, restrictive therapy, enhanced recovery pathways after surgery

Fluid regimes in major abdominal surgery

Relevant articles were searched for using the Pubmed database with the following terms: "liver resection", "liver surgery" , "goal-directed therapy", "fluid management" and "enhanced recovery after surgery". The results were independently assessed by the authors for scope and relevance.

Many factors influence the normal postoperative course of patients undergoing extensive liver surgery. One of those is a fluid infusion strategy; preoperatively – in urgent cases – intraoperatively and in the postoperative period. Transfusion of the optimal fluid volume during surgical procedures and in the postoperative period affects the course

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of the operation, as well as postoperative morbidity. Both excessive and insufficient fluid intake can be harmful [1, 2]. The main goal is to restore and maintain fluid volume to ensure homeostasis in terms of euvolemia, electrolyte balance and tissue perfusion. [3]. Intra- and postoperative fluid transfusion strategies have been the subject of numerous studies. Both surgeons and anesthesiologists have different approaches to fluid management. The confirmation of the thesis that fluid therapy depends mainly on individual preferences of the physician is a study by Lilot et al., which included a group of 5,912 patients undergoing various abdominal procedures. The authors concluded that a patient weighing 75 kg can receive from 500 to 5400 ml of crystalloids depending on the physicians preference [4]. There are generally three main strategies of perioperative fluid therapy: "liberal", "restrictive" and "goal-directed". Each of these strategies has its supporters and opponents, and each has been the subject of randomized trials. After years of a "liberal" approach, a paper by Brandstrup et al. was published comparing "liberal" and "restrictive" strategies. The results of the study clearly indicated a statistically significant increase in the number of complications in the patients from the "liberal" group [5]. Over the following years, the "restrictive strategy" has gained popularity, as one of the components of the "enhanced recovery after surgery" (ERAS) protocols. In 2018, a multicenter study was published comparing the two strategies. The study included a group of 3,000 patients. One of the key results of the study was the finding of a statistically higher incidence of acute kidney injury in patients who received fluids according to restriction protocol [6].

The adopted perioperative fluid therapy strategies have been extensively studied especially in patients undergoing gastrointestinal procedures. Some researchers believe that excessive fluid loading impairs the healing of intestinal anastomoses, delays the return of gastrointestinal motility, increases the overall incidence of complications, increases the length of hospital stay and the cost of treatment [7–9]. While this is true in patients undergoing procedures on the large intestine [10], it has been shown that the use of restrictive fluid therapy does not bring such benefits in cases of pancreatoduodenectomy [11, 12]. With regards to abdominal surgery, it should be noted that the specificity of individual procedures (the number of intestinal anastomoses, the need to open the retroperitoneal space, the presence of vascular anastomoses) affects the movement of fluids between compartments. In order to recommend a "surgery specific" fluid strategy, studies should be carried out in homogeneous groups.

Evolution of aim-directed fluid protocols. Optimization of oxygen delivery to tissues

In addition to the restrictive and liberal strategies discussed so far, or rather, as a result of the inconclusive results of conducted studies, a third strategy named goal-directed therapy (GDT) was introduced.

This strategy was created not only in response to the contradictory results of studies on the previously mentioned liberal and restrictive strategies, but also stemmed from in-depth analysis of the pathophysiology of the phenomena leading to increased number of complications, prolonged hospitalization and postoperative deaths in patients undergoing non-cardiac surgery. It was proven that intraoperative tissue perfusion (tissue blood flow), arterial oxygen saturation, hemoglobin concentration and cardiac output – components of the parameter referred to as oxygen tissue delivery (DO_2) – affect mortality and morbidity. The conducted studies have shown that perioperative fluid therapy, optimized on the basis of hemodynamic parameters significantly reduces the number of postoperative complications and the risk of death. At the same time, it has been shown that traditional parameters monitored intra- and postoperatively, i.e., blood pressure and heart rate, are not sensitive enough to detect moderate hypovolemia, which may cause inadequate tissue perfusion, especially in the visceral bed [13–15]. Goal-directed therapy is based on the premise that perioperative fluid administration is essential to maximizing DO_2. Therefore, it should be based on dynamic flow-dependent parameters, i.e., stroke volume (SV) and its variability in response to fluid bolus (stroke volume variation – SVV) [16, 17]. The results of randomized trials, where the primary endpoint was the occurrence of postoperative complications (as in other studies evaluating the liberal and restrictive strategy) are contradictory. The FEDORA study showed a statistically significant lower complication rate in patients from the GDT group who underwent abdominal procedures [15]. However, the work of Pestania et al. (POEMAS study) showed no such relationship [18].

Concept of perioperative euvolemia

Most studies refer to intraoperative fluid administration. Some papers treat this topic more broadly and include the preoperative and postoperative period as well. The protocols regarding the intake of fluids before abdominal surgery clearly indicate the benefits of the lack of restrictions in oral administration up to 2 hours before the induction of anesthesia [19]. Postoperative fluid therapy should continue as long as the patient is unable to tolerate oral intake. Its primary goal is to maintain intravascular volume while avoiding a positive fluid balance which, among others, leads to delayed healing of the wounds and anastomoses, consequently leading to a longer hospital stay, prolonged ileus and other complications [20]. In recent years the term "goal-directed therapy" has been introduced in literature in relation to intraoperative infusions, and "zero balance" – in relation to postoperative management.

Fluid therapy in liver surgery

The incidence of liver tumors is on the rise [21]. Indications to liver resections are mainly oncological, with the majority of cases being hepatocellular carcinoma and metastatic

tumors. The basic differences in the approach to intraoperative and postoperative fluid therapy in patients undergoing liver surgery will be presented below. Clinical situations related to patients who are hemodynamically unstable prior to emergency surgery will be intentionally omitted. Septic patients, as well as those receiving total parenteral nutrition will not be discussed either. Thus, we will concentrate on fluid therapy in ASA ≤3 patients undergoing elective liver procedures.

Liver surgery can be divided into hepatic parenchymal surgery, biliary tract surgery and cholecystectomy. The aim is to discuss the strategy of intra- and postoperative fluid therapy in large (including excision of more than 3 segments) liver resections.

Limitation of blood loss in liver surgery

One of the key aspects of liver surgery is the bloodless surgical field. The inflow to the liver may be controlled, e.g. by the Pringle maneuver (a temporary tightening of the hepatoduodenal ligament). Back bleeding from valveless hepatic veins is prevented by low central venous pressure. CVP of 5 mmHg is recommended to provide unobstructed outflow and limit blood loss. It has been shown that maintaining low central venous pressure effectively reduces bleeding, limiting the need for blood product transfusions, morbidity and postoperative mortality. At the same time, it has been shown that it does not significantly affect the incidence of postoperative acute kidney injury [22–27].

Looking for a silver bullet in fluid management

Recently, the role of central venous pressure (CVP) as a reliable parameter for assessing volemia has been increasingly questioned. Hemodynamic parameters as guides to volume management have gained popularity, although analysis of the literature reveals that these methods also have limitations. Problematic situations include mechanical ventilation and cardiac arrythmias to name a few [28].

Regardless of the monitoring methods used, the aim of the anesthetic technique is to maintain the free outflow of the blood through the hepatic veins. This is achieved by simultaneously employing several methods: fluid restriction, head-elevated patient positioning and ventilation techniques with pressure limitation in airways. Vasodilators (nitroglycerin) sublingually or intravenously are also used. It should be emphasized that these strategies are limited to the stage of parenchymal transection. Fluid infusion is being restricted to 1 ml/kg/h of buffered crystalloid plus additional volume to make up for the ongoing blood loss at a ratio 1:1. Intraoperative fluid therapy strategies are the subject of randomized trials. Correa-Galle et al. compared a conventional strategy with "goal-directed fluid therapy". Randomization was performed after the resection stage. The "conventional" group received an infusion of crystalloid at a dose of 6 ml/kg/h. The "goal-directed" group received infusion at a rate of 1 ml/kg/h with the simultaneous supplementation of albumin solution with an aim to restore stroke volume variation (SVV) to the level measured at the induction of anesthesia. In both groups, additional fluid volume was administered to maintain systolic blood pressure ≥90 mmHg or diuresis >25 ml/h. Red blood cell concentrate was also given to ensure hemoglobin concentration ≥7g/dl. In the postoperative period, conventional fluid therapy of 1.2 ml/kg/h was used with additional infusion in order to maintain the above-mentioned targets. There was no statistically significant difference in terms of the incidence of postoperative complications, the length of hospital stay or other variables specified in the study. A statistically significant difference was observed in the total volume of fluids infused during the post-hepatectomy phase. In the "goal-directed" group it was lower by an average of 900 ml [29]. Another study by Weinberg et al. compared the addition of a fluid restrictive intraoperative cardiac output-guided algorithm to standard fluid protocol. The "conventional care" group consisted of patients in whom the amount of fluid and catecholamines administration were at the discretion of the anesthesiologist. In both groups a higher incidence of postoperative complications was found, compared to the previously cited study, and these were mainly grade I and II complications according to the Clavien-Dindo classification. This trial showed a statistically significant lower fluid balance in the study group compared to the control group. There were no differences in the incidence of acute kidney injury between the groups [30].

Studies conducted by Kim Y. et al. [31] and Lilot M. et al. [32] showed that despite the recommendations regarding intraoperative fluid therapy in patients undergoing abdominal procedures, including liver resections, there is a very large discrepancy regarding the amount of fluids administered between individual centers and even physicians. Hepatic resections are procedures that can significantly affect hemodynamics, e.g. by compressing the inferior vena cava during surgical maneuvers, which causes a decrease in venous return and consequently cardiac output. In addition, the liver because of its metabolic function, i.e., contributing to lactate clearance, affects the acid-base balance.

Taking into account these facts and the protocols of enhanced recovery after surgery (ERAS) [33], which recommend intraoperative fluid restriction but not at the cost of organ hypoperfusion, the following can be suggested: the most appropriate approach to perioperative fluid therapy in liver resections should be goal-directed therapy with fluid restriction until transection completion (low central venous pressure) with subsequent volemia restoration under SVV guidance. Indicators of organ perfusion, e.g. serum lactate concentration should be monitored and included in decision-making regarding fluid therapy in the postoperative period with the aim to stabilize hemodynamic parameters, maintain diuresis and improve metabolic hemostasis [34, 35].

In the postoperative period, methods based on techniques that assess the diameter of the inferior vena cava,

its collapsibility, extensibility and the Doppler spectrum of the portal vein and hepatic veins can be used to guide fluid therapy [36, 37]. To date, there are no reports on the effectiveness of these methods in liver surgery.

There are no data concerning the impact of the applied fluid strategy on early and long-term prognosis in resections performed for oncological reasons. Restrictive and goal-oriented therapy facilitates visualization in the operating field, which may improve the radicality of the procedure. No studies have investigated the relation between the type of perioperative fluid regimen used as regards tumor recurrence risk. Further research in this direction is warranted.

Laparoscopic techniques

Laparoscopic liver resections have been gaining popularity. There are no randomized prospective studies comparing different strategies (liberal, restrictive and goal-directed) in resections performed laparoscopically. Nevertheless, in the published trials, the technique of maintaining low central venous pressure in the transection phase was adopted as a standard, with the aim of reducing bleeding. However, low central venous pressure together with increased intra-abdominal pressure increases the risk of gas embolism (carbon dioxide) [38, 39]. It seems prudent to use SVV rather than CVP monitoring as an indicator of vascular bed filling and use it as a guide to fluid therapy during the transection phase. In laparoscopic procedures, central venous pressure is notoriously unreliable due to the influence of the pneumoperitoneum on the inferior vena cava pressure [40, 41].

Challenges in cirrhosis

Data on fluid therapy in extensive resections in patients with cirrhosis is lacking. Published trials describe anesthesia complexity in this population, including strategies of fluid therapy [42, 43]. Taking into account the detailed data on the multiorgan consequences of cirrhosis and liver failure, it can be assumed that goal-directed therapy should be adopted.

Depending on the severity of cirrhosis and abnormal liver function (assessed according to the MELD or Child–Pugh scale), organ dysfunctions will vary, e.g. the presence of hepatorenal syndrome or the severity of hyperkinetic circulation with a relative or absolute intravascular volume deficit. Portal hypertension with collateral circulation, independently of other causes of coagulopathies, may increase the risk of bleeding at the stage of abdominal cavity incision. Multifactorial coagulopathy complicates anesthesia management. Vigilance over blood loss is essential with thresholds for red blood cells, platelets and plasma transfusions to maintain homeostasis. Fluid strategy, other than goal-directed, may exacerbate pathologies present in cirrhosis. The restrictive strategy may lead to hypoperfusion of vital organs, including the liver, intestines and kidneys, and as a result, lead to their failure. The liberal strategy, in addition to preexisting hypoalbuminemia, may lead to edema of the liver and the intestinal wall. Removal of the excess fluid may prove difficult, and, in some cases, impossible without implementing renal replacement therapy.

Performing major abdominal surgeries in patients with hepatic insufficiency, requires balancing the risk of exacerbation of liver failure and its organ consequences with expected benefits. Mortality in cirrhotic patients decreased due to advances in surgical techniques, anesthesia and postoperative care. In group C according to the Child–Pugh scale, it is expected to be 12%, in comparison to previous years, when it was estimated at 82% [44, 45]. However, these estimates do not refer to hepatic surgeries. Scheduled liver resections in C group are contraindicated.

Types of fluids

An increase in lactate concentration in patients undergoing liver resection is a common phenomenon. This is due to impaired lactate liver clearance but can also be caused by increased anaerobic metabolism associated with maintaining low central venous pressure and subsequent organ hypoperfusion. It is widely accepted to use balanced crystalloid solutions. A study by Weinberg et al. showed that acetate buffered crystalloids are recommended. Better biochemical and hematological indices are obtained in terms of electrolyte balance, acid-base balance and coagulation parameters compared to solutions buffered with lactates [46]. Data on the safety of hydroxyethyl starch solutions are conflicting and mainly drawn from studies of intensive care patients. However, most authors indicate a potentially higher risk of acute kidney injury and coagulation disorders in patients receiving these solutions [47–49]. No definitive conclusions can be drawn on gelatin solution use. Conclusive data from randomized trials is lacking. Acute kidney injury, coagulation disorders and remnant failure may complicate liver resection. Thus, in the author's opinion, the use of the above-mentioned solutions should not be encouraged during liver resection and in the postoperative period. Postoperative fluid therapy in patients undergoing laparoscopic liver resections does not differ significantly from what has been discussed previously. This technique results in fewer complications, faster recovery of gastrointestinal function, which encourages earlier oral fluid intake and a shorter hospital stay. The published results of studies on the safety of using albumin solutions cover mainly critically ill patients and patients undergoing abdominal surgery, not specifically liver resection [50, 51]. Although there are no studies on this group of patients, being aware of the possibility of liver failure after the procedure (sometimes before) and the physiological role of albumin i.e. in maintaining oncotic pressure, preventing the occurrence of edema, it can be assumed that their administration both intra- and postoperatively is beneficial – especially when large volumes of crystalloids would have to be used otherwise.

Conclusions

Fluid transfusion in the perioperative period in major liver resections is a complex topic. The chosen fluid strategy has

an impact on morbidity and the length of hospital stay. It is of the utmost importance to detect features of cirrhosis and its complications which may largely determine the type of strategy adopted. In extensive liver resections without cirrhosis, restrictive fluid therapy is most often used. During liver resection in cirrhotic livers, goal- directed therapy is preferred. It should be emphasized that only close cooperation between the surgeon and the anesthesiologist during the procedure enables the rational implementation of the adopted strategy, depending on the progress of surgery and clinical situation. The type of fluid is equally as important as the volume. The use of balanced crystalloid solutions is recommended with the exception of lactate-buffered solutions. In cirrhotic liver resection, it is important to maintain an adequate concentration of albumin in the serum, which is justified by the pathophysiology of cirrhosis and its consequences.

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Review article

Clinical nutrition in oncology

Anemia in cancer patients: addressing a neglected issue – diagnostics and therapeutic algorithm

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Cancer-related anemia (CRA) continues to be a critical concern despite advancements in oncology treatments. The prevalence of anemia varies from 30% to 90%, impacting the quality of life and prognosis of cancer patients. While CRA is often attributed to antineoplastic therapies, it can also result from the disease itself. Inflammation and the iron regulatory hormone hepcidin play significant roles in CRA pathogenesis. Treatment-induced anemia caused by chemotherapy, tyrosine kinase inhibitors (TKIs) and immunotherapy, pose additional challenges. Intravenous (IV) iron has emerged as an effective treatment option for CRA, overcoming limitations associated with oral iron supplementation. Combining IV iron and ESAs enhances treatment outcomes. Future directions involve exploring ESA safety and their immunomodulatory effects. Transfusions provide quick relief but might impact prognosis and immune response. Other considerations include incorporating physical activity and exploring hepcidin-directed therapy. In conclusion, CRA management necessitates a multifaceted approach to address deficiencies, optimize therapies and improve patient outcomes.

Key words: anemia, cancer, hepcidin, erythropoiesis-stimulating agents, blood transfusions

Introduction

Although modern oncology drugs employ mechanisms distinct from classical 20th-century cytotoxic therapies, cancer-related anemia (CRA) remains an underestimated issue. It is not always solely a consequence of antineoplastic treatments. The prevalence of anemia, varying from 30% to 90%, depends on factors such as neoplasm type, disease progression, or treatment method [1–4]. Anemia ranges from causing mild, persistent symptoms like fatigue to life-threatening conditions, especially for individuals with concurrent chronic diseases. Without a doubt, it significantly impairs quality of life (QOL) for cancer patients [5–6].

General definitions

According to the World Health Organization (WHO), anemia is a state where hemoglobin levels or red blood cell counts fall below the lower limits of normal (women <12 g/dl, men <13 g/dl) [7]. Cancer-related anemia (CRA) can result from cancer treatment (chemotherapy-induced anemia [CIA]) or the disease itself. Neoplasms can affect red blood cell (RBC) production (erythropoiesis), RBC breakdown (hemolysis), and blood loss (bleeding). For anemia resulting from oncological therapy, the Common Terminology Criteria for Adverse Events (CTCAE) grading system is used [8]. However, there are inconsistencies between WHO values and those of CTCAE (tab. I).

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Table I. Comparison of the values proposed by the World Health Organization and adapted by the Common Terminology Criteria for Adverse Events (CTCAE)

Severity of anemia	WHO (Hb)		CTCAE	CTCAE level
	women	men		
normal level	≥12 g/dl	≥13 g/dl	up to lower limit of normal (LLN)	0
mild	10–11.9 g/dl	10–12.9 g/dl	10 g/dl – LLN	1
moderate	8–9.9 g/dl	8–9.9 g/dl	8–9.9 g/dl	2
severe	6.5–7.9 g/dl	6.5–7.9 g/dl	<8 g/dl	3
life-threating	<6.5 g/dl	<6.5 g/dl	life-threating consequences	4

Pathogenesis and diagnostic approach

Anemia diagnosis must consider the intricate interplay of RBC production and usage across various organs (the intestines, liver, spleen, kidney, bone marrow) [9]. In most cases, CRA is primarily attributed to two causes – iron deficiency and concurrent antineoplastic therapy. Key indicators in CRA diagnosis are serum ferritin (SF) and transferrin saturation (TSAT; serum iron/total iron binding capacity x 100). Other iron-related parameters are often influenced by external factors and are unreliable predictors (e.g., MCV, soluble transferrin receptor) or are not routinely available (e.g., zinc protoporphyrin or hepcidin levels).

Functional and absolute iron deficiency

Typically, CRA patients exhibit normocytic anemia accompanied by iron deficiency (TSAT < 20%) and normal or elevated SF > 100 ng/ml [10–13]. This condition is referred to as functional iron deficiency anemia (FIDA). Another situation arises when TSAT is <20% and ferritin is <100 ng/ml, leading to absolute iron deficiency anemia (AIDA) [14]. These two clinical scenarios have distinct underlying causes. AIDA is usually linked to blood loss or inadequate iron intake/malabsorption. FIDA, on the other hand, arises due to iron sequestration driven by chronic inflammation (involving hepcidin) [15], and/or iron-restricted erythropoiesis prompted by endogenous erythropoietin production or erythropoiesis-stimulating agents [16].

Role of inflammation and hepcidin

Inflammation is a hallmark of cancer [17], impacting erythropoiesis *via* cytokines like IL-1, IL-6, IL-10, IFN-γ, TNF-α, and raising reactive oxygen species (ROS) levels. The levels of these cytokines can predict hemoglobin concentrations [18]. Hepcidin, a liver-produced iron regulatory hormone, is affected by both inflammatory cytokines and ROS. Hepcidin inhibits iron release to erythropoiesis from macrophages and hepatocytes, and also influences iron absorption in enterocytes. This hormone binds to ferroportin, an iron exporter, causing its degradation [19–20]. Consequently, oral iron absorption is limited in cancer patients, reducing its availability for dietary supplementation.

Treatment-induced anemia

In the past five years, over 200 cancer drugs have been approved, with 14% surpassing the prior standard of care [21]. Chemotherapy-induced anemia remains a significant concern, as it is still widely used, especially in neoadjuvant and adjuvant settings for solid tumors. Up to 90% of solid tumor patients experience anemia during chemotherapy [22], with incidence varying by regimen, tumor type and stage.

New agents like tyrosine kinase inhibitors (TKIs), small molecules and immunotherapy (ICI) can induce or exacerbate preexisting anemia differently from traditional cytotoxic agents. TKIs often lead to hematological toxicities [23], with mechanisms varying. Some TKIs, such as sunitinib, imatinib and pazopanib, can cause macrocytosis, which may serve as a predictor of patient survival [24–26]. The mechanism might relate to c-KIT inhibition [26]. Rarely do drugs like alectinib induce hemolytic anemia [27].

Immunotherapy can also lead to anemia via autoantibody-induced hemolysis, requiring treatment with steroids and rituximab [28]. In extremely rare cases, lethal aplastic anemia has been described [29].

CRA treatment

Three main strategies address CRA, either individually or in combination. Correcting deficiencies (iron, vitamin B_{12}, folate) is paramount. Erythropoiesis-stimulating agents (ESAs) and red blood cell concentrates (transfusions) follow.

Iron treatment

While oral iron is standard for general iron deficiency anemia treatment, it has limitations in cancer patients due to gastrointestinal (GI) intolerance. GI symptoms often accompany cancer treatments, making oral supplementation difficult [30]. Moreover, heightened hepcidin levels impair proper iron utilization. Studies suggest alternating dosing schedules could decrease hepcidin levels and enhance iron absorption [31–32]. Intravenous (*iv*) iron is preferred for CRA patients due to its more direct delivery and bypassing GI issues [33–34]. Intravenous iron, alone or with ESA, effectively treats chemotherapy-induced anemia, saves costs and improves QOL [35–38]. Intravenous iron suits both functional and absolute iron deficiency scenarios.

Intravenous iron treatment

Intravenous iron formulations have been utilized in human medicine for nearly a century; however, some physicians continue to harbor unnecessary concerns reminiscent of the early days of its introduction [39]. The prospective European ECAS study, conducted at the beginning of the 21st century to gather data on the prevalence and treatment of anemia, revealed that only 6.5% of patients received iron treatment [40]. These concerns likely stem from apprehensions about potential side effects.

Safety and side effects of intravenous iron supplementation

Contemporary iron products (as outlined in table II) all possess an iron core enveloped by a carbohydrate shell, a feature that distinguishes them from one another. Intravenous iron infusions seldom lead to hypersensitivity reactions, and although such reactions can be life-threatening, severe anaphylactic-type reactions are exceedingly rare [41]. High molecular weight iron dextrans, previously used, had significantly higher rates of serious adverse drug events, leading to their discontinuation. The new formulations are designed to be safer. A comprehensive systemic review that evaluated the safety of intravenous iron across randomized clinical trials established that intravenous iron is not correlated with an increased risk of serious adverse events [42]. The European Medical Agency has issued recommendations for managing allergic reactions associated with intravenous iron-containing medications, concluding that the benefits of these medications outweigh the associated risks [43]. As a result, administering a test dose with these new formulations is no longer advised.

Prevention and management protocols for infusion reactions have been well-delineated and align with approaches used in managing other infusion-related reactions observed in the field of oncology [44, 45]. There is contradictory data concerning cardiotoxicity and the risk of exacerbating infections when using intravenous iron [42, 46, 47]. Consequently, intravenous iron administration should be avoided in patients with active infections and on the same day as cardiotoxic chemotherapy administration.

In conclusion, the use of more recent intravenous iron formulations is regarded as safer compared to other commonly used methods in addressing anemia among cancer patients [42]. Nonetheless, determining the optimal dosing and treatment schedule for intravenous iron remains an ongoing effort, with variations among the different available products.

Erythropoiesis-stimulating agents

Erythropoietin (EPO), a hormone produced in the kidneys and liver, increases red blood cell production in response to hypoxia. Recombinant EPO was synthesized in the 1980s, revolutionizing chronic kidney disease treatment [48]. ESAs entered oncology in the 1990s, gaining popularity but later encountering safety concerns [49]. Modern erythropoiesis-stimulating agents (ESAs) (tab. III) are indicated for adult cancer patients with non-myeloid malignancies receiving chemotherapy, aiming to raise hemoglobin from 8–10 g/dl to no more than 12 g/dl. ESA treatment necessitates reevaluation after 4–6 weeks, adjusting doses based on response or cessation if no response is observed.

ESAs concerns

The most common side effects include allergic reactions and cardiovascular complications. Allergic reactions range from more commonly occurring mild local injection site reactions to rare but serious reactions that require prompt attention. Early reports regarding thrombotic risk [50] led to concerns about the safety of ESAs and their potential impact on the survival of cancer patients. A recent systematic review of randomized controlled trials revealed that although this type of therapy is associated with adverse cardiovascular effects, including venous thromboembolism (VTE), it does not affect patients' overall survival, and ESAs can be used safely [51]. Due to the lack of prospective trials, neither the National

Table II. Intravenous iron formulations: characteristics, dosing and comments. The information based on the summaries of product characteristics approved by the EMA and/or FDA

Preparation	Dosing	Comments
ferric carboximaltose	20 mg/kg up to 750–1000 mg intravenous infusion or single injection up to minimum 15 mins. Second dose might be administered after ≥ 7 days	may cause transient hypophosphataemia
derisomaltoze	500–2000 mg depending on the weight, infusion over 15 mins. (up to 1000 mg) and over 30 mins. (>1000 mg) or 500 mg bolus at a speed of 250 mg/min.	relatively a new product
iron sucrose	200 mg maximum dose in injection, 500 mg infusion of at least 3.5 h	commonly used in the USA
LMWID	depending on the preparation – 240–360 mins. infusion – complicated dosing (test dose recommended)	complicated dosing
ferric gluconate	125 mg in 60 mins., repeat in 2–3 weeks until a total dose of 1000 mg is obtained	associated with serious infusion reactions
ferumoxytol	510 mg in 15 mins. not available in the European Union	might influence MR results up to 3 months

LMWID – low molecular weight iron dextran; MR – magnetic resonance

Table III. Erythropoiesis-stimulating agents. The information is based on the summaries of product characteristics approved by the EMA and/or FDA

Erythropoiesis-stimulating agent (ESA)	Dosing	Dose escalation possibility
epoetin alfa	150 units/kg 3x/week or 30 000 units/week	300 units/kg 3x/week or 60 000 units/week
epoetin beta	30 000 units (450 units/kg)	60 000 units (900 units/kg/week)
epoetin theta	20 000 units/week	40 000 units/week (max. 60 000 units/week)
darbepoetin alpha	2.25 µg/kg/week or 500 µg/3 weeks	4.5 µg/kg/week

Comprehensive Cancer Network® (NCCN®) nor the European Society of Medical Oncology recommends the routine use of standard prophylactic anticoagulation in the absence of other risk factors [33, 52]. The use of validated scales predicting VTE events, such as the KHORANA scale, is strongly encouraged for patients receiving chemotherapy [53]. Another significant cardiovascular effect is arterial hypertension, which typically manifests at the beginning of therapy. The exact mechanism of this complication is not well understood. An important subgroup of patients includes those with chronic kidney disease or preexisting arterial hypertension. For these individuals, the introduction of ESAs should be cautious, and a gradual correction of anemia is advised [54].

ESAs and possible stimulation of cancer growth

Increased EPO signaling has been observed on cancer cells, particularly in the hypoxic regions of various tumors [55]. This observation led to the hypothesis of potential cancer growth stimulation. Early trials suggested inferior overall survival among patients receiving ESA during chemotherapy [56–57]. However, all trials that raised such concerns targeted hemoglobin levels above 12 g/dl. When ESAs are used within registered indications among patients receiving chemotherapy for non-myeloid cancers with hemoglobin levels below 10 g/dl and a target range up to 12 g/dl, no impact on overall survival was confirmed [51, 58–61]. Recent randomized, double-blinded, placebo-controlled studies focusing on this strategy appear to confirm the safety of ESAs and their lack of impact on overall survival (OS) and progression-free survival (PFS) for patients with solid tumors [62].

Combining intravenous iron and ESAs

Given the recommendation for correcting all deficiencies prior to initiating ESA treatment, a question arises about the combination of *iv* iron formulations and ESAs. This treatment approach should be administered on a regular daily basis, as demonstrated in a randomized controlled trial that showed significant improvements in both quality of life (QoL) and hemoglobin levels [16]. This combination also leads to a reduction in the need for transfusions when compared to the use of ESAs alone [63].

ESA future directions

Further research, particularly randomized controlled trials focused on the safety of ESAs, is necessary. With the growing interest in the potential immunomodulatory effects of erythropoietin (EPO) and its derivatives (given that ESAs might exhibit anti-inflammatory effects) [64], additional studies are required to determine the viability of their use in conjunction with modern treatment modalities like immunotherapy.

Transfusions

RBC transfusions are commonly used, because they provide quick relief, but come with risks like immune modulation [65, 66]. Transfusions negatively impact cancer patients, affecting progression-free and overall survival, recurrence and perioperative morbidity [67–74]. Some negative effects stem from immune activation, impacting oncology treatments [75–76]. Recent trials found decreased immunotherapy response rates with transfusions [77].

Considerations for optimizing RBC use in cancer patients

Although the precise hemoglobin (Hb) level or timing for blood transfusions in relation to the type of cancer treatment or disease stage has yet to be definitively established, there is existing data regarding different approaches to red blood cell (RBC) utilization.

Recognizing the adverse effects of transfusions on cancer patients at various stages of therapy, many healthcare professionals underscore the importance of adopting a more cautious approach to RBC transfusions. This approach is founded on the use of a lower Hb concentration as the threshold for initiating transfusions (typically around 7–8 g/dl), in contrast to a more liberal threshold (around 9–10 g/dl). Restrictive RBC transfusion strategies (Hb < 7–8 g/dl) align with reduced morbidity and mortality [78–79].

Foliate and vitamin B_{12} deficiency

Megaloblastic anemia stemming from deficiencies in vitamin B_{12} and folate is less frequent among cancer patients compared to iron deficiency. Such deficiencies may be linked to

disease progression and malnutrition, as well as increased cellular turnover, particularly in cases of lymphomas and leukemias. Individuals who have undergone gastrectomy or have experienced significant infiltration of the intestine may also experience such deficiencies due to the altered absorption of these vitamins in these parts of the digestive system. Certain cytotoxic drugs, commonly employed in cancer treatment such as 5-fluorouracyl, methotrexate and hydroxycarbamide, can induce megaloblastic anemia by interfering with DNA synthesis [80].

Additional considerations for the treatment of cancer-related anemia

While the primary modalities of addressing cancer-related anemia (ESA, iron supplementation and transfusions) form the foundation of management, there are several other noteworthy aspects to be taken into account. These encompass lifestyle interventions and a range of supplementary approaches.

Physical activity

Compelling evidence underscores the pivotal role of exercise and various forms of physical activity in cancer prevention and treatment, notably in enhancing patients' quality of life (primarily alleviating fatigue). Of all cancer-related fatalities worldwide, approximately 35% can be attributed to environmental factors, including sedentary lifestyles [81]. Different types of exercise have proven highly effective in mitigating cancer-related fatigue during treatment [82], as well as potentially improving overall cancer survival rates [83]. Given the key role inflammation plays in the development of cancer-related anemia, the potential anti-inflammatory effects of physical activity are noteworthy. Moreover, physical activity may influence hepcidin levels. Emerging data suggests that engaging in exercise can lead to improvements in hemoglobin levels in patients undergoing chemotherapy while using ESAs [84], in breast cancer patients during radiotherapy [85], and in breast cancer patients undergoing chemotherapy [86–87]. Nonetheless, an optimal type and intensity of physical activity has yet to be definitively established.

Hepcidin-directed therapy

Given the often-elevated levels of hepcidin in cancer patients, therapeutic approaches involving monoclonal antibodies that neutralize these proteins have gained attention. This form of treatment holds the potential to enhance ferroportin expression in enterocytes and macrophages, thereby facilitating the release of stored iron and promoting effective erythropoiesis. Initial clinical trials assessing the safety of such antibodies in addressing cancer-related anemia have yielded promising results [88]. Subsequent research in this domain is warranted, as it could potentially introduce another avenue for targeted treatment of cancer-related anemia.

Zinc deficiency

Zinc deficiency is prevalent in many countries and frequently coexists with iron deficiency. Among adults afflicted with chronic diseases, zinc deficiency has been associated with anemia [89]. While some recent analyses among non-cancer anemic patients have suggested a correlation between zinc levels and hemoglobin concentration [90], evidence in the context of cancer patients remains limited.

Conclusions

CRA's impact is significant, but awareness and treatment approach vary. There are three main pillars guide treatment: correcting deficiencies, using ESAs and transfusions. Intravenous iron addresses iron deficiency more effectively. ESAs have associated concerns but remain valuable. Transfusions provide relief but may affect prognosis. Future research focuses on enhancing interventions and combining treatments to optimize CRA management.

Article information and declarations

Author contributions

Konrad Tałasiewicz – conceptualization, visualization, writing – original draft, writing – reviewing and editing.
Aleksandra Kapała – conceptualization, supervision, writing – reviewing and editing.
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Review article

Cancer prevention and public health

The European Code Against Cancer – new evidence and recommendations

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Cancer is a major public health concern in the European Union (EU). There were 2.7 million new cancer cases and 1.3 million deaths in 2020 in the EU; of them, around 40% could have been prevented. Primary prevention is the most cost-effective long-term strategy for cancer control. The European Code Against Cancer (ECAC, 4th edition) is a health education tool aimed at raising awareness about evidence-based cancer prevention actions among EU citizens. The ECAC describes 12 ways individuals can reduce their cancer risk. Awareness of the ECAC (4th ed.) has been low (2–21%) and, therefore, efforts are needed to improve cancer prevention awareness throughout the region. Civil society and other stakeholders' engagement is key to improving cancer prevention in the region. Our aim is to propose recommendations to improve future ECAC editions to ensure an increase in cancer prevention literacy in the EU.

Key words: European Code Against Cancer, cancer prevention, health literacy

Introduction

Cancer is a major public health concern in the European Union (EU) since it is the second leading cause of mortality after cardiovascular diseases [1]. Europe accounts for approximately 10% of the global population but yet has 25% of the world's registered cancer cases [2]. In 2020, there were 2.7 million new cancer cases and 1.3 million deaths in the EU. Four cancer types were responsible for almost 50% of all cancer diagnoses. Breast cancer is the most commonly diagnosed cancer accounting for 13.3% of all cancer diagnoses (355,500 cases; females only), followed by colorectal (341,400; 12.7%), prostate (335,500; 12.5%) and lung (318,300; 11.9%) cancers.

In Poland, specifically, there were 204,575 new cancer cases and 119,319 deaths. Breast cancer is the most common cause of cancer death (11.8%), followed by lung cancer (11.4%) and colorectum cancer (10.4%) [3]. Poland has 8.7% lower age-adjusted incidence rate for all cancer types (excluding non-melanoma skin cancer) than the average in the EU. Highest differences in age-adjusted incidence rates were observed for skin melanoma (5.1 *vs.* 13.4), liver (3.5 *vs.* 5.8) and non-Hodgkin lymphoma (6.1 *vs.* 9.4) (figure 1; illustrated for all cancer types with an age-adjusted incidence rate of 5 per 100,000 persons per year or larger in the EU27) [1]. Given the significant risk-modifying effect of modifiable factors [4], it has been estimated that around 40% of all cancer cases in Europe could be prevented and mortality reduced [5].

Primary prevention, or the avoidance of cancer, is the most cost-effective long-term strategy for cancer control [6]; yet further comprehensive efforts are needed to address cancer burden, including secondary prevention interventions, such as screening programs followed by effective and early diagnoses and treatment [7]. Successful cancer prevention requires evidence-based effective preventive measures at the individual-level, to avoid or reduce certain exposures or unhealthy be-

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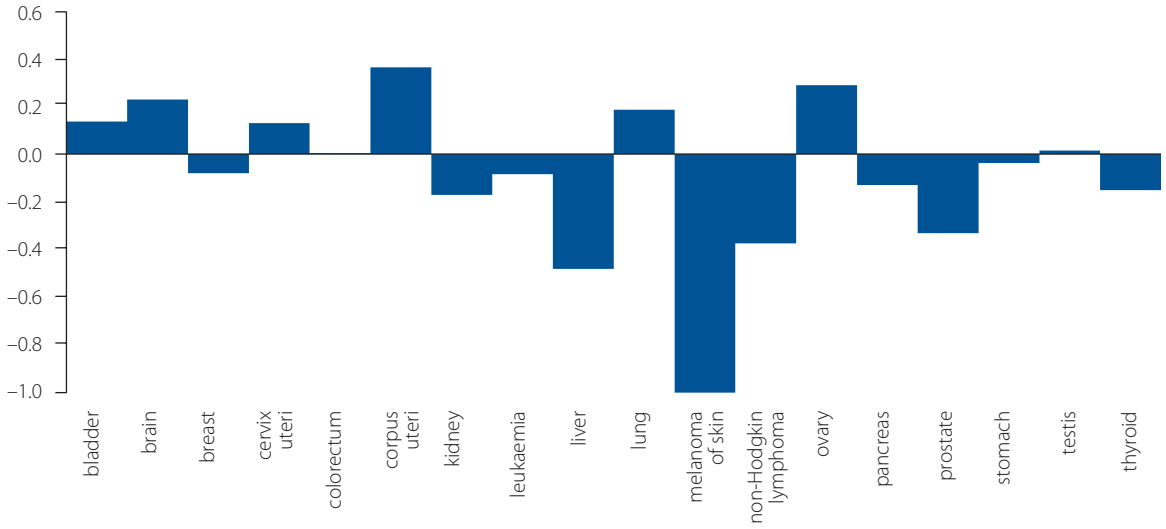

Figure 1. Difference in the age-adjusted incidence rates (expressed in %) between Poland and the EU27 in 2020; the figure shows the difference in cancer types with age-adjusted incidence rates of 5 per 100,000 persons per year or more [1]

haviours, as well as governmental policies and programmes at the population-level, to create the healthy environments and health care infrastructures needed to prevent cancer. However, significant investment is still required by EU Member states (MS) to raise awareness on major risk factors and available interventions, to implement and endorse policies that would support people in making healthier choices by default, and to encourage participation in cancer screening and immunization programmes. Without these actions in place, according to Europe's Beating Cancer Plan, cancer mortality within the EU is expected to increase by more than 24% by 2035 [5], making it the region's leading cause of death.

Improved cancer prevention in Europe requires both, addressing modifiable risk factors of cancer such as tobacco and alcohol consumption, lack of physical activity, being overweight, an unhealthy diet, exposure to ultraviolet radiation and air pollution, as well as strengthening cancer screening and vaccination programs. For individuals to engage in such preventive actions, they first need to be informed about those evidence-based actions and interventions that can reduce their risk of cancer. However, in today's media landscape, the amount of confusing, ambiguous, overwhelming, or even contradictory messages is escalating [8], making suitable advice based on the most up to date evidence and developed by authoritative organizations a key tool for cancer prevention. Offering information that is consistent with the best scientific evidence available at the time and providing access to high-quality health information that is relevant, trustworthy, and accessible [9, 10], is crucial for individuals to be able to make informed decisions on cancer prevention.

Yet knowledge alone will not suffice when it comes to promoting a change in unhealthy behaviours or engaging in healthy actions and interventions [11]. Indeed, behavioural change theories, such as the Integrated Theory of Health Behavior Change (ITHBC) [12] or the Behaviour Change Wheel [13], argue that healthy behaviours can be enhanced by fostering knowledge and understanding, since individuals are more likely to engage in recommended healthy actions and interventions if they have information about them. For example, understanding the health risks associated with smoking is essential in making a decision about quitting [14]. Similarly, evidence shows that providing information about established risk factors of cancer to individuals can improve the accuracy of risk perception, enhance response efficacy and increase intention to take action [15].

The European Code Against Cancer (ECAC) is an educational tool from credible authoritative sources, aimed at providing high-quality evidence-based information to the public, about cancer prevention actions that can be followed without specialised skills or advice. The aim of this work is to present the ECAC, assess the level of cancer prevention awareness among the European population, describe the role of civil society and other stakeholders' engagement in improving cancer prevention in the region, and propose recommendations for future interventions designed to boost cancer prevention literacy across the region.

The European Code Against Cancer

The ECAC is a health education tool aimed at raising awareness about evidence-based cancer prevention actions among EU citizens. The ECAC consists of a set of cancer prevention recommendations for the individuals to avoid or reduce exposures to established causes of cancer, adopt healthy behaviours to reduce cancer risk, and to participate in vaccination and screening programs under the appropriate national guidelines [8]. The ECAC has succeeded to inform policymakers and other

stakeholders to develop national health policies in cancer prevention [16, 17].

The ECAC, 4th edition, describes "12 ways to reduce your cancer risk", including avoiding or reducing unhealthy behaviours, such as:

- tobacco smoking and use of other forms of tobacco,
- exposure to second-hand smoke,
- drinking alcohol,
- exposure to ultraviolet radiation, high levels of radon and occupational carcinogens,
- limiting the use of hormone replacement therapy.

And protecting measures, such as:

- maintaining a healthy body weight,
- being physically active,
- eating a healthy diet,
- breastfeeding,
- participating in human papilloma virus (HPV) and hepatitis B virus (HBV) vaccination programmes, and bowel, breast, and cervical cancer screening.

The 4th edition also included a website, with over 200 questions and answers aimed at the public, explaining and providing additional information on the recommendations as well as cancer prevention topics not covered in the ECAC [8].

The ECAC is originally an initiative of the European Commission (EC) that provides a comprehensive synthesis of the available current evidence on cancer prevention and translates this into recommendations in an understandable way to the public following a standardized methodology developed to guide scientific assessments [18]. The International Agency for Research on Cancer (IARC), specialized cancer agency of the WHO, was mandated by the EC to produce the current 4th edition of the ECAC, introducing the objective to formulate the recommendations in clear, straightforward, and actionable language that can be understood by the general public without requiring specialised skills, knowledge, or training [8]. With the publication of Europe's Beating Cancer Plan [5], the IARC's mandate to provide the scientific coordination to update the ECAC was renewed, with the target of producing the 5th edition of ECAC by 2025.

In addition, the Innovative Partnership for Action Against Cancer (iPAAC) Joint Action (JA), commissioned to develop recommendations to ensure sustainability and monitoring of the ECAC [19], concluded that ongoing monitoring and evaluation of the ECAC are needed to ensure that the ECAC reaches its target population(s), as well as measure the impact of its use and inform routine updates [20]. In 2017, Ritchie et al. [16] evaluated for the first time the impact of the ECAC (4th ed.) at the EU level and found that, although the awareness of the ECAC was low – 2% in the United Kingdom (UK) to 21% in Hungary and Poland – willingness to make behavioural changes towards cancer prevention after reading the recommendations reached over 60%. These results highlight that we are still far from achieving Europe's Beating Cancer Plan's goal to making at least 80% of the population aware of the ECAC by 2025 [5].

The ECAC, 4th edition, provided an inspiring model to IARC for scaling up this tool to other regions of the world under the umbrella of a World Code Against Cancer Framework [21] to promote cancer prevention globally [22]. Despite disparities between regions, the experience of developing the ECAC 4th ed. provided the strategy, methodology and tools to expand these guidelines to other regions of the world. The European model has been recently adapted to the Latin America and the Caribbean (LAC) region [23]. The LAC Code Against Cancer will be launch during the second half of 2023.

Cancer prevention awareness in Europe

Currently, there is no psychometric instrument available based on the last edition of the ECAC; however, other surveys have been developed in relation to cancer and its risk factors, uptake of cancer screening and cancer prevention in general among the general population. Some examples include the Cancer Awareness Measure (CAM) [24], Attitudes and Beliefs about Cancer (ABC) [25] and national Cancer Barometers (France, Spain, or Belgium) [26–28].

Previous studies in European countries based on population-based surveys have assessed the public's knowledge of cancer risk factors and perceptions of symptoms, behaviours, and risks. Findings from Denmark, France, Ireland, Spain, Sweden and the UK reveal modest to low levels of public awareness of cancer risk factors [29–32]. Although most individuals perceived tobacco smoking as a main risk factor for cancer, they failed to identify other well-stablished modifiable risk factors, such as sexually transmitted viruses, alcohol, being overweight or environmental factors [29, 33]. Lifestyle determinants were commonly thought to be associated with cancer since the majority of French and Spanish respondents thought that physical inactivity, being overweight and having unhealthy diets played an important role; however, the protective association of breastfeeding with cancer was mostly unknown [33, 34]. Levels of awareness of modifiable risk factors of cancer demonstrated a sociodemographic gradient. Perceptions of the impact of these factors on the onset of cancer were lower among men, the elderly and those with a lower socio-economic status or education level [29, 31, 34]. Awareness was, therefore, lowest among those demographic groups at higher risk of developing cancer.

Health literacy (HL) is defined as "the ability to obtain, understand, process and apply health information to health decision-making" [35] and it is directly linked to engagement in cancer prevention behaviours. Previous studies have shown that limited levels of HL lead to lower adherence to risk-reducing behaviours and are related to smoking, a sedentary lifestyle and low fruit and vegetable consumption [36]. Low HL also contributes to a false perception of low risk from cancer and, therefore, lower adoption of cancer prevention actions

and interventions, since perceived risk is a key component in behavioural change theoretical models [37]. Finally, low HL has also been associated with cancer misconceptions and myths, less information-seeking and reduced perceived control over cancer risks [38]. All in all, despite the fact that individuals' knowledge and perceptions may not always match their actions [11], awareness of cancer risk factors is still essential for cancer prevention.

Efforts are needed to improve cancer prevention awareness throughout the EU. Policies and interventions within a universalism framework should be designed to reach all social segments of the population. In other words, due to the importance of sociodemographic factors on individuals' knowledge and perceptions, community-wide and tailored health education interventions on cancer prevention are needed to reduce socioeconomic disparities in cancer incidence and mortality [39], and to ensure that no country is left behind in the EU. The ECAC serves as a "toolbox" for policymakers, civil society and other stakeholders to prioritize the policies and strategies that will allow improving EU citizens' adherence to cancer prevention.

Civil society and cancer prevention

Civil society is a widely used term to denote the field of activity that is independent of both governmental and for-profit interests. Civil society organizations (CSOs) have, therefore, been defined as non-state, not-for-profit, voluntary organizations formed by people in a social sphere that is separate from both the state and the market [40]. Standing aside from the economic imperative to deliver a profit, and outside of the direct influence of governments, civil society is placed in a position of unique responsibility to act solely for social good.

CSOs have been instrumental in advancing cancer prevention, as recommended by the ECAC, through various means. As service providers, CSOs deliver programs and provide vital resources that are neglected or absent from governmental provision, particularly in resource-limited settings [41]. This work takes place at the grassroots level, whereby CSOs can enhance resilience in those communities by catalysing the implementation of, for instance, organized cancer screening programs [42], or by extending the scope of primary and secondary cancer prevention services to better address the needs of vulnerable or marginalized sections of society [43].

A further approach by which CSOs contribute towards cancer prevention is via the dissemination of evidence-based cancer prevention guidance to the general population as laid out by the ECAC. CSOs have been instrumental knowledge brokers for cancer prevention by developing understandable materials to heighten awareness of health determinants and cancer risk factors [16]. This capacity has proven to be an especially valuable asset when mitigating the effects of inaccurate information or the vested interests of stakeholders, which can be opposed to the objectives of cancer prevention [40]. For instance, in countries which have experienced a loss of confidence in the HPV vaccination programmes, CSOs have demonstrated success in developing campaigns that promote honest and reliable scientific information to the concerned public, which has resulted in regained trust and improved uptake of the HPV vaccination program [44].

CSOs not only provide information to the public but play a vital role in conveying the concerns and interest of wide sections of society to policymakers. Becoming advocates and enablers of change for the public good, further demonstrates how CSOs contribute to cancer prevention [45]. In recognition of the contribution of CSOs, the 2017 World Health Assembly resolution on "cancer prevention and control in the context of an integrated approach" calls upon member states of the WHO to foster partnerships with CSOs to improve the provision of services for cancer prevention and control [46]. This underscores the essential role CSOs have in promoting and sustaining cancer prevention as part of a "Whole of Society" approach [47].

Case-study in Poland

Cancer prevention advocates in Poland have had a long and proud history of disseminating the ECAC from its very beginnings – since the 1980s. Even before Poland became an EU member state in 2004, the ECAC was actively and widely disseminated across the country, with a special emphasis on communicating to children, adolescents and young adults. For the 3rd edition of ECAC, published in 2003, the programme "Schools promoting the recommendations of the European Code Against Cancer" was an especially successful initiative, which in the Małopolska voivodship reached approximately 80% of schools, 20,000 teachers, 300,000 students and 20,000 members of the local community [48]. Activities to promote the ECAC continued following the publication of the 4th edition in 2014. Of note was the informational brochure developed by experts in conjunction with Polish League Against Cancer, which describes the information of the ECAC in simple, easy to understand language, and was distributed free of charge to thousands of people throughout Poland (www.12sposobownazdrowie.pl/12_sposobow.pdf). Consequently, of those countries whose populations were surveyed regarding the awareness of the ECAC, Poland ranked as the joint highest, with a relatively high proportion (30%) of 25–34-year-olds surveyed, stating they knew of the ECAC [16]. This suggests that the consistent efforts to promote ECAC focused on children and young people in Poland have helped to maintain awareness of the ECAC.

Steps forward and recommendations

Experts and other stakeholders from the iPAAC JA [20], introduced above, suggested that the future ECAC editions:

- should broaden the scope to evidence-based individual and population level interventions and their implementation,

- have a multidisciplinary approach with synergies between cancer-targeted and NCDs-related recommendations,
- be tailored to different target groups and audiences (e.g., healthcare professionals and policymakers).

Finally, they recommended using the ECAC as a unifying tool for cancer prevention in the EU (the "toolbox" mentioned above). Most of these recommendations will not only be addressed in the new edition of the ECAC (5th edition), currently under development and due to launch in 2025 but will also inform the global methodology of the World Code Against Cancer Framework. The conclusions of the iPAAC JA were published in June 2021 and, since then, other initiatives have been introduced to improve the new edition of the ECAC and its further implementation. One example is the joint call by IARC, Institut National du Cancer (INCA) in France, and the Association of European Cancer Leagues (ECL) for the EC to commit to establishing a thorough, robust and systematic evaluation of the ECAC, which would be best served by the re-introduction of the ECAC-dedicated Eurobarometer survey to be implemented in 2024, before the launch of the 5th edition of the ECAC. Its results would be used as a baseline for EU citizens' level of awareness of cancer prevention and, ideally, through periodic surveys, monitoring and evaluating the impact of the ECAC across the EU will be possible.

Hence, monitoring and evaluating not only the impact of the Code on public awareness, but also its development process is key in ensuring ECAC's sustainability and a path to optimizing and enhancing its methodology.

Conclusions

The ECAC, under the umbrella of the World Code Against Cancer Framework, is a health education tool aimed at improving health literacy in cancer prevention to the public and nurturing the development of evidence-based cancer control policies. This initiative is constantly evolving to include the latest scientific data, and to respond to the needs of the European population and stakeholders as regards cancer prevention.

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Conflict of interest

None declared

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Rare case of recurrent myofibroblastoma in a female patient

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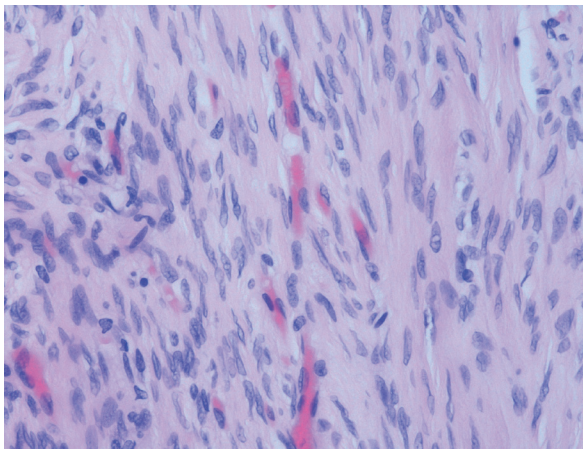

Figure 1. Microscopic display of hematoxylin and eosin-stained section of classic myofibroblastoma

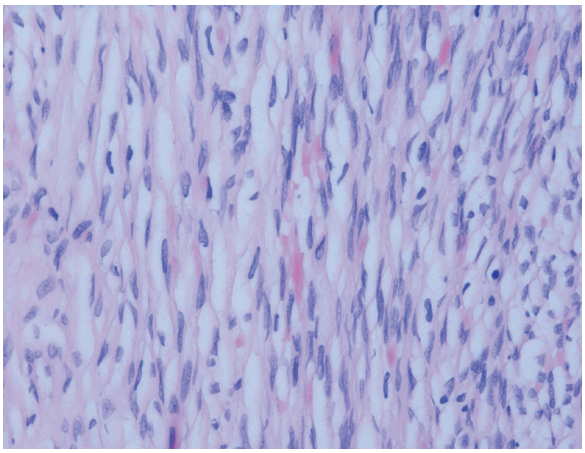

Figure 2. Spindle shaped, slender, blend and uniform cells closely packed in short fascicles intermixed with hyalinised, thick collagen bundles

A 61-year-old female patient presented with a painless lump located in the right breast. In 2015 she was diagnosed with mammary-type myofibroblastoma (MFB) in the right breast and underwent a resection. In 2016 there was a unilateral relapse and the second tumorectomy was performed. The patient underwent core needle biopsy, which indicated a non-epithelial spindle cell lesion with immunohistochemistry results CD34+;S100–; p63–; CKPAN–; ER–. On the MRI there was a lobular tumour (37 x 42 x 57 mm) with 2 satellite lesions. Due to the size of the tumour and previous breast surgeries, a nipple sparing mastectomy with reconstruction was performed. Histopathology confirmed MFB (fig. 1, fig. 2). MFB is a rare benign spindle cell tumour of the breast. Due to its rare incidence, no risk factors or genetic predispositions are identified [1]. As MFB is well encapsulated, the treatment of choice is surgery without further adjuvant therapy. Only one relapse of MFB has been reported in the literature so far [2]. There is little data concerning recurrence of MFB [2], therefore careful observation and documentation of recurrent MFBs could prove beneficial in studying the nature of MFB and treating patients.

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Pneumoconiosis mimicking lung metastases of medullary thyroid carcinoma

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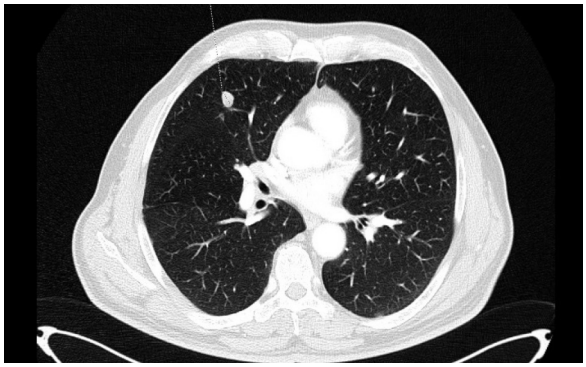

Figure 1. CT images of the thorax showing a pulmonary nodule in the 5R segment

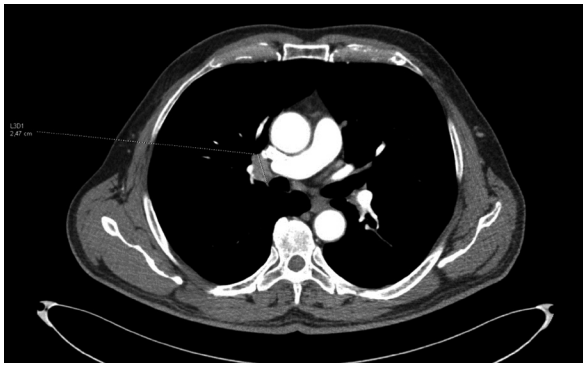

Figure 2. CT images of the thorax showing a right hilar lymphadenopathy

A 63-year-old man diagnosed with pT3N1b medullary thyroid carcinoma (MTC) was referred for further consultation three months after a total thyroidectomy with a left lateral lymphadenectomy. On admission the levels of carcinoembryonic antigen (CEA) and calcitonin (CT) were slightly elevated (CT – 51.1 pg/ml; CEA – 5.13 ng/ml). The patient underwent radiotherapy three months after surgical treatment. A follow-up CT of the thorax performed after the subsequent three months, revealed numerous pulmonary nodules (fig. 1) and a mediastinal lymphadenopathy (fig. 2) suspected of metastases. CT levels remained elevated (43 pg/ml) with a decrease of CEA level equally (3.61 ng/ml); the patient did not exhibit any respiratory symptoms. A histopathological examination of the retrieved lymph nodes did not show any abnormalities. Since the possibility of metastases could not be ruled out, the patient underwent an anterior thoracotomy. The removed lung masses unveiled black-grey nodules which turned out to be pneumoconiosis. The patient history revealed exposure to dust and fumes. This is the first described case of pneumoconiosis mimicking MTC metastases. What is particularly worthy of attention is the short period of time from the radical surgery to the occurrence of initially absent multiple pulmonary lesions with a relatively insignificant growth of calcitonin. This pattern is characteristic for singular nodular MTC metastases rather than multiple micronodular metastases in solid organs [1]. It is worth emphasizing that in such cases we should take into consideration different respiratory system comorbidities, including occupational diseases.

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