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Original article

Lung cancer

Lung cancer in the course of chronic obstructive pulmonary disease – the clinical picture in light of current diagnostic recommendations

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Introduction. Lung cancer and chronic obstructive pulmonary disease (COPD) are one of the most significant causes of death. The co-existence of COPD and lung cancer has a strong influence on treatment.
Material and methods. The data were collected retrospectively from patients diagnosed with lung tumors between 2016 and 2022. Of the 982 analyzed cases, 180 patients had co-existing primary lung cancer and COPD.
Results. 46.1% of the study group were women. 99.0% of patients presented a history of smoking. 46.7% patients were diagnosed with COPD during lung tumor diagnosis. 71.1% of patients suffered from non-small-cell lung cancer (NSCLC). The majority of patients had locally advanced or metastatic lung cancer.
Conclusions. The high incidences of COPD as well as lung cancer among women is striking. Almost half of the patients were diagnosed with COPD while diagnosing lung tumors. A long history of smoking is still the main factor as regards developing these diseases.

Key words: lung cancer, chronic obstructive pulmonary disease, spirometry, emphysema, non-small-cell lung cancer

Introduction

Lung cancer was the second most commonly diagnosed cancer in 2020, with 2,2 million new cases diagnosed yearly around the world (11.4% of all cancers), remaining the leading cause of cancer-related death, with an estimated 1.8 million deaths (18%) [1].The prognosis in lung cancer is very poor – only 10 to 20% of patients survive 5 years after diagnosis in most countries [1]. Chronic obstructive pulmonary disease (COPD) is the most commonly diagnosed chronic disease of the respiratory tract. Each year, COPD is diagnosed in 17.98 million patients. COPD is the third leading cause of death worldwide, with around 3.324 million deaths, which accounts for 6% of all deaths in 2019 [2].

There is a 4–6 fold greater risk of developing lung cancer in patients with coexistence of COPD in comparison with smokers with normal lung function. In patients with COPD, the 10-year risk of developing lung cancer is about 8.8%, while in patients with normal respiratory function only 2% [3]. Nevertheless, COPD will develop in only 20%, and lung cancer in 15% of cigarette smokers, though death from other smoking-related causes like stroke, heart disease and emphysema often occur in smokers [2, 3]. In patients with moderate COPD, lung cancer is the cause of death in around 30% of cases and it is the most common cause of death in COPD patients [2]. The co-existence of COPD and lung cancer has very important clinical

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consequences, and has a strong impact on diagnostic procedures and treatment. The most powerful therapeutic approach for non-small-cell lung carcinoma is surgical resection. This treatment is possible mainly in stage I, II and IIIA [1]. However, this option is associated with higher morbidity and mortality in patients with low ventilatory reserve, which is a common limiting factor for lung cancer surgery in patients with COPD [4]. Coexistence of lung cancer with COPD was described in many previous studies [5, 8–20]. Thus, we aimed to analyze the clinical characteristics of patients with coexistence of lung cancer and COPD in many aspects, taking into account current rules of diagnosis of both diseases and the possible specificity of the Polish population.

Material and methods

The demographic and clinical data were collected retrospectively from medical histories of patients hospitalized and diagnosed with lung tumors between January 1, 2016 and June 30, 2022 in a single lung disease department. A total of 982 patients with lung tumors were diagnosed in the years 2016–2022. Lung cancer was pathologically confirmed in 524 patients. COPD was confirmed in 180 patients (34.4%) of this group. Patients with co-existence of a primary lung cancer and COPD were included in further analysis (fig. 1). The following specifics were collected from medical records: age, sex, smoking status, lung cancer histological type, tumor size, disease stage, presence of metastases, treatment plan, co-existence of other diseases, results of pulmonary function tests and presence of emphysema in computed tomography (CT)

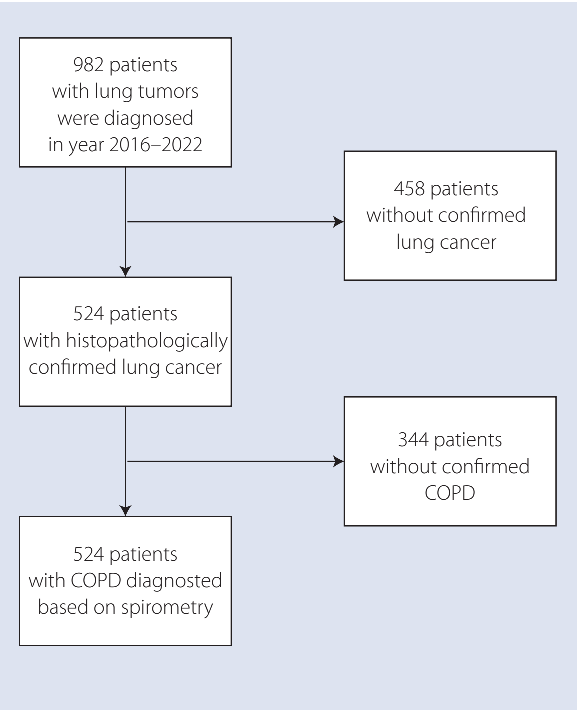

Figure 1. Patients selection to study group and reasons for patients exclusion

scans. The study was approved by the Committee of Research Ethics of the Medical University of Warsaw.

The diagnosis of lung cancer was confirmed pathologically in each case. The following subtypes of lung cancer were defined: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). NSCLC was further categorized as squamous-cell carcinoma (SCC), adenocarcinoma (ADC), large-cell carcinoma or not otherwise specified (NOS), or other [6]. The cancer stage was recorded using the TNM classification 8^{th} edition [7].

COPD was diagnosed based on an irreversible obstruction in spirometry (the FEV1%FVC less than 5 percentile after bronchodilation) in correspondence with clinical data. Spirometry values were recorded using European reference values. FVC and FEV1 were presented in liters and as a percentage of predicted values. GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria were used to assign a grade of clinical severity to COPD based on FEV1 [2]. Grade 1 was defined as having an FEV1 more or equal to 80%; grade 2 as more or equal to 50% FEV1 and less than 80%; grade 3 as more or equal to 30% FEV1 and less than 50%; and grade 4 as FEV1 less than 30%. Patients were classified as having COPD at lung cancer diagnosis if they had a previous diagnosis of COPD in their medical records or if they fulfilled the spirometric criteria during current diagnostic procedures. Patients with bronchial asthma or an obvious explanation for abnormality in spirometry, such as a central tumor or atelectasis were excluded from the study.

Patients were classified into four groups (tab. I): A,B,C, and D based on the level of symptoms, measured by the modified Medical Research Council dyspnea scale (mMRC) or the COPD Assessment Test (CAT), and the frequency of previous exacerbations [2].

Test

The presence of emphysema at lung cancer diagnosis was determined based on information from CT scans in medical records. All CT scans were reviewed at diagnosis by a radiologist experienced in pulmonary diseases. When emphysema was detected visually in the CT scan, the patient was classified as having emphysema.

Apart from the whole group characteristic, we performed a comparison of women with men, patients with emphysema and without emphysema, patients with different types of lung cancer. Unfortunately, not all data were available, thus we present in each table the number of patients with completed results of records or results of investigations.

Statistical analysis

Statistical analysis was performed using the STATISTICA 13.1, StatSoft software package. Descriptive statistics were used to describe the features of all participants. Proportions were expressed as percentages, continuous variables by mean if normally distributed or by median otherwise. For group comparison divided in terms of sex, presence of emphysema, lung

Table I. GOLD severity staging

Patients		Symptoms	
		CAT 0–9 mMRC < 2	CAT 10–40 mMRC ≥ 2
exacerbations (in past 12 months)	no hospital admission or ≤1 outpatient treatment	group A	group B
	≥1 hospital admission or ≥2 outpatient treatment	group C	group D

mMRC – modified Medical Research Council dyspnea scale; CAT – COPD assessment

cancer histological type, the Mann–Whitney test for continuous variables and the Fisher's exact test for categorical variables were used. A p-value of >0.05 was used as the removal criterion.

Results

Clinical characteristics

The process of qualification of patients to the study group is presented in figure 1. The general and clinical characteristics of the 180 patients finally enrolled in the study and the comparison between male and female are presented in tables II and III. The mean age of the group was 70.4 years. The largest (45.0%) age group of patients was between 65 and 75 years. There were 97 males (53.9%) and 83 females (46.1%). Ninety-nine percent of all patients presented with a history of smoking, whereas 58.7% were still active smokers, with 40.6% ex-smokers who ceased smoking at least 1 year previously. However 1.0% of non-smokers had been exposed to cigarette smoke as passive smokers; 77.7% of the group had a history of 20–60 pack-years, while 13.5% had more than 60 pack-years in their medical history. Males were exposed to significantly greater amounts of cigarette smoke than females (p = 0.001) in the Fisher exact test.

COPD characteristics

Almost half of all patients (46.7%) were diagnosed with COPD during lung tumor diagnosis. Table II lists characteristics of COPD and comparison between male and female. The distribution of patients with COPD according to the severity of the airway obstruction was as follows: grade 1 (FEV1 ≥ 80%)

Table II. Demographic characteristics and features of COPD in investigated group. Comparison of female with male using Mann–Whittney test for continuous variables and the Fisher's exact test for categorical variables. Only significant differences were shown (p < 0.05). Data are given as number and percentages or mean ± standard deviation

Patients	All	Female	Male	p-value
number of patients	180	83 (46.1%)	97 (53.9%)	–
age (years)	70.4 (8.6%)	70.0 (7.7%)	70.7 (9.3%)	–
≤55	7 (3.9%)	2 (2.4%)	5 (5.2%)	–
56 ≥ 65	43 (23.9%)	19 (22.9%)	24 (24.7%)	–
66 ≥ 75	83 (46.1%)	44 (53.0%)	39 (40.2%)	–
76 ≥ 85	37 (20.6%)	17 (20.5%)	20 (20.6%)	–
>85	10 (5.6%)	1 (1.2%)	9 (9.3%)	–
smoking status				
active	91 (58.7%)	42 (57.5%)	49 (59.8%)	–
former	63 (40.7%)	31 (42.5%)	32 (39.0%)	–
never	1 (0.6%)	0 (0.0%)	1 (1.2%)	–
no data*	25 (16.1%)			–
exposure – pack, years				
0 < 20	12 (8.2%)	10 (14.5%)	2 (2.6%)	p = 0.001

Table II cont. Demographic characteristics and features of COPD in investigated group. Comparison of female with male using Mann–Whittney test for continuous variables and the Fisher's exact test for categorical variables. Only significant differences were shown ($p < 0.05$). Data are given as number and percentages or mean ± standard deviation

Patients	All	Female	Male	p-value
21 < 40	58 (39.5%)	33 (47.8%)	25 (32.1%)	–
41 < 60	57 (38.8%)	22 (31.8%)	35 (44.9%)	–
61 < 80	6 (4.0%)	3 (4.4%)	3 (3.8%)	–
81 < 100	10 (6.8%)	0 (0.0%)	10 (12.8%)	–
<100	4 (2.7%)	1 (1.5%)	3 (3.8%)	–
no data	33 (18.3%)			–
COPD diagnosed during investigation of lung tumor				
yes	84 (46.7%)	37 (44.6%)	47 (48.5%)	–
no	96 (53.3%)	46 (55.4%)	50 (51.5%)	–
COPD severity (FEV1 range)				
grade 1 (>80%)	13 (10.0%)	8 (12.9%)	5 (7.4%)	–
grade 2 (50–80%)	73 (56.2%)	29 (46.8%)	44 (64.7%)	–
grade 3 (30–50%)	41 (31.5%)	24 (38.7%)	17 (25.0%)	–
grade 4 (<30%)	3 (2.3%)	1 (1.6%)	2 (2.9%)	–
no data	30 (16.67%)			–
emphysema				
yes	61 (44.2%)	35 (52.2%)	26 (36.6%)	p = 0.006
no	77 (55.8%)	32 (47.8%)	45 (63.4%)	–
no data	42 (23.3%)			–
GOLD				
A	20 (33.9%)	9 (32.1%)	11 (35.5%)	–
B	27 (45.7%)	13 (46.4%)	14 (45.2%)	–
C	3 (5.1%)	2 (7.1%)	1 (3.2%)	–
D	9 (15.3%)	4 (14.3%)	5 (16.1%)	–
no data	121 (67.2%)			–
number of comorbidities				
0	24 (13.3%)	11 (13.3%)	13 (13.4%)	–
1	38 (21.1%)	20 (24.1%)	18 (18.6%)	–
2	30 (16.7%)	12(14.5%)	18 (18.6%)	–
3	37 (20.6%)	21 (25.3%)	16 (16.4%)	–
4	22 (12.2%)	8 (9.6%)	14 (14.4%)	–
5	11 (6.1%)	5 (6.0%)	6 (6.2%)	–
6	7 (3.9%)	1 (1.2%)	6 (6.2%)	–
7	6 (3.3%)	4 (4.8%)	2 (2.0%)	–
8	2 (1.1%)	0 (0.0%)	2 (2.1%)	–
9	2 (1.1%)	0 (0.0%)	2 (2.1%)	–
10	1 (0.6%)	1 (1.2%)	0 (0.0%)	–

p-values are given for differences between female and male groups; * no data relate to the whole study group; COPD – chronic obstructive pulmonary disease; GOLD – Global Initiative for Chronic Obstructive Lung Disease

Table III. Lung cancer characteristics in the investigated group. Comparison of female with male using Mann–Whittney test for continuous variables and the Fisher's exact test for categorical variables. Data are given as number and percentages

Lung cancer	All patients	Female	Male	p-value
histological types	n = 180	83 (46.1%)	97 (53.9%)	–
NSCLC	128 (71.1%)	55 (66.3%)	73 (75.3%)	–
SCLC	52 (28.9%)	28 (33.7%)	24 (24.7%)	–
histological subtypes of NSCLC				
adenocarcinoma	47 (36.7%)	22 (40.0%)	25 (34.2%)	–
squamous-cell carcinoma	53 (41.4%)	20 (36.4%)	33 (45.2%)	–
not otherwise specified (NOS) NSCLS	19 (14.9%)	7 (12.7%)	12 (16.5%)	–
other	9 (7.0%)	6 (10.9%)	3 (4.1%)	–
central/peripheral tumor				
central	106 (60.2%)	51 (63.0%)	55 (57.9%)	–
peripheral	70 (39.8%)	30 (37.0%)	40 (42.1%)	–
no data*	4 (2.2%)			–
lung right/left				
right	86 (52.1%)	36 (46.2%)	50 (57.5%)	–
left	75 (45.5%)	40 (51.3%)	35 (40.2%)	–
right and left	4 (2.4%)	2 (2.5%)	2 (2.3%)	–
no data	25 (13.89%)			–
lobe				
superior	40 (48.2%)	18 (48.7%)	22 (47.8%)	–
inferior	35 (42.2%)	16 (43.2%)	19 (41.3%)	–
middle	8 (9.6%)	3 (8.1%)	5 (10.9%)	–
no data	97 (53.9%)			–
pleural effusion				
yes	62 (50.0%)	29 (51.8%)	33 (48.5%)	–
no	62 (50.0%)	27 (48.2%)	35 (51.5%)	–
no data	56 (31.1%)			–

p-values are given for differences between female and male groups; NSCLC – non-small-cell lung cancer; SCLC – small-cell lung cancer; COPD – chronic obstructive pulmonary disease; * no data relate to the whole study group

12 patients (3.9%); grade 2 (50% ≤ FEV1 < 80%) 74 patients (56.9%); grade 3 (30% ≤ FEV1 < 50%) 41 patients (31.6%); and grade 4 (FEV1 < 30%) 2 patients (2.3%). Emphysema was found in 55.9% of patients by CT. In terms of comorbid diseases, the number of patients with one or more comorbidities was 156 (86.7%), and 88 (48.9%) had three or more comorbid diseases. In particular, hypertension was the most common disease and occurred in 106 patients (58.9%) followed by heart failure – 39 (21.7%), diabetes type II – 34 (18.9%) and coronary heart disease – 31 (17.2%), followed by other diseases. There were no significant differences between males and females in age, sex, smoking status, COPD severity, presence of emphysema and number of comorbidities.

Lung cancer characteristics

In the study group there were 71.1% of patients with NSCLC, while in 28.9% of patients SCLC was diagnosed. Table III lists the characteristics of lung cancer in the whole group and a comparison between females and males. Of NSCLCs, squamous-cell carcinoma was the most dominant histological subtype of lung cancer – 41.4%, followed by adenocarcinoma – 36.7%, NOS –14.9% and large-cell carcinoma – 7.0%. Furthermore, in terms of cancer stage, stage III dominated in the group (52.5%), followed by stage IV (38.4%), stage I (5.7%), and stage II (3.4%). Substage IIIB was the most common in the group (28.8%), followed by IVA (23.7%). Potentially resectable cancers (stage I–IIIA) consisted of only 26.6%. Comparison

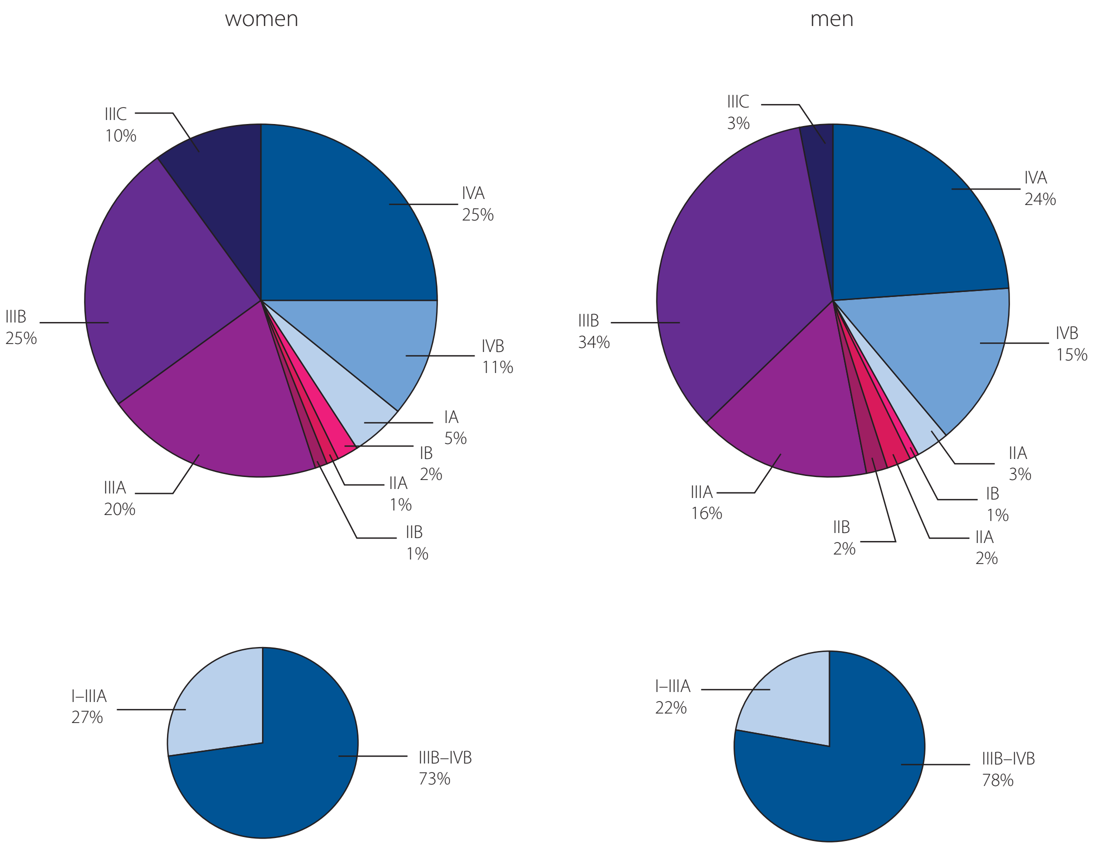

Figure 2. Lung cancer stages in patients with lung cancer in the course of COPD – comparison of men and women

of cancer stage between men and women is presented in figure 2. Cancer was mainly located centrally (60.2%), in the right lung (52.8%) and in the upper lobe (48.7%). Pleural effusion occurred in a minority of patients (38.8%). Additionally, metastases to the lung were most frequent (21.7% of all metastases), followed by metastases to the liver (15.3%), adrenal glands (14.4%), bones (14.4%), central nervous system (7.69%) and lymph nodes (7.69%). There were no significant differences between men and women as regards the histological type of cancer, tumor localization, presence of pleural effusion, lung cancer stage, number and localization of metastases.

Treatment and outcome

The records on treatment were available in 67 patients (37.2% of the whole group) and on outcome in 32 patients (17.8%). Of them only 10.9% of patients underwent surgical excision of the cancer even though 26.6% of patients were potentially resectable (stage I–IIIA). The most common treatment was the palliative approach (29.7%) which consisted of palliative care and palliative radiotherapy. Chemoradiotherapy was administered in 21.9% of patients. The overall outcome was positive in only 6.25% of patients, while 93.75% of patients died. There were no significant differences between men and women in treatment and outcome.

Comparison of patients with and without emphysema

When comparing patients with and without emphysema, no significant differences in demographic data, lung cancer characteristics and COPD stage were found. There were slightly more men than women in the emphysema group (tab. IV).

Comparison of patients between NSCLC and SCLC, and SCC and non-SCC

Patients with COPD and SCLC were in significantly more advanced stages of lung cancer than those with NSCLC ($p < 0.05$). The treatment was significantly different with chemotherapy as the most common in the SCLC group (obvious situation) and chemoradiotherapy as the most common in the NSCLC group ($p < 0.05$) (tab. V). There were no significant differences between groups in terms of age, sex, smoking status, COPD severity, number of metastases, treatment and outcome. The median pack-years in both groups was equal (45). There were no significant differences in patients with COPD between the two main NSCLC types – SCC and non-SCC – as regards age, sex, smoking status, COPD severity, lung cancer stage, number of metastases, treatment and outcome.

Table IV. Lung cancer in patients with COPD – comparison of patients with emphysema with without emphysema using Mann–Whittney test for continuous variables and the Fisher's exact test for categorical variables. Data are given as number and percentages or mean ± standard deviation

Patients	With emphysema	Without emphysema	p-value
n = 138	77	61	–
age	70.8 (8.2%)	70.3 (7.9%)	–
female	32 (41.6%)	35 (57.4%)	p = 0.06
male	45 (58.4%)	26 (42.6%)	–
smoking status			
active	39 (58.2%)	32 (58.2%)	–
former	27 (40.3%)	23 (41.8%)	–
never	1 (1.5%)	0 (0.0%)	–
no data*	16 (11.6%)		–
COPD severity (FEV1 range)			
grade 1 (>80%)	8 (13.8%)	3 (7.3%)	–
grade 2 (50–80%)	30 (51.7%)	25 (61.0%)	–
grade 3 (30–50%)	19 (32.8%)	13 (31.7%)	–
grade 4 (<30%)	1 (1.7%)	0 (0%)	–
no data	39 (28.3%)		–
histological types of lung cancer			
NSCLC	53 (68.8%)	43 (70.5%)	–
SCLC	24 (31.2%)	18 (29.5%)	–
histological subtypes of NSCLC			
adenocarcinoma	19 (35.8%)	13 (30.2%)	–
squamous-cell carcinoma	18 (34.0%)	22 (51.2%)	–
not otherwise specified (NOS) NSCLS	10 (18.9%)	7 (16.3%)	–
other	6 (11.3%)	1 (2.3%)	–
stage	77 (55.8%)	61 (44.2%)	–
IA	0 (0%)	5 (8.3%)	–
IB	1 (1.3%)	1 (1.7%)	–
IIA	2 (2.7%)	0 (0%)	–
IIB	1 (1.3%)	1 (1.7%)	–
IIIA	18 (23.7%)	6 (10.00%)	–
IIIB	18 (23.7%)	15 (25.00%)	–
IIIC	5 (6.6%)	3 (5.00%)	–
IVA	18 (23.7%)	20 (33.3%)	–
IVB	13 (17.0%)	9 (15.00%)	–
no data	2 (1.5%)		–
I–IIIA	19 (24.7%)	12 (19.7%)	–
IIIB–IVB	58 (75.3%)	49 (80.3%)	–

p-values are given for differences between with emphysema and without emphysema groups; NSCLC – non-small-cell lung cancer; SCLC – smal-cell lung cancer; * no data relate to the whole study group

Table V. COPD in two main types of lung cancer – comparison of SCLC and NSCLC using Mann–Whittney test for continuous variables and the Fisher's exact test for categorical variables. Data are given as number and percentages or mean ± standard deviation

Patients	SCLC	NSCLC	p-value
n = 178	52	126	–
age	70.6 (8.2%)	70.2 (8.9%)	–
female	28 (53.8%)	54 (42.1%)	–
male	24 (46.2%)	73 (57.9%)	–
smoking status	45	108	–
active	28 (62.2%)	63 (57.4%)	–
former	17 (37.8%)	45 (41.7%)	–
never	0 (0.0%)	1 (0.9%)	–
no data*	27 (15.2%)		–
COPD severity (FEV1 range)			
grade 1 (>80%)	2 (5.0%)	10 (11.4%)	–
grade 2 (50–80%)	21 (52.5%)	51 (57.9%)	–
grade 3 (30–50%)	16 (40.0%)	25 (28.4%)	–
grade 4 (<30%)	1 (2.5%)	2 (2.3%)	–
no data	52 (29.2%)		–
stage			
IA	0 (0.0%)	7 (5.7%)	–
IB	1 (2.0%)	1 (0.8%)	–
IIA	0 (0.0%)	3 (2.5%)	–
IIB	0 (0.0%)	3 (2.5%)	–
IIIA	6 (12.0%)	24 (19.7%)	–
IIIB	14 (28.0%)	36 (29.5%)	–
IIIC	5 (10.0%)	6 (4.9%)	–
IVA	13 (26.0%)	30 (24.6%)	–
IVB	11 (22.0%)	12 (9.8%)	–
no data	6 (3.4%)		–
I–IIIA	7 (13.7%)	35 (28.2%)	p = 0.041
IIIB–IVC	44 (86.3%)	89 (71.7%)	–
no data	3 (1.7%)		–
number of metastases			
1	11 (44.0%)	26 (60.5%)	–
2	7 (28.0%)	10 (23.2%)	–
3	6 (24.0%)	3 (7.0%)	–
4	1 (4.0%)	4 (9.3%)	–
no data	112 (62.9%)		–

p-values are given for differences between SCLC and NSCLC groups; n – number; NSCLC – non-small-cell lung cancer; SCLC – small-cell lung cancer; COPD – chronic obstructive pulmonary disease; * no data relate to the whole study group

Discussion

The coexistence of COPD and lung cancer is a known clinical observation. However, previous studies are sometimes incomplete with only selective data available or carried out on a small number of patients (8–21). We present a large group of patients with established COPD and lung cancer with precise characteristics of both diseases performed according to current guidelines [2]. The advantage of this study is its focus on the Polish population.

The main characteristics of patients with COPD and lung cancer from other studies was shown in table VI. In our study, we reported a similar mean age of patients as in other studies as well as sex distribution, which was almost equal in men and women. It is confirmed in a few studies [9, 11, 13], but most of them show a higher proportion of men [8, 10, 14–20]. Lung cancer and COPD are the diseases generally considered attributable to men. Our results indicate the tendency of high incidence of COPD as well as lung cancer among women which was confirmed by epidemiological studies [22]. In our study, the number of women and men was similar and the features of both serious diseases unexpectedly did not differ in statistical analysis. However, smoking exposure was significantly higher in men than in women, as in other studies [22]. In women, cigarette smoke has a greater influence on developing lung cancer because of the differences in lung anatomy and lung development, as well as other factors such as different hormonal effects due to estrogen playing an important role [23]. Our observation indicates women need to be perceived on the same level in the context of careful early diagnosis and screening programs in lung cancer as well as COPD. The common opinion among physicians should be verified.

Cigarette smoke is the main risk factor for developing COPD and lung cancer [22, 24]. In our study group, almost all of the patients were exposed to cigarette smoke. Interestingly most of the patients are still current smokers after establishing the diagnosis despite medical advice to quit smoking. COPD often remains undiagnosed for a long time [19, 25]. In our group of patients, almost 50% were diagnosed with COPD during the diagnosis of lung cancer. It is a striking number and underlines the importance of active COPD diagnosing in smokers and the need for multiple pulmonary function tests in every smoking patient over the years. COPD with predominance of emphysema are known to be a poor prognostic indicator in lung cancer patients [21, 26]. In our study, more than half of patients presented COPD phenotype with emphysema. However, groups with and without emphysema did not differ statistically in clinical characteristics. COPD with emphysema-predominant phenotype decreases the 5-year survival rate up to 5.4% [26] in stage III–IV, and to 65.2% in stage I–II [27]. In our study, the survival rate is low due to the high proportion of advanced cancer stages (III and IV) (fig. 2). Stage III and IV are the most common and represent almost 70% of newly diagnosed lung cancer [28], in patients with a coexistence of COPD even more: 68.5–88% [11, 13, 15, 17]. A similar observation was found in our study. Some explanation of more advanced stages in cases with coexistence of COPD than in lung cancer only could be a delayed diagnosis in patients with initially COPD. Patients attribute symptoms like cough and dyspnea to COPD, and vigilance for lung cancer is lower [25].

Thanks to increasing cancer vigilance and modern diagnostic methods, more lung cancers are diagnosed at the stages which are potentially resectable over the years. Surgery is the most effective treatment approach but it can only be used in patients with stages I–IIIA. 20.7% of lung cancer patients undergo surgery in USA [29], while in Poland it is about 20% [30]. In the majority of cases COPD is a serious and important contraindication for surgery, especially with severe and very severe obstruction. Because of that less patients are qualified to this radical treatment [4]. In our study, FEV1% of less than 30% was reported in only 3% of patients, but FEV1% 30–50% was reported in even 30% of patients, what had a serious influence on treatment choice. Finally, only 10% of our patients underwent surgical excision of lung cancer, which is not a satisfactory rate, but common among COPD patients [27].

SCLC represents about 13–15% of lung cancers [27]. Our study reports almost twice the incidence of SCLC in COPD patients. There are a few recent studies which analyze COPD with SCLC and NSCLC patients together [13, 16, 18]. The proportion of SCLC patients in these studies is as follows: 7.4%, 9.0%, 2.2%. The difference depends on the method of the selection of the study group. The credibility of our study is underlined by the examination of the full available database of consecutively admitted to our department patients without selection of patients. The high proportion of SCLC is undoubtedly connected with heavy smoking, also among women.

Similarly to the high proportion of SCLC in our group, we also noted the predominance of SCC in patients with NSCLC, probably as a result of the high burden of smoking history. We also compared patients with SCC versus non-SCC since SCC is much more connected with smoking than ADC. The more immunological dysfunctions and destruction of tissue present in COPD patients, the more that favors the development of SCC; for this group immunotherapy could be a promising treatment option [5]. SCC in our study group was no different from the others.

An important limitation of this study is its retrospective character. Thus, some data were lacking in some patients. It especially concerns lung cancer molecular characteristics, programmed death ligand 1 (PD-L1) expression, qualifications to modern therapies and patients' outcome.

Conclusions

In summary, COPD in patients with lung cancer is an important and growing clinical problem. High incidences of COPD as well as lung cancer among women is striking. The clinical pattern of lung cancer coexists with COPD. Lung cancer was

Table VI. Demographic data, lung cancer and COPD characteristics from articles published in years 2017–2023 focused on patients with coexistence of lung cancer and COPD. Data are given as number and percentages or mean ± standard deviation

Name, year	Patients number	M/F	Age (years)	Smoking history N/F/C (pack years)	SCLC/ NSCLC	ADC/ SCC/ other	STAGE I/II/III/IV	GOLD 1/2/3/4	Main finding
Dos Santos 2022 [15]	18	12/6	70.2 ± 9.2	69 (50–106)	ND	ND	ND	4/7/7/0	COPD with lung cancer was associated with elevated DNA damage in peripheral lymphocytes
Sandelin 2018 [16]	594	291/303	68.9 ± 8.5	ND	ND	ND	ND	ND	asthma diagnosis and use of inhaled corticosteroids were independently related to decreased risk of lung cancer in COPD patients, while the use of acetylsalicylic acid was associated with an increased risk
Yi 2018 [17]	170	154/16	70.4 ± 8.9	ND/18/152 ND/10.6%/89.4%	0/100%	60/94	0/0/70/ 100	35/103/24/8	high prevalence of COPD among patients with advanced NSCLC, COPD patients complained about various symptoms had diminished quality of life
Schwan Media 2018 [18]	329	191/138	69.4 ± 9.0	7/121/195 2.2%/37.5%/ 64.0% (40.6 ± 21.1)	0/100%	126/136	11.2%/20.5%/36.0%/32.5%	ND	COPD nor other common comorbidities are significantly associated with higher mortality in NSCLC patients
Sunmi 2018 [19]	57	52/5	67.5 ± 7.4	4/22/31 7.0%/38.6%/54.4% (49.5 ± 24.2)	100%/0	ND	24/33 LD/ED	19/21/16/4	although over half of the SCLC patients receiving chemotherapy had COPD, coexisting COPD had no impact on the survival of patients with SCLC
Lim 2019 [20]	68	30/38	75.2 (48–89)	ND	7.4%/92.6%	ND	15/5/9/39	FEV1% 78.4% ± 20.2	never-smoker NSCLC patients with COPD had shorter OS times, compared to non-COPD never-smoker NSCLC patients
Takegahara 2017 [21]	108	86/22	69.3 (46–84)	ND/63/45 ND/55.6%/44.4%	0/100%	53/38	73/23/12/0	ND	for lung cancer patients with COPD, preoperative management using LABA or LAMA bronchodilators and smoking cessation can reduce the frequency of postoperative pulmonary complications after surgical lung resection
Omote 2017 [22]	43	37/6	67 ± 8	(58.5 ± 37)	0/100%	28/7/8	4/1/9/29	27/16/0/0	mild to moderate COPD did not have a significant deleterious impact on toxicity and prognosis in NSCLC patients
Wang 2018 [23]	724	636/88	62.6 ± 8.5	31.1%/68.9% (N/F and C)	9%/81%	341/263/55	71.9%/21%/ 5.7% (I/II/III+IV)	75%/21%/4% (1/2/ 3 and 4)	COPD, especially emphysema-predominant phenotype, is an independent prognostic risk factor for squamous carcinoma only
Yuan 2022 [24]	20	20/0	66.3 ± 7	1/7/12	0/100%	10/6/4	2/15 (I–II/III–IV)	ND	coexistence of COPD leads to worse clinical manifestations and altered gene mutation profiles in patients with NSCLC

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Table VI cont. Demographic data, lung cancer and COPD characteristics from articles published in years 2017–2023 focused on patients with coexistence of lung cancer and COPD. Data are given as number and percentages or mean ± standard deviation

Suzuki 2022 [25]	132	125/7	70.5 ± 7	ND/85/47	3/132	69/52/8	98/24/9/1	66/58/8/0	the COPD phenotype with both emphysema and bronchial wall thickness on chest CT was associated with poorer performance status, greater extent of dyspnea, greater impairment of pulmonary function, and worse prognosis in patients after surgical resection of lung cancer
Yo 2022 [26]	221	200/ 21	70.7 ± 8.97	37/184 (N/F and C)	0/100%	77/117/27	0/0/106/115	51/121/44/4	pretreatment spirometry and maximal treatment for COPD may offer a chance of optimal management for patients with advanced NSCLC.
Hu 2018 [27]	643	551/92	64.9 ± 8.5	364/279 (N and F/C)	0/100%	302/206/35	378/117/139/9	ND	COPD is a common comorbidity of early stage lung cancer. Lung cancer patients with coexistence of COPD have obviously different clinicopathological features compared to patients without COPD, which requires special attention and management during the perioperative period of lung cancer

ADC – adenocarcinoma; COPD – chronic obstructive pulmonary disease; CT – computed tomography; C – current; DNA – deoxyribonucleic acid; F – female; F – former; GOLD – Global Initiative for Chronic Obstructive Lung Disease; LABA – long-acting beta agonists; LAMA – long-acting muscarinic antagonist; M – male; N – never; ND – no data; NSCLC – non-small-cell lung cancer; SCC – squamous-cell carcinoma; SCLC – small-cell lung cancer considered a male disease, however the frequency of lung cancer and COPD in women and men is similar. Almost half of cigarette smoking patients were diagnosed with COPD while simultaneously diagnosing lung tumors. A long history of smoking is still the main factor for developing both of these diseases. More epidemiological studies on large groups of patients are needed for a full understanding of the correlation between COPD and lung cancer.

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 Warsaw.

Author contributions

Robert Uliński – responsible for the concept and design of the study; involved in data collection; analyzed the data; was responsible for statistical analysis; wrote the manuscript.
Marta Dąbrowska – responsible for the concept and design of the study.
Joanna Domagała-Kulawik – responsible for the concept and design of the study; analyzed the data; wrote the manuscript.
All authors edited and approved the final version of the manuscript.

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Conflict of interest

Non declared

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Original article

Lung cancer

Analysis of the clinical and pathological characteristics of patients with the squamous-cell lung carcinoma including group survival rates and the occurrence of symptoms depending on the extent of the tumor

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Introduction. Non-small-cell lung carcinoma (NSCLC) constitutes 80% of all lung cancer cases, of which 25–30% are squamous-cell carcinoma (SCC). We investigated the impact of comorbidities and other risk factors on the survival of patients with SCC, including the correlation between symptoms and the maximum tumor size.

Materials and methods. The study cohort included 417 patients. The Kaplan-Meier method, the Log-rank test, Gehan's generalized Wilcoxon test, the Mann-Whitney U test, the t-test and Cox's model of proportionality of hazards were applied.

Results. The maximum tumor size exhibited a significant correlation with the presence of symptoms such as cough, hemoptysis, and weight loss. Patients who presented with a positive family history of cancer, a prior history of cancer, respiratory diseases, or hypertension experienced a notably reduced survival time.

Conclusions. Patient's symptoms and their medical history are important in predicting survival.

Key words: lung, carcinoma, squamous-cell, survival analysis

Introduction

According to the GLOBOCAN data for the year 2020, lung cancer constitutes 11.4% of all malignant tumors in terms of morbidity, and it is responsible for 18% of deaths caused by malignant tumors worldwide. Non-small-cell lung carcinoma (NSCLC) constitutes 80% of all lung carcinoma cases, of which 25–30% are squamous-cell carcinoma. The prognosis for patients diagnosed with lung cancer is unfavorable and is closely associated with the cancer's stage at the time of diagnosis, and the specific subtype of NSCLC. Men demonstrate a higher incidence of lung cancer compared to women, a discrepancy probably linked to lifestyle and genetic factors [1–5].

Among NSCLC, squamous-cell lung carcinoma (SCC) is the cancer most strongly associated with smoking. The role of classic or electronic cigarette fumes in the pathogenesis of SCC may be related to a decreased DNA methylation in regions strictly responsible for the proper functioning

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of the respiratory epithelium. In addition to active smoking, it is important to consider the role of passive smoking, which significantly influences the occurrence of lung cancer. There is substantial evidence suggesting that passive smoking has a greater impact on the development of adenocarcinoma than on the development of SCC. The SCC is also associated with environmental factors, genetic predisposition, i.e. a positive family history of cancer, positive cancer history, and also comorbidities – especially lung diseases [6–9].

Symptoms of centrally located tumors are most often a cough, as well as symptoms resulting from atelectasis or obstructive pneumonia, i.e. shortness of breath. Haemoptysis, which is often associated with lung cancer, may occur in SCC due to the extravasation of blood from the bronchial artery within the tumor or less often, from the pulmonary artery [4, 6].

The aim of the study was to determine the characteristics of patients with SCC and the characteristics of tumors such as size, TNM grade, and histopathological grade. The study also aimed to detect a possible relationship between exposure to risk factors and patient survival, so as to detect a correlation between patients' symptoms and maximum tumor size.

Materials and methods

The study included a cohort of 417 patients diagnosed with SCC who underwent radical anatomical resection of the lung tissue (segmentectomy, lobectomy, bilobectomy or pneumonectomy) due to lung cancer between May 2012 and December 2021. A dedicated database was established to compile the medical records of all patients who underwent surgery for lung cancer. Patients were observed for five years from the day of surgery. Data about patients' survival was collected up to 1st May 2022. All further outcomes were considered incomplete. Inclusion criteria: primary SCC confirmed histologically, lobectomy or pneumonectomy, age over 18. Exclusion criteria: histopathologically confirmed adenocarcinoma, histopathologically confirmed secondary lung cancer, the presence of more than one histologically different tumor in the specimen. Limits of our study: lack of information about patients after the end of the 5-year follow-up, lack of exact information about death, lack of exact data about chemotherapy. The detailed study design is presented in figure 1.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the Medical University of Silesia (No PCN/0022/KB/27/21).

Statistical analysis

Data is presented as the number of cases with percentage and for quantative variables as mean +/– SD or median with Q1 and Q3. The normality assumption was tested for each quantitative variable based on a graphical interpretation of the Q-Q plots and histograms. Odds ratios with 95% confidence intervals were calculated for categorical variables.

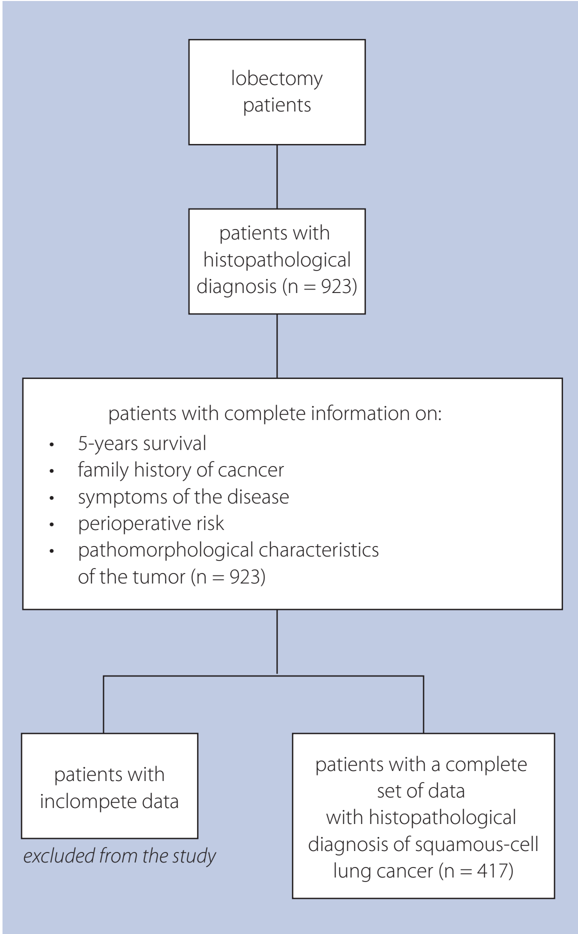

Figure 1. Study design flowchart

Pearson's chi-square test, the t-test and the Wilcoxon test were used to determine the significance of differences between groups with different selected characteristics. The Kaplan–Meier method was used to determine the probabilities of survival among the groups. The comparison of survival was performed using the Mantel-corrected log-rank test during which more than two groups were compared. To assess the impact of variables on patient survival, the Cox proportional hazards model was used. P-values less than 0.05 were considered significant. The analysis was carried out using the Rlanguage in the Rstudio software.

Results

The study encompassed 281 male and 136 female participants. Among the study participants, 81.5% were active cigarette smokers, while 73.4% had been exposed to second-hand smoke. Complications during the surgical procedure affected 33.3% of patients. The predominant T classifications for the cancer cases were T2 (36.1%) and T1 (33.6%). The majority of patients showed no neoplastic involvement in their lymph nodes (61.3%). Most patients presented with a histopathological malignancy of grade G2. A total of 1.4% of patients died during hospitalization. The mean age of the participants in the study was approximately 68 years. The median pack--years for smokers was approximately 40 years. The median maximum tumor size was 40.00 mm, and the median survival duration was 1321 days (approximately 3.5 years). Notably, no statistically significant differences were observed between the groups ($p > 0.05$) (tab. I).

Symptoms indicative of neoplastic disease were reported by 54.9% of the patients. A cough was the most frequently reported symptom, accounting for 41.0% of the total cases and prevalent among both smokers and non-smokers. The median of weight loss was 8.00 kg in the smoking group and 6.50 kg in the non-smoking group. The median of percentage weight loss was 10.00% in the smoking group and 9.00% in the non-smokers group. There were no significant differences observed between these groups ($p > 0.05$) (tab. I).

A positive cancer history concerned 15.8% of patients, while a positive family history of cancer was noted in 14.9% of patients. Surgical risk factors were identified in 58.3%

Table I. Characteristics of patients grouped by smoking status (n = 417)

Characteristic	Overall	Smoker		p-value
		No	Yes	
	n (%)	n (%)	n (%)	
smoking cigarettes	340 (81.5%)	–	–	–
second-hand smoking	306 (73.4%)	–	–	–
gender				0.664
male	281 (67.4%)	54 (70.1%)	227 (66.8%)	
female	136 (32.6%)	23 (29.9%)	113 (33.2%)	
surgery complication	139 (33.3%)	25 (32.5%)	114 (33.5%)	0.964
hemothorax requiring re-surgery	15 (3.6%)	4 (5.2%)	11 (3.2%)	0.621
blood tranfusion during or after surgery	36 (8.6%)	5 (6.5%)	31 (9.1%)	0.606
drainage	40 (9.6%)	12 (15.6%)	28 (8.2%)	0.078
disease symptoms	229 (54.9%)	35 (45.5%)	194 (57.1%)	0.085
pain	15 (3.6%)	1 (1.3%)	14 (4.1%)	0.389
hemoptysis	48 (11.5%)	6 (7.8%)	42 (12.4%)	0.350
dyspnoea	17 (4.1%)	3 (3.9%)	14 (4.1%)	1.000
cough	171 (41.0%)	30 (39.0%)	141 (41.5%)	0.783
weight loss	21 (5.0%)	2 (2.6%)	19 (5.6%)	0.427
TNM scale				
T feature				0.860
I	135 (33.6%)	23 (30.7%)	112 (34.3%)	
II	145 (36.1%)	27 (36.0%)	118 (36.1%)	
III	80 (19.9%)	18 (24.0%)	62 (19.0%)	
IV	41 (10.2%)	7 (9.3%)	34 (10.4%)	
x	1 (0.2%)	0 (0.0%)	1 (0.3%)	
N feature				0.719
0	253 (61.3%)	44 (57.1%)	209 (62.2%)	
I	87 (21.1%)	16 (20.8%)	71 (21.1%)	
II	5 (1.2%)	1 (1.3%)	4 (1.2%)	
x	68 (16.5%)	16 (20.8%)	52 (15.5%)	
M feature = x	410 (100.0%)	77 (100.0%)	333 (100.0%)	

→

Table I cont. Characteristics of patients grouped by smoking status (n = 417)

Characteristic	Overall	Smoker		p-value
		No	Yes	
	n (%)	n (%)	n (%)	
grade				
I	27 (6.5%)	3 (3.9%)	24 (7.1%)	0.301
II	222 (53.2%)	48 (62.3%)	174 (51.2%)	
III	141 (33.8%)	24 (31.2%)	117 (34.4%)	
IV	1 (0.2%)	0 (0.0%)	1 (0.3%)	
x	26 (6.2%)	2 (2.6%)	24 (7.1%)	
death during hospitalization	6 (1.4%)	1 (1.3%)	5 (1.5%)	1.000
quantitative characteristics				
pack-years				
median	30.00	–	–	–
q1	20.00	–	–	–
q3	45.00	–	–	–
age during surgery				
mean	67.77	68.44	67.62	0.387
stabilization of the disease (SD)	7.11	7.63	6.99	
weight loss (kg)				
median	8.00	6.50	8.00	0.586
q1	4.00	4.75	4.50	
q3	10.00	8.25	11.00	
weight loss (%)				
median	10.00	9.00	10.00	0.809
q1	5.00	6.00	6.50	
q3	15.00	12.00	16.50	
maximum tumor size (mm)				
median	40.00	40.00	40.00	0.987
q1	25.00	25.00	25.00	
q3	55.00	55.00	60.00	
5-year survival (days)				
median	1321.00	1251.00	1358.00	0.731
q1	623.00	684.00	622.00	
q3	1825.00	1825.00	1825.00	

x – feature cannot be assessed

of patients, with hypertension (60.2%), non-insulin-dependent diabetes mellitus (24.9%), respiratory system diseases (24.5%), and coronary artery disease (24.2%) being the prevailing factors. Statistically significant differences were observed between smokers and non-smokers who had experienced a myocardial infarction more than six months prior and those diagnosed with coronary artery disease. A higher percentage of patients who had a myocardial infarction six months earlier (p = 0.022) and a greater proportion of patients diagnosed with coronary artery disease (p = 0.044) were non-smokers (tab. II).

The median of the maximum tumor size was higher among patients who reported disease symptoms. The Wilcoxon test analysis revealed that these differences were highly significant

Table II. Overall medical history and depending on smoking status (n = 417)

Characteristic	Overall	Smoker		p-value
		No	Yes	
	n (%)	n (%)	n (%)	
positive cancer history	66 (15.8%)	17 (22.1%)	49 (14.4%)	0.136
positive family history of cancer	62 (14.9%)	10 (13.0%)	52 (15.3%)	0.737
surgery risk factors and comorbidities	243 (58.3%)	49 (63.6%)	194 (57.1%)	0.353
insulin-dependent diabetes	2 (0.5%)	1 (1.3%)	1 (0.3%)	0.811
insulin-independent diabetes	104 (24.9%)	26 (33.8%)	78 (22.9%)	0.066
cardiac infarction ≤6 months	2 (0.5%)	1 (1.3%)	1 (0.3%)	0.811
cardiac infarction >6 months	35 (8.4%)	12 (15.6%)	23 (6.8%)	0.022
epilepsy	1 (0.2%)	0 (0.0%)	1 (0.3%)	1.000
circulatory failure	8 (1.9%)	2 (2.6%)	6 (1.8%)	0.983
kidney failure	2 (0.5%)	1 (1.3%)	1 (0.3%)	0.811
COPD	83 (19.9%)	13 (16.9%)	70 (20.6%)	0.564
varicose veins and lower extremity venous insufficiency	10 (2.4%)	0 (0.0%)	10 (2.9%)	0.267
hypertension	251 (60.2%)	50 (64.9%)	201 (59.1%)	0.416
coronary artery disease	101 (24.2%)	26 (33.8%)	75 (22.1%)	0.044
respiratory system diseases	102 (24.5%)	17 (22.1%)	85 (25.0%)	0.695
chronic bronchitis	2 (0.5%)	0 (0.0%)	2 (0.6%)	1.000
bronchial asthma	18 (4.3%)	5 (6.5%)	13 (3.8%)	0.465
post-tuberculosis changes in the lungs	4 (1.0%)	0 (0.0%)	4 (1.2%)	0.757

COPD – chronic obstructive pulmonary disease

($p < 0.001$). The median of the maximum tumor size was significantly larger in the group of patients who reported hemoptysis ($p = 0.023$), a cough ($p = 0.0012$) and weight loss ($p = 0.002$) as disease symptoms (tab. S–I [supplementary files], fig. 2).

The median of the maximum tumor size was higher in the group of patients who reported pain ($p = 0.47$) and dyspnoea ($p = 0.054$) as disease symptoms. It is essential to note that these differences were not statistically significant (tab. S–I, fig. S–1 [supplementary files]). There were no statistically significant differences in survival duration observed between women and men ($p = 0.060$) (tab. III, fig. S–2 [supplementary files]). Patients with a positive cancer history were almost twice as likely to experience mortality compared to those with a negative cancer history ($p = 0.008$) (tab. III, fig. S–3 [supplementary files]). Likewise, patients with a positive family history of cancer had twice the risk of mortality in comparison to those with a negative family history of cancer ($p = 0.002$) (tab. III, fig. S–4 [supplementary files]). The group of patients exposed to second-hand smoking exhibited an almost sixfold higher risk of mortality compared to those who were not exposed to second-hand smoking ($p < 0.001$) (tab. III). Patients with surgical risk factors had a fivefold higher risk of death compared to patients without surgical risk factors ($p < 0.001$) (tab. III, fig. S–5 [supplementary files]).

Patients with hypertension had an approximately twofold higher risk of death compared to those without hypertension ($p = 0.011$) (tab. III–IV, fig. 3). The division of the patients by gender revealed a significant impact of hypertension on survival exclusively within the male group. There were no significant differences in survival between women with hypertension compared to the group of women without hypertension (fig. 4, S–6 [supplementary files]). Patients with respiratory system diseases had a mortality risk nearly twice as high as those without this group of comorbidities ($p = 0.035$) (tab. III, fig. 5).

Compared to patients with T1 cancer, patients with T2 had a twofold higher risk of death ($p = 0.006$), while T3 patients had an almost threefold higher risk ($p < 0.001$), and T4 patients had an almost fourfold higher risk of death ($p < 0.001$). Patients with the N feature at the N2 level had an approximately sevenfold higher risk of death compared to patients with N0 ($p < 0.001$) (tab. III, fig. S–7, S–8 [supplementary files]).

Patients with a tumor grade at G3 had an approximately threefold higher risk of death than patients with G1 ($p = 0.047$), while patients with G4 had a more than 100-times higher risk of death than patients with G1 ($p < 0.001$). Furthermore, patients with a larger maximum tumor size had a higher risk of death (tab. III, fig. S–9 [supplementary files]).

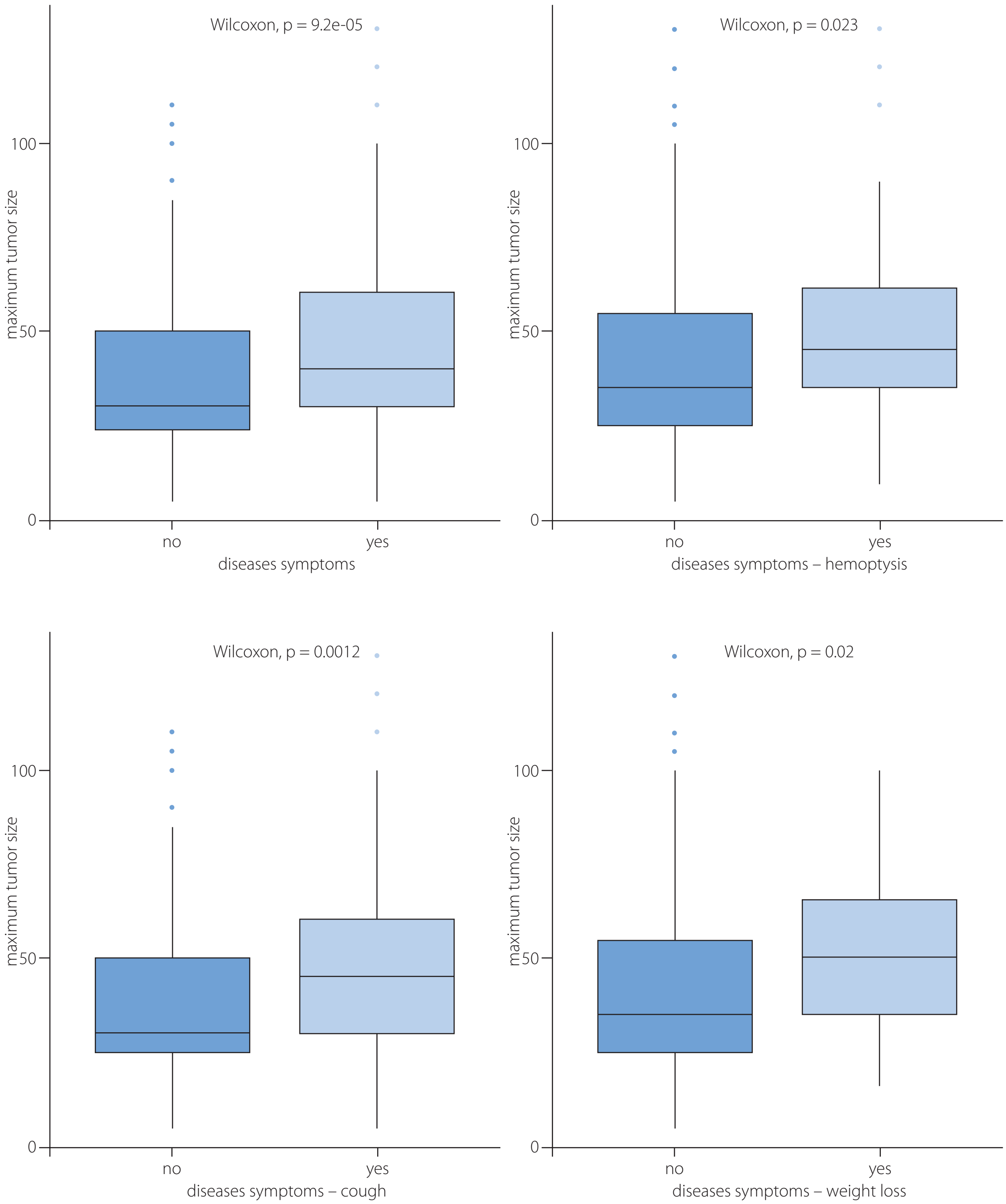

Figure 2. Disease symptoms such as hemoptysis, coughing, and weight loss depending on the maximum tumor size (n = 417), boxplot

Discussion

Our study focused on patients with SCC. However, given that the majority of previous studies in this field have been predominantly based on NSCLC studies in general, and considering the similarities between squamous and non-squamous tumors concerning factors influencing postoperative survival, we have concentrated on discussing studies primarily grounded in NSCLC research.

The article by Iachin et al. [10] from 2014 presented the conclusions that patients with cardiovascular disease presented higher mortality rates. The conclusions also show that patients with lung diseases have a higher mortality rate. In our work, we also highlighted different survival rates in these groups of patients. Another study showed that patients with congestive heart failure (CHD) had a higher mortality rate. Likewise, our research revealed varying survival rates among

Table III. Survival probability depending on specific features (n = 417)

Variable	Beta	HR (95% CI)	Wald. test	p-value
gender – female	–0.43	0.65 (0.42–1.00)	3.60	0.060
smoking cigarettes	–0.13	0.87 (0.54–1.40)	0.30	0.590
second-hand smoking	1.00	6.20 (2.90–13.00)	22.00	<0.001
positive cancer history	0.64	1.90 (1.20–3.00)	7.20	0.008
surgery risk factors and comorbidities	1.00	5.00 (2.90–8.40)	36.00	<0.001
hypertension	0.55	1.70 (1.10–2.70)	6.50	0.011
respiratory system disease	0.45	1.60 (1.00–2.40)	4.40	0.035
disease symptoms	–0.11	0.89 (0.6–1.30)	0.33	0.560
weight loss	-0.4×10^{-3}	1.00 (0.41–2.40)	0.00	0.990
positive family history of cancer	0.71	2.00 (1.30–3.20)	9.40	0.002
pack-years	–0.01	0.99 (0.99–1.00)	1.10	0.290
maximum tumor size	0.01	1.00 (1.00–1.00)	21.00	<0.001
T feature				
II	0.79	2.19 (1.25–3.84)	20.86	0.006
III	1.16	3.18 (1.76–5.76)		<0.001
IV	1.38	3.98 (2.07–7.65)		<0.001
x	–13.39	1.53×10^{-6} (0–Inf)		0.995
N feature				
I	0.06	1.06 (0.95–0.65)	15.56	0.822
II	1.99	7.34 (0.14–2.65)		<0.001
x	–0.15	0.86 (1.17–0.49)		0.594
grade				
II	0.48	1.61 (0.62–0.58)	23.40	0.360
III	1.04	2.82 (0.35–1.01)		0.047
IV	4.62	101.24 (0.01–10.22)		<0.001
x	0.35	1.42 (0.71–0.38)		0.604

x – feature cannot be assessed

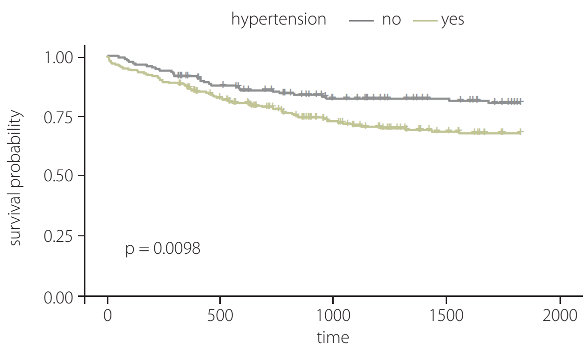

Figure 3. Survival probability depending on hypertension appearance, the Kaplan–Meier curve (n = 417)

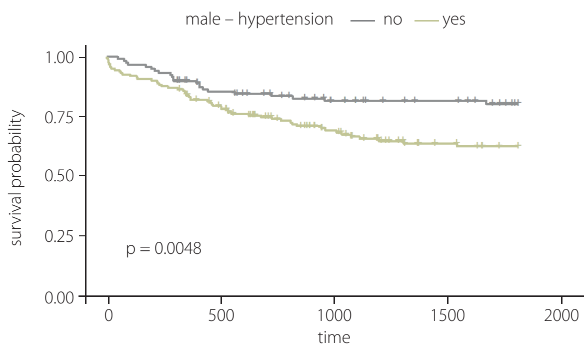

Figure 4. Survival probability for men depending on hypertension appearance, the Kaplan–Meier curve (n = 417)

groups of patients with similar comorbidities. Another study showed that patients with congestive heart failure (CHD) exhibited higher mortality rates. However, it was not possible to delve into this topic extensively in our work due to the limited

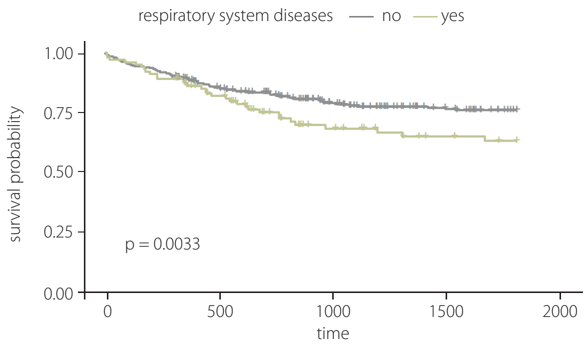

Figure 5. Survival probability depending on respiratory system disease appearance, the Kaplan–Meier curve (n = 417)

number of patients suffering from this condition. However, the assumption that cardiovascular diseases are a significantly negative prognostic factor in patients with lung cancer was clarify. A study by Tammemagi [12] showed that the presence of comorbidities negatively affects the survival of patients with lung cancer both in early and late stages of the disease. This observation presents an intriguing avenue for future investigations into the prevention of lung cancer, particularly regarding the prevention of diseases that frequently coexist with this condition [10–12]. Agarwal's study revealed a significant correlation between gender and survival outcome of patients with SCC. This conclusion could not be drawn from our work [13].

A subsequent study, conducted in 1999, presents valuable information, some of which is reflected in our work. This study examined aspects such as quality of life before the onset of lung cancer, the manifestation of disease symptoms, and their impact on survival. The findings from this study indicated that the onset of >5% weight loss and the presence of dyspnea were unfavorable prognostic factors. Despite the passage of time, this study remains a relevant up-to-date analysis of information on how we can predict the course of patients' disease [14].

A study conducted by Montazeri focused on the quality of life of lung cancer patients in relation to survival time. In the study, deceased patients were more likely to report symptoms such as fatigue, loss of appetite, a cough, shortness of breath and haemoptysis. This is reflected in our study, especially weight loss symptoms, shortness of breath and haemoptysis. Additionally, the author emphasizes that the quality of life before the cancer diagnosis significantly impacts survival after diagnosis. This is a relevant topic for future research [15].

A study conducted by Osowiecka, Rucińska, Każarnowicz et al. [16] focused on the influence of gender, T and N features. According to the presented analysis results, gender and T feature had no significant impact on the survival of patients with non-small-cell lung carcinoma treated with radiation. That said, the N feature turned out to have a significant impact on the survival of these patients. Compared to the results of our study, there was no significant effect of gender on the survival of patients with NSCLC but the N feature was significant. Unlike the presented study, the T feature was significant as well. Nevertheless, the similarity of survival depending on N feature despite treatment method is worth to be pointed out, which creates an interesting area of future research [16].

Conclusions

The maximum tumor size significantly influences specific symptoms of patients suffering from squamous-cell lung carcinoma including hemoptysis, weight loss, and coughing. Moreover, patients with a positive family history of cancer and respiratory diseases exhibit reduced survival time following lobectomy. The 5-year survival rate is comparable between women and men. As regards the prediction of patient survival in cases of squamous-cell lung carcinoma, the relationships should be properly considered.

Article information and declarations

Data availability statement

The data presented in this study are available in this article.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Medical University of Silesia (No PCN/0022/KB/27/21).

Author contributions

Weronika Targosz – data curation, funding acquisition, project administration, supervision.
Julia Świerczek – data curation, funding acquisition, project administration, supervision.
Błażej Ochman – formal analysis, methodology, writing – original draft.
Paweł Kiczmer – data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing—review & editing.
Paweł Ziora – data curation, resources, writing – review & editing.
Mateusz Rydel – resources, software.
Damian Czyżewski – resources, writing – original draft, validation.
Maciej Borowiecki – software.
Bogna Drozdowska – investigation, resources, validation, writing – review & editing.
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Conflict of interest

None declared

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Original article

Cancer epidemiology

Geographical disparities in survival rates for urological cancers in Poland from 2000 to 2015

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Introduction. In 2020 in Poland, urological cancers (testis, prostate, kidney, urinary bladder) accounted for 32% of cancer incidence among men and 5% among women. There has been an improvement in the survival rate for urological cancers in recent years. The aim of this study was to determine whether survival rates for urological cancers differ according to the region in Poland.

Material and methods. Data on 5-year relative survival come from the Polish National Cancer Registry and cover the patients diagnosed during period 2000–2014. The analysis was performed for four locations of urological cancers: prostate (C61), testis (C62), kidney (C64) and bladder (C67). Differences in survival rates are presented on maps divided into 16 voivodships.

Results. In the years 2000–2014, an increase in the 5-year survival rate of patients with urological cancer was recorded in Poland. A similar trend has been observed in other European countries, with the average survival rate of patients with prostate, bladder, kidney, and testicular cancer being lower in Poland than in the EU. We characterise the geographical differences between survival and the sex of the patient. In prostate, bladder, and kidney cancers, the highest survival rate was recorded in the Pomeranian Voivodship, regardless of gender and period.

Conclusions. In most of the analysed voivodships, survival rates for urological cancers increased in subsequent periods. This is proof that health care in Poland is continuously improving. The level of public knowledge in Poland about urological cancers is still low. National-scale educational and preventive campaigns are needed to achieve a greater increase in 5-year survival rates in the coming years.

Key words: urologic neoplasms, survival rate, Poland

Introduction

Regional differences in 5-year survival rates for the most common cancers are observed in most European countries. Among urinary tract cancers, an example is the survival rate for prostate cancer estimated in the Concord-3 project for selected European country regions analyzed for patients diagnosed in 2010–2014, for example France: 85.5% Somme region *vs.* 96.8% Herault region; Germany: 88.1% Bremen region *vs.* 93.9%

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Schleswig-Holstein region or Italy: 78.9% Latina region *vs.* 91.8% Ferrara region [1].

In 2020 in Poland, urological cancers (testis, prostate, kidney, urinary bladder) accounted for 32% of cancer incidence among men and 5% among women. Among men, the most common is prostate cancer. There is a continuing trend in which prostate cancer is the most frequently diagnosed cancer among men (19.6% of all incidences in 2020) [2]. Survival rates for testicular cancer, prostate cancer, kidney cancer, and bladder cancer are growing, as in other countries in Europe. In bladder cancer, the survival rate is higher among women than among men, unlike in Europe [3–6].

Survival studies show that survival rates for urologic cancer have improved in countries with the highest spending on health care [7]. In recent years, there has been an improvement in the survival rate for urological cancers, which may be related to the implementation of new drugs [8], and better health care facilities [9]. The purpose of this study was to determine whether survival rates for urological cancers differ depending on region and sex in Poland.

Material and methods

Data on 5-year relative survival come from the Polish National Cancer Registry [10]. The data cover patients diagnosed during the period 2000–2014 and are presented in three 5-year intervals (2000–2004, 2005–2009, 2010–2014). The Pohar-Perme estimator was used to calculate 5-year survival rates [11]. The analysis was performed for four locations of urological cancers: prostate (C61), testis (C62), kidney (C64) and bladder (C67). Differences in survival rates are presented on maps divided into 16 voivodships (fig. 1). All maps use the same percentage scale that corresponds to the same color. A color gradient was used to represent specific values in particular voivodships. All maps were prepared using Python software with the geopandas library [12]. The predefined Poland map was sourced from Chief Sanitary Inspectorate (Główny Inspektorat Sanitarny – GIS) support [13]. This website shares data from geoportal.gov.pl.

Results

Malignant neoplasm of the prostate (C61)

The 5-year survival rate for Poland was higher in each subsequent follow-up period. In the first observation period (2000–2004), the 5-year survival rate for prostate cancer was 70.6%. In the period (2005–2009) it was 76.6%, and in the last observation period (2010–2014) 81.8%.

During the initial observation period from 2000 to 2004, survival rates ranged between voivodeships from 57.5% to 76.8%. The Pomorskie Voivodeship and the Mazowieckie Voivodeship had the highest 5-year survival rates at 76.8% and 76.4%, respectively. Across all voivodeships, an improvement in the 5-year survival rate was observed at the end of the observation period compared to the initial period. The greatest improvement in the analyzed periods occurred in the Lubuskie Voivodship, with a significant increase of 28 percentage points (pp). Furthermore, this voivodeship was characterized by the highest 5-year survival rates in the final observation period (85.5%).

Malignant neoplasm of the testis (C62)

The 5-year survival rate for testicular cancer for Poland as a country was higher in each subsequent observation period. In subsequent observation periods, it was 85.3%, 86.2%, and 89.5%, respectively.

The 5-year survival rate for testicular cancer by voivodship was characterized by the greatest variability in the observed periods among the cancers analyzed. In the Pomorskie, Lubuskie, Lubelskie, and Opolskie Voivodships, the 5-year survival rate increased in the period 2005–2009 and then decreased in the most recent period. During the entire period, the greatest improvement in 5-year survival was observed in the Kujawsko-Pomorskie Voivodship (changed by 16.9 pp). In the last period, the highest 5-year survival rate was recorded in the Zachodniopomorskie Voivodship (99.4%), the Małopolskie Voivodship (95.2%), and the Podlaskie Voivodship (93.9%). In five voivodships (Łódzkie, Warmińsko-Mazurskie, Mazowieckie, Pomorskie, Lubuskie), the survival rate of the last observation period decreased compared to the initial observation period. The greatest reduction in the 5-year survival rate occurred in the Łódzkie Voivodship (reduction by 12.9 pp).

Malignant neoplasm of the kidney, except for the renal pelvis (C64)

The 5-year survival rate for kidney cancer increased in subsequent observation periods across both sexes. Among women in the first period (2000–2004), it was 59.3%, in the middle period (2005–2009) 65.6%, and in the last period (2010–2014) 70.6%. Among men during the same observation periods, survival rates were 54.3%, 58.8%, and 63.9% in the last period.

Over the years under observation, there was a gradual increase in the 5-year survival rate for kidney cancer among men. The largest increase in the 5-year survival rate occurred in the Pomorskie Voivodship (16.5 pp – 61.2% in the period [2000–2004], 77.7% in the period (2010–2014]). During the 2010–2014 period, the Pomorskie Voivodship also had the highest survival rate for this cancer. In the second period (2005–2009), compared to the first (2000–2004), three voivodships (Dolnośląskie, Opolskie, Lubuskie) showed a slight decline in the survival rate, respectively, 0.7, 1.9 and 2.4 pp. In the Podlaskie Voivodship, in the first two analyzed periods of 5-year survival (2000–2004, 2005–2009), the rates remained at the same level – 58.9%. For the period 2000–2005, the lowest survival rate was in the Zachodniopomorskie Voivodship – 45%. In the last observation period, this rate improved by 10 pp.

For women, a similar phenomenon was observed for this cancer site, and the 5-year survival rate increased with subsequent analyzed periods. The Świętokrzyskie Voivodship showed the greatest increase (by 22.5 pp), reaching 76.2% in the period 2010–2014. But the voivodeship with the highest survival rate in the last period was the Pomorskie Voivodeship – 81%. In the Dolnośląskie Voivodeship, which had the highest survival rate (64.1%) in the first observation period, no improvement was observed in the second observed period. The lowest survival rate in the period 2000–2004 occurred in the Lubuskie Voivodeship (47.7%), but over the following years it improved (by 21.2 pp), and in the last observed period the lowest value of the survival rate was observed in the Zachodniopomorskie Voivodeship (59.8%). Moreover, in Podlaskie and Zachodniopomorskie voivodeships, there were a decline in the survival rate between the periods 2005–2009 and 2010–2014, while in the rest of the voivodeships there was an improvement in this rate.

Malignant neoplasm of the bladder (C67)

The results regarding 5-year survival rates for the entire country increase regardless of gender in the second observation period compared to the first period (among men in the period [2000–2004] 60.4% and in the period [2005–2009] 63.7%; among women in the period [2000–2004] it was 63.1% and in the period [2005–2009] 66.0%). Among men in the third period, it was slightly higher than in the second period (63.3% for the period [2010–2014] compared to 63.1% for the period [2005–2009]). Among women in the last observation period, the 5-year survival rates were lower than in the second observation period (in the period [2005–2009] 66.0% and in the period [2010–2014] 64.9%).

In the last observation period, the 5-year survival rate for bladder cancer for both sexes in the country was similar (63.3% among men and 64.9% among women), but greater disproportions were observed among women depending on the region of Poland. Among both sexes, the highest 5-year survival in the last year of observation were recorded in the following voivodships: Lubelskie, Pomorskie, and Świętokrzyskie. Among men, the highest 5-year survival rates were also observed in the Kujawsko-Pomorskie Voivodship and among women in the Małopolskie and Podkarpackie Voivodships.

For men, the situation worsened in the following 5 voivodeships: Zachodniopomorskie (–9.3 pp, from 60% to 50.7%), Dolnośląskie (–5.7 pp, from 65.3% to 59.6%), Łódzkie (–2.3 pp, from 65.3% to 63%) Śląskie (–1.9 pp, from 60.6% to 58.7%), and Wielkopolskie (–1.7 pp, from 60.6% to 58.9%). The reduction in the 5-year survival rate among women in the last observation period in relation to the first observation period occurred in the six following voivodships: Mazowieckie (–8.1 pp, from 63.8% to 55.7%), Łódzkie (–7.3 pp, from 67.3% to 60%), Dolnośląskie (–6 pp, from 67.9% to 61.9%), Śląskie (–5.6 pp, from 60.9% to 55.3%), Opolskie (–5.5 pp, from 74.1% to 68.6%) and Podlaskie (–3.4 pp, from 66% to 62.6%).

Regardless of gender, the greatest improvement occurred in the Lubuskie Voivodship, 17.6 pp among men (from 43.2% to 60.8%), and 29.3 pp among women (from 36.5% to 65.8%).

Discussion

Survival serves as the most precise indicator of the future of the disease at a specific moment, deriving from data collected on all diagnosed individuals within a defined period and tracking their vital status until the conclusion of the observation period. Cancer mortality rates are crucial for guiding public health and health care priorities. They have proven valuable in recognizing potential distortions in metrics like cancer incidence and survival, such as the risk of overdiagnosis. When coupled with cancer survival data, cancer mortality rates can assess the long-term effectiveness of treatments [14]. The first work on the differentiation of medical care has dissatisfying results. Mortality rates have been observed since the end of the twentieth century, and regional differences within European countries have been observed for many years.

In the period 2000–2014, an increase in the 5-year survival rate of patients with urological cancer was recorded in Poland. A similar trend has been observed in other European countries, with the average survival rate of patients with prostate, bladder, kidney, and testicular cancer being lower in Poland than in the EU. In the CONCORD-3 study for the years 2000–2014, prostate cancer survival rates were higher than in Poland in 23 European countries [1].

The older EUROCARE-5 study for 2000–2007 noted that for testicular cancer, the age-standardized 5-year relative survival (RS) was 93% for patients from Northern Europe, 92% for those from Ireland/UK and from Central Europe, 89% for patients from Southern Europe, and 80% for patients from Eastern Europe. In Poland, the age-standardized 5-year RS was 78.3% [15]. However, for kidney cancer, the best prognosis was observed in Central Europe (64%), particularly in Austria and Germany showing figures ≥70%, and Southern Europe (64%). In Poland, the, age-standardized 5-year RS was 55.1%. For urinary bladder cancer, the best prognosis was observed in Southern and Northern Europe, particularly in Italy and Finland, where survival was ≥75%. In Poland, age-standardized 5-year RS was 61.5% [16].

The lead time is important to assess the survival rate, especially in the case of prostate cancer. Due to the small number of publications on this topic from Europe, we used data from the United States. In prostate cancer, after the introduction of PSA testing, the diagnostic advance is approximately 4.59 years for white people and 6.78 years for black people [17].

In kidney cancer, early stage diagnosis is strongly correlated with survival rates: 5-year cancer-specific survival rates for patients diagnosed with stage I and IV kidney cancer in Europe are 83% and 6%, respectively [18]. In bladder cancer, early detection by cystoscopy or urinary sediment cytology prolongs survival. The relative 5-year survival rates for whites *vs.* blacks are overall 81% *vs.* 58%; for localized disease, 88% *vs.* 74%; for regional disease, 44% *vs.* 30%; for distant disease, 9% *vs.* 8%; and for unknown stage, 61% *vs.* 35% [19].

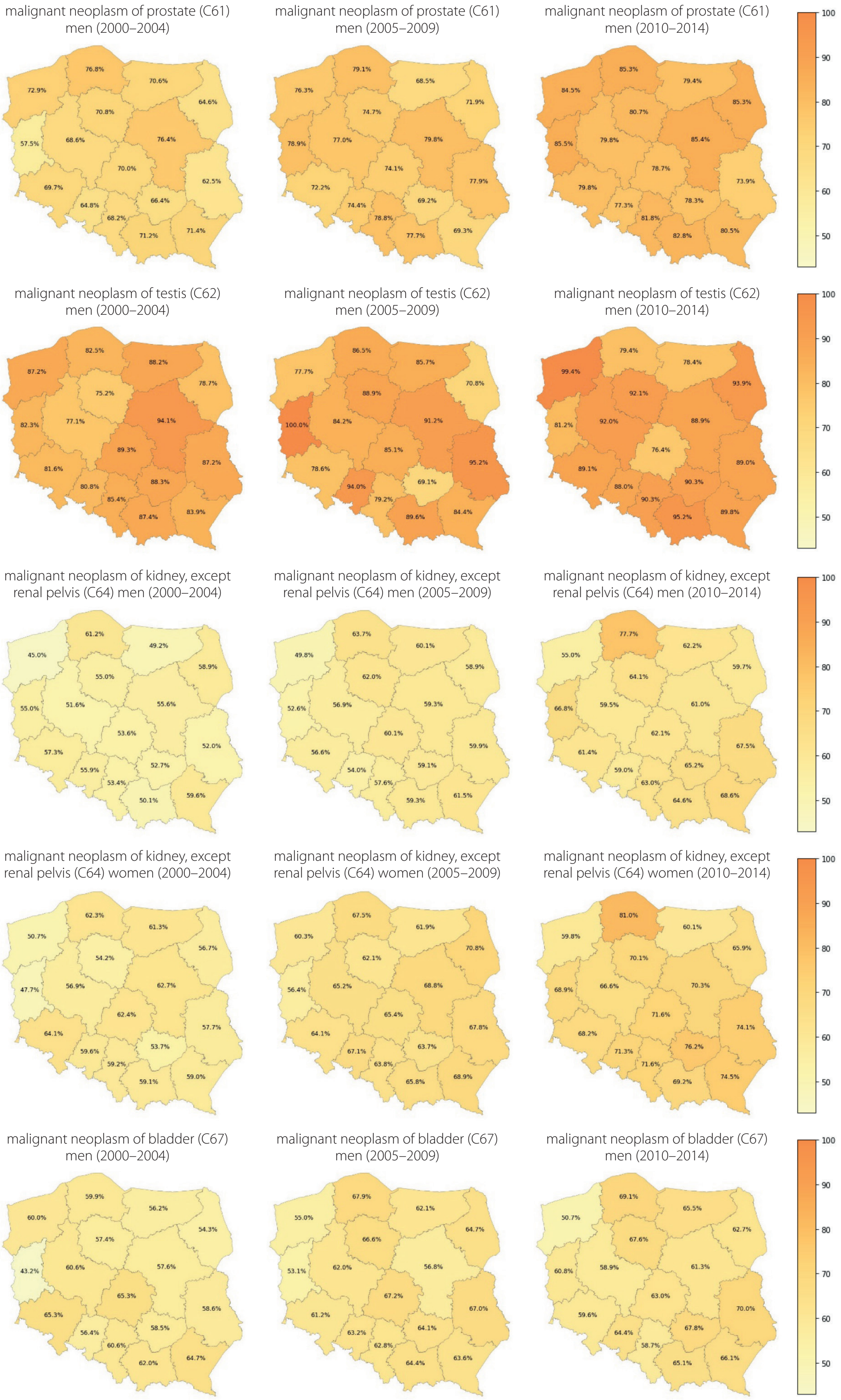

Figure 1. Differences in survival rates – divided into 16 voivodships

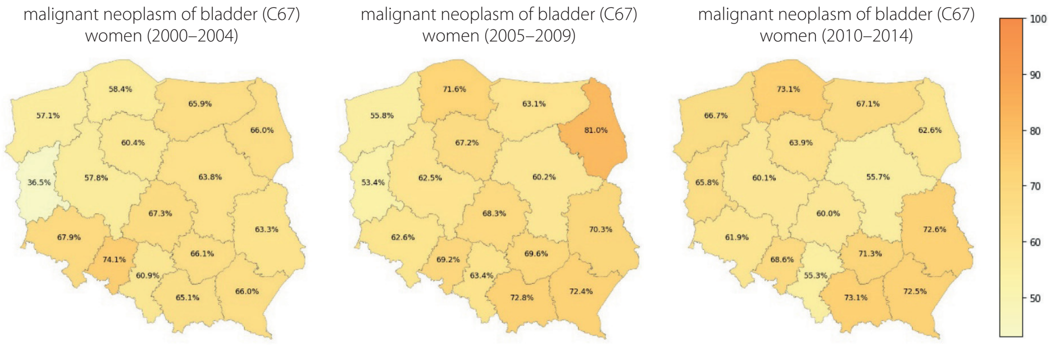

Figure 1 cont. Differences in survival rates – divided into 16 voivodships

The improved survival rate of prostate cancer in Poland can be explained by new treatments that have transformed prostate cancer into a chronic disease. We observe a constant increase in prostate cancer survival rates, due to progress in the treatment of metastatic castration resistant prostate cancer (docetaxel-based chemotherapy (2004), cabazitaxel registration (2010), the introduction of the latest generation of non-steroidal antiandrogen drugs into treatment (abiraterone acetate in 2011, enzalutamide in 2012) [20], and also due to the progress in surgical treatment of prostate cancer (2010 saw the first robot-assisted radical prostatectomy in Poland), the promotion and greater availability of serum PSA concentration determination, and transrectal ultrasound.

In the last period of observation (2010–2014), the highest survival rate was recorded in the Mazowieckie, Pomorskie, Podlaskie, Zachodniopomorskie, and Lubuskie Voivodships, and the lowest in the Lubelskie Voivodships. The phenomenon of highest survival in the Lubuskie Voivodship recorded a high percentage of consultations per 1,000 inhabitants and the highest number of oncology clinics in the country per 10,000. However, no entity meets the criteria of an urooncology center and the criterion of the minimum number of radical prostatectomy procedures.

The same survival rate in the Zachodniopomorskie and Mazowieckie Voivodship. Zachodniopomorskie is characterized by one of the highest percentages of urological consultations per 1,000 inhabitants, and in the Mazowieckie Voivodship we have the largest number of urological clinics in the country, the largest number of physicians working in the field of urology, the largest number of patients of the special drug B.56 program (treatment of patients with prostate cancer with apalutamide, darolutamide, enzalutamide, cabazitaxel, olaparib, radium [Ra-223] dichloride [21]), 6 centers that meet the criterion of the minimum number of radical prostatectomy procedures and one of two centers in Poland that perform robotic surgeries in urology at an expert level [22].

Survival rates in testicular cancer, lower in Poland than in Europe, may be justified by the low level of public knowledge of testicular cancer [23, 24].

Increased survival and decreased mortality in testicular cancer result from the introduction of cisplatin-based chemotherapy for the treatment of non-seminomas in the 1970s. The increase in survival is also due to the greater availability of scrotal ultrasound, the introduction of tumor markers for testicular cancer in diagnostics, and more frequent occurrence of seminomas (they have a better prognosis) than nonseminomas [25].

The greatest reduction in the 5-year survival rate occurred in the Łódź Voivodship by 12.9 pp. The highest survival rate was recorded in the Zachodniopomorskie and Podlaskie Voivodships, and the lowest in the Pomorskie, Łódźkie and Lubuskie Voivodships. The Zachodniopomorskie and Podlaskie Voivodships conduct large-scale preventive campaigns against testicular cancer (they support the Movember campaign, Męskie Zdrowie, Profilaktyka 40Plus, leaflets, educational films for patients, radio broadcasts, campaigns on social networks, teaching self-examination on dummies, etc.) [26, 27].

Survival rates in bladder cancer are lower than in Europe, probably due to the low level of knowledge about bladder cancer [28–30], 15–25% of patients who present in advanced stages of the disease [31], lack of reference centers [32], comprehensive specialist care [32] and long waiting times for radical cystectomy [33]. In bladder cancer, the increase in survival rates is due to intravesical immunostimulation with BCG instillations [34] and intravesical chemotherapy and immunotherapy in patients with locally advanced or metastatic bladder cancer [35]. Progress in surgical treatment did not improve survival rates [36, 37].

In Poland, survival rates among women with bladder cancer are higher than survival rates among men. This situation differs from the trend in Europe. Many studies have shown lower survival rates for women with bladder cancer than for men [3–6]. Among patients with kidney cancer, women also have higher survival rates, although urinary tract infections and nephrolithiasis among women are associated with a delay in the diagnosis of kidney cancer more often than among men [38]. However, this trend does not differ from the European trend. Among women, kidney cancer is detected at an earlier stage than among men, which in patients aged <59 years reduces mortality from renal cell carcinoma (RCC) by 19% compared to men [39].

The survival rate of kidney cancer patients is increasing in both sexes due to more frequent preventive examinations [18], including abdominal ultrasound and CT scans; many kidney cancers are detected accidentally during these examinations [40]. The reasons for increased survival also include modern drugs (molecularly targeted therapy [41], immunotherapy) [42] .

For both sexes, the survival rate is the highest in the Pomorskie Voivodship and the lowest in the Zachodniopomorskie Voivodship. In the Pomorskie Voivodship, in the years 2000–2015, the survival rate of kidney cancer in both sexes remained one of the highest in Poland.

Survival rates for urological cancers are lower in Poland than in other European countries due to a lack of coordination and centralization of services, low level of education, and early diagnosis, and because modern treatment is not reimbursed to the same extent as in Europe. To change this state of affairs, from May 2022, patients with advanced kidney cancer are covered by modern treatment under the special drug program B.10 (treatment of patients with kidney cancer with pembrolizumab [21]). Socioeconomic status influences the degree of advancement of urological cancers, as shown in many studies [43, 44].

In all urological cancers, efforts should be made to centralize surgical treatment, especially in rare cancers, as well as decentralize chemotherapy and radiotherapy and comprehensive specialist care for patients, which can contribute to increased 5-year survival rates in these cancers. It is also necessary to increase the spending on prevention, early diagnosis, and patient education.

Conclusions

Survival rates for patients with urinary tract cancer are lower in Poland than in Europe. In most of the analyzed voivodeships, survival rates for urological cancers increased in subsequent periods. This is proof that health care in Poland is continuously improving. The exception is the decrease in 5-year survival rates in the Łódzkie Voivodship. There is a need to conduct more studies on this phenomenon.

The level of public knowledge in Poland about urological cancers is still low compared to other European countries. National research on this topic should be conducted. Educational and preventive campaigns are also needed nationwide to achieve a greater increase in 5-year survival rates in the coming years.

Primary care physicians play an important role in referring patients with urological cancers to urologists [45]. There is an increasing need for the urologist to work closely with the primary care physician to prevent, identify, and manage urological cancer [46] because recognition and timely referral to primary care are crucial for early diagnosis of the cancer [47].

The limitation of this study is the use of historical data. The latest available 5-year survival analysis originating from the Polish National Cancer Registry covers the period 2010–2014 (end of observation 31.12.2019), i.e., there is a 10-year delay. A strength of the work is that it is the first voivodship analysis for urological cancers, with data coming from the most reliable source of information on cancer in Poland.

Article information and declarations

Data availability statement

Data available on onkologia.org.pl.

Ethics statement

No ethical issues or concerns were applicable to this research.

Author contributions

Klaudia Barańska – performed the analysis; wrote the manuscript with input from all authors.
Marta Miklewska – performed the analysis; wrote the manuscript with input from all authors.
Iwona Wnętrzak – wrote the manuscript with input from all authors.
Urszula Wojciechowska – devised the project, the main conceptual ideas and proof outline.
Joanna A. Didkowska – devised the project, the main conceptual ideas and proof outline.

Conflict of interest

None declared

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Review article

Tumor biology

Interactions between Notch and matrix metalloproteinases: the role in cancer

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Notch has its importance in the development and maintenance of cells and tissues. Either gain or loss of Notch signalling causes a wide range of abnormalities including cancer. To activate Notch signalling, the notch ligand must be processed by the family of proteases, ADAMs. Until recently, exclusively in a cancer context, a class of proteases, matrix metalloproteinases (MMPs) were known to cleave notch and trigger downstream signalling. Notch was found to regulate the expression of matrix metalloproteinases (through crosstalk. Studies have revealed that interactions between Notch and MMPs are associated with aggressive cancer traits such as invasion, metastasis, angiogenesis, and endothelial mesenchymal transition. In this review, we resummarise the studies which reveal the Notch-MMP interactions that have provided new perceptions into the mechanisms behind Notch-mediated aggressiveness in cancers.

Key words: angiogenesis, epithelial mesenchymal transition, invasion, matrix metalloproteinase, non-canonical Notch signalling

Introduction

The notch signalling pathway is a conserved signalling pathway that regulates normal development and maintains homeostasis by regulating cell fate decisions and cellular processes. It has an oncogenic role and tumour suppressor role depending in a cellular context [1]. Notch is activated *via* canonical and noncanonical ways that lead to the expression of the Notch target genes [2]. Inappropriate activation of Notch causes over-accumulation of the Notch intracellular domain (NICD) thereby activating abnormal cellular transformation and resultant morbid cellular traits. Knockdown of Notch or use of γ-secretase inhibitors reverses such caused morbid traits *in vitro* [3–5]. Matrix metalloproteinases (MMPs) can cleave the notch receptor and activate signalling leading to pathologic outcomes [6].

Matrix metalloproteinases (MMPs) are zinc-dependent proteases which have a role in normal tissue development and maintenance through remodelling an extracellular matrix (ECM) [7]. There are about 23 MMPs known in humans and their expression is stimulated *via* PI3/AKT, MAPK, and ERK signalling pathways, with turnover being regulated by endogenous MMP inhibitors, TIMPs [8]. Dysregulation in MMP turnover has a potential effect on tissue homeostasis and cell signalling dynamics [9–12]. Immunohistochemical (IHC) studies on tumour biopsies show that MMPs are critical role players in the breakage of tumour boundaries leading to tumour cell migration [13].

Role of matrix metalloproteinases in cancer

In general, matrix metalloproteinases contribute to cancer processes *via* migration, EMT, metastasis and angiogenesis. During the migration process, the cell-to-cell and cell-to-matrix adhesion has to be disrupted. MMPs can degrade ECM, and shed the adhesion molecules (cadherins and integrins), making them well-suited for the role during invasion

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and metastasis [14, 15]. MMP3 directly cleave the E-cadherin, an adhesion molecule of the epithelial cell. Loss of E-cadherin mediates the epithelial cell to acquire the mesenchymal phenotype [16]. MMP2, MMP9 and MT1-MMP degrade the basal membrane and interstitium and promote angiogenesis. The MMP knockout mice did not exhibit such a phenotype [17]. Clinical trials involving broad-spectrum MMP inhibitors have been unsuccessful so far. Not least, the MMP-specifically targeted therapeutics have their challenges such as MMP sub--type selectivity, metabolic risks and toxicity [18–20].

The canonical Notch cascade

Notch signalling occurs between the two juxtaposed cells or within the same cell caused by the interaction of the Notch receptor to its ligand. There are four Notch receptors Notch1, Notch2, Notch3, and Notch4 and five canonical ligands containing DSL-motif – DLL1, DLL3, DLL4, Jagged1, Jagged2, and many non-canonical ligands that lack the DSL-motif [21]. On the ligand binding to the Notch receptor, the NRR region of the receptor undergoes a conformational change to expose the S2 site for cleavage recognised by ADAM proteases. The NRR region protects the extracellular Notch S2 site from proteases until the NRR site is physically destabilised by the ligand binding and ligand endocytosis [22, 23]. The S2 cleavage typically requires ADAM10 and ADAM17, a disintegrin and metalloproteinase for Notch signalling, whereas Notch1 ligand-independent signalling requires ADAM17 [24]. The S2 cleavage is an important event for the succeeding S3 cleavage by γ-secretase [25]. The S3 cleavage liberates the NICD, translocates to the nucleus, interacts with the DNA binding proteins CSL/RBPJ and MAML to form a ternary complex [26, 27]. The ternary complex binds to DNA at the super-enhancer region and causes the transcription of target genes [28, 29]. Common targets of Notch signalling are transcription factors of the HES family – Hes1, Hes5, and Hes7 and HEY family – Hey1, Hey2, and HeyL that modulate fundamental cellular processes such as proliferation, stem cell maintenance, and differentiation during embryonic and adult development [2, 30].

Non-canonical processing of Notch by specific MMPs

Typically, Notch1 requires consecutive two cleavage steps post Notch ligand-receptor binding: first at the S2 site by ADAM protease ADAM10 or 17, and second at S3 by γ-secretase, which resultantly releases the Notch intracellular domain (NICD). ADAM 10 and ADAM17 have been regarded as canonical S2 proteases for cleavage at the S2 site on the Notch receptor which is regularly implied in normal development and tissue homeostasis *via* regulation of cell fate decisions and cellular processes occurring in drosophila, mice, and humans [25–31]. Many canonical and non-canonical Notch pathway components have been identified; the non-canonical ligands include DLK1, VE-cadherin, stanniocalcin-1 and the non-canonical proteases MMP7, MMP9, and MT1-MMP are mostly involved in pathogenesis [31–35]. Sawey and colleagues in 2008 found that MMP7 (matrilysin, an MMP) processes Notch1 independent of ADAMs which causes N1-NICD to be released and translocated to the nucleus [6]. On topical addition of recombinant MMP7 to COS-7 cells that are expressing Notch1 with C-terminal V5 tag underwent Notch activation including γ-secretase cleavage, NICD nuclear translocation, and resultant expression of Notch target genes. Moreover, the immunoblots of the Notch-V5 tag showed that cleavage of the Notch extracellular domain particularly occurred at the S2 site [36]. MMP7 is prevalently overexpressed in advanced cancers, with poor overall survival of patients, and is regarded as a prognostic biomarker in invasive and recurrent cancers [37–39]. MMP7 expression is controlled by PI3-K/AKT and/or ERK signalling *via* NF-κB transcription factor, and its loss of control is indicated in pathogenicity [40]. Similarly, like MMP7, the membrane-bound MT1-MMP (MMP14) can activate Notch by processing it independently of ADAMs (fig. 1). Changes in MT1-MMP expression affect the Notch signalling in melanoma cells. In the experiments, MT1-MMP processes the Notch1 actively in a Jagged1 ligand-dependent or independent manner. Moreover, when the full-length MT1-MMP was expressed in WM266-4 melanoma cells, it cleaved the Notch1. In the same experiment, the Notch processing intensity correlated to the expression of MT1-MMP. The resultant stimulation of the Notch target gene, HES, was confirmed by HES-reporter assay and gene expression analysis [41]. Non-canonical Notch processing by MT1-MMP not only affects cancer in the individuals but immunity too. It acts as a switch in normal B cell development in the bone marrow. Ectopic MT1-MMP cleaves the Notch ligand Delta-like 1 (DLL1) in bone marrow stem cells and thereby diminishes the Notch signalling by switching the B cell development [42].

Notch-MMP interactions: implications

Generally, MMPs are expressed at low levels in tissues, and their expression is induced by stimuli when required for ECM remodelling [11]. Matrix metalloproteinase expression demands multilevel regulation of various stimulating factors such as cell-ECM interactions, cell-cell interactions, ECM stimulation and other cellular environmental factors such as pH, ROS, cellular endopeptidases, lipid peroxidation, hyperglycemic, hypoxia, etc. [9]. MMP expression regulation may involve transcriptional regulatory elements, epigenetic regulation, post-transcriptional regulation, or different regulation occurring due to disease conditions involving gene mutations and promoter polymorphisms in MMP [43]. These external stimuli lead to downstream cell signalling; MMP turnovers are majorly regulated by protein kinases PKA, PKB/AKT, and PKC/MAPKs (JNKs, ERKs, and P38) signalling pathways [44]. Downstream of these signalling pathways, there are cell-type specific transcription factors-NF-κB, AP-1 subunits C-jun/C-fos, PEA3, ETS, and STAT that have binding sites on the promoters of specific MMPs. Moreover,

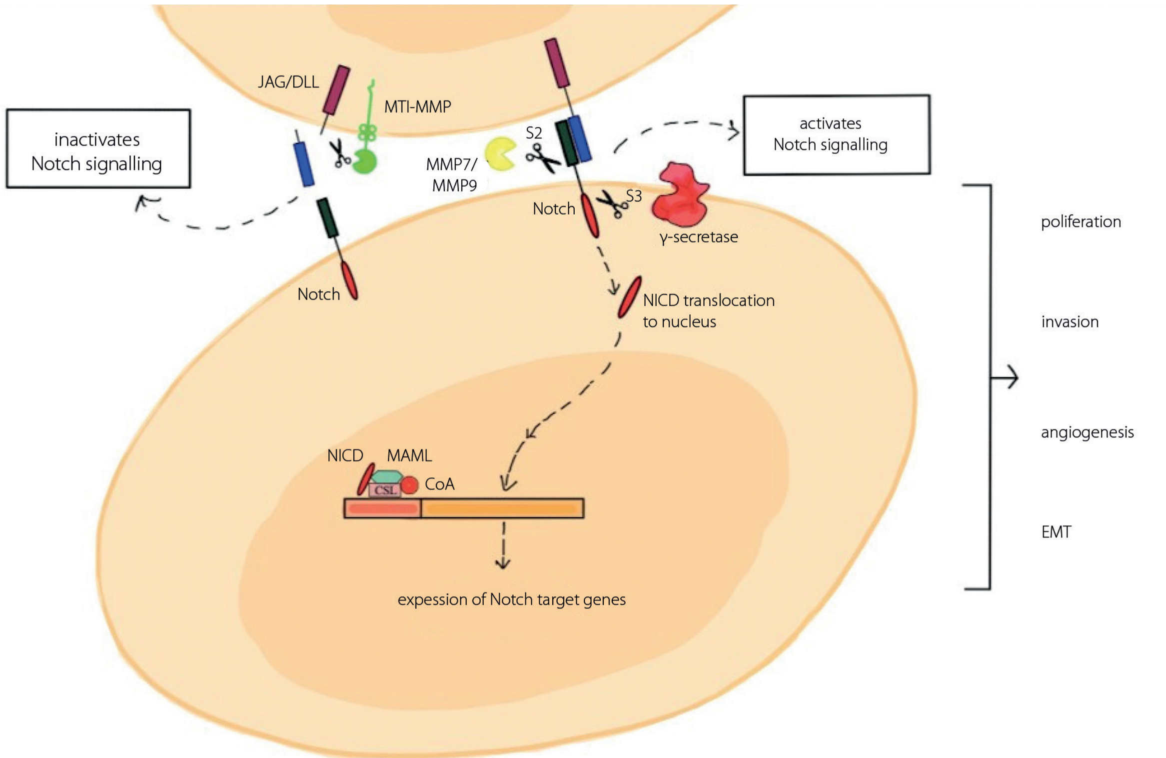

Figure 1. A diagram of the non-canonical Notch signalling pathway. This schematic shows a simplified overview of the main components of MMP-activated Notch signalling. Upon Notch ligand binding, a two-step proteolysis cleavage process i.e. S2 (small scissors within the juxtamembrane region, and the transmembrane domain of the Notch receptor is catalysed by members of the metalloproteases (MMP) family and the γ-secretase containing complex i.e. S3, respectively, then the Notch intracellular domain (NICD) is released from the membrane and translocates to the nucleus, where it forms a transcriptional activation complex with CSL and coactivators (CoA), thereby inducing the transcription of target genes causing proliferation, invasion, angiogenesis, and EMT in cancer

these transcription factors either upregulate or downregulate the expression of MMPs. Functional collaboration of more than one transcription factor may be required to regulate the gene--specific MMP expression. For example, regulatory interactions between AP-1 and cis-acting ETS elements on the MMP1 promoter are required to induce its expression [45].

Notch-NF-κB-MMP axis: invasion and migration

The notch signalling pathway critically participates in cell proliferation, apoptosis, cell invasion, and metastasis; studies show that notch pathway members are overexpressed [46–48]. Notch inhibition by downregulating Notch1 decreased invasion in prostate cancer [49]. The proliferation and invasion of cancer cells require remodelling of the extracellular matrix surrounding it through the action of MMPs. Studies show Notch controls the expression of ECM component-specific matrix metalloproteinases to bring about the rearrangements in the tumour environment through cross-talks with the NF-κB pathway [50–52]. NF-κB expression is driven by Notch. Also, the ectopic feeding of NICD, usually the nuclear-translocated part of Notch to the breast cancer cells, causes the cells to lose cell to cell adhesion and promotes migration and invasion [51, 53]. Notch1 is an upstream regulator of the NF-κB pathway where Notch1 and Notch3 induce transcription of NF-κB and its various subunits [54], moreover, NICD1 and NF-κB interaction leads to its NF-κB retention in the nucleus and enhances binding to the promoter of its target MMP genes [55, 56] (fig. 2). However, it is not clear whether in addition to retention of NF-κB, NICD1 and NF-κB complexed together is required for its transcriptional activity. That said, Notch1 downregulation leads to inhibition of NF-κB binding activity thereby inhibiting the expression of MMPs [53, 57]. NF-κB has a binding site on promoters of MMP1, MMP2, MMP7, and MMP9 to drive their expression [43, 52, 58]. Apart from MMPs, NF-κB drives the activity of cell adhesion molecules of ICAM, VCAM-1, and ECAM-1 which are essential for the cell migration process [59, 60].

Notch-VEGF and MMP axis: angiogenesis

Studies at the molecular level enable us to understand that Notch plays a pivotal role in sprouting angiogenesis; it maintains the functional integrity of leading apical endothelial cells and growing basal cells. Particularly, the VEGF--Notch axis allows the extravasation of MMPs that degrade the basal membrane and facilitate angiogenic sprouting. In the process, the apical endothelial cell (EC) maintains low--notch signalling and high VEGFR2 expression to preserve the sprouting phenotype. VEGFR2 helps the apical cell to migrate towards the VEGF-transmitting angiogenic centre.

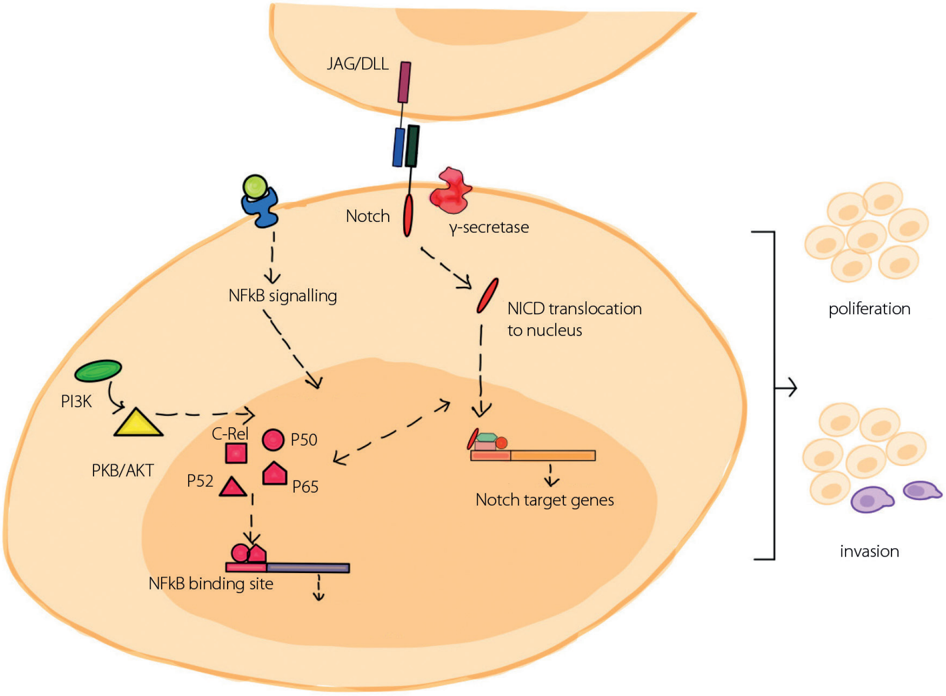

Figure 2. Schematic illustration of Notch signalling pathway to regulate MMP gene expression. This model summarises, through a literature survey, that Notch activation promotes malignant features such as proliferation and invasion in cancer *via* cross-talking the NF-κB signal pathway

It promotes the expression of MT1-MMP, MMP2 and MMP9 which are prime members that bring about the ECM remodelling for apical cell sprouting and migration. On the other hand, the basal EC maintains high Notch signalling, low VEGFR2, high VEGFR1, and low MMP expression to preserve the non-sprouting phenotype in the basal EC [61–63]. Thus, the positive and negative crosstalks between VEGF-Notch in the apical and basal endothelial cells regulate the expression of MMPs to preserve their functional integrity and promote sprouting angiogenesis (fig. 3).

Notch-HEY-MMP axis: epithelial to mesenchymal transition

Epithelial mesenchymal transition is the most aggressive trait in cancers. Epithelial cells acquire mesenchymal phenotype by undergoing remarkable changes. In the transition process, it loses various epithelial markers and gains mesenchymal markers. The loss of epithelial markers such as E-cadherin, γ-catenin, actin cytoskeleton organisation and the gain of vimentin, fibronectin, fibrillar collagen, N-cadherin, and the increased activity of MMPs (MMP2, MMP2, MMP9). The EMT is a complex process triggered by signalling molecules, proteases, and growth factors (fibroblast growth factor [FGF], platelet-derived growth factor [PDGF], transforming growth factor-β [TGF-β]) that trigger the downstream signalling such as TGF-β, Hedgehog, NF-κB and Notch signalling which involves crosstalks that lead to dynamic changes in the phenotype of the epithelial

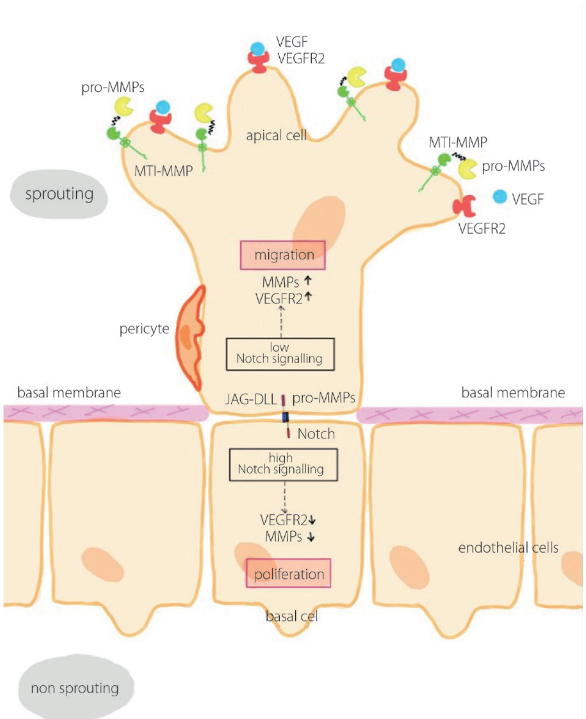

Figure 3. Schematic model of VEGF-Notch and MMP axis in vascular endothelial cell (EC) differentiation. In endothelial tip cells, Low-notch signalling *via* Notch1-DLL4 induces high levels of VEGFR2 and MMPs to promote migration towards the angiogenic centre. In endothelial basal cells, high levels of Notch signalling *via* Notch1-DLL4 suppresses differentiation toward an apical cell phenotype by inducing low expression of VEGFR2 and MMPs

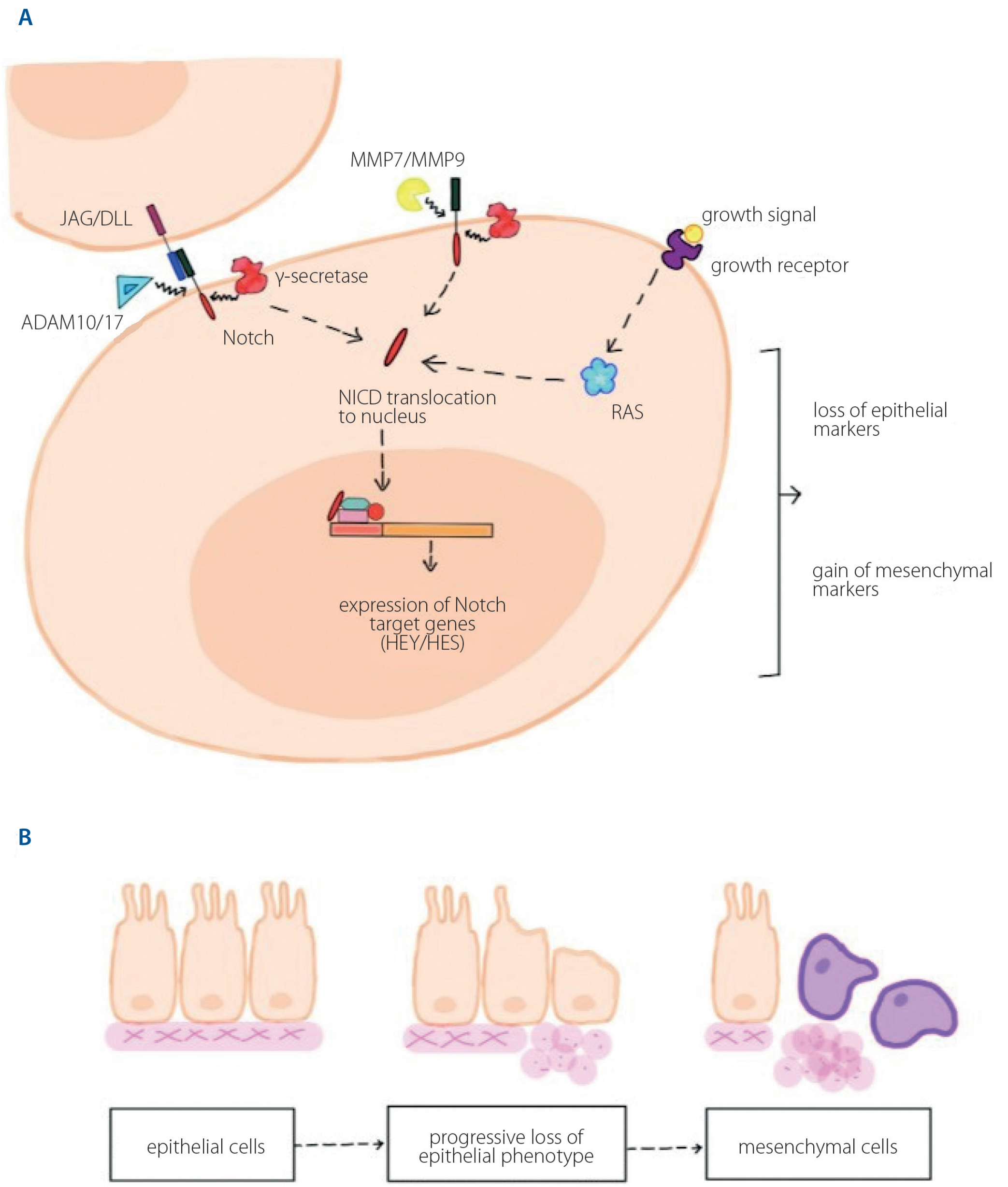

Figure 4. Notch-mediated epithelial-mesenchymal transition (EMT) cross-talk during carcinogenesis: **A.** The above diagram summarises the probable cross-talks between three ways that could drive EMT during carcinogenesis; viz., the canonical Notch signalling, the MMP-Notch-HEY/HES axis and the Growth Factor stimulation that induces notch signalling and translocation of NICD to the nucleus, where it forms a transcriptional activation complex with CSL and coactivators (CoA), thereby inducing the transcription of target genes HES/HEY. HES/HEY expression causes loss of epithelial markers and gain of mesenchymal markers in the epithelial cells leading to EMT. **B.** The EMT process primarily involves progressive loss of epithelial markers and gain of mesenchymal markers. Once the cells acquire a mesenchymal phenotype, they first intravasate and later extravasate from the blood vessel to establish a distant metastasis

cell [64] (fig. 4). Reports verify that down-regulating Notch signalling inhibits EMT by downregulating MMPs [65, 66]. The Notch target gene, HEY1, controls the expression of MMPs in salivary adenoid cystic carcinoma, on knockdown of HEY1 it suppressed the expression of MMP1, MMP2, MMP3, MMP9, MMP11, and MMP13 which may be involved in driving EMT [30, 67]. Similarly, numerous reports mention MMPs (MMP7, MMP9) having a role in triggering Notch signalling that leads to the induction of the EMT trait [36, 68] (fig. 4).

Conclusions and future perspective

MMP-mediated non-canonical Notch signalling and the involvement of Notch in the regulation of MMPs is associated with aggressive outcome in cancer (tab. I). Though, the MMP expression is majorly driven by NF-κB, MAPK, AKT signalling pathways and TIMPs are regulators of MMPs, it cannot be disregarded that under high Notch signalling, the NICD plays a primary role in retaining NF-κB subunits in the nucleus, which leads to uncontrolled expression of target MMPs.

Table I. Summary of Notch and matrix metalloproteinase interactions in human and mouse cancer models and associated functional phenotypes of those interactions

Matrix metalloproteinase	Axis	Phenotype	Type of cancer	Study model	Reference
MMP2, MMP9	Notch- PI3K/AKT/mTOR-MMP	invasion	bladder cancer	UMUC3 cell line	[71]
MMP2, MMP9	Notch-EMMPRIN-NF-κB/MMP	migration, invasion	human breast adenocarcinoma	MDA-MB-231 cell line	[72]
MMP2, MMP9	Notch-PI3/AKT-NF-κB-MMP	invasion, metastasis, angiogenesis	human breast adenocarcinoma	MDA-MB-231 cell line	[51, 53]
MMP9	Notch-NF-κB/uPA-MMP	invasion, metastasis	non-small-cell lung cancer	A549 and H1299 cell lines	[52]
MMP9	Notch-NF-κB/MMP	invasion	pancreatic cancer	BxPC-3 cell line	[64]
MMP9	Notch-NF-κB/MMP	cell growth, migration, invasion and induction of apoptosis	prostate cancer	PC-3, DU145, LNCaP, and C4-2B cell lines	[65]
MT1-MMP (MMP14)	MMP-Notch	cell growth and proliferation	melanoma cancer	WM115 and WM266-4 primary and metastatic cell lines	[41]
MT1-MMP	Notch-MMP	invasion, EMT	Kaposi sarcoma	lymphatic endothelial cell line	[68]
MMP9	Notch-NF-κB/MMP	invasion, angiogenesis	breast cancer	MDA-MB-231, MCF-7, SKBR-3 and T47D cell lines	[57]
MMP9	Notch-AKT-MMP	migration, metastasis, EMT	gastric cancer	SGC7901 and AGS cell lines; BALB/c mice	[66]
MMP7	Hey1-Notch1	self renewal, EMT, metastasis	salivary adenoid cystic carcinoma	SACC-LM cell line	[67]
MMP7	MMP-Notch1	EMT	pancreatic ductal adenocarcinoma	human primary acinar cell line and C57BL/6J mice	[36]

MMP – matrix metalloproteinase; EMT – epithelial-mesenchymal transition

Notch inhibition alone may not be enough; the negative outcomes of Notch inhibition have been reported in clinical studies which cannot be disregarded, firstly, Notch is a conserved pathway required for normal cell development and homeostasis of tissues by maintaining proliferation and apoptosis balance; due to, low notch activity under Notch inhibitors, the cells may acquire sprouting phenotype leading to angiogenesis. Moreover, several Notch inhibitors under clinical trials have exhibited adverse effects including gastrointestinal issues, infections, skin cancer-related problems, and tumour recurrence [69, 70].

The Notch-MMP axes play important roles in tumour processes like proliferation, migration, EMT, metastasis, and angiogenesis. It has come to our notice that these interactions are lethal impart aggressiveness and have added poorer prognoses to various cancers including those of the brain, breast, and pancreas. Understanding and targeting Notch-MMP interactions may be required to tailor target-specific drugs and combinational therapeutic approaches.

Article information and declarations

Author contributions

Jeeja Hernole – study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation, review and approval of the final version of the manuscript. Rajeswari Narayanappa – study conception and design, analysis and interpretation of results, draft manuscript preparation, review and approval of the final version of the manuscript.

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Conflict of interest

None declared

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Review article

Radiotherapy

Once upon a time in oncology: will we ever win the war against cancer? Critical review of the progresses in cancer therapies

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The aim of the present review of various classic and novel therapeutic strategies in oncology is critical discussion of its efficacy to answer the question: is it realistic and even possible to win the war against cancer. Although technological progress in radiotherapy (RT) has led to the development of many sophisticated 3D, 4D techniques, the use of RT as a sole modality has become more and more limited to the tumors in the early stage of disease, in favor of combined surgery-RT-chemotherapy (CHT) therapies. Nevertheless, patients' curability has never reached a level higher than 95% (stereotactic hypofractionated RT – limited to small tumors only). The CHT for solid malignant tumors is not effective enough, and therefore it is mainly combined with surgery and RT as a method of the boost. Common use of partial or complete regression (PR, CR) as end-points of its efficacy is irrelevant, since it is quasi-quantified tumor cell clearance but not cell kill effects, and the regrowth delay (the time the tumor takes to regrow to the size [volume] at the beginning of therapy) is the only proper end-point. The efficacy of various genetic, molecular, immuno, and antiangiogenic modalities tested in many clinical studies is critically discussed, and it has generally showed some therapeutic benefits, but somewhat unspectacular. It has been well documented that genotypes and phenotypes of the tumors (even within the same location, stage, and histology) are individually highly heterogeneous. Therefore, the term "average probability" referred to individual patients becomes meaningless, and moreover, this term has never been replaced by "certainty" yet. Statistics of many studies and trials consist of various pitfalls and biases. Thus, although we and our patients are more often winners on the individual battlefields, the winning, of the whole war against cancer seems to be possible (hope), but not for sure (real).

Key words: malignant solid tumors, efficacy of various therapeutic modalities, probability *vs.* certainty, statistical pitfalls and biases

The first thought which crosses one's mind as one tries to answer the title question might be "never say never", but "once upon a time" would sound more promising. A plethora of studies in many fields of oncology, genetics, molecular biology and tumor immunology have gathered large swathes of results and comments, which although looking promising, do not necessarily encourage. Therefore, to work out the dilemma whether one can win or not, one needs to consider and discuss

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the results and achievements of various classic, recent and novel therapeutic modalities used or tested in the realm of oncology.

Innovations in radiotherapy – physics but not only

Technological progress in radiotherapy has brought to the market a wide sort of high-tech accelerators emitting high energy photons, electrons, protons and particle beams, which have been used to develop a precise 3, 4D conformal IMRT, IGRT, IART techniques. Sophisticated algorithms optimizing dose distribution to maximize therapeutic differences between tumor and normal tissue responses have arrived to daily practice, based on an interplay of physics, biology, and clinical oncology [1–11]. It may look like the promise of a new era in radiotherapy. However, sometimes it remains as a promise only, although the RT offers a wide range of treatment time and dose intensity. Expectations of the outcome improvement are immutably based on the simple assumption (or even belief) that the tumor appearing on the CT/MRI images is limited to its bounds, which is often not true at all.

The RT seems to be an attractive offer, because it often claims a success, but it remains unclear what that "success" actually refers to: permanent curability or to local tumor control only. Withers [10], Le [11] and Glatstein [17] have warned that 3D conformal RT techniques result in a heterogeneous dose distribution, which hides discrepancy between physical and biological doses, and the risk of "overconformality". Some tumors with an indolent proliferation activity, such as prostate cancer, chordomas, meningiomas, acoustic neuromas, and some normal tissues as well, are highly sensitive to change in the dose per fraction, expressed by a low α/β ratio. For a long time, we have been convinced fans of the α/β concept. However, with the passing of time, some uncertainty has been steadily growing, suggesting that tumor and surrounding normal tissues consist of various cellular structures, as blood vessels and its epithelium, hypoxic cellular microlesions, muscles, nerves, etc., which respective α/β values differ, and therefore, an average α/β may also differ as well. Therefore, it is unknown, whether alpha, beta or perhaps even gamma value is correct [18], which can result in misleading conclusions and results. In fact, the α/β formalism is rather incidentally used in the daily RT planning.

The great leap forward in RT equipment and techniques is not supported by long-term local cure benefits, which turns out to be lower than expected. In the past, the results of a large number of the trials on altered fractionation was rather disappointing lesson, with an average 6% tumor control benefit [12–15]. Patients with generally poor prognosis are candidates to studies on new RT strategies. The question is whether objective evaluation of 3D IMRT, IGRT, IART efficacy has ever been done or not [18, 19]. There are obviously no convincing results regarding lung cancer [16–19], and some other advanced cancers, irrespective of any theoretical rationale for potential benefits.

Patients expected to live long (e.g., breast or pediatric cancers, etc.) may manifest some unforeseen morbidities that have not yet been precisely reported. Before the start of therapy, prediction of the events, (tumor control, late side effect) has in the past been based on the gathered incidences of such events, but it has never been judged whether a specific event will occur for sure, or not. There is true inconsistency between tumor control probability (TCP), expected before the treatment, and local tumor control (LTC), which is achieved as the result of therapy. The TCP or the risk of complication (NTCP) is the frequency of the event which may occur, and it is considered as a numerical mapping of the degree to which we believe the event will occur. Therefore, "Is this a game of chance?" – "No, it is the way we play it" (W.C. Fields in 36).

Radio-biological principles are rather rarely accounted for in RT planning. Assumption TCP, of let's say 99% (TCP = $e^{-0.01}$), suggests that 10 of 1000 patients, or 100 of 10,000 patients will fail, that means RT local curability is not universal. In the case of the SHRT, an LTC of 85–95% can be achieved using single dose or a few high fractions, but for small tumors only. On the other hand, using the 3D IMRT, IGRT, IART techniques, even a small "cold spot" within the PTV (overconformality), often missed during evaluation of the DVHs, can lead to a significant decrease in the TCP, and therefore, in the LTC as well. Heraclitus' sentence "you can't step in the same river twice" – means for RT, that the same tumor should not be irradiated twice, and reirradiation is seldom used and rarely effectively. The simple reason is that the planned reirradiation dose is inexplicably but commonly lower (40–50 Gy) than the curative one, although regrowing tumor cells proliferate much faster than native cancer cells, and therefore a recurrent tumor logically needs a higher radical dose than primarily delivered.

RT and surgery as local therapeutic modalities are directed to where the tumor exists, and the theoretical aim is complete elimination of clonogenic cancer cells, proliferating unlimitedly, which can theoretically lead to a cure for the patient. However, it remains unknown whether and how many microcolonies of cancer cells are beyond surgical or irradiated margins, and where they really are. Clinical situations, where RT or surgery is used alone, have been significantly reduced, replaced by pre- or post-operative radiotherapy, and/or chemotherapy. Such combinations of two or three modalities have been found to be successful for head and neck cancer, but not necessarily for lung or rectal cancers [20–23].

Till the mid 80s, various treatment modalities offered for locally advanced cancers were mainly palliative options. Then, reconstructive surgery initiated in the US in the 1980s, later in western European countries, and around 2000 in Poland, made a breakthrough in the treatment of these tumors, mainly H&N, sarcomas and childhood solid malignancies. But that method is limited to individually selected patients. Although the overall therapeutic benefit increased somewhat, it was not significant.

The major failure of many tumors is almost the same – distant metastases, which can subclinically be present even at the time of treatment or likely for some time before [21, 24]. It remains unknown how effective numerical eradication of clonogenic cancer cells is, being below the level of its clinical detection. If a few cancer cells survive, they will be the source of local recurrence for sure, and in the case of cell mutations, also the source of metastatic lesions. In the case of ovarian cancer, distant metastases are a major cause of failure, since the cancer cells spread over the whole abdominal cavity, and they grow intensively and reveal clinically as advanced disease. Thus, surgery is usually limited to palliative cytoreduction, followed by chemotherapy. There is no room for RT, although in the 60s some attempts were made, using the "moving strips" technique. However, that method was abandoned, because the strips overlapped and resulted in serious acute intestinal and bone marrow complications.

Among a long list of malignancies, glioblastoma multiforme is unique. Although surgery and/or RT, with or without temodal, are used with radical intent, neither long-term LTC nor DFS have ever been achieved and reported, and the OS is also very short. The enigma of this malignancy is that even if the gross tumor mass disappears as a result of local therapy, malignant glioma cells already circulate in the brain blood vessels network, controlled by the feedback regulatory system of the hypoxic and angiogenetic processes, which mutually activate each other.

Distant metastases are not the only attribute of advanced tumors. Even in the case of early stages of the cancer (e.g. breast cancer), distant metastases (DM) may occur early within the first 18 months of follow-up, with the rate of 8–23%, as was reported by Kryj et al. [26], suggesting that distant metastases can already be present at the time of surgery. Thomlinson [25] rightly pointed out, that breast cancer should be considered a systemic disease, and cytotoxic chemotherapy should be the modality used at the beginning of therapy. Therefore, it should not surprise, that in contrast to high-tech innovations, the use of RT as a sole treatment has been more and more limited in favor of combined therapies whose sequences are individually tailored, and defined as theragnostic oncology.

The power of chemotherapy – sequential or concurrent

Chemotherapy (CHT) acts within and out of the tumor bounds. In general, the candidates for that form of therapy are advanced tumors with a pronounced risk of dissemination. When cytotoxic agents are injected intravenously, there is however, no further control and a lack of knowledge about their destination. Therefore, the principal cause of CHT failure is inadequate delivery of the drug to some parts of the tumor because of poor local blood flow, which in clinical situations can sometimes only be deduced, but not measured. However, this is not the only reason.

Thomlinson [24, 25] designed and carried out a milestone study, which included 62,000 measurements of tumor volumes made in 239 breast cancer patients, treated with RT or CHT, producing 748 tumor regression curves. The Achilles' heel of the CHT is that multiagent cycles are spaced out by 1–3 weeks, to overcome epithelial and lymphopenia side effects, and to limit its severity to the level of patient tolerance. Making frequent measurements of tumor size (volume) of the breast cancers, Thomlinson [24] noted that tumors partly regress directly after each cycle of the CHT, and regrow later in a cyclic manner during sparing breaks between cycles (fig. 1C). This universal pattern was termed as "Jeffs phenomenon". It clearly shows that, although the intensity of the acute side effects decreases during breaks between the CHT cycles, clonogenic tumor cells do not sleep and wait, but repopulate pretty fast, resulting in tumor regrowth. Therefore, the resultant average tumor regression curve is much shallower than that noted directly after each single cycle. After surgery or RT, tumor deceleration is much deeper (fig. 1A and B), than after CHT, but the final number of surviving tumor cells also remains unknown. When the average number of surviving tumor cells would be equal to 0.001, then the LTC will raise to 99.9% (unrealistic). It means that 10 of 10,000 patients may fail after treatment, and, in fact, 100% cancer curability can never be predicted and achieved, since the cell survival rate is the result of random cell killing, and decreases asymptotically with no chance to reach zero.

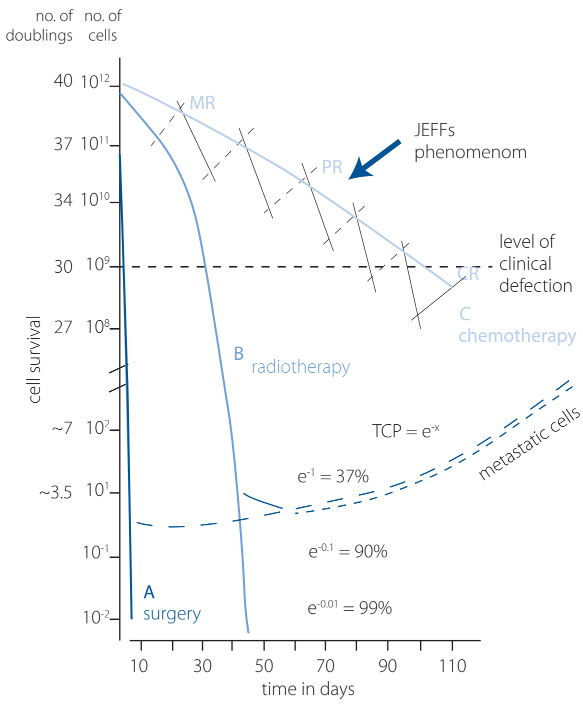

Figure 1. Theoretical tumor cell survival curves after: A – surgery; B – radiotherapy; C – chemotherapy. MR – minimal response; PR – partial regression; CR – complete regression; x – average number of survived cells. CHT curves-reprinted from Thomlinson [24]

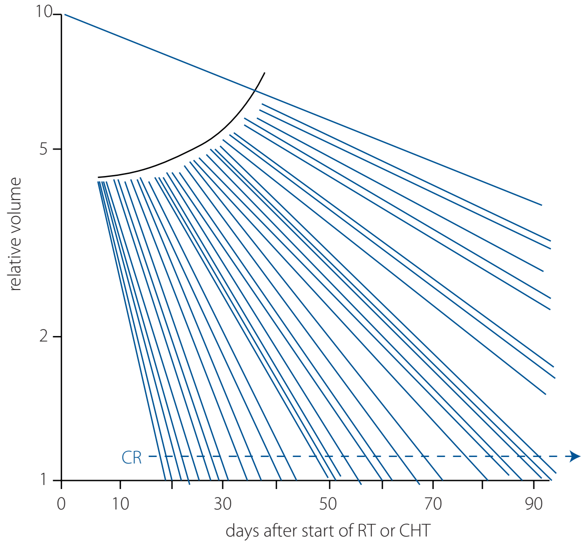

Figure 2. Spectrum of regression rate of breast cancers after delivery of a same and constant dose of the RT or CHT, estimated by Thomlinson [24, 25]

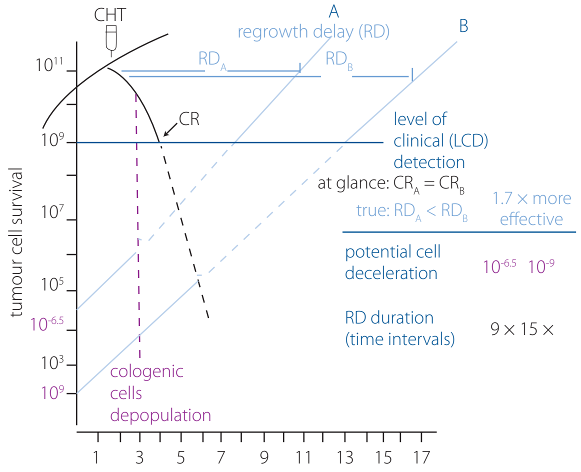

Figure 3. Scheme illustrating how to measure "regrowth delay" as the only quantitative end-point of CHT efficacy. Extrapolation of the tumor regrowth curves (dotted blue lines) back to the cell survival coordinate allows for an estimation of the approximate decrease in the cell kill effect of a given CHT

Tumor gets smaller (regression) during and after therapy, only when dead clonogenic cells are removed out of the tumor. Thomlinson [24, 25] clearly documented that the regression rate of the same tumor type varies individually, and its spectrum is about 50-fold wide after an identical and constant dose of RT or CHT (fig. 2). There are three formal, clinical end-points to quantify the CHT efficacy in the clinic, i.e. Minimal response (who knows what it quantitively means?), partial regression and complete regression (fig. 1C). This is astounding, that for more than 5 decades, the PR and CR have been persistently used in practice, despite the fact that they are clinically irrelevant and it makes no adds, since they mark the removal of already dead cells by various heterolytic processes only, resulting in the decrease of tumor doublings from about 35–36 (e.g. 3.5–4 cm tumor diameter) to 29–30 (0.5 cm^3 tumor), which is still not enough to achieve the local tumor control. Therefore, the PR and CR with no doubts, do not quantify the CHT cell kill effect. A long time ago, it was clearly pointed out that the only proper quantitative end-point for the CHT effect is the regrowth delay (RD), which measures the time period during which recurrent tumors regrow to the size (volume) at the start of the CHT (fig. 3). In the case of long-term LTC, the RD achieved infinity.

The CHT used as a sole modality to treat solid malignant tumors is not radical, curative therapy, except leukemias and some lymphomas. Therefore, it has often been used as neo- or adjuvant tools. However, metaanalysis of the CHT combined with RT [27] revealed only an average 2% therapeutic benefit after neo- or adjuvant CHT (the result seems to be within the range of statistical error). Concurrent chemo-radiation produces a bit higher LTC gain of about 6% [28]. Such, an average benefit looks suspectedly too low. Therefore, to check that results, we reviewed 15 well documented studies on concurrent RT-CHT (cisplatin, 5-Fu or paclitaxel) carried-out in world-leading cancer centers (3300 H&N cancers). The 3-year LTC has been higher by about 20% [11–26%] than the RT alone. So, previous metaanalysis results recommended as an "evidence" guide seem at least doubtful. A large number of studies suggest that surgery (fig. 1A) and radiotherapy (fig. 1B) have possible but not certain curative power (100% LTC has never been achieved), but not the CHT (fig. 1C). So, we can win some individual battles with cancer, but are not yet in a position to win the whole war.

Genetic and molecular tumor biology and therapeutic perspectives – belief on, or not

During the last 3–4 decades, enormous amount of data has been gathered regarding genomics, proteomics, radiomics and tumor biology [29–31]. Growing recognition of the heterogeneity of genotypes and phenotypes of tumor cells, tumor suppressor genes and intra-cellular multisignaling pathways has led to the initiation of many attempts to develop and test in practice various specific antibodies, which could modify and enhance the therapeutic power of classic treatment modalities. One of the most interesting approaches is targeting the signaling axes of cancer stem cells (CSC) alone or in combination with CHT and/or RT. It has been proven that the survival of even one CSC leads to recurrence for sure. Actually, the combination of CHT with CSC inhibitor GDC-0449 has been tested for the advanced, primary or recurrent small-cell lung cancer. In the case of melanoma, the use of immune check-point inhibitors targeting cytotoxic T-lymphocyte-associated protein CTL4 has clinically promising. Preclinical studies on TGF-β1-neutralizing antibodies have offered an interesting strategy to prevent radiation induced fibrosis. Some experimental studies have shown that the VEGFR2 blocking antibody may decrease the dose of fractionated radiotherapy. By contrast to the fear of destruction of tumor vasculature by antiangiogenic therapy, some studies have shown the normalization of tumor vasculature in various pilot clinical studies on HER2-negative breast cancer, NSCLC, rectal, hepatocellular, ovary cancers and glioblastoma multiforme. Regarding the last malignancy, a concept has developed that a block of more than one cellular receptors could be more efficient, and pilot the US study on anti-VEGFR2 together with anti-EGFR were combined with the RT. The results were highly disappointing, with no therapeutic benefit, but with a high rate, over 50% of brain lethal necrosis. It may likely suggest that the use of more than one antibody is too much to be tolerated by patients.

Many studies focused on antiangiogenic therapy (fig. 4), have finally shown a surprisingly short and disappointing extension of progression-free survival, by only 1.2–6 months, in addition to very low improvements in overall survival (by 1.4–4.7 months), achieved only for the selected patients [29], although many pilot and randomized studies documented the feasibility and reliability of molecular modifiers combined with CHT-RT for different malignant tumors [30–34]. Similarly, quests of validity molecular predictors [34] have shown that some of them correlate with higher LTC or even DFS. However, it has to be pointed out that an interpretation of the correlation's power may differ, and the correlation coefficient of r = 1.0 only, defines a strong and absolute "predictor-effect" relationship, whereas in many relevant studies, the factor r, even if it is higher than 0.5, has never reached 1.0. So far, the clinical power of the family of tested genetic and molecular predictors can only be interpreted in the category of "likelihood", but not as an absolute and undoubtful guideline. Numerous clinical studies, which extensively explore growing knowledge on genomics and the proteomics of human malignant tumors to test novel concepts of combined therapeutic strategies, are very important and should not be ignored, but the progress in the patients' curability can only be achieved by small steps forward, and for complete victory of the war against cancer we still have to wait.

An interesting aim of some experimental and clinical studies is to intensify processes of the host immune response against primary and metastatic cancer cells by immunotherapy combined with the RT and/or CHT. It has been found out that immunogenicity is mediated by the DNA exonuclease Trex1, which could be used as a potential biomodulator to optimize the RT combined with the CHT. The complimentary pathway is TGF-β, which promotes the RT to induce antitumor immunity. Actual results convince the stereotactic hypofractionated RT (SHRT) should be considered a potentially highly effective treatment, since the use of a large single dose or a few large fractions effectively boosts the tumor immune-response (fig. 5), triggering *in situ* vaccination, T-cell promising infiltration, and immunogenetic killing [30, 32]. Large doses of RT induce Fas-receptors which activate the T-cells. Pre- and clinical studies have shown a complexity of the processes optimizing radiation-immunotherapy interactions. The SHRT frequently used in the setting of limited extra- and intracranial metastases combined with immunotherapy could provide not only LTC improvement, but also distant control as well. Immune agents approved for cancer therapy include cytokines, oncolytic viruses, dendritic-cell vaccine and check-point inhibitors. There is well-grounded excitement regarding design studies exploring RT combined with available immunotherapeutic strategies.

Another fast-growing field in oncologic therapies is a combination of diagnostic and therapeutic modalities with nanoparticles [30]. The use of a nano-radiation dose enhancer (Nano-RDE) to improve RT efficacy has been one of the explored fields by experimental and pilot clinical studies, and has been termed as a "SMART combined modality therapy" [30]. Gold nano-particles (Au NP) have been tested to intensify

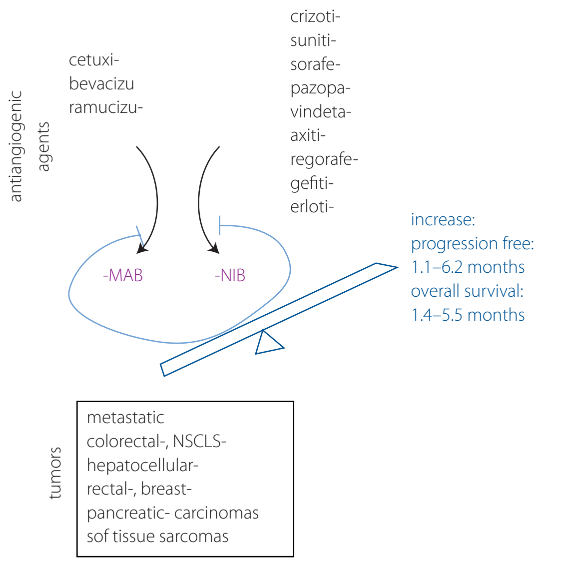

Figure 4. PFS and OS improvement after antiangiogenic therapy (taken from Jain et al. review [29])

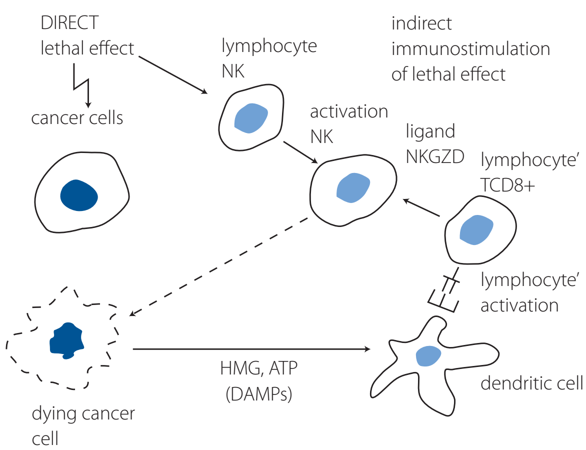

Figure 5. Scheme of immunostimulation of the indirect cancer cell death induced by high doses of the SHRT [32]. DAMPs – set of molecular factors which induce indirect immunological lethal effect

both the CHT and the RT efficacy. The TNFα – colloidal gold nanoparticle (CYT-6091) selectively delivered to the cancer cells intensifies the apoptotic effect of the RT dose. However, till now, such compounds are not used in routine daily RT practice yet. Nevertheless, an interesting approach concerns the use of direct conjugation of antibody labeled with radionuclide, compatible with SPECT or PET imaging, to localize antibodies in the tumor, inducing a cytoreductive and potentially curative effect (targeted drugs). Major obstacle is, however, insufficient dose delivery to solid tumors because of poor penetration. With no doubts, all these new approaches are very interesting and encouraging, but they are still at the beginning of "a long, long way to Tipperary". As it happened before, some of them will likely be abandoned, and others will be extensively explored. But, they still remain within probabilityland, and not in an absolute certaintyland of the victory.

The miracle of statistics – pitfalls and biases?

One may raise a query about statistical interpretations of clinical data [18, 19]. The roots of statistics' "cause-effect" relationships are in 19th-century laws of physics and mathematics, which are immutable. If something occurs, then that must follow. However, this does not happen in oncology at all. There is a lot of individual genetic, phenotypic, biological variables and pathways, which make a large number of more or less powerful variables of "cause-effect" relationships very difficult to be explicitly establish. Discussing the results of various brilliant concepts and attempts made to win the war against cancer, major question arises as to why the results of major therapeutic achievements are much lower than expected. It seems that one important reason is that the randomization and stratification routinely explored in the trials, produce only ostensibly homogenous groups of patients, whereas in fact, they are genetically, phenotypically and biologically highly individual tumors, and therefore highly heterogeneous, even if its localization, type, and stage are the same. Since the result of such widespread heterogeneities are usually quantified as "averages" or "median", one can generally be disappointed with the rather low therapeutic gain reported. The averages are usually recognized as significant when the "p" value is below 0.05. But according to Glatstein [18, 19], significance does not necessarily mean clinical importance. If, for example, the p-value is 0.06, the results are counted as insignificant. However, are the results really less clinically important when 94 instead of 95 out of 100 patients with cancer will be permanently cured? Somebody could say – "not at all statistically", since they differ by one patient only. But clinically – cure of the one is as important as a cure of the other 100 patients, and the p-value is just a statistical toy to play with the analyzed results of treatment.

Interpretations of the "averages" usually lead to uncertainties and doubts. It is a routine procedure to comment survival (LTC, DFS, OS) curves counting actuarial *vs.* crude survival. The first one often leads to underestimations, since the cases lost during the 3-, 5-, and 10-year follow-up are censored in about 50% as relapses, whereas they might be controlled during the assumed follow-up. Another point of criticism is that the interpretation of the survival curves simplifies their courses to the one number, which is a median value. It seems that the major problem is that the interpretation is focused on one point on the survival curve and its trail is usually ignored. Meanwhile, such a curve is surrounded by the "noise" of many points, representing individual patients. If, for example in some trial, the 5-year actuarial LTC of the H&N cancer was about 85% in the tested arm and 70% in the conventional one, then such a difference would be quantified for sure as statistically significant, in favor of a novel therapy. However, what is often ignored is that, for example, in the control arm a 15% rate of local recurrence has occurred during the first 18 months of follow-up [26]. It becomes clearly evident, based on biology, and the kinetics of tumor growth, that such small subclinical tumor cell lesions beyond the irradiated or excised mass likely already existed at the time of the start the therapy. Therefore, it should not be accounted for the efficacy of the conventional therapy. When such part of the LTC curve would be excluded, then both curve become close each other and significance disappears, and the advantage of the tested therapy as well. This is a simple example of the statistical bias, which often happens.

Important trouble with interpretation of the trials and metaanalyses results is that the actuarial statistics reflect wide biological and genetic heterogeneities of patients and maldistribution of various prognostic factors, although, at first glance, they look homogenous within each study group. For head and neck cancers, about 600 genetic and proteomic predictors were analyzed a couple of years ago, and none of them turned out to be absolute and the sole prognostic predictor. However, when Buffa et al. [34], analyzed that sets of data once again using sophisticated taxonomic cluster statistics, they clearly found overexpression of the four factors as a significant prognostic predictors of the LTC gain by 20%. Similarly, Suwiński et al. [35] designed the trial, to test efficacy of the 7 fractions per week *vs.* conventional 5 fractions per week, used in the postoperative radiotherapy for H&N cancer patients with the increased risk of local recurrences. Classic, actuarial statistics have shown no difference in the effectiveness of both schedules. But, when the authors designed molecular scoring for the overexpression of the four selected genetic predictors, then the score >2 of them predicted an enormous increase in the DFS after 7 fractions/week schedule, much higher (>40%) than after 5 fractions/week. In case of the score ≤2 there is in favor of any these two schedules. These examples, as well as many others, suggest that classic statistics may provide deceptive results. Therefore, a rhetorical question may arise: what can really be considered "evidence". It seems that in many studies the importance of "evidence" remains uncertain. Thus, clinicians should likely prefer clinical importance, experience, and common sense as guidelines, more than the results predominately based on the p-value. Glatstein [18, 19] strongly suggests that "evidence" should be weighed more carefully, and it seems that in the case of individual patients, the logic and own experience are often more important, but this does not mean that trials should be dismissed either.

Conclusions

Many years ago, the famous oncologist Vincent de Vita pointed out that "if we expect pronounced success in oncology, we have to be patient, because the progress will be realized in many small steps". For the last few decades, our knowledge on genetics, proteomics molecular predictors and modifiers has enormously increased, and we have unexpectedly learned that there are as many genetically and phenotypically different malignant diseases as there are patients suffering from them. It means, that effective combined therapy should be personally individualized, and that we are not able to win whole war against cancer just yet. However, that suggest, we should not lose hope and belief that it could happen in the future. There is a large number of winners on various, single oncologic battlefields, mainly those, which tumors are in very early stage of disease. Undoubtedly, we will likely achieve an important step forward when we will be able to replace "probabilityland" by "certaintyland", but not yet. We should also keep reasonable and limited belief on the statistics, and remember that the "averages" never represent individual heterogeneous characteristics. So far, real progress in cancer curability can likely be expected due to the increased activity and efficacy of prophylaxis and early detection of malignant tumors.

Article information and declarations

AAuthor contributions

Bogusław Maciejewski – was responsible for the main idea, writing and editing of the article.

Daniel Bula – was responsible for supportive writing and editing of the article.

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Review article

Tumor biology

Wnt pathways in focus – mapping current clinical trials across the cancer spectrum

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The Wnt pathway has a pivotal function in tissue development and homeostasis, overseeing cell growth or differentiation. Aberrant Wnt signalling pathways have been associated with the pathogenesis of diverse malignancies, influencing cell proliferation, differentiation, cancer stem cell renewal, the tumour microenvironment and thereby significantly impacting tumour development and therapeutic responsiveness. Promisingly, current research underscores the potential therapeutic value of targeting Wnt pathways, particularly canonical Wnt/β-catenin signalling, in the context of numerous cancer types. Key constituents of the Wnt pathway, such as the Wnt/receptor, β-catenin degradation or transcription complexes, have been focal points for interventions in preclinical studies. To comprehend potential therapeutic strategies, we conduct an analysis of ongoing clinical trials that specifically aim to target components of the Wnt pathways across a diverse spectrum of cancer types. By scrutinizing these trials, including their respective phases, targeted patient populations ,and observed outcomes, this review provides a consolidated overview of the current translational landscape of Wnt-targeted therapies, thus offering a roadmap for future research endeavours.

Key words: cancer, clinical trials, Wnt signalling pathways, targeted therapy

Introduction

Cancer is one of the main causes of death worldwide [1]. While chemotherapy remains the backbone of systemic treatment for both the radically and palliatively treated cancer patient population, new options including a growing number of molecularly targeted drugs have entered the market with new and new indications [2]. The journey from the initial discovery of a compound to its approval by regulatory bodies like the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) is an extensive process. It initiates with preclinical evaluations and advances through a multi-stage series of clinical trials involving human subjects. A significant proportion of compounds displaying promise in the preclinical phase ultimately do not achieve the specified endpoints during the clinical trial phases [3–6]. Figure 1 succinctly outlines this intricate progression.

There are numerous signaling pathways abrupted in cancer cells that have been already used as targets for different therapeutic strategies including kinase inhibitors (Kis), monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), drugs' nanoforms [2]. Activation of these pathways can induce

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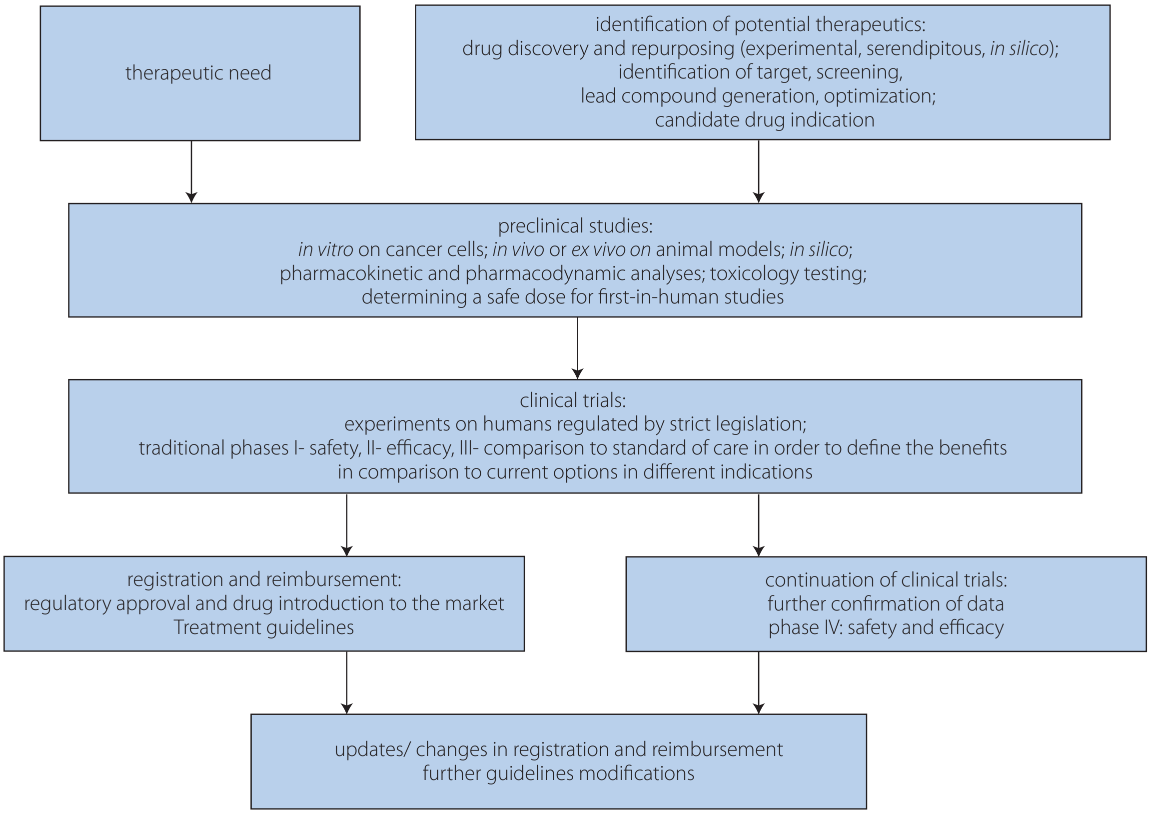

Figure 1. Sequential stages of drug discovery and registration [3–6]

alterations in cell survival capabilities, metabolic processes, cellular proliferation, differentiation, thereby impacting the tumor microenvironment. Moreover, it plays a role in angiogenesis, epithelial to mesenchymal transition, and the formation of metastases [7–10]. Among the numerous pathways with key components that are established targets for treatment, prominent examples comprise epidermal growth factor receptor/RAS/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (EGFR/RAS/RAF), human epidermal growth factor receptor 2 (HER2), sonic hedgehog (SHH), vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and protein kinase B/mammalian target of rapamycin (AKT/mTOR). It is noteworthy that the elements of these pathways often intersect during signal transduction [7–10]. Wnt represents a fundamental pathway crucial in both embryonic development and the onset of tumorigenesis [11]. Presently, there are no registered drugs specifically targeting the elements of this pathway, despite it presenting an apparent target for innovative anticancer agents. The objective of this review is to delve into the prospects of translating elements of the Wnt pathway from preclinical research to clinical applications. Through meticulous examination of these trials, encompassing their phases, targeted population, and the active drug studied, the review furnishes a comprehensive summary of the present translational panorama concerning therapies directed at the Wnt pathways.

Canonical and non-canonical Wnt signalling

The Wnt pathway plays a pivotal role in numerous developmental and homeostatic processes. Aberrations within this pathway have been implicated in a spectrum of pathological conditions, including cancers. The intricate balance and regulation of the Wnt pathway underscore its paramount importance in cellular homeostasis, presenting a potential target for therapeutic interventions in malignancies and other diseases.

There are in fact several signaling pathways that can be activated with the elements of Wnt. The canonical pathway is the most well-known (fig. 2). At the core of this pathway lies β-catenin, a key protein acting as a linchpin orchestrating downstream signaling events. Two other pathways are planar cell polarity (PCP) and calcium-related pathways [11–16].

Wnt proteins are categorized into canonical and noncanonical types, instigating both respective pathways by engaging Frizzled (FZD) receptors (tab. I). Frizzled receptors require a co--receptor, low-density lipoprotein receptor-related protein 5/6 (LRP5/6) for canonical signaling, and receptor tyrosine kinase-like orphan receptor 1/2 (ROR1/2) for non-canonical signaling, to transmit signals effectively [11–17].

Within the canonical pathway, upon activation, Wnt binding disrupts the β-catenin destruction complex, preventing the phosphorylation of β-catenin by GSK-3β, thereby averting its proteasomal degradation. Key components of the destruction complex include:

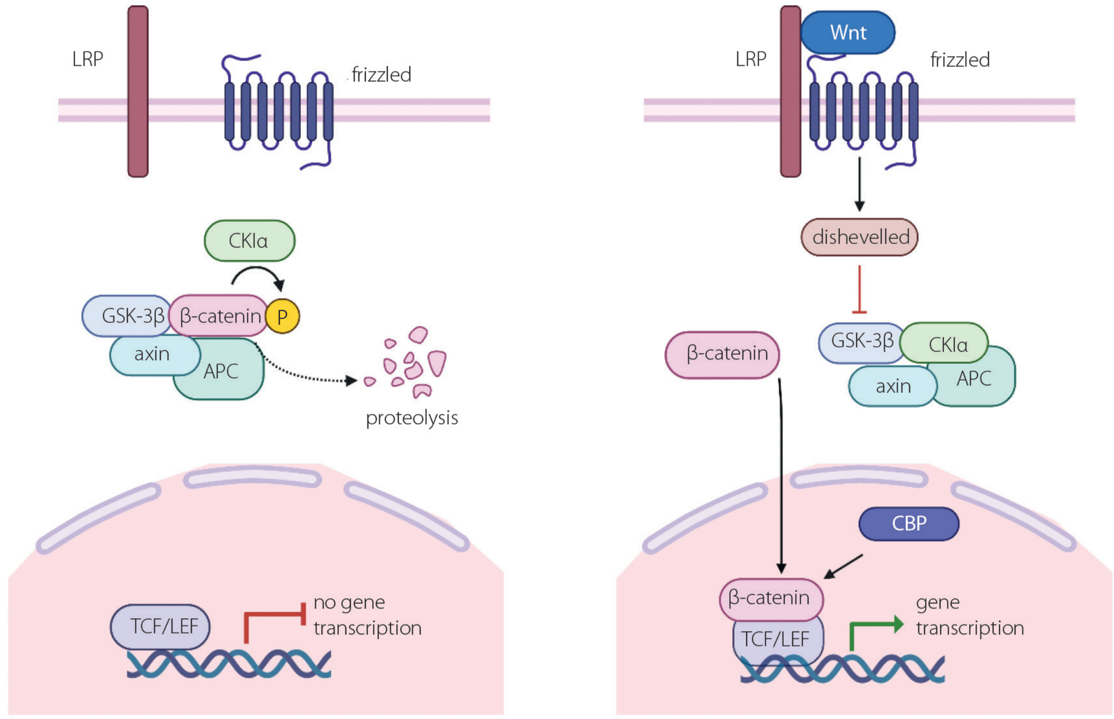

Figure 2. Canonical Wnt pathway inactive (on the left-hand side) and active (on the right-hand side) (created with BioRender) [11–16] APC – *adenomatous polyposis coli*; CBP – CREB-binding protein; CK1-α – casein kinase 1-alpha; GSK-3β – glycogen synthase kinase 3-beta; LEF – lymphoid enhancer factor; LRP – low-density lipoprotein receptor-related protein; TCF – T cell factor

Table I. Canonical and non-canonical elements of the Wnt family [11, 16]

Pathway		Proteins
canonical	Wnt / β-catenin	Wnt1, Wnt2, Wnt3, Wnt3a, Wnt8a, Wnt8b, Wnt10a, Wnt10b
non canonical	PCP, Wnt / Ca^{2+}	Wnt3, Wnt4, Wnt5a, Wnt5b, Wnt6, Wnt7a, Wnt7b, Wnt11

PCP – planar-cell polarity

- *adenomatous polyposis coli* (APC),
- glycogen synthase kinase 3-beta (GSK-3β),
- axin, casein kinase 1-alpha (CK1-α).

The accumulation of β-catenin in the cytoplasm enables its translocation into the nucleus, where it forms complexes with various transcription factors, primarily lymphoid enhancer factor/T-cell factor (LEF/TCF), initiating the transcription of vital Wnt/β-catenin target genes such as: cMyc, cyclin D1 (CCND1), and VEGF or programmed death-ligand 1 (PD-L1) [11–16].

Non-canonical Wnt pathways are Wnt / PCP and Wnt-cyclic guanosine monophosphate / calcium ion (Wnt-cGMP/Ca^{2+}) signaling. The targets for these non-canonical pathways can include matrix metalloproteinases (MMPs) or AKT/mTOR. These pathways are believed to exert an influence on processes such as epithelial-mesenchymal transition (EMT), cell migration, cell metabolism, chemo-resistance, or the formation of metastases [11, 16, 17].

Preclinical and clinical cancer studies regarding Wnt elements

Inhibition of the Wnt pathway represents an interesting and promising molecular target for novel anticancer therapies in various malignancies. Many new molecules have been investigated in preclinical studies or in clinical trials – mainly phase 1 (tab. II). Some of them have reached phase 2 clinical trials in the treatment of solid malignancies, as well as hematologic, but recruitment is ongoing or the results of those trials are expected to be soon published. An interesting approach represents the combination of Wnt inhibitors with chemotherapy of targeted therapies – PD-1/PD-L1 inhibitors (nivolumab / pembrolizumab) or EGFR inhibitors (cetuximab).

Katoh and Katoh divided Wnt-targeted agents into pan--Wnt inhibitors (like porcupine inhibitors), canonical (like β-catenin protein-protein inhibitor) and non-canonical (like ROR1 inhibitors) [12]. However, there is a significant group of compounds that modulate the signal indirectly or influence

Table II. Agents inhibiting the Wnt pathway which are under investigation. Complied on the basis of clinicaltrials.gov as of April 2023, unless otherwise specified

Name of agent	Mechanism of action	Development stage	Indications	Reference
PKF115–584, CGP049090, PKF222–815, PKF118–310, PKF118–744, ZTM000990	β-catenin – TCF antagonists	preclinical	colorectal cancer, breast cancer	[18, 19]
iCRT3, iCRT5, iCRT14	β-catenin – TCF antagonists	preclinical	colorectal cancer, triple negative breast cancer	[20, 21]
BC21	β-catenin – TCF antagonists	preclinical	colorectal cancer	[22]
FH535	β-catenin – TCF antagonists	preclinical	triple negative breast cancer, colorectal cancer, lung cancer, hepatocellular carcinoma	[23, 24]
CWP232228	β-catenin – TCF antagonists	preclinical	breast cancer	[25]
ICG-001	β-catenin / CBP inhibitor	preclinical	triple negative breast cancer	[26]
CG0009	glycogen synthase kinase 3α/β inhibitor	preclinical	breast cancer	[27]
niclosamide	inhibition the binding of a WNT ligand to LRP5/6 receptors	preclinical	breast cancer	[28]
salinomycin	inhibition the binding of a WNT ligand to LRP5/6 receptors	preclinical	breast cancer, prostate cancer, chronic lymphocytic leukemia	[29, 30]
LGK974 (WNT974)	inhibitor of the WNT-receptor complex (porcupine inhibitor)	phase 1 clinical trial, recruiting	pancreatic cancer, BRAF-mutant colorectal cancer, melanoma, triple negative breast cancer, head and neck squamous-cell cancer, cervical squamous-cell cancer, esophageal squamous-cell cancer, lung squamous-cell cancer	[31]
		phase 1 and 2 clinical trial + cetuximab, completed	BRAF-mutant metastatic colorectal cancer	[32]
		preclinical	Ewing sarcoma	[33]
		preclinical	clear cell, renal cell carcinoma	[34]
ETC-1922159	inhibitor of the WNT-receptor complex (porcupine inhibitor)	phase I clinical trial +/– pembrolizumab, recruiting	advanced solid tumors	[35]
CGX1321	Inhibitor of the WNT-receptor complex (porcupine inhibitor)	phase I clinical trial +/– pembrolizumab or encorafenib + cetuximab, recruiting	advanced gastrointestinal tumors	[36]
		phase 1 clinical trial, recruiting	advanced gastrointestinal tumors	[37]
RXC004	inhibitor of the WNT-receptor complex (porcupine inhibitor)	phase 1 clinical trial +/– nivolumab, recruiting	advanced solid tumors	[38]
		phase 2 clinical trial, recruiting	advanced solid tumors	[39]
		phase 2 clinical trial +/– nivolumab, recruiting	colorectal cancer	[40]
XNW7201	inhibitor of the WNT-receptor complex (porcupine inhibitor)	phase 1 clinical trial, active, not recruiting	advanced solid tumors	[41]
OMP-18R5 (vantictumab)	inhibitor of the WNT-receptor complex (antibody against WNT family proteins – namely FZD1, FZD2, FZD5, FZD7 and FZD8)	phase 1 clinical trial, completed	advanced solid tumors	[42]
		phase 1 clinical trial +/– nab-paklitaxel and gemcitabine, completed	advanced pancreatic cancer	[43, 44]
		phase 1b clinical trial + docetaxel, completed	non-small cell lung cancer	[45]
		phase 1b clinical trial, completed	metastatic breast cancer	[46]

→

Table II cont. Agents inhibiting the Wnt pathway which are under investigation. Complied on the basis of clinicaltrials.gov as of April 2023, unless otherwise specified

Name of agent	Mechanism of action	Development stage	Indications	Reference
OMP-54F28 (ipafricept)	inhibitor of the WNT-receptor complex (antibody against WNT family proteins – namely FZD 8 receptor)	phase 1 clinical trial, completed	advanced solid tumors	[47, 48]
		phase 1 clinical trial + sorafenib, completed	hepatocellular cancer	[49]
		phase 1 clinical trial + paclitaxel and carboplatin, completed	ovarian cancer	[50, 51]
		phase 1 clinical trial + nab-paclitaxel and gemcitabine, completed	pancreatic cancer	[52]
OTSA101	inhibitor of the WNT-receptor complex (antibody against Wnt family proteins – namely FZD 10 receptor)	phase 1 clinical trial, recruiting	synovial sarcoma	[53]
NVP-TNKS656	β-catenin-destruction complex inhibitors, namely tankyrase inhibitors (PARPs family)	preclinical	colorectal cancer	[54]
XAV939	β-catenin-destruction complex inhibitors, namely tankyrase inhibitors (PARPs family)	preclinical	breast cancer	[55]
PRI-724	inhibition of the CBP and β-catenin interaction	phase 1a/1b clinical trial, terminated	advanced solid tumors	[56, 57]
		phase 1 clinical trial + gemcitabine, completed	pancreatic cancer	[58, 59]
		phase 1 and 2 clinical trial, completed	acute myeloid leukemia, chronic myeloid leukemia	[60]
CWP232291	inhibitor of the Wnt pathway, induction of apoptosis *via* activation of caspases	phase 1 clinical trial, completed	refractory acute myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome, myelofibrosis	[61, 62]
		phase 1 clinical trial +/– lenalidomide, dexamethasone, completed	multiple myeloma	[63, 64]
		phase 1 and 2 clinical trial, active, not recruiting	acute myeloid leukemia	[65]
DKN-01	monoclonal antibody, inhibitor of the DKK1 activity, a modulator of Wnt / β-catenin signaling	phase 1 clinical trial +/– paclitaxel or pembrolizumab, completed	esophageal cancer gastroesophageal junction cancer, gastric adenocarcinoma with Wnt signaling alterations	[66, 67]
		phase 1 clinical trial + gemcitabine/cisplatine, completed	carcinoma primary to the intra- or exta-hepatic biliary system or gallbladder	[68, 69]
		phase 1b/2a clinical trial +/– docetaxel, recruiting	prostate cancer	[70, 71]
		phase 1 and 2 clinical trial +/– sorafenib, recruiting	advanced liver cancer	[72]
		phase 2 clinical trial + nivolumab, recruiting	advanced biliary tract cancer	[73]
		phase 2 clinical trial +/– paclitaxel, completed	endometrial cancer, uterine cancer, ovarian cancer, carcinosarcoma	[74]
		phase 2 clinical trial + tiselizumab +/– chemotherapy, recruiting	gastric cancer, gastroesophageal cancer	[75]
		phase 1 clinical trial, completed	multiple myeloma, solid tumors, non-small-cell lung cancer	[76, 77]
		phase 1 clinical trial + lenalidomide/dexamethasone, completed	relapsed or refractory multiple myeloma	[77]
		phase 1 and 2 clinical trial + atezolizumab, recruiting	metastatic esophageal cancer, metastatic gastric cancer	[78]

Table II cont. Agents inhibiting the Wnt pathway which are under investigation. Complied on the basis of clinicaltrials.gov as of April 2023, unless otherwise specified

Name of agent	Mechanism of action	Development stage	Indications	Reference
Foxy-5	WNT5A-mimicking peptide	phase 1 clinical trials, completed	breast cancer, colon cancer, prostate cancer	[79, 80]
		phase 2 clinical trial, recruiting	colon cancer (neoadjuvant setting)	[81]
UC-961 (cirmtuzumab)	monoclonal antibody against ROR1 of the non-canonical Wnt pathway	phase 2 clinical trial + docetaxel, not yet recruiting	metastatic castration resistant prostate cancer	[82]
		phase 1 clinical trial, completed	relapsed or refractory chronic lymphocytic leukemia	[83, 84]
		phase 1 and 2 clinical trial + ibrutinib, active, not recruiting	B-cell lymphoid malignancies	[85, 86]
		phase 2 clinical trial, recruiting	chronic lymphocytic leukemia, consolidation after venetoclaxs	[87]
		phase 1 clinical trial + paclitaxel, active, not recruiting	breast cancer	[88]
PRI-724	CBP / β-catenin antagonist	phase 2 clinical trial + FOLFOX and bevacizumab, withdrawn	metastatic colorectal cancer	[89]
		phase 1 clinical trial + gemcitabine, completed	advanced pancreatic cancer	[90, 91]
		phase 1 and 2 clinical trial, completed	acute myeloid leukemia, chronic myeloid leukemia	[92]
		phase 1 clinical trial, terminated	advanced solid tumors	[93]
PF-06647020 (cofetuzumab pelidotin)	monoclonal antibody against PTK7 – inhibition of non-canonical Wnt pathway	phase 1 clinical trial + gedatolisib, completed	triple negative breast cancer	[94–96]
		phase 1 clinical trial, completed	non-small cell lung cancer	[97, 98]
		phase 1 clinical trial, completed	advanced solid tumors	[99, 100]
GDC-0449 (vismodegib)	inhibitor of the hedgehog pathway	FDA and EMA registered	metastatic/locally advanced basal cell carcinoma	[101, 102]
		numerous clinical trials phase 1–3	advanced solid tumors (also advanced breast cancer) hematologic malignancies	#
LDE225 (sonidegib)	inhibitor of the hedgehog pathway	FDA and EMA registered	metastatic/locally advanced basal cell carcinoma	[103, 104]
		numerous clinical trials phase 1–3	advanced solid tumors (also advanced breast cancer) hematologic malignancies	#
itraconazole	antifungal medication, inhibitor of the hedgehog pathway	numerous clinical trials phase 1–3	prostate cancer, lung cancer, ovarian cancer, esophageal cancer, multiple myeloma, solid malignancies	#
PF-04449913 (glasdegib)	inhibitor of the hedgehog pathway	phase 1 and 2 clinical trials	hematologic malignancies	#
		phase 1 clinical trial, completed	solid tumors	[105, 106]
		phase 1 and 2 clinical trial + temozolomide, active, not recruiting	glioblastoma	[107]
IPI-926 (patidegib)	inhibitor of the hedgehog pathway	phase 1 clinical trial, completed	basal cell carcinoma	[108]
		phase 1 and 2 clinical trial + gemcitabine, completed	pancreatic cancer	[109, 110]
		phase 1 + FOLIFIRINOX, completed	pancreatic cancer	[111, 112]
		phase 1 clinical trial, completed	solid tumor malignancies	[113, 114]
		phase 1 clinical trial + cetuximab, completed	head and neck cancer	[115, 116]
		phase 2 clinical trial, completed	unresectable chondrosarcoma	[117]
LY2940680	inhibitor of the hedgehog pathway	phase 2 clinical trial, completed	solid tumor malignancies	[118]

Table II cont. Agents inhibiting the Wnt pathway which are under investigation. Complied on the basis of clinicaltrials.gov as of April 2023, unless otherwise specified

Name of agent	Mechanism of action	Development stage	Indications	Reference
ENV-101	inhibitor of the hedgehog pathway	phase 2 clinical trial, recruiting	advanced solid tumors harboring PTCH1 loss of function mutations	[119]
		phase 1 clinical trial, completed	breast cancer, colon cancer, cholangiocarcinoma, soft tissue sarcoma	[120]
		phase 1 and 2 clinical trial, completed	esophageal or gastroesophageal junction cancer	[121]
lycopene	naturally synthesized carotenoid (an active component of red fruits and vegetables) – suppression of β-catenin nuclear expression	phase 2 clinical trial, active, not recruiting	skin toxicity in patients with colorectal carcinoma treated with panitumumab	[122]
		preclinical	gastric cancer, breast cancer	[123, 124]
artesunate	antimalarial drug – suppression of Wnt pathway by downregulation of c-Myc and cyclin D1	phase 2 clinical trial, active, not recruiting	stage II/III colorectal cancer (pre-operative treatment)	[125, 126]
		phase 1 clinical trial, completed	advanced solid tumors	[127, 128]
		phase 1 clinical trial, completed	metastatic breast cancer	[129, 130]
resveratol	non-flavonoid polyphenol – suppression of Wnt pathway by decreasing the expression of β-catenin and cyclin D1	phase 1 clinical trial, completed	colon cancer	[131, 132]
		preclinical	breast cancer, gastric cancer	[133, 134]
quercetin	flavonoid (component of onion, red grapes, lettuce, tomato). Inhibition of the Notch1, PI3K/AKT and β-catenin signaling pathways	preclinical	breast cancer, ovarian cancer, B-cell lymphomas	[135–137]

CBP – CREB-binding protein; BRAF – B-Raf proto-oncogene, serine/threonine kinase; DKK1 – dickkopf-1 protein; EMA – European Medical Agency; FDA – Food and Drug Administration; FOLFOX – folinic acid, 5-fluorouracil and oxaliplatin; FOLFIRINOX – folinic acid, 5-fluorouracil, irinotecan and oxaliplatin; FZD – frizzled receptor; LRP5/6 – low-density lipoprotein receptor-related protein 5/6; PARPs – poly (ADP-ribose) polymerases; PI3K/AKT – phosphoinositide 3-kinase/protein kinase B; PTK7 – protein tyrosine kinase 7; TCF – T cell factor; # – for details see clinicaltrials.gov

Wnt signalling by interfering with other pathways (like SHH). β-catenin itself plays an important role as a signal transducer in other pathways including trophoblast cell surface antigen 2 (TROP-2) [138].

Current trials, as shown in table II, involve drugs acting on numerous levels of these signaling pathways:

- Outside the cancer cell / on the cell membrane level: Wnt--mimicking agents [79, 80]; monoclonal antibody against ROR1 (cirmtuzumab) [82–86]; Wnt proteins / receptors inhibitors like: porcupine inhibitors LGK974, ETC-1922159, CGX1321, RXC004, XNW7201 [31–41] or FZD inhibitors (vantictumab, ipafricept, OTSA101) [42–53]. Porcupine serves as a vital enzyme within the Wnt signaling pathway, aiding in the palmitoylation of Wnt proteins. This alteration is pivotal for the appropriate secretion of Wnt proteins and the initiation of the Wnt signaling pathway [139]. Monoclonal antibodies against protein tyrosine kinase 7 (PTK7) can also be included into that group. PTK-7 is a transmembrane receptor protein that has been implicated in the regulation of the Wnt signaling pathway (cofetuzumab pelidotin) [94–102].
- In the cytoplasm: dikkopf-1 (DKK1) modulators (DKN-01) [66–71]. Functioning as an extracellular antagonist, DKK1 binds to LRP5/6 co-receptors, interrupting their engagement with Wnt ligands and obstructing the activation of the canonical Wnt pathway. This impediment leads to a halt in the accumulation and nuclear movement of β-catenin [140].
- Within the nucleus e.g. inhibiting the target canonical pathway genes [125, 126] or CREB-binding protein (CBP) / β-catenin inhibitors (ICG-001, PRI-724, PRI-724 [26, 56–60, 89–96). CBP serves as a coactivator for transcription within the canonical Wnt pathway, collaborating with transcription factors such as β-catenin. It amplifies the transcription of Wnt target genes by modifying chromatin structure through the acetylation of histones [141].
- Within other signaling pathways that interact with Wnt including SHH (vismodegib, sonidegib, itraconazole, glasdegib, patidegib, LY2940680, ENV-101) as the most visible example [101–121].

While compounds acting on β-catenin degradation complex show activity in preclinical studies, their clinical activity has not been confirmed yet (NVP-TNKS656, XAV939) [54, 55]. Numerous limitations accompany the development of Wnt pathway inhibitors. They include: the non-obvious role of Wnt elements in cancer development and progression, its role in physiological processes, its complexity. Notably, WNT inhibitors have the potential to serve not only in cancer therapy but also in a supportive capacity to mitigate treatment-related toxicity [11–17, 142].

Numerous novel molecules have undergone scrutiny in either preclinical investigations or clinical trials. A portion of these compounds has progressed to phase 2 clinical trials, marking the mid-point in the translational process depicted in figure 1.

Conclusions

The precise equilibrium and meticulous regulation observed in the Wnt pathway underline its paramount importance in maintaining cellular homeostasis, thereby delineating it as a promising focal point for therapeutic interventions directed at malignancies. The Wnt pathway branches into canonical and noncanonical categories, each instigating distinctive signaling cascades through specific receptor engagement. A comprehensive understanding of these pathways and their constituent elements is imperative for discerning their potential therapeutic ramifications. Presently, preclinical and clinical inquiries into Wnt elements are progressing, presenting an enticing trajectory for the development of novel anticancer therapies. However, the intricate nature of Wnt signaling, its dual role in both disease and physiological homeostasis, and the complexities surrounding its inhibitors do pose formidable challenges. The number of trials and the variety of molecular targets related to Wnt pathways, as well as different cancer indications within the patient population (tab. II) provide grounds for optimism regarding the possibility of advancing beyond the early phases of clinical trials in the journey from bench to bedside (fig. 1).

Article information and declarations

Author contributions

Renata Pacholczak-Madej – study conception and design, material collection, analysis and interpretation of results: all authors; manuscript preparation.

Mirosława Püsküllüoğlu – study conception and design, material collection, analysis and interpretation of results: all authors; manuscript preparation.

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Review article

Liver tumors

Liver transplantation in metastatic liver tumors

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As transplant medicine has evolved in recent decades so too have the indications for liver transplantation (LT). Active or suspected malignancy has stopped being considered as a contraindication for organ transplantation, and nowadays LT plays a major role in the treatment strategies of liver malignancy, specially primary, but also metastatic. It offers excellent long-term outcomes for certain patients with neuroendocrine tumors liver metastases (NETLMs) and carefully selected patients with colorectal cancer liver metastases (CRLMs), who undergo neoadjuvant chemotherapy. Optimal patient selection has become the key issue to achieve the best possible outcomes and to deal with the alleviating shortage of organs. The recent tendency to incorporate markers of tumor biology into selection criteria, rather than simply focusing on tumor size and number, has led to further extension of indications for LT in patients with liver malignancy. This review article focuses on the current place of liver transplantation in the treatment strategy for patients with metastatic/secondary liver tumors.

Key words: liver transplantation, liver metastases, neuroendocrine tumor, colon cancer

Introduction

The idea of liver transplantation (LTx) as a method of treatment of unresectable tumor metastases limited only to this organ has been considered for several decades. However, due to significantly worse results, overall survival and high recurrence rates, LTs were initially abandoned [1–4]. At the turn of the century, however, the subject of liver transplantation as an effective "intent to cure" multiple metastases of neuroendocrine tumors to the liver (NELM) returned. The proven effectiveness of this procedure has even been reflected in Polish diagnostic and therapeutic recommendations for neuroendocrine tumors of the digestive system [5]. On the other hand, unresectable colon cancer metastases to the liver in the last 20 years of the 20th century were a contraindication to liver transplantation due to the described 5-year survival rate <20% [6, 7]. In 2006, recruitment for the SECA I study was launched in Norway to assess the effectiveness of orthotopic liver transplantation as a treatment for unresectable metastases of colorectal cancer to this organ in the current era of possible neo- and adjuvant therapies, various immunosuppression regimens and appropriate selection of recipients. Initial results showed overall survival of 60% [8]. Currently, about 20 clinical trials are being conducted worldwide to assess the effectiveness of treatment of unresectable metastases of colorectal cancer to the liver with orthotopic liver transplantation from a deceased donor, a fragment of a liver from a living donor and advanced surgical techniques: RAPID (resection and partial liver segment 2/3 transplantation with delayed total hepatectomy) and RAVAS (heterotopic transplantation of segments 2/3 using the splenic vein and artery after splenectomy and with delayed total hepatectomy), and the initial results are promising [9–11]. Currently, there is no trend to extend the indications for liver transplantation to other types of secondary, unresectable liver malignancies. Currently, research is focused on developing detailed recommendations regarding the selection of patients, organs and supportive

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therapies in order to obtain the overall survival values of patients after LTx due to unresectable cancer metastases similar to that in patients without cancer and the longest possible time without recurrence [12].

Transplant oncology

The transplant community has adopted a general guideline that survival at 5 years after liver transplantation by at least 50% of recipients justifies the use of expanded criteria organs (ECD). This principle applies both to transplants from living donors and from donors after brain death with maintained circulation and after cardiac arrest (DCD). From an oncological point of view, removal of the liver, extrahepatic bile ducts, and regional lymph nodes followed by transplantation would theoretically provide the best oncological eradication of primary and secondary hepatobiliary tumors. However, two main issues limit the possibility of using this method as the first line of treatment and the general acceptance of such a procedure. First, in most regions of the world, organ shortage limits the number of transplants and thus exposes waiting list cancer recipients to the progression of the above-mentioned cancer. Secondly, the benefits and risks of transplantation treatment should always be weighed in terms of patient survival, graft survival, the need for lifelong immunosuppression and the risk of recurrence of the underlying disease in immunocompromised patients.

Generally, there are two oncological indications for LT: primary (HCC and CCC according to the Mayo protocol) and secondary (discussed in this review) liver malignancy. Hepatocellular carcinoma (HCC), the most prevalent primary hepatic malignancy, represents 30% of indications for OLT in the United States since 2008 [13], with 5-year tumor recurrence-free survival rates (65–81%) comparable to those for general indications for end-stage liver disease (71–81%). Currently, only two indications for liver transplantation in the case of metastatic cancer are considered – neuroendocrine tumors (neuroendocrine liver metastases – NELM) and colorectal cancer (colorectal liver metastases – CLRM) [14]. LTx is an accepted definitive treatment for NELM as long as the primary NET has been resected and in the absence of more widespread disease. According to a recent systematic review, patients with NELM undergoing LTx provided 5-year overall survival rates between 49% and 97.2% and 5-year disease-free survival rates between 30% and 86.9% [14]. LTx results for CLRM have been discouraging so far. Moris et al. analyzed the data of 66 CLRM patients treated by LTx from 1972 to 2016 and described in 11 studies. Authors noted 1-, 3-, and 5-year overall survival of 85.2%, 48%, and 34.6%, respectively. Recurrence following LTx was very high as 66.7% (n = 44/66) patients recurred and 1-year DFS was only 38.9% [15]. However, according to a recent systematic review, patients with CLRM undergoing LTx provided 5-year overall survival rates between 50% and 83% and 5-year disease-free survival rates reaches 38% [16].

First time used by Hibi in 2017[17] the term of a new multidisciplinary branch of medicine, which is transplant oncology, should be introduced. It is a new concept including many disciplines of transplantation medicine and oncology, which aims to broaden the scope of treatment and research on cancer of the liver and bile ducts. Liver transplantation (LTx) in the case of primary and secondary malignant tumors of the liver and biliary tract is only part of this concept, and the whole critical elements of oncological transplantation are: the use of transplantation techniques in oncological surgery to extend the boundaries of conventional resection and the bridge connecting cancer and transplantation immunology, thus paving the way for a new anti-cancer strategy and genomic research platform based on new insights into cancer immunogenomics. This concept is intended to illustrate this new field of transplantation oncology and to highlight the importance of convening all relevant experts in the field of transplantation medicine and oncology, including transplant and hepatobiliary surgeons, medical oncologists and radiation therapists, hepatologists and gastroenterologists, immunologists, etc. to maximize care and cure cancer patients. In their concept, the authors emphasize the role of the four pillars of the new concept [18]: "The era of transplant oncology has just begun, and we are witnessing a paradigm shift in the treatment and research into hepatobiliary cancer. The 4 pillars of transplant oncology are:

1. evolution of multidisciplinary cancer care by integrating LT,
2. extending the limit of safe hepatobiliary resections by applying transplantation techniques to cancer surgery,
3. elucidation of self and nonself recognition system by linking tumor and transplant immunology, and
4. exploration of biomechanism of disease through genomic studies."

LTx for NELM – introduction

Neuroendocrine tumors/neoplasms (NETs/NENs) are a very heterogenous group of lesions including carcinoid, glucagonoma, gastrinoma, somatostatinoma, insulinoma, VIP-oma, ACTH-oma, pheochromocytoma and paraganglioma [19]. They originate from endocrine organs, the nervous system (peptidergic neurons) or from neuroendocrine cells of the diffuse endocrine system (DES) diffused throughout the whole body. Currently, The Surveillance, Epidemiology and End Results (SEER) program from US [20] states, that the incidence of NETs/NENs is estimated at 35 cases per 100,000 individuals per year.

Of all neuroendocrine neoplasms, about 70% are gastroenteropancreatic neuroendocrine neoplasms (GEP NENs), constituting only 2% of all gastrointestinal neoplasms, while most of them have blood drainage to the portal system and thus the possibility of metastases to the liver [21]. Among GEP-NENs, nearly half are intestinal and one third pancreatic. Among intestinal NENs only one fifth are hormone secreting. Out of pancreatic NENs only 10–30% are functional [22]. A majority of the NENs are non-functional indicating lack of symptoms of hormonal hypersecretion thus making diagnosis difficult [23]. Although NETs are relatively rare, slow-growing tumors, once they begin to metastasize, the liver is the most commonly affected organ (40–93%, mean over 50%) after lungs and bones [10, 24]. Especially GEP-NENs metastasize to the liver with up to 77% of patients developing neuroendocrine liver metastases (NELM) in their lifetime [25]. The appearance of NELM is a confirmed negative prognostic factor for long-term survival [26].

The classification of neuroendocrine neoplasms according to the WHO 2019 and AJCC 2017 distinguishes 4 subtypes of NETs/NENs depending on proliferation index Ki-67%: NET G1, NET G2, NET G3 and NEC(-ancer) [27, 28]. Only patients with unresectable NET G1, G2 metastases are considered as potential liver recipients for transplantation [29].

Careful selection of patients with advanced NETs for transplantation involves the use of high-quality imaging strategies to accurately depict disease burden, with an emphasis not only on distribution diseases within the liver, but also possible extrahepatic deposits, such that may prevent the patient from qualifying for a transplant. Morphological and functional imaging methods play an important role in the assessment of NETs and their metastases. Three growth types of NELM were identified radiologically and have relevance to prognosis and treatment options: single metastasis (type I), isolated metastatic bulk accompanied by smaller deposits (type II) and disseminated metastatic spread (type III) [30]. Since most NELMs are hypervascular lesions, computed tomography (CT) must take into account the phases of the hepatic artery [31]. In addition, diffusion-weighted magnetic resonance imaging (DW-MRI) should be systematically performed in any NELM assessment as it has the highest specificity of all MRI phases, even in tumors <1 cm [32]. Functional imaging with positron emission tomography (PET) 68-gallium radiolabeled DOTA peptides in association with CT represent gold standard, because it can detect morphological changes imaging modalities cannot, as well as those that have not been identified by somatostatin receptor scintigraphy [22, 33]. ^{68}Ga-DOTA PET/CT imaging detects NELM with high sensitivity between 82–100% and a specificity of 67–100%. And detects extrahepatic diseases with 85–100% sensitivity and specificity 67–90% [22]. In fact, the main advantage of ^{68}Ga-DOTA PET/CT in the condition for surgical selection is its ability to identify extrahepatic disease and thus change clinical strategies, which is especially important when considering multivisceral transplantation [34, 35]. In addition to detailed radiological imaging of the disease state, the patient's functional status and significant comorbidities should also be assessed general condition of patients qualified for transplantation.

In conclusion, the radiological evaluation of the disease should include computed tomography (hepatic artery phase, best three-phase), MRI (especially DW-MRI), somatostatin receptor scintigraphy (in the presence of receptors) and if available, ^{68}Ga-DOTA PET/CT. The latter is essential in patients under liver transplant consideration because it presents the best opportunity to reveal extrahepatic disease that could preclude transplantation.

Selection criteria for LTx for NELM

Most of the authors from several studies agree with Mazzaferro that meeting the Milan criteria by the liver recipient provides the longest overall and disease-free survival. The Milan group reported 5-year overall and disease-free survival of 97% and 89%, respectively, with their patient selection criteria (tab. I) [19, 36]. However, among 280 patients with NELMs, only 88 patients (31%) were on the waiting list for LTx, while 42 patients (15%) underwent OLT [26, 36]. In another report, a subgroup analysis the ELTR study in patients undergoing LTx (n = 106) showed a 5-year overall survival of 59%. When the criteria of Milan was applied retrospectively, the calculated survival rate increased to 79%, but it referred only to 36% of the recipients. Although this study suggests an extension of the Milan criteria, G3 histology grade is considered a contraindication to LTx [37]. In the US, the current OPTN/UNOS OLT guidelines for NELM (tab. I) are mainly based on the Milan-NET Criteria with a few additional conditions (OPTN/UNOS Liver and Intestinal Organ Transplantation Committee) [38]:

Table I. Summary outcomes reported from selected series on LTx for NELMs

First author	Year of publ.	Incl. period	Country	Patients (n)	1-year OS	3-years OS	5-years OS	1-year DFS	3-years DFS	5-years DFS
Nguyen	2011	1988–2011	US	184	79.5%	61.4%	49.2%	–	–	–
Le Treut	2013	1982–2005	Europe	213	81%	65%	52%	65%	40%	30%
Nobel	2016	2002–2014	US	230	87%	69%	63%	–	–	–
Mazzaferro	2016	1995–onwards	Italy	42	–	–	97.2%	–	–	86.9%
Valvi	2021	1988–2018	US	206	89%	75.3%	65%	74.9%	55.7%	43.9%
Maspero	2022	1984–2019	Italy	48	–	98%	95.5%	–	84%	75%
Eshmuminov	2022	1988–2021	international	225	–	–	73%	–	–	64.2%

OS – overall survival; DFS – disease-free survival

Milan-NET selection criteria (2007, revised in 2016):

- low grade NET (G1-G2) confirmed on histology,
- portal drainage of the primary tumor,
- primary tumor and all deposits radically removed in a separate operation before consideration for transplant,
- metastatic liver involvement <50% of liver volume,
- stable disease or response to treatment for at least 6 months prior to listing,
- age under 60 years (relative criteria).

Summary of UNOS guidelines for LT in NELM:

- common criteria with Milan-NET,
- additional criteria:
  - unresectable liver metastasis,
  - radiographic characteristics of NELM,
  - negative metastatic workup by PET scan,
  - lack of extrahepatic tumor recurrence during the past 3 months,
  - the presence of positive findings for lymph node metastases by PET scan,
  - the finding should become negative for 6 months before re-listing,
  - the presence of extrahepatic solid organ metastases (i.e., lungs or bones),
  - the case will be permanently delisted.

Literature review

To date, several studies have been published on OLT in NELM, including registry reports, multicenter series, and single center prospective and retrospective series (tab. I). The largest series reported in 2013 is the ELTR retrospective analysis by Le Treut et al. [39], which identified 213 patients who received OLT between 1982 and 2009. Before LT, 83% of patients underwent surgical treatment with removal of the primary tumor (n – 158) or liver metastases (n – 58); these included 23 cases of severe liver failure after resection (10.8%). In addition, 161 (76%) patients received non-surgical treatment, including somatostatin analogues in 63 patients, and transarterial chemoembolization (TACE) in 76 patients. 90-day post-operative mortality was 10%; significant risk factors included early retransplantation, exenteration, splenectomy, surgery duration over 10 h, margin of R1/R2 resection, hepatomegaly and additional surgeries after LTx. Regarding survival, the median OS after OLT was 67 months, with 1-, 3- and 5-year overall survival rates of 81%, 65%, and respectively 52%. Disease-free survival rates over the same time intervals were respectively 65%, 40%, and 30%. This ELTR study also demonstrated improved 5-year overall survival over time, with rates of 46% for recipients transplanted before 2000 in comparison to 59% for LTx done after 2000, respectively.

A 2011 analysis of the United Network for Organ Sharing (UNOS) database by Nguyen et al. [40] covered 184 patients with NELM (treated in 1988–2011). Overall survival rates at 1, 3, and 5 years were 79.5%, 61.4%, and 49.2% respectively.

Retrospective registry analysis performed by Nobel and Goldberg was reported in 2016. Authors studied the variable use of MELD exception points in patients with NELM and their impact on treatment outcomes; they showed 1-, 3, and 5-year posttransplant patient survival rates among all transplant recipients with metastatic NETs, regardless of exception points, at 87% (79–92%), 69% (59–77%), and 63% (53–72%), respectively. These rates were significantly (11%!) lower than national post-transplant survival rates for all first-time transplant recipients (80% and 74% 3- and 5-year survival, respectively, for all transplant recipients) [41]. In 2016, Mazzaferro et al. [36] evaluated 280 NELM patients referred for LTx consideration – the only prospective study with clearly defined selection criteria comparing transplanted and non-transplanted groups occurred (Milan NET criteria). In the end, 88 qualified and 42 actually passed the LTx. 5-year and 10-year overall survival rates in the transplant and non-transplant groups were 97.2% and 88.8% *vs.* 50.9% and 22.4%. The frequency of recurrence at 5 years and 10 years were 13.1% and 13.1% in the transplant group compared to 83.5% and 89% in the non-transplant group.

In 2022 Maspero et al. published a retrospective analysis comparing survival and disease recurrence in NELM patients undergoing transplantation (n – 48) or liver resection (n – 56) treated at the same center in 1984–2019. Patients undergoing LTx had better long-term outcomes compared to resected patients: 5-year and 10-year OS rates of 95.5% and 93% *vs.* 90% and 75%, respectively; 5-year and 10-year DFS rates of 75% and 52% *vs*. 33% and 18%, respectively.

In the aforementioned Milan group study, there was also a different pattern of cancer recurrence in the treatment groups. Multi-site recurrence was more frequent in patients after LTx (48% *vs.* 12%), in patients after resections mainly in the liver (88% *vs.* 8%), and recipients after LTx had longer median time-to recurrence (6.5 years *vs.* 2 years) than those undergoing only liver resection [42].

Also in 2022, Eshmuminov et al. analyzed a data pool from 15 large international centers on their NELM patients treated with LTx or liver resection (LR). Study concern 455 patients with NELM who underwent LTx (n – 225) or liver resection (n – 230) between 1988 and 2021. Multivariable analysis revealed negative prognostic factors: G2-NELM and LT outside Milan criteria for transplanted patients, while G3-NELM for resected patients. Comparison results are: 73% 5-year OS after LT *vs*. 52.8% 5-year OS after LR and 64.2% DFS after LT *vs.* 14,2% DFS after LR [43].

A favorable LTx result for NELM can be achieved by appropriate risk stratification in tumor biology, burden of the NELM, R0 resection feasibility, patient performance status, and expected waiting time for LTx. Based on the analysis of prognostic factors, the following was reported:

- LTx should be reserved for G1 and G2 NELM only based on mitotic and proliferative index (e.g. Ki-67). A Ki-67 index over 10% has been considered a marker of poor prognosis,

- the Milan group suggested that only liver metastases from NETs with
- portal venous drainage should be considered for LTx,
- functional involvement of the liver parenchyma at a level of 50% has been suggested as a cut-off point in considering to transplant. However, due to the subjectivity of the assessment this should not be considered as an absolute contraindication,
- resection of the primary tumor prior to LTx is recommended in order to
- monitor NELM biological response,
- LTx with R1 or R2 margins is not recommended,
- evidence of extrahepatic spread is a contraindication to LTx,
- the correct LTx time remains debatable. Some authors have proposed 6 months as the waiting time for observation of biological behavior of the tumor,
- there is no consensus on the importance and reasonable cut-off age for LTx [44].

LTx for CRLM – introduction

According to Global Cancer Statistics 2020, colorectal cancer is the third most common cancer in the world's population (out of 36 malignancies in 185 countries) and the second, after lung cancer, with the highest mortality [45]. Over the last quarter of a century, the incidence of colorectal cancer has been increasing, especially in the group of young adults [46]. The 5-year survival rate of patients with colon cancer according to the CONCORD 2 study (1995–2009) was slightly over 60% in twelve Western European countries. In Poland, this rate was 50% in patients with colon cancer and 47% in patients with rectal cancer [47]. The most common malignancy in the liver is metastasis of colorectal cancer [48], which will occur in more than 40% of patients with a primary tumor in the colon [49]. Technically feasible radical liver resection, presents the best treatment option, offering long-term survival [50–52]. More and more advanced parenchyma-sparing techniques are being used, which increase the percentage of patients in whom radical resection is possible [53, 54]. Despite nearly 50% of patients with colorectal liver metastases have unresectable disease [55–57]. This leads to an extremely unfavorable situation, because the 5-year overall survival of patients with CLRM treated only with systemic therapies is less than 20% [58]. In addition, 40–75% of patients experience a recurrence of the malignancy after surgery [59, 60], with more than half the recurrences involving the liver [61, 62]. Despite repeated resections, the prognosis is poor and depends on hepatic failure due to subsequent progression and recurrence. During the initial qualification for LTx of patients with CRLM, in order to exclude extrahepatic lesions, it is mandatory to perform a 3-phase angioCT, MRI and PET-CT with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). However, due to the possible false-negative results of involvement of the lymph nodes of the hepatic lymph confluence (hepatoduodenal ligament) in imaging studies, it is recommended to take a frozen section sample of the above-mentioned lymph nodes [63]. PET-CT is a valuable tool in evaluating extrahepatic metastases. In addition, from the data, PET-CT can be estimated by the so-called defined metabolic tumor volume (MTV) as an enhancement volume that is equal to or greater than 40% of the normalized maximum uptake volume [64]. This helps to assess the biological aggressiveness of the tumor, and MTV seems to be an effective predictor of poor prognosis after LTx in patients with CLRM. Cumulative MTV of all liver lesions per patient below 70 cm^3 clearly differentiates between better and worse long-term survival [65].

Selection criteria for LTx for CRLM

The prerequisite for qualifying a patient with CLRM to LTx is that the primary lesion was radically removed in accordance with the standards of care. The foregoing selection process basically aims to identify patients with favorable tumor biology which is hard to define term. Tumor biological behaviour associated to an array of clinicopathological and molecular features/properties characterized by high variability among patients and types of cancer. After the analysis of the qualification process and the results of trials: SECA II, RAPID, Compagnons group and preliminary data from LDLT trials in North America centers, the factors associated with poor prognosis after LTx for CRLM were given and divided into 4 groups [66].

Group 1 – characteristics of the primary tumor: primary tumor on right side of large intestine, lymph node positive primary tumor, time interval between primary resection to liver transplantation <2 years, signet ring cell carcinoma, BRAF mutation. Group 2 – characteristics of liver metastases: largest lesion >5 cm in size (Fong score) or 5.5 cm (Oslo score), more than one lesion, synchronous metastases, progression of metastases during chemotherapy, metabolic tumor volume (MTV) >70 cm^3. Group 3 – disease extent: presence of extrahepatic disease. Group 4 – molecular biomarkers: carcinoembryonic antigen.

Most of these factors are reflected in the scales used to qualify patients with CLRM to LTX. Mainly, the five-stage Fong scale (Fong Clinical Risk Score – FCRS), which was created in 1999, originally to assess the risk of recurrence of colorectal cancer after resection, and the four-stage Oslo Score (2020), which is the esult of the experience of the Norwegian group in LTx patients with CLRM (SECA I and SECA II studies). The four-stage Oslo score with each criterion value 1: largest lesion diameter >5.5 cm, pre-transplant CEA level >80 lg/ml, progression on chemotherapy, time from resection of primary tumor to transplant <24 months. The five-stage Fong Clinical Risk Score with each criterion value 1: node positive primary, interval from diagnosis of primary to liver metastasis <12 months, >1 liver metastasis, pre-resection CEA level >200 lg/ml, maximal lesion diameter >5.0 cm. For both scales, selection based on a score of 0 to 2 has been associated with 5- year survival outcomes comparable to other indications for liver transplantation [67].

Table II. Summary outcomes reported from selected series on LTx for CRLMs

First author	Year of publ.	Incl. period	Country/city	Patients (n)	1-year OS	3-years OS	5-years OS	1-year DFS	3-years DFS	5-years DFS
Hoti	2008	? –1994	ELTR data	50	62%	–	18%	–	–	–
Hagness	2013	2006–2011	Norway	21	95%	68%	60%	35%	–	–
Toso	2017	1995–2015	Lisbon, Coimbra, Paris, Geneva	12	83%	62%	50%	56%	38%	38%
Dueland	2020	2012–2016	Norway	15	100%	83%	83%	53%	44%	35%

OS – overall survival; DFS – disease-free survival

Literature review

To date, preliminary and longer-term results of only three major considerate studies of the efficacy of LTx in patients with unresectable CLRM have been reported (tab. II).

- SECA I [68]: in period 2006-2011, included 21 patients, Oslo/Norway, results: OS – 1-year 95%, 3-years 68%, 5-years 60%, DFS – 1-year 35%, 2-years 0%, conclusion: LTx is feasible for patients with unresectable CLRM.
- SECA II [69]: in the period 2012-2016, included 15 patients, Oslo/Norway, results: OS – 1-year 100%, 3-years 83%, 5-years 83%, DFS – 1-year 53%, 2-years 44%, 3-years 35%, conclusion: more restrictive selection criteria improve outcomes.
- Compagnons Hepato-Bilaires [70]: included 12 patients, Lisbon/Coimbra/Paris/Geneva, results: OS – 1-year 83%, 3-years 62%, 5-years 50%, DFS – 1-year 56%, 2-years 38%, 3-years 38%.

As mentioned, several studies of the effectiveness of LT in patients with CRLM are currently in progress and the preliminary results are still 2–3 years away. These are prospective, randomized studies on deceased donor liver transplantation, LDLT and Rapid procedure [71].

Conclusions and recommendations

In conclusion for neuroendocrine neoplasms, unresectable NELM resistant to conventional therapy with no evidence of extrahepatic disease is an accepted indication for LTx. However, the recommendations of the working group from the ILTS Transplant Oncology Consensus Conference should be used [72]:

1. "LT should be considered as a potentially curable treatment option for selected patients with unresectable metastatic NET of midgut/hindgut origin confined to the liver (moderate level of evidence and strong recommendation).
2. Selection criteria should consider ^{68}Ga-DOTATATE, Ki-67, histology, site of origin, and a certain time interval of stable disease or good response to therapies (moderate level of evidence and strong recommendation).
3. LT for selected patients with metastatic NET confined to the liver as part of multimodality therapy should achieve comparable outcomes as LT for other diagnoses (moderate level of evidence and strong recommendation).
4. Everolimus has achieved improvement in progression-free survival in NET and should be considered as part of immunosuppression after LT for NETLM (low level of evidence and strong recommendation).
5. Late recurrences beyond 5 years after LT are not uncommon, necessitating long-term follow-up with annual imaging (moderate level of evidence and strong recommendation)."

In conclusion for CRLM, LTx is an exciting therapeutic option for patients with unresectable metastases to the liver from the large intestine, and ultimately it can also be used for selected resectable patients. Current evidence is limited, but many studies are ongoing, and it is likely this field will grow significantly over the next decade with increasing experience and knowledge about outcomes, selection criteria and prognostic factors becoming available.

For liver transplantation due to CRLM, Transplant Oncology working group's guidelines have also been developed to point the way to an optimal selection of patients for LT and prepare the ground for future basic and clinical research [70,72], so quoting:

1. "LT can be a viable option in highly selected patients with unresectable CRLM with only liver involvement (moderate level of evidence and moderate recommendation).
2. LT for CRLM with low Oslo score ≤2 (maximum tumor diameter ≤5.5cm, pretransplant carcinoembryonic antigen ≤ 80 μg/L, response to chemotherapy, time interval: diagnosis to LT ≥ 2 y) may improve the 5-year overall survival rates over those achieved with the current standard of care (moderate level of evidence and moderate recommendation).
3. Minimization of immunosuppression is recommended (low level of evidence and moderate recommendation).
4. Aggressive treatment of all posttransplant resectable recurrences is recommended (low level of evidence and moderate recommendation).
5. There is a need for an international registry to coordinate data collection and design further studies on LT for CRLM (moderate level of evidence and moderate recommendation)."

Various forms of liver transplantation (orthotopic, partial, living related, auxiliary – RAPID/RAVAS) are a challenge and controversial (mainly ethical), but also potentially the most effective approach to cure patients with NELM or CRLM. Over time, we observe better patient selection (both in terms of transparency and stringency) and better immunosuppression strategies, which transfers to longer overall survival of patients and cancer recurrence-free survival. For patients with NELM, the role of neoadjuvant/adjuvant therapies in reducing post-transplant recurrence needs to be solved. For patients with CRLM, the completion of several ongoing prospective studies in 2–3 years will help to determine the effect of LTx compared to palliative chemotherapy, hepatic artery infusion (HAI) or other best possible therapy and the validity of the selection criteria.

Article information and declarations

Author contributions

Marcin Kotulski (70%) – concept of the study, review of the literature, writing and editing the manuscript.

Piotr Smoter (20%) – review of the literature, writing and editing the manuscript.

Tadeusz Wróblewski (5%) – review of the literature, writing and editing the manuscript.

Michał Grąt (5%) – review of the literature, writing and editing the manuscript.

Conflict of interest

None declared

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Review article

Clinical nutrition in oncology

Quality of life as an important goal of therapy for cancer patients on home enteral nutrition

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Nutritional support is increasingly recognized as an important component of multimodal cancer treatment. The number of cancer patients requiring home enteral nutrition (HEN) is increasing, particularly for head and neck (HNC) and upper gastrointestinal cancers. The quality of life (QoL) of these patients is emerging as a critical aspect that is influenced by the effective management of cancer-related symptoms, psychological support, and the socio-functional impact of HEN. Routine and standardized monitoring of QoL is highlighted as crucial for evaluating the effectiveness of HEN and for adapting treatment strategies. The interaction between nutritional status and other aspects of health such as physical functioning, psychological well-being, social engagement, and pain management is emphasized. Improving quality of life as a goal in palliative care should guide treatment strategies and the need for advanced nutritional support.

Key words: home enteral nutrition, quality of life, cancer, malnutrition

Introduction

The growing awareness of multimodal support in approaches has led to an increased focus on nutritional support, as underscored in European guidelines [1] and Polish recommendations [2–4]. Most oncology patients benefit from food fortification with the support of a clinical dietitian. However, enteral nutrition (EN) is indicated for malnourished patients or patients at risk of malnutrition who cannot meet their needs with oral nutrition and 'have a functioning digestive tract (tube, gastrostomy, jejunostomy) to a functioning digestive tract. If hospitalization is no longer required, these patients can transition to home enteral nutrition (HEN) [5]. In many countries, including Poland, HEN is reimbursed by health care provides. Home care supervised by specialized nutritional support teams (NST) reduces hospital admissions, the incidence of infectious complications, and treatment costs [8] by providing multidisciplinary care. Technological advances such as peristaltic feeding pumps or closed feeding systems can contribute to greater efficacy, safety, and patient comfort [6, 7] in long-term nutritional treatment. This can be achieved through appropriate training of patients and caregivers by specialized healthcare professionals. Improvement or preservation of nutritional status remain primary objectives of nutritional treatment. However, this review aims to draw attention to quality of life as an equally important issue, particularly in cancer patients.

Home enteral nutrition in cancer

Epidemiological studies indicate a worldwide increase in the number of patients requiring HEN [9, 10]. In the United States, the number of HEN patients increased from 463 in 1995 [11] to 1,385 per million citizens by 2017 (248,846 adult patients in total) [12]. This trend is consistent in Europe as reported by countries with national registries or long-term observations [5, 13]. Recent studies show that cancer patients have become

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a significant group among HEN recipients together with patients with neurological disorders [14]. HEN can be required due to obstruction in the gastrointestinal tract caused by tumor masses, such as in esophageal or gastric cancer, or due to mucosal damage and dysphagia caused by oncological therapy for head and neck cancer (HNC). In Poland, cancer patients accounted for 14% of all HEN cases in 2013 [15] and up to 33.9% in 2018 [16]. A particularly significant increase was seen in HNC patients (from 4.5% of all HEN patients in 2013 to 20% in 2018) and upper gastrointestinal tumors (from 5.2% to 11.7%). UK data also showed similar trends with the rate of oncological patients receiving HEN increasing from 25% in 2000 to 43% in 2015, and HNC patients clearly predominating this group (80% of oncological patients in 2015) [17, 18].

In those groups of cancer patients, especially during oncological treatment, a significant proportion may be unable to fulfill their nutritional requirements through oral intake alone. EN, especially in HNC patients, substantially contributes to therapeutic benefits by preventing chemotherapy dose reduction, excessive weight loss, and complications [19]. Postoperative body mass index (BMI), lean body mass, appendicular muscle mass and the postoperative pneumonia rates also improved in patients with esophageal cancer, compared to patients receiving only an oral diet [20]. In addition, a recent systematic review and meta-analysis has shown that HEN not only improves the postoperative nutritional status but also the physical, social, and role functions of patients with esophageal cancer [20].

The effectiveness of home EN depends on several factors such as diet tolerance, management of EN complications, appropriate pain management, mental health (depression) support, rehabilitation, and physical exercises. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends HEN for patients with a survival prognosis of at least one month [1]. For cancer cases where the remission or cure cannot be achieved, prolonged nutritional support aimed solely at improving or maintaining quality of life is considered beneficial [21].

Quality of life

Improving or maintaining quality of life is a major goal for cancer patients treated with HEN, especially in advanced stages of the disease. According to the ESPEN guidelines, QoL should be systematically monitored using validated assessment tools [26]. Due to the different populations of HEN patients, some NSTs use disease-specific assessment methods, for example IBDQ [27], QOL-EF for H&N [28], EuroQol-5D (EQ-5D) [29] or EORTC QLQ-C30 with modules for specific cancer types. NutriQoL is a validated and reliable quality of life assessment questionnaire that can be used to identify specific problems for HEN populations [30, 31].

Other studies have shown that QoL in HEN patients is generally worse than that of the general population, although this is dependent on demographics. Better QoL is observed in younger individuals, non-cancer patients, and those receiving care from multiple caregivers. In a study by Sharma et al., the quality of life of HNC patients was analyzed. Within the first three months of treatment, a significant deterioration in physical, emotional, social, and functional aspects was observed. One year after treatment, none of the subscales returned to baseline values. Surgery in combination with chemo-radiotherapy had the strongest impact on QoL among the treatment modalities [23]. Sensitivity problems, mouth opening, dry mouth, viscous saliva, pain, and weight problems can be observed even long after treatment [24]. The health-related quality of life of patients with locally advanced, non-metastatic gastric cancer deteriorated significantly after surgery and chemotherapy, improving after 6–12 months if no recurrence was diagnosed [25].

HEN significantly interferes with daily activities such as meals, sleep, travelling, and work, and often limits social activities due to long feeding times and concerns about damaging the EN tube [35, 36]. Enteral feeding affects social and family life, intimate relationships, and hobbies [32–34]. Nevertheless, patients observe an improvement in QoL during HEN [35–37], which was confirmed by a systematic review by Ojo and co-authors [38]. On the other hand, some studies indicate possible adverse effects, emphasizing the complexity of nutritional interventions in cancer treatment [36]. Lis showed in a systematic review that malnutrition significantly impairs the quality of life of patients with EN [39]. Weight loss is associated with poorer quality of life in patients with HNC and upper gastrointestinal cancer undergoing HEN [40]. Malnutrition assessed according to the Global Leadership Initiative on Malnutrition (GLIM) criteria correlated with QoL in HEN [41]. However, HEN can prevent further weight loss and thus, improve some aspects of QoL [42–43]. Studies on the effect of HEN on nutritional status and QoL in patients with esophageal cancer after esophagectomy found that HEN can stabilize or slightly improve nutritional status and physical performance as well as reduce fatigue [44, 45]. When nutritional support is initiated in the early stages of precachexia or cachexia, it can also improve performance status and survival [46].

Effective management of symptoms associated with cancer and its treatment, such as nausea, vomiting, pain, and digestive problems, is a critical component of QoL. In addition, the physical and mental health and QoL of cancer patients are related to sleeping problems. Sleep quality can be considered a prognostic factor for survival as it is related to cancer progression [25, 47]. More than half of cancer patients report poor sleep quality, and one third report functional impairment due to lack of sleep [48].

Chronic pain is another important factor contributing to the deterioration of quality of life in cancer patients [49, 50]. Although improvements in pain management have been noted in recent years, more than a third of cancer patients still do not receive adequate treatment [51, 52]. Inadequate pain management leads to further deterioration of QoL [53]. Pain and malnutrition contribute to depression and anxiety, which are common in cancer patients. In palliative stages, almost half of patients can be affected by these problems [54–56]. Psychological support can promote active coping and constructive strategies to manage difficult life situations during oncological treatment [22].

Nutritional support in palliative care requires experienced professionals as it can lead to poorer outcomes in some cases [57]. In cancer patients receiving palliative care, monitoring of QoL in HEN is particularly important. A significant decline in QoL, despite treatment, should prompt a reassessment of the need for more aggressive nutritional strategies. In end-stage disease, it may be more beneficial to prioritize supportive measures such as hydration and analgesia.

Conclusions

QoL is an important outcome for cancer patients receiving HEN. Regular, systematic assessment using validated instruments should be an integral part of patient monitoring. Strategies to improve QoL are essential components of care. Addressing problems affecting QoL like pain, sleeping disorders or depression is one of the key elements of care. HEN patients should have access to psychological support, especially in advanced stages of cancer. Deterioration of QoL can be a helpful parameter when deciding on the nature of palliative care.

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Review article

Cancer prevention and public health

Cancer patients and smoking cessation

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Abstinence from smoking is the most important element of cancer prevention. Tobacco smoking is responsible for at least 15 different types of cancer and almost 30% of all cancer deaths. There is evidence that not only does smoking after a cancer diagnosis pose negative effects for cancer treatment efficacy and tolerability, but quitting smoking after a cancer diagnosis has significant benefits. They include: increased survival rates and decrease overall mortality, decreased risk of another primary cancer, decreased risk of recurrence, increased tolerance to oncological treatments and increase of its efficacy, reduced pain. Quitting smoking improves quality of life too. Nicotine dependence is not only a patient's choice and lifestyle element but a chronic and relapsing disease. Failure to undertaken nicotine dependence treatment by the centre's staff may be treated as malpractice. Various evidence-based treatment options are available and they can, or even should, be adapted to the specificity of oncological patients.

Key words: cancer prevention, nicotine dependence, tobacco smoking, smoking cessation, cancer patients

Introduction – tobacco smoking and the health burden

In the European Code Against Cancer the first and most important recommendation for cancer prevention is abstinence from tobacco smoking. Tobacco smoking is responsible for almost 30% of all cancer deaths worldwide and is the single most significant factor of them [1]. Tobacco smoke, containing approximately 7,000 thousand chemical compounds, is classified by IARC as a human carcinogen. The scientific evidence is so extensive that it has been included in the highest of four groups of classifications. It means that there is no doubt that exposure to it is associated with a high risk of developing cancer. Approximately 70 carcinogenic substances found in tobacco smoke act as both initiators and promoters of the carcinogenesis process [2]. There are at least 15 different cancer localization in human body with a proven causal relationship with exposure to tobacco smoke. The highest risk is observed for lung cancer, with the risk attributed to be 90% in men and over 70% in women [3]. On average, a lifetime smoker has a 20-fold higher risk of developing lung cancer, compared with a lifetime non-smoker [4]. In the whole of Europe, lung cancer accounts for 24% of all cancer-related deaths and is the most common cause of death among men. In several European countries, including Poland, it is also the leading cause of cancer death among women [5, 6]. A slightly lower attributable risk, as much as 85%, is observed for head and neck cancers, e.g. mouth, throat, larynx, nasal cavity and apart from alcohol consumption, this is their most important cause. According to the results of many years of research conducted by the International Agency for Research on Cancer, tobacco smoking is also causally associated with other cancers, i.e., pancreas, bladder, stomach, liver, renal pelvis, colon, myeloid leukemia, ovary and cervix [7]. Tobacco smoking and tobacco-attributable cancer mortality remains one of the most significant health burdens in the Polish population. Annually, more than

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30 thousand Polish men and women die from cancer caused by smoking [8].

Despite many efforts to reduce smoking around the world and many successes in this field, the smoking population was 22.3% in 2020 (36.7% of all men and 7.8% of women) [9]. The prevalence of smoking among patients diagnosed with cancer is high – over 60% of them are smokers, former smokers or recent quitters [10]. Continuing to smoke after a cancer diagnosis is particularly disturbing. It seems that patients treat a cancer diagnosis as a death sentence and a condition in which it is too late to quit smoking.

Risk of smoking continuation after cancer diagnosis

Smoking has been linked not only to the development of disease, but also to prognosis upon diagnosis and risk of death during treatment. The adverse effects are found both in patients with smoking-related cancers and in those with nonsmoking-related cancers.

Overall mortality

Research data have proven that continued smoking by cancer patients is causally associated with all-cause and cancer-specific mortality. Continued smoking is among the strongest adverse predictors of survival in cancer patients [11]. For example, in patients with head and neck cancer who smoked during radiation treatment, the two-year survival rates were 39% compared to 66% in non-smokers. In a multivariate analysis, after taking into account age, disease stage and concomitant chemotherapy, the risk of death was 2.5 times higher in patients who continued smoking than in former smokers or never smokers [12].

Increased risk of second primary cancer

There is some evidence that smoking after cancer diagnosis increases not only the incidence of a first, but also a second primary cancer. The most frequent are tobacco related malignancies such as lung, head and neck, stomach and hematological cancers. A systematic review and meta-analysis of randomized and longitudinal observational studies demonstrated a four times higher risk of developing a second primary tumor for small-cell lung cancer patients who continued smoking, than for those who quit at diagnosis. [13] In the study done by Rice et al., a prospective analysis to investigate the risk of second primary cancer in a group of 569 patients with stage I non-small cell lung cancer who had undergone complete pulmonary resection was conducted. Over a median follow-up period of 5.9 years, 15% of the patients developed second primary tumors. Over half of them (56%) were additional lung cancers. The incidence of second primary lung cancers nearly doubled among current smokers compared to those who were former smokers [14].

If the patient was treated with radiation to the chest area, the risk of lung cancer as a second primary tumor increases 13 fold, if he smokes at the same time – 21 fold, in patients undergoing chemotherapy the risk increases 9–13 fold, and in patients who continue smoking – 19 fold [15]. Smoking by women cured of breast cancer increases the risk of lung cancer six fold, and if the patients were treated, among others, radiation to the chest area, this risk increases 9 fold [16]. Active smokers are at particularly high risk of developing lung cancer. In smokers who have been treated for Hodgkin's lymphoma in the past with, among others, radiotherapy, this risk increases 20 fold, and in the case of a combination of smoking, radiotherapy and chemotherapy with alkylating drugs, the risk increases 50 fold [16].

There is also a known relationship between smoking and the risk of prostate cancer recurrence. Men after radical prostatectomy who continue to smoke have a 30% greater risk of biochemical recurrence, a 2.5 times greater risk of resistance to anti-androgen treatment, a 2.5 times greater risk of distant metastases and a twice the risk of death during the course of cancer [17].

Stopping smoking at any stage of cancer reduces the risk of disease recurrence and secondary cancers.

Decreased effectiveness of therapy

The poorer effects of treatment with radiotherapy was observed in smoking patients compared to patients who stopped smoking or were never smokers. An adverse effect of smoking has been observed for efficacy of treatment with radiation and for systemic chemotherapy. In a study done by Browman et al. in smoking patients with head and neck cancer, the percentage of overall responses to treatment during radiation was 45% compared to 74% in non-smokers [12].

Smoking may interact with some drugs pharmacokinetics and can affect treatment outcomes, including cancer treatments. Smoking alters the drug metabolism due to affecting cytochrome P-450. Additionally, smoking increases the risk of drug resistance and the fluctuation of drug concentrations. Research on specific medications has indicated that the extent of pharmacokinetic disruption caused by smoking is comparable to that of other clinically significant drug interactions. This disruption is significant enough to influence recommended dosages. [18]. Lung cancer patients who persist in smoking demonstrate a more rapid elimination of erlotinib and gefitinib compared to non-smokers, potentially necessitating the administration of higher doses of these compounds to achieve comparable systemic levels. In this patient population, pharmacokinetic and toxicity profiles for smokers receiving erlotinib at a 300 mg daily dose is similar to that in nonsmokers receiving 150 mg daily, which could suggest that the daily dose of erlotinib in current smokers should be increased to 300 mg. Tobacco smoke was also demonstrated to affect the pharmacokinetics and toxicity of irinotecan, a topoisomerase-I inhibitor used in small-cell lung cancer [11].

Increased risk of complications in anticancer treatment

In patients with head and neck cancer, smoking during radiotherapy treatment significantly heightens the likelihood of experiencing radiotherapy-induced complications. These can include oral mucositis, weight loss, fatigue, xerostomia (dry mouth), altered taste sensation, and vocal difficulties [19]. Prostate cancer patients who were currently smoking, in contrast to those who had never smoked, exhibited a higher likelihood of encountering radiotherapy-related symptoms such as defecation urgency, diarrhea, a sensation of the bowel not being completely emptied after defecation, and abdominal cramps. On the other hand, former smokers did not show an elevated prevalence ratio for these symptoms [20].

An additional important issue is also the increased risk of surgical complications in smoking patients. Postoperative healing complications occur significantly more often in smokers compared with nonsmokers and in former smokers compared with those who never smoked. In a total of 140 cohort studies involving 479,150 patients, smokers and non-smokers were compared revealing the increased risk for following complications: almost a 4-fold risk of necrosis, double the healing delay and dehiscence, wound complications, hernia, and almost two and half times greater risk of lack of fistula or bone healing. The surgical site infection in smokers was almost twice that among non-smokers or ex-smokers [21].

In a population of 140,000 patients undergoing major surgical procedures, including oncological ones, cigarette smoking significantly increased the risk of at least one postoperative complication. The following oncological procedures were included in the analysis: removal of the esophagus, stomach, large intestine, pancreas, removal of the kidney or bladder, removal of the uterus and lung resection. In active smokers, compared to never smokers or smokers in the past, the following complications were significantly more common: cardiovascular, pulmonary, neurological, thromboembolic, septic (including septic shock), renal failure, urinary tract infections, need for blood transfusion, the need for reoperation, the need for rehospitalization, smokers required longer hospitalizations; only differences in peri-procedural mortality did not achieve statistical significance [22].

Quality of life and pain

Compared to never or former smokers, patients with head and neck cancer and lung cancer who continued smoking had poorer physical health, self-perception of their general health, emotional and social functioning, and vitality. Patients who continue smoking after a diagnosis of cancer also experience higher levels of cancer-related symptoms than nonsmokers or former smokers. Compared to never or former smokers, cancer patients who continued smoking have worse physical health, self-perception of their general health, and both social and emotional functioning. They also experience less vitality [23–25].

Smoking cessation and benefits for cancer patients

According to studies, evidence is sufficient to infer that smoking cessation reduces the risk of the following cancers: lung, laryngeal, oral cavity and pharynx, esophageal, pancreas, bladder, stomach, colon, liver, cervix, kidney and acute myeloid leukemia [26]. Apart from disease site and stage, abstinence from smoking is considered the strongest predictor of survival in cancer patients who have ever smoked [11]. Stopping smoking is associated with improved outcomes even among patients diagnosed with the most attributable to smoking cancer, i.e. lung cancer. Quitting smoking prolongs survival and reduces the incidence of cancer recurrence in this population of patients. A review of the literature showed that in patients diagnosed with early-stage non-small cell lung cancer, smoking cessation reduced overall mortality by 66% and the risk of recurrence or secondary lung cancer by 46%, compared to those who continued smoking. Similarly, in patients with small-cell lung cancer, smoking cessation reduced overall mortality by 46% and the risk of recurrence or primary lung cancer by 77% [27].

In a study examining the effectiveness and complications of radiotherapy in patients with advanced head and neck cancer, stopping smoking for at least one month was associated with a significant reduction in the duration of mucositis after radiotherapy [16].

In a study described by Daniel et al., moderate to severe pain was reported by 60% of persistent smokers with lung cancer while only 37% of nonsmoking patients reported it [28].

In summary – smoking cessation after cancer diagnosis is connected with many significant benefits like reduced risk of death by 30-40%, reduced risk of recurrence and second primary cancer, reduced risk of treatment complications, increased response for treatment, better quality of life and less pain. Although the benefits of smoking abstinence are evident regardless of stage and prognosis, they are undervalued by both health professional and patients themselves. In most cases the advice on smoking cessation provided by medical staff contains the information about risk of continuation of smoking rather than the information about benefits of quitting smoking. However, good medical practice requires informing the patient not only about the risk of deterioration of prognosis if they continue smoking, but also about the improved chance for anticancer treatment results.

Treatment of nicotine dependence

Smokers with life-threatening illnesses, which may in part be attributable to their use of tobacco, still have great difficulty in achieving permanent abstinence, with as many as about 50% of lung cancer patients returning to smoking after surgery [29]. It is mainly due to the nature of nicotine – a substance acknowledged to be as addictive as alcohol, heroin or cocaine [30]. Nicotine addiction is a disease included in the 11th revision of International Classification of Diseases (6C4A.2). It is characterized by a strong internal craving and impaired control over nicotine use. The need to take nicotine becomes a priority over other activities and a persistent habit despite the potential harm or negative consequences. The need to use nicotine results from a biological addiction, often accompanied by a subjective craving for its delivery, especially in certain social situations or emotional states. Addicted people often have physiological features of addiction, including tolerance to the effects of nicotine, withdrawal symptoms after stopping or reducing nicotine use. Withdrawal symptoms are a clinically significant set of symptoms, behaviors and physiological characteristics that occur after cessation or reduction of nicotine use in nicotine-dependent individuals. Nicotine withdrawal symptoms may include dysphoric mood, depression, insomnia, irritability, anger, anxiety, difficulty concentrating, restlessness, bradycardia, increased appetite and so-called nicotine craving. In the process of diagnosing nicotine addiction, in addition to determining its occurrence, it is recommended to determine the strength of nicotine addiction and the readiness to stop smoking. The strength of the biological addiction is assessed by the Fagerstrom Nicotine Dependence Test (FNDT), which the patient can complete independently while waiting for the appointment. The FNTD is widely used in clinical practice and in clinical and scientific research. The second important step is to determine the patient's readiness to stop smoking. Readiness to quit is, according to research, one of the important factors determining therapeutic success in maintaining long-term abstinence [31].

In the treatment of nicotine addiction, there is a selection of pharmacological methods available, the effectiveness and safety of which have been confirmed in clinical trials. Currently, those available are: nicotine replacement therapy (NRT), antidepressants and partial agonists of nicotine receptors.

Nicotine replacement therapy

The aim of nicotine replacement therapy (NRT) is to replace the nicotine that people who smoke usually get from cigarettes, so the urge to smoke is reduced and they can stop smoking completely. The main aims of NRT are three: craving reduction, withdrawal control, and abstinence promotion [32]. Nicotine replacement therapy products are available in transdermal form (patches), oral form (gum, lozenge, tablets, inhaler), and in some countries as a nasal spray. They provide nicotine, stabilizing its level in the blood in order to avoid a withdrawal syndrome after stopping smoking. As per producer suggestion, the treatment lasts for 10–12 weeks, but it can be prolonged to 6 or even 12 months. There are two types of product depending on the way of acting – long acting administrated once a day (patches) and short acting which are administrated multiple times per day (lozenges, pills, spray). Using nicotine patches together with another type of NRT (such as gum or lozenges) made it 17% to 37% more likely that a person would successfully stop smoking than if they used one type of NRT alone. Very few people experienced negative effects of using NRT during the quit attempt and there is no contraindications to the use of NRT in patients with cancer.

However, the use of oral, short-acting nicotine preparations may be considered questionable or contraindicated in people with damage to the larynx, esophagus and mucous membrane of the head and neck organs resulting from cancer or oncological therapy. In these patients, it is better to use another treatment with documented effectiveness. People who decide to use nicotine patches should know that they can only be used on intact skin, so they should not be used on areas undergoing radiotherapy. The patient should be aware of the potential risk of allergies in the area where the patch is applied; cases of local loss of subcutaneous fat tissue at the site of application have also been described, so it should be systematically changed.

When determining the initial dose of nicotine, we can use one of its metabolites – cotinine. It is an alkaloid with a long half-life, so its concentration in the blood or urine reflects exposure to the parent substance – nicotine. However, these determinations are not available or cheap, and we can successfully use the estimation method, according to which the daily dose of nicotine is determined based on the number of cigarettes smoked. The latest recommendation is to start from a maximum dose of nicotine and to combine the long- and short-acting form of NRT [33].

Bupropion

Bupropion is a selective inhibitor of noradrenaline and dopamine reuptake and has a minimal effect on serotonin reuptake. Bupropion is an antidepressant available in pills contains 150 mg of active substance. Bupropion administration begins 1–2 weeks before the patient's scheduled smoking cessation date. The treatment length is 12 weeks, but it can be prolonged if necessary. There is high-certainty evidence that bupropion increases smoking cessation rates when compared to a placebo or no pharmacological treatment in the general population [34]. In the cancer patient population, bupropion increases abstinence rates, lowers withdrawal, and increases the quality of life. However, abstinence rates among patients with depression symptoms were lower than in patients without depression symptoms at the beginning of treatment. Additionally, a systematic review of 7 studies proved that bupropion may be an effective and safe intervention for fatigue in cancer and non-cancer conditions. It is especially important since fatigue is a predominant and distressing symptom in cancer and non-cancer conditions for which there is a paucity of recommendations for pharmacological interventions [35]. Since bupropion is contraindicated for patients with seizure disorder, it should be avoided in patients with seizure risk, including those with brain metastases or primary brain tumors. There is evidence that bupropion combined with NRT increases the chance for successful quitting [36].

Partial agonists of nicotine receptor

There are two partial agonists of the nicotine receptor available for smoking dependence treatment – cytisine (herbal) and varenicline (synthetic). They help people to stop smoking by a combination of maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist). There is high-certainty evidence that varenicline helps in quitting smoking when compared to a placebo, but also shows superiority to bupropion and single form of nicotine replacement therapy. It is recommended also as safe and effective in the cancer patient population. However, varenicline has been withdrawn from the market due to Nitrosamine impurities and is no longer available. Cytisine is a herbal drug which works by the same mechanism as varenicline and is available for substantially less cost. It may lead to fewer people reporting SAEs than varenicline. There is moderate-certainty evidence (limited by heterogeneity) that cytisine helps more people quit smoking than a placebo. Based on studies that directly compared cytisine and varenicline, there may be no difference or benefit from either medication as regards quitting smoking [37]. The cytisine treatment regimen proposed by the producer is based on a very short, 25-day drug therapy. In some cases, extending the therapy helps to maintain abstinence and, consequently, increase the lasting effectiveness of the drug. Prolonged treatment could be particularly beneficial in oncological patients, but the daily dose should be limited to 6 tablets.

Although cytisine is not included in global guidelines for nicotine dependence treatment in the oncological population, it should be considered for use in cancer patients especially due safety of its use in the general population and its low price.

Electronic cigarettes and heat-not-burn products (HTP)

The use of e-cigarettes and HTPs is not recommended as a way of quitting smoking. There is currently insufficient evidence regarding the safety and effectiveness of their use as a smoking cessation aid in the general population or among patients diagnosed with cancer. Patients should always be advised to use evidence-based treatments for nicotine dependence [36].

Specificity of nicotine dependence treatment in the cancer patient population

Undoubtedly, cancer is connected with a particular physical and psychological burden for patients. A diagnosis of cancer requires patients and their relatives to face many challenges related to treatment, but also to face the diagnosis of a disease that can be fatal. Moreover, being diagnosed with cancers that are causally related to smoking involves the additional burden of dealing with other people's perceptions and feelings of guilt and shame. Although many diseases are related to lifestyle and daily habits, in public opinion, cancer patients, especially lung cancer patients, are most often blamed for their health problems [38]. The stigmatization of tobacco-related cancers and the self-stigmatization of patients is one of the factors that make it difficult to start treatment for nicotine dependence. They may intensify negative emotions, intensify depression and the mental crises that occur after a cancer diagnosis. Patients who feel blamed for their condition are reluctant to talk about addiction, and questions about their smoking history cause discomfort. Some patients, fearing negative evaluation, do not provide true information about addiction. The stigma associated with tobacco-related diseases may therefore significantly influence therapeutic decisions, including the decision to stop smoking. The non-judgmental attitude of medical staff and communication based on empathy and understanding of the fact that the patient is struggling with nicotine addiction is an essential condition for helping smoking cancer patients. It is important to focus on respecting the patient's subjectivity and using inclusive, non-judgmental language. Focusing solely on the negative consequences of continuing to smoke may make the patient feel judged for the development of the disease and lack understanding of how difficult it is to fight addiction. It is beneficial for the patient to discuss in detail the health benefits of quitting smoking in the context of a cancer diagnosis and the planned oncological treatment. Another key element of anti-smoking intervention is the subjective assessment of the patient's level of motivation to quit smoking. The patient's fears, resulting from, for example, past negative experiences in quitting smoking, or lack of confidence in one's own abilities, may be wrongly interpreted as a lack of motivation. Empathy, avoiding schematic thinking and authentic understanding of the difficulties encountered in quitting cigarettes (smoking, despite the harmful consequences, is defined as one of the symptoms of the disease that is nicotine addiction) are necessary conditions in communication with an addicted patient. Cancer diagnosis and anticancer treatment is considered one of the factors in the development of post-traumatic stress disorder (PTSD) [39]. At the same time, the feeling of a threat to one's life may provide an opportunity to reconsider the choice of one's basic life values and trigger changes in the area of health behavior, which may be referred to as post-traumatic growth. A traumatic event involving confrontation with the prospect of the end of life may lead to the activation of various adaptive behaviors. It is often called a teachable moment in people's life. A beneficial response style for the patient is to perceive the disease as a challenge and be ready to take active actions [40]. One such action may be trying to quit smoking. The condition is that patients understand that stopping smoking is important for the course of the disease and its treatment. The awareness that giving up cigarettes after cancer diagnosis may significantly affect the course and results of oncological treatment may be an important factor determining the motivation and willingness to change in smoking patients. Patients often think that "it is too late." Lack of understanding why quitting smoking is particularly important in the current health situation prevents people from taking the appropriate actions.

Equally important is the fact that a cancer diagnosis is a moment of loss of control and the ensuing sense of chaos. One way to regain control is to prepare for treatment and actively engage in the treatment process. Quitting smoking is an action that has a strong, positive impact on the prognosis, and can help the patient regain a sense of influence over his future. Most cancer patients quit or make an attempt to quit within a short time after diagnosis, so the most important message should be delivered as early as possible. Thus, it is necessary to involve medical staff in the process of identifying smoking cancer patients, providing non-judgmental support that includes information on the risks associated with continuing smoking after diagnosis and, above all, the benefits that the patient will receive. Unfortunately, despite the consensus that smoking cessation treatment should be an integral part of cancer care, most patients of cancer centers are not assessed for smoking-related behavior. A study carried out in Poland in 2023 shows that only 29% of oncology patients received information from medical staff about the negative impact of smoking on health, 15% received information about the negative impact of smoking on the effectiveness of oncological treatment, and 58% indicated that they were not talked to about smoking at all [41].

Obstacles to making anti-smoking interventions by medical staff may include beliefs that a cancer diagnosis is not the right time to discuss quitting smoking and talking about addiction would violate a patient's privacy, or that it is not part of their job duties. Health professionals may also have insufficient knowledge about the risks of continuing to smoke and the benefits of stopping smoking, or they may think that they do not have competence in the field of anti-tobacco interventions. Therefore, it is recommended that all physicians and other medical staff complete training in the evidence-based treatment of nicotine dependence. Increasing the level of anti-smoking counseling skills and updating knowledge on an ongoing basis are necessary to build a sense of competence among medical staff and thus ensure a readiness to discuss the issue of smoking addiction with patients. Participation in training has been shown to increase the involvement of health care professionals in smoking cessation counseling and also increase the percentage of patients quitting smoking [42]. Routine practice for cancer patients should be to identify those with an active smoking dependence, record their smoking status in the medical record, recommend smoking cessation and, ideally, offer treatment or discuss available treatment options.

Such interventions should be undertaken at every visit to the doctor and during hospitalization. Research shows that providing short (3 to 5 minutes) clear advice on quitting smoking by a member of the medical team increases both the patient's motivation to try to quit and their chances of achieving and maintaining abstinence [42, 43]. It has been proven that short counseling, so-called minimal intervention (5A's) is an effective way to initiate and monitor the effects of a quit attempt. An alternative to minimal intervention may be its shortened version called ask advise refer (AAR). The elements of the intervention include: routine assessment of smoking status among all patients and recording the information in medical records; brief, non-judgmental counseling on quitting smoking (focusing on the individual benefits of abstinence and indicating the risks associated with continuing smoking); referral of nicotine-dependent people to the National Quitline or other specialists [44].

Conclusions

The evidence is strong enough to incorporate tobacco dependence treatment into routine cancer care, but not many cancer centers report that they effectively identified tobacco use in their patients. Thus, tobacco cessation remains a challenging issue in the oncology population. Although there are many documented benefits of stopping smoking after a cancer diagnosis and the risks associated with continuing smoking, this topic is not often discussed by medical staff. If it is done, it is only during the first visit, however, due to the fact that the readiness of patients to quit smoking is changing over time and the importance of constantly motivating patients, it should be done at every contact with the patient. The message should be framed around the benefits of quitting smoking, not just the risks of continuing to smoke. Failure to inform the patient about the importance of stopping smoking for the effects of his anticancer treatment and overall survival should be considered as malpractice. Interventions should take into account not only those elements that are important in the treatment of smoking addiction in the general population, such as the depth of addiction or readiness to quit smoking, but also the specificity of patients diagnosed with cancer. These include higher levels of stress and anxiety, symptoms of depression, feelings of guilt, and the belief that it is too late to quit smoking. Anti-tobacco interventions conducted by an oncologist may be very short (1–1.5 minutes). It should contain only information conveyed in an empathetic and friendly way about the importance of stopping smoking for the effectiveness of anti-cancer treatment and advice on making a quit attempt with the help of a specialist. A more comprehensive intervention may be provided by a nurse or other specialist available in the hospital. It is important that healthcare professionals and educators continue to provide support and information to people affected by cancer to help them make and maintain positive changes in their health behaviors.

Recommendations

1. Nicotine addiction is a chronic and relapsing disease, thus every smoking patient should receive evidence-based treatment.
2. Nicotine dependence treatment should always include individualized pharmacotherapy, and behavioral counseling.

This may involve referring the patient for specialist help e.g. National Quitline.

3. Interventions aimed at stopping smoking should be carried out at every stage and throughout the patient's treatment process, by the entire team of the center – doctors, nurses, physiotherapists, radiotherapists, psycho-oncologists, health educators, etc.
4. Nicotine Replacement Therapy and/or cytisine should be available for patients during their stay in hospital.
5. The anti-smoking intervention should be tailored to the specificity of cancer patients, i.e. conducted in a non-judgmental way, not arousing a sense of guilt, taking into account the patient's mental state, i.e. higher levels of anxiety, depression, stress. The information should include information not only about further risks of continuing smoking but also about the benefits of quitting smoking for the effects and tolerability of cancer treatment.
6. The electronic database of patient records should enable not only the recording of the patient's smoking status, but also automatic activities supporting anti-smoking interventions for patients, such as, for example, an automatically generated referral to a specialist smoking cessation clinic, an information "leaflet" for patients about the positive impact of stopping smoking on the effects of anticancer treatment, information for primary care physicians on hospital discharge notes and others.
7. All health care professionals of cancers centers should be trained in smoking cessation intervention.

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Author contributions

Magdalena Cedzyńska – review of the literature. writing and editing the manuscript.

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Editorial

Breast cancer

Does an apple a day keep the doctor away? Cardiovascular prevention in breast cancer patients

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The aphorism "An apple a day keeps the doctor away", first in print coined as "Eat an apple on going to bed and you'll keep the doctor from earning his bread" as early as in 1866, has been tested by rigorous evidence-based approach [1]. Although the study was published on April Fool's Day in 2015 in JAMA Internal Medicine, it seriously tested the hypothesis that keeping to the rule above reduces the necessity of at least one visit per year. Unfortunately, the proverb did not pass the strict EBM threshold, although the study suggested that each-day-apple-consumers used fewer prescription medicines than the general population.

Dyrbuś et al. in this issue of *Nowotwory. Journal of Oncology* describe the variety of pharmacological preventive methods applied in contemporary cardio-oncology (*Pharmacological prevention methods in patients with cardiovascular disease with breast cancer – when, how, and for whom?*). The authors define when, how and for whom cardioprevention shall be applied; my insight here relates mainly to the question "Why?".

Since the beginning of cancer therapy, cardiotoxicity has been an issue of utmost importance. The first reports were related to post-anthracycline heart failure; the low magnitude of QRS complexes in ECG examination was the first considered, obviously not an early feature of this complication [2]. Polish oncological and cardiological community recognised the necessity of adequate patient monitoring. For example, Malinowski et al. analysed ECG data of patients treated by breast radiation between 1985 and 2002 and described the excess of ischemic features in patients with left-sided disease [3]. More recently, Kufel-Grabowska et al. studied the cardiotoxicity in patients treated with adjuvant trastuzumab after earlier anthracycline therapy [4]. The authors find significant differences in NT-proBNP concentrations at a post-treatment follow-up visit in patients with cardiotoxicity, while no such association for cardiac troponin levels. We have our Polish cardioprevention trials, both completed, e.g. ramipril study of Cracow team [5] or ongoing -- studies financed by Agency of Medical Research (EMPACT in Warsaw, MAINSTREAM in Zabrze, see clinicaltrials.gov).

In 2023 we can identify early signs of cardiotoxicity evoked by anti-cancer therapy and diminish its impact with effective preventive strategies. It was proven by some trials, which I refer to as "first generation". In second-generation studies, the population of patients for the intervention was selected by a marker of cardiotoxicity, with a defined population of high-risk patients eligible (see the review of Dyrbuś et al. for references). There comes a question – is the optimised management bringing benefit to patients' overall health? This issue is of raising importance, as last year European Society of Cardiology published comprehensive guidelines on cardio-oncology, developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). The document shows a complicated landscape of current cardio-oncology, with numerous procedures and classification schemes; many oncological practices and centres have problems fully implementing the algorithms into patient management pathways.

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We urgently need the trials of "third generation", where biomarkers/imaging strategies and pharmacological preventive approaches are linked to the tailoring of cancer therapy. There are many ways to adjust the intensity of cancer treatment, either adapting it to the response/toxicity or trying to make a perfect fit a priori, before initiating therapy. In breast cancer, we could easily avoid anthracyclines in HER2-positive patients (however, sometimes for a price of excess fatigue or non-cardiac toxicity), we may try to spare from cardiac burden patients with luminal cancers (although avoiding radiation or chemotherapy is not as straightforward, especially in premenopausal patients, where the potential long-term toxicity might be of utmost importance). Finally, in triple-negative individuals, where we usually apply relatively aggressive chemotherapy, we could add anti-PD-L1 immunotherapy or leave the patient without this additional cardiac risk factor. However, we deeply do not understand, what is the survival impact of every one of these decisions on patient survival. When decreasing the intensity of oncological therapy will provide a net benefit due to better cardiac health? Cardiologists sometimes joke that it is easier to fix the heart than cure cancer; however, we all know from epidemiological data that the death toll of late cardiac toxicity among cancer survivors is substantial. It holds true not only for the old cytotoxic chemotherapy but also for many novel targeted treatments [6].

I invite the readers of the article prepared by colleagues from Zabrze to get acquainted with cardiopreventive strategies and to apply them as broadly as possible, with benefit to the cardiac health of our patients. There shall also be a time for reflection, how is cardiology shaping oncology nowadays? Will cardiac specialists fix our failures or instead provide a critical selection gateway to the treatment? It is evident that merging both approaches is potentially the most effective; how to test it in clinical trials? And last but not least, it is critically vital that trials of oncological therapies will be open for wisely selected high-risk cardiac patients; only then we could learn whether in such a setting modifying the oncological treatment in parallel with maximal cardioprotection and effective rescue strategies provide a net health benefit.

And coming back to the role of a healthy lifestyle. There will be a time for fourth-generation trials, comparing pharmacological interventions with proactive exercise, diet, psychotherapy, education approach and testing which patients benefit, as well as providing rational advice on how to mix these strategies and provide patient compliance.

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Pictures in oncology

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The diagnostic dilemma of low-grade adrenal cortical carcinoma in a young female patient

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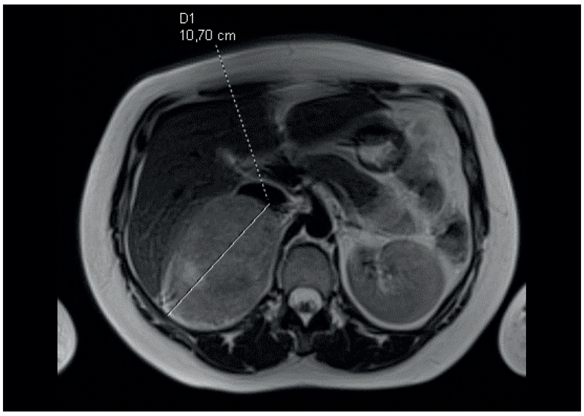

Figure 1. MRI, T_2-weighted image showing 11cm oval, well-circumscribed mass with high, heterogeneous signal, higher than the adjacent liver

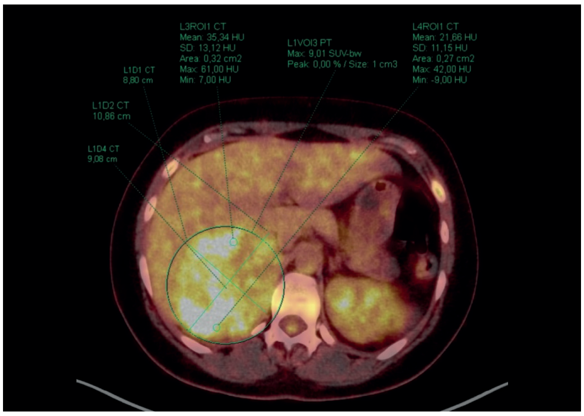

Figure 2. Fluorine-^{18}F-FDG-PET-CT PET-CT scan indicating high FDG uptake (SUV max 9.0), more than 3 times higher than the adjacent liver

A 33-year-old woman with hypertension and oligomenorrhea for last 6 months, with an incidentally diagnosed abdominal mass on ultrasound underwent an MRI and ^{18}F-FDG PET-CT (fig. 1, 2). No abnormalities were seen on lab tests. Initial diagnoses were ganglioneuroma, adrenal cortical carcinoma (ACC) and pheochromocytoma. Ganglioneuroma was supported by age, normal/lower level of adrenal hormones, well-circumscribed margins, progressive enhancement and persistent in delayed phase (in T_1w before and after dynamic administration of gadobutrol) and no evidence of metastasis [1, 2]. ACC was supported by haemorrhage on T_1w, heterogeneous T_2w signal – higher than an adjacent liver, enhanced density of periadrenal fat [1, 2]. Pheochromocytoma was less confident due to the relatively low signal on T_2w. High FDG uptake (SUVmax 9.0) suggested a malignant character. For all diagnosis parameters like lesion size (11 cm), there was no presence of drop of signal during out-of-phase sequence, no evidence of IVC invasion and local compressive symptoms showed imaging overlap [1, 2]. DWI revealed a high signal within the lesion, with a low signal on ADC maps. However, DWI does not help a lot in malignant/benign adrenal lesion differentiation [2]. ACC is a very rare and aggressive malignancy, with annual incidence 0.5–2 cases/ million [2]. Excision is a primary treatment for stage I–III disease with adjuvant therapy due to high risk of recurrence even with complete resection [2]. In this case, PET-CT showed adrenal/liver SUV ratio >1.8, indicating the malignant character of the lesion [2]. On laparotomy low-grade ACC, Weiss score 5, Ki-67: 11% was confirmed.

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Pictures in oncology

A pregnant woman with invasive cervical carcinoma

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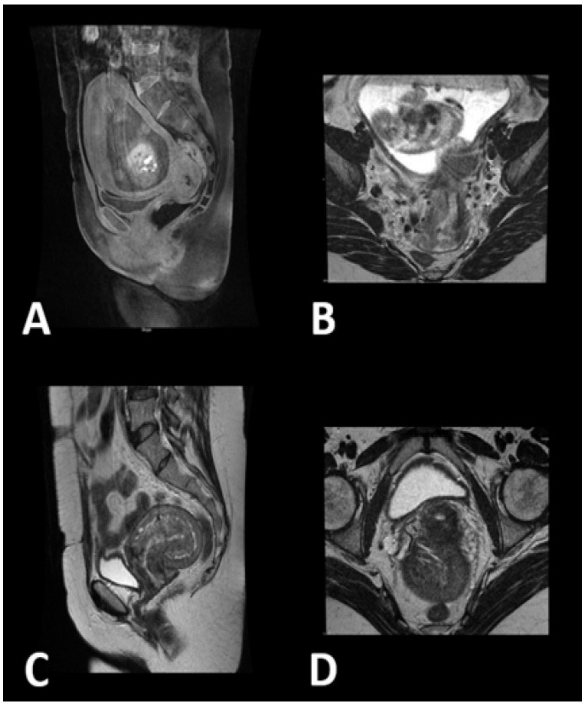

Figure 1. MRI before (A, B) and after (C, D) neoadjuvant chemotherapy

A 34-year-old woman in the 24th week of her third pregnancy was admitted to the Department of Gynecology and Obstetrics after a few episodes of short, vaginal bleeding, beginning in the 18th week, which raised a suspicion of cervical cancer. A routine cytology was performed during the 12th week of pregnancy (the first in the past 7 years), which yielded an inconclusive result. Therefore, it was recommended to extend the diagnostics. At admission, a gynecological examination showed uterine cervix shape deformation and immobilization, with visible nodular lesion on the cervical surface, confirmed as invasive squamous-cell carcinoma. The MRI of the pelvis and abdomen showed a circular neoplasm located in the upper part of the cervical canal, with a tumor measuring 37x46x48 mm (fig. 1). On the right side, the tumor infiltrates the parametria. Pelvical and abdominal lymphadenopathy were not observed, as well as distant metastases (stage IIB according to the FIGO Classification [1]). Therefore, the patient was qualified for neoadjuvant chemotherapy. The patient received three cycles of cisplatin and paclitaxel (the first cycle in the 24th week of pregnancy) in standard doses based on body weight, taking into account the weight of the fetus. The pregnancy ended with a planned caesarean section in the 34th week. The patient gave birth to a daughter (Apgar score of 9) with no complications during delivery and confinement. The post-chemotherapy MRI revealed a partial regression of the primary lesion to 25x14x14 mm. During confinement, the patient received teleradiotherapy for the pelvic region (45 Gy/25 fractions) with concomitant weekly cisplatin chemotherapy (40 mg/m^2) and a high dose rate (HDR) brachytherapy (28.5 Gy/4 fractions) (Ir 192, 3D planning). Complete remission in clinical and radiological control was observed 3 months after treatment completion. After 48 months, the patient's condition remains excellent, with no signs of relapse.

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