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Original article

Cancer genetics

Expression of cancer testis genes in gastric neoplasms — a preliminary study

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Introduction. Scientists are currently searching for new and improved diagnostic markers and treatment modalities for gastric cancer. One putative target are the cancer/testis genes (CTGs), whose expression is restricted to male germ cells, trophoblasts and ovaries. CTGs are also aberrantly expressed in several types of cancers. In healthy somatic tissues, CTGs expression is either not detected or present at low levels. About 270 CTGs have been described thus far.
The aim of this study was to investigate the expression levels of CTGs in stomach tissue samples from patients with gastric neoplasm, in relation to selected clinical and pathomorphological parameters.

Material and methods. 28 patients with histologically confirmed gastric neoplasms were included in this study. Total RNA was extracted from homogenates using the RNeasy Fibrous Tissue Mini Kit in accordance with the manufacturer's protocol. A quantitative assessment of mRNA levels for 35 genes was performed using real-time RT-PCR.

Results. We report that 11 out of 35 CTGs tested (*ATAD2*, *FBXO39*, *HORMAD1*, *IGSF11*, *IL13RA2*, *KIF2C*, *LDHC*, *OIP5*, *PLU1*, *SPAG9* and *TTK*) were significantly ($p \leq 0.05$) overexpressed in tumour tissue compared with healthy stomach samples isolated from the same patients. Additionally, our results indicated that overexpression of *OIP5* was associated with gastric adenocarcinoma in women. Moreover, two of the tested CTGs (*HORMAD1*, *TTK*) were significantly overexpressed in tubular gastric adenocarcinoma. Additional analysis showed a correlation between *KU-CT-1* expression in gastric adenocarcinoma and patient age at diagnosis.

Conclusions. Our results suggest that the overexpression of CTGs may be specific for gastric neoplasms, but it should be confirmed in larger numbers of patients.

Keywords: gastric neoplasm, genes, biomarkers, CTGs, expression

Introduction

For over a century, medical researchers have been searching for tumour markers. An ideal tumour marker is a marker with expression limited to the tumour tissue and, thus, could play a key role in the development of new methods aimed at stimulating the body's immune response against cancer cells. Over 160 years ago, Rudolf Virchow hypothesised that a certain pool of embryonic cells remains dormant in adult tissues and, upon reactivation, gives rise to various tumours [1]. In 1902, John Beard put forward a theory that all tumours originate from

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embryonic cells, basing his theory on observations of early placental development during pregnancy. Beard noticed that the formation of the placenta in the uterus resembles carcinogenesis, and that this process stops when enzymes produced by the foetus appear; otherwise, choriocarcinoma occurs [2]. In the 1970s, long-term research on this issue resulted in the discovery of cancer/testis antigens (CTAs) encoded in the human body by a heterogeneous group of cancer/testis genes (CTGs) [3]. According to the Ludwig Institute for Cancer Research Database, more than 270 CTGs have been identified thus far [4]. Some CTGs are located on the X chromosome and these encode the most immunogenic CTAs. These CTGs constitute more than 10% of the genes on the X chromosome, where they form so-called "gene families". Additional CTGs are located on the autosomes as well as the Y chromosome and most often occur in the form of single gene copies [5]. The high expression of CTGs is limited to multiple tumour types and their function is still largely unknown. Their limited expression in healthy tissue has made them potential candidates for biomarkers of gastric neoplasms. The function of the proteins encoded by CTGs is largely unknown, however, most often they are associated with meiosis and gametogenesis [6, 7]. Cancer/testis gene overexpression plays a key role in the processes of angiogenesis, metastasis, inhibition of apoptosis and cell proliferation in tumour tissues [8]. Moreover, overexpression of certain CTGs may produce differing effects in individual cells and tumour lines [9]. Cancer/testis genes encode surface antigens that can potentially be presented to the immune system with, among others, Class I and II human leukocyte antigens (HLAs). This process may lead to humoral responses as well as anti-tumour cytotoxic T cell effects against cancer cells [10]. Therefore, finding further immunodominant determinants for CTAs may be particularly important clinically [11]. Regulation of CTAs is associated with epigenetic mechanisms that either lead to changes in methylation of promoter regions or changes within histones. These mechanisms are part of a larger program of gene changes during carcinogenesis [10, 12, 13]. A large role in the carcinogenesis process is currently attributed to CTAs, particularly those encoded by CTGs located on the X chromosome. Expression of these CTAs is often characterized by high immunogenicity and is limited to malignant lesions [2].

Certain MAGE-A antigens may either regulate ubiquitin E3 ligase activity or disrupt cancer cell apoptosis via binding to procaspase-12 [8, 14]. Additional oncogenic functions have also been associated with cell proliferation through excessive levels of cyclins D1 and E. CTAs also affect genome instability resulting from chromosomal aberrations occurring during mitosis. CTAs may also be important in angiogenesis, a key process in metastasis [8, 15].

Gastric cancer is most often diagnosed at an advanced stage, which makes it one of the most common causes of death among cancer patients. More than half of all cases of gastric cancer occur in underdeveloped countries; the highest rates are in Eastern Europe, South America and East Asia, while the lowest incidence rates occur in Western Europe and North America [16]. Cancer diagnosis is difficult and involves a wide range of tests for accurate confirmation. Up to 75–85% of patients diagnosed with gastric cancer die within 5 years of disease onset [17]. Surgery is the most common treatment method, giving the best chance of recovery if the disease is diagnosed at an advanced stage. Chemotherapy and radiation therapy often constitute supplementary treatment, usually in a palliative manner. Early diagnosis is extremely important in disease management, and such diagnosis can be achieved by gastroscopy and histopathology. Many studies on new treatment methods have been conducted to investigate their effectiveness, including the use of molecularly-targeted drugs and CTGs may constitute one of the objectives [17, 18].

In the present study, the expression levels of 35 CTGs were determined in gastric neoplasm tissue from patients. The gene panel was determined based on the available literature, however, a decision was made to also include several new CTGs that are potential gastric tumour marker candidates. Our objective was to answer the question of whether certain CTGs may fit the previously mentioned biomarker specifications for specific gastric cancers. The results of our study suggest that expression levels of certain CTGs correlate with an increased risk of this disease. Our findings indicate that the research is still in its early phase. Our preliminary results are the first step in our research process. They show which genes should be confirmed in larger numbers of patients.

Material and methods

Patients

All samples were collected at the Department of Gastroenterology, Pomeranian Medical University in Szczecin. 28 patients with newly diagnosed gastric neoplasms were included in the study. The median age of the patients was 68 years (range 33–82 years) and 57% of the patients were male (Tab. I). All patients gave written informed consent to participate in the study. The study conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964). 19 samples (68%) were taken from the proximal part of the stomach and 9 samples (32%) were taken from the distal part of the stomach. The entire material collected during the research process included: 16 adenocarcinomas (14 intestinal-type, 2 diffuse type), 6 adenomas, 4 lymphomas [anaplastic large cell lymphoma (ALCL), diffuse large B-cell lymphoma (DLBCL), mucosa-associated lymphoid tissue (MALT), Burkitt's lymphoma) and 2 neuroendocrine tumours (G1 and G2). No patients included in the study had co-existing tumours and none of the patients received radiotherapy or immunotherapy before biopsy. The final diagnosis was made by the gastroenterologist after histopathological and gastroscopic examination. Two samples were taken from each patient at the time of the gastroscopy;

one sample from the gastric neoplasia and the other from normal stomach mucosa, located 5 cm away from the tumour's edge. Patient data are summarized in Table I.

RNA isolation

Tissue fragments were cut into small fragments and immediately stored in RNAlater® Solution (Invitrogen) at –80 °C until the time of genetic analysis. Samples were homogenized with the Ultra-Turrax T-10 basic (IKA®) dispersing tool in 600 µl RLT buffer (Qiagen) for 4 min at 30,000 rpm/min. Total RNA was extracted from homogenates using the RNeasy Fibrous Tissue Mini Kit (Qiagen) in accordance with the manufacturer's protocol. The concentration and purity of RNA samples was determined by measuring the absorbance using a spectrophotometer Perkin Elmer Lambda Bio+ (PerkinElmer). The obtained RNA was used for the reverse transcription reaction. 0.5 µg of RNA from each sample was reverse transcribed into cDNA with the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific) according to the manufacturer's instructions. The total reaction volume for each sample was 20 µL cDNA.

Real-time quantitative reverse transcription PCR (RQ-PCR)

Quantitative expression analysis of the selected genes, as well as the beta2-microglobulin reference gene, was performed using real-time reverse-transcription polymerase chain reaction (RT-PCR) on an ABI PRISM® Fast 7500 Sequence Detection System (Applied Biosystems). Real-time conditions

Table I. Clinicopathological characteristics of patients enrolled in the study

Feature	N
Age	Median value = 68 (range 33–82)
Gender	
Female	12
Male	16
Location	
Proximal	19
Distal	9
Types of neoplasia	
Adenocarcinomas	16
WHO classification (2019)	
Tubular	11
Papillary	1
Mucinous	3
Tubular/mucinous	1
Laurén classification	
Intestinal	14
Diffuse	2
Grading	
G1	5
G2	2
G3	1
Unknown	8
Gastritis	
Positive	5
Negative	11
Intestinal metaplasia	
Present	5
Absent	11
Peptic ulcer disease	
Present	3
Absent	13
Adenomas	
WHO classification (2019)	6
Tubular (minoris)	4
Tubular (minoris et majoris)	1
Tubular/villosum (minoris)	1
Neuroendocrine tumors	
Histologic grade (2019)	
NET G1	1
NET G2	1
Gastric lymphoma	
WHO classification (2019)	4
Anaplastic large-cell lymphoma	1
Diffuse large B-cell lymphoma	1
Mucosa associated lymphoid tissue lymphoma	1
Burkitt's lymphoma	1

WHO — World Health Organization; NET — neuroendocrine tumor

were as follows: 95°C (15 sec), 40 cycles at 95°C (15 sec) and 60°C (1 min). Melting point analysis confirmed only one PCR product under these conditions. To normalise mRNA levels between different samples, we used β-2 microglobulin as a reference gene. Each sample was analysed in two technical replicates. To calculate the values, two methods were used. Absolute expression ($2^{-\Delta Ct}$ method) and relative expression ($2^{-\Delta\Delta Ct}$ method).

Statistical analysis

Statistical analysis was performed with STATISTICA Version 12.5 data analysis software system. Data were analysed as gastric neoplasms absolute expression (AE) and gastric neoplasms relative expression (RE) to normal tissue in the same patient, calculated as the ratio of expression levels: neoplastic tissue/normal tissue. The Mann-Whitney test was used to compare CTG expression between tumour types. Cancer/testis gene expression data

Table II. Comparison between cancer/testis genes (CTGs) expressions in normal and adenocarcinoma tissue obtained during gastroscopy. RNA was isolated from cancer tissue and normal tissue located ~5 cm away and reverse transcribed and CTG expression was analyzed by real-time polymerase chain reaction (PCR). Differences with p value ≤ 0.05 (Wilcoxon signed-rank test) are in bold

	CTGs	Median	IQR	p value
Adenocarcinoma tissue versus normal	*CAGE1*	1.617	2.582	0.88
	MAGEA2	16.101	447.765	1
	MAGEA1	2.294	395.437	0.17
	TTK	2.13	6.367	**0.003**
	NY-ESO-1	7.122	279.465	0.33
	MAGEA3	2.309	451.499	0.17
	CXorf48	1.5	6.538	0.79
	DKKL1	2.847	10.939	0.22
	OIP5	1.781	3.654	**0.002**
	KU-CT-1	0.265	0.984	0.18
	FBXO39	3.305	7.021	**0.039**
	CAGE	1.652	6.062	0.5
	HAGE	1.434	5.883	0.39
	RGS22	0.965	2.676	0.38
	SSX4	1.901	18.467	0.37
	PLU1	2.021	1.551	**0.001**
	PLAC1	1.969	3.312	0.2
	LDHC	3.586	20.314	**0.007**
	CTAGE1	1.966	37.56	0.93
	SPAG4	1.567	0.924	0.14
	CCDC110	0.673	1.2	0.26
	SPA17	1.385	1.957	0.08
	SPAG9	1.962	2.429	**0.01**
	MAGEB6	1.561	18.177	0.23
	MAGEA11	2.556	11.463	0.46
	HORMAD1	6.755	8.353	**0.001**
	PRSS55	0.805	1.727	0.73
	IL13RA2	1.785	1.231	**0.003**
	HORMAD2	1.713	201.877	0.24
	KIF2C	2.958	8.916	**0.001**
	IGSF11	0.478	0.575	**0.035**
	SYCP1	1.617	8.081	0.64
	CALR3	1.324	2.666	0.64
	SPAG1	1.076	1.484	0.54
	ATAD2	3.712	5.838	**0.002**

Differences with p value ≤ 0.05 (Wilcoxon signed-rank test) are in bold; IQR — interquartile range

were compared between samples from adenocarcinoma tissue and normal stomach mucosa with the Wilcoxon signed-rank test. Correlations between CTG expression and patient age were analysed using the Spearman rank correlation coefficient (Rs). The relationships between CTG expression in patients with gastric adenocarcinoma and other clinical data were analysed using the Mann-Whitney test, and $p \leq 0.05$ was considered statistically significant.

Results

Cancer/testis gene expression in clinical samples

Sixteen adenocarcinomas, 6 adenomas, 4 lymphomas and 2 neuroendocrine tumours were confirmed histologically from the collected samples (Tab. I). We designed a panel of CTG candidates, including those previously shown to be expressed in gastric cancer [19–24] as well as some promising new targets, known to be expressed in various cancers [25–29]. A detailed statistical analysis was made only for adenocarcinoma, as this was the largest group.

Cancer/testis gene expression in gastric adenocarcinoma

Analyses of relative CTG expression in adenocarcinoma tissue versus healthy tissue (taken 5 cm from the tumour's edge) was carried out using the Wilcoxon signed-rank test and demonstrated statistically significant differences for 11 genes: *TTK*, *OIP5*, *FBXO39*, *PLU1*, *LDHC*, *SPAG9*, *HORMAD1*, *IL13RA2*, *KIF2C*, *IGSF11* and *ATAD2* (Tab. II). A correlation between CTG overexpression and patient age at which the gastric adenocarcinoma developed was also shown. The Spearman's rank correlation coefficient showed that AE for the genes *PLAC1*, *SPAG9*, *PRSS55* and *KIF2C* (Fig. 1) in tumour tissue increases with age. Additionally, increased relative expression of the gene *KU-CT-1* was observed in the tumour tissue (Fig. 2). Analyses of potential correlations between CTG expression and patient sex were then performed. Positive correlations were observed between adenocarcinoma occurrence in women and relative expression of the genes *OIP5* ($p = 0.050$) and *HAGE* ($p = 0.025$) (Tab. III). Additionally, patients were divided into 2 groups according to the histological type of adenocarcinoma: tubular and non-tubular. Overexpression of the genes *CAGE1*, *TTK*, *SPA17*, *SPAG9*, *MAGEB6* and *HORMAD1* was typical for tubular adenocarcinomas. When only AE was considered, significant results were obtained for the gene *RGS22* in non-tubular adenocarcinomas ($p = 0.036$) (Tab. III). Due to the small number of patients with G2 and G3 malignancies, the decision was made to combine them into a single group for analysis. The AE of *RGS22* was, however, significantly higher in the G2–G3 group,

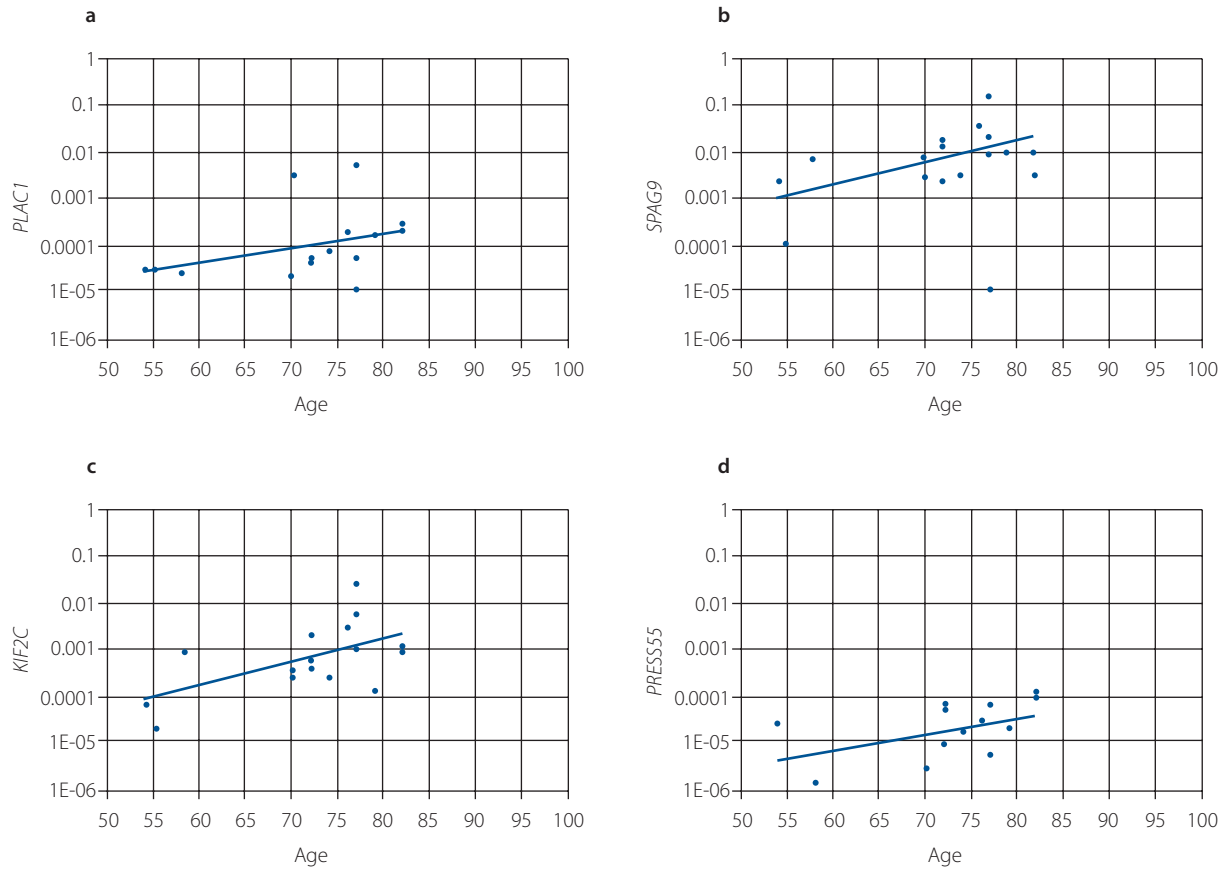

Figure 1. Positive correlation between absolute expressions (AE) of (**A**) *PLAC1* (Rs = 0.55; p = 0.029), (**B**) *SPAG9* (Rs = 0.53; p = 0.036), (**C**) *KIF2C* (Rs = 0.54; p = 0.029); (**d**) *PRSS55* (Rs = 0.60; p = 0.013) in adenocarcinoma tissue and patients' age. The Spearman rank correlation coefficient was used to analyze the correlation between age and cancer/testis gene (CTG) expression level

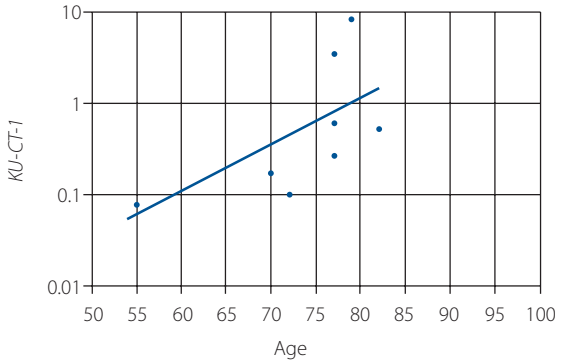

Figure 2. Positive correlation between relative expression (RE) of *KU-CT-1* (Rs = 0.76; p = 0.006) in adenocarcinoma tissue and patients' age. The Spearman rank correlation coefficient was used to analyze the correlation between age and cancer/testis gene (CTG) expression level

while the AE of *MAGEB6* was higher in the G1 group (Tab. III). In addition, the AE of *PLU1* and RE of *SSX4* and *CTAGE1* were typical for patients with adenocarcinoma without gastritis (Tab. III). Interestingly, the same patients were characterized by the absence of intestinal metaplasia, suggesting that the absence of intestinal metaplasia corresponds to increased expression of the same CTGs. Absolute overexpression of the gene *HORMAD2* (Tab. III) was typical for patients with gastric ulcers. No statistically significant differences in CTG expression in patients with adenocarcinoma were found based on the location from which the sample was collected or the occurrence of endothelial neoplasia.

Expression of cancer/testis genes in gastric adenocarcinoma and adenoma

We compared the expression of all the previously selected CTGs in gastric adenocarcinoma cases versus gastric adenoma. We noticed a much higher statistically significant RE in adenocarcinomas for the genes *CAGE1*, *FBXO39* and *PLU1* (Tab. IV).

Expression of cancer/testis genes in gastric adenocarcinoma and gastric lymphoma

In further statistical analysis, we compared the expression of all the previously selected CTGs in gastric adenocarcinomas with the expression of the same genes in gastric lymphomas. We noticed a much higher statistically significant RE in adenocarcinomas for *SPAG4* (Tab. V).

Expression of cancer/testis genes in gastric adenoma and gastric lymphoma

Finally, we compared the expression levels of all the previously selected CTGs in gastric adenomas with the expression of the same genes in gastric lymphomas. Again, a much higher statistically significant RE was observed in lymphomas for *SPAG4* (Tab. VI).

Discussion

The search for genetic markers that could potentially serve as characteristic biomarkers for specific cancer types has been ongoing for decades [30]; this was also one of the most important objectives of our current research. The salient observation of our study is the identification of new genes correlated with gastric neoplasms. We believe that the above-mentioned changes in gene expression can be considered as potential prognostic biomarkers. Moreover, our findings demonstrate that CTGs may be involved in development of gastric neoplasms. All these suggestions must be confirmed in larger numbers of patients.

First, we verified whether overexpression of the selected CTGs is limited to cancer tissues. If the antigens coded by these CTGs are also capable of invoking an immune response against cancer cells, it would place these markers in a group of very important molecules. We analysed the expression of CTGs in cancerous tissue, as well as healthy tissue, in patients with gastric adenocarcinoma. We examined the relationships between CTG expression in patients with gastric adenocarcinoma and the clinical course of their disease. Finally, we assessed differences in the expression of selected CTGs between different types of gastric neoplasm: adenocarcinoma and adenoma, lymphoma and adenoma, and adenocarcinoma and lymphoma.

Our results indicate a statistically significant overexpression of *TTK* (p = 0.003) in gastric adenocarcinoma compared to healthy tissue from the same patient. However, this increased expression was not characteristic of all tissues (a difference greater than 2 was observed in 9 of the 16 adenocarcinoma samples). Interestingly, we previously obtained very similar results for *TTK* (p < 0.001) in a similar study in patients with colorectal cancer [31]. High microsatellite instability is believed to induce mutations in many genes, including *TTK*, thereby causing cancer. Additionally, common frameshift mutations in the *TTK* gene have been confirmed in gastric and colorectal cancers [19, 32]. Moreover, these frameshift mutations correlate with increased expression of programmed cell death ligand 1 (PD-L1) in gastric cancers [33]. A very low level of *TTK* expression in normal, healthy gastric mucosa is confirmed not only by our study but also by Mills et al. [34]. In contrast, results obtained by Wang et al. [35] indicate that high expression of the *TTK* gene in gastric adenocarcinoma correlates with a better patient survival rate. These findings would explain why the results obtained here, where the RE of *TTK* was characteristic of tubular adenocarcinoma (p = 0.047), gave a much more favourable 5-year survival chance from disease diagnosis than seen for mucinous adenocarcinoma [36].

Interestingly, for tubular adenocarcinoma, a characteristic RE of *HORMAD1* has also been shown. Aung et al. [37] confirmed that the expression of *HORMAD1* in gastric cancer

Table III. Analysis of cancer/testis genes (CTGs) expression in relation to clinicopathological features

CTGs	Clinical feature		RE			AE		
			Median	IQR	p value	Median	IQR	p value
OIP5	Gender	F	2.844841	6.275311	**0.05**	0.000852	0.002245	0.49
		M	1.377583	0.796944		0.000687	0.001115	
HAGE		F	6.136988	11.77483	**0.025**	0.000082	0.001166	0.63
		M	0.869812	1.165361		0.000207	0.000143	
CAGE1	Histological type of adenocarcinoma	T	1.675143	2.930174	**0.047**	0.000026	0.000048	0.16
		NT	0.412256	0.455462		0.000003	0	
TTK		T	2.695605	6.463068	**0.047**	0.00323	0.003909	0.61
		NT	1.136899	0.842932		0.001927	0.000984	
RGS22		T	0.735397	1.218641	0.19	0.000005	0.000011	**0.036**
		NT	1.497796	4.473127		0.000023	0.000168	
SPA17		T	2.088386	2.120276	**0.015**	0.001396	0.006806	0.78
		NT	0.666488	0.253483		0.001641	0.003005	
SPAG9		T	2.201953	2.624137	**0.047**	0.009472	0.015327	0.13
		NT	0.658078	0.978798		0.002955	0.003761	
MAGEB6		T	9.616402	18.46288	**0.02**	0.000052	0.000138	0.46
		NT	0.748223	0.522369		0.000014	0.000025	
HORMAD1		T	7.177859	7.207974	**0.05**	0.000159	0.000497	0.19
		NT	1.969562	5.07031		0.000029	0.000125	
RGS22	Grading	G1	0.3778127	0.668473	0.18	0.000001	0.000005	**0.025**
		G2–G3	3.5319258	6.8011378		0.000028	0.00054	
MAGEB6		G1	5.6743783	15.689210	0.3	0.000072	0.000103	**0.025**
		G2–G3	0.5364804	5.6297952		0.000013	0.000014	
SSX4	Gastritis	GP	2.632287	17.51189	**0.025**	0	0.000002	0.53
		GN	0.594935	0.530141		0	0.000001	
PLU1		GP	2.021293	1.402366	0.53	0.011223	0.006718	**0.036**
		GN	1.190566	1.631837		0.004511	0.003733	
CTAGE1		GP	4.482278	230.5981	**0.048**	0.000059	0.000065	0.21
		GN	0.273115	0.799865		0.000004	0.000023	
CTAGE1	Intestinal metaplasia	IMP	4.482278	230.5981	**0.048**	0.000059	0.000065	0.21
		IMA	0.273115	0.799865		0.000004	0.000023	
SSX4		IMP	2.632287	17.51189	**0.025**	0	0.000002	0.53
		IMA	0.594935	0.530141		0	0.000001	
PLU1		IMP	2.021293	1.402366	0.53	0.011223	0.006718	**0.036**
		IMA	1.190566	1.631837		0.004511	0.003733	
HORMAD2	Peptic ulcer disease	P	1.043124	300.7225	0.93	0.000005	0.000008	**0.034**
		N	1.520991	2.436342		0.000017	0.000017	

Differences with p value ≤ 0.05 (Mann-Whitney U test) are in bold; RE — relative expressions; AE — absolute expression; IQR — interquartile range; F — female; M — male; T — tubular; NT — non-tubular; GP — gastritis positive; GN — gastritis negative; IMP — present intestinal metaplasia; IMA — absent intestinal metaplasia; P — positive peptic ulcer disease; N — negative peptic ulcer disease

Table IV. Comparison between cancer/testis gene (CTG) expressions in adenocarcinoma and adenoma

CTGs		RE			AE		
		Median	IQR	p value	Median	IQR	p value
CAGE1	ADMA	0.468405	0.694321	**0.027**	0.000007	0.000026	0.61
	ADCA	1.593094	2.347909		0.000016	0.000048	
FBXO39	ADMA	0.799568	1.369141	**0.012**	0.000126	0.000116	0.16
	ADCA	3.123984	5.828531		0.000249	0.000655	
PLU1	ADMA	0.873484	0.81754	**0.033**	0.010759	0.012407	0.82
	ADCA	1.926644	1.492435		0.010307	0.009317	

Differences with p value ≤ 0.05 (Mann-Whitney U test) are in bold; RE — relative expressions; AE — absolute expression; IQR — interquartile range; ADMA — adenoma; ADCA — adenocarcinoma

Table V. Comparison between cancer/testis gene (CTG) expressions in adenocarcinoma and lymphoma. Differences with *p* value ≤ 0.05 (Mann-Whitney U test) are in bold.

CTGs		RE			AE		
		Median	IQR	p value	Median	IQR	p value
SPAG4	ADCA	1.432069	0.997371	0.07	0.000082	0.000204	**0.047**
	LYMP	0.529842	0.401008		0.000001	0.000018	

Differences with p value ≤ 0.05 (Mann-Whitney U test) are in bold; RE — relative expressions; AE — absolute expression; IQR — interquartile range; ADMA — adenoma; ADCA — adenocarcinoma

Table VI. Comparison between cancer/testis gene (CTG) expressions in adenoma and lymphoma

		RE			AE		
		Median	IQR	p value	Median	IQR	p value
SPAG4	ADMA	1.02886	2.371437	0.29	0.000155	0.000916	**0.033**
	LYMP	0.529842	0.401008		0.000001	0.000018	

Differences with p value ≤ 0.05 (Mann-Whitney U test) are in bold; RE — relative expressions; AE — absolute expression; IQR — interquartile range; ADMA — adenoma; LYMP — lymphoma

is much higher than in 14 other non-cancerous tissues (including stomach tissue). These findings are in accordance with our results, which show that the RE of *HORMAD1* was higher in the adenocarcinoma tissue than in the healthy stomach tissue in 14/16 adenocarcinoma patients.

Expression of the *OIP5* gene has been confirmed in many stomach cancer cell lines, including: SNU1, SNU16, SNU216, SNU638 and AGS [20]. Studies of other groups have indicated that the *OIP5* is expressed in the gastric adenocarcinoma [38] and colorectal cancer [31]. Similar observations were made in our study. The RE of the *OIP5* gene was significantly increased in 7/16 patients with gastric adenocarcinoma (p = 0.002). Interestingly, the RE correlated with gender and was higher in women (p = 0.050). In another study, similar results were observed for patients with acute myeloid leukemia (AML), in a group where women constituted 41% of the examined individuals [25].

The RE of *FBXO39* in gastric adenocarcinoma was also found to be statistically significant when compared to healthy tissues from the same patients (*p*=0.039). Moreover, the RE of *FBXO39* was significantly higher in adenocarcinoma than in benign changes (adenoma) (p = 0.012).

Equally high results for *FBXO39* were obtained in an analysis of colon cancer [31]. Interestingly, anti-FBXO39 antibodies were not detected in the serum of patients with gastric cancer (antibodies were detected in 1/24 of patients), potentially making this CTG highly useful in research aimed at developing immune vaccines to stimulate immunogenicity against *FBXO39* [26]. On the other hand, according to Zheng et al. [39], knockout (gene silencing) of *FBXO39* promotes apoptosis and inhibits proliferation of cancer cells in the U-2OS cell line. Moreover, *FBXO39* predicts poor prognosis and correlates with tumour progression in cervical squamous cell carcinoma [40].

We found no statistically significant correlations between the RE of *PLU1* and either patient age at diagnosis or patient gender. Similarly, Wang et al. [21] found no connection between these parameters and the presence of the PLU1 protein in gastric cancer. Moreover, it has been found that the overexpression of *PLU1* is required in gastric cancer for proliferation and metastasis [21]. The results obtained by Wang et al. [21] correlate with our observations, in which the RE of *PLU1* was significantly higher in gastric adenocarcinoma than in benign changes (andenoma) ($p = 0.033$).

Our results indicated a positive correlation between the RE of *KU-CT-1* and the age of the patient at gastric adenocarcinoma diagnosis ($p = 0.006$). In our previous research, we also demonstrated a correlation between the AE of *KU-CT-1* and the age of the patient at diagnosis of colorectal cancer [31]. Nevertheless, the results of our work do not indicate a clear overexpression of *KU-CT-1* in gastric adenocarcinoma compared to healthy tissue. Similar results were obtained in a study by Okada et al. [27], where no expression of *KU-CT-1* was detected in any of the gastric or colorectal cancer tissue examined from the patients.

Another gene observed in our study to have increased expression in gastric adenocarcinoma is *LDHC*. Moreover, expression of *LDHC* has previously been demonstrated in breast, lung, ovarian, colorectal, cervical, thyroid, kidney and prostate cancers, as well as melanoma [41].

Additionally, we observed overexpression of the *SPAG9* gene in gastric adenocarcinoma samples ($p = 0.010$) and, according to the results obtained by Miao et al. [22], these findings may correlate with poor prognosis or even disease relapse following recovery. Moreover, increased expression of the *SPAG9* gene has also been observed in ovarian cancer [28], colorectal cancer [29], hepatocellular carcinoma [42], lung cancer [43], AML [44], breast cancer [45] and cervical cancer [46].

It is worth noting that detection of the protein product *IL13RA2* using immunohistochemical methods may serve as an independent prognostic factor for gastric cancer detection following surgical resection [47]. Overexpression of *IL13RA2*, confirmed by us in adenocarcinoma tissue , is characteristic of many tumours, including glioblastoma multiforme, astrocytoma, and colorectal and pancreatic cancers [48–51].

The expression of *KIF2C* is associated with lymphatic invasion, lymph node metastases and poor survival in patients with gastric cancer [23]. Overexpression of *KIF2C* (understood as expression levels twice as high) in our study was confirmed in 10/16 patients with adenocarcinoma. Interestingly, the AZ521 duodenal adenocarcinoma cell line (which does not demonstrate *KIF2C* expression), demonstrated a high proliferation rate ($p < 0.001$) and migration capacity ($p < 0.001$) compared to sham-transfected cells when transfected with the *KIF2C* gene [23].

IGSF11 expression has not been observed in many types of diffuse gastric cancer. On the other hand, it is believed that *IGSF11* may be a diagnostic marker for early-stage gastric cancer of the intestinal type [52, 53]. In our study, 14/16 adenocarcinoma samples were of the diffuse type. We observed higher RE of the *IGSF11* gene in lymphoma than in benign changes (adenoma).

Another gene analysed was *ATAD2*, whose function is associated with proliferation, invasion and cellular migration [54]. Numerous literature reports confirm the expression of *ATAD2* in gastric [24, 55], colorectal, breast, lung and uterine cancers [55]. Moreover, some subtypes of gastric cancer with drug resistance (GCIY, GPM1, MKN28) are characterized by high expression levels of *ATAD2*, thus expression of this gene is considered to be one cause of resistance to this drug [56].

Conclusions

Our results suggest that the overexpression of *ATAD2*, *FBXO39*, *HORMAD1*, *IGSF11*, *IL13RA2*, *KIF2C*, *LDHC*, *OIP5*, *PLU1*, *SPAG9* and *TTK* may be specific for gastric adenocarcinoma. Moreover, we found that the overexpression of *HORMAD1* and *TTK* were positively correlated with tubular gastric adenocarcinoma. Additionally, we observed positive correlations between the RE of *KU-CT-1* and patient age in adenocarcinoma. Our study had some limitations. A study with a small number of patients may not have sufficient statistical power to detect significant differences between the healthy and study group. However, preliminary results show which genes should be confirmed in larger numbers of patients.

Article information and declarations

Data availability statement

Available upon request.

Ethics statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee at the Pomeranian Medical University and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All patients gave written informed consent to participate in the study.

Author contributions

Michał Czerewaty — conceptualization, writing — original draft preparation, writing — review & editing, methodology, investigation, data curation, formal analysis.

Maciej Tarnowski — supervision, investigation, validation.

Krzysztof Safranow — software, formal analysis.

Elżbieta Urasińska — resources.

Bernardeta Chajnowska — resources.

Andrzej Pawlik — supervision.

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Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

None.

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Original article

Biomarkers

The expression of CDX-2 and p53 immunohistochemical markers — a useful diagnostic tool for glandular dysplasia in Barrett's oesophagus

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Introduction. Barret's esophagus (BE), is a common state, concerning roughly about 15% of GERD patients. The pathomechanism of BE is replacement of typical squamous-cell mucosa by a layer of intestinal-type glandular mucosa (intestinal metaplasia). In a number of cases the glands are prone to dysplasia which may lead to the occurrence of esophageal adenocarcinoma.

The golden standard in diagnosis of BE is endoscopy combined with histopathological examination of biopsy material of the altered Z line. Unfortunately, many guidelines do not recommend endoscopic treatment in most cases of BE in favor of long-term screening, reserving the need for treatment for dysplastic BE.

Material and methods. 53 patients suspected of BE (study group) and 45 patients without any macroscopic signs of BE (control group) underwent upper GI endoscopy during which several biopsies were taken from the elevated Z line. The study group was divided into 2 subgroups: I — without histopathological evidence of BE (n = 11); II — histopathologically confirmed BE (n = 42). In addition to the standard histopathological examination, the material was screened for levels of CDX2 and p53 expression.

Results. In the control group, none of the patients presented elevated CDX2 or p53 expression (0%). In the study group, 24 patients were CDX2 positive (45.28%) and 27 were p53 positive (50.94%). Both markers were positive in 21 cases (39.62%).

Conclusions. Standard histopathological examination combined with immunohistochemical examination can prove to be a useful tool in confirming the diagnosis of BE, diagnosing early glandular displasia and, in some cases, eliminating false negative results.

Keywords: Barrett's oesophagus, oesophageal adenocarcinoma, p53, CDX-2

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Introduction

Barrett's oesophagus (BE) is an acquired pathological condition. Histologically, it means a change in the structure of the distal oesophageal epithelium, just above the cardia. Typically, this means that the normal multi-layer squamous epithelial lining of the oesophagus is replaced with a single-layer columnar epithelium, typical for intestinal mucosa [1, 2]. The disease was named after British surgeon Norman Barrett, who in 1957 described an oesophagus with a "columnar epithelium" [3]. However, the first case of BE is believed to have been reported by another British doctor, Philip Allison, in 1948 [4]. It was found that BE is more frequent in male patients of 50+ years of age, obese patients, smokers and patients with gastroesophageal reflux disease (GERD) often also with a hiatal hernia (HHO) [5, 6].

It is estimated that approximately 1.3–1.9% of the European population might have BE. Interestingly, there is constant significant growth in the incidence of BE; in the 1990s, it was estimated to be around 0.3%. The risk of BE is drastically higher in patients with chronic GERD — approximately 15% [1, 6]. Moreover, in 76.9–96% of cases, patients with BE are also diagnosed with a hiatal hernia (HHO) [6].

The most frequent symptoms of Barrett's oesophagus are: heartburn, eructation, nausea and vomiting, upper abdominal and epigastric pain, dysphagia and halitosis. Less frequent symptoms may include: odynophagia, salivation, coughing, chronic pharyngitis and sinusitis (known also as laryngopharyngeal reflux). Sometimes the abovementioned symptoms are not present at all [7, 8].

According to the European Society of Gastrointestinal Endoscopy (ESGE), in BE a typical endoscopic view is a Z-line elevation of at least 10 mm together with the presence of tongues (dendritic shape, sometimes continent-shaped) that are easily visible in narrow-band imaging (NBI, i-scan). Sometimes, there is just one tongue and the Z line is not elevated. This is what is called a short segment Barrett's oesophagus [9, 10, 11].

In gastroscopy, in the event of suspected BE, the Z-line morphology is described according to the Prague Classification (CM). The two parameters: circumferential (C) and maximal (M) allow the indication of the elevation of the entire circumference of the Z line (C) and the elevation of its highest tongue (M). Distances should be indicated in centimetres, e.g. C2M4 [12].

If there are pathological alterations of the mucosa, a histological verification is necessary; therefore, biopsy samples are collected according to the Seattle protocol [13] — one sample from each Z-line quadrant every 1–2 cm: e.g. if the Z-line elevation is 5 cm, 3–5 samples should be collected from each quadrant.

In order to diagnose BE, it is critical that there be intestinal metaplasia, goblet cells or ectopic gastric glandular tissue. Most commonly, though, the decisive factor in diagnosing BE is the presence of typical intestinal metaplasia [14–17].

Material and methods

This study was approved by the Bioethical Committee of the Medical University in Łódź, No. RNN/51/20/KE.

The study included patients in which, during the screening gastroscopy, macroscopic features of BE were found (study group) as well as patients who did not present with these features but had a gastroscopy and a distal oesophageal biopsy performed for other reasons, e.g. because of an oesophageal erosion in the course of GERD (control group). In all patients, biopsy samples were collected from the same area of the oesophagus, adjacent to the stomach cardia, as indicated in the Seattle protocol [11].

A total of 98 patients were included in the study: 55 men (56.12%) and 43 women (43.88%). The mean age was 56.6 years (from 33 to 89 years, median 51 years).

The patients were divided into the following groups:

1) control group: 45 patients, 23 men (51.11%) and 22 women (48.89%), with no morphological changes in the cardia area (visible in endoscopy) and who had never reported gastroesophageal reflux. These patients were asymptomatic, undergoing a routine gastroscopy prior to a scheduled cholecystectomy;
2) study group: 53 patients, 32 men (58.18%), 21 women (41.82%); mean age 52.75 years (from 33 to 89 years, median 51 years) — patients who had macroscopically visible characteristics of BE during endoscopy**.** In the whole study group, immunohistochemical tests were performed retrospectively (based on preserved paraffin blocks).

Based on the outcome of the routine histological exam, the study group was divided into two subgroups:

1) group I (n = 11): 5 men (45.45%), 6 women (54.55%); mean age 54.36 years (from 37 to 89 years, median 48 years) — standard histopathological tests did not confirm BE (no intestinal metaplasia and/or goblet cells and no glandular dysplasia);
2) group II (n = 42): 25 men (59.52%), 16 women (40.48%); mean age 52.33 years (from 33 to 81 years, median 51 years) — patients with histological evidence and confirmation of BE, including those with confirmed glandular dysplasia.

Additionally, HHO features visible during endoscopy (for clinical reasons, only sliding and mixed type hernias) were taken into account.

Endoscopy

Endoscopy was performed with the PENTAX Medical EG29-i10 gastroscope. The patients received i.v. premedication with midazolam — 5 mg, phentanyl — 100 µg and hyoscine buthylbromide — 20 mg. During endoscopy, patients' heart rate and blood oxygenation were monitored (with a pulse oximeter). Additionally, before introducing the endoscope into the oesophagus, the patient's larynx was sprayed with 1% solution of lidocaine, a local anaesthetic. The endoscopic exam included the oesophagus, stomach and the proximal

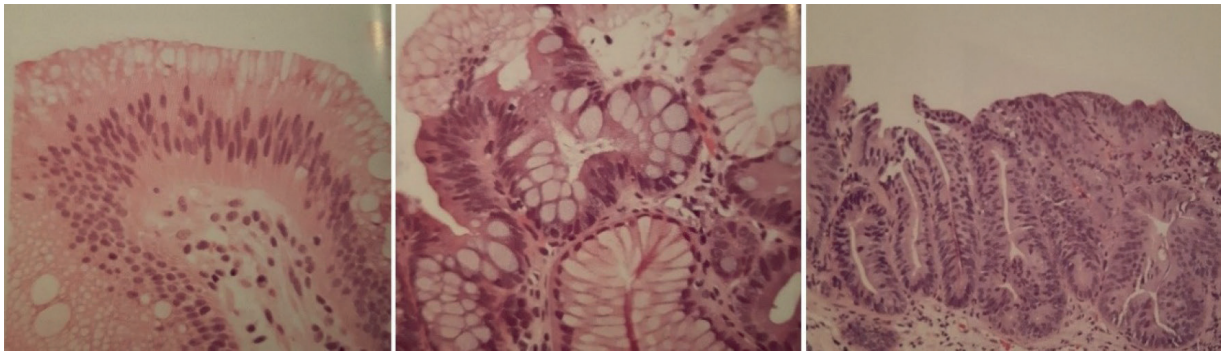

Figure 1. Histopathologic findings in Barrett's oesophagus (BE): intestinal metaplasia (left), low grade dysplasia (centre), high grade dysplasia (right)

part of the duodenum (duodenal papilla, the part behind it and the descending duodenum). If during endoscopy the Z-line morphology typical for BE was encountered, samples were collected according to the Seattle protocol, using Endo-Flex NEO230-G biopsy forceps. In case of the control group, 4 biopsies were taken from the borders of the normal "Z" line; similar to the Seattle protocol. Additionally, typical HHO features, such as a hernia ring or a bell-shaped, dilated gastroesophageal junction (GEJ) were recorded. The mean procedure time was 5 min 23 s (from 4 to 11 min). Oesophageal morphology was assessed using the Savary-Miller scale (S-M), and the Z line was described according to the Prague Classification (CM) [10].

Histological and immunohistochemical tests

Tissue biopsy samples collected during the endoscopy underwent standard histopathological staining with hematoxilline and eosine, followed by the paS-alcian blue staining. This method is aimed at identifying foci of intestinal metaplasia of the glandular gastric mucosa (in order to confirm the diagnosis of BE. European Society of Gastrointestinal Endoscopy criteria have been applied to the full diagnostics of BE (Fig.1).

Following the standard histopathological analysis, the material underwent immunohistochemical staining to assess the expression of CDX2 and p53 proteins using specific antibodies (tests performed in Autostainer by Dako) to indicate possible foci of glandular metaplasia. Because of the fact that the indicated proteins are only present in cellular nuclei, their expression was not routinely assessed in the patients' blood serum.

Biomarkers

The CDX2 protein, encoded by the CDX2 gene (chr13:27, 962, 137-27, 971, 139), is a transcription factor for intestinal cells (so-called goblet cells) actively involved in the correct organogenesis of the intestine. It is typically expressed in the nuclei of intestinal cells. CDX2 is a specific marker for colorectal cancer, but may be an indicator of lung, stomach, pancreatic or bile duct cancer as well [18, 19] (Fig. 2).

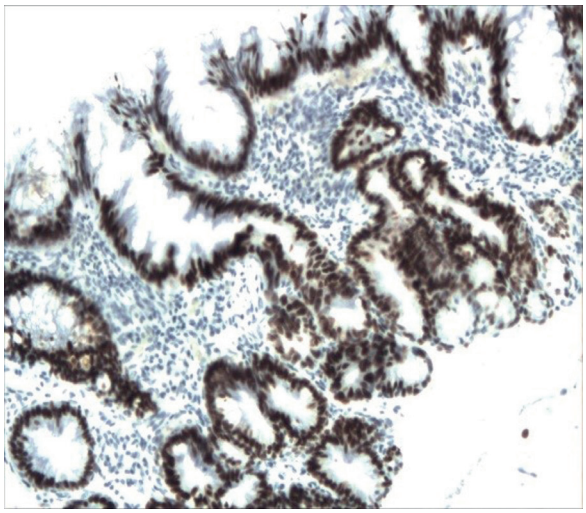

Figure 2. CDX2 positive stain: black nuclei visible represent the cells in which the transition between esophageal to intestinal type is in progress

The p53 protein, encoded by the TP53 gene (*chr17:7, 668, 401-7, 687, 549*), is a transcription factor known also as the "guardian of the genome" and a tumour suppressor. In homeostasis, p53 is inactive. It is only activated when there is a need to repair damaged cell DNA (it creates tetramers enabling the expression of genes such as hdm2, Fas, IGFBP-3, Bax, Cip1 or gadd45) or to induce cell apoptosis by means of cytochrome-C stimulated caspase activation. The expression of the p53 protein in the IH test is a useful marker in the diagnosis of colorectal, breast and lung cancer [20–22] (Fig. 3).

Results

Initially, each of the groups was analysed separately:

- control group: 0 cases (0%) CDX2 staining positive, 0 cases (0%) p53 staining positive, 0 cases (0%) both CDX2 and p53 staining positive;
- study group (overall): 24 cases (45.28%) CDX2 staining positive, 27 cases (50.94%) p53 staining positive, 21 cases (39.62%) both CDX2 and p53 staining positive;
- Group I: 1 case (9.09%) CDX2 staining positive, 5 cases (45.45%) p53 staining positive, 1 case (9.09%) both CDX2 and p53 staining positive;

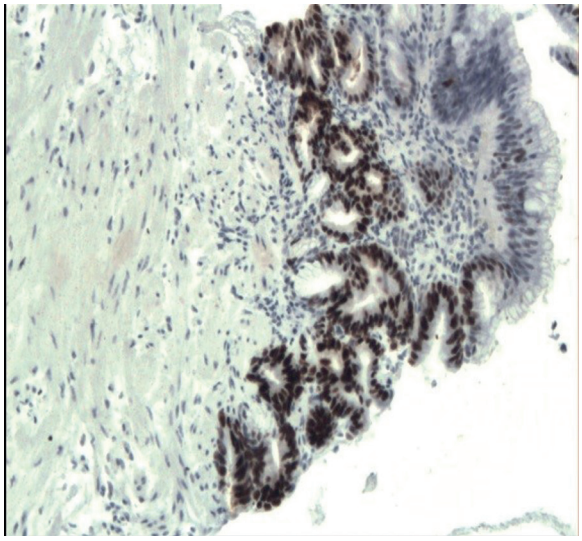

Figure 3. p53 positive stain: the black cells' nuclei indicate that in these the p53 factor is active

— Group II: 23 cases (54.76%) CDX2 staining positive, 22 cases (52.38%) p53 staining positive, 20 cases (47.62%) both CDX2 and p53 staining positive (Fig. 4).

In the samples from all cases of diagnosed glandular dysplasia (11.9% of all cases; n = 6) both markers stained positive.

Discussion

Firstly, concerning the results of our study, we wanted to comment on the specific findings and their clinical significance. In the control group there was no expression of the analysed markers. In group I (no histopathological confirmation of BE), the fact that in 1 case (9.09%) there was expression of CDX2 might be a result of an "omission" of an intestinal metaplasia (IM) focus in the preparation during the standard histopathological exam. This case should be considered a confirmed case of BE. All other cases where the result was CDX2-negative with p53 expression (45.45%) should be considered an invalid reaction, also referred to as a "wild reaction" — the expression of the p53 marker might be a consequence of another kind of chronic inflammation in the stomach cardia area (e.g. NERD/GERD).

In group II (histopathologically confirmed BE), the expression of CDX2 alone confirms the diagnosis of BE (54.76%). The expression of both CDX2 and p53 (47.62%) might suggest neoplasia at the cellular level, which might yet be invisible or "omitted" in the standard microscopic analysis.

In 19 patients (45.24%) from group II, intestinal metaplasia was not confirmed (CDX2-negative), and, as a consequence, it might be stated that the diagnosis of BE was incorrect.

Upon analysing the international guidelines for BE treatment, one might get the impression that this disease is not a significant threat to the population. Nevertheless, there are numerous international papers that indicate an increasing incidence of oesophageal adenocarcinoma. Between 1980 and 2005 the overall incidence of oesophageal adenocarcinoma increased from 1.2 cases per 100,000 people per year to 6 cases per 100,000 people per year — a fivefold increase [23, 24].

Some factors that increase the risk of oesophageal adenocarcinoma, apart from BE, are: male sex, Caucasian race, obesity and a lack of the *Helicobacter pylori* (HP) bacteria infection. According to the abovementioned authors, the presence

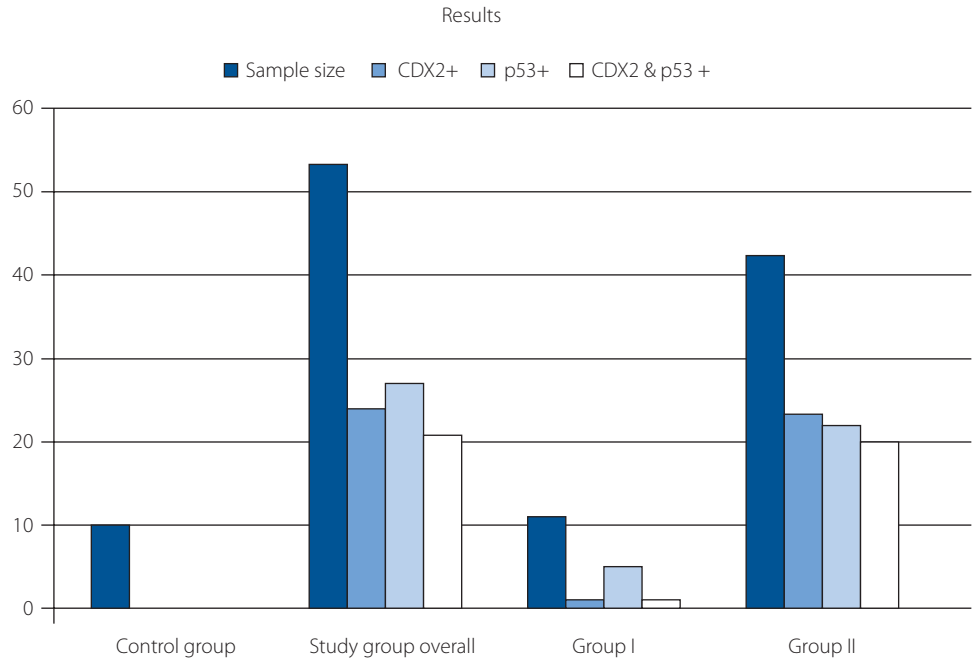

Figure 4. Visual representation of the results

of HP reduces the risk of oesophageal adenocarcinoma by 50% [24, 25].

This increase in incidence over 25 years is particularly surprising because it was an era of intense endoscopic surveillance of BE patients with a strong focus on conservative treatment. The results of one Polish paper confirm the abovementioned doubts relative to the efficacy of endoscopic surveillance in BE [26]. The authors reported that during 10 years of upper gastrointestinal (GI) tract endoscopic exams, they diagnosed 63 cases of BE. Of those 63, 51 qualified for endoscopic surveillance. Three (5.9%) patients developed oesophageal adenocarcinoma requiring extensive surgical treatment, even though their prior condition could have been treated in a simple and less invasive way. Similar conclusions can be drawn from the analysis of foreign studies. Researchers from Denmark [27] and Sweden [28] via screening diagnosed 167 (out of 11,028 cases of BE) and 82 (out of 7,932 cases of BE) cases of oesophageal cancer. In both countries it was also noticed that cases of adenocarcinoma were diagnosed at the very beginning (before month 3) of surveillance. The authors stated that the majority of cancer cases were a result of inaccurate diagnostics of BE. There is more data on discovering adenocarcinoma cases during the period of BE surveillance [29–31], even though in the phase of neoplasia (state directly prior to cancerogenesis), patients should undergo treatment.

So far, the clinical and theoretical usefulness of immunohistochemical markers expression in the diagnosis of BE has been proven, but none of the numerous papers published are mentioned in the international guidelines for BE. What is more, there are not enough publications on the usefulness of simultaneous testing for the expression of CDX-2 and p53 in the clinical practice of BE diagnostics. The only available study that simultaneously analyses the expression of both CDX-2 and p53 is a paper by Fabio Terabe et al. [29] on an animal model — mice C57B1/6J. In 135 mice, gastroesophageal reflux was surgically induced (by performing oesophagogastrojejunostomy, oesophagojejunostomy without gastrectomy or oesophagojejunostomy with gastrectomy) and then after 40 weeks the mice were euthanised. Samples collected from their stomach cardia area were analysed in histopathological and immunohistochemical tests. Intestinal metaplasia had developed in 21 out of the 110 mice (19%), of which most cases (45.5%) were in mice who had had undergone oesophagogastrojejunostomy. In all cases of intestinal metaplasia, expression of the CDX-2 was present. In 8 out of 110 (7.2%) glandular dysplasia developed; most of the cases were reported (7 of 33; 21%) in the group that had had undergone oesophagogastrojejunostomy. In all dysplasia cases, expression of the p53 protein was present. Additionally, in 62% cases of intestinal dysplasia, expression of the p53 protein was present. In 50% of glandular dysplasia cases there was no expression of the CDX-2 protein. The results presented by Terabe et al. coincide perfectly with the results of my work.

Conclusions

Routine histopathological testing can sometimes give both a false positive and a false negative result in the diagnosis of BE. Testing the expression of the CDX2 and p53 markers with immunohistochemical methods in cases of BE may help detect intestinal metaplasia and potential glandular dysplasia overlooked under standard histopathological procedures.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Article information and declarations

Data availability statement

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

Ethics statement

This study protocol was reviewed and approved by the Committee of Research Ethics of the Medical University of Łódź.

Authors contributions

Tomasz Klimczak — conceptualization, data curation, formal analysis, project administration, writing — original draft preparation.

Jerzy Klimczak — conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, writing — review & editing.

Marian Danilewicz — conceptualization, data curation, formal analysis, methodology, project administration, supervision, validation, writing — review & editing.

Lech Pomorski — conceptualization, formal analysis, investigation, methodology, project administration, supervision, writing — original draft preparation, writing — review & editing.

Jacek Śmigielski — data curation, methodology, resources, writing — review & editing.

Wojciech Ciesielski — data curation, formal analysis, methodology, writing — original draft preparation.

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Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

None.

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Review article

Cancer prevention and public health

The impact of cell phone use on the formation of brain tumors

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Cell phone use is increasing and now includes nearly 6.9 billion subscribers. A common concern is the effect of long-lasting phone calls on the formation of brain tumors, due to the proximity of this region. The aim of the following review was to verify this association along with a potential molecular background. The results of epidemiological studies are inconclusive. Most of them do not indicate a significantly increased risk of central nervous system cancers in phone users. However, some indicate that there is an increased risk of gliomas and a worse prognosis for patients with long-term phone use (in terms of cumulative hours and number of calls). Experimental studies show that radiation emitted by phones is able to induce changes in cell biology by generating oxidative stress, causing DNA damage and affecting gene expression. Therefore, further observation of the population and evaluation of the results of ongoing studies is needed to accurately assess this risk.

Keywords: brain tumors, cell phones, carcinogenesis, public health

Introduction

Tumors of the central nervous system (CNS) are a group of more than a hundred histologically distinct subtypes of neoplasms with varying clinical characteristics, treatment and epidemiology. While their incidence in the world community is relatively low, they have a disproportionately high mortality rate (only 1 in 3 patients achieve survival of at least 5 years from diagnosis) [1]. They are the most common solid tumors diagnosed in children aged 0–14 years and the second most common in adolescents aged 15–19 years in the world pediatric population. What is more, they are the eighth most common among all cancers (3%) in the world adult population above 40 years of age. They are three times more frequent in men than in women [2, 3]. In Poland, their frequency is estimated on 2% of all tumors [2]. The most frequent type is glioma (up to 70% of primary brain tumors worldwide, 40% in Poland) [2, 3]. It is a group of neoplasms originating from glial cells. The World Health Organization (WHO) has made a four-stage classification for their grade of malignancy, where grade I is considered to be a benign lesion, while grade IV is the highest and represents lesions with very high malignancy (the most common malignant brain tumor, glioblastoma multiforme, is also in this category) [3]. Other malignant lesions, such as anaplastic astrocytomas and oligodendrogliomas, are far less common. Although their localization can be the entire CNS, their most common location is in the supratentorial region of the brain [1]. Non-malignant lesions (22.38 per 100 000) are far more common than malignant

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ones (8.5 per 100 000) among patients form around the world [3]. Malignant brain cancer is the sixth most common cause of death in people over the age of 40 in the world. Despite its poor prognosis (average life expectancy estimated at 12.6 months after diagnosis), in recent years there has been an increase in survival rates in Western developed countries due to significant improvements in medical care [4, 5].

Many risk factors for the disease have been discovered to date — both environmental and genetic. However, interestingly, the exact etiology of these tumors is still not understood [5]. Approximately 5% of gliomas are family-related, while an even smaller percentage are associated with so-called Mendelian disorders and hereditary syndromes [3, 6]. Recent studies have coherently demonstrated that increased birth weight (> 4000 g) leads to increased risk of CNS tumors, as confirmed by a meta-analysis by Georgakis et al [7]. Caucasians are at higher risk for the disease. It has also been proven that the incidence is higher in people before 12 and after 65 years of age. The only fully confirmed environmental risk factor for all brain tumors is ionizing radiation. This correlation is most strongly seen in children receiving cranial radiotherapy as part of treatment for acute lymphoblastic leukemia [8]. Research is constantly being conducted to identify other factors that may influence the increased risk of brain tumors. One such factor might be electromagnetic radiation from cell phones. This radiation was classified by the International Agency for Research on Cancer as a potential carcinogen [9].

Since the first introduction of cell phones in the mid-1980s, they have become an irreplaceable part of daily life in developed countries. Numerous studies have been done since then to prove the relationship between cell phone use and the increased incidence of brain tumors in the world population. The main aim of this paper was to explore if any relationship exists between cell phone use and the incidence of brain cancer.

Material and methods

A review of scientific publications in PubMed and Google Scholar databases and relevant data published by the WHO and the National Cancer Institute [10–12] was conducted. The following keywords were used to search for articles: "mobile phone," "cell phone," "brain cancer," "glioma," "risk," and a combination of these. Initially, 541 articles from 1993–2014 were found, and then repeated articles and abstracts were eliminated, obtaining 396 articles. The time criterion was set to 2014–2024 (the review was conducted in March 2024). Finally, 141 articles were found, which were analyzed substantively by title and abstract. Finally, 38 articles were included in the review.

Cell phone use and formation of CNS tumors

Cell phone usage is extremely widespread, accounting for up to 97% of US adults and about 6.9 billion people worldwide [10, 11]. Phones also used by younger and younger children. There are equally prevalent concerns about the impact of cell phones on CNS tumors due to the proximity of the head during calls. Cell phones emit radiofrequency non-ionizing electromagnetic radiation (450–2700 MHz) with a peak power of 0.1–2 W [11]. The controversial fifth-generation (5G) phones use frequencies above 80 GHz. However, it is still far lower than that of ionizing radiation, a proven risk factor for CNS tumors [12, 13]. The different types of wireless phone technology generations and frequencies they use are shown in Table I.

Experimental studies

Ionizing radiation is a known factor affecting the cycle and function of cells [13]. Researchers are also trying to answer the question of such an effect induced by radiofrequency radiation (RFR). In a study on mice [frequency (f) = 1900 MHz, specific absorption rate (SAR) = 2.5/5/10 W/kg] and rat (f = 900 MHz, SAR = 1.5/3/6 W/kg) models, it was shown that exposure to RFR for 10 hours a day after 14 (mice) and 19 weeks (rats) caused a significant increase in DNA damage in the cortex cells of the frontal lobes of mouse brains and the hippocampus of rat brains. The frequencies mentioned above correspond to the 2nd and 3rd generations of telephone network technology (2G and 3G), but the exposure was of a much higher dose and duration than standard cell phone usage [14]. The probable mechanisms are the production of reactive oxygen species (ROS) and the resulting oxidative stress which cause oxidative damage to DNA cells as well as disruption of the repair of damaged DNA [15, 16]. Some authors indicate that even short-term exposure to

Table I. Types of wireless phone technology generations [32]

Abbreviation	Full name	Date of introduction	Frequency (f)
1G	Analog-Advanced Mobile Phone Service (AMPS)	1980′	800 MHz
2G	Global System for Mobile Communications (GSM) and Code Division Multiple Access (CDMA)	1990′	850–1900 MHz
3G	Universal Mobile Telecommunications Service (UMTS)	1998	800–2100 MHz
4G	Long Term Evolution (LTE)	2008	700–2690 MHz
5G	Device-to-Device Communication	2018	> 30 GHz (even to 300 GHz)

this type of radiation is capable of increasing ROS levels, causing DNA damage [17–19]. Such exposure is able to induce the activation of p53-related pathways and, with longer exposure, activation of Bcl-2, Ras and Akt1-related pathways, thus promoting cell survival and impairing apoptosis. Radiofrequency radiation is also able to affect the genes responsible for angiogenesis (inhibition of *VEGF*, *TNFSF15*, stimulation of *EPO*, *IL8*, *STAT5B*, *HPSE*) [20]. Moreover, the thermal effect generated by RFR is also noted, leading to increased ROS production and enhanced neuronal cell excitability [20]. Furthermore, RFR can cause an increase in intracellular nitric oxide (NO) levels in neurons and activation of the CaM/NO/cGMP signaling pathway, thereby impairing the response of nerve cells to ischemic or injury damage. This can affect not only the process of neurogenesis and cognitive function, but also the development of CNS tumors [21]. Gupta et al. [22] observed that f = 2450 MHz radiation results in changes in neuronal structure and function. It is caused by destroying mitochondria and releasing cytochrome-c, activating the apoptotic agents caspase-3 and caspase-9 in hippocampal cells [22]. Similar conclusions were reached by Zhao et al. [23] as they observed increased expression of caspase-2, caspase-6 and Asc protein genes in neurons and astrocytes, and Bax protein only in astrocytes after 2-hour exposure to RFR with f = 1900 MHz. This shows that even short-term exposure to RFR can increase the expression of genes encoding apoptotic proteins. However, Durdik et al. [24] indicated that RFR induces ROS and oxidative stress, but not DNA damage and apoptosis of CD34+ bone marrow progenitor cells. Hou et al. [25] observed a significant increase in ROS levels after 1-hour exposure to RFR at f = 1800 MHz and enhanced apoptosis of NIH/3T3 mouse fibroblasts. Shahabi et al. [26] noted that another morphological change in rat neural cells induced by long-term exposure (6 hours a day for 4 and 8 weeks) to RFR (f = 900 MHz) is their vacuolization, although with an unknown pathophysiological role. In addition, Falcioni et al. [27] indicated that with exposure to RFR (f = 1.8 GHz) in rats, there was an increase in the incidence of cardiac schwannoma and proliferation of cardiac Schwann cells and brain glial tissue, which also indicates the induction of radiation-induced changes in neurons. The effects of RFR on glioblastoma multiforme cells have also been explored. Al-Serori et al. [28] showed that RFR at f = 1950 MHz caused DNA damage in the U87 cell line, one of the most common among malignant brain tumors. However, the results of a study by Liu et al. [29] contradict these observations. Ouadah et al. [30] while testing rats with implanted glioma cells noted that exposure to f = 900 MHz radiation did not affect the survival, tumor volume, mitotic index, vascularization and necrosis of tumor cells. There is much more concern about the widespread introduction of 5G technology. Karipidis et al. [31], in a review of 107 experimental and 31 epidemiological studies, concluded that there is no confirmed evidence of any harm from this type of radiation on the human body, including the CNS. Russell, on the other hand, noted that the effects of 5G exposure have not been sufficiently studied, although there are reports of induced oxidative stress and altered gene expression [32]. While the results of the above are ambiguous, they show that RFR exposure is capable of inducing changes in cell biology that may have a potential impact on the onset of CNS diseases, including neurodegenerative disorders and tumors. The effects of RFR on cell biology are shown in Figure 1.

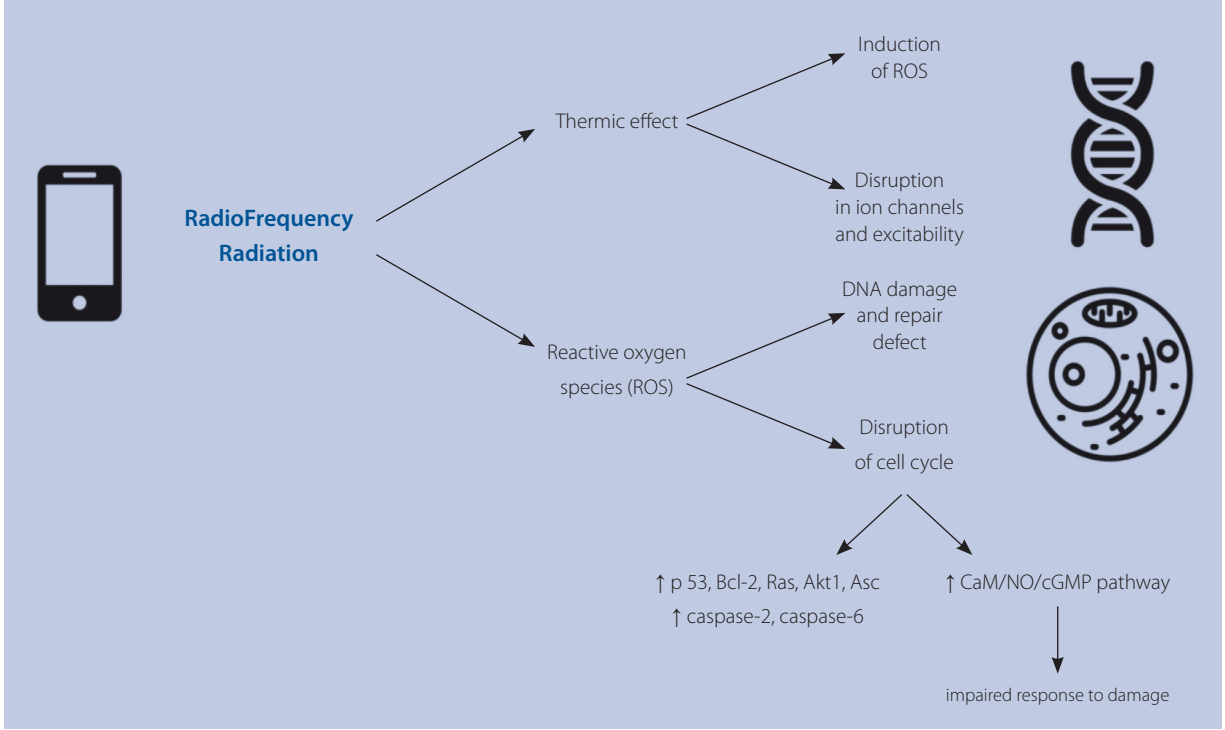

Figure 1. The effects of radiofrequency radiation (RFR) on cell biology [15–32]

Epidemiological studies

Data on the impact of cell phone radiation on the growth of CNS tumors is still controversial. Some authors categorically state that it is one of the factors of carcinogenesis and should be restricted [33]. Moon, who analyzed the nationwide cell phone subscription rate and the incidence of CNS tumors, observed a statistically significant correlation between these variables for benign tumors [benign meningeal neoplasm (ICD-10: D32. 0); benign neoplasm of the brain and other parts of the central nervous system (ICD-10: D33)] and malignant ones [malignant neoplasm of the brain except lobes and ventricles (ICD-10: C71.0), frontal lobe (ICD-10: C71.1), temporal lobe (ICD-10: C71.2)]. The strongest correlation was reported for tumors of the frontal lobe [r = 0.85; 95% confidence interval (CI): 0.63–0.93], a region exposed to close contact with the phone during conversation [34]. In contrast, Schüz et al. [35] in a study in a group of 776,156 women during a 14-year follow-up, noted that the relative risk of ever or never using a cell phone for all brain tumors was close to 1.0 [relative risk (RR) = 0.97; 95% CI: 0.90–1.04]. No significant increase or decrease in the risk of the disease was observed for daily phone use or > 10 years. No difference in tumor location was also noted [35]. Feychting et al. [36] found that phone use for > 15 years did not affect the risk of formation of CNS tumors: glioma [hazard ratio (HR) = 0.97; 95% CI: 0.62–1.52], meningioma (HR = 1.24; 95% CI: 0.60-2.59) and acoustic neuroma (HR = 0.76; 95% CI: 0.33–1.73). Villeneuve et al. [37] came to similar conclusions when they analyzed the increase in the number of phone users and the incidence of brain gliomas in Canada. They indicated that the increase in incidence was mainly related to the aging of the population, rather than phone use [37]. Choi et al. [38] conducted a similar study in South Korea's population. They observed that the age-adjusted incidence rate for brain tumors increased almost by 4% in people > 60 years old, but this was not correlated with cell phone use [38]. In another Korean study, Yoon et al. [39] noted that the age-adjusted odds ratio (aOR) for the development of glioma for regular phone users was 1.17 (95% CI: 0.63–2.14). They found no association with time of use or type of phone. However, a statistically insignificant increase was observed for urban residents (aOR = 1.42; 95% CI: 0.66–2.89) compared to rural residents (aOR = 0.50; 95% CI: 0.22–1.13). In addition, they found a statistically insignificant, although noticeable, difference in aOR between prevalence of tumors located ipsilateral and contralateral to the side of the head on which the cell phone was used most often [39]. Karipidis et al. [40], in an Australian ecological study (n = 16825), found no increase in the incidence of gliomas during the period of intensive cell phone expansion (2003–2013) in that country [annual percentage change (APC) = –0.6; 95% CI: –1.4 to 0.2). There was also no correlation with the incidence of temporal lobe tumors (APC = 0.5; 95% CI: –1.3 to 2.3). Elwood et al. [41], in a New Zealand study (n = 6677), similarly found no association between the increase in cell phone use (in 2006 almost the entire country's population) and the incidence of gliomas. What is more, the results suggested a decline in the 10–69 age group, the most intensive users of mobile devices [41]. Most interestingly, Uddin et al. [42] analyzed Taiwan's epidemiological data, finding that as the number of phone users increased by each percent (in 2002, the number of phone subscribers exceeded the population), there was a 0.5% increase in the incidence of brain tumors. However, the authors noted that further research was needed, and the conclusions so far are ambiguous [42]. A similar study conducted in Nordic countries by Deltour et al. [43] found no significant association between cell phone use and the incidence of gliomas, including among the most intensive users of mobile devices. The observations apply not only to gliomas, but also to other intracranial tumors. Shrestha et al. [44] investigated the effect of cell phone use on the development of pituitary tumors. They determined that the risk did not increase over at least 10 years of phone use [odds ratio (OR) = 0.69; 95% CI: 0.25–1.89] in relation to duration, total hours of use, cumulative number of calls and type of device [44]. Pettersson et al. [45] verified the correlation between the occurrence of acoustic neuromas and phone use for at least 6 months. They identified this risk as OR = 1.18 (95% CI: 0.88–1.59), and for histopathologically verified tumors as OR = 0.99 (95% CI: 0.65–1.52). For exposures lasting at least 10 years, the risk was OR = 1.11 (95% CI: 0.76–1.61). The authors also found no correlation between tumor location and the side of the head to which the phone was being held [45]. In a similar way, Carlberg et al. [46] found no statistically significant increase in meningioma risk (OR = 1.0; 95% CI: 0.8–1.2). They observed an increase in OR for cell phone use for > 25 years, but this was not statistically significant, and neither was the difference in tumor location [46]. Some authors suggest that there is no increased risk of CNS tumor development in casual, moderate phone use. Instead, it appears in the group of users who use these devices most intensively. A French study by Coureau et al. [47] showed that there was no significant increase in the risk of gliomas (OR = 1.24; 95% CI: 0.86–1.77) or meningiomas (OR = 0.90; 95% CI: 0.61–1.34) for normal phone users. On the other hand, it was significantly higher for intensive cell phone use, considering the cumulative time > 896 h (OR = 2.89; 95% CI: 1.41–5.93 for gliomas; OR = 2.57; 95% CI: 1.02–6.44 for meningiomas) and > 18360 calls (OR = 2.10; 95% CI: 1.03–4.31) [47]. Furthermore, Momoli et al. [48] in the Canadian subgroup of the INTERPHONE study noted an increased risk of glioma formation in a group of people who used the phone for at least 558 hours of cumulative use (OR = 2.0; 95% CI: 1.2–3.4). Alarming results were observed by Hardell and Carlberg [49] in a study in a group of 1,380 glioma patients. They found a significantly higher risk of this tumor on the ipsilateral side relative to phone use (OR = 1.8; 95% CI: 1.4–2.2), especially in the 18–39 age group (OR = 2.2; 95% CI: 1.2–3.8) [49]. Similar observations were noted by de Voght [50], who indicated that there was a 35% increase

in the incidence of parietal lobe tumors over a 10-year period, corresponding to 188 additional cases per year. A statistically significant increase in the incidence of tumors on the ipsilateral side was also found by Grell et al. [51] in a study in the INTERPHONE group (n = 792) (α = 9.66; 95% CI: 2.84–39.3). This association was unrelated to cumulative time and number of calls [51]. In addition, Carlberg and Hardell [52] noted that cell phone use >20 years was associated with lower survival for patients with gliomas in general (HR = 1.8; 95% CI: 1.3–2.5) and glioblastoma multiforme (HR = 2.0; 95% CI: 1.4–2.9). The major concerns about phone use are among the youngest users. However, Castaño-Vinyals et al. [53] in a study in a group of 899 patients with CNS tumors aged 10–24 years did not observe a significantly increased risk of developing gliomas (OR = 0.85; 95% CI: 0.62–1.18) — regardless of the duration and intensity of phone use and RFR dose. In fact, the risk seemed to decrease in the 15–19 age group with increasing number and duration of calls [53]. Similar conclusions were reached by Sato et al. [54] in a Japanese study in a group of children aged 6–18 years (n = 82). Data from the above studies are summarized in Table II.

It should not be forgotten that most experimental and epidemiological studies have their limitations. The results of experimental studies on animal models are often hard to relate to the human body, while studies on human cell lines are rare. In addition, they often take into account the extremes of exposure, practically impossible to replicate in the daily use of phones. Many epidemiological studies report a long latency period (> 15 years), ignore rare subtypes of brain tumors, and overlook the impact of phone use in childhood, during the period of greatest CNS development [55].

Table II. The impact of cell phone use on brain tumors formation [34–54]

Study	Country	Test group	Observation period	Conclusions
Moon 2023 [34]	South Korea	Nationwide cell phone subscription rate	10 years	↑ benign tumors ↑ malignant tumors of the temporal and frontal regions
Schüz et al. 2022 [35]	The United Kingdom	n = 776 156	14 years	No risk
Feychting et al. 2024 [36]	The United Kingdom, Denmark, Finland, the Netherlands, Switzerland	n = 264 574	7 years	No risk
Villenueve et al. 2021 [37]	Canada	Nationwide cell phone subscription rate, patients with gliomas (n = 43 350)	23 years	No risk
Choi et al. 2021 [38]	South Korea	Patients with brain tumors (n = 29 721)	18 years	No risk
Yoon et al. 2015 [39]	South Korea	Patients with gliomas (n = 285)	5 years	No risk
Karipidis et al. 2018 [40]	Australia	Patients with gliomas (n = 16 825)	10 years	No risk
Elwood et al. 2022 [41]	New Zealand	Patients with gliomas (n = 6677)	25 years	No risk, ↓ incidence in 10–69 age group
Uddin et al. 2023 [42]	Taiwan	Nationwide cell phone subscription rate	20 years	Correlation cannot be excluded
Deltour et al. 2022 [43]	Sweden, Finland, Norway, Denmark	Patients with gliomas (n = 18 232)	20 years	No risk
Shrestha et al. 2015 [44]	Finland	Patients with pituitary tumors (n = 80), healthy controls (n = 240)	10 years	No risk
Pettersson et al. 2014 [45]	Sweden	Patients with neuromas (n = 451), healthy controls (n = 710)	> 6 months	No risk

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Table II cont. The impact of cell phone use on brain tumors formation [34–54]

Study	Country	Test group	Observation period	Conclusions
Carlberg et al. 2015 [46]	Sweden	Patients with meningiomas (n = 1625), healthy controls (n = 3530)	9 years (881 hours of calls)	No risk
Coureau et al. 2014 [47]	France	Patients with gliomas (n = 253), patients with meningiomas (n = 194), healthy controls (n = 892)	2 years (> 896 hours of calls)	No risk for normal use, ↑ risk in the group with the longest time of use
Momoli et al. 2017 [48]	Canada	Patients with gliomas (n = 253)	3 years (> 558 hours of calls)	↑ risk in the group with the longest time of use
Hardell et al. 2017 [49]	Sweden	Patients with gliomas (n = 1380)	17 years	↑ risk on the ipsilateral side
Grell et al. 2016 [51]	Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, the United Kingdom	Patients with gliomas (n = 792)	4 years	↑ risk on the ipsilateral side
Carlberg et al. 2016 [52]	Sweden	Patients with gliomas (n = 1678)	20 years	↓ survival of glioma patients
Castaño-Vinyals et al. 2022 [53]	Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, the Netherlands, New Zealand, Spain	Patients aged 10–24 with brain tumors (n = 899), healthy controls (n = 1910)	5 years	No risk
Sato et al. 2017 [54]	Japan	Patients aged 6–18 with brain tumors (n = 82)	5 years	No risk

Summary

The majority of available epidemiological studies do not identify an increased risk of developing brain tumors in the context of cell phone use. However, experimental studies and some epidemiological studies suggest the effects of radiation emitted by phones on neural cells (oxidative stress, thermal effect) and the potential impact on the formation of CNS tumors with long-term use. It should also be remembered that widespread mobile telecommunication is a new invention, available for about 20 years, and brain tumors are characterized by a long latency period. Therefore, it is necessary to conduct further studies and evaluate the results of previous ones in order to further define the impact of cell phone use on the formation of brain tumors.

Article information and declarations

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

Supplementary material

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Review article

Cancer prevention and public health

Integrating smoking cessation counseling into oncology practice — benefits and barriers

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Exposure to tobacco smoke, which contains around 70 carcinogenic components, leads to approximately 8 million deaths worldwide annually. Poland ranks among the top countries with the highest tobacco-related DALY (Disability-Adjusted Life Years) rates. Despite the well-documented risks of continuing to smoke after a cancer diagnosis and the benefits of quitting, many cancer patients continue to smoke. The benefits of quitting smoking for cancer patients are significant: improved survival rates, better treatment efficacy, reduced complications, lower risk of recurrence and secondary cancers, enhanced quality of life, and long-term health benefits such as lower risk of cardiovascular and respiratory diseases. Abstinence from smoking is considered the strongest predictor of survival in cancer patients who have ever smoked. However, the topic of smoking cessation is not frequently discussed by medical staff. A study conducted in Poland found that only 11% patients were informed about its negative impact on oncological treatment. This suggests a low level of awareness among medical personnel regarding the consequences of continued smoking on treatment outcomes and possible concerns about discouraging patients. Incorporating smoking cessation counseling into prehabilitation for oncology patients is crucial. Personalized information about improving treatment outcomes and the availability of specialist help could significantly increase patients' chances of quitting smoking. Tailored counseling approaches and psychological support are essential to address individual concerns and overcome barriers to quitting, especially during the „teachable moment" of a chronic disease diagnosis. Time constraints during patient visits pose a challenge for oncologists and healthcare providers. However, delivering a personalized message about the benefits of quitting smoking and available support services can be done in under a minute. This message should be framed to avoid inducing guilt in patients. Despite the clear benefits of smoking cessation for cancer patients, Poland lacks an organized system of assistance. Integrating smoking cessation into oncology practice requires systemic changes. Ideally, oncology centers should refer smoking patients to dedicated cessation support centers staffed by trained health educators, psychologists, and nurses. Training sessions by the National Institute of Oncology can support this integration. In conclusion, integrating smoking cessation counseling into oncology practice is essential for improving cancer treatment outcomes and overall patient health. Overcoming barriers through education, dedicated resources, patient-centered approaches, and policy support can make smoking cessation a standard part of cancer care.

Keywords: smoking cessation, cancer care, benefits of quitting

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Exposure to tobacco smoke components, around 70 of which are carcinogenic, causes approximately 8 million deaths worldwide annually. Poland is a country with a very high burden of smoking-related consequences — it ranks among the dozen or so countries with the highest tobacco-related DALY (Disability-Adjusted Life Years) rates in the world [1]. Tobacco smoke is classified by the International Agency for Research on Cancer (IARC) in Lyon as a carcinogenic factor that unequivocally initiates and promotes the process of carcinogenesis. This knowledge is well-established and known among medical personnel. Unfortunately, despite well-documented risks associated with continuing smoking after a cancer diagnosis and the benefits of quitting smoking among cancer patients, many continue to smoke. International and Polish studies have shown that between 30% and 60% of patients do not quit smoking after a cancer diagnosis. The benefits experienced by patients who stop smoking are invaluable: improved survival rates and treatment efficacy, reduced complications and side effects, reduced risk of disease recurrence and secondary cancers, enhanced quality of life, and long-term health benefits including a lower risk of cardiovascular disease, respiratory issues, and other smoking-related illnesses [2]. Apart from disease site and stage, abstinence from smoking is considered the strongest predictor of survival in cancer patients who have ever smoked [3].

Although the aforementioned benefits of stopping smoking after a cancer diagnosis and the risks associated with continuing smoking are well documented, this topic is rarely discussed by medical staff. A study, conducted by Fundacja Wygrajmy Zdrowie, on Polish cancer patients indicates that only 40% received information about the harmful impact of smoking on health at the oncology center, and even fewer, only 11%, received information from medical staff about the negative impact of smoking on the effectiveness of oncological treatment. These data may suggest a potentially low level of awareness among medical personnel at these centers regarding the consequences of continued smoking on cancer treatment outcomes, as well as concerns about discouraging patients. Additionally, the small number of places where the patient can get help is a factor that makes it difficult to undertake smoking cessation activities. Nevertheless, there is a high probability that if patients received personalized information about the possibility of improving treatment outcomes and the availability of specialist help, their chances of quitting smoking could significantly increase. Incorporating smoking cessation counseling into prehabilitation for oncology patients is essential to address this gap. By doing so, patients can be better prepared — both physically and mentally — for the rigors of cancer treatment.

It is worth noting, however, that even organized programs cannot help all patients. Many factors influence the effectiveness of smoking cessation programs. These factors lie not only with the medical staff but also with the patients themselves and the organization of the healthcare system. Medical staff should bear in mind that cancer patients are unique, differing from the general population attempting to quit smoking. Patients may be resistant to quitting smoking due to addiction, fear of withdrawal symptoms, or a lack of motivation, particularly when dealing with the stress of a cancer diagnosis. Tailored counseling approaches that address individual concerns and provide psychological support are essential to overcoming this barrier.

On the other hand, it is important to remember that a chronic disease diagnosis is a so-called "teachable moment," when patients are more receptive and willing to make health-related changes in their lives. Therefore, delivering a message about the necessity of quitting smoking during this critical moment should become good medical practice. Tailoring smoking cessation interventions to individual patient needs and preferences can improve their effectiveness.

Oncologists and healthcare providers often face time constraints during patient visits, making it challenging to incorporate smoking cessation counseling into routine practice. However, a properly constructed message containing only personalized information about the benefits of quitting smoking and the availability of nicotine addiction treatment and support services, such as Quitline (Telefoniczna Poradnia Pomocy Palącym), takes no more than a minute. It is especially important that the message is constructed in a way that does not induce feelings of guilt in the patient, particularly in cases of cancers obviously related to smoking.

Unfortunately, despite the clear benefits of smoking cessation for patients undergoing cancer treatment, there is no organized system of assistance in Poland. Integrating smoking cessation into oncology practice requires systemic changes, including modifying clinic workflows and establishing referral systems to cessation programs. Ideally, every oncology center should identify smoking patients and refer them to a smoking cessation support center located within the oncology center. Such a center does not necessarily require the involvement of an oncologist; health educators, psychologists, and nurses trained in nicotine addiction treatment can and should be the ones to provide this support. Training sessions are regularly organized by the team at the National Institute of Oncology as part of the National Health Program.

In conclusion, integrating smoking cessation counseling into oncology practice is a critical step toward improving cancer treatment outcomes and overall patient health. While there are significant barriers to overcome, the benefits of such integration are substantial. By addressing these challenges through education, dedicated resources, patient-centered approaches, and policy support, healthcare providers can effectively incorporate smoking cessation into cancer care.

Article information and declarations

Author contributions

M.C. — conceptualization, writing — original draft preparation.
I.A.P. — conceptualization.

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Review article

Radiotherapy

Do malignant tumors need oxygen to survive radiotherapy?

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The pathological vascular network in malignant tumors is generally irregular and chaotic. Euoxic clonogenic tumor cells (radiosensitive) are gathered around the vessels, which are unevenly distributed within the tumor volume. The results of many clinical studies [mainly on head and neck (H&N) cancers] have convincingly shown that extension of the overall irradiation time (OTT) needs a pronounced increase in the total dose (TD). It was strongly suggested that the results reflect an accelerated clonogens repopulation, which likely neutralizes about 30% of the cell kill effect of each dose fraction, and it potentially increases to even 80% towards the end of conventional irradiation. However so far, this mechanism's activity seems to be quantitatively exaggerated, since towards the end of irradiation, residual 10^1–10^2 cancer cells likely become hypoxic and highly resistant to 2 Gy fractions. Thus, local hypoxia should likely be considered as a dominant process responsible for clinical failure. Accelerated repopulation of only a few cellular survivors does not seem reliable. The efficacy of various chemical radiosensitizers, bioreductive drugs, and immuno-boosts are presented and discussed. Finally, it becomes clear that conventional 2 Gy fractionated radiotherapy should no longer be considered as an effective regimen to achieve local tumor control of locally advanced cancer higher than 50%. Pronounced improvement of the RT might be expected using an initial conventional dose of 50 Gy given in 25 fractions followed by a boost of 4–5 large dose (hypo) fractions of 5–6 Gy or by local brachytherapy.

Keywords: tumor oxygenation, cell kill effect, hypoxia, radiosensitizers, immuno-boosts

The impact of oxygen on tumor response to radiotherapy

Since the early 1950s, the role of oxygen pressure in the tumor and its impact on cancer cells' radiosensitivity has been extensively studied *in vitro* and *in vivo*. Thomlinson, Gray and Denekamp [1, 2] clearly documented that the growing solid tumors develope own vascular network to supply the tumor's metabolism and cell proliferation; the neo-vascular network is generally chaotic with an uneven pattern.

An imbalance usually exists between blood vessel branching and the kinetics of tumor cell proliferation. Analyzing the histological sections of human bronchus cancer, Thomlinson and Gray designed the 70–90 µm cylindrical model of highly proliferative euoxic cancer cells clustered around the blood vessels [1], and therefore radiosensitive due to the O_2 pressure of about 20 µm Hg or higher. Further increases of oxygen pressure does not however increase their radiosensitivity (Fig. 1). But if the O_2 gets below 10 mm Hg cell radiosensitivity dramatically decreases, and the cells turn into poorly oxygenated, hypoxic and finally anoxic cells (< 5 mm Hg), with death being irreversible.

Euoxic cancer cells are the principal targets of radiation, e.g. induced secondary electrons [3]. Theoretically, consecutive

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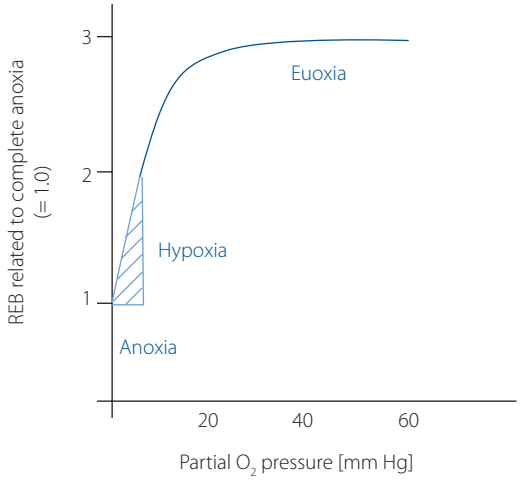

Figure 1. Dependence of the oxygen enhancement ratio (OER) on partial O_2 pressure [OER = dose in CO_2/dose in O_2] (adopted from Denekamp [2]); RBE – relative biological effectivenes

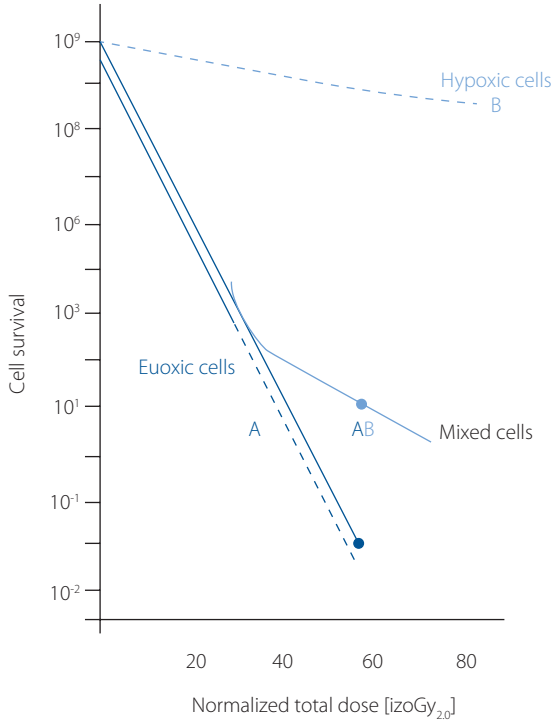

Figure 2. Cell survival after 2 Gy fractions depending on hypoxic and mixed euoxic/hypoxic cells (based on Horsman et al. [3])

fractions of, e.g. 2 Gy, should definitely eliminate (kill) the same rate of euoxic epithelial cancer cells (0.5). The same rate does not however mean the same number of cells. If the tumor contains initially 1 bln cells (10^9), after 2 Gy will survive 500 mln cells ($10^{8.7}$), but after 4–5 weeks of its number is reduced to 1000 cells (10^3), and to 500 cells ($10^{2.7}$) after the next 2 Gy fraction. It has essential sense when one wants to compare the numerical cell kill effects of 2 Gy fractions during the first 2–3 weeks of irradiation with the effect of the same number of fractions but during the last two weeks of conventional irradiation. When the euoxic cells are killed by successive fraction doses, then the hypoxic ones may get closer to the vascular network and may transform into being well oxygenated. This phenomenon was termed as reoxygenation. Generally, it is a pretty fast process within a few hours, and highly effective during the first few fractions [2]. However, it has never been quantitatively measured in human tumors, yet. Moreover, during treatment, radiation also deteriorates vascular network by killing the vessels endothelium. Thus reoxygenation might but may not necessarily be effective. It seems more and more reliable that a "final battle" against the surviving cancer cells (mainly hypoxic) occurs during the last few fractions of conventional radiotherapy.

Figure 2 illustrates the responses of oxic and hypoxic tumor cells to 2 Gy fractions [3]. This radiobiologically idealistic model *in vitro*, likely assumes that after 2 Gy (SF_2) a surviving fraction of the oxic cells equals 0.5, and oxygen enhancement ratio (OER) is 2.8–3 higher compared with the fully hypoxic fraction. If the tumor would contained only oxic cells, they will be completely eliminated (Fig. 3, curve A), which theoretically should lead to permanent local tumor control (LTC). But tumors also contain a few hypoxic cells (< 0.1%). Each successive 2 Gy fraction likely kills fewer and fewer clonogens accompanied with progressive reduction of vascular density. Consequently the number of hypoxic cells increases (Fig. 3, curve AB). If the tumor is completely hypoxic, it will ignore 2 Gy fractions and the LTC gain can likely never be expected. This plausible model is based on reliable values of the D_{10} of about 5–7 Gy for oxic tumor cells, and about 15 Gy for hypoxic cells, as proposed by Overgaard [4]. However, such a model does not directly reflect situations in clinical radiotherapy, thus an important question arises, whether at least some radiobiological principles (and which specifically) work in the clinic? To solve such a dilemma, results of the head and neck cancer radiotherapy seem be a suitable model, since the tumors are localized in a single part of the body, the vast majority of them are squamous cell cancers, and its metastases develop, at first, in the regional neck lymph nodes.

Once the tumor gets larger, the number of hypoxic cells will increase, which are usually chaotically spread within the tumor volume, and its precise quantitation is not possible, so far. The probability of LTC and the respective dose (TCD) can only be assessed on average, since radiation cell killing is random in nature and focused on proliferating, euoxic cells as the targets, whereas radioresistant hypoxic cells are unaffected and in fact ignore small 2 Gy fractions. They can only be killed by much higher doses (D_{10} ~ 15 Gy). Thus, after conventionally fractionated doses, the LTC of head and neck (H&N) cancers are usually lower than theoretically assumed. For T_1–T_2 tumors, the LTC may reach a level of 80–90%, but for advanced T_3–T_4 tumors, the LTCs rarely reach levels higher than 30–45%.

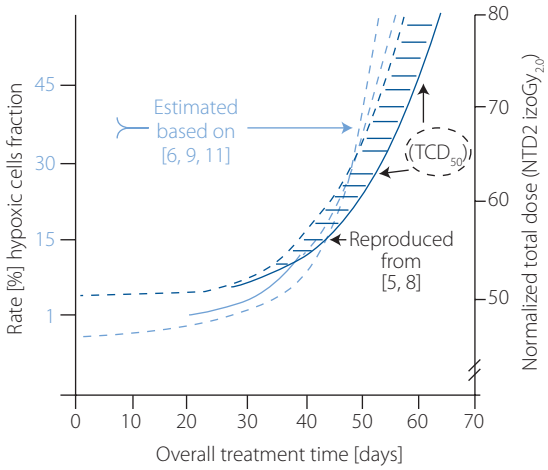

Figure 3. The dose-time relationship for 50% (TCD_{50}) [50% local tumor control (LTC) *versus* overall treatment time (OTT)]. Hypoxic fractions (red line) related to the OTT (estimated from the reports [6, 9, 11])

The first sign of what happens during irradiation at the cellular level below the clinically evident "sea surface" was experimentally documented in 1969 by Hermens and Bardensen [5]. They clearly counted clonogenic tumor cells which intensively repopulated during clinically evident regression of the gross tumor. This observation has generally been ignored until the 1990s, when Maciejewski, Withers [6–12] and Trott [13] analyzed the retrospective results of about 850 patients with H&N cancer treated in a single institution with RT alone. They showed that for a given total dose (TD), an extension of overall treatment time (OTT) leads to a dramatic decrease in 3-year LTC by about 1.5% per each additional day of time extension. The results of these quantitative analyses [6–8, 11–19] were used to estimate a bi-phasic dose-tumor response curve (Fig. 3, black curve). This has led to the conclusion that after the first two-three weeks of fractionated irradiation, the dose controlling 50% or 90% of the H&N cancer (TCD_{50} or TCD_{90}) sharply increases with the OTT extension. This tendency has been interpreted as the result of accelerated repopulation of euoxic tumor clonogens [4, 9]. From the bi-phasic LTC-DOSE curve, it was estimated that repopulation around the third week of irradiation counterbalances the cell kill effect of about 0.6 Gy of each daily 2 Gy fraction, and it continuously increases to even 1.4–1.6 Gy/day around week 6 of the OTT and longer. It was estimated from the results of the Cox et al. [14] trial 83–13, which showed that although the TD increased by 9.6 Gy during an extra 6 days, the LTC of 44% remained unchanged. It likely suggests that the effect of 1.6 Gy of daily 2 Gy might be neutralized by the repopulation. Thus, it was widely agreed that repopulation seems to be a major process responsible for local tumor failures. Such conviction led to many altered fractionation schedules tested in clinical trials. After over 25 years and over 50 studies, overall therapeutic gain appeared surprisingly low (7%) and disappointing. No improvement in the LTC after the TD higher than 60 Gy graphically reflects the flattened shape of the dose-response curve [15–17], which Suwiński and Withers [18] the defined as "effect plateau".

It must be emphasized that the effectiveness of the proliferative potential of euoxic tumor clonogens as a dominant or a single process induced by irradiation has only been deduced but not proven. Moreover, the events of self-sensitizing of the quiescent tumor cells and its reoxygenation have been anticipated but never quantitated as yet. Despite the belief that the increase of the total dose may overcome the repopulation, the LTC for advanced H&N cancers immutably remains around 50%, although many various sophisticated techniques and dose fractionation regimes have been tested since 1980. Through all these years, it remains intriguing as to why the use of more and more aggressive fractionated regimens did not resulted in a higher local control rate of the advanced tumors; conventional dose fractionation regimes have deliberately been continued, based on the assumption only that the each dose fraction kills a constant rate of the cancer cells. As a matter of fact, radiation effects relate to the cell numbers, which are not constant but markedly decrease during fractionated irradiation.

It has to be remembered that irradiation eliminates not only tumor clonogens but also vascular endothelial cells, with the network of oxygen supply becoming weaker and weaker, and therefore an "army" of hypoxic cells increases and begin to dominate towards the end of irradiation (Fig. 3, dotted curve). Undoubtedly, these cells are about 3 times more resistant to 2 Gy fractions than euoxic clonogens. Therefore, the logical conclusion would be that natural tumor growth definitely needs oxygen, but during fractionated irradiation, and oxygen assigns cancers cells to death a few moments after the radiation beam is delivered, and it does not give them a comfort to survive.

Hypoxia supports cancer cells to survive the course of radiotherapy

The first clear evidence that hypoxic cells exist in malignant tumors was documented by Thomlinson and Gray in 1955 [1]. Denekamp [2] pointed out that tumors' hypoxic cells are radioresistant as the result of vascular insufficiency. Chaotic and very primitive patterns of pathologic tumor neo-vasculature is not efficient enough to provide the increasing nutrient needed for the rapidly growing cancer cells. Microregional cellular foci within the tumor mass become nutritionally deprived what promotes the increasing number of hypoxic cells. They may stay alive, and when microenvironmental conditions will improve they may proliferate once again due to reoxygenation (e.g. local recurrence).

The radiation response of the hypoxic tumor cells is represented by cell survival curve B on Figure 2, which shows no cell kill after low fraction doses (≤ 2.5 Gy). Next, the bi-phasic cell survival curve (Fig. 2, AB) illustrates a mixed cell population, inflected by a proportion of resistant hypoxic cells.

Generally, curve A on Figure 2 seems to be relevant to a selected group of small (≤ 2.5 cm in diameter) epithelial cancers. On the contrary, the theoretical curve B represents a purely hypoxic tumor with LTC probability almost close to zero after conventional 2 Gy fractionated schedules.

Advanced tumors are usually heterogeneous with a mixed population of euoxic and hypoxic cells. During the first three--four weeks of irradiation, the initial part of curve AB (Fig. 2) is similar to curve A. However, towards the end of irradiation, hypoxic cells begin to dominate and the respective cell survival curve bends horizontally. An important question arises, whether any clinical results reflect these purely radiobiological principles, and the answer is "yes", there are a few.

Following the Thomlinson's recommendations [20], the present author [21] has measured the volumes of over 600 H&N tumors and more than 280 metastatic lymph nodes during the period of 1975–1986. The normalized total doses for 90% Local Nodal Control (NTD_{90}) were estimated and plotted against initial nodal volumes. Figure 4 shows that the nodal dose-response curve clearly reflects experimental estimates (Fig. 2, AB). Nodes with volume larger than 10 cm^3 (2.5 cm in diameter) characterize "the tail" on Figure 4, which suggests that the larger nodal metastases may likely contain some rate of the hypoxic cells, and they should need an extra dose of about 10 Gy to be locally controlled.

On the other hand, some other authors [17, 22] documented the adverse impact of lymph node involvement on local control of the primary H&N tumors compared to those with the N_0 stage. When total nodal volume increased above 30 cm^3, then a primary tumor needed an extra 6–7 Gy to be controlled with the same rate as those with the N_0 stage. This is still ignored in the clinical settings. Peters et al. [22, 23] pointed out that one plausible explanation of such an adverse effect could be that some "joungly" cancer cells escape into lymphatics to develop metastatic lesions, whereas the cells which remain in the primary tumor likely become synchronized in the most resistant phase of the cell cycle (G_0), and become even more resistant than hypoxic cells. Peters defined it as "probabilistic radioresistance".

The final "cell kill battle" concerns the last few dose fractions, delivered to a few surviving tumor cells of about 10^1–10^2. It is radiobiologically impossible that a smaller and smaller number of cells have the potential to repopulate faster and faster to neutralize about 80% of successive 2 Gy doses. It could theoretically happen only if the cell cycle turnover time was shortened by 15–20 times, but it is biological nonsense, since its duration is always constant throughout the whole treatment. Therefore, the belief that tumor clonogens intensively repopulate during the whole course of treatment and accelerate towards the end of conventional 2 Gy irradiation (Fig. 3) is not entirely credible and true. Conventional 1.5–2 Gy fractions are too weak to trigger cell-kill of residual hypoxic and radioresistant cells, and any increase of a conventionally fractionated

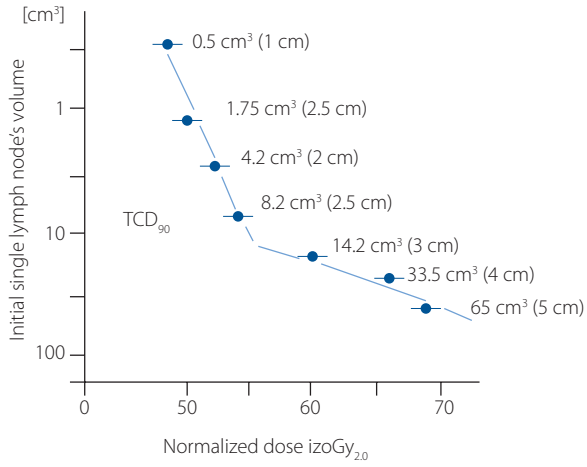

Figure 4. The local nodal control (LNC) Doses (TCD_{90}) related to initial node volumes (from Maciejewski [21]); TCD_{90} – tumor cure dose for 90% patients

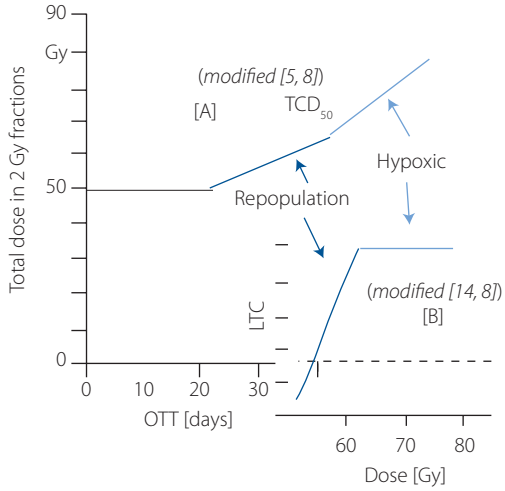

Figure 5. Modified (**A**) dose-time relationship for 50% (TCD_{50}) and (**B**) local tumor control (LTC) — dose "effect plateau" for head and neck (H&N) cancers; Blue — reflects effect of repopulation; red — reflects effect of hypoxia; OTT — overall irradiation time

total dose with an extension of the OTT above week 5 is likely wasted and seems clinically useless.

If 1 or 3 hypoxic cells survive at the end of irradiation, which may likely happen in locally advanced H&N cancers, then the LTC of about 37% should not surprise ($TCP = e^{-x} = e^{-1} = 0.37$). Such final cellular pattern calls for modification of the LTC-DOSE relationship (at least for the H&N cancers), shown on Figure 5. When the tumor completely regresses, the only one or a few hypoxic cells will survive, then they likely will lead to the tumor regrowth, and finally to local recurrence and/or dissemination [24, 25]. In humans, many biological and molecular changes during hypoxia are controlled by activation the HIF family of transcription factors. Both HIF-1 and HIF-2 regulate more than 100 different genes during hypoxia, controlling several processes including erythropoiesis, angiogenesis, metabolic activity cell invasion, proliferation

and survival of hypoxic cells. It suggests the credible and cautious conclusion that the hypoxic cells likely dominate towards the end of irradiation, what likely is an important or even a key hallmark of advanced malignant (at least epithelial) tumors, and the LTC gain above 45–50 % can never be achieved using conventional radiotherapy, which should be modify to strengthen its efficacy.

Hypoxia radiosensitizers

Since the role of hypoxic cancer cells was recognized as a meaningful factor for radiotherapy failure, a number of various approaches have been clinically tested to overcome hypoxic radioresistance [26]. One of the earliest clinical attempts proposed in 1968 by Churchill Davidson was hyperbaric oxygen therapy (HBO) [27]. High oxygen breathing (usually 95% oxygen + 5% carbon dioxide) was clinically tested to radiosensitize tumors. Over 20 trials including almost 3000 patients, mainly with locally advanced cancers, were carried out by the British Medical Research Council (MRC). Because of high oxygen pressure up to about 3 atmospheres, HBO radiotherapy was delivered through a glass window in a hermetic capsule. The overall benefit in LTC was unexpectedly low (7%) (Tab. I). No benefit was achieved in bladder, lung and esophageal cancer [28–31]. Relatively higher LTC (28%) was noted for uterine cervix cancer only [31], however it was not possible settle the doubts whether the LTC gain attributes to the HBO or rather the use of a few large daily fractions. Finally, HBO therapy was discontinued because of the high rate of serious complications (life-threatening complications caused by patient's decompression during leaving the capsule) and since chemical radiosensitizers [26] have appeared on the therapeutic market.

In 1969, the concept of chemical radiosensitizers was developed by Adams and Cooke [26]. They found certain compounds were able to mimic oxygen, and therefore to enhance radiation damage of primarily hypoxic cancer cells. The nitroimidazoles were the first electron-affinic compounds, which experimentally showed a radiosensitizing effect. Animal studies indicated misonidazole as the most promising, with a sensitizing enhancement ratio (SER) of > 2.0, and toxicity mainly directed at hypoxic cells. However once again, many clinical trials did not document the LTC benefit [28, 29, 31], as the misonidazole dose was found to be too low to sensitize hypoxic cells, but the use of higher doses immediately resulted in serious neurotoxicity as the first effect.

Failure of these clinical trials has led to test more effective radiosensitizers. Among many compounds, nimorazole, etanidazole and pimonidazole have been found to be the most promising. The first was tested in the DAHANCA 5 trial [28, 30, 31] and resulted in a highly significant benefit in the LTC, and nimorazole became a part of standard therapy for H&N cancers in Denmark. In contrast to this compound, the use of etanidazole or pimonidazole did not produce any clinical benefit (Tab. I). Moreover, the trial on pimonidazole combined with radiotherapy for cervix cancer was stopped, since the preliminary results were worse than that noted for the control group.

Results on the use of oxygen-mimic agents have generally been disappointing, and therefore bioreductive drugs became the next option of clinical interest, since they occurred to be highly cytotoxic to hypoxic cells [32–34]. Mitomicin-C, Nicotinamide (ARCON) and Tirapazamine were recognized as clinically effective, producing an increase in the LTC of H&N cancers by 18–20% (Tab. I). The interest was mainly focused

Table I. Clinical results [3 years local tumor control (LTC) gain due to the use of hypoxic sensitizers combined with fractionated radiotherapy]

Hypoxia sensitizers	No. trials (patients)	3 years LTC improvement *vs.* control
HBO [25, 27–31] Cervix cancer	24 (~ 2700 pts) 4 (~ 290 pts)	9% (58 *vs.* 49%) 28% (76 *vs.* 48%)
OXYGEN [27, 30–32] Mimetic sensitizers	41 (5970 pts)	7% (49 *vs.* 42%)
— misonidazole [29]	5 (626 pts)	No gain
— nimorazole [31]	2 (414 pts)	19% (52 *vs.* 33%)
— etanidazole [33]	1 (523 pts)	No gain
— pimonidazole [31]	1 (~ 80 pts)	Worse LTC (trial stopped)
BIOREDUCTIVE agents — mitomycin C [34]	3 (480 pts)	17–22% (76 *vs.* 54%) (48 *vs.* 31%)
— ARCON [32] (nicotinamide)	1 (215 pts)	20–25% (70 *vs.* 45%) (larynx, hypopharynx only)
— tirapazamine [34]	1 (230 pts)	18% (84 *vs.* 66%) (early H&N cancer)
TRANSFUSION [25, 31] Hb increase	2 (235 pts)	15% (84 *vs.* 69%) (early H&N cancer)

HBO — hyperbaric oxygen therapy; H&N — head and neck; Hb — hemoglobin

on the ARCON, which combines three potentially successful strategies, i.e. accelerated RT, HBO and a bioreductive drug. Clinical trials on agents modifying tumor hypoxia enrolled more than 11 000 patients in 91 randomized trials. The results have shown significant LTC improvement for the cervix and head and neck cancers only. The variability of the results may suggest considerable genetic heterogeneity of tumors within the same localization and histology. In order to optimize future clinical projects, detection of the hypoxic cell subpopulation and capacity for reoxygenation appears to be a key issue, something which is, however, still not quantified. Diagnostic positron emission tomography (PET) with Miso-radiotracers illuminates hypoxic cells chaotically spread within one tumor volume prior to therapy, and densely gathered within the residual volume towards the end of therapy; it would be useful to design the individual shape of the radiation beams and dose distribution but this is not routinely used in practice, yet.

One of the earlier approaches to counteract the adverse impact of hypoxia on the efficacy of RT also focused on the hemoglobin (Hb) concentration. Although mechanism of the relations between the Hb level and tumor hypoxia, is not clear, clinical studies [30, 35, 36] showed that Hb concentration below 12 g/L significantly reduces local tumor control and survival after radiotherapy. It seems that the efficacy of the oxygen homogenously delivered to the tumor by its own vascular network can be considered a key factor in intensifying radiation cell kill effect. A few clinical trials on the effect of blood transfusions in patients with low Hb levels [25, 31, 35, 36] have shown significant improvement in the LTC in cases when the advanced cervix cancer is accompanied with anemia. However, in the DAHANCA 5 trial on blood transfusions given several days prior to the RT, although indicating a rapid, albeit transient, increase of the Hb level, it finally failed to show a pronounced LTC benefit in H&N cancer patients. Low Hb level prior to the RT is commonly considered as a poor prognostic factor. However, patients with initially normal Hb levels (~ 12 g/L), and their gradual but sharp decrease during RT has been recognized as even more pronounced risk factor. An interesting but transient approach was the use of erytropoetin (EPO) producing a gradual increase in the Hb of patients with H&N cancer, but final RT results were disappointing, and the patients with EPO+ had even poorer outcomes than those with the EPO(–).

Since inadequate tumor vasculature and insufficient oxygen supply have been proven as important factors for tumor hypoxia, both angiogenesis inhibiting agents (AIA; e.g. bevacuzimab, avastin, angiostatin) and vascular disrupting agents (VDA; e.g. combrestatin, tumor necrosis factor) have been recognized as an attractive option for targeted therapy. Although some preclinical radiotherapy studies have shown that tumor oxygenation increases, the final results did not document any improvement or even deterioration in tumor oxygenation. The role of hypoxia in combination with AIA and VDA with radiation is not fully recognized, but it seems that the sequencing and timing of these two modalities looks critical in optimizing the most beneficial effects of therapy.

Immuno-boost

For decades, the importance of the immuno-modulation induced by conventional radiotherapy has been appreciated, however, local radiation is not the only immunosuppressive factor, particularly when large volumes are irradiated. During the RT, immunocompetent T-cells are severely depleted. With the advent of new imaging and radiation techniques, stereotactic-hypofractionated radiotherapy (SHRT) using single or a few large dose fractions [37] became an attractive therapeutic option producing very high LTC, but only for small tumor sizes (≤ 4 cm). The SHRT has been recognized as an "effective weapon" against residual hypoxic cells. The experimental data have indicated that high doses may effectively also induce local immunoresponse [37] activating TCD8+ lymphocytes and natural killer (NK) cells. Such a combined circle of "immunomodulated" response may contribute to more effective cell kill, but the power of such impact is not very impressive. Also, the effect of radiation outside the irradiated volume (abscopal effect) is recognized, but not strong enough and frequent to create the background for meaningful therapeutic gain.

The advent of novel immunocompetent drugs has changed the attitude of radiation oncologists towards the immunomodulative role of radiation. A convincing example of advantageous cooperation between radiotherapy and immunocompetent drugs is a randomized clinical trial carried out in a group of patients with stage III NSCLC [38]. Conventionally fractionated curative chemoradiotherapy as a control arm has been tested compared with the same schedule but followed by the maintenance with durvalumab for a period of 12 months. Twelve-month progression-free survival was 55.9% in the durvalumab arm and 35.3% for chemoradiotherapy alone. Such improvement attributes to immunoeffects, which have been often ignored in previous radiotherapy trials. Previous altered radiotherapy or chemoradiation did not result in a such high LTC magnitude. The NCLC results strongly suggest that immunoresponse should be considered as one of the most important processes affecting locoregional control in radiotherapy, substantially overshadowing repopulation effects.

Comments

It is obvious that oxygen is fundamental to the physiological function of normal tissues and organs, and ultimately the healthy life of human beings. But in malignant tumors, oxygen is not evenly distributed within the tumor, and some cells can already be hypoxic and radioresistant, but at the beginning of irradiation they rate is rather small. Tumor hypoxia is moved to the "shadow" because since the 90s, the general belief was begun dominate that accelerated repopulation of cancer cells counterbalances an increasing rate of 2 Gy fractions, towards

the end of fractionated radiotherapy. This process has been considered as a major (or even the only) factor leading to an increment of the total dose with overall time extension. For over 30 years, this concept has been unquestioned, however nowadays, it looks highly doubtful. It is reliable that during the last few days of irradiation, the number of hypoxic cells and their radioresistance to conventional 2 Gy fractions dominates over the kinetics of previously euoxic cells. Thus, a fair comment is that oxygen does not protect tumor cells but rather marks them to being killed by radiation.

For over 30 years the fact that the number of hypoxic tumor cells, increases during radiotherapy, even to more than 50–70% towards the end of treatment (Fig. 3) has been somehow ignored. It is radiobiologically illogical that towards the end of irradiation a few surviving cancer cells (undoubtedly hypoxic) have suddenly got enormous potential to repopulate faster than millions of euoxic clonogens during week 3 or 4 of treatment. It is amazing that up until now, nobody, including the present authors, has ever questioned that.

It seems plausible that a small number of resistant hypoxic cancer cells likely ignore and do not respond to 2 Gy [6, 9, 10, 14], and therefore any increase of the total dose, let's say above 63–65 Gy, is therefore likely to be wasted and useless. Thus, the "effect plateau", documented by Suwiński et al. [18] and Cox et al. [14], illustrates a resistance of the hypoxic cancer cells to 2 Gy fractions but not an accelerated repopulation. The minimal therapeutic gain noted after many altered fractionation schedules tested over 25 years is likely a convincing argument. Although these trials were fairly randomized and stratified, nevertheless both arms biologically remain highly heterogeneous, and it should not be surprising that fraction doses within the very narrow range of 1.15–2.0 Gy are ignored by resistant hypoxic cells.

Radiobiological concepts and clinical achievements gathered over the decades lead to the logical assumption that there is no longer room for conventional 2 Gy radiotherapy (CRT) as an effective, radical treatment for locally advanced tumors (not only for H&N cancers). Since towards the end of fractionated irradiation, hypoxic cancer cells likely dominate, the last 5–6 fractions become essential. Thus, it seems reasonable to consider a combined schedule of conventional (CRT), i.e. 50 Gy in 25 fractions (when repopulation works) followed by the last 5–6 fractions of 4–6 Gy each (SHRT anti-hypoxic boost), as a rational solution. Such doses can be delivered using external irradiation (CRT + SHRT) or brachytherapy (CRT + BRT).

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Supplementary material

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Review article

Clinical nutrition in oncology

Obesity in breast cancer patients after oncological treatment. How to conduct a nutritional intervention?

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Obesity in breast cancer patients is a significant predictor of morbidity as well as adverse treatment outcomes. It correlates with poorer response to treatment, particularly affecting survival length and quality of life. This paper aims to describe the relationship between obesity and breast cancer prognosis, highlighting the importance of integrated prehabilitation strategies. Prehabilitation, which includes nutritional counseling, psychological support, and physical activity, is proposed as a proactive approach to prepare patients for the rigors of cancer treatment, such as surgery, chemotherapy, and radiation therapy. The results emphasize the need to maintain optimal weight and body composition through dietary adjustments, particularly high protein intake, and physical rehabilitation. An interdisciplinary approach, including the involvement of oncologists, nutritionists, psychologists, and physiotherapists, is crucial for successful treatment outcomes.

Keywords: obesity breast cancer, prehabilitation

Obesity among patients with breast cancer

Obesity is defined as a pathological increase in adipose tissue in women exceeding 25% of ideal body weight (IBW), which increases the risk of breast cancer by up to 3-fold [1, 2]. Insulin resistance, hyperglycemia, and hyperinsulinemia are key factors leading, on the one hand, to obesity, and, on the other, to the development of cancer. Therefore, it is not surprising that, despite the disease, 15–45% of the European population's cancer patients are overweight and obese [3].

Obese women have the pooled relative risk (RR) of breast cancer 1.41, while overweight women have a much lower risk 1.07, according to a Chan et al. [4] study. Another important factor is the timing of obesity onset: when it occurs before menopause it increases the risk of breast cancer (BC) more than in the postmenopausal period (RR pre-menopause 1.75, post menopause 1.34) [4]. Increased body weight is not only associated with a more frequent diagnosis of breast cancer but also with an unfavorable treatment outcome. An increase in body weight (by 5 kg/m^2) before diagnosis of BC is associated with a 17% increase in total risk of death, up to 12 months after diagnosis and over this time by 11% and 8% respectively [4]. Both the time of gaining weight and the intensity of this process are important. Women with obesity in II and III class have a 58% increased risk of breast cancer [5]. Interestingly,

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women with a body mass index (BMI) > 35 kg/m^2 had a higher risk of breast cancer with the expression of estrogen (ER) and progesterone receptors (PR). There was no association between weight gain and an increased risk of cancer without the estrogen receptors expression. Additionally, no correlation was found between premenopausal hormone therapy, BMI, and breast cancer [5].

In the case of patients with a higher BMI, tumors of larger dimensions, less differentiation and more frequent lymph node metastases were diagnosed [5].

Obesity after oncological treatment

The body composition of female patients undergoing and after oncological treatment undergoes dangerous changes [6]. Catabolic processes, prolonged periods of weakness or bedrest, increased inflammatory state, loss of appetite, and changes in taste during the disease causes reduction in nutrient intake and an inability to engage in regular physical activity. This leads to unfavorable changes in body composition [7, 8] such as:

- loss of muscle mass (LBM) and strength;
- decreased physical performance;
- increase in fat tissue content.

These changes are characteristic for sarcopenia or sarcopenic obesity and have a negative impact on treatment course. The International guidelines for the assessment of nutritional status (GLIM) highlight the importance of assessing muscle mass by including its measurement as one of the phenotypic criteria for this assessment on a par with weight loss (> 5% within six months, or > 10% beyond six months), low BMI (< 20 if < 70 years, or < 22 if > 70 years) [9]. Assessing malnutrition using only BMI is insufficient because loss of lean body mass may be masked by excess fat mass [10]. Therefore, an obese patient according to the GLIM criteria (due to loss of muscle mass) could also be considered a malnourished patient.

The incidence of sarcopenia in breast cancer patients varies, depending on the measurement techniques from 15.9% to 47.8% (dual X-ray absorptiometry scans *vs.* CT scans), event to 58% [10, 11]. Sarcopenia increases the risk of complications (postoperative complications, chemotherapy toxicity, cardiovascular disease e.g., hypertension — the reduction in muscle mass also reduces the expression of myokines, including irisin, involved in the maintenance of vagal tone and in the parasympathetic modulation of cardiac function) and prolongs rehabilitation. It reduces the percentage of patients responding to treatment, overall survival (OS), progression-free survival (PFS), quality of life (QoL), increases the risk of depression, and overall mortality in breast cancer survivors [12].

Unintentional loss of body weight, which is often accompanied by loss of muscle tissue, shouxld automatically alert the therapeutic team. Monitoring patients (weight, muscle mass) and promptly addressing any abnormalities in body weight and body composition is crucial to providing optimal care [13]. Adequate nutrient supply, particularly protein, and regular physical activity are crucial during and after treatment, as the adverse effects of chemotherapy and radiotherapy may result in undesirable changes in body composition that have been demonstrated to persist for months or even years [14].

Prehabilitation as a method of supporting therapy

Prehabilitation is a comprehensive process that prepares patients for surgery and long-term oncological treatment, including chemotherapy, immunotherapy, and radiotherapy (Fig. 1). The fundamental premise of this process is to ensure the optimal state of health of patients, enabling successful surgical procedures without complications. Prehabilitation facilitates the implementation of therapy, helps minimize adverse events (AE) and contributes to a faster return to optimal psycho-physical condition [15, 16]. The effectiveness of this process depends on the cooperation between the interdisciplinary prehabilitation team, which should include: a physician (surgeon, oncologist, anesthesiologist), clinical dietitian, physiotherapist, psychologist, nurse, and the patient. Prehabilitation is based on four inseparable pillars:

- elimination of addictions;
- psychological support;
- nutritional preparation;
- physical activity.

Every single pillar has an individual character and guidelines which are adapted to the patient's current condition and the expected effect [17]. Each element of prehabilitation is crucial, but special attention is focused on nutritional and physical preparation for treatment.

Nutritional preparation is an extremely important pillar of prehabilitation, although it is often overlooked. The patient's nutrition in the perioperative period, before and during chemotherapy and radiotherapy, has a direct impact on the course and effectiveness of treatment [17]. All patients before starting any planned treatment should be under the supervision of a clinical dietitian. The clinical dietitian will determine the patient's nutritional status and individual needs (for macro-, micronutrients and fluids). Particular attention should be paid during this period to patients with low muscle mass (malnourished according to the GLIM criteria [9] and high body mass which are associated with worse treatment outcomes [11, 12, 19, 20]. American studies indicate that if breast cancer patients > 50 years of age maintained a BMI < 25 kg/m^2, approximately 11–18 thousand deaths could be avoided per year [21]. Therefore, both during preparation for surgery and other oncological treatments, in the case of obese patients, the goal is to reduce body weight with maintaining or rebuilding muscle mass [22]. For this purpose, nutritional treatment should focus on an adequate supply of protein and supplementation of omega-3 fatty acids.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients

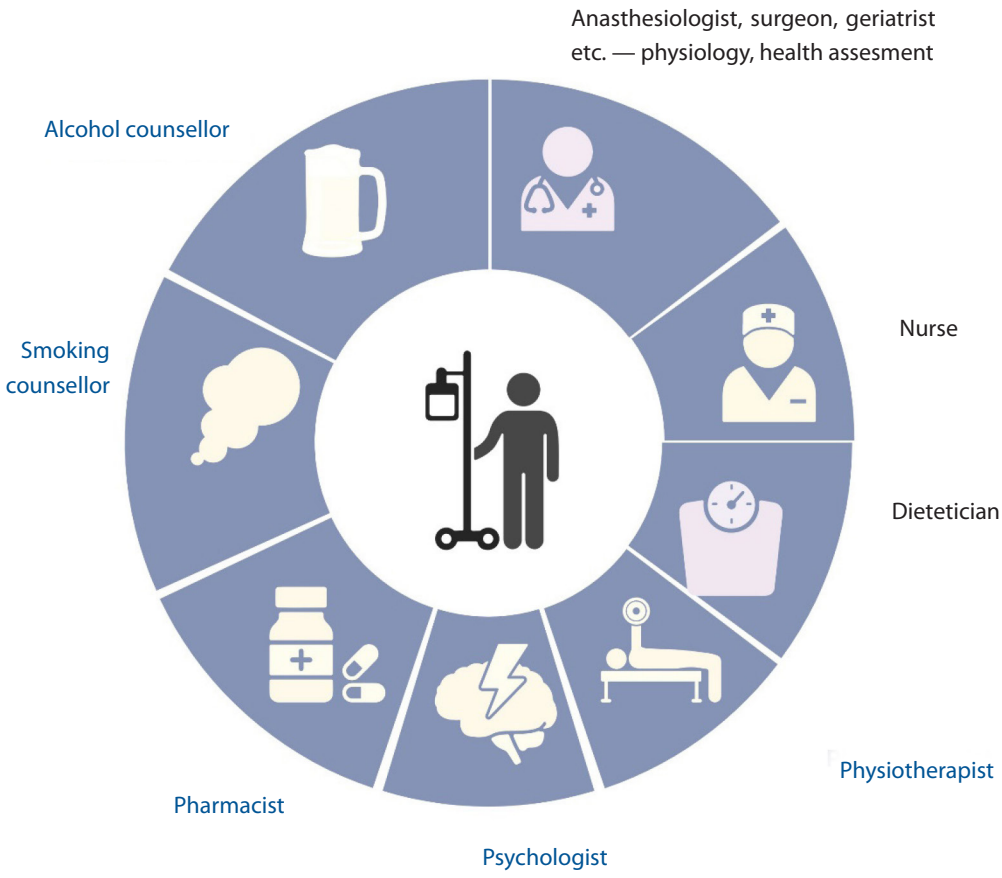

Figure 1. Multidisciplinary team, Durrand J. et al., 2019 [18]

recommends protein intake above 1 g/kg body weight/day and if possible, up to 1.5 g/kg body weight/day [23]. The synthesis of muscle tissue in oncological patients is extremely difficult due to the inflammation associated with the disease. It is also important to consider that the synthesis of muscle tissue in the geriatric population requires an increased supply of protein per kilogram of body weight compared to younger individuals. This is due to several factors, including disturbed intracellular signalling, impaired circulation of nutrients in the blood, the presence of chronic inflammation, and reduced physical activity [24]. In this population, to maximize skeletal muscle protein synthesis, an intake of 25–30 g of high-quality protein per meal is required [25].

One of the amino acids that is often used in the perioperative period is arginine. This amino acid contributes to the wound healing process at every stage (synthesis of nitric oxide, growth factors, collagen), and is an essential amino acid for the proliferation and activation of immune system cells. Due to this effect, it is used as a common component of immunonutrition. However, it must be noted that arginine supplementation is not recommended for routine use. Some types of cancer cells are dependent on external arginine sources (arginine auxotrophy) due to the inability of its synthesis to internally. In other words, some type of cancer cells may respond to Arg supplementation with growth. Deficiencies of the key enzymes in the synthesis of arginine [arginine succinate synthetase (ASS1)] have been found in some cancer types e.g., hepatocellular, prostate, pancreatic, head and neck carcinoma, malignant melanoma [26]. Moreover, breast cancer expresses high levels of another enzyme arginase (ARG1), which is associated with polyamine production (growth factors) and inhibition of the NO generation by macrophages. This leads to cancer cell proliferation, Arg deprivation in the tumor microenvironment, inhibition of T-cell proliferation and impairment of their functions [27]. Other components of immunomodulatory diets are beta-glucans, or more precisely, the dectin-1 receptor, which are responsible for triggering immunostimulatory effects. Immunonutrition also uses ingredients such as selenium, zinc, and vitamin C, which will regenerate wounds and support the immune system [2].

Supplementation with omega-3 fatty acids (another immunomodulatory component) is recommended in patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished (ESPEN, Clinical Nutrition in cancer, 2021) [23]. The consumption of omega-3 fatty acids improves appetite, food intake, increases lean body mass and body weight. These fatty acids, on the one hand, reduce

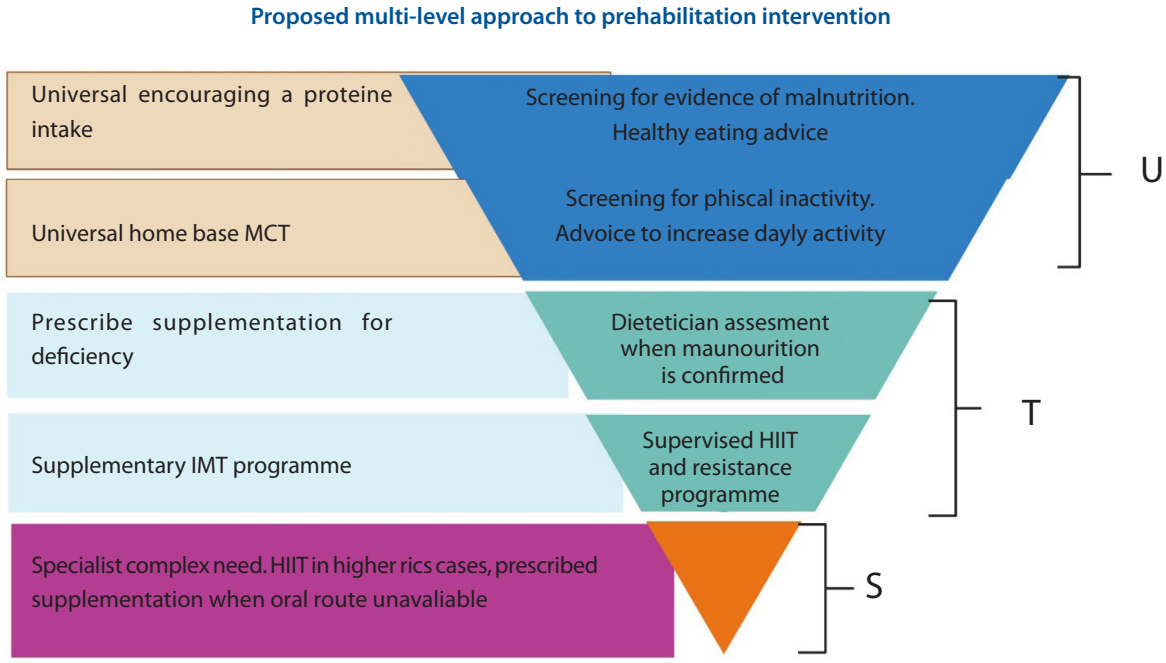

Figure 2. Proposed multi-level approach to prehabilitation intervention (nutritional support and exercise used as examples) (Durrand et al., 2019 [18]); HIIT — high intensity interval training; IMT — inspiratory muscle training; MCT — moderate continuous training; S — specialist; T — targeted; U — universal

synthesis of pro-inflammatory mediators [2], and, on the other, have the ability to increase (even double) the anabolic response in reaction to increased amino acid and insulin concentrations [28]. However, the anabolic effect of omega-3 fatty acids requires long-term intervention. A change in the structure of the myocyte cell membrane and, therefore, a change in their sensitivity to anabolic signals (increased concentration of amino acids in the blood) occurs over a period of 4–6 weeks, with supplementation of 5 g of omega-3/day [28] (Fig. 2).

The diet of a prehabilitated patient should, first be individually tailored to the patient's health condition and needs. The frequently used intervention is a modification of the usual diet (often a reduction diet) with high protein content and supplementation with omega-3 acids (1–2 g/d) Doses exceeding 2 g/day of eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) are generally required to reduce levels of prostaglandin E2. In the treatment of hypertriglyceridemia or inflammatory disorders, the most commonly administered dosage is 3.0 to 3.5 g/day of EPA + DHA. The European Union has established that doses of EPA and DHA up to 5 g per day are safe [29, 30]. As long as BC patients consume an adequate amount of protein and follow dietary recommendations, dietary fortification is rarely required. It is also worth noting that each patient should be educated on the importance of hydration which influence e.g., taste perception, especially during chemotherapy. It is recommended that oncology patients should drink 30–40 ml/kg body weight/day [8, 31].

According to ESPEN and Enhance Recovery After Surgery Society (ERAS Society) recommendations, providing increased nutritional support (especially protein intake) prior to planned surgery is beneficial in many clinical situations but depends on a number of variables. However, if the patient is malnourished or at risk of malnutrition, surgery can be postponed for 10–14 days [32]. On the day before surgery and 2–3 hours before the procedure, it is recommended that the patient should consume an oral carbohydrate solution. This approach minimizes the body's response to injury, postoperative insulin resistance and hyperglycemia, and has a protective effect on muscle tissue [32, 33].

The fourth pillar of prehabilitation is physical activity. Lack of physical physical strength the sensitivity of muscle cells to anabolic signals such as an increase in amino acid concentration in the blood. Additionally poor physical function is a predictor of adverse events in the perioperative period [34] and poor outcomes in the long term. Moderate physical activity (3–5 h/week) will influence the effectiveness of treatment, including OS, especially in patients with hormone-dependent cancer [35] and it is a cost-effective procedure [36]. Muscle tissue has an important impact on the functioning of the immune system, mediated by myokines. Physically active patients after diagnosis of breast cancer have a higher survival rate than physically inactive patients, and these effects are mediated by regulation of natural killer cells. The breast cancer survivors can also mobilize NK cells to the circulation to the same degree as age-matched healthy controls by exercise [37, 38].

Therefore, each patient should have an individually prescribed set of exercises adapted to their health condition and physical predispositions aimed at changing the body mass

composition (resistance training), and increasing the patient's aerobic capacity (aerobic training). Most patients preparing for surgery or the entire treatment process, require consultation with a physiotherapist [39]. Appropriately selected physical exercises performed daily for a minimum 2 week period (optimally 4–6 weeks) will help eliminate the side effects of surgical treatment e.g., the most common respiratory complications. These is why a form of resistance training of the diaphragm, respiratory muscles, and intercostal muscles — inspiratory muscle training should be especially included in the prehabilitation exercise program [40]. Physical activity may also be an effective remedy for chronic fatigue frequently reported by BC patients [41].

Treatment methods and effects on body weight

Treatment of breast cancer includes a wide range of interventions as surgical treatment, radiotherapy, and systemic treatment [hormone therapy (HT), immunotherapy, chemotherapy (CT) as neoadjuvant or adjuvant treatment]. There are many regimens due to dynamic development of personalized treatment which are based on receptor expression on cancer cells [42]. Due to such a large variety of therapies and drugs used to treat breast cancer, we can expect various adverse events and, consequently, different effects on body weight.

Weight gain during treatment is most common in hormone receptor (HR)-positive_(HR+) breast cancer treatment, however studies indicate an ambiguous relationship between e.g. tamoxifen (TMX) therapy and weight gain (Tab. I). It is also worth noting that patients with adjuvant CT prior to TMX for the first 3 years were more obese than those who had not undergone CT and this may be due to the prolonged effects of chemotherapy [43].

Other adverse events accompanying oncological treatment which affect nutritional status (body weight and body composition) are vomiting [19, 44, 45], decreased appetite [44, 46–48], anorexia [49], feeling of fullness [50], xerostomia [51], diarrhea [19, 44, 46, 47, 52], constipation [53], loss or change of taste [47, 48, 54], mucositis [55]. These events, through

Table I. Adverse events affecting body weight in distinct therapeutic regimens

Breast cancer type	Author	Therapy	AE affecting body weight	
HR+	Nyrop et al., 2016 [56]	TMX	Weight gain	• 18–52% of patients in 1st year • 7–55% of patients in the 5th year
	Raghavendra et al., 2018 [57]			• in pre-menopausal patients weight gain > 5% is 1.4 times higher than post-menopausal
HR+ recurrence	Baselga et al., 2012 [47]	Steroidal aromatase inhibitor (SAI) + mTOR inhibitor (everolimus)	Weight loss	• 19% of patients in everolimus + exemestane • 5% of patients in placebo + exemestane
			Other AE	• stomatitis • decreased appetite • diarrhea • dysgeusia
HER+ advanced, metastatic	Swain et al., 2020 [48]	Pertuzumab + transtuzumab + docetaxel	Diarrhea	• 68.4% of patients: mild to moderate • patients > 65 years of age > probability of diarrhea
			Other AE	In pertuzumab arm: • nausea • stomatitis • loss or change of taste • decreased appetite
Unresectable HER+ or HER2–low (IHC1+ OR IHC 2+/ISH–)	Hurvitz et al., 2023 [44]	Second line: T-Dxd (conjugated deruxtecan with trastuzumab)	Weight loss	• 23% of patients in group T-Dxd • 9% trastuzumab–emtansine
			Other AE	• nausea 77% • vomiting 52% • diarrhea 32% • lack of appetite 30%
TNBC	Cortes et al., 2022 [58]	ICI: pembrolizumab (neoadjuvant or adjuvant [58]) Atezolizumab with nab-paclitaxel	Other AE	Pembrolizumab: • nausea • abdominal pain • diarrhea • decreased appetite [46] • Atezolizumab: • decreased appetite • nausea • diarrhea • vomiting (19)

AE — adverse events; HER+ — human epidermal growth factor receptor positive; HR+ — hormone receptor (HR)-positive; ICI — immune checkpoint inhibitors; IHC1+ or 2+ — immunohistochemistry evaluation of the degree of protein expression; ISH — *in situ* hybridization; TMX — tamoxifen; TNBC — triple negative breast cancer

Table II. Differences between diet with preventive effects, lowering breast cancer (BC) recurrence, cancer-related mortality

Diet with preventive effects and lowering breast cancer recurrence, breast cancer-related mortality [71–73]	Diet increasing breast cancer risk (pro-inflammatory), elevating risk of cancer recurrence [71, 72, 74]
Diet rich in: • fresh vegetables (green-leafy, cruciferous) • fruit • nuts • fish (EPA, DHA) • dietary fiber • soy • whole grain products • eggs • lean meats	Diet rich in: • highly processed foods (with salt and sugar) • high glycemic index, including fruit juice • red and processed meat • alcohol • saturated fatty acids • total fat

DHA — docosahexaenoic acid; EPA — eicosapentaenoic acid

their negative impact on adequate protein and energy intake affect the results of oncological treatment.

Nutritional guidelines for obese patients during and after completion of therapy

Diet may, on the one hand, be a factor influencing the risk of developing breast cancer and, on the other hand, be a factor influencing the course of oncological treatment (Tab. II) [59]. Weight gain (overweight or obesity) during or after cancer treatment increases the risk of the disease (HR+), is a predictor of poor prognosis, increases recurrence, and reduces the OS [60]. Moreover, women who survive breast cancer have a 30% higher risk of developing another type of cancer [61]. For this reason, the oncologist should recommend a reduction diet, with adequate protein intake by a clinical dietitian [62], and lifestyle changes including physical activity and psychosocial support.

Inadequate protein supply will affect the functioning of the immune system both during treatment [e.g., with checkpoint inhibitors (ICI)] and after its completion. Lack of sufficient protein delivery leads to atrophy of the thymus, reduction of thymus-dependent areas in lymphatic organs, a decreased number of T lymphocytes, inability to produce responses to T-dependent antigens, cell-mediated responses, activity of macrophage system, complement system (C1, C2, C4, C3) [63]. Insufficient protein intake not only weakens the immune system, but also contributes to the depletion of muscle tissue. Muscle mass loss is associated with high neutrophil to lymphocyte ratios or proteolytic cascades (increase TNF-α), which promote tumor migration and invasion [11]. If one considers that muscle tissue has an important impact on the function of the immune system (mediated by myokines), the need to preserve this tissue becomes obvious. Interventions such as adequate protein and energy supply and physical activity ("exercise oncology") are necessary, and it should be perceived as multidisciplinary supportive care during and after treatment [64].

Maintaining the appropriate energy balance and thus proper body weight is related to improving BC patient prognosis and quality of life [65–69]. Consumption of foods rich in dietary fiber, soy, lower consumption of saturated fatty acids and total fats are related to higher survival after BC [60, 65]. A meta-analysis by Xing et al. [70] suggests that following a low-fat diet after a BC diagnosis can improve survival by reducing the risk of disease recurrence by 23%. Breast cancer survivors whose diet was characterized by the highest dietary quality index had a 23% lower mortality rate compared to women with the lowest dietary quality index category [65, 71–74].

A meta-analysis by Lee et al. [75] showed that following the DASH diet and Chinese Pagoda Guidelines can reduce breast cancer-related mortality. This relationship turned out to be particularly important in older people, physically fit and women with cancer call with estrogen (ER+) and human epidermal growth factor 2 receptors expression (HER2+), and without progesterone receptor expression (PR–) [75]. A diet based on the Mediterranean model was able to improve the body's antioxidant capacity as well as the glycemic profile [76].

The above-mentioned dietary models are based on the consumption of vegetables, fruit, whole grain products, eggs, fish, lean meats, and dairy products, as well as limiting the consumption of salt, fat, sugar, and alcohol. The Pagoda guidelines additionally recommend at least: 150 minutes of physical activity per week and performing at least 6000 steps a day [1, 6, 77].

The study, conducted as part of the Nurses' Health Study (NHS; 1980–2010) and NHSII (1991–2011) involved 8,927 women with stage I-III breast cancer, concluded that total fruit and vegetable (green, leafy, and cruciferous vegetables) intake was associated with lower all-cause mortality (ACM) but not with breast cancer-specific mortality. It is worth highlighting that a higher consumption of fruit juices (except orange juice) was associated with worse breast cancer- and non-breast cancer-related survival [4].

The composition of the microbiota found in the mammary glands seems to be diverse and may influence both the development of BC and the course of treatment. Researchers will confirm the hypothesis that intestinal dysbiosis is the source of the development of BC. Disturbed microbiota activate mast cells in the breast, which will facilitate the spread of cancer cells [78]. Diets rich in dietary fiber may have a beneficial effect on composition (increased diversity) and functioning of the intestinal microbiota and therefore on the functioning of the immune system [79, 80]. For this reason, the consumption of various sources of fiber is crucial before and after BC treatment.

Better diet quality after cancer diagnosis appears to be associated with lower levels of inflammation measured by the C-reactive protein (CRP), regardless of BMI or physical activity [5, 78, 81, 82]the association between DII and cancer recurrence and mortality among patients with breast cancer has not been investigated. Therefore, the present study aimed to investigate whether DII was positively associated with risk for cancer recurrence and overall mortality among patients with breast cancer. Among 511 women (51.9 ± 10.7 years; stage 0–3. On the other hand, the high risk of cancer recurrence in obese patients may be caused by pro-inflammatory cytokines e.g., CRP, IL-3, IL-6, IL-8, as well as TNFα [83].

Conclusions

Increased body weight is not only associated with a more frequent diagnosis of breast cancer but also with an unfavorable treatment outcome [decreased QoL, disease free survival (DFS), and OS]. The time of gaining weight (before or after menopause) and the intensity of this process influences treatment results. Therefore, maintaining the appropriate energy balance and proper body weight and composition of BC patients is crucial. In this area, the support of a clinical dietitian and physiotherapist is necessary. The oncologist should recommend a reduction diet with adequate protein intake (1,2 g/kg body weight/day and if possible up to 1.5 g/kg body weight /day) by a clinical dietitian and lifestyle changes including physical activity. Clinical dietitians' support during and after breast cancer treatment is an essential element that can improve the patient's prognosis.

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Authors contributions

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Natalia Komorniak — writing — review and editing.
Natalia Jakubiak — visualization.
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Conflicts of interest

None declared.

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VIA MEDICA

Letter to the Editor

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The existence of "bosom malignancy" — a "tortured phrase" in breast cancer literature

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Independent researcher

Dear *Nowotwory. Journal of Oncology* Editors,

One of the corner-stones of the integrity of biomedical literature, including that related to cancer and oncology, lies in the precision of descriptors. This can be measured by the selection of appropriate technical terms or jargon, and then their accurate use and application, which would allow scientific output to be transmitted more precisely [1]. The impact (and thus integrity) of biomedical literature becomes compromised or reduced when inappropriate or inaccurate terms are used, also colloquially known as "tortured phrases", which may replace existing technical terms, either accidentally (i.e., due to a lack of knowledge) or intentionally (e.g., to masquerade plagiarism) [2, 3]. While users and readers of such literature might not notice or pay attention to such — sometimes subtle — deviations from established scientific terminology, the greater risk is that they might be propagated into downstream literature, through text reuse or citation. Peer reviewers and editors are thus tasked to scrutinize papers carefully before accepting and publishing them.

Among several issues plaguing the integrity of cancer research, one issue has not yet been widely debated, namely the erosion of scientific precision due to the presence of "tortured phrases", which distort the accuracy of established oncological terms and jargon. To gain a micro-appreciation of the extent of this phenomenon in oncological literature, or in literature of other fields of study (e.g., computer science, etc.) discuss cancer-related topics, a search was conducted for one "tortured phrase" — "bosom malignancy" (including other variants such as "bosom malignant", "bosom disease", etc.), which most likely represents breast cancer. Open access examples are listed in Table I. From an initial discovery of 115 samples, 34 were open access, and from those, 12 had to date (16 May 2024) been retracted. Two instances were in preprints, which have also shown to be vulnerable to being populated by "tortured phrases" [4].

While the issue of "tortured phrases" might appear to be minor or trivial when seen alongside larger issues impacting trust in cancer research, such as the lack of reproducibility [5], encompassing aspects like erroneous nucleotide sequences [6], this issue is nonetheless important and worthy of wider debate. Even though "tortured phrases" might exist in a text, undetectable by an untrained or uncritical eye, they may reveal additional issues with that manuscript that may further degrade its integrity, such as the undeclared use of paraphrasing software to avoid the detection of plagiarism [2], or the undeclared use of third party services, like language editing companies. For that reason, "tortured phrases" can serve as "epistemic markers" or useful (but crude) primers to evaluate or measure one aspect of the integrity of a paper, particularly its scientific linguistic integrity [7].

Effective detection methods are needed to identify synonymized text or "tortured phrases". The discovery that ChatGPT, a large language model, has the ability to reverse them [8] is worrisome because it would allow cheating authors to cover up their unethical behaviour with the assistance of AI.

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Table I. Open access papers related to cancer and oncology containing one "tortured phrase" ("bosom malignancy")[1]

Paper DOI Year of publication	*Journal* Publisher	Country(ies) of affiliation(s)
10.21767/2254-6081.100032*,[2] 2015	*Archives in Cancer Research* Insight Medical Publishing (OMICS International)	Egypt, Saudi Arabia
10.9790/0661-1903015970 2017	*IOSR Journal of Computer Engineering* IOSR Journals	India
10.4172/2472-0429.1000126 2018	*Advances in Cancer Prevention* OMICS International	India
10.1080/21691401.2018.1478420 2018	*Artificial Cells, Nanomedicine, and Biotechnology* Taylor & Francis	Malaysia, Pakistan
10.22034/APJCP.2018.19.4.969 2018	*Asian Pacific Journal of Cancer Prevention* Asian Pacific Organization for Cancer Prevention	China
10.4172/2167-0501.1000246 2018	*Biochemistry & Pharmacology: Open Access* Longdom (OMICS International)	Pakistan
10.21608/bjas.2020.136251 2020[3]	*Benha Journal of Applied Sciences* Egyptian Knowledge Bank	Egypt
10.21608/bjas.2020.187219 2020[4]	*Benha Journal of Applied Sciences* Egyptian Knowledge Bank	Egypt
10.1186/s43094-020-00113-2 2020	*Future Journal of Pharmaceutical Sciences* BMC/Springer Nature	India
10.18844/gjit.v10i1.4533 2020	*Global Journal of Information Technology: Emerging Technologies* Birlesik Dunya Yenilik Arastirma ve Yayincilik Merkezi	Australia
10.35940/ijitee.h6160.069820 2020	*International Journal of Innovative Technology and Exploring Engineering* Blue Eyes Intelligence Engineering and Sciences Engineering and Sciences Publication	India
10.1088/1757-899x/994/1/012036 2020*	*IOP Conference Series: Materials Science and Engineering* IOP Science	India
10.21608/jfds.2020.160391 2020	*Journal of Food and Dairy Sciences* Egyptian Knowledge Bank	Egypt
10.1155/2020/8017496 2020	*Journal of Healthcare Engineering* Hindawi (Wiley)	Pakistan
10.1016/j.micpro.2020.103137 2020*	*Microprocessors and Microsystems* Elsevier	India
10.1016/j.procs.2020.04.270 2020	*Procedia Computer Science* Elsevier	India
10.2139/ssrn.3564459 2020	*SSRN*# Elsevier	India
10.21608/bjas.2021.169132 2021[5]	*Benha Journal of Applied Sciences* Egyptian Knowledge Bank	Egypt
10.1051/e3sconf/202130901075 2021	*E3S Web of Conferences* EDP Sciences	India
10.24018/clinicmed.2021.2.3.59 2021	*European Journal of Clinical Medicine* European Open Science Publishing	Bangladesh
10.30699/fhi.v10i1.296 2021	*Frontiers in Health Informatics* Farname	Iran
10.1088/1757-899x/1084/1/012023 2021*	*IOP Conference Series: Materials Science and Engineering* IOP Science	India
10.1088/1742-6596/1916/1/012092 2021*	*Journal of Physics: Conference Series* IOP Science	India
10.1088/1742-6596/1916/1/012101 2021*	*Journal of Physics: Conference Series* IOP Science	India
10.1016/j.micpro.2020.103537 2021*	*Microprocessors and Microsystems* Elsevier	China
10.17762/turcomat.v12i1s.1562 2021	*Turkish Journal of Computer and Mathematics Education* Ninety Nine Publication	Not indicated
10.21203/rs.3.rs-1555234/v1 2022	*Research Square*# Springer Nature	India

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Table I cont. Open access papers related to cancer and oncology containing one "tortured phrase" ("bosom malignancy")[1]

Paper DOI Year of publication	*Journal* Publisher	Country(ies) of affiliation(s)
10.1177/15330338221132078 2022*	*Technology in Cancer Research & Treatment* SAGE Publications Inc.	Pakistan
10.7759/cureus.28875 2022*,[6]	*Cureus* Springer Nature	India
10.1186/s12906-022-03810-y 2022	*BMC Complementary Medicine and Therapies* BMC/Springer Nature	India
10.1155/2022/4217529 2022*	*Journal of Nanomaterials* Hindawi (Wiley)	Bangladesh, Pakistan
10.1016/j.dajour.2023.100177 2023*	*Decision Analytics Journal* Elsevier	India
10.1155/2023/3875525 2023	*Journal of Healthcare Engineering* Hindawi (Wiley)	India, Kenya, Saudi Arabia
10.1007/s12652-018-1066-y 2024*	*Journal of Ambient Intelligence and Humanized Computing* Springer Nature	India, USA

*Retracted; #Preprint; [1]Sourced and discovered with the Problematic Paper Screener (https://dbrech.irit.fr/pls/apex/f?p=9999:24:::NO:::) using the search term "bosom malignancy". Only open access journal articles were included to allow for open and public verification; [2]The article appears to have been silently retracted [9], but an archived version exists on the Internet Archive: https://web.archive.org/web/20180604062320/https://www.acanceresearch.com/cancer-research/roles-biomarkers-in-basic-and-clinical-research-for-breast-cancer.php?aid=7754; [3]At the time of analysis (16 May 2024), the article and journal websites were not accessible, but a copy is available on the Internet Archive: https://web.archive.org/web/20210118201919/https://bjas.journals.ekb.eg/article_136251.html; [4]At the time of analysis (16 May 2024), the article and journal websites were not accessible, but a copy is available on the Internet Archive: https://web.archive.org/web/20210812024850/https://bjas.journals.ekb.eg/article_187219.html; [5]At the time of analysis (16 May 2024), the article and journal websites were not accessible, but a copy is available on the Internet Archive: https://web.archive.org/web/20210527114817/https://bjas.journals.ekb.eg/article_169132.html; [6]Although the retraction notice alludes to the presence of tortured phrases, precisely which tortured phrases are not specified: https://www.cureus.com/articles/109423-causes-of-cancer-in-the-world-comparative-risk-assessment-of-nine-behavioral-and-environmental-risk-factors/retraction#!/; the paper remains unretracted at PubMed Commons (16 May 2024) (https://pubmed.ncbi.nlm.nih.gov/36225498/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9540511/), even though retraction took place on 19 April 2024. This ineffective bibliometric mismanagement accentuates concerns about the curation management of that popular biomedical database [10]

Article information and declarations

Author contributions

Jaime A. Teixeira da Silva — conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing — original draft preparation, writing — review & editing.

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Conflict of interest

The author declares no conflict of interest.

Supplementary material

None.

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Pictures in Oncology

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Advanced renal cancer as a chronic disease — long-term disease control with a tyrosine kinase inhibitor (TKI) inhibitor

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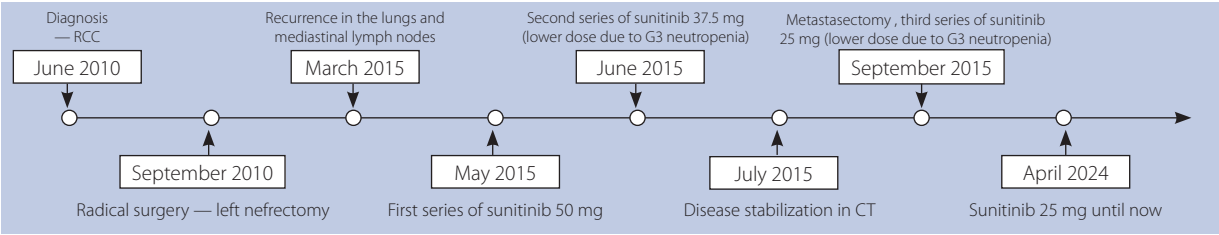

Figure 1. Treatment history — timeline; RCC — renal cell carcinoma; CT — computed tomography

A 68-year-old female patient diagnosed with clear cell renal cell carcinoma in June 2010 underwent radical left nephrectomy in September 2010. Computed tomography (CT) performed in March 2015, revealed metastases to the right lung and mediastinal lymph nodes, which confirmed disease recurrence. Treatment with sunitinib commenced in May 2015, initially at a dosage of 50 mg. One month after initiating therapy, the patient required the commencement of antihypertensive medications due to the onset of hypertension. During the treatment the dose was de-escalated twice due to the occurrence of Grade 3 adverse effects (neutropenia) as per the Common Terminology Criteria for Adverse Events (CTCEA) (Fig 1). A CT performed in July 2015 indicated disease stability according to the Response Evaluation Criteria in Solid Tumors (RECIST).

In September 2015, an R1 metastasectomy was performed, and CT has shown stabilization (according to RECIST 1.1 — stable disease) up to now.

Currently the patient is taking the 25 mg of sunitinib every other day. Disease stabilization is maintained.

In conclusion: 1) long-term administration of sunitinib at reduced doses is safe and leads to sustained responses; 2) hypertension is a common cardiological complication associated with sunitinib use and, at the same time, a favorable prognostic factor for treatment response. Therefore, support from an internist is essential [1, 2].

Contemporary oncological treatments frequently enable individuals with advanced cancer to achieve prolonged survival, effectively transforming cancer into a chronic ailment.

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Synchronous adenocarcinomas of the sigmoid colon coexisting with rectal melanoma

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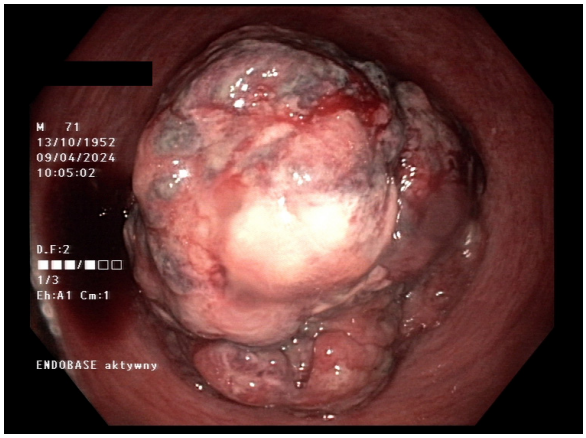

Figure 1. Endoscopic image of an amelanocytic mass observed in the rectum (on biopsy it proved to be primary rectal melanoma)

Melanomas of the gastrointestinal tract (GIT) are usually metastatic, while primary GIT melanoma are rare (0.2–3.0% of all melanomas; 0.1–4.6% of all anorectal malignancies) and associated with poor prognosis [1–3]. Its rarity in the large bowel results from the absence of melanoblasts in this segment of GIT, however a detailed pathogenesis of GIT melanomas remains uncertain [2]. Synchronous multifocal colorectal cancers coexisting with GIT melanoma have been extremely uncommon, with only a few cases described so far [1, 3].

A 71-year-old male patient with a long history of *colitis ulcerosa* treated with sulfasalazin and prednison had numerous polyps and tumors of various sizes, ulcerations and a massive rectal tumor seen on the colonoscopy (Fig. 1). Biopsies revealed typical lesions for *colitis ulcerosa* plus sigmoid invasive adenocarcinoma (rectosigmoid junction tumor), adenocarcinoma in polyp located in sigmoid and — additionally — melanoma (rectal large mass). A massive systematic spread to the liver was seen on staging. Due to symptoms of chronic bleeding from a rectal tumor, the patient underwent a total proctocolectomy; on pathology there were coexisting adenocarcinoma G2 (R0 resection) and melanoma in the rectum. The adenocarcinoma in the polyp was radically removed during endoscopy.

Rapid progression was seen postoperatively, and apart from best supportive care no other disease-oriented therapy was instituted. The patient died from rapid disease progression in the early postoperative period.

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