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Original article

Cancer epidemiology

Cancer incidence and mortality in Poland in 2023

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Introduction. Cancers are a real global health problem. Europe accounts for ⅒ of the world's population, but ¼ of all cancer cases occurs in this region. Poland is in the group of countries where cancer mortality is the highest. The aim of this article is to present a summary of the epidemiological indicators of malignant neoplasms in Poland in 2023.

Material and methods. This report presents observed morbidity and mortality data for 2010–2021, and also estimated values two years ahead (2022–2023). Data aggregation was carried out according to sex, age, cancer site, or administrative division of Poland. Time trends were determined using joinpoint regression. The Polish National Cancer Registry is responsible for gathering cancer morbidity data in Poland; mortality data came from Statistics Poland.

Results. The Polish National Cancer Registry reported about 171,558 new cases and 93,652 cancer deaths in 2021. The most common cancers in men were prostate, lung, and colon cancer. The most common cancers in women were breast, lung, and colorectal cancers. The prediction of morbidity and mortality for 2023 indicates a continuation of long-term trends.

Conclusions. The increase in the number of cases (approximately 25,000) and the number of deaths (by approximately 6000) observed in 2021 compared to 2020 indicates the huge impact of the COVID-19 pandemic on health indicators in Poland. However, the year 2021 shows the characteristics of the previous trend among cancer data.

Key words: mortality, morbidity, neoplasms, Poland

Introduction

Cancers are a real global health problem. Europe accounts for ⅒ of the world's population, but ¼ of all cancer cases occurs in this region [1]. In addition, 23% of deaths in Europe are caused by cancers (data from 2020) [2–4]. Poland is in the group of countries where cancer mortality is the highest [1]. The impact of COVID-19 on the mortality rate of the Polish population continues. Deaths from COVID accounted for almost the same percentage as deaths from cancer (17.0% *vs.* 18.7%). In 2021, for every 100,000 inhabitants, 452 people were diagnosed with cancer [5]. The purpose of the article is to present a summary of the epidemiological indicators of malignant neoplasms in Poland in 2021.

Materials and methods

Source of data and identification of cancer cases

The Polish National Cancer Registry (PNCR) is the source of cancer morbidity data. In Poland, the entire country has a unified protocol, allowing us to maintain the same principles of cancer registration in every region. Cancer mortality data comes from

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Statistics Poland [3]. All the data presented were collected dufing the 10th revision of the International Classification of Diseases and Health Problems [6].

Statistical analysis

The basic statistical measurements presented in this report are absolute numbers, percentages, crude and age-standardized (revised European Standard Population (ESP2013) [7]) rates. The projected data for 2022–2023 were estimated based on linear regression. Time trends were determined using Joinpoint regression [2] using Joinpoint Trend Analysis Software.

Results

Overall national analysis

In Poland, cancer is still a growing social problem and a challenge to both economic and health systems. The most common cancers in men in 2021 were (listed as the most common):

- prostate (21%),
- lung (15%),
- colon (7%),
- bladder cancers (6%).

In women, these were:

- breast (24%),
- lung (9%),
- corpus uteri (7%),
- colon (6%),
- thyroid gland (4%),
- ovarian (4%) cancers.

Skin cancers also constitute a high percentage in both groups, in each sex they constitute approximately 8% of cases (tab. I).

Among the main causes of death, the most common cancer sites were in men: lung cancer (27%) and prostate cancer (11%), in women: breast cancer (16%) and lung cancer (18%) (tab. II). Detailed data on morbidity and mortality in women and men are presented in tables I and II, respectively.

Table I. Cancer incidence in Poland in 2021

Site	ICD-10	Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
		Males			Females		
all cancers	C00–C97, D00–D09	84,275	458.9	549.5	87,283	444.7	419.7
all cancers but skin	C00–C97, D00–D09 excluded C44	77,610	422.6	499.3	80,408	409.7	386.9
oral cavity and pharynx	C00–C14	3,173	17.3	18.7	1,357	6.9	6.5
lip	C00	171	0.9	1.2	85	0.4	0.4
tongue	C01–C02	618	3.4	3.6	239	1.2	1.1
pharynx	C10–C13	780	4.2	4.4	173	0.9	0.8
digestive organs	C15–C26	17,696	96.4	116.3	13,749	70.1	65.6
oesophagus	C15	1,046	5.7	6.4	324	1.7	1.5
stomach	C16	3,010	16.4	19.8	1,747	8.9	8.3
small intestine	C17	224	1.2	1.4	215	1.1	1.0
colon	C18	5,607	30.5	38.1	4,990	25.4	24.0
rectosigmoid junction	C19	901	4.9	6.0	649	3.3	3.1
rectum	C20	3,428	18.7	22.2	2,133	10.9	10.2
anus and anal canal	C21	73	0.4	0.5	226	1.2	1.1
colorectum	C18–C21	10,009	54.5	66.6	7,998	40.8	38.4
liver	C22	828	4.5	5.3	534	2.7	2.5
gallbladder and biliary tract	C23–C24	595	3.2	4.1	880	4.5	4.2
pancreas	C25	1,864	10.2	11.9	1,923	9.8	9.1
respiratory system	C30–C39	14,417	78.5	91.9	8,791	44.8	41.0
larynx	C32	1,743	9.5	10.6	316	1.6	1.5
trachea and lung	C33–C34	12,344	67.2	79.2	8,248	42.0	38.5
bone and articular cartilage	C40–C41	214	1.2	1.2	190	1.0	1.0

→

Table I cont. Cancer incidence in Poland in 2021

Site	ICD-10	Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
		Males			Females		
neoplasms of skin	C43–C44	8,541	46.5	62.2	9,093	46.3	43.5
melanoma	C43	1,876	10.2	11.9	2,218	11.3	10.8
other neoplasms of skin	C44	6,665	36.3	50.2	6,875	35.0	32.8
mesothelial and soft tissue	C45–C49	926	5.0	5.7	842	4.3	4.1
breast	C50	167	0.9	1.1	21,079	107.4	102.2
female genital organs	C51–C58	–	–	–	12,662	64.5	61.0
vulva and vagina	C51–C52	–	–	–	620	3.2	2.9
cervix uteri	C53	–	–	–	2,160	11.0	10.4
corpus uteri	C54	–	–	–	6,024	30.7	29.0
ovary	C56	–	–	–	3,624	18.5	17.6
male genital organs	C60–C63	19,416	105.7	124.9	–	–	–
penis	C60	259	1.4	1.6	–	–	–
prostate	C61	17,832	97.1	116.7	–	–	–
testis	C62	1,303	7.1	6.5	–	–	–
urinary tract	C64–C68	8,662	47.2	57.1	3,940	20.1	18.8
kidney and renal pelvis	C64–C65	3,235	17.6	20.0	2,107	10.7	10.2
bladder	C67	5,301	28.9	36.3	1,742	8.9	8.2
eye	C69	238	1.3	1.5	260	1.3	1.2
central nervous system	C70–C72	1,469	8.0	8.7	1,300	6.6	6.4
brain	C71	1,375	7.5	8.1	1,195	6.1	5.8
endocrine glands	C73–C75	950	5.2	5.3	4,019	20.5	19.9
thyroid gland	C73	842	4.6	4.6	3,871	19.7	19.1
ill-defined, secondary and unspecified sites	C76–C80	1,014	5.5	6.6	1,094	5.6	5.2
lymphoid, haematopoietic and related tissue	C81–C96	5,295	28.8	33.8	4,871	24.8	23.7
Hodgkin lymphoma	C81	372	2.0	2.0	378	1.9	2.0
non-Hodgkin lymphoma	C82–C86, C96	1,863	10.1	11.8	1,768	9.0	8.5
immunoproliferative diseases	C88	69	0.4	0.4	98	0.5	0.5
multiple myeloma	C90	855	4.7	5.5	878	4.5	4.2
lymphoid leukaemia	C91	1,324	7.2	8.7	1,002	5.1	4.9
myeloid leukaemia	C92	681	3.7	4.4	645	3.3	3.1
all leukaemias	C91–C95	2,136	11.6	14.0	1,749	8.9	8.5
carcinoma *in situ*	D00–D09	1,504	8.2	10.5	3,486	17.8	17.0

Predictions for 2023

The publication of PNCR data has two-year intervals compared to the current year, the last year reported is 2021. Precise data for 2022 and 2023 are incomplete due to the data collection process. We have made forecasts for these years to illustrate the situation in Poland. The basis for these predictions was the years 2010–2021. Tables III and IV present the observed cases in 2021 and expected in 2023.

It is estimated that in 2023 the number of cancer cases will increase and the most frequently diagnosed cancer cases in men will remain prostate (23%), lung (14%), and colorectal cancer (12%); in women, breast (24%), lung (10%),

Table II. Cancer deaths in Poland in 2021

Site	ICD-10	Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
		Males			Females		
all cancers	C00–C97, D00–D09	50,581	275.4	355.0	43,071	219.5	203.3
all cancers but skin	C00–C97, D00–D09 excluded C44	50,484	274.9	354.1	42,988	219.0	202.9
oral cavity and pharynx	C00–C14	2,300	12.5	13.9	789	4.0	3.7
lip	C00	68	0.4	0.6	40	0.2	0.2
tongue	C01–C02	467	2.5	2.8	164	0.8	0.8
pharynx	C10–C13	653	3.6	3.9	145	0.7	0.7
digestive organs	C15–C26	15,101	82.2	105.3	11,640	59.3	54.9
oesophagus	C15	1,157	6.3	7.3	340	1.7	1.6
stomach	C16	2,820	15.4	19.6	1,539	7.8	7.3
small intestine	C17	122	0.7	0.8	115	0.6	0.5
colon	C18	4,262	23.2	31.3	3,491	17.8	16.5
rectosigmoid junction	C19	249	1.4	1.8	176	0.9	0.8
rectum	C20	1,966	10.7	14.0	1,247	6.4	5.9
anus and anal canal	C21	93	0.5	0.6	108	0.6	0.5
colorectum	C18–C21	6,570	35.8	47.7	5,022	25.6	23.8
liver	C22	1,219	6.6	8.2	876	4.5	4.1
gallbladder and biliary tract	C23–C24	575	3.1	4.0	1,035	5.3	4.9
pancreas	C25	2,328	12.7	15.4	2,363	12.0	11.1
respiratory system	C30–C39	14,644	79.7	97.1	8,218	41.9	38.4
larynx	C32	1,220	6.6	7.8	197	1.0	0.9
trachea and lung	C33–C34	13,059	71.1	86.8	7,807	39.8	36.5
bone and articular cartilage	C40–C41	179	1.0	1.2	117	0.6	0.6
neoplasms of skin	C43–C44	758	4.1	5.8	699	3.6	3.3
melanoma	C43	661	3.6	4.9	616	3.1	2.9
other neoplasms of skin	C44	97	0.5	0.9	83	0.4	0.4
mesothelial and soft tissue	C45–C49	601	3.3	4.1	473	2.4	2.3
breast	C50	63	0.3	0.5	6,406	32.6	30.5
female genital organs	C51–C58	–	–	–	6,415	32.7	30.5
vulva and vagina	C51–C52	–	–	–	401	2.0	1.9
cervix uteri	C53	–	–	–	1,361	6.9	6.5
corpus uteri	C54	–	–	–	1,647	8.4	7.8
ovary	C56	–	–	–	2,639	13.4	12.7
male genital organs	C60–C63	5,764	31.4	47.0	–	–	–
penis	C60	138	0.8	1.0	–	–	–
prostate	C61	5,458	29.7	45.1	–	–	–
testis	C62	146	0.8	0.8	–	–	–

→

Table II cont. Cancer deaths in Poland in 2021

Site	ICD-10	Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
		Males			Females		
urinary tract	C64–C68	4,558	24.8	34.1	1,849	9.4	8.6
kidney and renal pelvis	C64–C65	1,491	8.1	10.4	891	4.5	4.2
bladder	C67	2,978	16.2	23.1	889	4.5	4.1
eye	C69	64	0.3	0.5	56	0.3	0.3
central nervous system	C70–C72	1,471	8.0	9.3	1,376	7.0	6.6
brain	C71	1,369	7.5	8.5	1,285	6.5	6.2
endocrine glands	C73–C75	134	0.7	0.9	273	1.4	1.3
thyroid gland	C73	75	0.4	0.6	200	1.0	0.9
ill-defined, secondary and unspecified sites	C76–C80	2,065	11.2	14.8	2,048	10.4	9.6
lymphoid, haematopoietic and related tissue	C81–C96	2,845	15.5	20.4	2,683	13.7	12.7
Hodgkin lymphoma	C81	64	0.3	0.4	60	0.3	0.3
non-Hodgkin lymphoma	C82–C85, C96	817	4.4	5.8	814	4.1	3.9
immunoproliferative diseases	C88	24	0.1	0.2	19	0.1	0.1
multiple myeloma	C90	604	3.3	4.3	664	3.4	3.1
lymphoid leukaemia	C91	671	3.7	5.1	472	2.4	2.2
myeloid leukaemia	C92	548	3.0	3.8	547	2.8	2.6
all leukaemias	C91–C95	1,336	7.3	9.7	1,126	5.7	5.3
carcinoma *in situ*	D00–D09	0	0.0	0.0	0	0.0	0.0

Table III. Estimated cancer cases and deaths numbers in 2023 from the most common cancers among men and women

Males					
Cancer cases			Cancer deaths		
Site	Absolute number	Percents	Site	Absolute number	Percents
all cancers	84,390	100%	all cancers	53,399	100%
prostate	19,745	23%	lung	14,525	27%
lung	11,525	14%	colorectum	7,375	14%
colorectum	10,304	12%	prostate	6,134	11%
bladder	5,389	6%	bladder	3,312	6%
kidney	3,108	4%	stomach	3,024	6%
stomach	2,819	3%	pancreas	2,494	5%
leukaemias	1,978	2%	leukaemias	1,543	3%
melanoma	1,969	2%	kidney	1,527	3%
pancreas	1,836	2%	brain	1,524	3%
non-Hodgkin lymphomas	1,757	2%	larynx	1,351	3%

→

Table III cont. Estimated cancer cases and deaths numbers in 2023 from the most common cancers among men and women

Females					
Cancer cases			Cancer deaths		
Site	Absolute number	Percents	Site	Absolute number	Percents
all cancers	86,697	100%	all cancers	46,434	100%
breast	20,530	24%	lung	8,872	19%
lung	8,835	10%	breast	7,355	16%
colorectum	8,097	9%	colorectum	5,358	12%
corpus uteri	6,161	7%	ovary	2,783	6%
thyroid gland	3,969	5%	pancreas	2,586	6%
ovary	3,507	4%	corpus uteri	2,109	5%
melanoma	2,223	3%	stomach	1,555	3%
kidney	1,994	2%	cervix uteri	1,402	3%
pancreas	1,971	2%	brain	1,301	3%
bladder	1,916	2%	thyroid	1,301	3%
cervix uteri	1,875	2%	leukaemias	1,268	3%
stomach	1,733	2%	bladder	1,044	2%

and colorectal cancer (9%). These cancer sites will also be the leading causes of death (tab. III). Based on the crude rate (cases per 100,000), the number of cases primarily of stomach, larynx, and lung cancer in men will be noticeably lower in 2023 than in 2021. Most of the rest of the cancer sites show an increase in incidence in 2023. There will be a reduction in cases of breast and ovarian cancers by comparing crude rates among women. Mortality will increase for every cancer site in both sexes, except gallbladder in women (tab. IV and V).

The number of cancer cases increases throughout the observation period in both sexes. Until 2007, the number of cases among men was higher than among women, after which both became equal. In 2020, due to the COVID-19 pandemic, there was a break in the trend, but the estimated data for 2021 indicate a return to the previous trend. The change in the number of deaths shows a similar trend for both sexes, an increase until 2003 and then a slowdown, although there is a clear difference in the absolute number, approximately 10,000 more deaths in men (fig. 1).

The standardized incidence rate among both sexes increased until 2013, with varying annual percentage changes. Then, among men, this rate began to decline, and among women, the incidence rate remained at a similar level. Among men, the standardized mortality rate showed an increasing trend until 2002, when it became decreasing. Among women, the trend in the standardized mortality rate has remained at a similar level since 1980 (fig. 1). The three cancer sites with the highest incidence rate in men are: prostate, lungs, and colorectum. This order of occurrence has been maintained since 2013. Previously, lung cancer took first place, followed by prostate cancer. This change was caused by a favorable reversal of the trend in lung cancer incidence and a decrease in the incidence value since 1995 (fig. 2).

The highest incidence rate in women is in breast cancer; the trend has been constantly increasing since 1980. The difference between the incidence of breast cancer and other cancers in women is noticeable (fig. 3). The next cancer sites with the highest incidence rates are the lung and colorectum. For the last 30 years, colorectal cancer has taken second place, but according to predictions, in 2022 this will change and lung cancer will be the second most frequently diagnosed cancer among women (fig. 3).

Since the early 1970s, the most common cause of death among Polish men has been lung cancer. Since the beginning of the 21st century, we have been observing a decline in mortality due to this cancer. Data from 2021 and forecasts indicate that the trend has leveled out in the following years (fig. 4). The next causes of death are colon and prostate cancer. In the case of colorectal cancer, a slowdown in the increasing trend in mortality has been observed since 2003, and a decrease in mortality has been observed since 2018 (annual percentage change – APC = –3.6% [CI: –5.3; –1.1]) (fig. 6). After a period of stabilization of the coefficient values, an increase in mortality due to prostate cancer has been observed since 2012 (APC = 1.5

Table IV. Estimated number of cancer cases in Poland in 2023 comparing to observed data in 2021

Males							
Site	ICD-10	2021 – observed			2023 – expected		
		Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
all cancers	C00–D09	84,275	458.9	549.5	84,390	463.9	526.4
oesophagus	C15	1,046	5.7	6.4	1,083	6.0	6.4
stomach	C16	3,010	16.4	19.8	2,819	15.5	17.9
colorectum	C18–C21	10,009	54.5	66.6	10,304	56.6	65.4
pancreas	C25	1,864	10.2	11.9	1,836	10.1	11.2
larynx	C32	1,743	9.5	10.6	1,514	8.3	9.0
lung	C33–C34	12,344	67.2	79.2	11,525	63.4	70.9
melanoma	C43	1,876	10.2	11.9	1,969	10.8	12.2
prostate	C61	17,832	97.1	116.7	19,745	108.6	121.1
kidney	C64	3,054	16.6	18.8	3,108	17.1	18.3
bladder	C67	5,301	28.9	36.3	5,389	29.6	35.1
brain	C71	1,375	7.5	8.1	1,285	7.1	7.4
Hodgkin lymphoma	C81	372	2.0	2.0	344	1.9	1.9
non-Hodgkin lymphomas	C82–C86+C96	1,863	10.1	11.8	1,757	9.7	10.8
leukaemias	C91–C95	2,136	11.6	14.0	1,978	10.9	12.4
Females							
Site	ICD-10	2021 – observed			2023 – expected		
		Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
all cancers	C00–D09	87,283	444.7	419.7	86,697	445.5	406.1
stomach	C16	1,747	8.9	8.3	1,733	8.9	8.0
colorectum	C18–C21	7,998	40.8	38.4	8,097	41.6	37.5
gallbladder	C23–C24	880	4.5	4.2	664	3.4	3.0
pancreas	C25	1,923	9.8	9.1	1,971	10.1	9.0
lung	C33–C34	8,248	42.0	38.5	8,835	45.4	39.6
melanoma	C43	2,218	11.3	10.8	2,223	11.4	10.6
breast	C50	21,079	107.4	102.2	20,530	105.5	97.3
cervix uteri	C53	2,160	11.0	10.4	1,875	9.6	8.9
corpus uteri	C54	6,024	30.7	29.0	6,161	31.7	28.9
ovary	C56	3,624	18.5	17.6	3,507	18.0	16.7
kidney	C64	1,984	10.1	9.6	1,994	10.2	9.3
bladder	C67	1,742	8.9	8.2	1,916	9.8	8.7
brain	C71	1,195	6.1	5.8	1,106	5.7	5.3
thyroid gland	C73	3,871	19.7	19.1	3,969	20.4	19.7
Hodgkin lymphoma	C81	378	1.9	2.0	345	1.8	1.8
non-Hodgkin lymphomas	C82–C86+C96	1,768	9.0	8.5	1,717	8.8	8.0
leukaemias	C91–C95	1,749	8.9	8.5	1,626	8.4	7.7

Table V. Estimated number of cancer deaths in Poland in 2023 comparing to observed data in 2021

Males							
Site	ICD-10	2021 – observed			2023 – expected		
		Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
all cancers	C00–D09	50,581	275.4	355.0	53,399	293.6	362.6
oesophagus	C15	1,157	6.3	7.3	1,249	6.9	7.6
stomach	C16	2,820	15.4	19.6	3,024	16.6	20.3
colorectum	C18–C21	6,570	35.8	47.7	7,375	40.5	51.4
pancreas	C25	2,328	12.7	15.4	2,494	13.7	15.9
larynx	C32	1,220	6.6	7.8	1,351	7.4	8.3
lung	C33–C34	13,059	71.1	86.8	14,525	79.9	92.7
melanoma	C43	661	3.6	4.9	780	4.3	5.5
prostate	C61	5,458	29.7	45.1	6,134	33.7	47.8
kidney	C64	1,418	7.7	9.8	1,527	8.4	10.2
bladder	C67	2,978	16.2	23.1	3,312	18.2	24.5
brain	C71	1,369	7.5	8.5	1,524	8.4	9.3
Hodgkin lymphoma	C81	64	0.3	0.4	86	0.5	0.5
non-Hodgkin lymphomas	C82–C86+C96	817	4.4	5.8	1,038	5.7	7.0
leukaemias	C91–C95	1,336	7.3	9.7	1,543	8.5	10.8
Females							
Site	ICD-10	2021 – observed			2023 – expected		
		Absolute number	Crude rate	Stand. rate (ESP2013)	Absolute number	Crude rate	Stand. rate (ESP2013)
all cancers	C00–D09	43,071	219.5	203.3	46,434	238.6	211.9
stomach	C16	1,539	7.8	7.3	1,555	8.0	7.1
colorectum	C18–C21	5,022	25.6	23.8	5,358	27.5	24.5
gallbladder	C23–C24	1,035	5.3	4.9	948	4.9	4.3
pancreas	C25	2,363	12.0	11.1	2,586	13.3	11.8
lung	C33–C34	7,807	39.8	36.5	8,872	45.6	39.8
melanoma	C43	616	3.1	2.9	684	3.5	3.1
breast	C50	6,406	32.6	30.5	7,355	37.8	34.0
cervix uteri	C53	1,361	6.9	6.5	1,402	7.2	6.5
corpus uteri	C54	1,647	8.4	7.8	2,109	10.8	9.6
ovary	C56	2,639	13.4	12.7	2,783	14.3	12.9
kidney	C64	848	4.3	4.0	883	4.5	4.0
bladder	C67	889	4.5	4.1	1,044	5.4	4.7
brain	C71	1,285	6.5	6.2	1,301	6.7	6.1
thyroid gland	C73	200	1.0	0.9	228	1.2	1.0
Hodgkin lymphoma	C81	60	0.3	0.3	65	0.3	0.3
non-Hodgkin lymphomas	C82–C86+C96	814	4.1	3.9	893	4.6	4.1
leukaemias	C91–C95	1,126	5.7	5.3	1,268	6.5	5.8

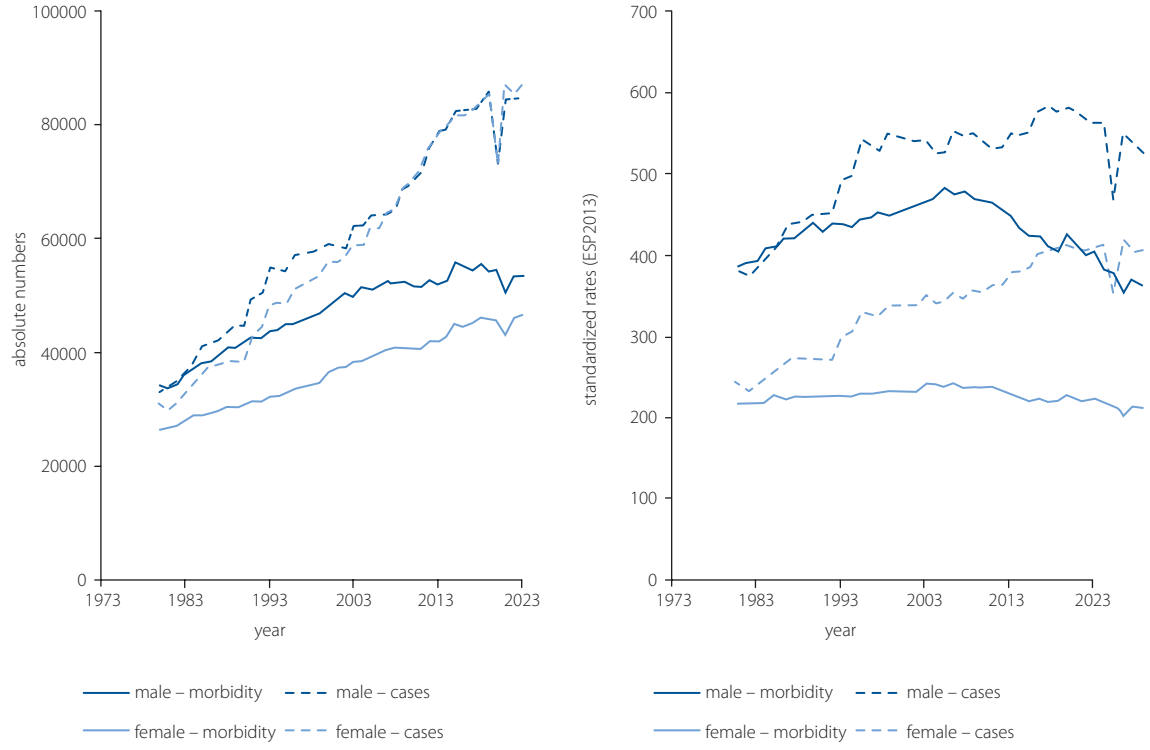

Figure 1. Cancer morbidity and mortality trends in Poland in 1980–2023*

*Values for 2022–2023 estimated based on trends in 2010–2021

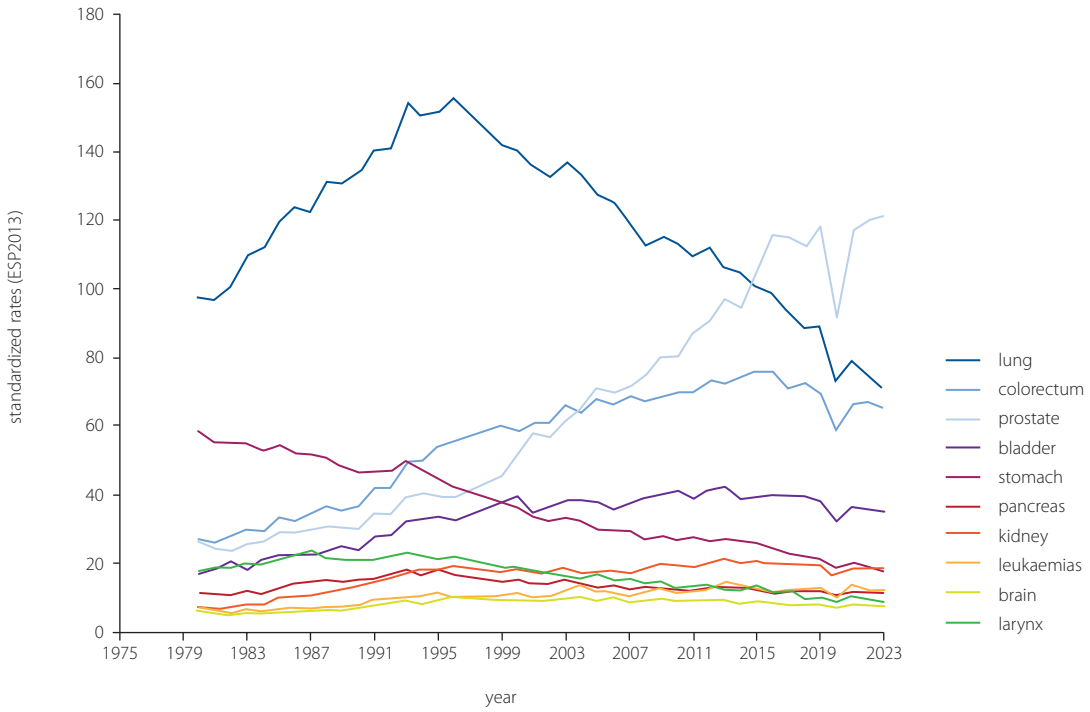

Figure 2. Incidence trends of the leading cancer sites for males, Poland 1980–2023 (2022–2023 estimation)

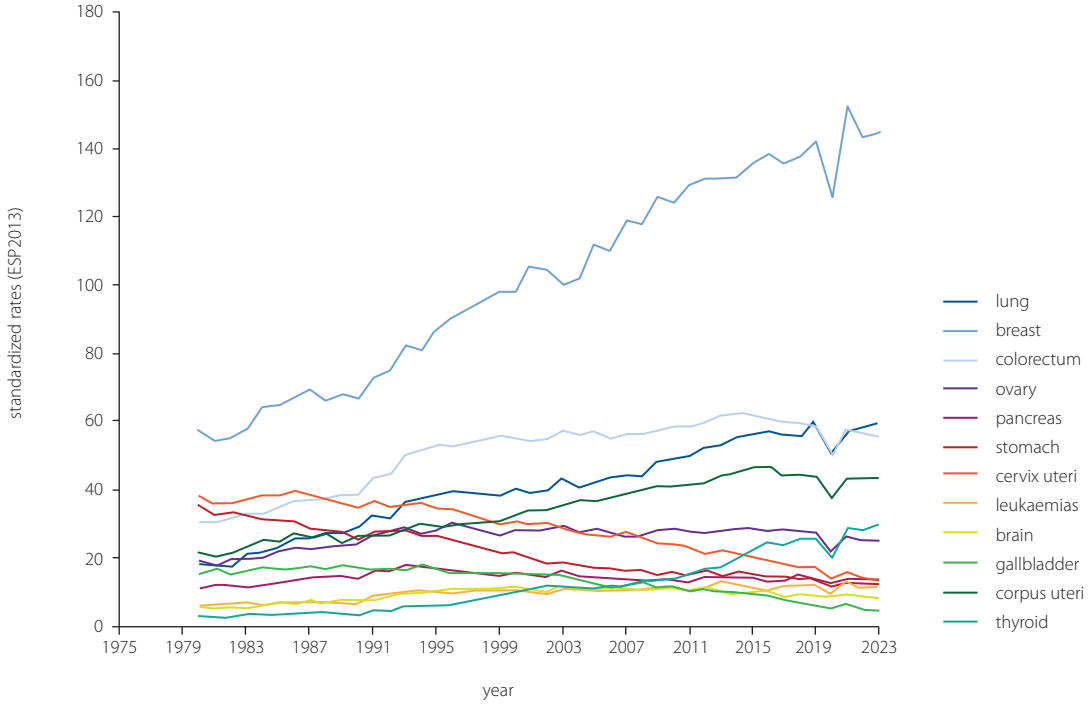

Figure 3. Incidence trends of the leading cancer sites for females, Poland 1980–2023 (2022–2023 estimation)

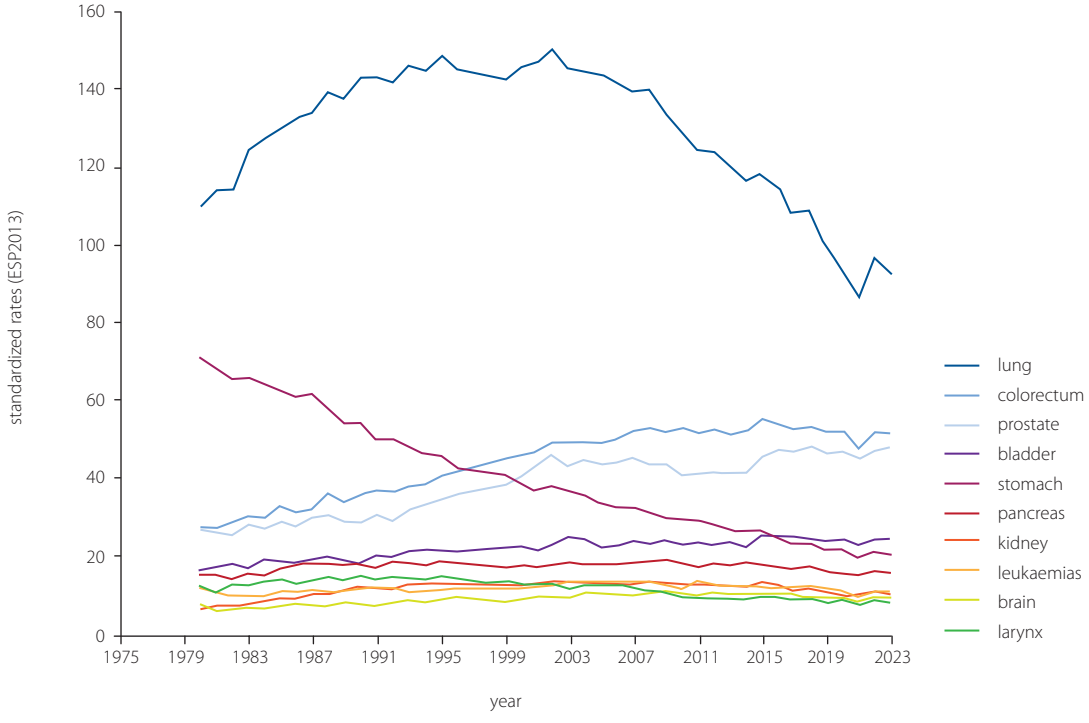

Figure 4. Mortality trends of the leading cancer sites for males, Poland 1980–2023 (2022–2023 estimation)

[CI: 0.6; 3.9]) (chart 6). It is also worth emphasizing the long-term downward trend in the case of stomach cancer, which became the 5th cause of death in 2015 (fig. 4).

In women, as in men, a temporary decrease in cancer mortality can be observed among all analyzed cancers during the COVID-19 pandemic. Data from 2021 and forecasts indicate that mortality rates will return to pre-pandemic levels in the coming years. Since 2007, lung cancer has been the first cause of cancer death in women. The mortality and incidence rates for lung cancer are very similar. Breast cancer remains the second cause of death, with an increasing trend in mortality since 2010 (APC = 1.1 [CI: 0.6; 2.5]) (fig. 6). Although colorectal cancer

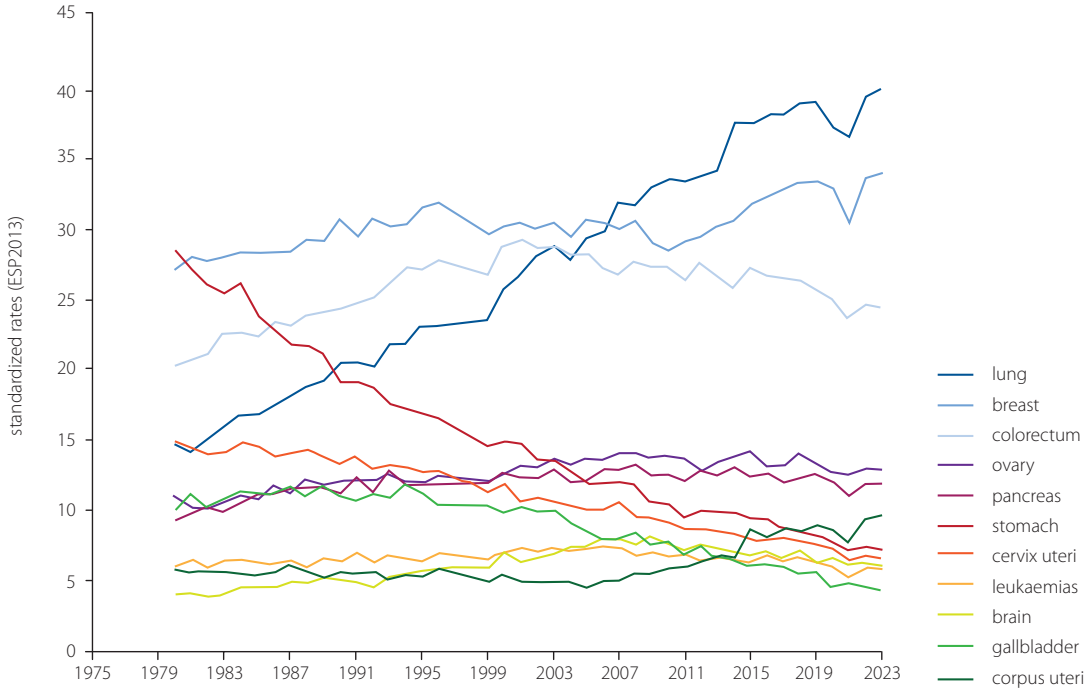

Figure 5. Mortality trends of the leading cancer sites for females, Poland 1980–2023 (2022–2023 estimation)

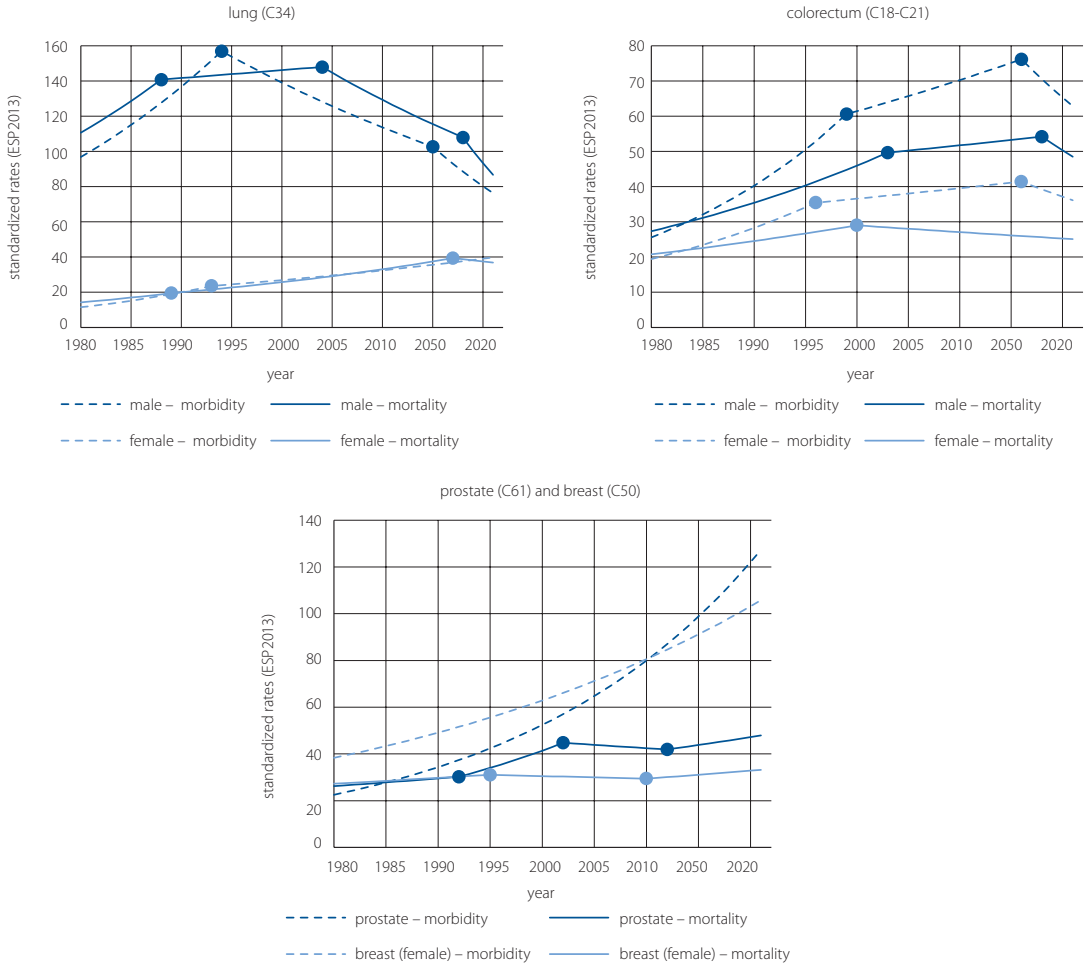

Figure 6. Time trends in incidence and mortality standardized rates (ESP2013) from lung, colorectal, prostate and breast cancer in 1980–2021 based on Joinpoint regression analysis

still ranks third in terms of mortality, a downward trend has been observed since 2000 (APC = –0.7% [CI: –0.9; –0.5] (fig. 6). Similarly to among men, a steady decline in stomach cancer mortality has been observed for over 6 decades.

Age group analysis

In both girls and boys (0–19 years of age), the most common cancer diagnoses are leukemia, brain and central nervous system (CNS) tumors. The same cancers are also the most common causes of death in children. In women, breast cancer ranks first among all age groups older than 20 years. In men, the most common diagnoses vary according to age. Testicular cancer is most common in the 20–44 age group (24%), and prostate cancer is most common in older groups (over 45 years). Among the five most common cancers in adult men aged 20 to 44 years, there are also cancers of the thyroid, skin, colorectum, brain, and CNS. In women, these include thyroid cancer, skin cancer, cervix uteri cancer and cancers *in situ*.

In the 45+ age group in men, the first three sites of incidence include prostate, lung, and colorectal cancer, which coincides with the most common causes of death, with the exception of prostate cancer in men aged 45–64, which is characterized by a much lower mortality rate in this group, and its place in the top three in terms of mortality is taken by pancreatic cancer.

In women 45+ years, the most common cancers depend on the age group. In the 45–64 group, the most common breast cancer survivors are corpus uteri and lung cancer, and in the 65+ group, lung and colorectal cancer. The first two causes of cancer death in women over 40 years of age are lung and breast cancer. The exact incidence and mortality values for the most common cancers by sex and age are presented in tables VI and VII, respectively.

Geographical analysis

In 2021, the most cancer cases were recorded in the Śląskie and Mazowieckie Voivodship, which also have the largest population. The fewest cases were recorded in the Lubuskie Voivodship. Among the most common cancers in Poland, especially in the Mazowieckie, Śląskie, and Dolnośląskie Voivodships, lung cancer ranks high, where the highest mortality rate is also observed (tab. VIII).

Breast cancer is the most common form of cancer among women, with the highest incidence in the Mazowieckie, Śląskie, and Wielkopolskie Voivodships, accounting for a total of 35% of cases throughout the country. However, in terms of women's mortality, the leader is lung cancer, which is responsible for 14.6% of deaths in the Mazowieckie Voivodship (tab. IX).

In most voivodships, the most common malignant tumor in men in 2021 was prostate cancer, with the largest share in the Wielkopolskie Voivodship (27%). Only in the Warmińsko-Mazurskie Voivodship is lung cancer the most common disease, with a share of approximately 18% (tab. X).

The structure of cancer incidence in women by voivodship repeats one pattern: in all voivodships, breast cancer comes first, with its share ranging from 21% (Warmińsko-Mazurskie Voivodship) to 27% (Mazowieckie Voivodship), and the second place is lung cancer, from 7% to 13%, followed by colorectal cancer, 8–10% (tab. XI).

Discussion

In 2021, the number of new cancer cases and deaths was similar to the data for 2019, the year before the COVID-19 pandemic. In 2021, the Polish National Cancer Registry registered 171,558 new cancer incidences and 93,652 deaths, while in 2019 it was 171,218 new cancer cases and 100,324 deaths [8].

The morbidity trends observed over many years and the mortality rate due to malignant tumors in Poland are determined by both the age structure of the population and changes in the Polish population's exposure to carcinogens, mainly associated with smoking (in 2023 the percentage of men and women smoking was equal, 21% of adults smoke). In 2021, the number of women who died of lung cancer exceeded that of women who died of breast cancer by 1389 deaths.

The most common disease in men is prostate cancer with 21%, characterized by a dynamic increase in incidence and a plateau in long-term mortality, which, however, has been increasing since 2004. In the male population, a reduction in the incidence and mortality rate of lung cancer has been observed in the last 15 years, mainly attributable to the reduction in the percentage of men who smoke in recent decades.

In the female population, the main cancer sites are still breast, lung, colorectum, and cervix uteri. Lung cancer is still the leading cause of death in women (18%) and is superior to breast cancer (14.9%). Breast cancer dominates women and has been characterized by ever-increasing incidence over the past half century. The mortality rate of breast cancer has changed several times over the past 30 years. The initial increase in mortality was stopped in the mid-1990s, and a decline in mortality was recorded in the years 1996–2010. During the period 2010–2021, there was an unfavorable change in the trend. Colorectal cancer has been the third most common cause of cancer death in recent years.

Infection with the SARS-Cov2 virus among cancer patients in 2021 caused 11,640 deaths. Most deaths due to COVID-19 were found in patients with digestive system cancers (17%), lymphatic, lymphatic tissue and related tissue cancers (15%), cancers of the respiratory system (14%), and male genital cancers (14%).

Table VI. The incidence of the 5 most common cancer sites in Poland in 2021, depending on sex and age

Males							
0–19 years		20–44 years		45–64 years		65+ years	
Number	Percents	Number	Percents	Number	Percents	Number	Percents
all cancers		all cancers		all cancers		all cancers	
691	100%	4,199	100%	23,891	100%	55,494	100%
leukaemias (C91–C95)		testis (C62)		prostate (C61)		prostate (C61)	
180	26%	1,001	24%	4,091	17%	13,715	25%
brain and CNS (C71–C72)		thyroid (C73)		lung (C33–C34)		lung (C33–C34)	
117	16%	277	7%	3,571	15%	8,668	16%
non-Hodgkin lymphomas (C82–C85+C96)		melanoma (C43)		colorectum (C18–C21)		colorectum (C18–C21)	
72	10%	273	7%	2,955	12%	6,783	12%
Hodgkin lymphoma (C81)		colorectum (C18–C21)		kidney and renal pelvis (C64–C65)		other and unspecified malignant neoplasm of skin (C44)	
56	8%	267	6%	1,271	5%	5,225	9%
other connective and soft tissue (C49)		brain and CNS (C71–C72)		other and unspecified malignant neoplasm of skin (C44)		bladder (C67)	
45	7%	257	6%	1,231	5%	3,756	7%
Females							
0–19 years		20–44 years		45–64 years		65+ years	
Number	Percents	Number	Percents	Number	Percents	Number	Percents
all cancers		all cancers		all cancers		all cancers	
605	100%	8,934	100%	28,912	100%	48,832	100%
leukaemias (C91–C95)		breast (C50)		breast (C50)		breast (C50)	
148	24%	2,501	28%	9,104	31%	9,472	19%
brain and CNS (C71–C72)		thyroid (C73)		corpus uteri (C54)		lung (C33–C34)	
92	15%	1,631	18%	2,464	9%	5,969	12%
thyroid (C73)		cancer *in situ* (D00–D09)		lung (C33–C34)		colorectum (C18–C21)	
56	9%	1,010	11%	2,190	8%	5,561	11%
Hodgkin lymphoma (C81)		melanoma (C43)		colorectum (C18–C21)		other and unspecified malignant neoplasm of skin (C44)	
52	9%	503	6%	2,126	7%	5,206	11%
kidney and renal pelvis (C64–C65)		cervix uteri (C53)		ovary (C56)		corpus uteri (C54)	
34	6%	437	5%	1,533	5%	3,342	7%

Table VII. The mortality of the 5 most common cancer sites in Poland in 2021, depending on sex and age

Males							
0–19 years		20–44 years		45–64 years		65+ years	
Number	Percents	Number	Percents	Number	Percents	Number	Percents
all cancers		all cancers		all cancers		all cancers	
107	100%	974	100%	12,665	100%	36,835	100%
brain and CNS (C71–C72)		brain and CNS (C71–C72)		lung (C33–C34)		lung (C33–C34)	
34	32%	131	13%	3,580	28%	9,419	26%
leukaemias (C91–C95)		colorectum (C18–C21)		colorectum (C18–C21)		colorectum (C18–C21)	
25	23%	100	10%	1,411	11%	5,057	14%
bone and articular cartilage (C40–C41)		testis (C62)		pancreas (C25)		prostate (C61)	
12	11%	93	10%	763	6%	4,989	14%
other connective and soft tissue (C49)		lung (C33–C34)		stomach (C16)		bladder (C67)	
12	11%	60	6%	759	6%	2,008	5%
liver (C22)		leukaemias (C91–C95)		brain and CNS (C71–C72)		stomach (C16)	
5	5%	58	6%	516	4%	1,815	5%
Females							
0–19 years		20–44 years		45–64 years		65+ years	
Number	Percents	Number	Percents	Number	Percents	Number	Percents
all cancers		all cancers		all cancers		all cancers	
75	100%	1,084		9,633		32,279	
brain and CNS (C71–C72)		breast (C50)		lung (C33–C34)		lung (C33–C34)	
31	41%	287	26%	1,830	19%	5,931	18%
leukaemias (C91–C95)		cervix uteri (C53)		breast (C50)		breast (C50)	
16	21%	114	11%	1,706	18%	4,413	14%
other connective and soft tissue (C49)		colorectum (C18–C21)		ovary (C56)		colorectum (C18–C21)	
4	5%	96	9%	856	9%	4,070	13%
kidney and renal pelvis (C64–C65)		brain and CNS (C71–C72)		colorectum (C18–C21)		pancreas (C25)	
4	5%	89	8%	855	9%	1,849	6%
non-Hodgkin lymphomas (C82–C85+C96)		ovary (C56)		cervix uteri (C53)		ovary (C56)	
4	3%	75	7%	501	5%	1,706	5%

Table VIII. Numbers of incidences and deaths for the most common malignant tumors among men in 2021 by voivodships

Voivodship	All cancers	Stomach	Colorectum[1]	Pancreas	Lung	Melanoma	Prostate	Kidney	Bladder	non-Hodgkin lymphomas[2]	Leukaemias[3]
Incidence											
Dolnośląskie	6,543	215	774	154	1,005	200	1,275	249	468	152	172
Kujawsko-Pomorskie	5,080	197	566	95	893	108	994	195	348	94	68
Lubelskie	4,667	151	488	81	585	80	1,158	197	369	93	125
Lubuskie	1,939	83	236	48	283	27	458	103	110	29	32
Łódzkie	5,462	204	665	119	759	150	1,067	187	304	139	251
Małopolskie	6,759	228	749	151	882	142	1,321	220	380	201	167
Mazowieckie	9,994	370	1,193	245	1,611	242	1,994	345	545	279	249
Opolskie	2,390	75	303	47	309	60	474	89	165	46	55
Podkarpackie	4,369	161	541	118	562	122	881	183	200	113	124
Podlaskie	2,647	65	352	61	312	59	652	110	165	46	53
Pomorskie	6,018	191	566	88	861	105	1,629	225	510	105	73
Śląskie	10,605	427	1,447	246	1,561	199	2,240	320	670	238	314
Świętokrzyskie	3,368	117	383	76	470	66	802	100	228	80	89
Warmińsko-Mazurskie	2,980	98	381	54	533	61	520	104	172	63	111
Wielkopolskie	8,229	292	1,025	226	1,091	183	1,675	313	455	154	209
Zachodniopomorskie	3,225	136	340	55	627	72	692	114	212	31	44
Poland	84,275	3,010	10,009	1,864	12,344	1,876	17,832	3,054	5,301	1,863	2,136
Deaths											
Dolnośląskie	3,940	231	497	219	1,013	48	426	117	226	55	82
Kujawsko-Pomorskie	2,828	158	344	146	860	36	306	59	182	50	75
Lubelskie	2,657	129	368	112	643	30	290	105	140	36	83
Lubuskie	1,205	61	142	56	369	16	132	21	65	23	25
Łódzkie	3,404	198	487	136	926	36	322	83	205	46	98
Małopolskie	4,283	253	516	179	997	63	510	125	303	65	125
Mazowieckie	6,747	358	852	328	1,825	94	713	166	399	120	178
Opolskie	1,284	67	186	45	305	18	140	40	83	20	41
Podkarpackie	2,395	160	320	97	517	39	297	63	121	47	59
Podlaskie	1,488	76	198	59	369	23	179	45	88	22	45
Pomorskie	3,090	169	353	180	816	39	339	86	171	42	90
Śląskie	6,599	404	894	270	1,597	83	653	172	372	94	161
Świętokrzyskie	1,839	98	231	84	454	19	234	61	122	33	43
Warmińsko-Mazurskie	1,862	97	257	75	516	28	220	58	89	66	47
Wielkopolskie	4,571	233	636	231	1,180	54	461	142	295	63	119
Zachodniopomorskie	2,389	128	289	111	672	35	236	75	117	35	65
Poland	50,581	2,820	6,570	2,328	13,059	661	5,458	1,418	2,978	817	1,336

[1]colorectum C18–C21; [2]non-Hodgkin lymphomas C82–C85 + C96; [3]leukaemias C91–C95

Table IX. Number of incidences and deaths for the most common malignant tumors among women in 2021 by voivodships

Voivodship	All cancers	Colorectum[1]	Lung	Breast	Cervix uteri	Corpus uteri	Ovary	Kidney	Bladder	non-Hodgkin lymphomas[2]	Leukaemias[3]
Incidence											
Dolnośląskie	7,276	637	720	1,808	167	451	313	156	166	142	173
Kujawsko-Pomorskie	5,468	445	662	1,254	117	317	245	144	116	83	43
Lubelskie	4,431	375	371	1,035	98	335	189	138	97	103	115
Lubuskie	1,913	171	194	451	55	115	92	73	47	24	33
Łódzkie	6,162	543	546	1,539	156	440	296	119	114	138	207
Małopolskie	7,376	649	526	1,727	147	531	298	124	103	173	141
Mazowieckie	10,987	886	1,146	2,990	258	732	325	207	170	251	242
Opolskie	2,275	241	194	541	63	209	94	49	30	53	42
Podkarpackie	4,288	396	277	1,014	84	374	192	98	64	113	107
Podlaskie	2,716	262	189	629	75	193	121	74	54	34	25
Pomorskie	5,547	471	703	1,300	151	309	182	149	178	106	55
Śląskie	10,315	1,152	1,019	2,336	283	768	559	226	240	212	207
Świętokrzyskie	3,015	293	234	643	90	241	118	94	57	69	71
Warmińsko-Mazurskie	3,299	309	353	702	96	169	145	67	66	76	105
Wielkopolskie	8,373	828	663	2,137	213	568	324	193	139	151	153
Zachodniopomorskie	3,842	340	451	973	107	272	131	73	101	40	30
Poland	87,283	7,998	8,248	21,079	2,160	6,024	3,624	1,984	1,742	1,768	1,749
Deaths											
Dolnośląskie	3,511	403	662	451	91	128	217	79	72	59	80
Kujawsko-Pomorskie	2,462	293	570	356	64	76	139	46	30	44	60
Lubelskie	2,154	255	337	307	83	104	160	31	31	36	69
Lubuskie	1,053	119	215	143	34	31	66	24	27	21	27
Łódzkie	3,004	354	553	459	88	97	189	54	54	37	100
Małopolskie	3,666	410	540	550	117	179	225	74	78	84	110
Mazowieckie	5,830	652	1,143	895	192	223	335	117	106	116	142
Opolskie	1,140	153	178	184	44	40	58	33	19	20	33
Podkarpackie	1,899	221	242	295	62	108	124	40	31	43	63
Podlaskie	1,214	169	177	196	51	50	73	29	27	22	39
Pomorskie	2,548	291	540	337	89	75	144	43	57	49	57
Śląskie	5,691	689	938	908	157	227	384	103	122	84	128
Świętokrzyskie	1,365	153	185	214	49	72	104	28	33	23	46
Warmińsko-Mazurskie	1,507	154	305	206	51	58	70	43	43	71	36
Wielkopolskie	3,934	475	745	641	122	114	246	64	106	64	81
Zachodniopomorskie	2,093	231	477	264	67	65	105	40	53	41	55
Poland	43,071	5,022	7,807	6,406	1,361	1,647	2,639	848	889	814	1,126

[1]colorectum C18–C21; [2]non-Hodgkin lymphomas C82–C85 + C96; [3]leukaemias C91–C95

Table X. Standardized rates of morbidity and mortality for the most common malignant neoplasms in men in Poland in 2021 by voivodships

Voivodship	All cancers	Stomach	Colorectum[1]	Pancreas	Lung	Melanoma	Prostate	Kidney	Bladder	non-Hodgkin lymphomas[2]	Leukaemias[3]
Incidence rates (ESP2013)											
Dolnośląskie	556.3	18.5	66.9	12.9	84.7	16.3	108.1	20.4	41.0	12.6	15.6
Kujawsko-Pomorskie	618.3	24.0	70.8	11.6	105.8	13.1	118.5	22.5	45.3	10.7	8.7
Lubelskie	544.9	17.2	58.6	9.1	65.6	9.1	137.0	21.9	46.2	10.8	14.6
Lubuskie	482.3	22.0	58.7	11.4	70.0	7.4	112.3	23.8	28.2	8.8	9.1
Łódzkie	528.0	20.1	65.7	11.9	71.6	14.6	102.1	17.0	30.9	13.0	24.6
Małopolskie	511.5	17.7	57.9	11.5	66.6	10.7	101.8	15.8	30.9	14.5	12.1
Mazowieckie	469.6	17.6	56.6	11.5	75.5	10.7	94.2	15.3	26.6	13.0	12.3
Opolskie	589.7	19.6	76.7	11.6	76.1	14.7	113.6	20.1	41.2	10.2	14.7
Podkarpackie	528.5	19.8	67.1	14.2	69.4	14.3	109.9	20.4	25.4	13.2	14.0
Podlaskie	565.7	14.2	76.0	11.8	66.9	12.3	141.7	22.7	36.1	9.2	10.9
Pomorskie	674.3	20.5	65.3	9.6	95.8	11.0	182.5	23.6	61.7	11.0	8.2
Śląskie	562.9	23.0	78.4	12.4	81.1	10.3	120.5	16.1	36.6	12.5	16.3
Świętokrzyskie	624.9	22.2	71.5	14.5	84.6	12.0	143.6	17.9	43.5	15.1	16.3
Warmińsko-Mazurskie	553.8	17.2	70.7	9.7	93.8	11.9	98.9	17.9	34.2	11.0	21.4
Wielkopolskie	619.1	22.2	80.4	16.6	80.8	13.4	125.8	22.1	36.2	10.5	15.7
Zachodniopomorskie	455.8	19.5	49.0	7.5	85.3	10.0	99.0	14.5	30.3	4.3	6.7
Poland	549.5	19.8	66.6	11.9	79.2	11.9	116.7	18.8	36.3	11.8	14.0
Mortality rates (ESP2013)											
Dolnośląskie	363.6	21.2	47.0	19.1	89.2	5.2	46.0	10.8	23.5	5.2	8.2
Kujawsko-Pomorskie	371.3	19.8	47.0	18.6	108.1	5.2	48.3	7.1	27.7	5.9	10.6
Lubelskie	331.3	15.3	47.5	13.9	76.2	4.0	42.5	13.1	19.3	4.8	10.6
Lubuskie	331.8	17.1	39.9	13.7	94.7	5.0	46.6	5.4	19.7	5.6	7.4
Łódzkie	352.2	20.7	51.7	13.8	90.4	3.6	38.0	8.2	24.0	4.7	10.3
Małopolskie	352.9	20.5	43.3	14.1	78.7	5.7	48.6	10.5	27.4	5.3	10.3
Mazowieckie	337.5	17.7	44.3	15.7	87.4	4.8	40.9	8.1	21.8	6.1	9.1
Opolskie	337.1	17.3	50.7	11.3	75.5	4.9	42.3	10.2	22.8	5.1	11.1
Podkarpackie	315.0	20.3	43.0	11.5	64.0	5.0	45.6	8.1	18.2	6.8	8.0
Podlaskie	340.3	18.3	47.3	13.4	80.6	5.7	45.1	10.0	21.2	4.6	10.8
Pomorskie	368.8	19.5	44.3	20.3	92.6	4.5	48.8	10.4	22.4	5.1	11.1
Śląskie	374.0	23.0	52.6	13.9	86.6	5.1	43.1	9.6	22.1	5.6	9.3
Świętokrzyskie	368.4	20.2	47.4	15.5	83.7	3.7	54.6	12.1	27.3	7.3	9.1
Warmińsko-Mazurskie	384.9	18.9	55.5	14.2	96.7	5.3	59.5	10.9	20.8	13.2	10.6
Wielkopolskie	368.2	18.6	53.9	17.4	89.8	4.7	44.0	11.5	26.7	5.1	9.8
Zachodniopomorskie	365.2	20.2	43.8	16.2	96.1	6.3	44.3	11.6	19.9	6.0	10.0
Poland	355.0	19.6	47.7	15.4	86.8	4.9	45.1	9.8	23.1	5.8	9.7

[1]colorectum C18–C21; [2]non-Hodgkin lymphomas C82–C85 + C96; [3]leukaemias C91–C95

Table XI. Standardized rates of morbidity and mortality for the most common malignant neoplasms in women in Poland in 2021 by voivodships

Voivodship	All cancers	Colorectum[1]	Lung	Breast	Cervix uteri	Corpus uteri	Ovary	Kidney	Bladder	non-Hodgkin lymphomas[2]	Leukaemias[3]
Incidence rates (ESP2013)											
Dolnośląskie	444.9	38.6	42.1	112.0	10.0	10.0	19.2	9.8	9.7	8.8	10.9
Kujawsko-Pomorskie	493.3	40.0	57.8	113.7	10.6	10.6	22.2	12.9	10.2	7.7	4.2
Lubelskie	381.9	32.0	30.9	90.8	8.3	8.3	16.4	12.2	8.1	8.8	9.9
Lubuskie	351.6	31.8	34.8	82.5	9.9	9.9	16.7	13.6	8.4	4.3	6.5
Łódzkie	429.1	37.1	35.8	108.7	11.2	11.2	21.1	8.5	7.9	9.9	15.0
Małopolskie	417.6	37.0	29.9	97.8	8.2	8.2	17.4	7.2	5.8	9.9	8.0
Mazowieckie	373.1	30.0	38.1	102.7	8.8	8.8	11.3	7.0	5.7	8.5	8.2
Opolskie	416.5	43.8	34.5	99.3	12.1	12.1	17.2	8.7	5.6	10.0	7.5
Podkarpackie	390.9	36.0	25.2	92.8	7.7	7.7	17.5	8.9	5.7	10.6	9.9
Podlaskie	426.4	41.2	29.3	99.5	12.2	12.2	19.4	11.9	8.1	5.2	3.7
Pomorskie	462.7	39.9	57.4	109.6	12.5	12.5	15.4	12.4	15.0	8.9	4.6
Śląskie	407.4	45.0	38.4	92.8	11.6	11.6	22.3	8.9	9.2	8.4	8.6
Świętokrzyskie	435.9	41.6	32.1	95.1	13.3	13.3	17.1	13.4	7.8	9.6	10.2
Warmińsko-Mazurskie	444.5	42.2	46.2	95.3	12.8	12.8	19.3	8.9	8.6	10.1	14.2
Wielkopolskie	462.4	46.4	36.2	118.6	11.6	11.6	17.6	10.8	7.4	8.1	8.3
Zachodniopomorskie	413.2	36.0	45.2	105.8	11.6	11.6	14.2	8.0	11.1	4.5	3.4
Poland	419.7	38.4	38.5	102.2	10.4	10.4	17.6	9.6	8.2	8.5	8.5
Mortality rates (ESP2013)											
Dolnośląskie	210.4	24.3	39.6	27.2	5.4	7.6	13.2	4.8	4.2	3.4	4.7
Kujawsko-Pomorskie	219.1	26.6	50.0	31.5	5.6	6.7	12.8	3.9	2.6	3.9	5.4
Lubelskie	180.1	21.2	28.1	25.6	7.2	8.6	13.8	2.8	2.4	3.0	5.8
Lubuskie	195.5	22.5	39.1	25.9	6.1	5.9	12.0	4.7	5.3	4.1	5.3
Łódzkie	198.5	23.3	35.7	31.2	5.9	6.4	12.6	3.7	3.5	2.4	6.8
Małopolskie	203.3	22.6	30.4	30.5	6.5	10.0	12.6	4.1	4.2	4.8	6.0
Mazowieckie	193.2	21.3	38.0	30.0	6.5	7.4	11.5	3.9	3.4	3.8	4.5
Opolskie	204.2	27.0	31.0	33.2	8.1	7.4	10.2	5.8	3.4	3.6	6.1
Podkarpackie	170.4	20.1	22.0	26.9	5.5	9.4	11.2	3.6	2.6	3.8	5.4
Podlaskie	181.9	24.9	27.3	29.3	8.0	7.2	11.1	4.2	4.0	3.3	6.0
Pomorskie	212.3	24.8	44.3	28.2	7.3	6.1	11.9	3.6	4.6	4.1	4.7
Śląskie	220.5	26.8	35.6	35.4	6.2	8.8	15.1	3.9	4.7	3.3	5.0
Świętokrzyskie	187.9	20.7	25.1	29.5	6.8	9.8	14.6	3.6	4.4	3.1	6.5
Warmińsko-Mazurskie	202.8	21.0	40.2	28.1	6.9	7.7	9.4	5.5	6.0	9.6	4.7
Wielkopolskie	218.2	26.9	40.5	35.9	6.8	6.4	13.8	3.6	5.8	3.6	4.4
Zachodniopomorskie	223.4	24.5	49.9	28.6	7.1	7.1	11.3	4.3	5.5	4.5	6.2
Poland	203.3	23.8	36.5	30.5	6.5	7.8	12.7	4.0	4.1	3.9	5.3

[1]colorectum C18–C21; [2]non-Hodgkin lymphomas C82–C85 + C96; [3]leukaemias C91–C95

Conclusions

Deaths from COVID-19 are still a competitive cause of death compared to cancer. Both data from 2021 and forecasts until 2023 indicate that after a temporary reduction in cancer morbidity and mortality during the COVID-19 pandemic, both values will return to the trends presented before the pandemic.

In Poland in 2021, the most frequently diagnosed cancers among men were prostate, lung, and colorectal cancers. Among women, the main cancer sites remain: breast, lung, and colorectum. Mortality from colorectal cancer has been on downward trend since 2015, and this decreasing trend continues. A still disturbing phenomenon is the higher mortality rate than morbidity for lung cancer among men, and the similar number of lung cancer cases and deaths in women.

Strengths and limitations of the report

The analysis covers the entire population of Poland, and is the best source of cancer incidence data. Cancer registration in the Polish National Cancer Registry (PNCR) is mandatory, ensuring a high level of completeness of the data.

Article information and declarations

Data availability statement

The presented data come from the Polish National Cancer Registry (PNCR) and is available at https://onkologia.org.pl/.

Author contributions

Joanna A. Didkowska – devised the project, the main conceptual ideas and proof outline.

Klaudia Barańska – performed the analysis, wrote the manuscript with input from all authors.

Marta J. Miklewska – performed the analysis, wrote the manuscript with input from all authors.

Urszula Wojciechowska – performed the analysis, devised the project, the main conceptual ideas and proof outline.

Conflict of interest

None declared

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References

1. Dyba T, Randi G, Bray F, et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer. 2021; 157: 308–347, doi: 10.1016/j.ejca.2021.07.039, indexed in Pubmed: 34560371.
2. Kim HJ, Fay M, Feuer E, et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med. 2001; 19(3): 335–351, doi: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z.
3. Statistics Poland. https://stat.gov.pl/en/ (22.01.2024).
4. Causes of death statistics. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Causes_of_death_statistics (22.01.2024).
5. Didkowska J, Wojciechowska U, Barańska K. Nowotwory złośliwe w Polsce w 2021 roku [Cancer in Poland in 2021]. Krajowy Rejestr Nowotworów [Polish National Cancer Registry], Warszawa 2023.
6. International statistical classification of diseases and related health problems. World Health Organization, 2015. https://iris.who.int/handle/10665/246208 (22.01.2024).
7. European Commission, Eurostat. Revision of the European Standard Population: report of Eurostat's task force: 2013 edition. LU: Publications Office, 2013. https://data.europa.eu/doi/10.2785/11470 (25.10.2022).
8. Didkowska J, Wojciechowska U, Olasek P, et al. Nowotwory złośliwe w Polsce w 2019 roku [Cancer in Poland in 2019]. Krajowy Rejestr Nowotworów [Polish National Cancer Registry] 2021. https://onkologia.org.pl/sites/default/files/publications/2022-05/Nowotwory_2019.pdf.

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Original article

Breast cancer

Factors that may contribute to non-radical resections in patients undergoing breast-conserving treatment for breast cancer

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Introduction. Breast-conserving treatment in breast cancer consists of radical removal of the cancerous tumor combined with a satisfactory aesthetic result. This study aimed to retrospectively analyze factors that may contribute to non-radical resections in patients undergoing breast-conserving treatment for infiltrating breast cancer and carcinoma *in situ*.

Material and methods. This retrospective study analyzed the medical records of 1,312 patients with stage I and II breast cancer and patients with ductal carcinoma *in situ* (DCIS) who underwent breast-conserving treatment from January 2013 to December 2022.

Results. The number of non-radical resections (R1) was 6.4% (80 cases out of 1,237). Fifty-five (4.4%) of R1 patients were re-operated with larger margins and 25 (2%) had a mastectomy. Analysis of factors contributing to a non-radical resection showed a significant correlation with age, histological type, multifocality, preoperative treatment and clinically detectable lesions.

Conclusions. The use of contrast-enhanced spectral mammography as a standard method in surgical planning of breast cancer treatment, taking into account R1 resection risk factors, will allow better selection of patients eligible for breast-conserving treatment.

Key words: breast cancer, breast-conserving treatment, resection margin, contrast-enhanced spectral mammography

Introduction

Breast cancer is the most common malignancy and accounts for as many as 22.9% of cancer cases in women. The peak incidence is between the ages of 50 and 69 [1, 2].

The choice of local or systemic therapy for each stage of breast cancer depends on the clinical and pathomorphological assessment, taking into account the histological type, the degree of malignancy of the cancer, the receptor status,

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the size of the primary tumor and the status of the regional lymph nodes, the presence and extent of metastases in distant organs. It also depends on the patient's age, menopausal status, fitness, past and coexisting diseases, as well as preferences. Any decision taken on the extent of surgical treatment between breast-conserving treatment and a mastectomy primarily depends on the size of the tumor and the exclusion of the multicentricity of tumor lesions [3–5]. According to Breast Cancer Unit (BCU) recommendations in breast cancer centers, approximately 60% of patients should be treated using breast-conserving techniques [6]. Careful planning as regards the type of surgical procedure is important for treatment outcomes, and translates directly into a reduction in the incidence of local recurrence [7, 8]. In most centers, breast-conserving treatment is planned based on digital mammography, whose sensitivity in assessing tumor size and the presence of additional foci is not high, which may result in a non-radical resection [9, 10]. In the authors' own practice, the imaging method on the basis of which breast-conserving treatment was planned was contrast-enhanced spectral mammography (CESM). Contrast-enhanced spectral mammographyis based on a dual-energy technique that utilizes the difference in X-ray attenuation of breast tissue and iodine. It provides not only morphological information analogous to conventional mammography, but also additionally allows the imaging of breast areas that show increased contrast uptake usually associated with neoangiogenesis, similarly to breast magnetic resonance imaging (MRI) [11].

Breast-conserving treatment aims to radically remove the cancerous tumor while achieving a good aesthetic result [12]. According to current recommendations, a negative margin in infiltrating breast cancer is defined as the absence of cancerous tissue in the line of excision confirmed by postoperative histopathological examination [13]. For ductal carcinoma *in situ* (DCIS), the minimum margin should not be smaller than 2 mm [14].

Material and methods

This study aimed to retrospectively analyze factors that may contribute to non-radical resections in patients undergoing breast-conserving surgery for infiltrating breast cancer and carcinoma *in situ* (DCIS).

This retrospective study analyzed the medical records of 1,312 patients with stage I and II breast cancer and patients with DCIS who underwent breast-conserving treatment. Patients who had preoperative diagnostics performed outside our center were excluded from the study. A total of 1,237 patients with primary operable cancer as well as those undergoing preoperative systemic treatment were included in the study. The procedures were carried out at the Department of Oncological Surgery of Prof. K. Gibinski University Clinical Centre of the Medical University of Silesia in Katowice from January 2013 to December 2022. All patients included in the study had preoperative diagnostic tests performed at the Hospital Oncology Surgery Outpatient Clinic, which included: history-taking, physical examination, imaging studies including contrast-enhanced spectral mammography (CESM) and core needle biopsy (CNB). The procedures were performed by the same team of four surgeons with many years of experience in breast surgery. All surgically removed lesions were marked with threads to identify the resection margins, and the bed of the removed tumor was marked with metal clips. For lesions not clinically detectable, an anchor was placed on the day of surgery in the radiology department under ultrasound or mammography guidance. All removed clinically undetectable lesions were evaluated intraoperatively with the use of mammography to assess the presence of a tracer in the tumor and the size of the margins. Tumor removal procedures were combined with a sentinel node procedure or with the removal of the axillary lymphatic system, depending on the cN category. The postoperative histopathological examination was performed at the Department of Histopathology of the Medical University of Silesia. The preparations were assessed by 2 experienced pathologists. The study included infiltrating carcinomas and carcinomas *in situ*. R0 resection in infiltrating carcinomas meant that there was no ink in the tumor margins in DCIS margins of no less than 2 mm. The number of non-radical procedures, the number of re-operations with breast conservation and the number of amputations were assessed. It was investigated whether non-radical margins were dependent on age, histopathological type of cancer, grading, biological subtype, preoperative treatment, multifocality, clinically palpable lesion or nonpalpable lesion requiring anchorage.

Statistical analysis

Because the variables describing the characteristics under study were not measured on quotient scales and did not meet the assumption of normality of distributions, non-parametric statistical tests were used in the calculations. A non-parametric test of independence was used to assess whether the counts in the study groups differed significantly from each other. P-values <0.05 were considered statistically significant.

Results

The age distribution of the participants was not a normal distribution, with a median of 63.23 (±11.5) years (the minimum age in the sample was 29 years, the maximum 91 years). There were 80 (6.4%) cases of R1 resection confirmed by the postoperative histopathology report. 55 (4.4%) of the 80 R1 patients were re-operated with larger margins and 25 (2%) had a mastectomy. The investigated variables that may affect the radicality of resection are shown in table I.

Discussion

In this study, the rate of re-operation due to non-radical margins was 6.4%, far from the data available in the literature that indicate a resection rate of 20% in invasive carcinoma of no

Table I. The analysis of variables that may contribute to non-radical resection

Characteristics	Total number n = 1,237	Resection R1 n = 80	Resection R0 n = 1,157	Statistical significance
age – yy, M (± SD)	63.23 (±11.5)	62.98 (±11.5)	66.80 (±11.2)	p < 0.11
histopathological size – mm, M (± SD)	21.0 (±14.3)	18.7 (±14.3)	21.2 (±14.4)	NS
histopathological type of cancer:				p < 0.0001
NST	65.8%	3.6%	62.2%	–
lobular	13.3%	0.4%	12.9%	–
ductolobular	7.1%	0.7%	6.4%	–
special subtype	6.3%	1.0%	5.3%	–
DCIS	3.0%	0.8%	2.2%	–
HG	0.3%	0.0%	0.3%	–
LG	4.2%	0.0%	4.2%	–
grading:				NS
G1	7.5%	0.6%	6.9%	–
G2	74.3%	3.9%	70.4%	–
G3	18.2%	0.6%	17.6%	–
biological subtype:				NS
luminal A	40.2%	3.4%	36.8%	–
luminal B (HER-negative)	34.3%	1.3%	33.0%	–
triple-negative	11.4%	0.6%	10.8%	–
luminal B (HER-positive)	12.1%	0.6%	11.5%	–
non-luminal (HER-positive)	2.0%	0.1%	1.9%	–
multifocal	84.9%	6.3%	76.0%	p < 0.029
monofocal	18.3%	0.6%	17.1%	–
clinically palpable	98.7%	10.4%	88.3%	p < 0.0001
clinically impalpable (anchor)	1.3%	1.3%	0.0%	–
treated preoperatively	26.5%	1.9%	24.6%	p < 0.037
not treated preoperatively	73.5%	9.8%	63.6%	–

yy – years; M – mean; mm – millimetres; SD – standard deviation; R0 – radical resections; R1 – non-radical resections; NST – no special type; DCIS – ductal carcinoma *in situ*; HG – high grade; LG – low grade

special type (NST) and often higher in infiltrating lobular carcinoma and DCIS [14, 16 ,17]. Such a low percentage should be explained by the considerable experience of the surgeons, who perform more than 80 breast cancer procedures per year, and treatment planning on the basis of CESM, whose sensitivity in determining the size of the tumor lesion and additional tumor foci is far superior to classical digital mammography [8, 18].

The authors' analysis of the causes of R1 resection indicates a higher risk of non-radical resection in patients under 62 years of age. The glandular-adipose structure of the breast, more common at this age, may be the reason for the difficulty in identifying the extent of the cancerous lesion. Cancers at younger ages are also characterized by greater aggressiveness than those at later ages [19]. In the conducted analysis, the size of the tumor lesion was not a significant factor in increasing the risk of non-radical resection. Histopathological type was a significant factor confirming a higher risk of non-radical resection in invasive lobular carcinoma and DCIS. This should be associated with the clinical picture and radiological features of these lesions as confirmed by numerous studies [20–22]. The grade of malignancy (G) in our analysis was not a significant factor for the increased risk of R1 resection; a higher risk in more aggressive G2–3 carcinomas was to be expected. This is probably to be explained by the relatively small study group.

Data available in the literature indicate that luminal carcinoma is diagnosed more frequently than other biological types, is associated with a lower clinical and pathological stage of the disease, and thus allows more frequent use of breast-conserving treatment [22–23]. In this study, the biological subtype was not a significant factor in increasing the risk of non-radical resection. Perhaps this should also be attributed to the small size of the study group.

Multifocality in the presented analysis was associated with a higher incidence of R1 resection. Identification of additional microscopic foci of cancer is sometimes possible on the basis of postoperative histopathology alone. The authors believed that with a CESM result in each patient, with a very high sensitivity in detecting additional cancer foci, comparable to that of MRI as shown in this study, non-radical procedures in these cases could be reduced completely. However, as can be seen, this is not always possible [24].

When analyzing patients who were operated on with clinically palpable lesions compared to nonpalpable lesions requiring anchor placement, a significantly higher number of R1 resections were observed for the former. Apparently, macroscopic assessment is less accurate compared to intraoperative mammographic assessment. Furthermore, for lesions with anchor placement, when the radiologist signals during intraoperative

mammography that any of the margins appear too narrow or that there is no marker in the tumor, there is always the possibility of expanding the margin during the same procedure [25].

In the group of patients undergoing systemic treatment prior to surgery, non-radical resections were observed significantly less frequently compared to patients undergoing primary surgery. This is most likely related to the fact that the majority of postoperative procedures were performed with anchor placement, where intraoperative radiographic verification minimized the possibility of non-radical margins [26].

A limitation of the study was the relatively small group of patients; moreover, the volume of the mammary glands and the technique of the procedure – oncoplastic surgery *versus* tumorectomy – were not taken into account. Despite the incomplete elimination of non-radical procedures in the analyzed group, the re-operation rate of 6.4% is not high. The use of CESM as a standard method to assess the extent of the disease seems to minimize the number of non-radical resections and significantly alter the extent of planned surgery as shown in the authors' previous studies [27, 28].

Conclusions

The use of contrast-enhanced spectral mammography as a standard method in surgical planning of breast cancer treatment taking into account R1 resection risk factors will allow better selection of patients eligible for breast-conserving treatment.

Article information and declarations

Ethics statement

The authors declare that the study, due to its retrospective nature, did not require the approval of the Ethics Committee. All research procedures were carried out in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and its subsequent amendments.

Author contributions

Andrzej J. Lorek – conceptualization, data curation, writing – original draft preparation.
Katarzyna Steinhof-Radwańska – conceptualization, data curation.
Wojciech Zarębski – data curation, formal analysis.
Joanna Lorek – writing – original draft preparation.
Zoran Stojcev – writing – review and editing.

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Conflict of interest

None declared

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References

1. Wojciechowska UJ. Cancer incidence and mortality in Poland. Polish National Cancer Registry, Oncology Center – Maria Skłodowska-Curie Institute [Online]. http://onkologia.org.pl.
2. Miklewska MJ, Barańska K, Wojciechowska U, et al. Morbidity and mortality trends of the most common cancers in 1990-2019. Poland's position compared to other European countries. Nowotwory. Journal of Oncology. 2023; 73(1): 46–55, doi: 10.5603/NJO.a2022.0065.
3. Curigliano G, Burstein HJ, Winer EP, et al. St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2017. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. Ann Oncol. 2017; 28(8): 1700–1712, doi: 10.1093/annonc/mdx308, indexed in Pubmed: 28838210.
4. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002; 347(16): 1233–1241, doi: 10.1056/NEJMoa022152, indexed in Pubmed: 12393820.
5. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002; 347(16): 1227–1232, doi: 10.1056/NEJMoa020989, indexed in Pubmed: 12393819.
6. Biganzoli L, Cardoso F, Beishon M, et al. The requirements of a specialist breast centre. Breast. 2020; 51: 65–84, doi: 10.1016/j.breast.2020.02.003, indexed in Pubmed: 32217457.
7. Houben IPl, Vanwetswinkel S, Kalia V, et al. Contrast-enhanced spectral mammography in the evaluation of breast suspicious calcifications: diagnostic accuracy and impact on surgical management. Acta Radiol. 2019; 60(9): 1110–1117, doi: 10.1177/0284185118822639, indexed in Pubmed: 30678480.
8. Lorek A, Steinhof-Radwańska K, Barczyk-Gutkowska A, et al. The Usefulness of Spectral Mammography in Surgical Planning of Breast Cancer Treatment-Analysis of 999 Patients with Primary Operable Breast Cancer. Curr Oncol. 2021; 28(4): 2548–2559, doi: 10.3390/curroncol28040232, indexed in Pubmed: 34287253.
9. Cuesta AC, Ríos MM, Meseguer MN, et al. Accuracy of Tumor Size Measurements Performed by Magnetic Resonance, Ultrasound and Mammography, and Their Correlation With Pathological Size in Primary Breast Cancer. Cirugía Española (English Edition). 2019; 97(7): 391–396, doi: 10.1016/j.cireng.2019.08.001.
10. Iacconi C, Galman L, Zheng J, et al. Multicentric Cancer Detected at Breast MR Imaging and Not at Mammography: Important or Not? Radiology. 2016; 279(2): 378–384, doi: 10.1148/radiol.2015150796, indexed in Pubmed: 26605912.
11. Łuczyńska E, Heinze-Paluchowska S, Hendrick E, et al. Comparison between Breast MRI and Contrast-Enhanced Spectral Mammography. Med Sci Monit. 2015; 21: 1358–1367, doi: 10.12659/msm.893018.
12. Povoski SP, Jimenez RE, Wang WP, et al. Standardized and reproducible methodology for the comprehensive and systematic assessment of surgical resection margins during breast-conserving surgery for invasive breast cancer. BMC Cancer. 2009; 9: 254, doi: 10.1186/1471-2407-9-254, indexed in Pubmed: 19635166.
13. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Ann Surg Oncol. 2014; 21(3): 704–716, doi: 10.1245/s10434-014-3481-4, indexed in Pubmed: 24515565.
14. Sachańbiński T, Radecka B. A review of methods of intraoperative margin assessment in breast conserving surgery. Nowotwory. Journal of Oncology. 2021; 71(4): 225–231, doi: 10.5603/njo.a2021.0040.
15. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. Ann Surg Oncol. 2016; 23(12): 3801–3810, doi: 10.1245/s10434-016-5449-z, indexed in Pubmed: 27527714.

16. Cody HS, Van Zee KJ. Reexcision--The Other Breast Cancer Epidemic. N Engl J Med. 2015; 373(6): 568–569, doi: 10.1056/NEJMe1507190, indexed in Pubmed: 26244311.
17. Landercasper J, Attai D, Atisha D, et al. Toolbox to Reduce Lumpectomy Reoperations and Improve Cosmetic Outcome in Breast Cancer Patients: The American Society of Breast Surgeons Consensus Conference. Ann Surg Oncol. 2015; 22(10): 3174–3183, doi: 10.1245/s10434-015-4759-x, indexed in Pubmed: 26215198.
18. Kaczmarski K, Wang P, Gilmore R, et al. Surgeon Re-Excision Rates after Breast-Conserving Surgery: A Measure of Low-Value Care. J Am Coll Surg. 2019; 228(4): 504–512.e2, doi: 10.1016/j.jamcollsurg.2018.12.043, indexed in Pubmed: 30703538.
19. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011; 29(29): 3885–3891, doi: 10.1200/JCO.2011.36.1105, indexed in Pubmed: 21900114.
20. Park S, Park HS, Kim SII, et al. The impact of a focally positive resection margin on the local control in patients treated with breast-conserving therapy. Jpn J Clin Oncol. 2011; 41(5): 600–608, doi: 10.1093/jjco/hyr018, indexed in Pubmed: 21355001.
21. Melstrom LG, Melstrom KA, Wang EC, et al. Ductal carcinoma in situ: size and resection volume predict margin status. Am J Clin Oncol. 2010; 33(5): 438–442, doi: 10.1097/COC.0b013e3181b9cf31, indexed in Pubmed: 20023569.
22. Seo M, Cho N, Bae MS, et al. Features of Undiagnosed Breast Cancers at Screening Breast MR Imaging and Potential Utility of Computer-Aided Evaluation. Korean J Radiol. 2016; 17(1): 59–68, doi: 10.3348/kjr.2016.17.1.59, indexed in Pubmed: 26798217.
23. Nowikiewicz T, Chmielowska E, Andrusewicz H, et al. Prevalence of biological types of breast cancer and their influence on disease staging and therapeutic management – a single-center study. Pol J Pathol. 2017; 68(1): 16–25, doi: 10.5114/pjp.2017.67611, indexed in Pubmed: 28547976.
24. Steinhof-Radwańska K, Lorek A, Holecki M, et al. Comparison of the efficiency of mammography and contrast-enhanced spectral mammography in female patients with multifocal and multicentral breast cancer. Pol Arch Intern Med. 2021; 131(7-8): 759–761, doi: 10.20452/pamw.16011, indexed in Pubmed: 34057323.
25. Theunissen CI, Rust EAZ, Edens MA, et al. Radioactive seed localization is the preferred technique in nonpalpable breast cancer compared with wire-guided localization and radioguided occult lesion localization. Nucl Med Commun. 2017; 38(5): 396–401, doi: 10.1097/MNM.0000000000000659, indexed in Pubmed: 28362718.
26. Davey MG, O'Donnell JPM, Boland MR, et al. Optimal localization strategies for non-palpable breast cancers -A network meta-analysis of randomized controlled trials. Breast. 2022; 62: 103–113, doi: 10.1016/j.breast.2022.02.004, indexed in Pubmed: 35151049.
27. Steinhof-Radwańska K, Grażyńska A, Barczyk-Gutkowska A, et al. The new method, the old problem - role of contrast-enhanced spectral mammography in the diagnosis of breast cancer among Polish women. Pol J Radiol. 2020; 85: e381–e386, doi: 10.5114/pjr.2020.97941, indexed in Pubmed: 32817772.
28. Steinhof-Radwańska K, Grażyńska A, Lorek A, et al. Contrast-Enhanced Spectral Mammography Assessment of Patients Treated with Neoadjuvant Chemotherapy for Breast Cancer. Curr Oncol. 2021; 28(5): 3448–3462, doi: 10.3390/curroncol28050298, indexed in Pubmed: 34590596.

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Original article

Tumor biology

Warthin tumors – risk factors, diagnostics, treatment

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Introduction. Warthin tumors are the second most common benign tumor of the salivary gland, located mainly in the parotid glands, sometimes bilaterally. The main risk factor is nicotine addiction. The aim of the study was to present our own experience in the diagnosis and treatment of salivary gland neoplasm, and to analyze the risk factors for the development of Warthin tumors.

Materials and methods. The study group consisted of 55 patients operated on with Warthin tumors (between 2009 and 2023). 55 control individuals with no Warthin tumors were recruited. The patients underwent a retrospective analysis of risk factors for head and neck cancer.

Results. Warthin tumor patients reported salivary gland diseases, such as urolithiasis, inflammation, dry mouth, nicotine addiction, and chronic diseases, such as hypercholesterolemia. In 83% of cases of fine-needle aspiration biopsy (FNAB) of Warthin tumors, results were confirmed by postoperative histopathological diagnosis. The therapy included extracapsular tumor removal, partial parotidectomy with preservation of the facial nerve, and removal of the submandibular gland. Postoperative complications were a cutaneous fistula and paresis of the marginal branch of the facial nerve.

Conclusions. The study confirmed that nicotine addiction (smoking duration and number of cigarettes smoked per day) was the main risk factor for developing Warthin tumors. An increase in body-mass index (BMI), hypercholesterolemia, salivary gland diseases, and dry mouth symptoms manifested Warthin tumors. FNAB, ultrasonography (USG) and computer tomography (CT) or magnetic resonance imaging (MRI) with contrast were essential in the diagnostics and planning therapeutic strategy. The main treatment used in the clinic was extracapsular tumor removal.

Key words: Warthin tumors, salivary gland neoplasm, diagnostic, surgery treatment

Introduction

Salivary gland neoplasm account for 6% of all head and neck neoplasm. More than 80% of large salivary gland tumors are benign [1]. After pleomorphic adenoma (PA), the second most common is Warthin tumors (WT) [2]. In recent years, a predominance of Warthin tumors has been observed in certain regions of Germany, 44.9–48% compared to 17.3–23% pleomorphic adenomas [3]. In Poland, according to the Registry of Non-Malignant Tumors of Major Salivary Glands, Warthin tumors (37.1%) rank second after pleomorphic adenoma (217/585) [4]. Warthin tumors were first described in 1895 by Hildebrand. It is located mainly in the parotid glands (it accounts for 2–15% of parotid tumors), rarely in the submandibular glands. Isolated cases of Warthin tumors were described in the oral cavity, larynx, nasopharynx, eyelids and perisalivary lymph nodes [5].

One of the theories of the pathogenesis of tumors is their development from the cells of the salivary gland ducts present in the intra- and peri-parotid lymph nodes [6]. Another theory suggests it is an active process based on an inflammatory reaction leading to neoplasm proliferation [7]. Warthin tumors grow slowly and are not painful whereas large tumors may cause discomfort and distort facial features. It is estimated

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that approximately 0.3% of tumors undergo transformation into malignancy [8]. Diagnostics is based on an interview, physical examination, fine-needle aspiration biopsy (FANB) under ultrasound guidance, computer tomography (CT) or magnetic resonance imaging (MRI) with contrast. Treatment involves surgical removal of the tumor – depending on the location of the lesion: extracapsular removal of the tumor along with a margin of healthy tissue or partial parotidectomy with preservation of the facial nerve. These methods are usually chosen to protect the facial nerve [9].

The aim of the study was to present our own experience in the diagnosis and treatment of salivary gland neoplasm, and to analyze the risk factors for the development of Warthin tumors.

Materials and methods

One hundred and ten individuals were recruited for the study. They were divided into 2 groups, the study group and the control group. The study group consisted of 55 patients, 24 (44%) females aged 27–85 years (mean age 60.1 years) and 31 (56%) males aged 40–78 years (mean age 52 years) treated for Warthin tumors of the salivary glands at the Department of Otolaryngology and Laryngological Oncology, Audiology and Phoniatrics, Medical University of Lodz. Pre-operative diagnosis involved a history and physical examination, laboratory tests (morphology, creatinine, CRP) and additional tests: ultrasound guided FNAB examination, CT or MRI with contrast. In all cases, surgical treatment was performed – extracapsular tumor removal or partial parotidectomy with preservation of the facial nerve. Post-operative care included: suction drainage (24 h), postoperative wound care (changing the dressing, rinsing with Octenisept), check-up and removal of stitches 7 days after the procedure, also a conservative lifestyle was recommended (2 weeks).

The control group consisted of 55 individuals, the so-called healthy volunteers (the criterion for inclusion was the absence of a salivary gland tumor confirmed by imaging; the patients and the controls were matched according to gender and age). The comparison group consisted of 24 females aged 27–75 years (mean age 58.2 years) and 31 males aged 24–71 years (mean age 53.4 years). The patients completed a questionnaire regarding the risk of head and neck cancer. The study was granted the consent of the bioethics committee of the Medical University of Lodz (RAN/222/17/KE).

Statistical analysis: for statistical analysis STATISTICA 12.0 software, the chi-square test was used and the V-Cramer coefficient was calculated. $P < 0.05$ was considered statistically significant.

Results

Statistical analysis ($p < 0.05$) showed that patients with Warthin tumors had a higher BMI, tendency to obesity, suffered from hypercholesterolemia, reported symptoms in the salivary glands (i.e. stones, inflammation) and dry mouth. They were also addicted to smoking, they smoked more cigarettes per day for a longer time than the control group (tab. I). Among smokers, more than half (52%) have been smoking more than 10 cigarettes a day for 10 years.

No statistically significant differences between the groups were found in: gender, thyroid disease, diabetes, hypertension, education, alcohol consumption, number of sexual partners, exposure to ionizing factors, UV, radiotherapy, exposure to the automotive industry, rubber industry, exposure to nickel, chromium, cement dust, asbestos dust, work in a hairdressing salon, treatment for cancer, head and neck cancer, and the incidence of Epstein-Barr virus. A physical examination revealed a tumor with a soft or taut consistency, movable in relation to the ground. Facial expressions were preserved. No cervical lymphadenopathy was observed. In most patients, tumor growth was painless (49/55), 6 individuals reported pain within the tumor. The lesions were located in the parotid (52/55) and in the submandibular glands (3/55) (tab. II). Synchronous tumors were observed in 6 and metachronous in 2 patients. Multiple tumors in a single salivary gland were present in 6 cases. The average time of tumor growth was 2.2 years. Based on neck CT with contrast or USG, the average tumor volume was estimated at 5.97 cm^3 [4], and the mean tumor size was 2.56 cm. A history of autoimmune diseases revealed hypothyroidism (13/55) and hyperthyroidism (2/55). The FNAB results were confirmed in postoperative histopathological diagnosis in 49 patients (83%). The following surgical procedures were performed: extracapsular removal of the tumor (50/55), superficial parotidectomy with preservation of the facial nerve (2/55) – parotidectomy II according to the ESGS classification and removal of the submandibular gland (3/55). Postoperative complications included, cutaneous fistula (2/7) and paresis of the marginal branch of the facial nerve (5/7). In patients with a cutaneous fistula, a strip dressing was applied, in those with paresis of the VII^{th} nerve, galantamine injections (Nivalin) and rehabilitation were recommended. All subjects regained normal facial nerve function. Recurrence of Warthin tumor was observed in two patients.

Discussion

Warthin tumors constitute approximately 17% of all salivary gland tumors. It is a benign, encapsulated tumor composed of oncocytic epithelium surrounded by lymphoid stroma with active germinal centers [10]. The risk of malignancy in case of the epithelial component is 0.3%; mucoepidermoid carcinoma, squamous-cell carcinoma, adenocarcinoma, oncocytic carcinoma were observed; the lymphatic component may undergo transformation towards malignant lymphoma [11]. Cases of coexistence of Hodgkin's lymphoma or non-Hodgkin's lymphoma with Warthin tumors are also known [12]. In the examined material, Warthin tumors and Hodgkin's lymphoma of the parotid gland were detected in one patient.

Table I. Characteristic elements of the physical examination of patients in the study groups

Analyzed trait	Study group n = 55	Control group n = 55	p < 0.05*
	number (SD)	number (SD)	
gender: female male	 24 31	 24 31	1
age in years – mean	58.64	56.22	0.6572
education: primary secondary higher	 13/55 27/55 15/55	 7/55 31/55 17/55	0.3853
BMI – mean	28.5	25.4	0.0451*
normal weight (BMI 18–25) overweight (BMI 25–30) obesity (BMI > 30) metabolic syndrome	12 29 12 2	24 28 3 0	0.0533
smoking status "yes"	41/55	17/55	6.231e-08*
duration smoking – in years	15.1	7.3	1.882e-04*
number of cigarettes per day – mean	12.1	8.2	1.424e-11*
alcohol consumption: never <30 U/week >30 U/week	 21/55 33/55 1/55	 24/55 30/55 1/55	0.733
thyroid disease: hyperthyroidism hypothyroidism	 2/55 13/55	 2/55 3/55	0.0887
diabetes: diabetes 1 diabetes 2	0/55 6/55	1/55 3/55	0.6214
hypercholesterolemia	16/55	4/55	0.0055*
hypertension artery	11/55	6/55	0.1531
number of sexual partners: 1–3 3–7 >7	 36/55 13/55 6/55	 35/55 15/55 5/55	0.2565
oral sexual activity	19/55	22/55	0.4321
salivary gland disease (inflammation, stones)	29/55	4/55	4.26e-05*
dry mouth	28/55	6/55	0.003145*
oncological treatment among patient's family (parents, grandparents, siblings)	12/55	4/55	0.08482
treatment for head and neck neoplasm among patient's family (parents, grandparents, siblings)	7/55	3/55	0.2998
oncological treatment in the past	7/55	2/55	0.05661
treatment of head and neck neoplasm in the past	1/55	1/55	1
exposure to: radiotherapy UV ionizing factors	 4/55 10/55 3/55	 1/55 9/55 1/55	0.2166 0.2773 0.1457
Epstein-Barr virus infection	2/55	1/55	0.4652
exposure to: the automotive industry, rubber industry, exposure to nickel, chromium, dust cement, asbestos dust, work in a hairdressing salon	14/55	3/55	0.0642

Table II. Clinical features of Warthin tumors in the study group

Tumor location										Features of tumors		
parotid gland*								submandibular gland		soft consistency	taut consistency	movable in relation to the surround tissue
right				left				right	left	38	17	49
I	II	III	IV	I	II	III	IV	0	3			
9	11	4	–	10	17	1	–					

* Region of parotid gland according to the ESGS classification I, II, III, IV

Epstein-Barr virus infection was found to cause multiple occurrences of Warthin tumors [13]. The main risk factor is nicotine addiction. Other risk factors comprise autoimmune diseases, inflammatory diseases and ionizing radiation [14] as well as an increase in BMI (average value 29.1), obesity and diseases related to the metabolic syndrome (hypertension, diabetes, coronary heart disease). Based on a database of smoking addiction in Austria (from 23.5% in 1972 to 24.3% in 2014) and the occurrence of Warthin tumors (from 1970 to 2015, a 3.9-fold increase in tumors was observed) it was concluded that other factors including increased BMI may influence the development of tumors [15]. *Mycobacterium tuberculosis* infections were detected in a Warthin tumor in one patient. In tobacco smokers, the occurrence of Warthin tumors was 8 times more frequent than mixed tumors, exacerbating factors include: benzopyrene, arsenic, and N-nitrosoguanidines present in tobacco smoke that affect the transformation of gland tissue [16].

The neoplasm develops mainly in men in the 5th and 6th decade of life. There has been an increase in Warthin tumor cases in women. The male to female Warthin tumor patient ratio ranged from 2.3:1, 1.8:1 to 12.6:1 [3, 17]. In our study, Warthin tumors were found in 56% of men aged 27–75 years (mean age was 54.3 years) and the male to female ratio was 1.3:1.

The first symptoms of Warthin's tumor are changes in the shape of the face – a palpable tumor in the area of the salivary gland. These lesions are oval, soft [18], and usually grow asymptomatically. It was found that approximately 7% of tumors may be painful, then malignant growth should be ruled out. Warthin tumors tend to be multifocal (12–20% of cases) and bilateral (5–14% of cases) [19]. The tumors are most often located in the superficial lobe, in the lower part, the so-called tail of the parotid gland (level II according to the European Classification of Salivary Glands), where intrasalivary lymph nodes are present. WT recurrences are observed in 5–10% patients [20].

In the diagnosis of monomorphic adenoma, additional tests are recommended: FNAB, ultrasound. According to the Milan Classification it is category IV.A – "benign tumor" or category IV.B "salivary gland tumor with uncertain malignant potential (SUMP)" [21]. Cells characteristic of Warthin tumors are lymphocytes and oncocytic cells. The FNAB results were consistent with the postoperative diagnosis at 95% to 74% [22]. In our study it was 83%. Although no statistically significant differences were observed between CT with contrast and MRI, due to the benefits for the patient (no radiation, no contrast containing iodine), magnetic resonance imaging is recommended [23].

The first choice treatment is surgical removal of the tumor. Depending on the location of the tumor, different techniques are recommended: partial parotidectomy is when the tumor is in the lower part of the salivary gland (tail), superficial parotidectomy when it affects the superficial lobe or, in the case of tumors located in the deep lobe, total paratidectomy with preservation of the facial nerve [24]. Based on meta-analysis, Quer et al. proposed parotidectomy II (partial parotidectomy) or extracapsular tumor removal (extracapsular dissection – ECD) when a single tumor is located in area I or II; parotidectomy depending on the size of the lesion when a single tumor is in area II or IV or intrasalivary; parotidectomy II (partial lateral parotidectomy) or ECD when a single lesion is larger than 3 cm and is located in the tail of the salivary gland; in the case of multifocal lesions in the superficial lobe, parotidectomy I or II (lateral or superficial parotidectomy), when multifocal lesions affecting the superficial and deep lobe are present, parotidectomy I, II, III, IV (total parotidectomy) are indicated [8]. Wierzbicka et al. described surgery for salivary gland tumors using new technologies such as VITOM 3D [28] and also emphasized the importance of synoptic reporting in the surgery of recurrent salivary gland tumors [29]. Mantsopoulos et al. recommend ECD using neuromonitoring as a procedure with the lowest risk of complications (including Frey syndrome) [25]. Postoperative complications include facial nerve damage, sialocele, postoperative hematoma, cutaneous fistula, Frey syndrome and scarring [31]. It is recommended to describe procedures for benign salivary gland tumors according to the ESGS classification [32]. Patients who do not decide to undergo the procedure or those with contraindications for general anesthesia should be observed and development of the tumor monitored by imaging tests [28].

In recent years, minimally invasive treatment procedures were used. There are isolated cases of treatment of Warthin tumors by ethanol sclerotherapy under ultrasound guidance with satisfactory results (reduction of tumor size, patient satisfaction

resulting from changes in appearance) [29] and ablation of tumors using radiofrequency [30] or microwaves [31].

Conclusions

In the operated patients, nicotine addiction (duration of smoking and number of cigarettes smoked per day) was the main risk factor for Warthin tumors. Increased BMI (including obesity), hypercholesterolemia, salivary gland diseases, and the presence of dry mouth were observed (statistically significant) in the group of patients with Warthin tumors. FNAB, USG and neck CT/MRI with contrast are essential in diagnosing and planning the therapy. The main treatment method was extracapsular tumor removal (according to the ESGS classification).

Article information and declarations

Author contributions

Katarzyna Kolary-Siekierska – conceptualization, formal analysis, funding acquisition, investigation, methodology, writing – original draft, writing – review and editing.
Anna Jałocha-Kaczka – methodology, writing – review and editing.
Piotr Niewiadomski – formal analysis, writing – review and editing.
Jarosław Miłoński – conceptualization, formal analysis, funding acquisition, investigation, methodology, writing – original draft, writing – review and editing.

Data availability statement

Data were collected from a questionnaire, a retrospective analysis was conducted.

Ethics statement

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 Lodz (protocol code RNN / 222/17/KE).

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Conflicts of Interest

None declared

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References

1. Faquin WC, Rossi ED, Baloch Z, et al. The Milan System for Reporting Salivary Gland Cytopathology. 2018, doi: 10.1007/978-3-319-71285-7.
2. Kordzińska-Cisek I, Grzybowska-Szatkowska L. Salivary gland cancer — epidemiology. Nowotwory. Journal of Oncology. 2018; 68(1): 22–27, doi: 10.5603/njo.2018.0005.
3. Psychogios G, Vlastos I, Thölken R, et al. Warthin's tumour seems to be the most common benign neoplasm of the parotid gland in Germany. Eur Arch Otorhinolaryngol. 2020; 277(7): 2081–2084, doi: 10.1007/s00405-020-05894-z, indexed in Pubmed: 32189070.
4. Piwowarczyk K, Bartkowiak E, Klimza H, et al. Review and characteristics of 585 salivarygland neoplasms from a tertiary hospitalregistered in the Polish National MajorSalivary Gland Benign Tumors Registry overa period of 5 years: a prospective study. Otolaryngologia Polska. 2020; 74(5): 1–6, doi: 10.5604/01.3001.0014.1261.
5. Limaiem F, Jain P. Warthin Tumor. StatPearls 2021.
6. Stachura J, Domagała W. Patologia znaczy słowo o chorobie. Polska Akademia Umiejętności w Krakowie 2009.
7. Thompson AS, Bryant HC. Histogenesis of the Papillary Cystadenoma Lymphomatosum (Warthin's Tumor) of the Parotid Salivary Gland. Am J Pathol. 1950; 26(5): 807–849, indexed in Pubmed: 15432614.
8. Quer M, Hernandez-Prera JC, Silver CE, et al. Current Trends and Controversies in the Management of Warthin Tumor of the Parotid Gland. Diagnostics (Basel). 2021; 11(8), doi: 10.3390/diagnostics11081467, indexed in Pubmed: 34441400.
9. Smółka W, Markowski J, Piotrowska-Seweryn A, et al. Mucoepidermoid carcinoma in Warthin tumor of the parotid gland. Arch Med Sci. 2015; 11(3): 691–695, doi: 10.5114/aoms.2015.52379, indexed in Pubmed: 26170867.
10. Wang YL, Zhu YX, Chen TZ, et al. Clinicopathologic study of 1176 salivary gland tumors in a Chinese population: experience of one cancer center 1997-2007. Acta Otolaryngol. 2012; 132(8): 879–886, doi: 10.3109/00016489.2012.662715, indexed in Pubmed: 22497626.
11. Mohapatra M, Satyanarayana S. Low grade mucoepidermoid carcinoma in a setting of Warthin's tumor. Indian J Pathol Microbiol. 2012; 55(3): 392, doi: 10.4103/0377-4929.101756.
12. Park CK, Manning JT, Battifora H, et al. Follicle center lymphoma and Warthin tumor involving the same anatomic site. Report of two cases and review of the literature. Am J Clin Pathol. 2000; 113(1): 113–119, doi: 10.1309/MJH0-RQGX-U128-VFC6, indexed in Pubmed: 10631864.
13. Sava A, Nemțoi A, Stan CI, et al. Clinical-pathological correlations in Warthin tumors of parotid gland: a series of 10 cases. Rom J Morphol Embryol. 2019; 60(2): 445–453, indexed in Pubmed: 31658317.
14. Orabona GD, Abbate V, Piombino P, et al. Warthin's tumour: Aetiopathogenesis dilemma, ten years of our experience. J Craniomaxillofac Surg. 2015; 43(4): 427–431, doi: 10.1016/j.jcms.2014.11.019, indexed in Pubmed: 25814196.
15. Kadletz L, Grasl S, Perisanidis C, et al. Rising incidences of Warthin's tumors may be linked to obesity: a single-institutional experience. Eur Arch Otorhinolaryngol. 2019; 276(4): 1191–1196, doi: 10.1007/s00405-019-05319-6, indexed in Pubmed: 30734098.
16. Yu GY, Liu XB, Li ZL, et al. Smoking and the development of Warthin's tumour of the parotid gland. Br J Oral Maxillofac Surg. 1998; 36(3): 183–185, doi: 10.1016/s0266-4356(98)90494-6, indexed in Pubmed: 9678882.
17. Luers JC, Guntinas-Lichius O, Klussmann JP, et al. The incidence of Warthin tumours and pleomorphic adenomas in the parotid gland over a 25-year period. Clin Otolaryngol. 2016; 41(6): 793–797, doi: 10.1111/coa.12694, indexed in Pubmed: 27343470.
18. Liu X, Du D, Lin X. Large and multiple Warthin's tumors of bilateral parotid glands: A case report of bilateral regional excision of the parotid. Oral Maxillofac Surg Cases. 2018; 4(3): 118–123, doi: 10.1016/j.omsc.2017.10.001.
19. Köybaşioğlu FF, Önal B, Han Ü, et al. Cytomorphological findings in diagnosis of Warthin tumor. Turk J Med Sci. 2020; 50(1): 148–154, doi: 10.3906/sag-1901-215, indexed in Pubmed: 31769640.
20. Quer M, Guntinas-Lichius O, Marchal F, et al. Classification of parotidectomies: a proposal of the European Salivary Gland Society. Eur Arch Otorhinolaryngol. 2016; 273(10): 3307–3312, doi: 10.1007/s00405-016-3916-6, indexed in Pubmed: 26861548.
21. Rossi E, Baloch Z, Pusztaszeri M, et al. The Milan System for Reporting Salivary Gland Cytopathology (MSRSGC): An ASC-IAC-Sponsored System for Reporting Salivary Gland Fine-Needle Aspiration. Acta Cytol. 2018; 62(3): 157–165, doi: 10.1159/000488969.
22. Flezar M, Pogacnik A. Warthin's tumour: unusual vs. common morphological findings in fine needle aspiration biopsies. Cytopathology.

2002; 13(4): 232–241, doi: 10.1046/j.1365-2303.2002.00415.x, indexed in Pubmed: 12269895.
23. Liu Y, Zheng J, Lu X, et al. Radiomics-based comparison of MRI and CT for differentiating pleomorphic adenomas and Warthin tumors of the parotid gland: a retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021; 131(5): 591–599, doi: 10.1016/j.oooo.2021.01.014, indexed in Pubmed: 33602604.
24. Lee DH, Yoon TMi, Lee JK, et al. Surgical treatment strategy in Warthin tumor of the parotid gland. Braz J Otorhinolaryngol. 2019; 85(5): 546–550, doi: 10.1016/j.bjorl.2018.04.004, indexed in Pubmed: 29807810.
25. Mantsopoulos K, Koch M, Klintworth N, et al. Evolution and changing trends in surgery for benign parotid tumors. Laryngoscope. 2015; 125(1): 122–127, doi: 10.1002/lary.24837, indexed in Pubmed: 25043324.
26. Ruohoalho J, Mäkitie AA, Aro K, et al. Complications after surgery for benign parotid gland neoplasms: A prospective cohort study. Head Neck. 2017; 39(1): 170–176, doi: 10.1002/hed.24496, indexed in Pubmed: 27131221.
27. Olejniczak I, Leduchowska A, Kozłowski Z, et al. Evaluation of benign tumors of large salivary glands according to the new classification of the European Salivary Glands Society. Otolaryngol Pol. 2021; 75(4): 7–13, doi: 10.5604/01.3001.0014.7889, indexed in Pubmed: 34344837.
28. Ringel B, Kraus D. Observation Rather than Surgery for Benign Parotid Tumors: Why, When, and How. Otolaryngol Clin North Am. 2021; 54(3): 593–604, doi: 10.1016/j.otc.2021.02.004, indexed in Pubmed: 34024486.
29. Mamidi IS, Lee E, Benito DA, et al. Ultrasound-guided ethanol sclerotherapy for non-surgical treatment of Warthin's tumor. Am J Otolaryngol. 2021; 42(1): 102813, doi: 10.1016/j.amjoto.2020.102813, indexed in Pubmed: 33130530.
30. Tung YC, Luo SD, Su YY, et al. Evaluation of Outcomes following Radiofrequency Ablation for Treatment of Parotid Tail Warthin Tumors. J Vasc Interv Radiol. 2019; 30(10): 1574–1580, doi: 10.1016/j.jvir.2019.04.031, indexed in Pubmed: 31471194.
31. Jin M, Fu J, Lu J, et al. Ultrasound-guided percutaneous microwave ablation of parotid gland adenolymphoma: A case report. Medicine (Baltimore). 2019; 98(35): e16757, doi: 10.1097/MD.0000000000016757, indexed in Pubmed: 31464905.

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Outcomes of treatment, laboratory results, adverse effects, and tolerability of cancer treatment in patients with metastatic renal-cell carcinoma treated with sunitinib after cytoreductive nephrectomy

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Introduction. This publication aims to present the results of a retrospective analysis of the treatment outcomes of patients with metastatic renal-cell carcinoma (RCC) who underwent cytoreductive nephrectomy (CN) followed by systemic treatment with sunitinib.

Material and methods. The retrospective analysis includes the results of 67 patients treated and followed up at the Institute of Oncology in Poznan University of Medical Sciences.

Results. Among the 67 patients included in the study, 24 were female (35.82%) and 43 were male (64.18%). The patients treated with sunitinib experienced several adverse effects, including weight loss, anaemia, neutropenia, hypokalemia, and thyroid dysfunction. For these reasons, some patients (n = 32, 47.76%) required a reduction in the dose of sunitinib. The most common reason for sunitinib discontinuation was disease progression (n = 52,77.61%).

Conclusions. Treatment with sunitinib requires regular clinical and laboratory monitoring to appropriately reduce the drug dose or increase the interval between drug cycles in the event of adverse effects.

Key words: sunitinib, metastatic renal-cell carcinoma, cytoreductive nephrectomy, CARMENA, SURTIME

Introduction

Renal-cell carcinoma (RCC) is a significant challenge in oncology. According to current literature, an estimated 30% of patients with RCC have metastases at the time of diagnosis [1]. In 2020, 4,770 cases of kidney cancer were recorded in Poland, and 2,522 people died from this cancer [27]. In recent years, significant progress has been made in understanding the molecular mechanisms underlying the development of this cancer. RCC is characterized by losing the *VHL* gene, leading to increased angiogenesis [2]. As our understanding of the biology of RCC deepens, innovative therapies that target specific molecules involved in cancer cell proliferation and angiogenesis processes emerge. One of the directions in treating RCC is sunitinib – an anti-angiogenic drug that represents a group of medicines known as tyrosine kinase inhibitors. Sunitinib can inhibit a number of key signaling pathways involved in the processes of cancer development and growth. It works by inhibiting angiogenesis – forming new blood vessels that supply blood and nutrients to the tumor – limiting tumor growth and inhibiting cancer cell proliferation. The U.S. Food

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and Drug Administration (FDA) approved the drug in 2006 as a first-line treatment for patients with advanced RCC. The approval of sunitinib in this indication was based on the results of a phase 3 study in which patients treated with sunitinib had a significantly longer median progression-free survival (PFS) – 11 months – than patients treated with interferon-α (INF-α) – 5 months – previously the leading systemic treatment for metastatic RCC [3]. Regarding secondary endpoints, 28% of patients showed significant tumor shrinkage with sunitinib compared to 5% of patients treated with IFN-α. At the end of the study, the primary endpoint of median PFS was still better with sunitinib (11 months *vs.* 5 months for IFN-α, $p < 0.000001$) [4].

In addition to treating RCC, sunitinib is also used to treat gastrointestinal stromal tumors and pancreatic neuroendocrine tumors [5]. What is more, reports suggest the use of sunitinib in treating thyroid cancer [6]. Although sunitinib has low toxicity compared to chemotherapy, it can cause systemic complications such as cardiotoxicity, heart failure, and hypertension [7]. The toxic effect of sunitinib on thyroid function, resulting in iatrogenic hypothyroidism, is also significant [8]. Other adverse effects include weakness, diarrhea, nausea, vomiting, skin lesions, mucositis, and hand–foot syndrome [9]. The classic treatment regimen for metastatic RCC is a daily dose of 50 mg of sunitinib for 4 consecutive weeks, followed by a 2-week interval, so one cycle lasts an average of 6 weeks. If adverse effects occur, the dose can be reduced to 37.5 mg or even 25 mg, but the cycle duration remains unchanged (4 weeks of drug administration, then 2 weeks off). In special situations, such as poor patient health or significant toxicity from sunitinib, the interval between cycles may be extended at the treating physician's discretion.

Sunitinib was part of two prospective randomized clinical trials, CARMENA and SURTIME, which evaluated the role of cytoreductive nephrectomy (CN) in patients with metastatic RCC treated with sunitinib [10, 11]. The CARMENA study enrolled 450 patients (an intermediate and poor prognosis group according to the Memorial Sloan Kettering Cancer Center – MSKCC) randomly assigned to an experimental arm (radical nephrectomy + sunitinib – 226 patients in total) and a control arm (sunitinib only, no surgical treatment – 224 patients in total). The study was designed to test whether sunitinib alone is not inferior (non-inferiority) to nephrectomy followed by sunitinib. The results were surprising – median overall survival was shorter in patients who received cytoreductive nephrectomy (CN) in combination with systemic treatment with sunitinib compared to patients who received systemic treatment alone without nephrectomy. Therefore, it was concluded that sunitinib alone is not worse than nephrectomy followed by sunitinib, thus questioning the validity of performing CN in patients with metastatic RCC, previously the gold standard of care until the above results were published. Therefore, it was concluded that patients in the poor and intermediate prognosis group, according to the MSKCC, should not undergo surgery but only receive systemic treatment.

In another clinical trial evaluating the role of CN in patients with metastatic RCC treated with sunitinib – SURTIME – patients were randomized into two groups: in the first group (experimental group), sunitinib treatment was started before CN and continued after the procedure. The second group of patients (the control group) did not receive the initial therapy with sunitinib but instead received CN followed by sunitinib. A total of 99 patients were enrolled in the SURTIME study, and their treatment outcomes were compared with respect to the assumed 28-week PFS. The primary objective of the SURTIME study was to determine whether pretreatment with sunitinib prior to CN improves prognosis. Another study objective was to identify patients refractory to systemic therapy who are unlikely to benefit clinically from CN. Previous single-arm phase 2 studies of delayed CN after preoperative sunitinib showed that this approach is safe and helps avoid CN in people with early resistance to tyrosine kinase inhibitors (VEGFR) [12, 13]. In addition, the approach of delayed CN after initiating preoperative treatment with sunitinib may reduce the size and vascularity of the primary tumor, thereby facilitating the procedure and reducing the perioperative risk [14, 15]. No differences in progression-free survival were observed between the two groups in the SURTIME study (experimental and control). However, there was a reduction in the relative risk of death in patients in the experimental group (patients treated with sunitinib prior to CN) compared to patients in the control group. Median overall survival was significantly longer in patients treated with sunitinib prior to nephrectomy – 32.4 months, compared to the control group, where median survival was 15 months. The SURTIME study also showed that delaying the initiation of systemic treatment by performing CN may put some patients at risk of not receiving systemic treatment. The results of the SURTIME study suggest that the delayed CN approach, in which patients are started on sunitinib and offered nephrectomy only if their disease does not progress, may be better than performing the procedure upfront in every patient and then including sunitinib.

Both the CARMENA and SURTIME studies had limitations and inconsistencies, so their results should be interpreted with great caution by urologists and oncologists. However, since the publication of the results of these two prospective randomized studies, the role of CN and the indications for its use in patients with metastatic RCC have become an integral part of discussions among physicians treating RCC.

Material and methods

In this study, we present the results of a retrospective analysis of the cancer treatment of patients with metastatic RCC who underwent CN and subsequently received systemic treatment with sunitinib. The retrospective analysis includes the results of 67 patients diagnosed with metastatic RCC who were

treated and followed up at the Institute of Oncology in Poznań University of Medical Sciences in 2022 and 2023.

The software used for statistical analysis was Dell Inc. (2016), Dell Statistica (data analysis software system) version 13. software.dell.com and Cytel Studio version 11.1.0. The normality of the distributions of the variables studied was tested using the Shapiro–Wilk test. Quantitative variables with a normal distribution were presented using the mean and standard deviation, and the remaining quantitative variables were presented using the median (minimum-maximum). Categorical parameters were described as n (%). The statistical significance of the relationships and differences studied was checked at the level of significance $\alpha = 0.05$.

Results

Among the 67 patients diagnosed with metastatic RCC, there were 24 women (35.82%) and 43 men (64.18%). The mean age of the patients at the initiation of sunitinib treatment was 63.16 years (ranging from 49 years to 84 years). The mean age of women and men was similar – the mean age of women was 63.25 years, and the mean age of men was 63.12 years. In most patients (n = 35, 52.24%), the tumor was located in the right kidney, while left-sided tumors were less common (n = 32, 47.76%). All patients included in the study (n = 67, 100%) underwent CN before initiating systemic treatment with sunitinib. The mean duration of sunitinib treatment was 23.00 months (ranging from 0.73 months to 113.67 months), with a mean duration of treatment of 16.18 months in women and 26.80 months in men (p = 0.083). The most common reasons for sunitinib discontinuation were disease progression (n = 52, 77.61%), less frequently cardiac complications (n = 6, 8.95%), poor tolerability (n = 3, 4.48%), death due to unrelated causes (n = 3, 4.48%), or other reasons (n = 3, 4.48%). Among all patients, 54 (80.60%) were qualified to continue treatment with another drug (including axitinib, nivolumab, cabozantinib). In the analyzed patient group, 3 patients (4.48%) discontinued sunitinib treatment during the first cycle. They were, therefore, excluded from the comparative analysis of laboratory test results at baseline and at the end of sunitinib treatment. The laboratory test results of the remaining patients (n = 64) at baseline and the end of treatment were subjected to statistical analysis; the collected results are presented in table I.

Among the patients included in the study, a statistically significant decrease in body weight was observed during systemic treatment with sunitinib (p = 0.001) (tab. I). Moreover, a statistically significant decrease in hemoglobin levels (p < 0.001), hematocrit levels (p < 0.001), platelet count (p = 0.001) and blood smear neutrophil count (p < 0.001) was also revealed in patients treated with sunitinib. A statistically significant decrease was also observed in serum albumin levels (p < 0.001). Importantly, a statistical increase in aspartate aminotransferase (AST) was found (p = 0.007). In addition, there was a statistical decrease in alkaline phosphatase (p < 0.001) and a statistical increase in lactate dehydrogenase (p < 0.001). Importantly, statistically significant potassium levels were also revealed during sunitinib treatment (p = 0.004). There were no statistical differences in creatinine levels at baseline and at the end of treatment, indicating that sunitinib did not cause statistically significant renal toxicity in the patient population analyzed. There were also no statistically significant changes in liver parameters such as alanine aminotransferase (ALT) or bilirubin; however, given the statistically significant increase in AST during sunitinib treatment, the effect of this drug on liver toxicity remains unclear. Importantly, short-term liver toxicity was observed in several patients during treatment, requiring a reduction in sunitinib dosage or an increase in the interval between cycles, which may indicate a negative effect of sunitinib on liver function. No statistically significant effect was found on serum sodium and calcium levels. Sunitinib treatment was associated with significant thyroid dysfunction manifested by iatrogenic hypothyroidism, most of which required thyroid hormone replacement. The TSH test was used as the reference parameter. At the start of sunitinib treatment, the mean TSH level was 1.89 (μlU/ml), while at the end of treatment, the mean TSH level was 6.27 (μlU/ml) – p < 0.001. It should be noted that most patients required thyroid hormone replacement during sunitinib treatment, so the final mean TSH appears to be significantly underestimated. Sunitinib-related adverse effects required dose reductions in 32 patients (47.76%). In addition to the above-mentioned laboratory abnormalities, the following adverse effects were observed in patients treated with sunitinib: weakness, hand–foot syndrome, diarrhea, decreased appetite, numbness of the upper and lower limbs, skin lesions, hypertension, oral mucosal lesions, musculoskeletal pain, and abdominal pain.

The study also analyzed factors that may have influenced the need to reduce the dose of sunitinib during treatment because of the adverse effects caused by the drug. The need to reduce the dose of sunitinib during treatment was observed to be correlated with patient age at the initiation of treatment – patients whose dose of sunitinib was reduced were older at the start of sunitinib treatment than patients whose dose of sunitinib was not reduced during the treatment (p = 0.038) (fig. 1).

The study also analyzed factors that may influence the presence or absence of cancer progression during sunitinib treatment. A correlation was found between patient age at the start of sunitinib treatment and the occurrence of disease progression – patients with disease progression during sunitinib treatment were younger at the start of sunitinib treatment. Therefore, the prognosis of younger patients treated with sunitinib is statistically worse than that of older patients (p = 0.004) (fig. 2).

Discussion

The retrospective analysis of the treatment outcomes of patients with metastatic RCC treated with sunitinib allowed us to identify the adverse effects of the drug that require special attention during the treatment process. A better understanding

Table I. The laboratory test results at baseline and sunitinib treatment's end

Laboratory test	n	Mean	Median	Minimum	Maximum	Stabilization of the disease	p-value
body weight (start of treatment) (kg)	64	82.82	83.50	45.00	124.00	17.56	0.001
body weight (end of treatment) (kg)	64	79.50	76.50	49.00	114.00	14.25	
hemoglobin (start of treatment) (mmol/l)	64	8.63	8.65	6.00	11.30	1.09	<0.001
hemoglobin (end of treatment) (mmol/l)	64	7.57	7.60	5.40	10.50	1.16	
hematocrit (start of treatment) (L/l)	64	0.41	0.41	0.27	0.55	0.05	<0.001
hematocrit (end of treatment) (L/l)	64	0.37	0.37	0.27	0.50	0.06	
platelets (start of treatment) (10^9/l)	64	265.38	249.00	126.00	508.00	74.63	0.001
platelets (end of treatment) (10^9/l)	64	231.25	211.50	72.00	533.00	81.73	
neutrophils (start of treatment) (10^9/l)	64	4.69	4.64	1.72	11.07	1.67	<0.001
neutrophils (end of treatment) (10^9/l)	64	2.82	2.39	0.58	14.98	1.99	
creatinine (start of treatment) (µmol/l)	64	107.45	106.00	60.00	247.00	29.17	0.521
creatinine (end of treatment) (µmol/l)	64	114.44	106.00	58.00	281.00	42.27	
albumin (start of treatment) (g/l)	64	38.85	39.30	25.50	49.00	4.15	<0.001
albumin (end of treatment) (g/l)	64	35.13	36.05	19.00	43.00	5.57	
ALT (start of treatment) (IU/l)	64	33.40	25.50	10.00	134.00	25.13	0.342
ALT (end of treatment) (IU/l)	64	31.23	25.00	8.00	113.00	21.05	
AST (start of treatment) (IU/l)	64	26.67	21.00	11.00	118.00	18.96	0.007
AST (end of treatment) (IU/l)	64	30.11	25.00	12.00	104.00	16.94	
bilirubin (start of treatment) (µmol/l)	64	10.71	10.10	4.00	23.00	4.09	0.946
bilirubin (end of treatment) (µmol/l)	64	10.87	9.00	4.40	30.00	5.59	
natrium (start of treatment) (mmol/l)	64	140.31	140.50	133.00	146.00	2.77	0.140
natrium (end of treatment) (mmoll)	64	140.81	141.00	130.00	146.00	3.17	
potassium (start of treatment) (mmol/l)	64	4.59	4.60	3.90	5.50	0.39	0.004
potassium (end of treatment) (mmol/l)	64	4.39	4.35	3.50	5.30	0.43	
alkaline phosphatase (start of treatment) (IU/l)	64	106.03	92.00	48.00	427.00	56.38	<0.001
alkaline phosphatase (end of treatment) (IU/l)	64	98.25	88.50	34.00	430.00	66.23	
lactate dehydrogenase (start of treatment) (IU/l)	64	187.11	184.00	106.00	280.00	37.04	<0.001
lactate dehydrogenase (end of treatment) (IU/l)	64	222.17	211.50	132.00	386.00	55.22	
calcium (start of treatment) (mmol/l)	64	2.42	2.42	2.14	2.75	0.15	0.954
calcium (end of treatment) (mmol/l)	64	2.42	2.41	2.12	2.92	0.16	
TSH (start of treatment) (µIU/ml)	64	1.89	1.64	0.01	6.44	1.35	<0.001
TSH (end of treatment) (µIU/ml)	64	6.27	2.87	0.01	88.08	11.80	

of the molecular mechanisms underlying sunitinib-related adverse effects helps physicians maximize the efficacy of sunitinib, and minimize the occurrence of adverse effects, thereby improving patients' quality of life. The analysis of the results collected allows us to conclude that, due to the adverse effects caused by sunitinib, appropriate qualification for treatment is necessary and that, when using sunitinib, it is absolutely essential to constantly monitor laboratory test results to reduce the dose of the drug or extend the interval between cycles in case of drug toxicity.

The adverse effects observed in the analyzed group of patients, such as weight loss, anemia, thrombocytopenia,

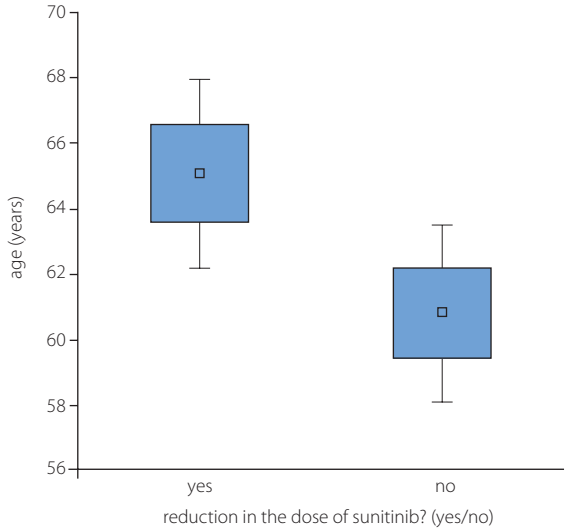

Figure 1. Correlation of the need to reduce the dose of sunitinib with a patient's age at the initiation of treatment

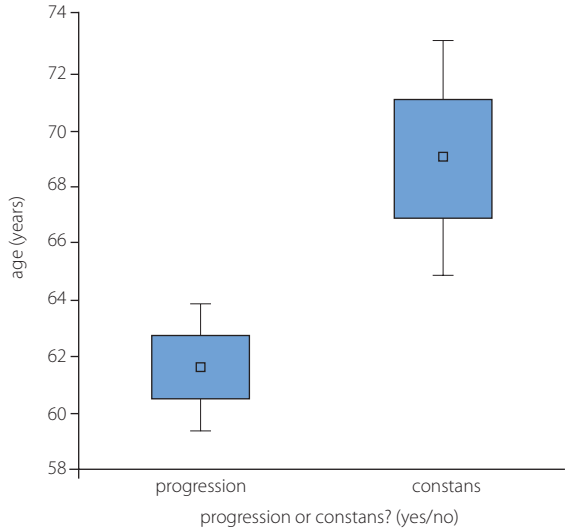

Figure 2. Correlation between a patient's age at the start of sunitinib treatment and the occurrence of disease progression

decreased neutrophil count, decreased albumin levels, increased liver function test values (ALT), electrolyte imbalance (hypokalemia), increased lactate dehydrogenase levels, or decreased alkaline phosphatase levels, may be related to the neoplastic process or its progression and not necessarily to the use of sunitinib. However, the adverse effects of sunitinib described in the study are consistent with reports in the literature regarding sunitinib [3, 4].

The thyroid toxicity of sunitinib is of particular interest in the results analyzed. The vast majority of patients developed iatrogenic hypothyroidism requiring thyroid hormone replacement. This observation is consistent with reports in the literature. Sunitinib causes iatrogenic hypothyroidism and even atrophy of the gland. The mechanism of this adverse effect is not fully understood. According to literature reports, the causes may include the antiangiogenic effect of sunitinib [16, 17], inhibition of iodine uptake [18], induction of destructive thyroid inflammation [19], inhibition of thyroid peroxidase activity [20], or reduced vascularization of thyroid cells due to regression or narrowing of blood vessels [16, 21]. Because of iatrogenic hypothyroidism in patients, screening for hypothyroidism is mandatory during sunitinib treatment, and any laboratory abnormalities or symptoms reported by patients suggesting hypothyroidism require levothyroxine supplementation [8].

The CheckMate 214 study compared nivolumab + ipilimumab with sunitinib in patients with metastatic RCC. A total of 1096 patients with metastatic RCC were enrolled between October 2014 and February 2016. The patients were randomized into two groups – those treated with nivolumab + ipilimumab (550 people) and those treated with sunitinib (546 people). The study showed that immunotherapy (nivolumab + ipilimumab) was significantly more effective than sunitinib in patients with intermediate and poor prognosis, according to the IMDC (International Metastatic RCC Database Consortium) scale in terms of overall survival, progression-free survival, and clinical response rate [22]. In addition, patients treated with the nivolumab + ipilimumab regimen had a statistically better quality of life compared to sunitinib [23].

Another phase 3 study – COMPARZ – compared sunitinib with another antiangiogenic drug – pazopanib [24]. Among the 1,110 patients with metastatic RCC enrolled in the study, 557 received pazopanib, and 553 received sunitinib. Pazopanib was shown to be non-significantly inferior to sunitinib in terms of progression-free survival and overall survival. However, pazopanib treatment was better tolerated, and fewer adverse effects were reported by pazopanib-treated patients compared to sunitinib-treated patients. Patients treated with sunitinib when compared to pazopanib, had a higher incidence of fatigue (63% *vs*. 55%), hand-foot syndrome (50% *vs*. 29%), and thrombocytopenia (78% *vs*. 41%), while patients treated with pazopanib had a higher incidence of ALT elevations (60% *vs*. 43% with sunitinib). The overall analysis of the COMPARZ study results concluded that pazopanib and sunitinib had similar efficacy. However, the safety profile, number of adverse effects, and patients' quality of life during treatment favored pazopanib.

Another clinical trial – CABOSUN – compared sunitinib with another antiangiogenic drug – cabozantinib, as initial therapy for advanced RCC of intermediate and poor prognosis according to the IMDC scale. A total of 157 patients were randomized 1:1 to cabozantinib (n = 79) or sunitinib (n = 78). In this trial, cabozantinib treatment significantly prolonged PFS compared with sunitinib as initial systemic therapy for advanced RCC of poor or intermediate risk [25].

Due to the emergence of drugs with higher efficacy and fewer adverse effects compared to sunitinib, the use of sunitinib

has been limited in recent years. However, this drug is still used in the following clinical situations:

- patients with advanced RCC in good and intermediate prognosis groups (I, A),
- patients with advanced RCC in intermediate prognosis group without access to cabozantinib, immunotherapy, or immunotherapy combined with kinase inhibitors (I, B) [26].

Tailored oncological treatment based on molecularly targeted therapies and immunotherapies (for example ipilimumab and nivolumab) play an increasing role in the multidisciplinary approach to patients with advanced RCC, so the use of sunitinib has recently been limited. The use of immune checkpoint inhibitors (ICI), i.e. ipilimumab and nivolumab, in the therapy of metastatic kidney cancer, has revolutionized treatment recommendations due to the high effectiveness of these drugs. Treatment personalization extends the scope of therapy and extends the survival of patients. Tremendous progress in molecular biology and the development of new molecularly targeted drugs allow treatment personalization for very narrow, genetically selected groups of cancer patients [28].

The study's main limitation is that it was conducted retrospectively, assessing the results of previous oncological treatments without the possibility of prospective assessment. There was no assessment of the quality of life in patients receiving sunitinib, which is clinically very important in the treatment of advanced cancer. Moreover, only patients who had previously undergone CN were included in the study. To increase the study's scientific value in the future, it seems reasonable to expand the experimental group to include additional patients with metastatic RCC treated with sunitinib who did not undergo CN, and to compare patients treated with sunitinib after CN and without CN in the past.

Conclusions

Since sunitinib was approved by the U.S. Food and Drug Administration (FDA) in 2006 as a first-line treatment for advanced RCC, the recommendations for its use have been modified several times in response to new clinical and literature data. Despite the emergence of immunomodulatory drugs, particularly ipilimumab and nivolumab, which are increasingly being introduced in the treatment of advanced RCC, sunitinib is still used with good results in patients with metastatic RCC in the aforementioned prognostic groups.

The complexity of the mechanisms associated with metastatic RCC forces researchers, oncologists, and urologists to constantly monitor the clinical effectiveness of the treatment regimens implemented. Since the introduction of sunitinib into widespread use, many studies have been published evaluating the efficacy of this drug. That said, all the reasons for the success or failure of the oncological treatment of patients with metastatic RCC receiving sunitinib still remain unknown. Therefore, the efficacy of sunitinib treatment in patients with metastatic RCC should continue to be evaluated and monitored, preferably using prospective randomized studies, the results of which are the most reliable from a scientific and clinical point of view.

Qualification to the correct prognostic group and the subsequent initiation of appropriate systemic treatment of metastatic renal-cell carcinoma requires a thorough analysis, which should be performed by a multidisciplinary oncology team (case conference). Treatment with sunitinib requires regular clinical and laboratory follow-ups, monitoring of the occurrence of adverse effects, and assessment of the patient's quality of life to appropriately reduce the dose of the drug or increase the interval between cycles in the event of adverse effects; this includes the possible implementation of the appropriate pharmacological treatment aimed at reversing the adverse effects of the drug.

Article information and declarations

Author contributions

Maciej Michalak – planning the study, collecting data, statistical analysis, writing an article.
Piotr Tomczak – planning the study, writing an article, content supervision.
Tomasz Milecki – planning the study, statistical analysis, writing an article.
Andrzej Antczak – planning the study, writing an article, content supervision.

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author, Maciej Michalak.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki. The opinion of the Ethics Committee was obtained that there were no features of a medical experiment.

Conflict of interest

None declared

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References

1. Osawa T, Takeuchi A, Kojima T, et al. Overview of current and future systemic therapy for metastatic renal cell carcinoma. Jpn J Clin Oncol. 2019; 49(5): 395–403, doi: 10.1093/jjco/hyz013, indexed in Pubmed: 30722031.
2. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med. 2017; 376(4): 354–366, doi: 10.1056/NEJMra1601333, indexed in Pubmed: 28121507.

3. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007; 356(2): 115–124, doi: 10.1056/NEJMoa065044, indexed in Pubmed: 17215529.
4. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22): 3584–3590, doi: 10.1200/JCO.2008.20.1293, indexed in Pubmed: 19487381.
5. Motzer RJ, Escudier B, Gannon A, et al. Sunitinib: Ten Years of Successful Clinical Use and Study in Advanced Renal Cell Carcinoma. Oncologist. 2017; 22(1): 41–52, doi: 10.1634/theoncologist.2016-0197, indexed in Pubmed: 27807302.
6. Ferrari SM, Centanni M, Virili C, et al. Sunitinib in the Treatment of Thyroid Cancer. Curr Med Chem. 2019; 26(6): 963–972, doi: 10.2174/0929867324666171006165942, indexed in Pubmed: 28990511.
7. Touyz RM, Herrmann J. Cardiotoxicity with vascular endothelial growth factor inhibitor therapy. NPJ Precis Oncol. 2018; 2: 13, doi: 10.1038/s41698-018-0056-z, indexed in Pubmed: 30202791.
8. Cohen R, Bihan H, Uzzan B, et al. [Sunitinib and hypothyroidism]. Ann Endocrinol (Paris). 2007; 68(5): 332–336, doi: 10.1016/j.ando.2007.06.027, indexed in Pubmed: 17707761.
9. Fallahi P, Ferrari SM, Vita R, et al. Thyroid dysfunctions induced by tyrosine kinase inhibitors. Expert Opin Drug Saf. 2014; 13(6): 723–733, doi: 10.1517/14740338.2014.913021, indexed in Pubmed: 24821006.
10. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018; 379(5): 417–427, doi: 10.1056/NEJMoa1803675, indexed in Pubmed: 29860937.
11. Bex A, Mulders P, Jewett M, et al. Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncol. 2019; 5(2): 164–170, doi: 10.1001/jamaoncol.2018.5543, indexed in Pubmed: 30543350.
12. Powles T, Kayani I, Blank C, et al. The safety and efficacy of sunitinib before planned nephrectomy in metastatic clear cell renal cancer. Ann Oncol. 2011; 22(5): 1041–1047, doi: 10.1093/annonc/mdq564, indexed in Pubmed: 21242586.
13. Powles T, Blank C, Chowdhury S, et al. The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer. Eur Urol. 2011; 60(3): 448–454, doi: 10.1016/j.eururo.2011.05.028, indexed in Pubmed: 21612860.
14. Shuch B, Riggs SB, LaRochelle JC, et al. Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm. BJU Int. 2008; 102(6): 692–696, doi: 10.1111/j.1464-410X.2008.07660.x, indexed in Pubmed: 18410444.
15. Patard JJ, Thuret R, Raffi A, et al. Treatment with sunitinib enabled complete resection of massive lymphadenopathy not previously amenable to excision in a patient with renal cell carcinoma. Eur Urol. 2009; 55(1): 237–9; quiz 239, doi: 10.1016/j.eururo.2008.09.006, indexed in Pubmed: 18804907.
16. Jebreel A, England J, Bedford K, et al. Vascular endothelial growth factor (VEGF), VEGF receptors expression and microvascular density in benign and malignant thyroid diseases. Int J Exp Pathol. 2007; 88(4): 271–277, doi: 10.1111/j.1365-2613.2007.00533.x, indexed in Pubmed: 17696908.
17. Yamada E, Yamazaki K, Takano K, et al. Iodide inhibits vascular endothelial growth factor-A expression in cultured human thyroid follicles: a microarray search for effects of thyrotropin and iodide on angiogenesis factors. Thyroid. 2006; 16(6): 545–554, doi: 10.1089/thy.2006.16.545, indexed in Pubmed: 16839256.
18. Mannavola D, Coco P, Vannucchi G, et al. A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab. 2007; 92(9): 3531–3534, doi: 10.1210/jc.2007-0586, indexed in Pubmed: 17595247.
19. Desai J, Yassa L, Marqusee E, et al. Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med. 2006; 145(9): 660–664, doi: 10.7326/0003-4819-145-9-200611070-00008, indexed in Pubmed: 17088579.
20. Wong E, Rosen LS, Mulay M, et al. Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. Thyroid. 2007; 17(4): 351–355, doi: 10.1089/thy.2006.0308, indexed in Pubmed: 17465866.
21. Makita N, Miyakawa M, Fujita T, et al. Sunitinib induces hypothyroidism with a markedly reduced vascularity. Thyroid. 2010; 20(3): 323–326, doi: 10.1089/thy.2009.0414, indexed in Pubmed: 20187785.
22. Motzer RJ, Rini BI, McDermott DF, et al. CheckMate 214 investigators. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019; 20(10): 1370–1385, doi: 10.1016/S1470-2045(19)30413-9, indexed in Pubmed: 31427204.
23. Cella D, Grünwald V, Escudier B, et al. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. Lancet Oncol. 2019; 20(2): 297–310, doi: 10.1016/S1470-2045(18)30778-2, indexed in Pubmed: 30658932.
24. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013; 369(8): 722–731, doi: 10.1056/NEJMoa1303989, indexed in Pubmed: 23964934.
25. Choueiri T, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. European Journal of Cancer. 2018; 94: 115–125, doi: 10.1016/j.ejca.2018.02.012.
26. Wysocki P, Chłosta P, Chrzan R, et al. Zalecenia postępowania diagnostyczno-terapeutycznego w raku nerkowokomórkowym — aktualizacja. Onkol Prakt Klin Edu. 2022; 8(6): 424–457.
27. Wojciechowska U, Barańska K, Miklewska M, et al. Cancer incidence and mortality in Poland in 2020. Nowotwory. Journal of Oncology. 2023; 73(3): 129–145, doi: 10.5603/njo.2023.0026.
28. Krawczyk P. Only one step from tailored oncological therapies. Nowotwory. Journal of Oncology. 2018; 68(1): 42–45, doi: 10.5603/njo.2018.0009.

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Review article

Tumor pathology

Cytology of thyroid and parathyroid glands in oncology diagnosis – a contemporary review of updates and innovations

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Fine needle aspiration (FNA) is widely used in the examination of head and neck lesions and has been considered an important diagnostic tool in the evaluation of thyroid and parathyroid nodules. Thyroid nodules are frequent findings in the general population, although 90-95% of these nodules are benign. FNA plays a crucial role to determine which nodules are at greatest risk of malignancy and which nodules are benign and do not require surgical intervention. In the case of the parathyroid glands, the US-guided parathyroid FNA is an effective method for the identification of intrathyroidal or ectopic parathyroid tissue, and distinguish it from thyroid and other surrounding anatomical structures. In addition, the use of FNA can significantly increase the accuracy of parathyroid gland location in patients with hyperparathyroidism who are candidates for surgical treatment in cases where imaging techniques fail to identify the parathyroid. Widespread US guidance in FNA procedures, constellation of clearly defined, reproducible key diagnostic cytopathological criteria for individual lesions in conjunction with images and clinical data as well as evolutions in FNA techniques and ancillary tests facilitate further diagnostic and clinical management. This paper aims to review the current state of the art in cytological evaluation of thyroid and parathyroid lesions.

Key words: cytology, fine needle aspiration, thyroid, parathyroid, cytological diagnosis

Introduction

Most thyroid and parathyroid nodules represent benign colloid nodules and parathyroid adenomas or hyperplastic parathyroid glands respectively. Malignant tumors represent less than 5% of all thyroid tumors and less than 1% of parathyroid tumors [1–4]. The selection of patients with malignant thyroid tumors and parathyroid tumors who are eligible for surgical treatment is the greatest challenge in the work up of thyroid and parathyroid nodules. Surgical treatment can result in complications such as post-operative thyroid hormone imbalance, hypoparathyroidism, recurrent laryngeal nerve injury, bleeding and infection. Surgical treatment of benign tumors should be limited to cases of hyperthyroidism and hyperparathyroidism, nodular lesions in conjunction with Graves's disease and patients

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with compressive symptoms. Numerous studies have found fine needle aspiration (FNA) to be a minimally invasive, safe, accurate, and cost-effective diagnostic tool for management of thyroid and parathyroid nodules. As ultrasound-guided (US--guided) thyroid FNA is recommended for initial evaluation of thyroid nodules and to triage patients based on its results [5,6], the cytologic examination of parathyroid has not been recommended in the past [7–9]. Dense fibrotic reaction to the needle, disruption of the lesion and seeding along the needle tract has been reported as complications caused by parathyroid FNA [10–15]. However, FNA is an efficient technique for the identification of parathyroid tissue in patients with intrathyroidal or ectopic parathyroid gland location, and to distinguish it from thyroid and other surrounding anatomical structures. In cases of persistent hypercalcemia after a failed surgery or in a recurrent disease when neck anatomy is distorted, the use of US-guided FNA can significantly increase the accuracy of parathyroid gland localization [16–21].

Clinical perspectives and role of image studies

Thyroid

Thyroid nodules are common with a higher prevalence in woman, and with palpable nodules found in 4–7% of adults [1, 3, 22–25] and subclinical nodules identified in approximately 70% of adults [26, 27]. Although 90–95% of thyroid nodules are benign, the rate of thyroid cancer has been on the rise over the last 3 decades [5, 27, 28]. Factors such as an increase in radiation exposure and more frequent diagnostic imaging with higher resolution US as well as overall diagnostic improvements contribute to this trend. Increased detection of microcarcinomas is also attributed to increasing prevalence of thyroid cancer worldwide [28–31].

Thyroid nodules are more frequent in women than in men and the female risk of carcinoma is approximately 3-fold compared to that of men. Pregnancy and the effect of estrogen have been suggested as factors associated with increased risk of malignancy [32]. Chronic iodine deficiency has been known to be a risk factor for goiter and follicular thyroid carcinoma [32, 33]. On the other hand, according to some epidemiologic studies, iodine excess might increase the incidence of papillary thyroid carcinoma [34]. Other risk factors include environmental factors such as ionizing radiation. The risk of radiation-related thyroid carcinoma was shown to be 3-fold higher in iodine deficient areas than elsewhere [35–37].

Tumors of the thyroid gland are the most common endocrine neoplasm. The majority of these derived from follicular epithelial cells, a smaller number from calcitonin-secreting C cells and rarely from both follicular and C cells [38]. Somatic rearrangements of the *RET* proto-oncogene occur in about 35% and *BRAV* V600E mutations in 45% of adult sporadic papillary carcinoma [38–42]. Follicular thyroid carcinoma and thyroid neoplasms with follicular architecture and an expansive but not infiltrative growth pattern are characterized by a high incidence of *RAS* mutations [43]. Medullary thyroid carcinoma, tumor derived from C cells, is characterized by *RET* and *RAS* mutations being detected in 80–90% of cases [44].

US examination provides valuable information about the sonographic characteristics of thyroid nodules. Sonographic characteristics for suspicious malignant nodules include irregular margins, solid structure, markedly hypoechogenicity, microcalcifications, larger vertical than horizontal dimensions and dominant central vascularity. Benign nodules are usually well-defined, isoechoic, with regular borders, without microcalcifications and commonly cystic.

In 2009 a standardized risk-stratification system for thyroid lesions (TI-RADS), assessing the risk of malignancy of thyroid nodules based on ultrasound features, was proposed. TI-RADS scale informs practitioners about the risk of malignancy and further management of the lesion. Since then, there have been various modifications to this scale, and similar systems were established by the European Thyroid Association (EU-TI-RADS), the American College of Radiology (ACR-TI-RADS), the American Thyroid Association (ATA guidelines) and the Korean Society of Thyroid Radiology (K-TI--RADS) [45–48]. In 2022, Polish Scientific Societies and the National Oncological Strategy introduced updated recommendations referring to diagnosis and treatment of thyroid cancer in adult patients. In that guideline, the EU-TI-RADS-PL classification, modified based on EU-TIRADS classifier, was introduced. According to EU-TI-RADS-PL, the malignancy risks of thyroid lesions are evaluated as non-suspicious (TR2), low-risk (TR3), intermediate-risk (TR4) and high-risk (TR5) nodules. The most significant modification, compared to EU-TI-RADS, referred to EU-TIRADS-PL 5 class with indication for FNA in TR5 nodules of dimension ≥5 mm (instead of ≥10 mm in EU-TI-RADS 5 lesions) [49].

Parathyroid

Typically, parathyroid glands are small, weighing between 30–50 mg, with an oval or kidney-shaped appearance, and their color ranges from yellow to brown. They usually measure 2–7 mm in size. It's common for a person to have four parathyroid glands, but variations exist, and about 15% of individuals may have additional parathyroid glands. The upper parathyroid glans, which emerge from the fourth branchial pouches alongside the thyroid gland lateral anlages, are generally found behind the middle section of the thyroid at the level of isthmus. Less than 2% of upper glands occur in ectopic location. Conversely, the lower parathyroids and the thymus originate from the third branchial pouch, usually located lateral to, or less commonly slightly below the thyroid's lower pole. Due to their shared embryonic origins with the thyroid gland and thymus, ectopic parathyroid glands can be found in locations like the mediastinum or near the carotid sheath in the aortopulmonary window in 10–20% of individuals. A small subset of intrathyroidal parathyroids account for about 2% of all cases.

Sporadic hyperparathyroidism is a leading cause of hypercalcemia, with parathyroid adenomas being identified

in the majority (more than 85%) of primary hyperparathyroidism cases. Hyperactivity in all four glands is the second most common cause of primary hyperparathyroidism (10% to 15%) while parathyroid carcinoma is found in less than 1% of cases [16, 50, 51]. The diagnosis of hyperparathyroidism hinges on elevated levels of parathyroid hormone (PTH) and calcium in the blood. Both PTH and calcium are elevated in the majority of the cases. The standard care of primary hyperparathyroidism is preoperatively identification and subsequent surgical removal of the affected gland or glands. Surgical removal of the affected glands has evolved from extensive, bilateral neck explorations to less invasive techniques such as minimally invasive parathyroidectomy.

A different approach including radical surgery is required in cases of suspicious parathyroid carcinoma The localization of parathyroid abnormalities in patients with primary hyperparathyroidism is essential for surgical planning. Techniques like ultrasound (US) and Technetium 99 m sestamibi scans (^{99}Tc-MIBI) are commonly employed, with other methods including 4-dimensional computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) serving as alternatives, especially when initial imaging is inconclusive [7, 16]. Both US and sestamibi scintigraphy studies show that the effectiveness of these imaging modalities varies by the specific location of pathologic parathyroid glands. Both methods are more sensitive in detecting lower left adenomas than upper right ones. Overall, the positive predictive value for all parathyroid gland sites is approximately 54% for sestamibi scintigraphy and 59% for US, respectively. High-resolution US, in particular, has demonstrated a broad range of sensitivity and specificity between 51% and 87% and between 90% and 98% respectively. The PET/CT scans with ^{18}F-labeled choline analogues might be considered as the alternative imaging method of parathyroid glands, especially in patients with negative or equivocal first-line imaging tool findings [19, 20, 52, 53]. The size of the parathyroid glands does not necessarily correlate with their function, and common limitations of US are the identification of small, multiple, or ectopic parathyroid glands and to differentiate parathyroid tissue from thyroid nodules or other neck structures. Although imaging studies are used to localize the lesion and not to diagnose hyperplasia or parathyroid neoplasms, up to 25% of parathyroid adenomas might not be detectable *via* US or sestamibi scans, highlighting the challenges evident in localizing these glands [16, 52, 53].

The role of cytopathology and sampling techniques

FNA is widely accepted as a safe, cost-effective, and accurate diagnostic modality that may be performed in an outpatient setting.

For FNA of thyroid and parathyroid lesions, 27- to 22-gauge (0.4–0.7 mm) needles are suitable, either using a capillary technique without aspiration or a plastic disposable 10- or 20-ml syringe attached to a plastic or metal syringe holder (FNA with aspiration). Both air-dried and alcohol-fixed smears as well as liquid-based preparations have been used in evaluating thyroid and parathyroid FNAs. Adjunct use of cell block preparations may also be helpful in certain situations. There are two common fixation methods: air drying or wet fixing using either 95% ethanol or ethanol based Cytospray as a fixative. Both fixation methods are largely determined by local practice patterns and provide comparable results for a reliable diagnosis performance. Wet fixation usually better demonstrates such details as nuclear pattern, chromatin structure and nucleoli, and match nuclear and cytoplasmic structures observed in histologic sections. Air-dried specimens give better information on cytoplasmic details and the background material. Air dried smears can be stained with Diff-Quik or May-Grünwald-Giemsa (MGG), and wet fixed smears with hematoxylin and eosin (H&E) or Papanicolaou (Pap) [54].

The liquid-based preparation techniques have been reported as a valid method for cytologic diagnosis of thyroid and parathyroid lesions. Cellular morphology and nuclear details may appear more prominent, and the architectural pattern may show only minor differences as compared to conventional smears. However, smears from thyroid nodules may contain less colloid, the nuclear hallmarks of papillary carcinomas may be vague, and cell shrinkage and disruption of the cytoplasm may be more pronounced.

In many institutions, aspirations are routinely performed by a clinician or radiologist without the assistance of a cytopathologist or cytotechnologist. A less skilled aspirator may see a higher percentage of unsatisfactory FNA smears, and on-site adequacy evaluations (ROSE) can be helpful in reducing the number of nondiagnostic specimens. ROSE allows the cytopathologists to achieve important clinical information and is a prerequisite for the multimodal approach. The ROSE procedure, however, is costly and time-consuming with divergent results in respect to the FNA adequacy rate. The benefit of on-site evaluations depends on the experience of the operator and the skill and expertise of the interpreting cytopathologist or cytotechnologist [55–57].

FNA of the thyroid has emerged as a minimally invasive, precise and reliable method for managing thyroid nodules. Cytopathology has a low false-negative rate for diagnosis of thyroid malignancy and offers crucial insights into the characteristics of thyroid nodules, aiding in the differentiation between benign and suspicious nodules. US-guided FNA has significantly increased the triage efficiency, decreased the rate of unnecessary surgery for benign thyroid nodules and helped to identify nodules that are most appropriate for surgical management [54]. In cases of benign FNA, the recommendation is to monitor the patient periodically with imaging. In cases of malignant FNA or suspicion of malignancy, the recommendation is to undergo surgical treatment such as lobectomy or total thyroidectomy. Controversy still exists regarding the accuracy of FNA, and the clinical management for thyroid nodules

smaller than 1 cm or greater than 4 cm [6, 58]. FNA of a palpable thyroid mass may be performed by any clinician or cytopathologist with appropriate experience and in the past, aspirations were often performed only with manual aid. In the last decades, thyroid FNA is increasingly performed using ultrasound US guidance. The US-guided FNA is a safe and effective method that has proven to be superior to palpation-guided FNA to reduce inadequate sampling and the need for repeated FNA with inadequate sample rates of 14–21% *versus* 32–50%, respectively [57–60]. Complications due to FNA of the thyroid gland are rare and may include persistent pain, hematoma, infection, and recurrent laryngeal nerve palsy.

In the past, thyroid FNA reporting generated much confusion for both clinicians and pathologists due to multiple different reporting schemes and descriptive reports that did not clearly convey malignancy risk. In 2007, more uniform and evidence-based reporting schemes have been instituted, including the widely implemented six-tiered Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), arising from the National Cancer Institute in Bethesda, Maryland. As a result, the Bethesda system provides clarity of communication, facilitating the exchange of data across institutions, as well as having an implicit cancer risk associated with each category to guide appropriate clinical management [54]. Since its introduction and publishing the first edition of TBSRTC, two additional editions of the Bethesda system have been published. The updated 3rd edition published in 2023 [61, 62] reflects advances in the field of thyroid cytology in the last decade such as the expanded use of ancillary testing in the cytological diagnosis of neoplastic disease. A simplified reporting structure; updated and recalculated risk of malignancy (ROM) for each category and harmonization of nomenclature with the 2022 World Health Organization classification of thyroid tumors [38, 61] (tab. I) are important topics that have been expanded and updated in the 3rd edition of TBSRTC. After the introduction of TBSRTC, the system has been most widely accepted in Poland with some minor modifications. Polish scientific society recommendations regarding the cytological diagnosis of thyroid nodules and treatment of thyroid malignancies were updated and published in 2022 [48]. The terminology, diagnostic categories, risk of malignancy and patient management are consistent with the Bethesda recommendations.

FNA diagnosis of many thyroid lesions is based on cytological patterns and the distinctive cytological features of FNA smears, and can be a precise match to the endocrine pathology diagnosis. In others, the cytological examination can show a particular pattern that can help to place the lesion in a specific diagnostic category of TBSRTC but may not provide a specific histological diagnosis [61, 62].

Normal components of a thyroid FNA are comprised of follicular cells and colloid. Follicular cells may appear as intact macrofollicles or flat sheets of uniformly spaced follicular cells with small round nuclei and condensed chromatin. Microfollicles composed of 15 or fewer follicular cells are absent or only a minor component in aspirates of non-neoplastic thyroid nodules. Follicular cells that underwent oncocytic metaplasia show abundant granular cytoplasm with enlarged, round, eccentrically placed nuclei with prominent nucleoli. Colloid has a variable appearance and may appear as rounded or irregular aggregates with a jagged "cracking" artifact. Smears of common cystic thyroid nodules exhibit hemosiderin-laden

Table I. Diagnostic categories in the 3rd edition of the Bethesda System for Reporting Thyroid Cytopathology*

Nondiagnostic
cyst fluid only
virtually acellular specimen
other (obscuring blood, clotting artifact, drying artifact, etc.)
Benign
consistent with follicular nodular disease (includes adenomatoid nodule, colloid nodule, etc.)
consistent with chronic lymphocytic (Hashimoto) thyroiditis in the proper clinical context
consistent with granulomatous (subacute) thyroiditis
other
Atypia of undetermined significance
specify if AUS-nuclear atypia or AUS-other
Follicular neoplasm
specify if oncocytic (formerly Hürthle cell) type
Suspicious for malignancy
suspicious for papillary thyroid carcinoma
suspicious for medullary thyroid carcinoma
suspicious for metastatic carcinoma
suspicious for lymphoma
other
Malignant
papillary thyroid carcinoma
high-grade follicular-derived carcinoma
medullary thyroid carcinoma
undifferentiated (anaplastic) carcinoma
squamous-cell carcinoma
carcinoma with mixed features (specify)
metastatic malignancy
non-Hodgkin lymphoma
other

* Adapted from Ali SZ, VanderLaan PA. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes, 3rd ed. Springer: New York, NY, USA; 2023

macrophages and "cyst-lining" cells with elongated, drawn-out cytoplasm. Multinucleated giant cells may be seen in thyroid aspirates, although these cells are not specific for either benignity or malignancy. Nonthyroidal elements may be obtained through transit of the needle to the target lesion. Of nonthyroidal elements, smears of parathyroid nodules and lymph nodes may mimic thyroid lesions [54].

Adequacy in thyroid aspirates generally requires identification of six or more groups of at least 10 follicular cells per group. Any aspirate with a diagnostic abnormality is counted as adequate regardless of cellularity. Classification of cystic lesions lacking adequate follicular cells as nondiagnostic has been a controversial topic and in the 3rd edition of TBSRTC, FNA smears of colloid nodules that consist of abundant colloid without minimum number of follicular cells are considered satisfactory for evaluation and benign (TBSRTC category II).

Key diagnostic cytopathological features and ancillary tests

Key cytological description and clearly defined and reproducible cytological criteria are established for most benign and malignant diagnoses in thyroid pathology. Benign diagnoses with distinctive cytologic diagnostic criteria include follicular nodular diseases, colloid cysts, and thyroiditis. Papillary carcinoma accounts for 80% of all thyroid cancers and has readily recognizable cytologic features. (fig. 1A–D) Several histologic variants of papillary carcinoma have been described. The cytologic features of most of these overlap and specific recognition of subtypes is difficult or impossible. However, diagnosis of a specific subtype of papillary carcinoma is not clinically necessary in most instances [54].

In the new 2022 WHO classification scheme, tumors of the thyroid gland are stratified into the following main categories:

- follicular cell-derived neoplasms,
- C-cell-derived neoplasms,
- mixed medullary and follicular cell-derived neoplasms,
- salivary gland type carcinomas,
- thyroid tumors of uncertain histogenesis,
- thymic tumors within the thyroid, and
- embryonal thyroid neoplasms.

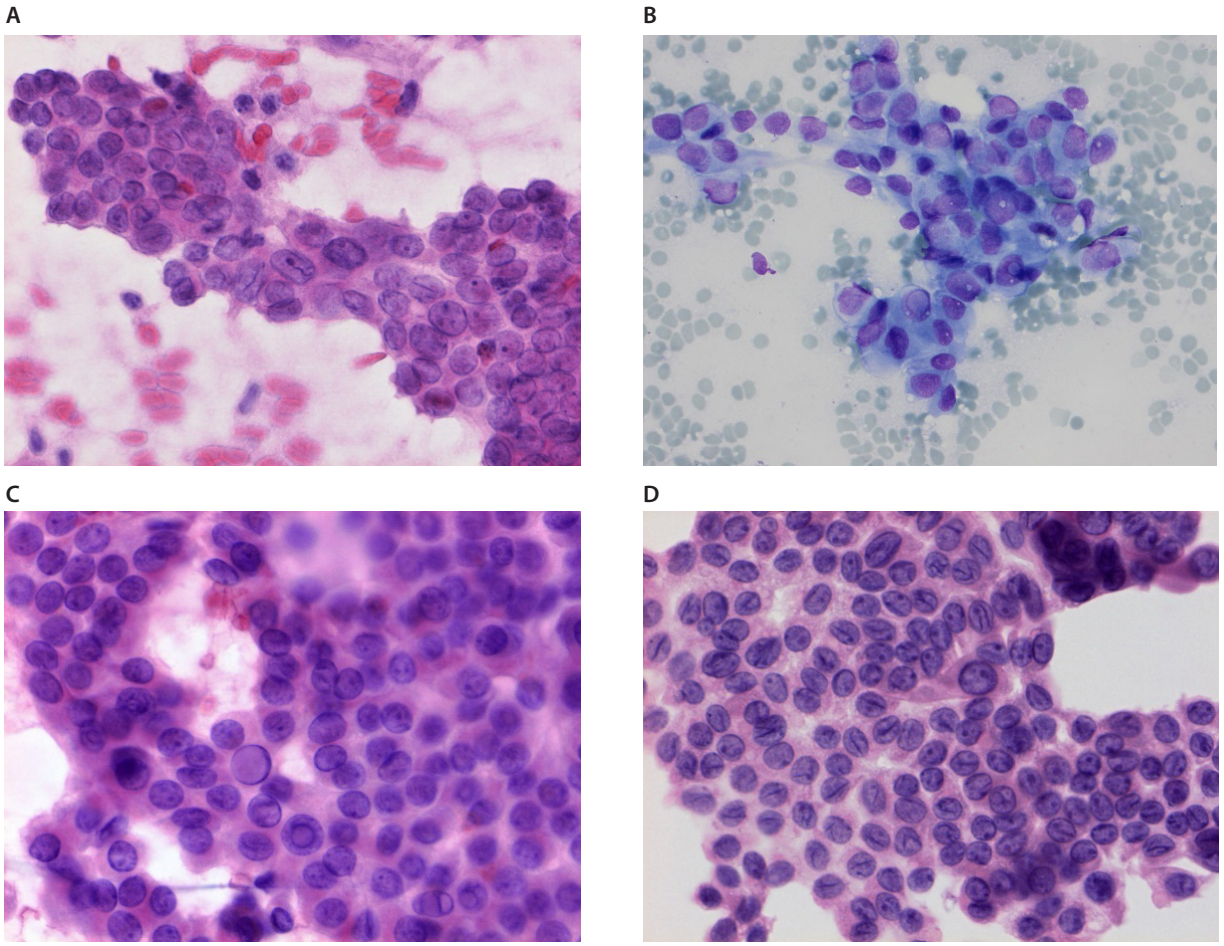

Figure 1. FNA of papillary thyroid carcinoma. **A** – tumor sheets with extensive nuclear changes of papillary carcinoma: grooves, nuclear membrane abnormalities, powdery chromatin, crowding, and nuclear enlargement. (hematoxilin and eosin staining). The most specific nuclear finding of papillary carcinoma is that of intranuclear pseudoinclusions; **B** –this air-dried smear juxtaposes two; **C** – alcohol fixed smear three true nuclear pseudoinclusions. (MGG and hematoxilin and eosin stains); **D** – another case of papillary thyroid carcinoma which also exhibits the common nuclear features of papillary carcinoma: nuclear enlargement, pale and powdery chromatin and irregular nuclear membranes with grooves. (hematoxilin and eosin stain)

Even though cytologic criteria for most malignant entities exists, specific and accurate diagnosis of some thyroid malignancies requires synergies with immunocytochemistry and molecular tests [63–72]. Thyroglobulin indicates follicular thyroid cells and calcitonin parafollicular cells with high specificity. Thyroglobulin positivity occur in most follicular neoplasms of the thyroid, and for the columnar cell variant of papillary carcinoma. Thyroid neoplasms of follicular origin show immunopositivity for thyroid transcription factor-1 (TTF-1) and the cells of oncocytic tumors for thyroglobulin and for low-molecular-weight keratin. TTF-1 shows nuclear expression by IHC in thyroid follicular and parafollicular cells and lungs. TTF-1 is diffusely expressed in papillary thyroid carcinoma, follicular thyroid carcinoma, high-grade follicular-derived non-anaplastic thyroid carcinoma, and medullary thyroid carcinoma. Immunopositivity for calcitonin, carcinoembryonic antigen (CEA) and neuroendocrine markers, such as chromogranin, synaptophysin, and rarely CD56 is appropriate for the diagnosis of medullary carcinoma. In addition, the second-generation neuroendocrine markers insulinoma-associated protein 1 (INSM1) is a highly sensitive and specific marker in the diagnosis of medullary thyroid carcinoma and C-cell hyperplasia. The anaplastic type of thyroid cancer shows inconsistent positive reactivity for cytokeratin, PAX8, p53 and occasionally TTF-1. An immunopanel comprising thyroglobulin, TTF-1, GATA-3, PTH and chromogranin is helpful to distinguish cells of thyroid origin from those of parathyroid origin [63-65]. Example of immunoprofiles for primary thyroid neoplasms and parathyroid lesions are presented in table 2. In addition, the selective panels of antibodies may be applicable to differentiate tumors of thyroid origin from neoplasms metastatic to the thyroid gland. For example, panel of CK7, CK20, TTF-1, CDX2, CEA, MUC1, MUC5AC, SATB2 and MOC31 helps to distinguish secondary esophagus, stomach and colorectal malignancies from primary thyroid neoplasms; panel of CK7, CK20, GATA3, mammaglobin, GCDFP15, ER, PR, TTF-1 and TG, metastasis of mammary carcinoma from primary thyroid neoplasms and panel of SOX10, Melan-A, S100, HMB45, CK7 and CK20, metastatic melanoma from primary thyroid neoplasms.

The TBSRTC may reliably establish a benign or malignant nodule diagnosis in 70–80% of all cases. The FNA diagnosis for the remaining 20–25% of nodules, falls in indeterminate cytology categories such as follicular lesion of undetermined significance/atypia of uncertain significance (FLUS/AUS, Bethesda category III), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN, Bethesda category IV) [61, 62, 66].

The majority of lesions representative of these categories are benign on surgical pathology, indicating unnecessary surgical interventions [67]. Molecular tests have been increasingly applied to complement cytopathology [68] and improve risk-based stratification of indeterminate thyroid nodules [69, 70]. Molecular tests are based on detection of thyroid tumor specific mutations, sometimes added by gene expression profiling (Mutations in papillary thyroid carcinoma: *BRAF* mutation (29–69%), *RET* rearrangement (13–43%), *NTRK1* rearrangement (5–13%), *RAS* mutation (0–21%), the infiltrative follicular variant of papillary carcinoma (higher rates of *BRAF* than *RAS* mutations), follicular thyroid carcinoma: *RAS* mutation (40–53%), *PPARG* rearrangement (25–63%) [41–43, 71–73]. Although molecular testing has been useful for the diagnosis of indeterminate thyroid FNA, there are no molecular panel confidently discriminate malignancy.

While cytopathology offers valuable insights in the evaluation of head and neck masses, it has been of limited value in the diagnosis of parathyroid disorders as the differentiation between normal, hyperplastic, or neoplastic parathyroid tissue solely on FNA samples can be challenging or impossible [16, 74–76]. However, FNA guided by US can enhance the precision of locating parathyroid glands prior to potential surgical

Table II. Examples of immunoprofile of thyroid tumors and parathyroid

Thyroid tumors	Immunoprofiles
thyroid tumors of follicular cells origin	CK7+, CK20–, TTF-1+, PAX8+, thyroglobulin+, calcitonin–, synaptophysin–, chromogranin–
thyroid tumors of parafollicular C-cells origin	CK7+, TTF-1+, PAX8–, calcitonin+, CEA+, synaptophysin+, chromogranin+, thyroglobulin–
mixed medullary and follicular cell-derived thyroid carcinomas	calcitonin+, TTF-1+, thyroglobulin+
oncocytic carcinoma	TTF-1+, PAX8+, CK7+, thyroglobulin+, calcitonin–
high-grade follicular cell-derived non-anaplastic carcinoma	TTF-1+, PAX8+, CK7+, thyroglobulin+, calcitonin–
anaplastic thyroid carcinoma	inconsistent positive reactivity; CK+ (75% of cases), PAX8+ (50% of cases with epithelioid morphology), P53+ (50% of cases), squamous-cell carcinoma phenotype: P63+, P40+, 34BE12+, CK5/6+
cribriform morular thyroid carcinoma	b-catenin, TTF-1+ (mainly in cribriform components), PAX8–, thyroglobulin–
hyalinizing trabecular tumor	TTF-1+, PAX8+, thyroglobulin+, MIB1 (membranous)
parathyroid	TTF-1–, PAX8–, thyroglobulin–, calcitonin– (rarely +), PTH+, GATA3+, chromogranin+, synaptophysin+

treatment of hyperparathyroidism, especially in complex cases such as recurrent disease or following unsuccessful surgeries. Yet, certain cytomorphologic characteristics can help differentiate parathyroid tissue from thyroid and other anatomical structures in cases of unintentional aspiration of intrathyroidal and ectopic parathyroid glands, although overlaps exist [16–21].

The effectiveness of FNA for cytopathological analysis can be hindered by factors like the small size, divergent location and number of parathyroid glands, as well as coexisting lesions of the thyroid gland or previous neck surgeries. An experience and skill of the aspirator in US-guided FNA and the expertise of the interpreting cytopathologist may significantly affect the adequacy and accuracy of the procedure.

Potential complications of parathyroid FNA include hematoma, parathyroid abscess, disruption of the lesion and seeding along the needle tract (parathyromatosis) or dense fibrotic reaction to the needle [11–15]. The number of needle pass, the size of the needle and the skill of the aspirator may influence these complications. However, these uncommon events may rarely convert a minimally invasive surgery to a standard surgical approach, and in the majority of reported series of parathyroid FNA no severe complication occurred associated with FNA procedure of parathyroid gland [16].

Recent studies have addressed the cytomorphological aspects of parathyroid lesions, revealing a range of diagnostic sensitivities (40.4–88.9%) in identifying parathyroid tissue [16–18, 76–78]. The availability of clinical and radiological data at the time of FNA can improve diagnostic accuracy. In two reported series, sensitivity was found to be 50% and 71% in cases without clinical and radiologic data and 86.7% and 88.9%, respectively, in cases with available serum PTH and results of the US examination [7, 77]. Distinguishing parathyroid and thyroid lesions is not easy because of their adjacent anatomical location and the overlapping of cytological and radiological features. Knowledge of cytomorphologic features of parathyroid is essential in distinguishing parathyroid from thyroid lesions and to avoid misdiagnosis. Many studies have focused on the cytomorphological aspects of parathyroid lesions. Yet, certain cytomorphologic characteristics enhance the accuracy of FNA in identifying parathyroid tissue and distinguishing parathyroid and thyroid lesions [7, 16, 77, 79–84].

Three-dimensional tight or loose fragments with variable architectural patterns are common in parathyroid aspirates, whereas flat sheets are more common in thyroid. A mixture of scattered cells and naked nuclei in the background and nuclei with stippled chromatin are common features of parathyroid aspirates, while microfollicles, papillary and papillary-like features may be present in both thyroid and parathyroid aspirates [16, 77, 80, 85]. According to the studies published to date, FNA smears of the parathyroid show certain reproducible architectural patterns, as well as characteristic features of individual cells, nuclei, and background of the smears. Consistent cytomorphology comprises high to moderate cellular smears consisting of tight or loose three-dimensional clusters with cribriform, trabecular and wedge-shaped architectural patterns. These cohesive or loose cellular clusters of round, uniform, or slightly pleomorphic cells, have an overlapping appearance with numerous naked nuclei and/or isolated single cells in the background (fig. 2A). Less common findings include disorganized or follicular/microfollicular sheets, papillary fragments with fibrovascular cores, and capillary networks with associated epithelial cells [16–18, 77–81, 84]. Parathyroid cells in FNA smears are smaller than cells from thyroid follicular lesions and are usually round to oval in shape. The cells have a moderate to high nuclear to cytoplasmic ratio with pale to finely granular, occasionally oxyphilic cytoplasm and uncommon cytoplasmic vacuoles.

The nuclei are uniform with regular nuclear membrane, absent or inconspicuous nucleoli, coarsely granular, and typically stippled chromatin. Nuclear grooves, nuclear molding, and nuclear inclusions are fewer common features, while anisonucleosis may be seen in relatively many cases [7, 16, 17, 78]. Colloid-like material, macrophages and lymphocytes may be occasionally present in the background of the smears [16, 79–81, 84]. Cytologic pitfalls leading to misdiagnosis include the presence of cells with oxyphilic cytoplasm (oncocytic pattern) [16, 83–85]. Some reported series describes possible diagnostic criteria to classify parathyroid lesions and to distinguish benign parathyroid lesions from parathyroid carcinoma. The preliminary observations suggested that evident nucleoli, mitoses and possibly a papillary-solid pattern may guide the differentiation between parathyroid adenoma and parathyroid carcinoma [17, 18, 20, 77]. Differentiating between benign and malignant parathyroid lesions, however, remains complex due to overlapping cytomorphological features of parathyroid hyperplasia, parathyroid adenoma and parathyroid carcinoma [16]. Most parathyroid lesions can be highly variable in terms of cytomorphologic features and many different patterns may be seen in an aspirated specimen from one lesion. True Parathyroid cysts are rare and most represent non-functional cysts. Parathyroid cysts usually yield thin water-clear fluid as opposed to the thick colloid or bloody or colored cystic fluid with macrophages obtained from cystic thyroid lesions. A pathologically altered parathyroid gland can take on the form of a cystic or partly cystic lesion which in our experience may yield bloody fluid as opposed to water-clear fluid of pure parathyroid cysts. Such cystic parathyroid lesions may be difficult to distinguish from cystic lesions of the thyroid, especially if the FNA material is just a fluid without cells on microscopic examination. In such cases, the high level of PTH in the needle rinsed fluid speak for the parathyroid cyst [16].

Assessing PTH levels in the needle washout fluid (FNA--PTH assay) and applying immunocytochemistry (IC) to the aspirated material are ancillary techniques that enhance

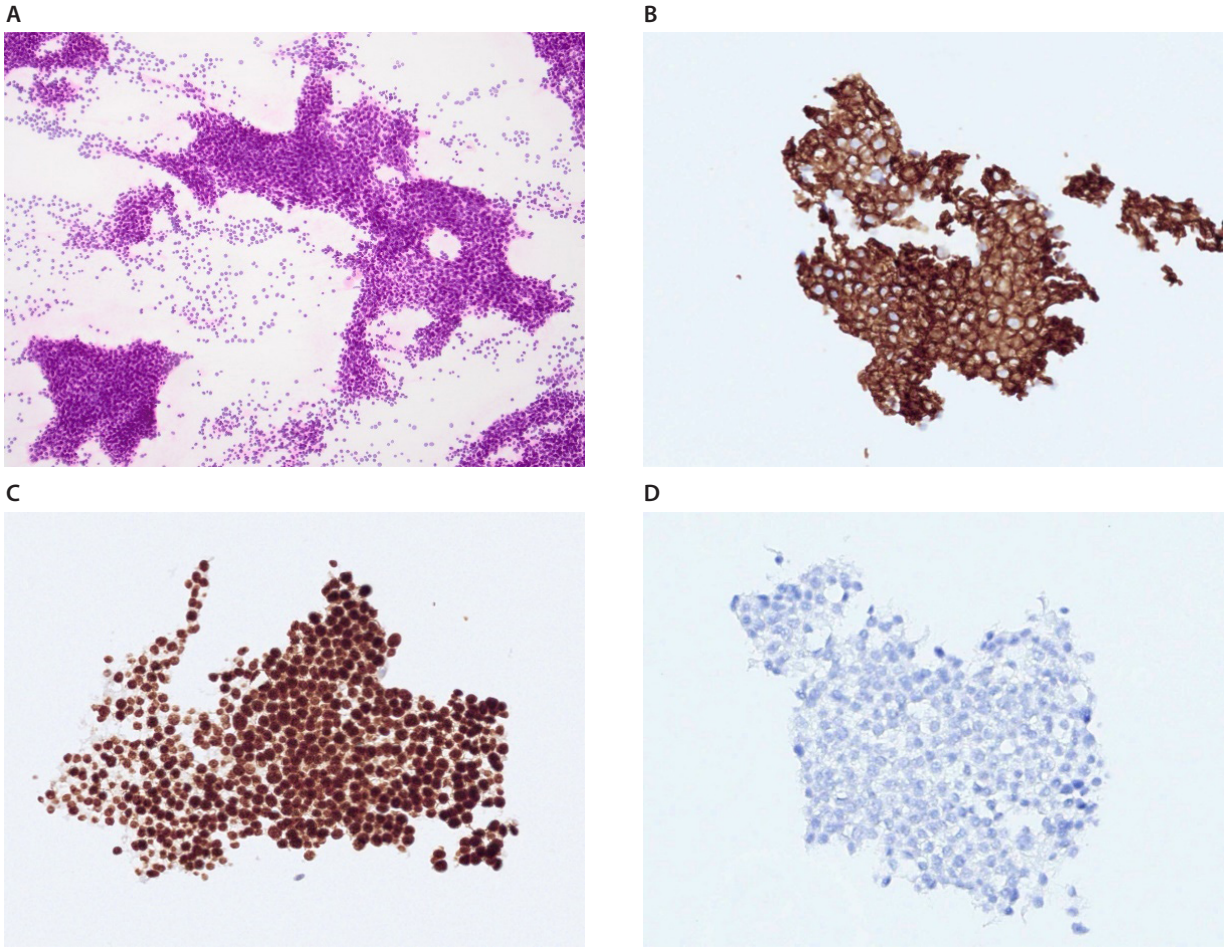

Figure 2. FNA of parathyroid. **A** – three-dimensional, crowded and loose clusters of uniform cells with small round nuclei without nucleoli and scant granular cytoplasm (hematoxilin and eosin staining). Cell block sections. Positive immunostainings; **B** – parathyroid hormone; **C** – GATA-3; **D** – negative TTF-1, confirming parathyroid tissue (cell block, PTH+, GATA-3+, TTF-1–)

the accuracy of FNA in identifying parathyroid lesions. Immunohistochemistry, in particular, helps distinguish parathyroid from thyroid tissue by testing for specific markers. Parathyroid cells are immunoreactive for PTH, GATA-3, and chromogranin (98%) [86–88] and negative for TTF-1, INSM1, and thyroglobulin. A small subset of parathyroid tissue is immunoreactive for synaptophysin. IC can be applied to any of the several types of preparations such as direct smears, cytospin, liquid-based preparations or cell blocks (fig. 2B–D).

The usefulness of detecting PTH in the rinse material obtained from FNAB has been a well established technique with a strong correlation observed between levels of PTH and the cytologic findings [7, 16, 21, 80–83]. The FNA-PTH assay is especially useful in the location of pathological parathyroid glands while immunostainings on aspirated material can improve the discrimination between parathyroid and thyroid nodules. There are studies suggesting that the FNA procedure with PTH assay is more sensitive than parathyroid scanning or US alone and is also superior to FNA alone. [16, 21, 89–91] The PTH washout greater than 436.5 pg/ml has been reported to be 90% sensitive and 89% specific in localizing parathyroid tissue [89, 91].

Conclusions

US-guided FNA is a reliable and sensitive method to diagnose thyroid nodules and to detect parathyroid lesions. A key role of cytopathology in evaluation of thyroid nodules depends in part on evolutions in reporting criteria and the creation of uniform reporting systems such as TIRADS and TBSRTC. Those reporting systems facilitate easier and more reliable interpreting and sharing the results of FNA examination of thyroid with clinicians and improve patient management. In addition, the recent development of thyroid cytopathology and the growing role of parathyroid cytopathology includes widespread US guidance in FNA procedures, improved resolution of US for nodule detection, evolutions in FNA techniques and increasingly growing ancillary tests on cytopathology samples. However, clinical judgment remains of crucial importance in interpreting FNA results.

Article information and declarations

Author contributions

Elwira B. Bakuła-Zalewska – conceptualization, writing – original draft preparation, writing – review and editing.
Agnieszka Żyłka – writing – original draft preparation, writing – review and editing.
Marek Dedecjus – conceptualization.
Piotr Góralski – data curation.
Jacek Gałczyński – data curation.
Joanna Długosińska – data curation.
Monika Durzyńska – writing – original draft preparation, writing – review and editing.
Monika Prochorec-Sobieszek – writing – original draft preparation, writing – review and editing.
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Conflicts of Interest

None declared

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References

1. Ogilvie JB, Piatigorsky EJ, Clark OH. Current status of fine needle aspiration for thyroid nodules. Adv Surg. 2006; 40: 223–238, doi: 10.1016/j.yasu.2006.06.003, indexed in Pubmed: 17163105.
2. Sclabas GM, Staerkel GA, Shapiro SE, et al. Fine-needle aspiration of the thyroid and correlation with histopathology in a contemporary series of 240 patients. Am J Surg. 2003; 186(6): 702–9; discussion 709, doi: 10.1016/j.amjsurg.2003.08.015, indexed in Pubmed: 14672783.
3. Gharib H, Goellner JR. Fine-needle aspiration biopsy of the thyroid: an appraisal. Ann Intern Med. 1993; 118(4): 282–289, doi: 10.7326/0003-4819-118-4-199302150-00007, indexed in Pubmed: 8420446.
4. Guilmette J, Sadow PM. Parathyroid Pathology. Surg Pathol Clin. 2019; 12(4): 1007–1019, doi: 10.1016/j.path.2019.08.006, indexed in Pubmed: 31672291.
5. Cooper DS, Doherty GM, Haugen BR, et al. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19(11): 1167–1214, doi: 10.1089/thy.2009.0110, indexed in Pubmed: 19860577.
6. Luster M, Aktolun C, Amendoeira I, et al. European Perspective on 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: Proceedings of an Interactive International Symposium. Thyroid. 2019; 29(1): 7–26, doi: 10.1089/thy.2017.0129, indexed in Pubmed: 30484394.
7. Suzuki A, Hirokawa M, Kanematsu R, et al. Fine-needle aspiration of parathyroid adenomas: Indications as a diagnostic approach. Diagn Cytopathol. 2021; 49(1): 70–76, doi: 10.1002/dc.24595, indexed in Pubmed: 32833315.
8. Patel KN, Yip L, Lubitz CC, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. Ann Surg. 2020; 271(3): e21–e93, doi: 10.1097/SLA.0000000000003580, indexed in Pubmed: 32079830.
9. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016; 151(10): 959–968, doi: 10.1001/jamasurg.2016.2310, indexed in Pubmed: 27532368.
10. Park JiY, Choi W, Hong AR, et al. A Comprehensive Assessment of the Harms of Fine-Needle Aspiration Biopsy for Thyroid Nodules: A Systematic Review. Endocrinol Metab (Seoul). 2023; 38(1): 104–116, doi: 10.3803/EnM.2023.1669, indexed in Pubmed: 36891657.
11. Alwaheeb S, Rambaldini G, Boerner S, et al. Worrisome histologic alterations following fine-needle aspiration of the parathyroid. J Clin Pathol. 2006; 59(10): 1094–1096, doi: 10.1136/jcp.2005.029017, indexed in Pubmed: 17021134.
12. Hirokawa M, Suzuki A, Higuchi M, et al. Histological alterations following fine-needle aspiration for parathyroid adenoma: Incidence and diagnostic problems. Pathol Int. 2021; 71(6): 400–405, doi: 10.1111/pin.13091, indexed in Pubmed: 33740321.
13. Kim J, Horowitz G, Hong M, et al. The dangers of parathyroid biopsy. J Otolaryngol Head Neck Surg. 2017; 46(1): 4, doi: 10.1186/s40463-016-0178-7, indexed in Pubmed: 28061891.
14. Spinelli C, Bonadio AG, Berti P, et al. Cutaneous spreading of parathyroid carcinoma after fine needle aspiration cytology. J Endocrinol Invest. 2000; 23(4): 255–257, doi: 10.1007/BF03343718, indexed in Pubmed: 10853713.
15. Agarwal G, Dhingra S, Mishra SK, et al. Implantation of parathyroid carcinoma along fine needle aspiration track. Langenbecks Arch Surg. 2006; 391(6): 623–626, doi: 10.1007/s00423-006-0095-8, indexed in Pubmed: 17021789.
16. Bakuła-Zalewska E, Długosińska J, Stanek-Widera A, et al. Fine needle aspiration biopsy of parathyroid; is it meaningful? A cytologic study of 81 cases with histological and clinical correlations. Cytopathology. 2024; 35(3): 362–370, doi: 10.1111/cyt.13356, indexed in Pubmed: 38213192.
17. Caleo A, Vitale M, Valvano L, et al. Fine needle cytology pre-surgical differentiation of parathyroid neoplasms: Is it reliable? Cytopathology. 2017; 28(4): 273–279, doi: 10.1111/cyt.12413, indexed in Pubmed: 28217943.
18. Tseng FY, Hsiao YL, Chang TC. Ultrasound-guided fine needle aspiration cytology of parathyroid lesions. A review of 72 cases. Acta Cytol. 2002; 46(6): 1029–1036, doi: 10.1159/000327103, indexed in Pubmed: 12462078.
19. Abraham D, Sharma PK, Bentz J, et al. Utility of ultrasound-guided fine-needle aspiration of parathyroid adenomas for localization before minimally invasive parathyroidectomy. Endocr Pract. 2007; 13(4): 333–337, doi: 10.4158/EP.13.4.333, indexed in Pubmed: 17669707.
20. Li W, Zhu Q, Lai X, et al. Value of preoperative ultrasound-guided fine-needle aspiration for localization in Tc-99m MIBI-negative primary hyperparathyroidism patients. Medicine (Baltimore). 2017; 96(49): e9051, doi: 10.1097/MD.0000000000009051, indexed in Pubmed: 29245309.
21. Obołończyk Ł, Karwacka I, Wiśniewski P, et al. The Current Role of Parathyroid Fine-Needle Biopsy (P-FNAB) with iPTH-Washout Concentration (iPTH-WC) in Primary Hyperparathyroidism: A Single Center Experience and Literature Review. Biomedicines. 2022; 10(1), doi: 10.3390/biomedicines10010123, indexed in Pubmed: 35052802.
22. Lew JI, Snyder RA, Sanchez YM, et al. Fine needle aspiration of the thyroid: correlation with final histopathology in a surgical series of 797 patients. J Am Coll Surg. 2011; 213(1): 188–94; discussion 194, doi: 10.1016/j.jamcollsurg.2011.04.029, indexed in Pubmed: 21601489.
23. Porterfield JR, Grant CS, Dean DS, et al. Reliability of benign fine needle aspiration cytology of large thyroid nodules. Surgery. 2008; 144(6): 963–8; discussion 968, doi: 10.1016/j.surg.2008.09.006, indexed in Pubmed: 19041004.
24. Hegedüs L. Clinical practice. The thyroid nodule. N Engl J Med. 2004; 351(17): 1764–1771, doi: 10.1056/NEJMcp031436, indexed in Pubmed: 15496625.
25. Bouvet M, Feldman JI, Gill GN, et al. Surgical management of the thyroid nodule: patient selection based on the results of fine-needle aspiration cytology. Laryngoscope. 1992; 102(12 Pt 1): 1353–1356, doi: 10.1288/00005537-199212000-00008, indexed in Pubmed: 1453841.
26. Goldfarb M, Gondek S, Solorzano C, et al. Surgeon-performed ultrasound can predict benignity in thyroid nodules. Surgery. 2011; 150(3): 436–441, doi: 10.1016/j.surg.2011.07.002, indexed in Pubmed: 21878228.
27. Yassa L, Cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer. 2007; 111(6): 508–516, doi: 10.1002/cncr.23116, indexed in Pubmed: 17999413.

28. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Canadian Cancer Society, Toronto 2013.
29. Elisei R, Molinaro E, Agate L, et al. Are the clinical and pathological features of differentiated thyroid carcinoma really changed over the last 35 years? Study on 4187 patients from a single Italian institution to answer this question. J Clin Endocrinol Metab. 2010; 95(4): 1516–1527, doi: 10.1210/jc.2009-1536, indexed in Pubmed: 20156922.
30. Roy R, Kouniavsky G, Venkat R, et al. The role of preoperative neck ultrasounds to assess lymph nodes in patients with suspicious or indeterminate thyroid nodules. J Surg Oncol. 2012; 105(6): 601–605, doi: 10.1002/jso.22115, indexed in Pubmed: 22006435.
31. Wang CCC, Friedman L, Kennedy GC, et al. A large multicenter correlation study of thyroid nodule cytopathology and histopathology. Thyroid. 2011; 21(3): 243–251, doi: 10.1089/thy.2010.0243, indexed in Pubmed: 21190442.
32. Nagataki S, Nyström E. Epidemiology and primary prevention of thyroid cancer. Thyroid. 2002; 12(10): 889–896, doi: 10.1089/10507250276101 6511, indexed in Pubmed: 12487771.
33. Feldt-Rasmussen U. Iodine and cancer. Thyroid. 2001; 11(5): 483–486, doi: 10.1089/105072501300176435, indexed in Pubmed: 11396706.
34. Lee JH, Hwang Y, Song RY, et al. Relationship between iodine levels and papillary thyroid carcinoma: A systematic review and meta-analysis. Head Neck. 2017; 39(8): 1711–1718, doi: 10.1002/hed.24797, indexed in Pubmed: 28513893.
35. Ron E, Lubin J, Shore R, et al. Thyroid Cancer after Exposure to External Radiation: A Pooled Analysis of Seven Studies. Radiat Res. 1995; 141(3): 259–277, doi: 10.2307/3579003, indexed in Pubmed: 7871153.
36. Mirkatouli NB, Hirota S, Yoshinaga S. Thyroid cancer risk after radiation exposure in adults-systematic review and meta-analysis. J Radiat Res. 2023; 64(6): 893–903, doi: 10.1093/jrr/rrad073, indexed in Pubmed: 37816676.
37. de Vathaire F, Zidane M, Xhaard C, et al. Assessment of Differentiated Thyroid Carcinomas in French Polynesia After Atmospheric Nuclear Tests Performed by France. JAMA Netw Open. 2023; 6(5): e2311908, doi: 10.1001/jamanetworkopen.2023.11908, indexed in Pubmed: 37145599.
38. Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol. 2022; 33(1): 27–63, doi: 10.1007/s12022-022-09707-3, indexed in Pubmed: 35288841.
39. Nikiforov YE. RET/PTC rearrangement in thyroid tumors. Endocr Pathol. 2002; 13(1): 3–16, doi: 10.1385/ep:13:1:03, indexed in Pubmed: 12114746.
40. Khan MS, Qadri Q, Makhdoomi MJ, et al. RET/PTC Gene Rearrangements in Thyroid Carcinogenesis: Assessment and Clinico-Pathological Correlations. Pathol Oncol Res. 2020; 26(1): 507–513, doi: 10.1007/s12253-018-0540-3, indexed in Pubmed: 30467698.
41. Agrawal N, Akbani R, Aksoy B, et al. Integrated Genomic Characterization of Papillary Thyroid Carcinoma. Cell. 2014; 159(3): 676–690, doi: 10.1016/j.cell.2014.09.050, indexed in Pubmed: 25417114.
42. Abdullah MI, Junit SM, Ng KL, et al. Papillary Thyroid Cancer: Genetic Alterations and Molecular Biomarker Investigations. Int J Med Sci. 2019; 16(3): 450–460, doi: 10.7150/ijms.29935, indexed in Pubmed: 30911279.
43. Rajab M, Payne RJ, Forest VI, et al. Molecular Testing for Thyroid Nodules: The Experience at McGill University Teaching Hospitals in Canada. Cancers (Basel). 2022; 14(17), doi: 10.3390/cancers14174140, indexed in Pubmed: 36077677.
44. Ciampi R, Romei C, Ramone T, et al. Genetic Landscape of Somatic Mutations in a Large Cohort of Sporadic Medullary Thyroid Carcinomas Studied by Next-Generation Targeted Sequencing. iScience. 2019; 20: 324–336, doi: 10.1016/j.isci.2019.09.030, indexed in Pubmed: 31605946.
45. Tessler FN, Middleton WD, Grant EG, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. J Am Coll Radiol. 2017; 14(5): 587–595, doi: 10.1016/j.jacr.2017.01.046, indexed in Pubmed: 28372962.
46. Chen F, Sun Y, Chen G, et al. The Diagnostic Efficacy of the American College of Radiology (ACR) Thyroid Imaging Report and Data System (TI-RADS) and the American Thyroid Association (ATA) Risk Stratification Systems for Thyroid Nodules. Comput Math Methods Med. 2022; 2022: 9995962, doi: 10.1155/2022/9995962, indexed in Pubmed: 35075371.
47. Russ G, Bonnema SJ, Erdogan MF, et al. European Thyroid Association Guidelines for Ultrasound Malignancy Risk Stratification of Thyroid Nodules in Adults: The EU-TIRADS. Eur Thyroid J. 2017; 6(5): 225–237, doi: 10.1159/000478927, indexed in Pubmed: 29167761.
48. Middleton WD, Teefey SA, Reading CC, et al. Comparison of Performance Characteristics of American College of Radiology TI-RADS, Korean Society of Thyroid Radiology TIRADS, and American Thyroid Association Guidelines. AJR Am J Roentgenol. 2018; 210(5): 1148–1154, doi: 10.2214/AJR.17.18822, indexed in Pubmed: 29629797.
49. Jarząb B, Dedecjus M, Lewiński A, et al. Diagnosis and treatment of thyroid cancer in adult patients - Recommendations of Polish Scientific Societies and the National Oncological Strategy. 2022 Update [Diagnostyka i leczenie raka tarczycy u chorych dorosłych - Rekomendacje Polskich Towarzystw Naukowych oraz Narodowej Strategii Onkologicznej. Aktualizacja na rok 2022]. Endokrynol Pol. 2022; 73(2): 173–300, doi: 10.5603/EP.a2022.0028, indexed in Pubmed: 35593680.
50. Ruda JM, Hollenbeak CS, Stack BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg. 2005; 132(3): 359–372, doi: 10.1016/j.otohns.2004.10.005, indexed in Pubmed: 15746845.
51. Rao SD. Epidemiology of parathyroid disorders. Best Pract Res Clin Endocrinol Metab. 2018; 32(6): 773–780, doi: 10.1016/j.beem.2018.12.003, indexed in Pubmed: 30559041.
52. Domanski HA, Qian X, Stanley DE. Chapter 1. Introduction; VanderLaan PA, Krane JF. Chapter 5: Head and Neck: Thyroid. In: Domanski HA. ed. Atlas of fine needle aspiration cytology. 2nd ed. Springer, London 2019.
53. Ghaheri BA, Koslin DB, Wood AH, et al. Preoperative ultrasound is worthwhile for reoperative parathyroid surgery. Laryngoscope. 2004; 114(12): 2168–2171, doi: 10.1097/01.mlg.0000149451.45264.90, indexed in Pubmed: 15564838.
54. Petranović Ovčariček P, Giovanella L, Carrió Gasset I, et al. The EANM practice guidelines for parathyroid imaging. Eur J Nucl Med Mol Imaging. 2021; 48(9): 2801–2822, doi: 10.1007/s00259-021-05334-y, indexed in Pubmed: 33839893.
55. Feletti F, Mellini L, Pironi F, et al. Role of the cytopathologist during the procedure of fine-needle aspiration biopsy of thyroid nodules. Insights Imaging. 2021; 12(1): 111, doi: 10.1186/s13244-021-01053-y, indexed in Pubmed: 34370089.
56. Witt BL, Schmidt RL. Rapid onsite evaluation improves the adequacy of fine-needle aspiration for thyroid lesions: a systematic review and meta-analysis. Thyroid. 2013; 23(4): 428–435, doi: 10.1089/thy.2012.0211, indexed in Pubmed: 23043247.
57. Zargham R, Johnson H, Anderson S, et al. Conditions associated with the need for additional needle passes in ultrasound-guided thyroid fine-needle aspiration with rapid on-site pathology evaluation. Diagn Cytopathol. 2021; 49(1): 105–108, doi: 10.1002/dc.24605, indexed in Pubmed: 32870607.
58. Hambleton C, Kandil E. Appropriate and accurate diagnosis of thyroid nodules: a review of thyroid fine-needle aspiration. Int J Clin Exp Med. 2013; 6(6): 413–422, indexed in Pubmed: 23844264.
59. Cesur M, Corapcioglu D, Bulut S, et al. Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. Thyroid. 2006; 16(6): 555–561, doi: 10.1089/thy.2006.16.555, indexed in Pubmed: 16839257.
60. Robitschek J, Straub M, Wirtz E, et al. Diagnostic efficacy of surgeon-performed ultrasound-guided fine needle aspiration: a randomized controlled trial. Otolaryngol Head Neck Surg. 2010; 142(3): 306–309, doi: 10.1016/j.otohns.2009.11.011, indexed in Pubmed: 20172371.
61. Ali SZ, VanderLaan PA. The Bethesda System for ReportingThyroid Cytopathology: Definitions, Criteria, and Explana-tory Notes, 3rd ed. Springer, New York 2023.
62. Ali SZ, Baloch ZW, Cochand-Priollet B, et al. The 2023 Bethesda System for Reporting Thyroid Cytopathology. Thyroid. 2023; 33(9): 1039–1044, doi: 10.1089/thy.2023.0141, indexed in Pubmed: 37427847.
63. Crescenzi A, Baloch Z. Immunohistochemistry in the pathologic diagnosis and management of thyroid neoplasms. Front Endocrinol (Lausanne). 2023; 14: 1198099, doi: 10.3389/fendo.2023.1198099, indexed in Pubmed: 37324272.
64. Nishino M, Krane JF. Role of Ancillary Techniques in Thyroid Cytology Specimens. Acta Cytol. 2020; 64(1-2): 40–51, doi: 10.1159/000496502, indexed in Pubmed: 30947167.
65. Baloch Z, Mete O, Asa SL. Immunohistochemical Biomarkers in Thyroid Pathology. Endocr Pathol. 2018; 29(2): 91–112, doi: 10.1007/s12022-018-9532-9, indexed in Pubmed: 29744727.
66. Bongiovanni M, Spitale A, Faquin WC, et al. The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. Acta Cytol. 2012; 56(4): 333–339, doi: 10.1159/000339959, indexed in Pubmed: 22846422.
67. Schneider DF, Cherney Stafford LM, Brys N, et al. GAUGING THE EXTENT OF THYROIDECTOMY FOR INDETERMINATE THYROID NODULES: AN ONCOLOGIC PERSPECTIVE. Endocr Pract. 2017; 23(4): 442–450, doi: 10.4158/EP161540.OR, indexed in Pubmed: 28095042.

68. Tysarowski A, Szumera-Ciećkiewicz A, Marszałek A, et al. Molecular diagnostics of cancers – practical approach. Nowotwory. Journal of Oncology. 2023; 73(3): 174–186, doi: 10.5603/njo.2023.0028.
69. Ferraz C. Molecular testing for thyroid nodules: Where are we now? Rev Endocr Metab Disord. 2024; 25(1): 149–159, doi: 10.1007/s11154-023-09842-0, indexed in Pubmed: 37902897.
70. Trimboli P, Scappaticcio L, Treglia G, et al. Testing for BRAF (V600E) Mutation in Thyroid Nodules with Fine-Needle Aspiration (FNA) Read as Suspicious for Malignancy (Bethesda V, Thy4, TIR4): a Systematic Review and Meta-analysis. Endocr Pathol. 2020; 31(1): 57–66, doi: 10.1007/s12022-019-09596-z, indexed in Pubmed: 31811566.
71. Rivera M, Ricarte-Filho J, Knauf J, et al. Molecular genotyping of papillary thyroid carcinoma follicular variant according to its histological subtypes (encapsulated vs infiltrative) reveals distinct BRAF and RAS mutation patterns. Mod Pathol. 2010; 23(9): 1191–1200, doi: 10.1038/modpathol.2010.112, indexed in Pubmed: 20526288.
72. Agarwal S, Bychkov A, Jung CK. Emerging Biomarkers in Thyroid Practice and Research. Cancers (Basel). 2021; 14(1), doi: 10.3390/cancers14010204, indexed in Pubmed: 35008368.
73. Giordano TJ. Genomic Hallmarks of Thyroid Neoplasia. Annu Rev Pathol. 2018; 13: 141–162, doi: 10.1146/annurev-pathol-121808-102139, indexed in Pubmed: 29083981.
74. Fagin JA, Wells SA. Biologic and Clinical Perspectives on Thyroid Cancer. N Engl J Med. 2016; 375(11): 1054–1067, doi: 10.1056/NEJMra1501993, indexed in Pubmed: 27626519.
75. Patel KN, Yip L, Lubitz CC, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. Ann Surg. 2020; 271(3): e21–e93, doi: 10.1097/SLA.0000000000003580, indexed in Pubmed: 32079830.
76. Wilhelm SM, Wang TS, Ruan DT, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016; 151(10): 959–968, doi: 10.1001/jamasurg.2016.2310, indexed in Pubmed: 27532368.
77. Ha HJ, Kim EJu, Kim JS, et al. Major Clues and Pitfalls in the Differential Diagnosis of Parathyroid and Thyroid Lesions Using Fine Needle Aspiration Cytology. Medicina (Kaunas). 2020; 56(11), doi: 10.3390/medicina56110558, indexed in Pubmed: 33114338.
78. Heo I, Park S, Jung CW, et al. Fine needle aspiration cytology of parathyroid lesions. Korean J Pathol. 2013; 47(5): 466–471, doi: 10.4132/KoreanJPathol.2013.47.5.466, indexed in Pubmed: 24255635.
79. Agarwal AM, Bentz JS, Hungerford R, et al. Parathyroid fine-needle aspiration cytology in the evaluation of parathyroid adenoma: cytologic findings from 53 patients. Diagn Cytopathol. 2009; 37(6): 407–410, doi: 10.1002/dc.21020, indexed in Pubmed: 19283690.
80. Cho M, Oweity T, Brandler TC, et al. Distinguishing parathyroid and thyroid lesions on ultrasound-guided fine-needle aspiration: A correlation of clinical data, ancillary studies, and molecular analysis. Cancer Cytopathol. 2017; 125(9): 674–682, doi: 10.1002/cncy.21888, indexed in Pubmed: 28621914.
81. Layfield LJ. Fine needle aspiration cytology of cystic parathyroid lesions. A cytomorphologic overlap with cystic lesions of the thyroid. Acta Cytol. 1991; 35(4): 447–450, indexed in Pubmed: 1927181.
82. Domingo RP, Ogden LL, Been LC, et al. Identification of parathyroid tissue in thyroid fine-needle aspiration: A combined approach using cytology, immunohistochemical, and molecular methods. Diagn Cytopathol. 2017; 45(6): 526–532, doi: 10.1002/dc.23711, indexed in Pubmed: 28371486.
83. Owens CL, Rekhtman N, Sokoll L, et al. Parathyroid hormone assay in fine-needle aspirate is useful in differentiating inadvertently sampled parathyroid tissue from thyroid lesions. Diagn Cytopathol. 2008; 36(4): 227–231, doi: 10.1002/dc.20783, indexed in Pubmed: 18335560.
84. Dimashkieh H, Krishnamurthy S. Ultrasound guided fine needle aspiration biopsy of parathyroid gland and lesions. Cytojournal. 2006; 3: 6, doi: 10.1186/1742-6413-3-6, indexed in Pubmed: 16569241.
85. Paker I, Yilmazer D, Yandakci K, et al. Intrathyroidal oncocytic parathyroid adenoma: a diagnostic pitfall on fine-needle aspiration. Diagn Cytopathol. 2010; 38(11): 833–836, doi: 10.1002/dc.21338, indexed in Pubmed: 20301208.
86. Abati A, Skarulis MC, Shawker T, et al. Ultrasound-guided fine-needle aspiration of parathyroid lesions: a morphological and immunocytochemical approach. Hum Pathol. 1995; 26(3): 338–343, doi: 10.1016/0046-8177(95)90068-3, indexed in Pubmed: 7890288.
87. Erdogan-Durmus S, Ramazanoglu SR, Barut HY. Diagnostic significance of GATA 3, TTF-1, PTH, chromogranin expressions in parathyroid fine needle aspirations via immuonocytochemical method. Diagn Cytopathol. 2023; 51(7): 449–454, doi: 10.1002/dc.25140, indexed in Pubmed: 37042181.
88. Shi Y, Brandler TC, Yee-Chang M, et al. Application of GATA 3 and TTF-1 in differentiating parathyroid and thyroid nodules on cytology specimens. Diagn Cytopathol. 2020; 48(2): 128–137, doi: 10.1002/dc.24338, indexed in Pubmed: 31713988.
89. Knezević-Obad A, Tomić-Brzac H, Zarković K, et al. Diagnostic pitfalls in parathyroid gland cytology. Coll Antropol. 2010; 34(1): 25–29, indexed in Pubmed: 20432729.
90. Trimboli P, D'Aurizio F, Tozzoli R, et al. Measurement of thyroglobulin, calcitonin, and PTH in FNA washout fluids. Clin Chem Lab Med. 2017; 55(7): 914–925, doi: 10.1515/cclm-2016-0543, indexed in Pubmed: 27802177.
91. Gökçay Canpolat A, Şahin M, Ediboğlu E, et al. Diagnostic accuracy of parathyroid hormone levels in washout samples of suspicious parathyroid adenomas: A single-centre retrospective cohort study. Clin Endocrinol (Oxf). 2018; 89(4): 489–495, doi: 10.1111/cen.13812, indexed in Pubmed: 30004132.

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Review article

Radiotherapy

Re-irradiation: the "some like it hot – others not" dilemma

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Although re-irradiation as a therapeutic procedure has already been explored over a few decades, it still remains a field of various uncertainties, and the majority of retrospective clinical studies contain quite a lot of "blank points". The critical point of this therapy is the severity of the radiation response of the normal organs at risk, which limits the planned and delivered dose. Re-irradiation is often considered a palliative treatment, although the results of the stereotactic hypofractionation (SHRT) strongly suggest that it can easily be used with radical intent. While tolerance doses (TD) were more or less arbitrarily established (not estimated) many years ago, they have not been verified during the passing time, but at least accounted for the ⅔ or ⅓ volume of the organ at risk. Regarding the so-called "remembered dose", it becomes crucial when the primary and re-irradiated volume of normal organs overlap. Knowledge of that parameter contains many loopholes. Such "doses" have mainly been approximately deduced from experimental and some clinical studies, and for a few organs at risk only. Present review the selected studies including 8,427 recurrences reported in a small number of the retrospective studies providing complete factors and parameters of the primary and re-irradiation procedures. The review's results are presented and discussed. In 2022, the ESTRO/EORTC experts council defined re-irradiation procedures including three therapeutic scenarios, which are presently discussed. That consensus provides at least the detailed basics to optimize and improve quantitative knowledge on re-irradiation, which is the major aim of this paper.

Key words: re-irradiation, tolerance doses, remembered dose, ESTRO/EORTC therapeutic scenarios

Introduction

For many decades, the use of re-irradiation after radical radiotherapy has generally been considered taboo because of the strong belief and fear that re-irradiation may inevitably often induce severe late radiation sequelae (complications) in normal tissues/organs (organs at risk – OAR) surrounding recurrent tumors or metastasis. However, the progressive increase of experimental and clinical studies challenges this prevailing dogma, revealing at least partial capability of some normal tissues to repair radiation sublethal and potentially lethal damages (SLD, PLD).

Currently, conformal (CRT), dose modulated (IMRT) and arc (VMAT) techniques are widely used in radiotherapy and result in a higher rate of local tumor control and in prolonged overall survival. Particularly stereotactic hypofractionated radiotherapy (SHRT) is more often applied, since it tailors the dose focused on the tumor volume, with a large dose gradient beyond its margins. Despite substantial improvements in radiotherapeutic efficacy, the risks of local recurrences, distant metastases and secondary primary tumors still remain (e.g. a secondary primary tumor develops in more than 20% of irradiated patients with a primary cancer, among which 80% occurred in the H&N region). To a certain degree, these three types of failure may occur out of the initially irradiated volumes, and therefore "re-treatment" in such cases can be considered similar

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to the primary radiotherapy. On the other hand, recurrence may develop within the organ which is the site of the previous primary tumor, or even frequently, within or close to its original volume [1–12].

During recent years, re-irradiation has been more often explored in clinical practice. Two main scenarios are considered by radiation oncologists. Some of them advocate re-irradiation as a "Luke Warm Bath", by using palliative biological total doses (often with low fraction doses delivered twice-a-day – b.i.d.), because of a justified fear of severe late normal tissue toxicities. This scenario has usually been forced for a large recurrence (metastasis) developed close or within the previously irradiated volume. Sometimes it can be well grounded, since the risk of late complications (late radiation effects – LRE) can be more or less precisely predicted, but not eliminated. Moreover, various complications are individually scored in the different studies, and therefore they can be unreliable. This scenario does not seem reasonable in the case of a chance of long-term cure or durable palliation. Moderate total doses (e.g. 40–50 Gy) usually produce a partial regression of the recurrence only or a stable status of the disease. Such effects cannot be satisfied, since the survived tumor clonogens repopulate much faster than those of the untreated primary tumor. Furthermore, It should be remembered that possible morbidity from tumor progression is frequently greater and more severe than the re-irradiation toxicity. Thus, it encourages the consideration of higher doses, even if the price of such decisions might involve a higher risk of the LRE.

According to radiobiological principles, local recurrence (also metastasis) occurs when the primary dose is not radical enough, at least within a part of the tumor volume (e.g. a geographical miss), and results in the survival of some tumor clonogenic cells. Even one, well oxygenated tumor clonogen is definitely able to initiate a growth of the recurrent tumor, due to accelerated repopulation. It may likely suggest their higher radiosensitivity (more clonogens actively participate in the cell cycle), but also their aggressiveness and fast growth. On the other hand, some tumors recurring within or close to a previously irradiated volume may sometimes arise from radioresistant clonogens (e.g. the salivary gland) and make re-irradiation ineffective. The biology and kinetics of the recurrent malignant lesions suggest a radical scenario of the re-irradiation, called "Hot Bath-Therapy", with total doses higher than that previously. This may immediately raise a fear of much higher risk (~50%) of serious late complications (LRE), since the delivered dose comes closer or even above tolerance level of the $TD_{50/5}$ (50% risk within 5-year follow-up). But such potentially high incidence of severe late complications has not been reported yet.

The debate on the optimal re-irradiation dose fractionation continues. Different "Hot Bath" schedules have been explored to re-irradiate recurrent tumors (mainly in the head and neck region), among which hyperfractionated schedules have been recommended [2, 4, 6, 8, 10, 11, 29, 30, 34, 36], and its effectiveness has recently proven by the result of a Chinese trial [39]. The dose of at least 72 Gy in 60 fractions (1.2 Gy per fraction) given twice-a-day with a 6-hour interval is strongly advised by Benson et al. [2]. Hyperfractionation with two daily fractions below 1.8 Gy allows for the delivery of a high biological dose [18], since solid malignant tumors are usually much less sensitive to change in dose per fraction (high α/β ratio) than the majority of late responding normal tissues (very low α/β ratio, high rate of the β effects reflecting sublethal damages), and moreover it improves the sparing effect in normal tissues. For example, 72 Gy in 60 fractions delivered to normal tissue (organ) or to a part of it, is in fact, biologically equivalent to dose EQD_2 of 57 $izoGy_2$. It can lead to the escalation of a physical total dose to even 80–85 Gy. Moreover, low fraction doses lead to more effective repair of the sublethal and potentially lethal damage of the normal tissues, and also improve their functional recovery.

The next hypofractionation (single or a few large fractions) was widely used during the early years of the orthovoltage radiotherapy (geometrically regular fields). However, it resulted on an unacceptably high rate of serious and lethal late complications (severe deep necrosis), and therefore it was abandoned around 1920–1925. After about 80 years, hypofractionation came back to the market due to technologically innovative tools in the linacs (IMRT, VMAT) or stereotactic accelerators (CyberKnife), and became considered as a radical option offering a higher rate local control (>80–85%), including the recurrent tumors or multiple metastases [5, 14–16, 19, 20, 33, 35, 38]. Moreover, a major advantage of stereotactic hypofractionated radiotherapy (SHRT) of multiple metastases (e.g. in the liver, lung, brain or bone) is that a single high dose (~10–15 Gy) or a few large fractions can be delivered to each of a few lesions at the same time during the patient's set-up on therapeutic table and on each session of the irradiation. Another advantage of the SHRT is a specific dose distribution within the irradiated volume, characterized by a dose focused on the recurrent lesion, with a high dose gradient within a narrow tissue strip beyond the recurrence margins. It significantly improves the normal tissue sparing effect [11, 12, 17–21]. However, this advantage of the SHRT is that it is addressed to limited volumes of malignant lesions [14, 15, 16, 19–20], smaller than 4 cm in diameter.

An important and required basis for a proper and optimal selection of the re-irradiation scenario is detailed knowledge on the morphological and functional structure of the normal tissues (organs), and the radiobiological mechanisms of their response and tolerance to irradiation.

Late normal tissue's (organ's) radiation effects – tolerance doses

In contrast to acutely responding hierarchical epithelial tissues, late radiation effects (LRE) (injuries) develop in the mature tissues (organs) termed "flexible" (type F), and they can manifest

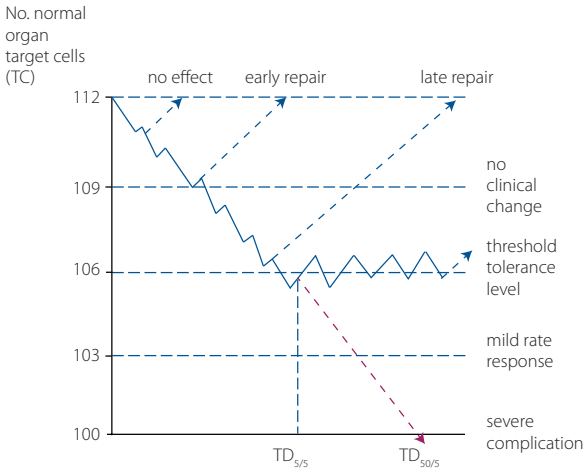

Figure 1. Radiation-induced target cell (TC) depletion in normal organ (tissue), and clinical manifestation of late radiation effect (LRE) – adopted from Rubin [24] If the TC depletion reaches the threshold tolerance level, it results in a 5% risk of late complications (LC) during 5-year follow-up ($TD_{5/5}$). After higher dose ($TD_{50/5}$) depletion, the TC continues and leads to a 50% risk of LC

months or even years after completing treatment [18, 22, 23, 29, 30]. Mature morphology does not however deny a component of the stem cells with retained proliferative potential. That said, the more affected the cells the deeper the cellular depletion. Some of them retain the potential to repair the SLD, PLD and to regenerate (fig. 1), and if such cellular and functional recovery reaches the threshold (tolerance) level, late effects may still not occur. But when the cellular damage progresses and continues, and the cellular reserve is completely depleted, then moderate or severe late complication occurs.

The severity and latency time of the LRE depend on the initial number of normal, so-called target cells (TC) with proliferative potential [14], which set-up the functional subunits (FSU). The higher the dose, the shorter the latency of the LRE. Moreover, residual, partly injured target cells may increasingly be recruited to the proliferative pool (when environmental conditions become favorable), to enter into a cascade (avalanche) of cell death, which speeds up morphological and functional tissue (organ) disorders. Surgery, chemotherapy, infection, or physical trauma usually accelerate the LRE severity.

Withers pointed out [23] that the tolerance dose (TD) for a given normal organ mainly depends on the number of their TCs per unit of the FSU rather than on the number of the FSUs. It may explain the relatively low TD for organs (e.g. hair follicles kidney, lung, liver) with a small number of the TCs within each FSU. Organs at risk (OARs) with acinar or alveolar structure (e.g. the salivary glands, pancreas, testis, mammary epithelium) respond to irradiation in a similar way to the kidney, in which the nephrons are well defined the structural FSUs with relatively small number of the TCs. It is well-known that among other factors, the risk of late effects depends on the irradiated volume of the OAR. The larger it is, the lower the delivered dose should be [23]. This condition can be fulfilled using the advanced 3D-radiotherapy techniques (IMRT, VMAT), brachytherapy and the SHRT as well, which offer significant dose gradient within a narrow strip of the normal tissues beyond the tumor margins.

An additional important factor, is the arrangement of the FSUs into serial or parallel networks within the OARs. The threshold tolerance-dose and volume of the re-irradiated OARs arranged in the parallel FSUs such as liver, kidney and lung can objectively be achieved, and the use of advanced RT techniques improves sparing effect in these organs [11, 14, 30]. Quite the reverse, if the FSUs are arranged in the series, like links in a chain (e.g. nerve tracts, spinal cord, cylindrical sheets of the peritoneum in the small intestine, named arteries), the loss of even one subunit may result in overt functional injury of the other subunits in the series. Post-irradiation small bowel obstruction or carotid blowout are examples of such volume effect. The key-point is that higher doses to previously irradiated volumes may not affect the function of the organs arranged in the parallel FSUs, but they can definitely be catastrophic for organs arranged in the serial FSUs. Tolerable re-irradiation of serial organs needs particular caution and should be focused on whether whole or a part of their volumes are involved within the irradiated volume.

It seems that the TCs and FSUs structure may by analogy also be referred to the primary malignant solid tumor and considered as a single, large FSU, within which even one surviving tumor clonogenic stem cell (TC) may lead to recurrence (on average 67% of irradiated tumors, since recurrence rate = 1 – TCP = 1 – e^{-1} = 0.67). However, the malignant TCs differ significantly from the normal ones, because they are highly heterogeneous regarding cellular radiosensitivity, oxygen consumption and proliferative potential. Nevertheless, both primary and recurrent tumors require a suitably high total dose to achieve a radical effect and complete local tumor control. The only limiting factor is the tolerance and volume of normal tissues (organs) surrounding the tumor and its impact on late complications, and on the quality of life after primary or re-irradiation.

Although many years passed off, the tolerance doses for normal tissues referred to the primary radiotherapy (fig. 2A) have not been precisely defined yet, but mainly interpreted only based on the results of various retrospective clinical studies [17, 23, 24, 25], and therefore their values are likely inaccurate. It is astounding that for over 50–60 years, TD values have not been as yet verified, and they remain as more or less approximate guidelines for clinical practice [24]. It means that after completing radiotherapy we have to wait for the occurrence of some failures (recurrence, metastases), or not, but we are unable to precisely *a priori* predict such events. There is a lack of clinical studies testing different dose fractionations to establish (not to deduce) an optimal TD, and therefore the tolerance doses for re-irradiation are still uncertain [10, 11, 14, 16, 17, 26, 28]. Some TD came from animal experiments

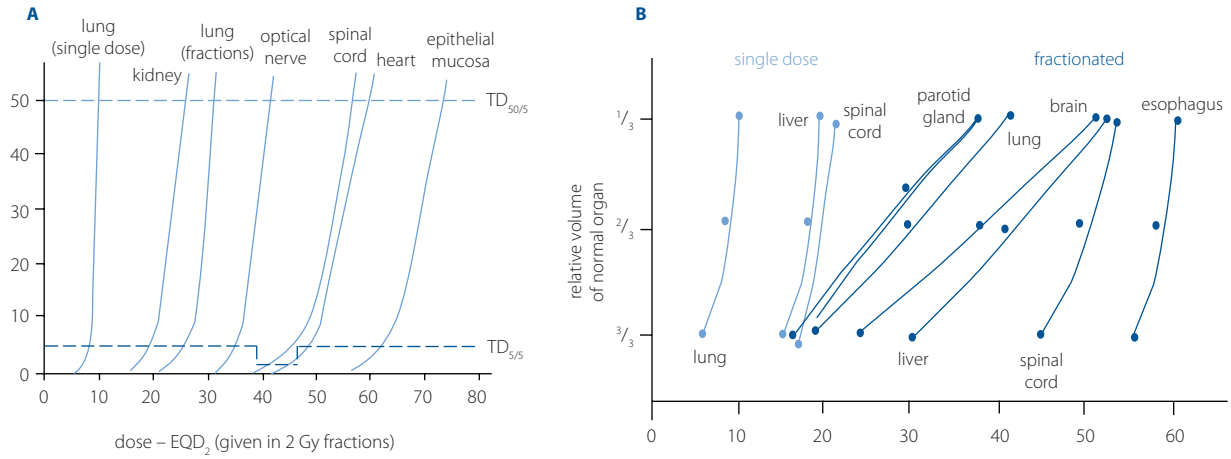

Figure 2. Tolerance dose ($TD_{5/5}$ and $TD_{50/5}$). **A** – whole volumes of the selected normal organs – according to Mc Bride, Withers [23] and Rubin [24]; **B** – the $TD_{5/5}$ in relation to the volume of the irradiated normal organs – according to Emami [17]

[22, 25–28], but they cannot be simply and directly transferred to clinical practice.

Despite some uncertainties, two levels of the Tolerance Dose have been proposed, i.e. the $TD_{5/5}$ referring to a low risk (5%), and $TD_{50/5}$ to a high risk (50%) of late complications, which may occur during the 5-year follow-up. Figure 2A shows a wide spectrum of the $TD_{5/5}$. We had to wait until 1990 when Emami et al. [17] defined $TD_{5/5}$ values depending on the volume of irradiated normal organs (fig. 2B). The smaller irradiated volume of the OARs, the higher $TD_{5/5}$ can be planned and delivered.

Apart from the volumetric factor, fraction size (d_{fx}) has also been found to have an important impact on the radiation response of the OARs, which are much more sensitive to change in the dose per fraction (d_{fx}) than malignant solid tumors. The lower the "d_{fx}", the more effective the sparing effect in the OARs. However, the physical doses expressed in the Gy do not necessarily correspond with bioequivalent doses [23, 25]. For example, 70 Gy in 35 fractions is not biologically equivalent to 70 Gy in 50 fractions, which is equal to 66.5 $izoGy_{2.0}$ for the tumor (α/β = 10.0 Gy) and 59.5 $izoGy_{2.0}$ for the normal organ (α/β = 2.0 Gy). Since the dose is not homogeneously distributed within the irradiated volume, it becomes practically important to convert physical Gy_s into bioequivalent $izoGy_{2.0}$, (if given in 2 Gy fractions) based on simple formulas:

$$EQD_{2.0} = TD_{phys}\,(d_{fx} + \alpha/\beta)\,/\,(2.0\ Gy + \alpha/\beta),$$

or in the case of the SHRT:

$$BED = TD_{phys}\,(1 + d_{fx}/\,\alpha/\beta)$$

(biological effective dose)

For example, if the planned total dose is e.g. 80 Gy, given in 40 fractions, and the DVH shows 56 Gy within a 5 cm length of the spinal cord (α/β = 2.0 Gy), the first thought would be to revise such a treatment plan, since 56 Gy is higher than a $TD_{5/5}$ of 50 Gy. However, the bioequivalent dose $EQR_{2.0}$ is equal to only 42 $izoGy_{2.0}$ [56 Gy x (80 Gy/40_{fx} + 2.0) / (2.0 Gy + 2.0)], that is below $TD_{5/5}$, and the original plan can be accepted with any doubts.

A belief in the sparing effect of a dose per fraction lower than 2.0 Gy has sometimes led in the past to a trap. Twenty years ago, Nguyen et al. [31] designed a super-hyperfractionated schedule of 40 fractions of 0.9 Gy delivered every 2 hours, 8 fractions per day, during 5 days, up to 36 Gy. After a 4-week break they repeated once again the same cycle, up to a total dose of 72 Gy. The authors used this schedule to treat 178 patients with advanced H&N cancer (mainly nasopharyngeal). Although a high rate of local tumor control was achieved, the price paid was tragic, mostly lethal late complications (wide and deep necrosis) which developed in about 80% of patients. Seven years later, Horiot et al. [32] also used small fractions of 1.15 Gy. given twice-a-day, but with 6–8 hour intervals, up to a total dose of 80.5 Gy. The 5-year local tumor control of the advanced H&N cancers was close to 50%, but in contrast to the Nguyen study, late complications were mild and their rate was low. It shows that the major and critical difference between these two quoted studies was too short a time interval between 8 daily fractions used by Nguyen et al.

Radiobiologically, mucosal "half-time" repair ($T_{1/2}$) of the epithelial cells is 1.5 hour. During short 2-hour intervals, a sublethal damage repair in the majority of cells is incomplete (~50%), which is increasingly accumulated through consecutive fractions, and finally leads to lethal necroses. Moreover, although at first glance it looks the 72 Gy given by Nguyen et al. is at the upper limit of the mucosal tolerance, about 50% of the incomplete repair should not be referred to the daily fraction of 0.9 Gy, but to about 3.6 Gy (0.5 x 7.2 Gy of the daily dose), which may raise the total $EQD_{2.0}$ to even 86.4 $izoGy_{2.0}$, in contrast to the Horiot study, in which the bioequivalent total dose $EQD_{2.0}$ reduces to 71.9 $izoGy_{2.0}$. These intentionally presented examples should be treated as a warning that even a single one risk factor missed or biased leads to much higher risk of the LRE than assumed. The situation remains even more

risky when a few OARs (with various α/β indices and $TD_{5/5}$) are within the irradiated volume. Current 3D-techniques nowadays allow for the complete exclusion of the cervical spinal cord from the irradiated area, but not other OARs. When re-irradiation is considered, fear and uncertainties arise, since one does not know, even intuitively, what may radiobiologically happen in the OARs during and after primary radiotherapy, and what proportion of the re-irradiated total dose can be delivered without pronounced increase in the risk of the LRE. It claims that re-irradiation still appears to be a really challenging approach.

Remembered dose mystery

There is still a common conviction that the OARs primarily irradiated to the upper limit of the $TD_{5/5}$ may not tolerate re-irradiation. Such a fear gets even stronger when the recurrence (metastasis) develops early and/or within or close to the previously irradiated volume, as often happens in the case of malignant brain tumors and their metastases. Recurrence or metastasis develops from surviving cancer cells, therefore they, like the original tumor, may likely not remember the primarily delivered dose. It logically suggests that the tumor (primary or recurrent) does not need any dose restriction, but the OARs absolutely do. Some functionally advanced normal tissues (organs) do retain residual proliferative potential due to redifferentiation of some of the mature cells into proliferative status (e.g. fibrocytes into fibroblasts), whereas some other organs can never do that (e.g. neurons). In fact, a proliferative activity plays a marginal role (by contrast with malignant tumors), with favor on capacity of the repair of the sublethal and potentially lethal (SLD, PLD) damages [11, 23, 25, 30]. The lower the dose and irradiated volume of the OAR, the higher the rate of the delivered dose which can be offset by the repair processes (fig. 3). The remaining part of the delivered but not repaired dose is termed the "remembered dose (RD)" [18, 23]. The lower the RD is the broader the "therapeutic window" becomes for re-irradiation. However, both kinetics of the OAR repair and the RD values are not precisely quantitated, but only approximately identified based on the results of animal experiments and fragmentary clinical studies on only a few OARs, and they practically remain unprecise.

Spinal cord tolerance to re-irradiation was intensively and experimentally tested on non-human primates [1, 22, 26, 28, 30]. The results suggest that the "remembered dose" by the spinal cord is close to 50% of the primary dose (fig. 4), if the interval between two types of irradiation is not shorter than 12 months. No myelopathy has occurred after a cumulative total-EQD_{2tot} <172%. Moreover, the pronounced sparing effect was noted [23, 27, 28, 30, 37] after twice-a-day hyperfractionation. Spinal cord re-irradiation using the SHRT [19, 33] can be safe if the cumulative $EQD_{2.0}$ does not exceed approximately 70–75 Gy. Generally, spinal cord re-irradiation practically limits to the recurrences in the spinal canal or spinal cord metastases. For re-irradiation of recurrences within the head and neck region, spinal cord tolerance is no longer a problem, since the cord can easily be left out of the irradiated volume. For example, for nasopharyngeal recurrences, a high dose re-irradiation is recommended [39], despite the treatment related morbidity. Re-irradiation to the cumulative dose EQD_2 of about 120 Gy (re-irradiation total dose of 60–65 Gy) generally resulted in retreatment complications lower than expected (e.g. risk of the carotid blowout of <3%), particularly when the intertreatment interval was longer than 2 years and the hyperfractionation schedule with 1.5 Gy per fraction (b.i.d.) was

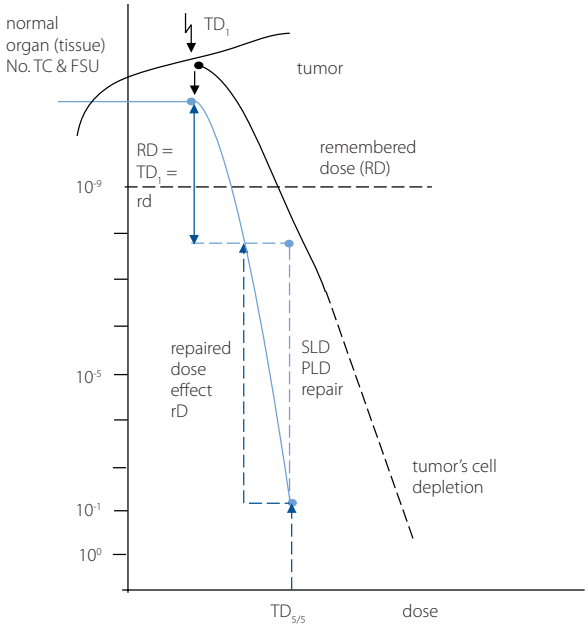

Figure 3. Theoretical scheme of critical organ (tissue) response to the primary total dose (TD_1) Part of the total dose (rD) absorbed by normal organ (tissue) is counterbalanced by the effective SLD and PLD repair, and therefore the remembered dose – rD = TD_1 – rD

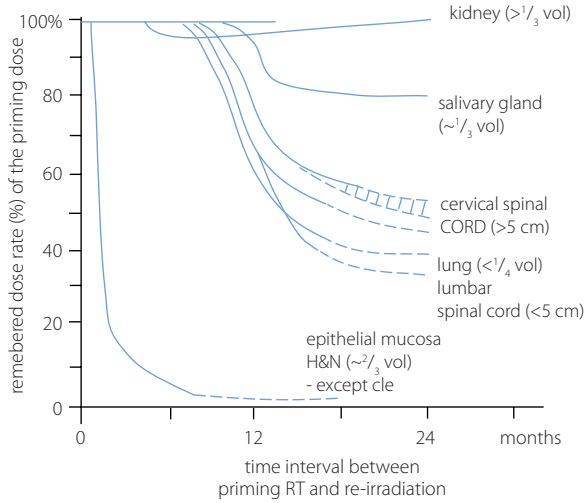

Figure 4. Remembered Dose for selected normal organs (tissues) depending on the time interval between primary and re-irradiation

used with a total dose higher than 60 Gy [1, 8, 11, 14, 25, 30], which can produce 35–50% of local tumor control. By contrast, lower total doses turned out to be definitely ineffective. Stereotactic hypofractionated re-irradiation (SHRT) has been recommended [15, 16, 19, 33, 35, 37, 38] for recurrent cancers, mainly localized beyond the previously irradiated area, with a relatively safe dose of BED < 130 Gy.

The "remembered dose" for the lung (fig. 4) was infrequently tested using the animal model [22]. Both the size of the priming dose and the time interval had a significant impact on the post-re-irradiation response [22, 25, 30, 34]. After a low primary single dose of 6 Gy, the lung tolerates re-irradiation as it was not previously irradiated. At least 1 month after the primary dose of 10 Gy, about half of that dose (25–75%) is remembered as a persistent residual damage. However, transferring quantitative experimental results to a clinic setting seems risky. Jackson and Ball's study on re-irradiation of recurrent non-small-cell lung cancer [34] has revealed a relatively large recovery potential of the occult injury. The re-irradiation dose $EQD_{2.0}$ of 20–30 Gy, delivered 18 months after the priming dose $EQD_{2.0}$ of 55 Gy did not cause any symptomatic radiation pneumonitis [22, 34]. However, re-irradiation of the lung can be a serious problem for patients who suffer(ed) from benign pulmonary diseases or heavy smokers.

Some experimental studies showed that kidney and salivary glands are the organs with a vestigial repair capacity [22], and the rate of remembered dose after priming irradiation can be high and close to 90% (fig. 4). Some functional recovery of the salivary glands may however occur 1 year after re-irradiation, if the cumulative $EQD_{2.0}$ did not exceed 40 Gy. Slight xerostomia has occurred after 10–15 Gy, if more than 30% of the gland was within the irradiated volume.

The kidney is classified as a highly radiosensitive organ (low number of the TC within a large number of the FSU), but the latent period before expression of the clinical late radiation injury can take years, particularly after low doses. Progressive renal damage may even develop many years after irradiation. For example, after an initial dose of 6 Gy (25% of the EQD_{2tot}), the tolerance to re-irradiation decreases during about 26 weeks, which may suggest continuous progression of the occult damage. Thus far, ⅓ of the kidney volume should not receive a cumulative dose higher than 30 Gy, and re-irradiation of the kidney, similar to the salivary gland, must be considered with extreme caution, or not at all.

Figure 4 shows the remembered doses, but for the selected tissues (organs) only, and they are rather deduced than quantitively estimated based on the available fragmentary clinical and experimental data, and therefore must be considered with a limited certainty. By contrast with the kidney and other mature tissues, the epithelium (head and neck aero-digestive mucosa) is a unique one with enormous repair and proliferative capacity, which effectively balances radiation cell kill and sublethal damage. The epithelial cells repopulate fast after the primary dose, and it is almost forgotten after a few weeks. This means that the remembered dose can drop close to zero (fig. 4), unless dose fractionation accelerates and is incessantly continued (including weekends). In such a case, the reserve of the epithelial cells completely depletes and radiation cellular effects gradually progress into a "consequential late effect" (CLE). Therefore, the CLE area (even if healed) should not be included in the re-irradiated volume.

Re-irradiation – know-how dilemma

Despite a few decades passed, clinical studies on re-irradiation still remain fragmentary. Although some animal experiments have been carried out, tolerance estimates and the remembered doses cannot be simply and directly transposed to clinical radiotherapy. Knowledge on the re-irradiation and underlying radiobiological mechanisms are incomplete, mostly limited to experimental and a few retrospective clinical studies. The majority of clinical guidelines are rather approximations based on expert opinions, but with uncertain reliability [3, 11, 22, 24, 29, 30]. Thus with a few exceptions, objective dose constraints (cumulative biological doses) for re-irradiation, prostate recurrence, radical thoracic re-irradiation of non-small-cell lung cancer, locally recurrent nasopharyngeal cancer, recurrent breast cancer, SHRT for spinal metastases and recurrent cervix cancer are generally sparse [4, 5, 15, 18, 19, 29, 30, 33, 34, 36, 37]. High-level evidence on re-irradiation is incidentally available, especially regarding optimal patient selection and the safety of high cumulative doses, since the entire spectrum of dose fractionations has been retrospectively explored and assigned to more or less precisely defined risk of the severe late complications. Although technological advances in radiotherapy offer the delivery of higher and radical biological doses to the tumor with improved sparing effects for normal tissues, radiation oncologists are understandably reluctant to re-irradiate tissues which primarily received high doses, especially if surgery can effectively be applied. There is still a scarcity of precise, quantitative data regarding the time interval between treatments, the dose fractionation pattern, the type of normal tissue at risk, incidence and severity of late complications after the priming irradiation [17] and the patient's life expectancy and quality.

Regarding retreatment, the following terms have been practically used in radiotherapy: re-irradiation, retreatment, salvage, recurrent, palliative, metastases' radiotherapy [3]. Andratschke et al. [21] pointed out that specific recommendations for re-irradiation did not exist until 2022, despite having been urgently needed to ensure common standards. The ESTRO and EORTC Delphi consensus of international experts (21) proposed the definition that: "re-irradiation is a new course of radiotherapy, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity", which should fulfil the following four criteria:

- irradiated region defined,

- prescribed dose,
- time interval between treatments, and
- degree of the overlap of irradiated volumes.

Three scenarios of re-irradiation have been proposed (fig. 5):

- type 1 is a new course of RT that has geometrically overlapped with part or the whole of a previously irradiated volume,
- type 2 relates to a new course, with concerns of toxicity from the cumulative doses, but with no overlap of the irradiated volumes, and
- type 3 relates to the following two options:
  - repeat organ irradiation which is a new course of RT to a previously irradiated organ but with no overlap of the irradiated volumes, and
  - repeat irradiation means a new course of RT to a previously unirradiated organ, and without concerns for toxicity from the cumulative dose.

This decision-tree based on three binary questions (fig. 5) should help to classify the available treatment factors (at least 4 criteria previously mentioned), and to choose a proper scenario of a repeat course of RT.

Type 1 scenario relates to a complete or partial overlap of the irradiated volumes. It raises a challenging dilemma whether a radical (high) or palliative dose should be applied. The time interval between treatments is a crucial factor. It seems that at least a 12-month interval is reasonable. If it is shorter than 6 months, re-irradiation becomes riskier. However, if the recurrence (metastatic lesion) volume is small and the overlap is a small part of a previously irradiated volume, then precise 3D-IMRT, VMAT, SHRT offer the radiation beam(s) a direct focus on the tumor mass with sharp-down dose-gradient beyond. For larger re-irradiated volumes, radical hyperfractionation with a dose per fraction of 1.5 Gy (b.i.d.) or less is advocated as optimal.

The ESTRO and EORTC re-irradiation scenarios were established and published in 2022 [21]. In the previous years, although the number of clinical studies on re-irradiation has increased, the majority of them were retrospective and heterogeneous regarding the entire spectrum of dose fractionation schedules and treatment outcomes. Moreover, when recurrence developed in the organ with the primary tumor, the information as to whether primary and secondary volumes overlapped was not usually recorded, and the situation became even more difficult when the interval was short and allowed for little to no forgiveness of the prior RT, making the re-irradiation riskier and highly challenging. There are many reasons for such situations. A review of many retrospective studies [6–8, 10–13, 29, 30, 34] raises serious uncertainties since more than 9% of them were focused on a single anatomical site of recurrence, mainly the head and neck or brain. Only 14% of studies reported constraints for OARs and cumulative doses to the OARs were infrequently and inconsistently reported (17%); quality of life after re-irradiation was evaluated in only 8% of the reports. Such a deficit of information makes decision regarding re-irradiation quite challenging. When a type 1 scenario is chosen then the remembered dose of the OARs within the planned re-irradiation volume most be considered as an essential parameter. Thereby after 20 years or more, the RDs can only be anticipated and for a few OARs only (fig. 4). In case of the type 1 scenario, a deficiency of important information on the choice of the optimal total dose seems to be unattainable. If a high risk of complications is apprehended, a "Luke Warm Bath" with a dose of 50 Gy or less is chosen, instead of a "hot shower". One should keep in mind that such palliative doses (except the SHRT) are usually ineffective, but they can be an overload for late responding normal tissues. Such a dilemma might be solved by using 3D-IMRT, VMAT or SHRT, which offer the delivery of effective biological doses to maximize the chance of durable local control, and to achieve high and safe therapeutic gain.

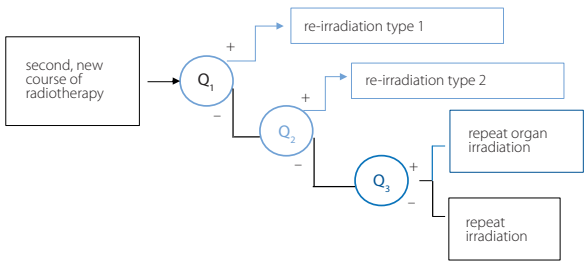

Figure 5. Decision tree for 4 scenarios of re-irradiation according to the ESTRO/EORTC consensus [21]

The type 2 and 3 scenarios of repeat- or re-irradiation are much less risky since the priming and recurrent volumes are not overlapped. Metastases in various normal organs are a "growing family of the customers" for these two types of repeat – or re-irradiation scenarios. For a few reasons (mentioned earlier), stereotactic hypofractionation (SHRT) has been recognized and documented as a highly effective option. Moreover, the SHRT significantly shortens overall treatment time from weeks to day(s), thereby providing an opportunity for out-patient therapy.

The sources of brain metastases are various primary tumors origins. The use of the SHRT reduces neurocognitive toxicities due to a significant reduction of the irradiated volume, and it can be used as a radical or salvage re-irradiation with high 1-year local control rates between 60% and 91% [3, 30], and with a low risk (8%) of radionecrosis. A few small metastatic lesions can easily be eradicated by a single dose or a few SHRT fractions, in contrast to a single metastasis but with a much larger volume (if in both situations the total volumes are equal), which would need a rather more conventionally fractionated dose than SHRT, and a local control of which is much lower.

Re-irradiation using the SHRT has also turned out to be effective for spinal cord with no risk of radiation myelopathy and liver metastases with the retained adequate function [19, 27, 30, 33, 35, 37]. For single or multiple bone metastases, the SHRT with

a single dose of 10–15 Gy or 3 fractions of 8–15 Gy has widely been accepted as an effective therapy with 58–65% complete pain relief, lasting 15–22 weeks [3, 20, 30].

Many studies, mainly retrospective, were not included since their results were incomplete or at least uncertain, and/or sample sizes were too small to accept the results as valid. Nevertheless, the selected number of respective studies [1, 3–8, 11, 17, 21, 30, 34, 37] fulfilled all established criteria for 8427 recurrent tumors, although they referred to a few normal organs only. They are presented in table I. The majority of parameters in that table are deduced rather than estimated. Among the various RT methods, the IMRT and the SHRT were the most often used. The relatively low incidence of the LRE may suggest that the re-irradiation doses were suboptimal and they can be higher. As a rule, the factors and parameters in table I should rather be interpreted as suggestions but not recommended standards, since there is a lack of information in the majority of studies regarding primary and re-irradiated lesions overlapping or not, is essential prerequisite for the type 1 re-irradiation scenario.

Table I. Review of the primary and re-irradiation parameters, cumulative doses, outcomes and risk of late complications for the selected normal organs (tissues) [1, 3, 7, 11, 13, 15, 21, 27, 29, 30, 34, 38, 39]

Organ at risk	First course RT, TD/no/fx	Time interval beetween first and second course of RT (months)	Re-irradiation second course TD/no/fx	Cumulative dose $EQD2_{(\alpha/\beta)}$ $BED_{(\alpha/\beta)}$	Outcomes in years	Risk of LRE (%)	Technique
brain stem (230 GMB), atrocytm	50–60 Gy/ 25–30 fx 40.5 Gy/15 fx	>12 mo	<10–50 Gy/ 20–25 fx 12 Gy/1 fx 18–24 Gy/3 fx	$EQD2_{/3}$ = 100 Gy_3 135 Gy_3	1 yr PFS – 17% 1 yr OS – 36%	radionecrosis 2–5%	3D-IMRT SHRS
brain metastases (626 pts), various origins	various primary tumors, doses irrelevant	9–20 mo >100 mo	15–20 Gy/1 fx 21–30 Gy/3 fx 21–24 Gy 3 fx	BED_3 – 110–160 Gy BED_3 ~ 100 Gy	2 yr LC – 70–80% 2 yr OS – 30–52%	radionecrosis ~ 8.5% radionecrosis	SHRS
spinal cord (227 pts), rodents experiments – lumbar	40–45 Gy/2–22 fx (cervical) 10–12% higher	>6 mo >18 mo	20–35 Gy/ 12–14 fx 26–30 Gy/ 13–15 fx	BED_2 ~ 130–145 Gy_2 BED_2 ~ 140–150 Gy_2	2 yr LC ~ 85% 2 yr ~ 60%	~ 0.8% radiolopathy neuropathy <1%	SHRS IMRT SHRS
bone metastases (2672 pts), primary tumor: lung, prostate, breast, kidney	various primary tumors and doses irrelevant	unimportant	10 Gy/1 fx 10–10, 20 Gy/3 fx 30 Gy/10 fx	$BED_{2.5}$ ~ 30–70 $Gy_{2.5}$	complete pain relief ~ 30–50%	osteonecrosis bone fracture ~ <3%	IMRT SHRS
head and neck (2992 pts), • mandible • carotid arter • parotid	60–70 Gy/ 30–38 fx 50–60 Gy/ 25–30 fx 50–55 Gy/ 25–27 fx ~30 Gy/30 fx	>6 mo >1 year >1 year	60–72.4 Gy/ 50 fx (b.i.d.) 50–56 Gy/ 34–37 fx 50–56 Gy/ 34–37 fx 30 Gy (1/2 vol.) after >2 yrs salvage surgery 30–35%	BED_3 ~ 125–175 Gy_3 <120 BED_3 <100–125 BED_3 BED_3 ≤ 120 Gy_3	3 yrs LRC – 35–69% 3 yrs OS – 25–39%	osteonecrosis 8–12% carotid blowout ~ 3% xerostomia <10%	IMRT (hyper fx) SHRT
lung – non--small-cell cancer (704 pts), organs: • lung • heart • great vessels • trachea • brachial plexus	50–65 Gy/ 25–37 fx 40 Gy/16 fx 48 Gy/3–5 fx ± chemotherapy	>6–12 mo	not well defined 48–56 Gy/ 30–35 fx (b.i.d.) 30–45 Gy/3–5 fx	IMRT SHRT	BED_4 < 14 $5Gy_4$ V_{20} < 20% V_{40} < 50% BED_{max} < 120 Gy BED_{max} < 110 Gy BED_{max} < 85 Gy	symptomatic response 60–75% 3 yr OS – 35% 1 yr LTC after SHRS > 70% mainly peripheral localisation	various LRE 7–21%
breast – local (482 pts)	45–50 Gy/ 25–28 fx + 16 Gy boost (IORT BRT) ± hormono--chemotherapy,	various usually >6 mo	optimal re-RT unclear >60 Gy 30 Gy + HPT ± chemotherapy	IMRT SHRT BRT	BED_5 < 150 Gy_5 <30 Gy for ⅓ vol. of lung <30 Gy for 15% vol. of heart	3 yr LC 63–75%	~ 10-25% teleangiectosis skin fabrosis & contracture cardiac disfunction

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Table I cont. Review of the primary and re-irradiation parameters, cumulative doses, outcomes and risk of late complications for the selected normal organs (tissues) [1, 3, 7, 11, 13, 15, 21, 27, 29, 30, 34, 38, 39]

Organ at risk	First course RT, TD / no.fx	Time interval beetween first and second course of RT (months)	Re-irradiation second course TD/no/fx	Cumulative dose $EQD_2(\alpha/\beta)$ $BED(\alpha/\beta)$	Outcomes in years	Risk of LRE (%)	Technique
	surgery, depending on stage of disease						lung local fibrosis
liver – hepatocellular cancer (575 pts), metastases	50 Gy/5 fx, 40–45 Gy/ 5 fx 30 Gy/5 fx (<½ vol.)	>8 mo	30 Gy/20 fx (b.i.d.) 25 Gy/ 156 fx Gy/3 fx 15 Gy/3 fx 20 Gy/6 fx 21 Gy/7 fx	SHRT IMRT (hiperfx) SHRT	EQD_2 98–105 Gy $D_{0.5max}$ < 10–15 Gy D_{800} < 9–13 Gy stomach	3 yr OS 28–56% 2 yr LC 80%	stomach perforation 7–10% radiat. induced liver disease 10–15%
pelvis (575 pts), mainly cervix ca OAR: bladder, rectum, kidney	54–76 Gy/ 27–38 fx BRT – 27–35 Gy	>18 mo	36 Gy/5 fx, 42 Gy/7 fx 40 Gy/4–6 fx 39 Gy/3 fx, 20 Gy/4 fx 40.8 Gy/34 fx (b.i.d.)	IMRT, BRT, SHRT chemotherapy hyperfx	kidney (½ vol.) < 15 Gy bladder BED_3 <120 Gy rectum D_{2cc} < 75 Gy sigmoid femoral head BED < 100 Gy	cervix ca: 3 yr LC ~ 75% OC ~ 33%	grade 3–4 toxicity 15–17% obturation perforation

TD – total dose in Gy; fx – number of fractions; $EQD_{2.0}$ – equivalent effective dose if given in 2.0 Gy fractions; BED_x – biologically effective dose for (x) – α/β value; LC – local control; OS – overall survival, LRE – late radiation effects; IMRT – intensity modulated radiotherapy; SHRT – stereotactic hypofractionated radiotherapy; BRT – brachytherapy; RT – fractionated radiotherapy

Conclusions

Knowledge on re-irradiation as one among various radiotherapy modalities has mainly been based on fragmentary results of retrospective clinical studies and some animal experiments until 2022; from that point ESTRO/EORTC experts defined what re-irradiation means and proposed a decision-tree for four clinical scenarios that fulfil the criteria for re-irradiation to be considered as obligatory, and parameters and clinical factors must be accounted for and reported (tab. II), before the choice one among four re-irradiation scenarios. If life expectancy is short, then symptoms referred to the re-irradiation might be considered without concerns for irreversible toxicity despite excessive cumulative doses. The ESTRO/EORTC guidelines and re-irradiation scenarios clarify some uncertainties and are important and useful for actual and prospective studies as a source of precise data and growing experience in the field of re-irradiation. However, nowadays we are still condemned to retrospective sources of re-irradiation using a spectrum of dose fractionations. Data on the remembered dose, so important for the type 1 scenario, dose tolerance constraints, cumulative biological dose for both treatments are fragmentary, often uncertain and sometimes are even "blank points". Therefore the palliative "bath" or a "hot" radical shower dilemma remains, since it is not easy to clarify immediately all uncertainties involved. However, the ESTRO/EORTC guidelines (tab. I and II) raise promising perspectives when all required factors

Table II. Factors and parameters required to select an optimal re-irradiation scenario and to report the results (according to the ESTRO/EORTC consensus [21])

Patient characteristics
age, sex, performance status
life style (drinking, smoking)
estimated life expectemcy
Tumor characteristics
primary tumor site location and histology
local recurrence, or metastases or new primary tumor
in field marginal or out-field lesion
retreatment target volume
Previous radiotherapy or other treatments
number of courses
dose, time, fractionation
standardised toxicity persisent or not
time interval since priming RT
previous surgical and/ on systemic therapies
RT technique
Indication to retreatment
treatment intent curative, palliative
goal local control symptom relief or prevention prolongation survival
type 1, 2 or 3 scenario (ESTRO, EORTC)

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Table II cont. Factors and parameters required to select an optimal re-irradiation scenario and to report the results (according to the ESTRO/EORTC consensus [21])

Re-irradiation planning
dose, fractionation targets of organs at risk and dose constraints
RT modality and technique
biological dose estimation
cumulative dose(s) of both treatments
organs at risk and its cumulative doses
Follow-up
standardised reports of toxicity
follow-up intervals and duration

and parameters of priming and re-irradiation treatments will be accurately recorded and collected. Crane [11] pointed out that the most practical way to solve the challenge in the field of the state-of the art practice of re-irradiation is to try to reach consensus among clinicians who see and treat such patients on a regular basis, and are confronted with optimal decisions.

Article information and declarations

Author contributions

Bogusław A. Maciejewski – concept of the work, determination of $TD_{5/5}$ and $TD_{50/5}$ doses and remembered doses, preliminary and final version of the manuscript.

Dorota Gabryś – development of the ESTRO/EORTC consensus and the radiobiological part of the response and health protection to radiotherapy, participation in proofreading the manuscript.

Aleksandra Napieralska – an addition to radiotherapy, IMRT and SHRT for palliative and radical recurrence and metastases.

Conflict of interest

None declared

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References

1. Nieder C, Dragun AE. Re-irradiation. In: Dragun AE. ed. Perez and Brady's Principle and Practice of Radiation Oncology. Wolters Kluwer, Lippincolt Williams and Wilkins, Philadelphia 2013: 695–704.
2. Benson R, Giridhar P, Venkatesulu BP, et al. Re-irradiation for head and neck squamous cell carcinoma. J Egypt Natl Canc Inst. 2017; 29(1): 1–9, doi: 10.1016/j.jnci.2016.07.002, indexed in Pubmed: 27595192.
3. Armstrong S, Hoskin P. Complex Clinical Decision-Making Process of Re-Irradiation. Clin Oncol (R Coll Radiol). 2020; 32(11): 688–703, doi: 10.1016/j.clon.2020.07.023, indexed in Pubmed: 32893056.
4. Fontanesi J, Hetzler D, Ross J. Effect of dose rate on local control and complications in the reirradiation of head and neck tumors with interstitial iridium-192. Int J Radiat Oncol Biol Phys. 1989; 17(2): 365–369, doi: 10.1016/0360-3016(89)90452-5, indexed in Pubmed: 2753760.
5. Stevens KR, Britsch A, Moss WT. High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys. 1994; 29(4): 687–698, doi: 10.1016/0360-3016(94)90555-x, indexed in Pubmed: 8040014.
6. Langendijk JA, Kasperts N, Leemans CR, et al. A phase II study of primary reirradiation in squamous cell carcinoma of head and neck. Radiother Oncol. 2006; 78(3): 306–312, doi: 10.1016/j.radonc.2006.02.003, indexed in Pubmed: 16524634.
7. Lee N, Chan K, Bekelman J, et al. Salvage Re-Irradiation for Recurrent Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2007; 68(3): 731–740, doi: 10.1016/j.ijrobp.2006.12.055, indexed in Pubmed: 17379449.
8. Dawson LA, Myers LL, Bradford CR, et al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001; 50(2): 377–385, doi: 10.1016/s0360-3016(01)01456-0, indexed in Pubmed: 11380224.
9. Creak AL, Harrington K, Nutting C. Treatment of recurrent head and neck cancer: re-irradiation or chemotherapy? Clin Oncol (R Coll Radiol). 2005; 17(3): 138–147, doi: 10.1016/j.clon.2004.10.008, indexed in Pubmed: 15900996.
10. Abusaris H, Storchi PRM, Brandwijk RP, et al. Second re-irradiation: efficacy, dose and toxicity in patients who received three courses of radiotherapy with overlapping fields. Radiother Oncol. 2011; 99(2): 235–239, doi: 10.1016/j.radonc.2011.03.010, indexed in Pubmed: 21497928.
11. Crane C, Tepper JE. Radiation Therapy. Retreatment. Semin Radiat Oncol. 2020; 30: 201–261.
12. Bots WTC, van den Bosch S, Zwijnenburg EM, et al. Reirradiation of head and neck cancer: Long-term disease control and toxicity. Head Neck. 2017; 39(6): 1122–1130, doi: 10.1002/hed.24733, indexed in Pubmed: 28263446.
13. Shen Z, Qu A, Jiang P, et al. Re-Irradiation for Recurrent Cervical Cancer: A State-of-the-Art Review. Curr Oncol. 2022; 29(8): 5262–5277, doi: 10.3390/curroncol29080418, indexed in Pubmed: 35892987.
14. Duprez F, Berwouts D, Madani I, et al. High-dose reirradiation with intensity-modulated radiotherapy for recurrent head-and-neck cancer: disease control, survival and toxicity. Radiother Oncol. 2014; 111(3): 388–392, doi: 10.1016/j.radonc.2014.04.018, indexed in Pubmed: 24998706.
15. Heron DE, Ferris RL, Karamouzis M, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. Int J Radiat Oncol Biol Phys. 2009; 75(5): 1493–1500, doi: 10.1016/j.ijrobp.2008.12.075, indexed in Pubmed: 19464819.
16. Liu F, Xiao Jp, Xu Gz, et al. Fractionated stereotactic radiosurgery for 50 patients with recurrent or residual nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2001; 51(1): 164–170, doi: 10.1016/s0360-3016(01)01623-6, indexed in Pubmed: 11516866.
17. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991; 21(1): 109–122, doi: 10.1016/0360-3016(91)90171-y, indexed in Pubmed: 2032882.
18. Mc Bride WH, Withers HR, Schane D. Biologic basis of radiation therapy. In: Schane D. ed. VII ed Perez and Brady's Principles and Practice of Radiation Oncology. Wolters and Kluwer, Lippincott, Philadelphia 2019: 87–111.
19. Hashmi A, Guckenberger M, Kersh R, et al. Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis. J Neurosurg Spine. 2016; 25(5): 646–653, doi: 10.3171/2016.4.SPINE151523, indexed in Pubmed: 27341054.
20. Hharsell WF, Yajnik S. Palliation of Bone Metastases. In: Yajnik S. ed. V ed. Perez and Brady's Principles and Practice of Radiation Oncology. Wolters Kluwer, Philadelphia 2008: 1986–1999.
21. Andratschke N, Willmann J, Appelt AL, et al. European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making. Lancet Oncol. 2022; 23(10): e469–e478, doi: 10.1016/S1470-2045(22)00447-8, indexed in Pubmed: 36174633.
22. Dorr W, Gabryś D, Stewart FA. Retreatment tolerance of normal. In: Joiner MC, van der Kogel AJ. ed. Basic Clinical Radiobiology V ed. Tandor and Francis Group LLC 2019: 272–285.
23. Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance. Int J Radiat Oncol Biol Phys. 1988; 14(4): 751–759, doi: 10.1016/0360-3016(88)90098-3, indexed in Pubmed: 3350731.
24. Rubin P, Casarelts GW. Clinical radiation pathology, vol 1 and 2. WB Sounders, Philadelphia 1968.

25. Kirkpatrich JP, Millena MT, Coustina ML. Late effects and QUANTEC. In: VI ed. Perez and Brady's Principle and Practice of Radiation Oncology. Wolters Kluwer, Lippincolt Williams and Wilkins, Philadelphia 2013: 296–328.
26. Schultheiss TE, Stephens LC. Invited review: permanent radiation myelopathy. Br J Radiol. 1992; 65(777): 737–753, doi: 10.1259/0007-1285-65-777-737, indexed in Pubmed: 1393407.
27. Nieder C, Grosu AL, Andratschke NH, et al. Proposal of human spinal cord reirradiation dose based on collection of data from 40 patients. Int J Radiat Oncol Biol Phys. 2005; 61(3): 851–855, doi: 10.1016/j.ijrobp.2004.06.016, indexed in Pubmed: 15708265.
28. Ang KK, Jiang GL, Feng Y, et al. Extent and kinetics of recovery of occult spinal cord injury. Int J Radiat Oncol Biol Phys. 2001; 50(4): 1013–1020, doi: 10.1016/s0360-3016(01)01599-1, indexed in Pubmed: 11429229.
29. Dionisi F, Fiorica F, D'Angelo E, et al. Organs at risk's tolerance and dose limits for head and neck cancer re-irradiation: A literature review. Oral Oncol. 2019; 98: 35–47, doi: 10.1016/j.oraloncology.2019.08.017, indexed in Pubmed: 31536844.
30. Nieder C, Milas L, Ang K. Tissue tolerance to reirradiation. Semin Radiat Oncol. 2000; 10(3): 200–209, doi: 10.1053/srao.2000.6593.
31. Nguyen TD, Demange L, Froissart D, et al. Rapid hyperfractionated radiotherapy. Clinical results in 178 advanced squamous cell carcinomas of the head and neck. Cancer. 1985; 56(1): 16–19, doi: 10.1002/1097-0142(19850701)56:1<16::aid-cncr2820560104>3.0.co;2-w, indexed in Pubmed: 4005785.
32. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol. 1992; 25(4): 231–241, doi: 10.1016/0167-8140(92)90242-m, indexed in Pubmed: 1480768.
33. Hashmi A, Guckenberger M, Kersh R, et al. Re-irradiation stereotactic body radiotherapy for spinal metastases: a multi-institutional outcome analysis. J Neurosurg Spine. 2016; 25(5): 646–653, doi: 10.3171/2016.4.SPINE151523, indexed in Pubmed: 27341054.
34. Jackson MA, Ball DL. Palliative retreatment of locally-recurrent lung cancer after radical radiotherapy. Med J Aust. 1987; 147(8): 391–394, doi: 10.5694/j.1326-5377.1987.tb133559.x, indexed in Pubmed: 2443823.
35. Medin PM, Foster RD, van der Kogel AJ, et al. Spinal cord tolerance to reirradiation with single-fraction radiosurgery: a swine model. Int J Radiat Oncol Biol Phys. 2012; 83(3): 1031–1037, doi: 10.1016/j.ijrobp.2011.08.030, indexed in Pubmed: 22197239.
36. Shen Z, Qu A, Jiang P, et al. Re-Irradiation for Recurrent Cervical Cancer: A State-of-the-Art Review. Curr Oncol. 2022; 29(8): 5262–5277, doi: 10.3390/curroncol29080418, indexed in Pubmed: 35892987.
37. Sminia P, Oldenburger F, Slotman BJ, et al. Re-irradiation of the human spinal cord. Strahlenther Onkol. 2002; 178(8): 453–456, doi: 10.1007/s00066-002-0948-1, indexed in Pubmed: 12240552.
38. Mitsuhashi N, Sakurai H, Katano S, et al. Stereotactic radiotherapy for locally recurrent nasopharyngeal carcinoma. Laryngoscope. 1999; 109(5): 805–809, doi: 10.1097/00005537-199905000-00023, indexed in Pubmed: 10334235.
39. You R, Liu YP, Xie YL, et al. Hyperfractionation compared with standard fractionation in intensity-modulated radiotherapy for patients with locally advanced recurrent nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2023; 401(10380): 917–927, doi: 10.1016/S0140-6736(23)00269-6, indexed in Pubmed: 36842439.

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Review article

Liver tumors

Current role of chemoembolization in the treatment of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) accounts for 75% to 85% of primary liver cancers. Recent years have shown a significant increase in the incidence of HCC in Europe and the United States. The algorithm used most commonly in the treatment of HCC is the one developed in 1999 by Barcelona Clinic Liver Cancer (BCLC), updated from clinical trials. The last update is from 2022. Among the available treatments, depending on the stage of HCC, are liver transplantation, resection, thermal ablation, transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT) as well as systemic treatment. The use of irreversible electroporation (IRE), a method involving disruption of cell membrane integrity is currently undergoing research. According to the BCLC, TACE is recommended for patients with BCLC stage-B (more than three lesions, preserved portal vein flow, preserved Child–Pugh A–B liver function and no extrahepatic lesions) and with BCLC stage 0 and stage 1 as an option after failure or not feasible for the first treatment option. In this article, we will try to explain in more detail what the chemoembolization method is and what the indications for its implementation are.

Key words: liver, embolization, chemoembolization, transarterial chemoembolization, Barcelona Clinic Liver Cancer

Introduction

Hepatocellular carcinoma (HCC) accounts for 75% to 85% of primary liver cancers [1]. In Poland, there are between 2,000 and 3,000 new cases per year, while globally in 2020, HCC will account for around 900,000 new cases and around 830,000 deaths [2, 3]. HCC is the sixth most common cancer and third/fourth most common cause of death among cancers [4, 5].

It is three times more frequent in men. Recent years have shown a significant increase in the incidence of HCC in Europe and the United States. Between 2000 and 2016, mortality from HCC in the United States increased by 43% [6]. HCC is associated with chronic liver disease and cirrhosis in 80–90% of cases. Major risk factors include hepatitis B and C, alcohol abuse, non-alcoholic steatohepatitis (NASH), as well as diabetes, obesity and aflatoxin B1. It is estimated that approximately one-third of patients with cirrhosis may develop HCC with a one-year rate of 1–8% [7]. Elevated α-fetoprotein levels are found in 70–80% of patients with HCC.

There is also a variant of HCC – fibrolamellar carcinoma (FLC) – unrelated to cirrhosis, occurring mainly in young people with a slight predominance in women. This form has a different pathology and histopathology, and also a different prognosis. α-fetoprotein levels remain normal.

The algorithm used most commonly in the treatment of HCC is one developed in 1999 by The Barcelona Clinic of Liver Cancer (BCLC), updated from clinical trials. The last update from 2022 is presented in figure 1 [8]. Among the available treatments, depending on the stage of HCC, are liver

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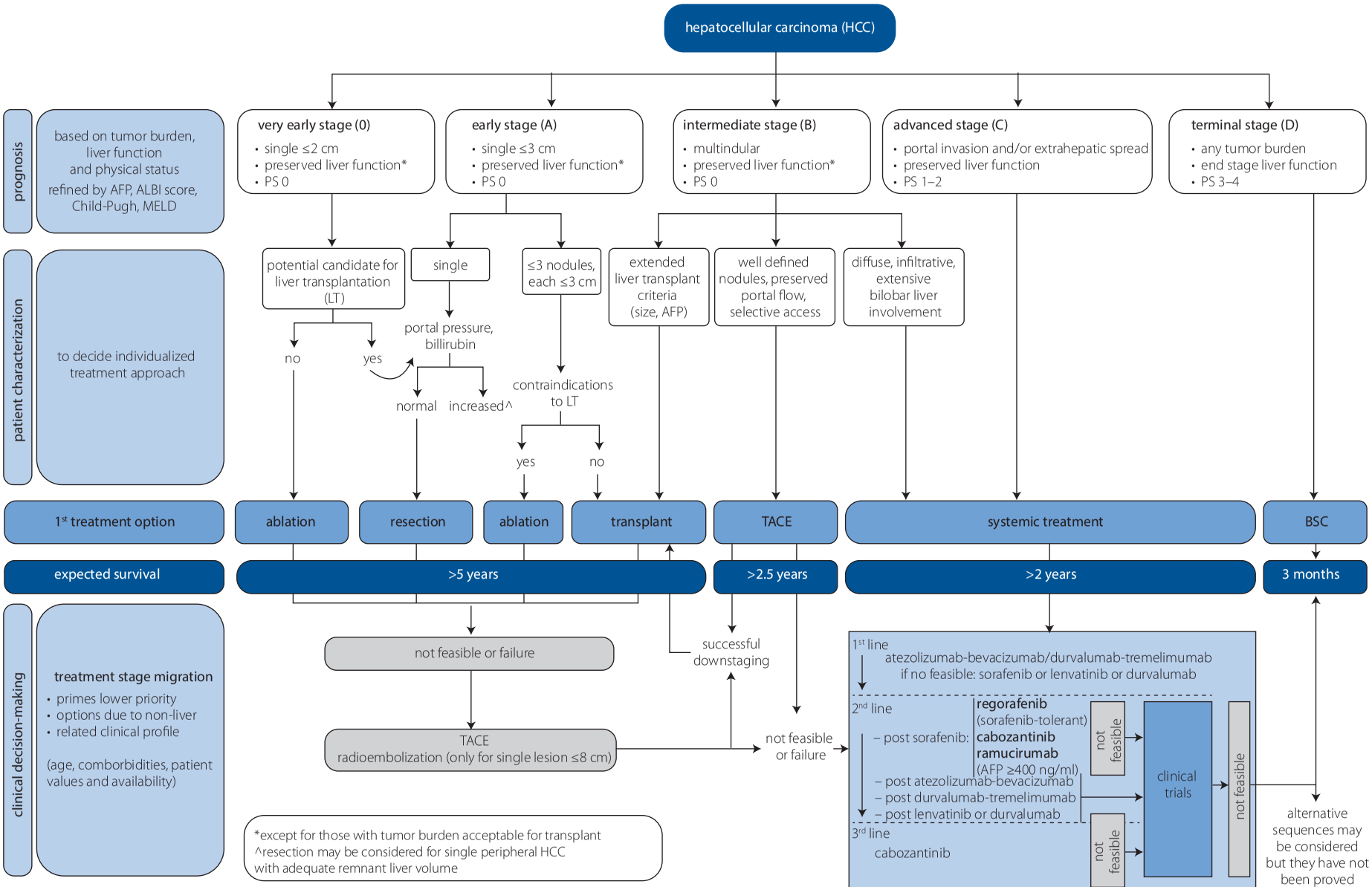

Figure 1. Barcelona Clinic Liver Cancer (BCLC) – updated from clinical trials (2022)

transplantation, resection, thermal ablation (microwave [MWA], radiofrequency [RFA] and laser ablation), transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT) as well as systemic treatment. The use of irreversible electroporation (IRE), a method involving disruption of cell membrane integrity [9, 10], is currently undergoing research. According to the BCLC, TACE (transarterial chemoembolization) is recommended for patients with BCLC stage-B (more than three lesions, preserved portal vein flow, preserved Child-Pugh A–B liver function and no extrahepatic lesions) [11–15], and with BCLC stage 0 and stage 1 as a option after failure or not feasible for the first treatment option [8].

Treatment strategy for HCC

An understanding of the liver's vascularity and HCC is necessary for the correct choice of treatment strategy for HCC. Healthy liver parenchyma is nourished approximately 75% from the portal vein branch, with only the remainder coming from the hepatic artery branch [16]. The terminal branches of the hepatic artery are divided into two sections. The first section accompanies the portal vessels and supplies the peribiliary vascular plexus (PBP), the interstitial tissue of the portal system and the walls of the portal vessels. The second section, named the isolated artery, penetrates the liver parenchyma independently of the portal vein branch. In the cirrhotic liver, PBPs are more developed which provides a link between the arterial and portal systems, and favors tumour survival in the event of arterial occlusion. The development of HCC in a cirrhotic liver progresses in several stages from a regenerative nodule undergoing transformation initially to a dysplastic nodule with a low and then high degree of dysplasia. In subsequent stages, a foci of HCC, known as nodule-in-nodule, appears within the dysplastic nodule to eventually progress to a large HCC. With this process, the proportions of vascularization change – the role of the portal system gradually declines in favor of the arterial system. In poorly and moderately differentiated HCC, portal vascularization almost completely disappears [17]. HCC can grow in an expanding, infiltrating or mixed form. The first form is encapsulated and compresses the surrounding parenchyma, while the second form is poorly differentiated without a capsule with blurred outlines. This differentiation makes some HCCs, especially encapsulated, well-differentiated and extracapsular infiltrating HCCs having partially preserved portal vascularization.

The mode of enhancement has an obvious impact on HCC characteristics in imaging studies. In patients at risk, LI-RADS criteria are used in the assessment of liver lesions. These take into account lesion size, non-rim arterial phase hyperenhancement (APHE), non-peripheral washout, enhancing capsule and threshold growth. Using the above as a basis, the lesion can be assigned to one of the groups from LI-RADS 1, defined as definitely benign, to LI-RADS 5, defined as definitely HCC [18].

The first reports of hepatic artery embolization in the treatment of hepatic cancers date back to 1974. In the 1970s, the first doses of chemotherapeutic agents were administered *via* the hepatic artery, and results showed that even single procedures gave better results than multiple cycles of systemic therapy [19–22]. There are currently two types of TACE procedures resulting from the embolization material used. Conventional TACE (cTACE) in which the chemotherapeutic agent is mixed with Lipiodol – an oily, thick contrast agent to act as a drug carrier.

Drug eluting bead TACE (DEB TACE) – drug-soaked microspheres which, when injected into the vasculature, close the vasculature and then release the chemotherapeutic agent into the tumour in a controlled manner. The microspheres require the addition of a contrast agent to visualize the mixture.

Both procedures can be performed using a standard microcatheter or with a balloon-tipped microcatheter that, when inflated, changes regional hemodynamic conditions in the catheterized vessel or can be used as a safeguard against reflux. This method is called ballon occluded TACE (b-TACE). There is a difference in the distribution of embolization material in cTACE and DEB-TACE. In cTACE, the emulsion, formed at a ratio of one part chemotherapeutic agent to two parts Lipiodol, selectively injected into the arteries is initially deposited in the tumor's sinusoids and then passes into the tumor's draining vessels on the side of the portal system and, *via* PBP, enters the portal system of healthy liver tissue in the tumor's immediate vicinity and into the arterial anastomoses [23–25]. This results in the prevention of flow reversal in the outflow pathway, the tumors necrosis and the increased margin of healthy liver surrounding the tumour. There is also an opportunity to potentially identify other tumour feeding routes that were not originally visible [26]. In the case of richly vascularized lesions, where the mixture's full dose is not sufficient to close the tumor's vascular bed, embolization can be completed using particles or Spongostan. As this mechanism also causes necrosis of healthy hepatocytes surrounding the tumour, ultra-selective embolization of the feeding vessels to minimize liver damage is very important [27].

DEB-TACE involves injecting embolization material saturated with a chemotherapeutic agent (usually doxorubicin but also epirubicin, mitomycin, cisplatin) through a catheter directly into the branch of the hepatic artery feeding the tumour. In DEB-TACE, it is possible to select the size of microspheres (from 40 µm to 900 µm). Smaller microspheres result in more peripheral vascular closure (i.e. closer to the tumor's centre) resulting in better deposition of the chemotherapeutic agent, but also significantly more necrosis of the liver parenchyma compared to the procedure performed with larger particles [28]. With smaller microspheres, there may also be an increased risk of biliary necrosis and blockages outside the liver. At the same time, microspheres are unable to block outflow from the tumour in DEB-TACE. Closing only the arterial vessels

enables reverse flow to be generated from the surrounding hepatic sinuses and portal veins to the tumor's peripheral part. Arterial micro-anastomoses can also be difficult to block. Peripheral tumour tissues can therefore survive due to retained vascularization. Admittedly, the chemotherapeutics released from the microspheres in DEB-TACE can induce necrosis of surviving tumour cells, but this requires depositing them close to the living part of the tumour. DEB TACE also causes more arterial damage than cTACE and a higher risk of arteriovenous fistulae [29–31].

The procedure is performed under local anaesthesia with fluoroscopy guidance. After a percutaneous puncture of the femoral or radial artery, the interventional radiologist inserts a vascular sheath 5 Fr (2 mm in diameter) to prevent blood loss while providing access for subsequent instruments. A guidewire and catheter of appropriate curvature are inserted through the sheath, with fluoroscopy guidance, obtained with an angiographic apparatus. As an a-traumatic tool, the guidewire allows for safe navigation through the vascular system while providing guidance for the catheter, through which the contrast agent is administered. Aortic nephrography is performed first to assess possible routes for feeding the lesion. The visceral trunk is catheterized first, followed by the common hepatic artery. Angiography is performed by administering 25 ml of contrast for 5 seconds. This allows for an accurate assessment of the liver's vascular bed and the tumor's vascularization. If the vascularization is not complete, arteriography of the superior mesenteric artery is also performed in search of the right hepatic artery. This is the most common anatomical variation. Once the vessels feeding the HCC have been identified, the catheter tip is inserted as close to the tumour as possible using a micro-catheter, while avoiding the vessels feeding the healthy liver parenchyma. Once the micro-catheter's correct location is confirmed, a slow infusion of embolization material (beads soaked in a cytostatic agent) mixed with contrast begins, thereby enabling observation of the material's distribution. Chemoembolization using slow-release drug particles produces a synergistic effect: it closes or reduces the arterial blood supply to the tumour with simultaneous deposition of the chemotherapeutic agent in the tumour area and reduced washout.

Depending on the number, size and degree of vascularization of the lesions, the authors perform 1 to 3 procedures at intervals of 4–6 weeks per TACE cycle. A follow-up examination is performed after the last procedure, preferably using the same technique as the eligibility examination. MRI is the preferred method. If there is no enhancement after embolization and the tumour regresses, a follow-up examination is performed after another 3 months.

If enhancement of the residual tumour tissue is visualized, thermal ablation is used or further TACE sessions are performed, depending on the tissue's extent and availability. Two thermal ablation systems can be used: Emprint Medtronic (tMVA) and Echo Laser Elesta. In BCLC stage A patients, a complementary TACE procedure, after thermal ablation of lesions with borderline indications, is used. The efficacy of such combination therapy is confirmed in the available literature [32–37].

The causes of TACE failure and incomplete tumor necrosis can be divided into two groups. The first group includes reasons related to the technical side of the procedure. These include: incomplete, overly rapid embolization which results in compaction of the embolization material and blood supply into the vessels proximally feeding the lesion. Another reason may be the catheterization of the abnormal vessel (this occurs when tumors have a poor vascularization) or embolization of not all the vessels feeding the lesion, particularly marginal, subcostal lesions, where additional feeding may come from arterial anastomoses or from extrahepatic arteries, e.g. from the internal thoracic or diaphragmatic artery, which is usually given off directly from the aorta.

The second group can be described as dependent on the form of HCC. A proportion of HCCs, especially encapsulated, well-differentiated and extracapsular infiltrating HHCs have partially preserved portal vascularization.

In other cases, arterial inflow closure may result in portal vascularization of the tumour due to reversed flow in the small vessels on the portal system side and in the surrounding hepatic sinusoids [38–40]. Although TACE enables obtaining high concentrations of chemotherapeutic agents in the tumor not achievable with systemic treatment and relatively low concentrations outside the tumour area, it is the ischaemia caused by embolization that contributes significantly to HCC necrosis [41].

The mRECIST criteria, in which areas undergoing contrast enhancement are considered as a viable tumour, are adopted to assess the response to treatment [42]. This is of great importance, as necrosis caused by TACE often leads to tumour swelling and an increase in tumour size which can be incorrectly treated as progression. Unintentional chemoembolization of a healthy part of the liver, and a concentrated dose of the cytostatic agent can lead to local liver damage and the formation of perfusion lesions in the healthy part of the liver, or lesions that mimic new foci.

Hence, it is extremely important that imaging examinations are evaluated by radiologists who are familiar with the specifics of the procedures and are members of multidisciplinary teams.

The efficacy of both TACE and also TAE methods has been evaluated in a number of studies.

In a five-year follow-up of 173 patients treated with DEB--TACE with Child-Pugh class A/B (102/71 [59/41%]), and mean lesion diameter 7.6 ± 2.1 cm, Malagari and her team obtained the following results: Overall survival at 1, 2, 3, 4, and 5 years was 93.6, 83.8, 62, 41.04, and 22.5 %, with higher rates achieved in Child class A compared with Child class B patients. Mean overall survival was 43.8 months (range 1.2–64.8). Cumulative survival was better for Child class A compared to Child class B patients ($p = 0.029$). For patients with dominant lesions

≤5 cm 1-, 2-, 3-, 4-, and 5-year survival rates were 100, 95.2, 71.4, 66.6, and 47.6 % for Child class A and 94.1, 88.2, 58.8, 41.2, 29.4, and 23.5% for Child class B patients. Regarding DEB-DOX treatment, multivariate analysis identified a number of lesions ($p = 0.033$), lesion vascularity ($p < 0.0001$), initially achieved complete response ($p < 0.0001$), and objective response ($p = 0.046$) as significant and independent determinants of 5-year survival (43).

The PRECISION V study compared cTACE with DEB-TACE. The microsphere treated group showed higher rates of complete response (27% *vs.* 22%), objective response (52% *vs.* 44%) and disease control (63% *vs.* 52%) compared to the cTACE treated group. The hypothesis of a DEB TACE advantage was not confirmed (unilateral $p = 0.11$). Nevertheless, patients with cirrhosis and Child-Pugh class B, ECOG 1 performance, lesions in both lobes of the liver and disease recurrence showed a significant increase in objective response ($p = 0.038$) compared to cTACE. The use of microspheres was associated with improved tolerability, a significant reduction in severe liver toxicity ($p < 0.001$) and a significantly lower rate of doxorubicin-related side effects ($p = 0.0001$) [44].

In a randomized controlled trial (RCT) conducted between 1996 and 2000, Llovet and his team compared the efficacy of TAE, TACE and conservative treatment. Of the 903 patients, 112 were eligible for the study. Survival probabilities at 1 year and 2 years were 75% and 50% for embolization; 82% and 63% for chemoembolization, and 63% and 27% for control (chemoembolization *vs* control $p = 0.009$). chemoembolization induced objective responses sustained for at least 6 months in 35% [14] of cases, and was associated with a significantly lower rate of portal-vein invasion than conservative treatment [45].

The systematic review and meta-analysis presented by Bzeizi and co-authors included 34 studies involving 4,841 patients with HCC, and an average follow-up period of 1.5 to 18 months. There were no significant differences between DEB-TACE and cTACE in terms of complete response, partial response and disease stability. However, disease control (OR: 1.42, 95% CI: 1.03, 1.96) and objective response (odds ratio [OR]: 1.33, 95% confidence interval [CI]: 0.99, 1.79) were significantly more successful with DEB-TACE treatment with fewer major complications and overall mortality. A pooled analysis showed no superiority of DEB-TACE in terms of complete or partial response, disease stability, disease progression control or mortality at 30 days or at the end of the study [46].

However, the results showed that DEB-TACE was associated with better objective response, disease control and lower overall mortality compared to C-TACE treatment with fewer major complications. DEB-TACE shows less systemic exposure to the chemotherapeutic agent. Furthermore, it shows a standardized release of the chemotherapeutic agent from microspheres, resulting in prolonged retention in the tumor as well as lower liver toxicity. An important aspect is the ability to select the size of the microspheres.

Our extensive experience also shows the advantage of DEB-TACE in terms of controlling the rate and volume of microspheres administered [44].

In vivo studies performed on pigs have shown the spread of doxorubicin to a distance of 600 µm from the edge of the microsphere, with a very rapid decrease in the first 100–200 µm around the particle, and a very slow decrease in the next 400 µm. A sudden drop in drug concentration suggests the presence of barriers to drug diffusion [47]. Particles released 43% of the initial doxorubicin load within the first month and 89% within 3 months of the procedure, consistent with *in vitro* tests predicting a 50% release within 2–3 months [48, 49].

However, it should be noted that the above study took place on healthy pig livers without a tumor. HCC occurring in a cirrhotic liver has a different vascularization from healthy tissue, and the permeability and sensitivity of tumor cells to doxorubicin is also different [50–52]. The above work suggests that when deciding on the type of TACE (cTACE *vs.* DEB-TACE), an in-depth analysis of imaging examinations, in particular, is required to optimally select the procedure technique due to the heterogeneity of the BCLC B group. Despite the clear advantages of DEB-TACE, some authors identify groups of patients in whom they prioritize cTACE.

Adverse effects associated with TACE include post-embolism syndrome, which is the body's natural response to tumor embolization. It can manifest in a number of ways: abdominal pain, raised body temperature, vomiting or temporary deterioration of liver function. The duration of symptoms is highly individual, ranging from 2–3 days to 2 weeks. The incidence ranges from 5 to about 22% [53]. It is important to adequately provide patients with painkillers. More serious complications include liver abscesses requiring drainage, acute pancreatitis or acute cholecystitis, liver failure, kidney failure. Their incidence ranges from 2% to 4% [53]. Vascular dissection and punctures are even rarer.

Monier et al. in their study assess adverse effects of forming biloma, portal vein trombosis, portal vein branch narrowing, and bile duct dilatation. They assess incidence range up to 5% and for global hepatic damages up to 15% [54]. In order to detect potential side effects quickly, patients require regular monitoring after TACE, especially of liver parameters. Due to the contrast agent used during the procedure, contrast-induced nephropathy should be excluded in patients at risk. It is defined as an increase in creatinine concentration by ≤0.5 mg/dl or more than 25% from the baseline within 2–3 days of contrast agent administration. The evaluation of liver function is done according to the Child-Pugh scale correlated with the pre-treatment results. The ALBI score also shows great usefulness in post-treatment evaluation [55].

Conclusions

In case of TACE failure and disease progression at BCLC stage C and Child-Pugh liver stage A–B, the patient receives systemic treatment. Systemic therapy should be considered as a first line over TACE in patients where: HCC exceeds "up to seven" criteria, tumor(s) is/are larger then 5 cm, contiguous multinodular tumors, poorly differentiated or undifferentiated HCC and if there is no objective response after two consecutive TACE treatments [56].

Sorafenib was initially used, being the first multi-kinase inhibitor available for the treatment of advanced HCC. Currently, a atezolizumab and bevacizumab combination is the preferred treatment method, superior to Sorafenib, and demonstrating prolonged overall survival. On the other hand, in the presence of sorafenib contraindications, lenvatinib remains the preferred drug of choice. Second-line treatment includes using regorafenib, cabozantinib, nivolumab, pembrolizumab, ramucirumab and combination therapies [57].

Article information and declarations

Author contributions

Rafał Kidziński – writing – original draft preparation, writing – review and editing.

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Conflict of interest

None declared

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References

1. Smoter P, Kotulski M, Smoter K, et al. Liver transplantation in primary liver tumors. Nowotwory. Journal of Oncology. 2023; 73(4): 248–254, doi: 10.5603/njo.95859.
2. Ferlay J, Ervik M, Lam F. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer, Lyon 2018: 1–6.
3. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
4. Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019; 380(15): 1450–1462, doi: 10.1056/NEJMra1713263, indexed in Pubmed: 30970190.
5. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018; 391(10127): 1301–1314, doi: 10.1016/s0140-6736(18)30010-2, indexed in Pubmed: 29307467.
6. Centers for Disease Control and Pre- vention, National Center for Health Statistics. Trends in liver cancer mortality among adults aged 25 and over in the United States, 2000–2016. July 2018. https:// www.cdc.gov/nchs/products/databriefs/ db314.htm.
7. Ioannou GN, Green P, Lowy E, et al. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS One. 2018; 13(9): e0204412, doi: 10.1371/journal.pone.0204412, indexed in Pubmed: 30260995.
8. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022; 76(3): 681–693, doi: 10.1016/j.jhep.2021.11.018, indexed in Pubmed: 34801630.
9. Bhutiani N, Philips P, Scoggins CR, et al. Evaluation of tolerability and efficacy of irreversible electroporation (IRE) in treatment of Child-Pugh B (7/8) hepatocellular carcinoma (HCC). HPB (Oxford). 2016; 18(7): 593–599, doi: 10.1016/j.hpb.2016.03.609, indexed in Pubmed: 27346140.
10. Lencioni R, Cioni D, Della Pina C, et al. Hepatocellular carcinoma: new options for image-guided ablation. J Hepatobiliary Pancreat Sci. 2010; 17(4): 399–403, doi: 10.1007/s00534-009-0233-0, indexed in Pubmed: 20091187.
11. Burrel M, Reig M, Forner A, et al. Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002; 359(9319): 1734–1739, doi: 10.1016/S0140-6736(02)08649-X, indexed in Pubmed: 12049862.
12. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002; 35(5): 1164–1171, doi: 10.1053/jhep.2002.33156, indexed in Pubmed: 11981766.
13. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002; 224(1): 47–54, doi: 10.1148/radiol.2241011262, indexed in Pubmed: 12091661.
14. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology. 2003; 37(2): 429–442, doi: 10.1053/jhep.2003.50047, indexed in Pubmed: 12540794.
15. Huang YH, Chen CH, Chang TT, et al. The role of transcatheter arterial embolization for patients with unresectable hepatocellular carcinoma: a nationwide, multicentre study evaluated by cancer stage. Aliment Pharmacol Ther. 2005; 21(6): 687–694, doi: 10.1111/j.1365-2036.2005.02404.x, indexed in Pubmed: 15771754.
16. Matsui O, Kobayashi S, Sanada J, et al. Hepatocelluar nodules in liver cirrhosis: hemodynamic evaluation (angiography-assisted CT) with special reference to multi-step hepatocarcinogenesis. Abdom Imaging. 2011; 36(3): 264–272, doi: 10.1007/s00261-011-9685-1, indexed in Pubmed: 21267562.
17. Miyayama S. Treatment Strategy of Transarterial Chemoembolization for Hepatocellular Carcinoma. Applied Sciences. 2020; 10(20): 7337, doi: 10.3390/app10207337.
18. American College of Radiology Committee on LI-RADS® (Liver). https://www.acr.org/-/media/ACR/Files/Clinical-Resources/LIRADS/LI-RADS-2018-Manual-5Dec18.pdf.
19. Doyon D, Mouzon A, Jourde AM, et al. [Hepatic, arterial embolization in patients with malignant liver tumours (author's transl)]. Ann Radiol (Paris). 1974; 17(6): 593–603, indexed in Pubmed: 4142843.
20. Friedman MA, Volberding PA, Cassidy MJ, et al. Therapy for hepatocellular cancer with intrahepatic arterial adriamycin and 5-fluorouracil combined with whole-liver irradiation: a Northern California Oncology Group Study. Cancer Treat Rep. 1979; 63(11-12): 1885–1888.
21. Misra NC, Jaiswal M, Singh RV, et al. Intrahepatic arterial infusion of combination of mitomycin-C and 5-fluorouracil in treatment of primary and metastatic liver carcinoma. Cancer. 1977; 39(4): 1425–1429, doi: 10.1002/1097-0142(197704)39:4<1425::aid-cncr2820390411>3.0.co;2-k.
22. Hirose H, Aoyama M, Oshima K, et al. [Chemotherapy of hepatocellular carcinoma--with special reference to one-shot intra-arterial infusion of a high dose of adriamycin]. Gan To Kagaku Ryoho. 1982; 9(12): 2216–2221, indexed in Pubmed: 6307182.
23. Terayama N, Matsui O, Gabata T, et al. Accumulation of iodized oil within the nonneoplastic liver adjacent to hepatocellular carcinoma via the drainage routes of the tumor after transcatheter arterial embolization. Cardiovasc Intervent Radiol. 2001; 24(6): 383–387, doi: 10.1007/s00270-001-0070-2, indexed in Pubmed: 11907744.
24. Miyayama S, Matsui O, Yamashiro M, et al. Ultraselective transcatheter arterial chemoembolization with a 2-f tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol. 2007; 18(3): 365–376, doi: 10.1016/j.jvir.2006.12.004, indexed in Pubmed: 17377182.

25. Miyayama S, Yamashiro M, Okuda M, et al. Anastomosis between the hepatic artery and the extrahepatic collateral or between extrahepatic collaterals: observation on angiography. J Med Imaging Radiat Oncol. 2009; 53(3): 271–282, doi: 10.1111/j.1754-9485.2009.02073.x, indexed in Pubmed: 19624293.
26. Miyayama S, Matsui O. Superselective Conventional Transarterial Chemoembolization for Hepatocellular Carcinoma: Rationale, Technique, and Outcome. J Vasc Interv Radiol. 2016; 27(9): 1269–1278, doi: 10.1016/j.jvir.2016.04.014, indexed in Pubmed: 27345337.
27. Yoshida K, Matsui O, Miyayama S, et al. Isolated Arteries Originating from the Intrahepatic Arteries: Anatomy, Function, and Importance in Intervention. J Vasc Interv Radiol. 2018; 29(4): 531–537.e1, doi: 10.1016/j.jvir.2017.12.002, indexed in Pubmed: 29477620.
28. Namur J, Wassef M, Millot JM, et al. Drug-eluting beads for liver embolization: concentration of doxorubicin in tissue and in beads in a pig model. J Vasc Interv Radiol. 2010; 21(2): 259–267, doi: 10.1016/j.jvir.2009.10.026, indexed in Pubmed: 20123210.
29. Minamiguchi K, Tanaka T, Nishiofuku H, et al. Comparison of embolic effect between water-in-oil emulsion and microspheres in transarterial embolization for rat hepatocellular carcinoma model. Hepatol Res. 2020; 50(11): 1297–1305, doi: 10.1111/hepr.13561, indexed in Pubmed: 32822527.
30. Miyayma S, Matsui O. Applying superselective conventional TACE. Endovasc Today. 2017; 16: 52–56.
31. Shimose S, Iwamoto H, Tanaka M, et al. Increased Arterio-Portal Shunt Formation after Drug-Eluting Beads TACE for Hepatocellular Carcinoma. Oncology. 2020; 98(8): 558–565, doi: 10.1159/000507262, indexed in Pubmed: 32422633.
32. Helmberger T, Dogan S, Straub G, et al. Liver resection or combined chemoembolization and radiofrequency ablation improve survival in patients with hepatocellular carcinoma. Digestion. 2007; 75(2-3): 104–112, doi: 10.1159/000104730, indexed in Pubmed: 17598962.
33. Lu Z, Wen F, Guo Q, et al. Radiofrequency ablation plus chemo- embolization versus radiofrequency ablation alone for hepatocellular carcinoma: a meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2013; 25(2): 187–194, doi: 10.1097/MEG.0b013e32835a0a07, indexed in Pubmed: 23134976.
34. Lencioni R, Crocetti L, Petruzzi P, et al. Doxorubicin-eluting bead-enhanced radiofrequency ablation of hepatocellular carcinoma: a pilot clinical study. J Hepatol. 2008; 49(2): 217–222, doi: 10.1016/j.jhep.2008.03.021, indexed in Pubmed: 18486261.
35. Iezzi R, Pompili M, Posa A, et al. Combined locoregional treatment of patients with hepatocellular carcinoma: State of the art. World J Gastroenterol. 2016; 22(6): 1935–1942, doi: 10.3748/wjg.v22.i6.1935, indexed in Pubmed: 26877601.
36. Thamtorawat S, Hicks RM, Yu J, et al. Preliminary Outcome of Microwave Ablation of Hepatocellular Carcinoma: Breaking the 3-cm Barrier? J Vasc Interv Radiol. 2016; 27(5): 623–630, doi: 10.1016/j.jvir.2016.01.011, indexed in Pubmed: 27013403.
37. Zhang NN, Lu W, Cheng XJ, et al. High-powered microwave ablation of larger hepatocellular carcinoma: evaluation of recurrence rate and factors related to recurrence. Clin Radiol. 2015; 70(11): 1237–1243, doi: 10.1016/j.crad.2015.06.092, indexed in Pubmed: 26220125.
38. Goseki N, Nosaka T, Endo M, et al. Nourishment of hepatocellular carcinoma cells through the portal blood flow with and without transcatheter arterial embolization. Cancer. 1995; 76(5): 736–742, doi: 10.1002/1097-0142(19950901)76:5<736::aid-cncr2820760505>3.0.co;2-q.
39. Ekelund L, Lin G, Jeppsson B. Blood supply of experimental liver tumors after intraarterial embolization with gelfoam powder and absolute ethanol. Cardiovasc Intervent Radiol. 1984; 7(5): 234–239, doi: 10.1007/BF02553141, indexed in Pubmed: 6498867.
40. Yoshida K, Matsui O, Miyayama S, et al. Isolated Arteries Originating from the Intrahepatic Arteries: Anatomy, Function, and Importance in Intervention. J Vasc Interv Radiol. 2018; 29(4): 531–537.e1, doi: 10.1016/j.jvir.2017.12.002, indexed in Pubmed: 29477620.
41. Kluger MD, Halazun KJ, Barroso RT, et al. Bland embolization versus chemoembolization of hepatocellular carcinoma before transplantation. Liver Transpl. 2014; 20(5): 536–543, doi: 10.1002/lt.23846, indexed in Pubmed: 24493271.
42. Gregory J, Dioguardi Burgio M, Corrias G, et al. Evaluation of liver tumour response by imaging. JHEP Rep. 2020; 2(3): 100100, doi: 10.1016/j.jhepr.2020.100100, indexed in Pubmed: 32514496.
43. Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol. 2012; 35(5): 1119–1128, doi: 10.1007/s00270-012-0394-0, indexed in Pubmed: 22614031.
44. Lammer J, Malagari K, Vogl T, et al. PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol. 2010; 33(1): 41–52, doi: 10.1007/s00270-009-9711-7, indexed in Pubmed: 19908093.
45. Llovet JM, Real MI, Montañá X, et al. Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002; 359(9319): 1734–1739, doi: 10.1016/S0140-6736(02)08649-X, indexed in Pubmed: 12049862.
46. Bzeizi KI, Arabi M, Jamshidi N, et al. Conventional Transarterial Chemoembolization Versus Drug-Eluting Beads in Patients with Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. Cancers (Basel). 2021; 13(24), doi: 10.3390/cancers13246172, indexed in Pubmed: 34944792.
47. Namur J, Wassef M, Millot JM, et al. Drug-eluting beads for liver embolization: concentration of doxorubicin in tissue and in beads in a pig model. J Vasc Interv Radiol. 2010; 21(2): 259–267, doi: 10.1016/j.jvir.2009.10.026, indexed in Pubmed: 20123210.
48. Gonzalez MV, Tang Y, Phillips GJ, et al. Doxorubicin eluting beads-2: methods for evaluating drug elution and in-vitro:in-vivo correlation. J Mater Sci Mater Med. 2008; 19(2): 767–775, doi: 10.1007/s10856-006-0040-y, indexed in Pubmed: 17653626.
49. Lewis AL, Gonzalez MV, Lloyd AW, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol. 2006; 17(2 Pt 1): 335–342, doi: 10.1097/01.RVI.0000195323.46152.B3, indexed in Pubmed: 16517780.
50. Nakashima T, Kojiro M. Pathologic Characteristics of Hepatocellular Carcinoma. Seminars in Liver Disease. 2008; 6(03): 259–266, doi: 10.1055/s-2008-1040608.
51. Jain RK. Transport of molecules in 45. the tumor interstitium: a review. Cancer Res. 1987; 47: 3039–3051.
52. Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer. 2006; 6(8): 583–592, doi: 10.1038/nrc1893, indexed in Pubmed: 16862189.
53. Quinto AM, Nutu OA, Manso RS, et al. Complicaciones de la quimioembolización transarterial (QETA) en el tratamiento de los tumores hepáticos. Cirugía Española. 2018; 96(9): 560–567, doi: 10.1016/j.ciresp.2018.06.004.
54. Monier A, Guiu B, Duran R, et al. Liver and biliary damages following transarterial chemoembolization of hepatocellular carcinoma: comparison between drug-eluting beads and lipiodol emulsion. Eur Radiol. 2017; 27(4): 1431–1439, doi: 10.1007/s00330-016-4488-y, indexed in Pubmed: 27436016.
55. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015; 33(6): 550–558, doi: 10.1200/JCO.2014.57.9151, indexed in Pubmed: 25512453.
56. Silk T, Silk M, Wu J. Up to seven criteria in selection of systemic therapy for hepatocellular carcinoma. World J Gastroenterol. 2022; 28(23): 2561–2568, doi: 10.3748/wjg.v28.i23.2561, indexed in Pubmed: 35949352.
57. Cheng AL, Qin S, Ikeda M, et al. IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med. 2020; 382(20): 1894–1905, doi: 10.1056/NEJMoa1915745, indexed in Pubmed: 32402160.

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Review article

Clinical nutrition in oncology

Probiotics – when and for whom in the oncological patient population

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The human microbiome contains trillions of microorganisms. These organisms vary from person to person like fingerprints, and their composition depends on both host and environmental factors, of which diet plays a crucial role. Knowledge of the human microbiome is possible thanks to the introduction of new DNA sequencing methods, which have been developed over the last decade (Human Microbiome Project). This is when the notion of dysbiosis, which is not quite correct, was coined, i.e. disruption of the normal human microbiota. In the absence of standards for the composition and function of the microbiome, dysbiosis is a conventional term describing the differences in the composition and function of the microbiome between a healthy population and a population affected by, for example, a disease; despite its imperfections, this definition is quite suitable for describing changes in the microbiome in the case of various diseases, including cancer.

The microbiome can influence the development and course of cancer through direct oncogenic effects, pro-inflammatory effects on mucous membranes, generation of metabolic abnormalities, modulation of the immune response and efficacy of anticancer treatment. Both tumour tissue and neighbouring tissues contain their own microbiome, and the same applies to other tissues and body fluids, which, through the microbiome and its metabolites, antigens, etc., can influence tumour development, progression and response to treatment. The gut microbiome is an important regulator of the immune response. It can also influence tumours and their treatment in distant organs. Due to the link between the microbiome and cancer, the potential of its modification in oncological treatment is of great interest to researchers and clinicians.

The aim of this paper is to present the current state of knowledge of one of the most popular methods of modifying the microbiome-probiotics, which are commonly used by oncology patients. The safety aspects of the use of probiotics and current meta-analyses on this group of products are mainly discussed.

Key words: probiotics, cancer, chemotherapy, radiotherapy, surgery

Introduction

The human microbiome contains trillions of microorganisms [1]. These organisms vary from person to person like fingerprints, and their composition depends on both host and environmental factors, of which diet plays a crucial role [2]. Knowledge of the human microbiome is possible thanks to the introduction of new DNA sequencing methods, which have been developed over the last decade (Human Microbiome Project). This is when the notion of dysbiosis, which is not quite correct, was coined, i.e. disruption

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of the normal human microbiota. In the absence of standards for the composition and function of the microbiome, dysbiosis is a conventional term describing the differences in the composition and function of the microbiome between a healthy population and a population affected by, for example, a disease; despite its imperfections, this definition is quite suitable for describing changes in the microbiome in the case of various diseases, including cancer [2]. The microbiome can influence the development and course of cancer through direct oncogenic effects, pro-inflammatory effects on mucous membranes, generation of metabolic abnormalities, modulation of the immune response and efficacy of anticancer treatment [1, 2]. Both tumour tissue and neighbouring tissues contain their own microbiome, and the same applies to other tissues and body fluids, which, through the microbiome and its metabolites, antigens, etc., can influence tumour development, progression and response to treatment. The gut microbiome is an important regulator of the immune response. It can also influence tumours and their treatment in distant organs [2]. Due to the link between the microbiome and cancer, the potential of its modification in oncological treatment is of great interest to researchers and clinicians. The aim of this paper is to present the current state of knowledge of one of the most popular methods of modifying the microbiome--probiotics, which are commonly used by oncology patients. The safety aspects of the use of probiotics and current meta--analyses on this group of products are mainly discussed.

Material and methods

This paper is a literature review. The articles for this paper were chosen based on whether they evaluate the mechanisms of probiotic action and their effects mainly on oncological patients. The keywords used in the search queries included "probiotics", "cancer", "radiation", "chemotherapy", "surgery", "tumor", "mucositis", and related articles were identified by searching PubMed, NCBI (National Center for Biotechnology Information), and Google Scholar. Boolean terms included "And, Or, Not." We focused on meta-analyses, systematic reviews and original contributions.

Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit [3]. Probiotics must contain live bacteria that, in the digestive tract, provide an appropriate physiological effect (e.g. biofilm formation, secretion of bioactive substances, antagonism against pathogens). The amount of probiotics declared by the producer in a given product should be maintained in the indicated amount throughout its shelf life. The health benefits of taking probiotic bacteria are strain-dependent (fig. 1), and should be demonstrated after analysis of the effects of the product on the target group taking it, based on the results of well-designed and conducted clinical trials preferably supported by the results of a meta-analysis [4].

Probiotic strains should be fully genetically characterized using molecular biology methods. It is necessary to confirm the safety of the strain based on toxicological studies [6] and to exclude the possibility of transmission of antibiotic resistance genes, as described later in this article. The efficacy of a probiotic should be confirmed in at least one randomized clinical trial. The Oxford EBM Centre describes five levels of evidence of probiotic efficacy (from highest to lowest) [7]:

1. systematic review of RCTs, 'n-of-1' studies,
2. RCT/observational study with a 'very favorable' outcome,
3. non-randomized cohort study, follow-up study,

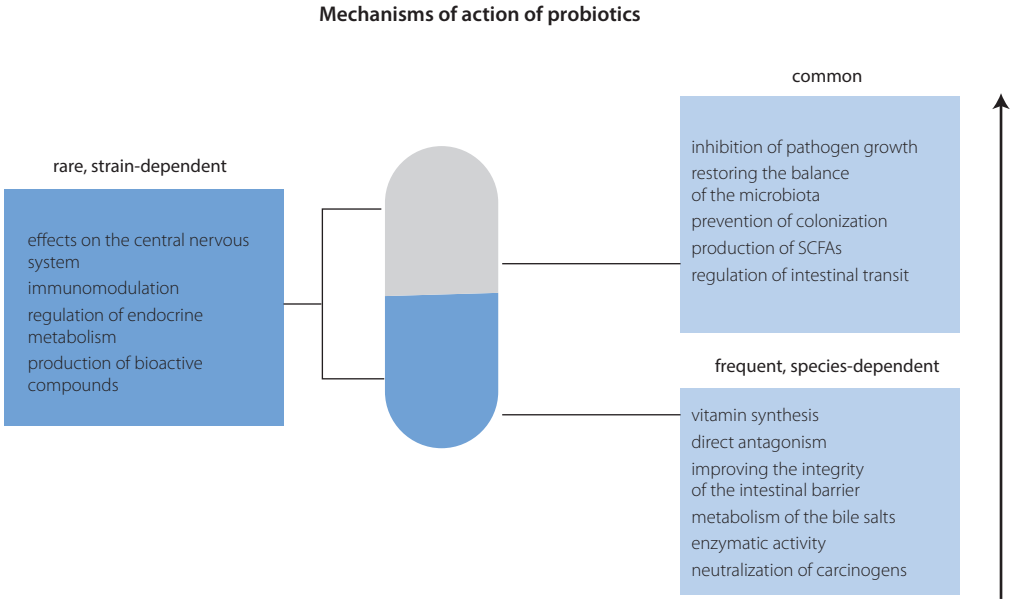

Figure 1. Overall mechanisms of probiotic action. Own elaboration based on literature (acc. Hill et al.) [5] in BioRender

4. case reports, case-control,
5. inference based on mechanism of action.

Although there are probiotics on the market with different levels of evidence, probiotics with a level 1 or 2 should be used in oncological patients. In certain cases it is acceptable to use a probiotic with a level of evidence 3, when its efficacy was tested in a large population and the adverse effects were well characterized in this study. Although there are probiotics on the market with different levels of evidence, probiotics with a level 1 or 2 should be used in oncological patients. In certain cases it is acceptable to use a probiotic with a level of evidence 3, when its efficacy was tested in a large population and the adverse effects were well characterized. Of note, that probiotics most often have the registration status of dietary supplements rather than medicines, which is due, on the one hand, to the nature of these products, which contain live bacteria, causing standardization problems from the point of view of pharmacopeial requirements and, above all, to the impossibility of patenting probiotic strains, which, occurring in nature, cannot be subject to patent restrictions, which, in turn, makes the very costly investment involved in the process of developing an innovative medicine uneconomic. The average research and development (R&D) to marketplace cost for a new medicine is nearly $4 billion, and can sometimes exceed $10 billion [8]. Due to legal requirements in the EU, manufacturers are not allowed to advertise the beneficial effects of probiotics on the body. This is a very complex issue at the intersection of medicine, law and health policy, a detailed discussion of which is beyond the scope of this paper.

To illustrate only a part of this problem, we would like to cite the assumptions of The European Food Safety Authority (EFSA) regarding health claims in accordance with the Regulation of the European Parliament and of the Council (WE) Nr 1924/2006 and (EU) nr 1169/2011 (EU) (https://www.efsa.europa.eu/sites/default/files/event/190118-ax.pdf):

1. they must not refer to a disease,
2. disease risk reduction claims must not refer to a reduction in disease risk, but to a reduction in a disease risk factor,
3. sick people must not be the target population for food claims,
4. claims should refer to the general (healthy) population or subgroups thereof.

Due to such limitations, the only sources of information on the efficacy of probiotics are scientific studies. At this point, it should be emphasized that, for example, yoghurts, pickles and other foods that contain bacterial strains with undocumented beneficial health effects are not probiotics. Unlike fermented foods, probiotic products must meet a number of quality requirements as well as those concerning the safety and efficacy of their use. These requirements are particularly important in the use of probiotics for oncological patients, who are burdened not only by the underlying disease but also by treatment with often high risks and severe side effects and complications.

The effect of probiotics is strain-dependent, so the results obtained from studies of other strains should not be extrapolated even to those that are taxonomically closely related to them. Therefore, both clinical trials and descriptions of probiotics should always give their full taxonomic names. The same problem applies to meta-analyses that describe collectively the effects of different probiotics. Such meta-analyses are, of course, of great value, especially when they contain data on their mechanism of action, but only when they include papers on a specific strain or a preparation of different strains can they be helpful to clinicians in making therapeutic decisions.

Probiotics are primarily used to supplement microbial deficiencies that may be the cause of specific conditions. A classic example of this approach is the concept of taking probiotics prophylactically during antibiotic therapy or chemotherapy, which disrupts the patient's microbiota. However, a cause-and-effect relationship between the microbiota and the disease should always be identified. Probiotic administration often does not result in changes in the composition of the microbiota [8], and may be associated with the production of metabolites that enter the interactions with the host's metabolism and immune system. However, probiotics can affect gut microbiota gene expression, with potential anti-inflammatory effects. Moreover, probiotic intervention alters the influence of microbiota on biochemical, physiological and immunological parameters [9]. Furthermore, probiotic strains are administered to patients because of their antagonistic properties towards pathogenic bacteria. An excellent example is one of the best studied probiotic strains *Lactiplantibacillus plantarum* 299v. On the surface of this bacterium are mannose adhesins encoded by the *Msa* gene that have an affinity for receptors located on intestinal mucosal cells. *L. plantarum* 299v, by binding to these receptors, inhibits the competitive adhesion of bacteria (*Escherichia coli* – ETEC/EPEC, *Salmonella enterica serovar Enteritidis*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Saccharomyces cerevisiae*) and *Candida albicans*. Other adhesins present on the surface *L. plantarum* 299v are glycolytic enzymes: 3-phosphoglycerate aldehyde dehydrogenase (GAPDH), enolase (ENO) and phosphoglycerate kinase (PGK). GAPDH inhibits competitively the adhesion of group A streptococci, staphylococci, *Candida albicans* and *Schistosoma mansoni*. ENO prevents adhesion of streptococci, *Streptococcus pneumoniae*, *Streptococcus aureus* and *Candida albicans*. Moreover, *L. plantarum* 299v enhances the production of mucin in intestinal epithelial cells, which explains the antagonistic effect of this bacterium towards the *Escherichia coli*. Probiotic bacteria are also recommended to increase the production of short-chain fatty acids (SCFAs) in the gut, which improve the integrity of the intestinal epithelium, reduce bacterial translocation, regulate epithelial cell proliferation and differentiation, improve nutrient absorption, are energy substrates for the liver, skeletal

muscle, heart, brain, prevent hyperinsulinemia and have anti-inflammatory effects [10–11]. According to Dogra et al. [12], probiotics can increase the resistance of the microbiome to stress factors and/or improve its ability to recover. The mechanisms of action of probiotics can be divided into rare, which are strain-dependent:

- immunomodulation,
- endocrine action,
- production of bioactive compounds,
- effects on the central nervous system;

frequent, species-dependent:

- vitamin synthesis,
- direct antagonism,
- enzymatic activity,
- metabolism of bile salts,
- neutralization of carcinogens,
- improvement of intestinal barrier integration;

and common to many probiotics: production of non-short-chain fatty acids, prevention of intestinal colonization by pathogens, regulation of intestinal transit, inhibition of pathogen growth, restoration of intestinal microbiota balance, improvement of intestinal epithelial renewal [5]. Given the complexity of cancer and the consequences of its treatment, all of these mechanisms can benefit oncological patients.

Safety

The safety of probiotic usage must be determined on the basis of established scientific principles, including the conduct of appropriate studies. A large number of species of lactic acid bacteria, bifidobacteria and yeast are available in many common dietary supplements and foods, meaning that they are safe for consumption. The EFSA has maintained and updated a list of species considered safe for human consumption since 2007. The main classifications are QPS (*qualified presumption of safety*) and novel food [13]. These qualifications are based on taxonomic identification and a comprehensive scientific data on the safety of the strain in question, which include:

1. genotypic and phenotypic identification,
2. detection of virulence-related genes by validated whole-genome sequencing (WGS), toxin production potential (toxin production potential must be considered for novel foods with respect to potentially adverse metabolic properties),
3. animal toxicity tests may be required for novel foods,
4. assessment of the risk of antimicrobial resistance is required for all; identification of intrinsic or acquired resistance and potential transferable antimicrobial resistance genes.

It seems that since the effect of probiotics is strain-dependent, the safety of their use should also be determined on a strain-by-strain basis. The only method is to conduct *in vitro* toxicological studies and clinical trials. End-product-specific studies are particularly important, especially when probiotics are used in groups of seriously ill people. Reference can be made to studies of the probiotic *L. plantarum* 299v, which, when administered to kidney transplant patients, reduced the incidence of infections caused by *Clostridium difficile* [14–15]. In addition, no risk of endocarditis was identified for this strain and the risk of use in critically ill patients [15].

In contrast, the use of *Saccharomyces boulardii* is not recommended in patients with a catheter inserted into a central vein, in critical condition or with significantly weakened immunity. Great caution is also recommended for the use of this probiotic in patients with impaired intestinal barrier integrity, which is often seen in patients treated with chemotherapy or radiotherapy [16]. Adverse reactions caused by the administration of a probiotic strain do not necessarily result in its being deprived of QPS status. For instance, cases of bacteraemia have been observed following the use of the *Lacticaseibacillus rhamnosus* GG strain and endocarditis, however, conditions predisposing to opportunistic infections were noted in all of these cases, leaving the QPS status of species previously included in the genus Lactobacillus spp. and now belonging to any of the derived genera unchanged [17].

Meta-analysis confirms the safety of probiotics in oncological patients. Wang et al. found in eleven studies of probiotics used for prevention of chemoradiotherapy-induced diarrhoea in people with abdominal and pelvic cancer, including 1612 people (873 receiving probiotics and 739 not receiving probiotics) that in seven studies no adverse events (AEs) caused by probiotics were observed. In four studies varying degrees of AEs were reported in both placebo and probiotic groups. The authors concluded that despite the rare occurrence of AEs after probiotic treatment, caution should be considered as many cancer patients are immunocompromised [18]. In a subsequent systematic review and meta-analysis involving twenty-five studies (n = 2,242) in patients with different types of cancer, 237 adverse events were observed in those consuming probiotics and 314 adverse events in those not consuming probiotics. No deaths related to probiotic intake were observed and infection events were not clearly related to the intervention [19]. It must be added, however, that the reporting of adverse effects in this group of patients is difficult, and distinguishing their cause is often impossible. Therefore, probiotics should not be used, and it is certainly necessary to assess the balance of benefits and losses before their possible use, in patients:

- with immunodeficiency,
- in a severe general condition hospitalized in an intensive care unit,
- with a central venous catheter.

Probiotic therapy in meta-analyses

Some papers on cancer prevention by probiotics have been published so far. One of the most interesting is the meta-analysis by Gheisary Z. et al. on the prevention of oral cancer [20], which showed a statistically significant reduction in lesions after probiotic therapy. Probiotic-mitigated changes included

a reduction in the number of subgingival periodontopathogens *P. gingivalis* (SMD = 0.402), *F. nucleatum* (SMD = 0.392), and *T. forsythia* (SMD = 0.341), immunological markers MMP-8 (SMD = 0.819), and IL-6 (SMD = 0.361). The results of this study suggest that probiotic supplementation improves clinical parameters and reduces the burden of periodontopathogens and proinflammatory markers in patients with periodontal disease. Among the bacteria analyzed in the meta-analysis are the following *B. bifidum*, *L. acidophilus*, *L. casei*, *L. rhamnosus*, *L. salivarius Bifidobacterium*, *B. longum*, *L. acidophilus*, *L. bulgaricus*, *L. casei.*

Another meta-analysis [21] estimated the potential effect of probiotics on inhibiting oral carcinogenesis. Although the studies included in the meta-analysis are of moderate quality, it was possible to select bacterial species with potentially carcinogenesis-preventing effects, included *Acetobacter syzygii,* AJ2, *Lactobacillus plantarum* and *Lactobacillus salivarius* REN. Among them, the use of *L. salivarius* REN resulted in a 95% lower risk of developing oral cancer ($p < 0.05$).

Interestingly, another study showed that probiotics can be effective in the prevention and treatment of oral mucositis caused by chemotherapy, radiation therapy and chemo-radiotherapy [22]. Five studies involving 435 patients that were included in the meta-analysis indicated that the use of probiotics reduced the risk of inflammation.

Treatment – surgery, chemotherapy and radiation

One of the most common and typical side effects associated with chemotherapy or radiation therapy in cancer patients is diarrhea (up to 80% of treated patients). Diarrhea can lead to some severe consequences: loss of fluids and electrolytes, creation of nutritional deficiencies, increased risk of infections or delays in treatment, reduction of dosage or discontinuation of treatment. Probiotics have long been used in gastrointestinal guidelines to relieve diarrhea [23]. However, can probiotics be effective in the treatment of diarrhea in oncological patients?

In 2018, based on the results collected in the Cochrane database [24],evidence supporting the effectiveness of probiotics in preventing or treating diarrhea associated with cancer treatment was shown to be lacking. However, according to the authors, probiotics appear to be safe, as no studies have shown serious side effects. Three studies analyzed in this paper where probiotics were compared with other drugs in preventing diarrhea in patients treated with radiation therapy – with or without chemotherapy – found beneficial effects of probiotics. Remarkably, no study reported serious adverse events or deaths related to diarrhea.

Another interesting meta-analysis on the reduction of diarrhea induced by chemotherapy and or radiotherapy or chemo--radiotherapy among individuals with abdominal and pelvic cancer was published in 2016 [18]. The authors concluded that probiotics may have a beneficial effect in preventing chemo--radiotherapy-induced diarrhea, especially in cases of grade ≥2 diarrhea with rarely cause side effects. An interesting meta-analysis was conducted by Skonieczna-Zydecka et al. [25], who evaluated the effectiveness of probiotic use in the prevention of postoperative complications. The authors found a reduction in the incidence of postoperative complications like abdominal distress, diarrhea, pneumonia, sepsis, surgical wound infections and urinary tract infections. They also observed shorter duration of antibiotic therapy, occurrence of fever, administration of infusions, hospitalization, shorter times for introducing solid foods and also lower levels of C-reactive protein (CRP) and interleukin (IL) – 6. This meta-analysis shows that prophylactic administration of probiotics counteracts postoperative complications by modulating the intestinal immune response and production of [SCFAs]. In a study by Gan et al. [26], administration of probiotics before surgery was shown to reduce the incidence of infections after liver resection, and may reduce the duration of hospitalization and antibiotic use [26]. In the probiotic group, infection rates were 11.7%, while in the placebo group they were 30.3% respectively ($p < 0.001$). The rate of wound infection decreased the length of hospital stay (–0.57 days) and antibiotic use (mean difference: –3.89 days, 95% CI: –4.17 to –3.60; $p < 0.001$) were shortened in the group of patients using probiotics. The probiotics used are *L. Casei Shirota* and synbiotic *Pediococcus pentoseceus* 5–33:3, *Leuconostoc mesenteroides* 32–77:1 *L. paracasei* ssp paracasei 19 and *L. plantarum* 2362, as well as 2.5 g inulin, oat bran, pectin and resistant starch.

Similar results were obtained in Chen's 2022 meta-analysis [27] in which it was shown that the use of probiotic therapy [including synbiotic therapy] is associated with a significant reduction in the risk of postoperative infectious complications by 37% (relative risk [RR] = 0.63, 95% confidence interval [CI] 0.54–0.74, $p < 0.001$). Probiotic administration was shown to be effective in reducing the incision infection, central line infection, pneumonia infection, urinary infection and incidence of diarrhea septicemia. A meta-analysis [28] evaluated the effect of probiotic therapy on reducing postoperative infectious complications in patients who underwent colorectal cancer surgery. In these patients, probiotics may result in reducing overall postoperative complications, but may result in little to no difference in hospital length of stay (LOS) and postoperative quality of life (QOL). The authors conclude that perioperative administration of probiotics can reduce infectious complications in patients undergoing colorectal cancer surgery. In addition, compared to standard of care or placebo, probiotics may have similar effects on perioperative mortality and procedure-related complications such as anastomotic leakage, hospital length of stay, and quality of life. In contrast, the meta-analysis of Yang [3] found that probiotics (*Bifidobacterium*, *Lactobacillus* and *Streptococcus* species) can more effectively reduce inflammation associated with gastric cancer by increasing levels of cluster of differentiation 4+ and significantly reducing levels of IL-6.

Table I. Summary of the effect of probiotics in gastrointestinal cancers

Type of article	Aim of the study	Number of studies analyzed	Type of sample used	Probiotic strain (examples)	Outcomes	Conclusions	References
systematic review and meta-analysis	investigating the effect of probiotics on inhibiting oral carcinogenesis	studies included in qualitative synthesis (n = 5) studies included in quantitative synthesis (meta-analysis) (n = 2)	4-nitroquioline-1-oxide (4NQO)-induced oral carcinogenesis in male F344 rats and TCA-8113 (human tongue squamous carcinoma)	*Lactocasieibacillus salivarius* REN	inhibition of oral carcinogenesis induced by 4-nitroquioline-1-oxide	the study found that the 4 strains described here show potential therapeutic activity in oral carcinogenesis. The ability of *L. salivarius* REN to inhibit oral cancer suggests that this bacterium may be a potential inhibitor of oral carcinogenesis	[21] Wan Mohd Kamaluddin et al. 2020
			human oral KB cancer cell line	*Lactocaseibacillus plantarum*	reduction of proliferation and induction of apoptosis to the cancer cell [TCA-8113]; enhancing cytotoxicity expect		
			human oral cancer cell line (KB) and human normal epithelial cell line (KDR)	*Acetobacter syzygii*	the metabolites of *Acetobacter syzygii* induced apoptosis		
			NK cells and monocytes from healthy human donors; humanized-BLT (hu-BLT; human bone marrow/ liver/ thymus) mice; nodscid gamma mouse (immunodeficient laboratory mice)	AJ2- mix of *Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaricus*	super-charged NK cells inhibit OSCSCs tumor growth and improved immune system of hu-BLT mice		
systematic review, meta-analysis, and meta-regression	verify that probiotics and/or synbiotics reduce the incidence of surgical site infections and other surgery-related complications	35 trials included 3,028 adult patients; interventions were probiotics (n = 16) and synbiotics (n = 19 trials)	adult patients with hepatopancreatobillary surgery; or colorectal surgery; or oesophagectomia	*Enterococcus faecalis* T110, *Clostridium butyricum* TOA, *Bacillus mesentericus* TOA	probiotic treatment can reduce superficial incisional SSIs in patients undergoing CRC surgery; perioperative probiotic treatment can enhance immune responses and improve the intestinal microbial environment	the study found a reduction in the incidence of postoperative complications like abdominal distress, diarrhea, pneumonia, sepsis, surgical wound infections, urinary tract infections; shorter duration of antibiotic therapy, occurrence of fever, administration of infusions, hospitalization, shorter time to introduce solid foods and also lower levels of C-reactive protein (CRP) and interleukin (IL-6)	[25] Skonieczna-Żydecka et al. 2018
				Lactobacillus casei strain Shirota, *Bifidobacterium breve* strain Yakult; prebiotic: GOS	perioperative administration of synbiotics in patients with esophagectomy is useful because they suppress excessive inflammatory response and relieve uncomfortable abdominal symptoms through the adjustment of the intestinal microfloral environment		
				Lactobacillus casei strain Shirota, *Bifidobacterium breve* strain Yakult; prebiotic: GOS	perioperative synbiotic treatment attenuated the decrease in intestinal integrity and reduced the rate of infectious complications in patients with or without liver cirrhosis who underwent hepatic surgery		

Table I cont. Summary of the effect of probiotics in gastrointestinal cancers

Type of article	Aim of the study	Number of studies analyzed	Type of sample used	Probiotic strain (examples)	Outcomes	Conclusions	References
systematic review and meta--analysis	to investigate whether the use of probiotics and synbiotics can have an impact on the prevention of infectious complications in patients with colorectal cancer	studies included in meta-analysis (n = 14) 1,566 patients	human	*Lactobacillus plantarum* (CGMCC No 1258), *Lactobacillus acidophilus* (LA-11), and *Bifidobacterium longum* (BL-88)	compared with the control group, the probiotic group had increased transepithelial resistance, reduced bacterial translocation, decreased ileal-bile acid binding protein; they had decreased blood enteropathogenic bacteria and increased fecal bacterial variety; the post-operative recovery of peristalsis, incidence of diarrhea/ infectious-related complications were improved	significant reduction in the risk of postoperative infectious complications by 37% reducing the incision infection, central line infection, pneumonia infection, urinary infection, and incidence of diarrhea septicemia	[27] Chen et al. 2022
				Bifidobacterium longum, *Lactobacillus acidophilus*, and *Enterococcus faecalis*	the use of probiotics can reduce the occurrence of infectious complications		
systematic review and meta--analysis	the primary outcome measures included perioperative mortality, postoperative infectious complications, and probiotics--related adverse events. postoperative outcomes between patients with and without perioperative probiotic administration during colorectal cancer surgery. Secondary outcome measures included overall postoperative complications, hospital length of stay, and postoperative quality of life	studies included (n = 20)	human	*Bifidobacterium animalis, lactis*, *Lactobacillus casei*, and *Lactobacillus plantarum*	changes in the microbiota (typically occur over time in CRC patients) and inflammatory responses are modified by the use of probiotics before and after surgery. It reduces postoperative bowel discomfort	perioperative probiotic administration may reduce complications, including overall infectious complications, in patients undergoing colorectal cancer surgery without any additional adverse effects; probiotics may have similar effects on perioperative mortality; procedure--related complications such as anastomotic leakage, and hospital LOS; or improve the QOL	[28] An et al. 2019
				Lactobacillus acidophilus NCFM, *Lactobacillus rhamnosus HN001*, *Lactobacillus paracasei LPC-37*, and *Bifidobacterium lactis HN019* + *oligosaccharide*	the perioperative administration of synbiotics significantly reduced postoperative infection rates in patients with colorectal cancer		
				Pediococcus pentosaceus, *Leuconostoc mesenteroides*, *Lactobacillus paracasei spp. paracasei*, and *Lactobacillus plantarum*, and 2.5 g of each of the four fermentable fibers (prebiotics)	patients who use synbiotics had a better Gastro-Intestinal Quality of Life Index compared with placebo; synbiotics administration may have a beneficial effect on the post-colectomy gastrointestinal function (mainly diarrhea)		

SSIs – surgical site infections; CRC – colorectal cancer; LOS – length of stay; QOL – quality of life

In table I, we have summarized the results of systematic review and meta-analyses focusing on the potential benefits of probiotics for cancers located in the gastrointestinal tract. As can be seen, undoubtedly further research on this topic is needed, although already the effect of probiotic therapy on improving quality of life, reducing gastrointestinal complaints or the impact on reducing the frequency of infectious complications seems promising.

Other clinical work on probiotic therapy in cancer patients

Bajramagic et al. studied the effect of probiotics in patients with colorectal adenocarcinoma [29]. This study included 78 participants divided into two groups. Patients (n = 39) from the first group received a probiotic product containing *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium lactis, Bifidobacterium bifidum, Bifidobacterium breve, Streptococcusthermophilus*. The second group (n = 39) did not consume probiotics. It was observed that the length of postoperative hospitalization was shorter in the probiotic group compared to the rest of the studied patients ($p < 0.05$). Moreover, the authors reported that probiotics are able to reduce postoperative complications, however this effect depends on the localization of the tumor (i.e. *rectum* –33.3% whereas ascending colon –16.7% and sigmoid colon –12.5%) [29]. Complex multidisciplinary anti-cancer treatment should also be focused on improvement of quality of life. In Kaźmierczak-Siedlecka et al., a double-blind, randomized and placebo-controlled trial studied the effects of the bacterial probiotic strain – *L. plantarum* 299v on nutritional status, tolerance of enteral nutrition and quality of life in cancer patients who received home enteral nutrition [30]. This study included 35 patients divided into 2 groups: first received probiotics and the second a placebo for 4 weeks. Probiotic *L. plantarum* 299v was administered in doses of 2 capsules per day (1 capsule contains 10 x ^{10} CFU). After 4 weeks of probiotic supplementation, a statistically significant increase of serum albumin concentration was observed ($p = 0.032$). Additionally, in patients who received probiotics, the frequency of gastrointestinal symptoms, such as flatulence and vomiting, was reduced at week 4 in comparison to the baseline ($p = 0.0117$). Nevertheless, quality of life was improved across both groups of participants [30]. It could be associated with the introduction of enteral nutrition, not only the administration of probiotics/placebo. The effects of enteral nutrition in combination with probiotics was also analyzed in a study by Xie et al., with regards to gastric cancer patients (n = 140; n = 70 probiotics and enteral nutrition; n = 70 received only enteral nutrition) in the postoperative period [31]. It was observed that the incidence of enteral nutrition-related diarrhea was less common in patients who received probiotics. There was no difference between groups regarding nutritional status before and after intervention ($p > 0.05$) [31]. However, this result may be associated with the fact that probiotics were administered only for 8 days.

Oral mucositis is one of the side effects of anti-cancer therapy, which may be induced by chemotherapy and radiotherapy [32]. It is estimated that 40% of head and neck patients will develop oral mucositis 1–2 weeks after starting radiotherapy and 5–10 days after starting chemotherapy [33]. According to other data, it can occur even in 80% of patients treated with high-dose chemotherapy [32]. Oral mucositis is related to low food intake, and, as a consequence, it contributes to weight loss. Recently, in a systematic review and meta-analysis by Liu et al. (n = 708, 8 trials; finally 7 trials were included to meta-analysis) the role of probiotics as a preventive method for oral mucositis induced by anti-cancer treatment was assessed [34]. The incidence of oral mucositis in the probiotic group was significantly low (risk ratio (RR) = 0.84, 95% confidence interval (CI) = 0.77–0.93, $p = 0.0004$) in 3 trials in which Lactobacilli-based probiotics were investigated. Moreover, incidence of severe oral mucositis was significantly lower in patients who received probiotics, which was shown in 7 trials (RR = 0.65, 95% CI = 0.53–0.81, $p < 0.0001$). Therefore, the use of probiotics to limit side effects of anti-cancer treatment, such as oral mucositis, is promising.

In a meta-analysis by Lu et al. (13 trials, n = 1024), it was reported that probiotics are effective in the prevention of diarrhea induced by chemotherapy [35]. Notably, the administration of probiotics reduced both the total rate of diarrhea in these patients and diarrhea grade III–IV, however no statistically significant effect was observed in the case of diarrhea grade I–II [35]. The positive effect of probiotics on reduction of diarrhea associated with chemotherapy was also noted recently in 2023 in Huang et al., where a trial regarding colorectal cancer patients was undertaken (n = 100; n = 50 probiotics, n = 50 placebo) [36]. In this study, gut microbiota using 16S rRNA sequencing and SCFAs in the preoperative period and after the first circle of chemotherapy in the postoperative period were analyzed. Notably, chemotherapy affects gut microbiota causing dysbiotic changes observed by a reduction of microbial diversity and a decrease in the level of Firmicutes. It was noted that probiotics affect not only the composition of gut microbiota but also contribute to the production of SCFAs ($p < 0.0001$) [36]. The stimulation of SCFAs production seems to be significant in colorectal cancer patients. Recently, in 2023, in a study by Kaźmierczak-Siedlecka et al., gut microbiota-derived metabolites in 15 colorectal cancer patients in the preoperative period were analyzed [37]. Stool samples were stored in –80°C and the subsequent analysis of SCFAs was conducted by using gas chromatography. The normal proportion between SCFAs is 3:1:1 for acetate, propionate, butyrate (respectively), but in colorectal cancer patients the abnormal proportion between SCFAs was observed (based on this proportion, in 93.33% of patients the result <1 for butyrate was found) [37]. These results indicate

Table II. Use of probiotics in support of mental health

Aim of the study	Study group	Probiotic strain	Dosage	Outcomes	References
assess the effect of a psychobiotic formulation specifically on well-being	studies included 134 patients	*L. helveticus R00052* and *B. longum R0175*	3 billion CFU once a day (dissolve in a 300 ml glass of water) for 4 weeks	no significant effects of probiotic intake in whole sample outcomes; the linear mixed-effects model showed that the interaction between high scores in Healthy Behaviors and probiotic intake was the single significant predictor of positive effects on anxiety, emotional regulation and mindfulness in post-treatment outcomes	[45] Morales-Torres et. al. 2023
assess the effects of probiotic intake on symptoms of depression and metabolic status in patients with major depressive disorders	studies included 40 patients with major depressive disorder	*L. acidophilus, L. casei, B. bifidum*	6 x 10^9 CFU a day for 8 weeks (in capsules)	beneficial effects on Beck Depression Inventory, insulin, hs-CRP concentrations and glutathione concentrations	[46] Akkasheh et al. 2016
determine the effect of consumption of probiotic supplements (Winclove's Ecologic® Barrier) on depressive symptoms in a sample of participants with mild to severe depression	studies included 71 patients with depressive symptoms	*B. bifidum W23, B. lactis W51, B. lactis W52, L. acidophilus W37, L. brevis W63, L. casei W56, L. salivarius W24, L. lactis W19* and *L. lactis W58*	10^{10} CFU in powder for 8 weeks	after probiotic use participants demonstrated a significantly greater reduction in cognitive reactivity compared with the placebo group	[47] Chahwan et al. 2019
to examine whether the use of probiotic yogurt will have an impact on immune system function and mental and physical disorders caused by stress.	studies included 224 healthy adults	*L. gasseri SBT2055, B. longum SBT2928*	≥5.0 × 10^8 CFU for 12 weeks in yogurt	the NK cell activities of the test yogurt group were higher than those of the placebo yogurt group, and their serum ACTH levels were significantly decreased by the test yogurt	[48] Nishihira et al. 2014
determine the impact *of L. rhamnosus* on stress-related behaviors, physiology, inflammatory response, cognitive performance and brain activity patterns in healthy male participants.	studies included 29 healthy adults	*L. rhamnosus (JB-1)*	1 × 10^9 CFU in capsule for 8 weeks	no significant effects of probiotics on BDI scores. There was no overall effect of probiotic treatment on measures of mood, anxiety, stress or sleep quality	[49] Kelly et al. 2016
evaluate the efficacy and health benefits of the use of a tablet containing *Lactobacillus gasseri CP2305* in healthy young adults	studies included 60 medical students preparing for the exam	*L. gasseri CP2305*	1 x 10^{10} CFU per 2 tablets for 24 weeks	taking probiotics significantly reduced anxiety and sleep disturbance relative to placebo. CP2305 administration attenuated the stress-induced decline of *Bifidobacterium spp.* and the stress-induced elevation of *Streptococcus spp.*	[50] Nishida et al. 2019
determine the effects of *L. acidophilus NCFM* on irritable bowel syndrome symptoms and quality of life	studies included 340 volunteers who were diagnosed with IBS	*L. acidophilus NCFM*	*L. acidophilus NCFM* (ATCC 700,396) high dose (10^{10} CFU) and low dose (10^9 CFU) for 12 weeks	NCFM alleviates moderate to severe abdominal pain, consistent with earlier observations of this strain mitigating visceral pain through increased analgesic receptor expression	[51] Lyra et al. 2016

NK – natural killer; ACTH – adrenocorticotrophic hormone; BDI – beck depression inventory; CFU – colony-forming units

that it is reasonable to consider the administration of butyrate in the preoperative period.

Mental well being

Stress and depressive disorders accompany patients at various stages of cancer. In these cases, an important and safe option to help patients is the use of psychobiotics. Psychobiotics are probiotics that benefit mental health. Due to the high heterogeneity and limited number of studies, as well as the complex and complicated nature of the concept of using psychobiotics (effects on the brain-gut axis), their use, is not a routine procedure. In one of the first meta-analysis [38], a systematic review of existing evidence on the effect of probiotic-based interventions on depressive symptoms was conducted. The meta-analysis showed that probiotics significantly reduced depression scale scores in the study subjects. Psychobiotics had an effect on both the healthy population and patients with depression (MDD). The effect of psychobiotics was observed in the population under 60 years of age, while no effect was confirmed in the elderly. In another meta-analysis McKean et al. [39] showed that psychobiotics reduce subclinical symptoms of depression, anxiety and stress in healthy individuals.

Nikolova et al. [40] published a meta-analysis of studies involving 404 people with depression in which they confirmed that psychobiotics are effective in reducing the symptoms of this illness when administered together with antidepressants, but yet do not appear to be effective in monotherapy. Potential mechanisms of action may take place through an increase in brain-derived neurotrophic factor (BDNF) and a decrease in CRP, although the evidence currently available is quite sparse. Misera et al. [41] evaluated the effect of psychobiotics on psychometric scales in patients with MDD, showing that psychobiotics could alleviate MDD symptoms. Therapy tended to be more depending on the duration of psychobiotic supplementation. Psychobiotics have great potential in the treatment of MDD and they are also a safe form of intervention. One of the best studied bacterial strains in the psychobiotic group are *L. heleveticus* Rosell-52 and *B. longum* Rosell-175. Administration of *L. heleveticus* Rosell-52 to animals exposed to stress has been shown to reduce adhesion of pathogens to intestinal epithelial cells, preventing their translocation and reducing the synthesis of pro-inflammatory cytokines, thereby potentially having a protective effect on limbic system structures exposed to prolonged stress [42]. Clinical studies have shown that administration to healthy individuals of the bacterial strains *L. heleveticus* Rosell-52 and *B. longum* Rosell-175 reduces gastrointestinal discomfort caused by excessive stress [43]. The administration of these bacterial strains has been observed to have a positive effect on the subjects' mood, reduce the severity of anxiety and decrease cortisol excretion. In March 2016, the Canadian Directorate of Non-Prescription Natural and Health Products made the following recommendations for its use: [1] helps relieve general symptoms of anxiety; [2] relieves gastrointestinal symptoms caused by stress; and [3] promotes emotional balance.

Research indicates that psychobiotics may play an important therapeutic role in the treatment of depression and anxiety [44]. Table II summarizes studies focusing on the potential use of probiotics in supporting mental functioning.

Conclusions

There is a link between gut microbiota and the development, prognosis and treatment of cancer. Probiotics can be used in the prevention and treatment of cancer due to their clinical effectiveness and safety. When using probiotics in oncological patients, it is important to take into account the QPS status, novel foods, EFSA opinion, relevant quality, the opinions of scientific bodies and the results of clinical trials to evaluate the balance of benefits and losses. Quality aspects related to the products' manufacture should also be taken into account. This topic undoubtedly requires further research. At the moment, we do not have standards/recommendations for probiotic therapy of oncology patients.

Article information and declarations

Author contributions

Igor Łoniewski – development of the concept of the paper, drafting.
Karolina Kaźmierczak-Siedlecka – development of the concept of the paper, drafting.
Natalia Komorniak – revision of manuscript.
Ewa Stachowska – development of the concept of the paper, drafting and revision of manuscript.
Authorship requires substantial contributions to the development of the concept of the paper, the analysis and interpretation of data and the drafting and revision of manuscript submissions.

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Conflict of interest

None declared

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References:

1. McDonald D, Hyde E, Debelius JW, et al. American Gut Consortium. American Gut: an Open Platform for Citizen Science Microbiome

Research. mSystems. 2018; 3(3), doi: 10.1128/mSystems.00031-18, indexed in Pubmed: 29795809.
2. Picardo SL, Coburn B, Hansen AR. The microbiome and cancer for clinicians. Crit Rev Oncol Hematol. 2019; 141: 1–12, doi: 10.1016/j.critrevonc.2019.06.004, indexed in Pubmed: 31202124.
3. Yang D, Meng XY, Wang Y, et al. Effects of probiotics on gastric cancer-related inflammation: A systematic review and meta-analysis. J Food Biochem. 2022; 46(5): e14034, doi: 10.1111/jfbc.14034, indexed in Pubmed: 35277873.
4. Fenster K, Freeburg B, Hollard C, et al. The Production and Delivery of Probiotics: A Review of a Practical Approach. Microorganisms. 2019; 7(3), doi: 10.3390/microorganisms7030083, indexed in Pubmed: 30884906.
5. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11(8): 506–514, doi: 10.1038/nrgastro.2014.66, indexed in Pubmed: 24912386.
6. Binda S, Hill C, Johansen E, et al. Criteria to Qualify Microorganisms as „Probiotic" in Foods and Dietary Supplements. Front Microbiol. 2020; 11: 1662, doi: 10.3389/fmicb.2020.01662, indexed in Pubmed: 32793153.
7. World Gastroenterology Organisation (WGO) . https://www.worldgastroenterology.org (5.07.2023).
8. Average Research and Development Costs for Pharmaceutical Companies. https://www.investopedia.com/ask/answers/060115/how-much-drug-companys-spending-allocated-research-and-development-average.asp (5.07.2023).
9. Kaczmarczyk M, Szulińska M, Łoniewski I, et al. Treatment With Multi-Species Probiotics Changes the Functions, Not the Composition of Gut Microbiota in Postmenopausal Women With Obesity: A Randomized, Double-Blind, Placebo-Controlled Study. Front Cell Infect Microbiol. 2022; 12: 815798, doi: 10.3389/fcimb.2022.815798, indexed in Pubmed: 35360106.
10. Marlicz W, Yung DE, Skonieczna-Żydecka K, et al. From clinical uncertainties to precision medicine: the emerging role of the gut barrier and microbiome in small bowel functional diseases. Expert Rev Gastroenterol Hepatol. 2017; 11(10): 961–978, doi: 10.1080/17474124.2017.1343664, indexed in Pubmed: 28618973.
11. Nordström EA, Teixeira C, Montelius C, et al. 299v (LP299V): three decades of research. Benef Microbes. 2021; 12(5): 441–465, doi: 10.3920/BM2020.0191, indexed in Pubmed: 34365915.
12. Dogra SK, Doré J, Damak S. Gut Microbiota Resilience: Definition, Link to Health and Strategies for Intervention. Front Microbiol. 2020; 11: 572921, doi: 10.3389/fmicb.2020.572921, indexed in Pubmed: 33042082.
13. Panel EB, Koutsoumanis K, Allende A, et al. The list of QPS status recommended biological agents for safety risk assessments carried out by EFSA [Internet]. Zenodo, 2021. https://zenodo.org/record/4428353 (5.07.2023).
14. Kujawa-Szewieczek A, Adamczak M, Kwiecień K, et al. The Effect of Lactobacillus plantarum 299v on the Incidence of Clostridium difficile Infection in High Risk Patients Treated with Antibiotics. Nutrients. 2015; 7(12): 10179–10188, doi: 10.3390/nu7125526, indexed in Pubmed: 26690209.
15. Dudzicz S, Kujawa-Szewieczek A, Kwiecień K, et al. Reduces the Incidence of Infection in Nephrology and Transplantation Ward-Results of One Year Extended Study. Nutrients. 2018; 10(11), doi: 10.3390/nu10111574, indexed in Pubmed: 30355985.
16. Rannikko J, Holmberg V, Karppelin M, et al. Fungemia and Other Fungal Infections Associated with Use of Saccharomyces boulardii Probiotic Supplements. Emerg Infect Dis. 2021; 27(8): 2090–2096, doi: 10.3201/eid2708.210018, indexed in Pubmed: 34287140.
17. Koutsoumanis K, Allende A, Alvarez-Ordóñez A, et al. Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 13: suitability of taxonomic units notified to EFSA until September 2020. EFSA Journal. 2021; 19(1), doi: 10.2903/j.efsa.2021.6377.
18. Wang YH, Yao N, Wei KK, et al. The efficacy and safety of probiotics for prevention of chemoradiotherapy-induced diarrhea in people with abdominal and pelvic cancer: a systematic review and meta-analysis. Eur J Clin Nutr. 2016; 70(11): 1246–1253, doi: 10.1038/ejcn.2016.102, indexed in Pubmed: 27329608.
19. Hassan H, Rompola M, Glaser AW, et al. Systematic review and meta-analysis investigating the efficacy and safety of probiotics in people with cancer. Support Care Cancer. 2018; 26(8): 2503–2509, doi: 10.1007/s00520-018-4216-z, indexed in Pubmed: 29704110.
20. Gheisary Z, Mahmood R, Harri Shivanantham A, et al. The Clinical, Microbiological, and Immunological Effects of Probiotic Supplementation on Prevention and Treatment of Periodontal Diseases: A Systematic Review and Meta-Analysis. Nutrients. 2022; 14(5), doi: 10.3390/nu14051036, indexed in Pubmed: 35268009.
21. Wan Mohd Kamaluddin WN, Rismayuddin NA, Ismail AF, et al. Probiotic inhibits oral carcinogenesis: A systematic review and meta-analysis. Arch Oral Biol. 2020; 118: 104855, doi: 10.1016/j.archoralbio.2020.104855, indexed in Pubmed: 32801092.
22. Shu Z, Li P, Yu B, et al. The effectiveness of probiotics in prevention and treatment of cancer therapy-induced oral mucositis: A systematic review and meta-analysis. Oral Oncol. 2020; 102: 104559, doi: 10.1016/j.oraloncology.2019.104559, indexed in Pubmed: 31923856.
23. Hungin APS, Mulligan C, Pot B, et al. European Society for Primary Care Gastroenterology. Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice -- an evidence-based international guide. Aliment Pharmacol Ther. 2013; 38(8): 864–886, doi: 10.1111/apt.12460, indexed in Pubmed: 23981066.
24. Wei D, Heus P, van de Wetering FT, et al. Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. Cochrane Database Syst Rev. 2018; 8(8): CD008831, doi: 10.1002/14651858.CD008831.pub3, indexed in Pubmed: 30168576.
25. Skonieczna-Żydecka K, Kaczmarczyk M, Łoniewski I, et al. A Systematic Review, Meta-Analysis, and Meta-Regression Evaluating the Efficacy and Mechanisms of Action of Probiotics and Synbiotics in the Prevention of Surgical Site Infections and Surgery-Related Complications. J Clin Med. 2018; 7(12), doi: 10.3390/jcm7120556, indexed in Pubmed: 30558358.
26. Gan Yu, Su S, Li Bo, et al. Efficacy of Probiotics and Prebiotics in Prevention of Infectious Complications Following Hepatic Resections: Systematic Review and Meta-Analysis. J Gastrointestin Liver Dis. 2019; 28: 205–211, doi: 10.15403/jgld-182, indexed in Pubmed: 31204407.
27. Chen Y, Qi A, Teng D, et al. Probiotics and synbiotics for preventing postoperative infectious complications in colorectal cancer patients: a systematic review and meta-analysis. Tech Coloproctol. 2022; 26(6): 425–436, doi: 10.1007/s10151-022-02585-1, indexed in Pubmed: 35348943.
28. An S, Kim K, Kim MHa, et al. Perioperative Probiotics Application for Preventing Postoperative Complications in Patients with Colorectal Cancer: A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2022; 58(11), doi: 10.3390/medicina58111644, indexed in Pubmed: 36422183.
29. Bajramagic S, Hodzic E, Mulabdic A, et al. Usage of Probiotics and its Clinical Significance at Surgically Treated Patients Sufferig from Colorectal Carcinoma. Med Arch. 2019; 73(5): 316–320, doi: 10.5455/medarh.2019.73.316-320, indexed in Pubmed: 31819304.
30. Kaźmierczak-Siedlecka K, Daca A, Folwarski M, et al. Immunonutritional support as an important part of multidisciplinary anti-cancer therapy. Cent Eur J Immunol. 2020; 45(4): 454–460, doi: 10.5114/ceji.2020.103339, indexed in Pubmed: 33613095.
31. Xie H, Lu Q, Wang H, et al. Effects of probiotics combined with enteral nutrition on immune function and inflammatory response in postoperative patients with gastric cancer. J BUON. 2018; 23(3): 678–683, indexed in Pubmed: 30003737.
32. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, et al. Prevention and Treatment of Chemotherapy and Radiotherapy Induced Oral Mucositis. Medicina (Kaunas). 2019; 55(2), doi: 10.3390/medicina55020025, indexed in Pubmed: 30678228.
33. Bolton L. Managing Oral Mucositis in Patients With Cancer. Wounds. 2021; 33(5): 136–138, indexed in Pubmed: 34370681.
34. Liu YC, Wu CR, Huang TW. Preventive Effect of Probiotics on Oral Mucositis Induced by Cancer Treatment: A Systematic Review and Meta-Analysis. Int J Mol Sci. 2022; 23(21), doi: 10.3390/ijms232113268, indexed in Pubmed: 36362057.
35. Lu D, Yan J, Liu F, et al. Probiotics in preventing and treating chemotherapy-induced diarrhea: a meta-analysis. Asia Pac J Clin Nutr. 2019; 28(4): 701–710, doi: 10.6133/apjcn.201912_28(4).0005, indexed in Pubmed: 31826366.
36. Huang F, Li S, Chen W, et al. Postoperative Probiotics Administration Attenuates Gastrointestinal Complications and Gut Microbiota Dysbiosis Caused by Chemotherapy in Colorectal Cancer Patients. Nutrients. 2023; 15(2), doi: 10.3390/nu15020356, indexed in Pubmed: 36678227.
37. Kaźmierczak-Siedlecka K, Skonieczna-Żydecka K, Palma J, et al. Microbiota-derived metabolites in colorectal cancer patients in preoperative period. Eur Rev Med Pharmacol Sci. 2023; 27(4): 1443–1449, doi: 10.26355/eurrev_202302_31384, indexed in Pubmed: 36876684.

38. Huang R, Wang Ke, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016; 8(8), doi: 10.3390/nu8080483, indexed in Pubmed: 27509521.
39. McKean J, Naug H, Nikbakht E, et al. Probiotics and Subclinical Psychological Symptoms in Healthy Participants: A Systematic Review and Meta-Analysis. J Altern Complement Med. 2017; 23(4): 249–258, doi: 10.1089/acm.2016.0023, indexed in Pubmed: 27841940.
40. Nikolova VL, Cleare AJ, Young AH, et al. Updated Review and Meta-Analysis of Probiotics for the Treatment of Clinical Depression: Adjunctive vs. Stand-Alone Treatment. J Clin Med. 2021; 10(4), doi: 10.3390/jcm10040647, indexed in Pubmed: 33567631.
41. Misera A, Liśkiewicz P, Łoniewski I, et al. Effect of Psychobiotics on Psychometric Tests and Inflammatory Markers in Major Depressive Disorder: Meta-Analysis of Randomized Controlled Trials with Meta-Regression. Pharmaceuticals (Basel). 2021; 14(10), doi: 10.3390/ph14100952, indexed in Pubmed: 34681176.
42. Girard SA, Bah TM, Kaloustian S, et al. Lactobacillus helveticus and Bifidobacterium longum taken in combination reduce the apoptosis propensity in the limbic system after myocardial infarction in a rat model. Br J Nutr. 2009; 102(10): 1420–1425, doi: 10.1017/S0007114509990766, indexed in Pubmed: 19563693.
43. Diop L, Guillou S, Durand H. Probiotic food supplement reduces stress-induced gastrointestinal symptoms in volunteers: a double-blind, placebo-controlled, randomized trial. Nutr Res. 2008; 28(1): 1–5, doi: 10.1016/j.nutres.2007.10.001, indexed in Pubmed: 19083380.
44. Ross K. Psychobiotics: Are they the future intervention for managing depression and anxiety? A literature review. Explore (NY). 2023; 19(5): 669–680, doi: 10.1016/j.explore.2023.02.007, indexed in Pubmed: 36868988.
45. Morales-Torres R, Carrasco-Gubernatis C, Grasso-Cladera A, et al. Psychobiotic Effects on Anxiety Are Modulated by Lifestyle Behaviors: A Randomized Placebo-Controlled Trial on Healthy Adults. Nutrients. 2023; 15(7), doi: 10.3390/nu15071706, indexed in Pubmed: 37049546.
46. Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition. 2016; 32(3): 315–320, doi: 10.1016/j.nut.2015.09.003, indexed in Pubmed: 26706022.
47. Chahwan B, Kwan S, Isik A, et al. Gut feelings: A randomised, triple-blind, placebo-controlled trial of probiotics for depressive symptoms. J Affect Disord. 2019; 253: 317–326, doi: 10.1016/j.jad.2019.04.097, indexed in Pubmed: 31078831.
48. Nishihira J, Kagami-Katsuyama H, Tanaka A, et al. Elevation of natural killer cell activity and alleviation of mental stress by the consumption of yogurt containing Lactobacillus gasseri SBT2055 and Bifidobacterium longum SBT2928 in a double-blind, placebo-controlled clinical trial. J Funct Food. 2014; 11: 261–268, doi: 10.1016/j.jff.2014.09.002.
49. Kelly JR, Allen AP, Temko A, et al. Lost in translation? The potential psychobiotic Lactobacillus rhamnosus (JB-1) fails to modulate stress or cognitive performance in healthy male subjects. Brain Behav Immun. 2017; 61: 50–59, doi: 10.1016/j.bbi.2016.11.018, indexed in Pubmed: 27865949.
50. Nishida K, Sawada D, Kuwano Y, et al. Health Benefits of CP2305 Tablets in Young Adults Exposed to Chronic Stress: A Randomized, Double-Blind, Placebo-Controlled Study. Nutrients. 2019; 11(8), doi: 10.3390/nu11081859, indexed in Pubmed: 31405122.
51. Lyra A, Hillilä M, Huttunen T, et al. Irritable bowel syndrome symptom severity improves equally with probiotic and placebo. World J Gastroenterol. 2016; 22(48): 10631–10642, doi: 10.3748/wjg.v22.i48.10631, indexed in Pubmed: 28082816.

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Review article

Cancer prevention and public health

E-cigarettes – their use and harmfulness. A brief summary of current scientific knowledge

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The consumption of e-cigarettes has rapidly increased in the last years, both worldwide and in Poland, especially among adolescents and youth. Many e-cigarette users also smoke conventional cigarettes ("dual use"). Some researchers argue that e-cigarette vaping, where tobacco burning seems to be eliminated, significantly reduces the number and content of toxic substances when compared to combustible tobacco products. They also underline that consumption of less harmful tobacco and nicotine products can substantially reduce the health consequences of tobacco smoking when the cigarette smoking would be substituted by the e-cigarette use. However, the number of studies that prove negative health consequences of e-cigarette use is steadily increasing. Many carcinogenic, cardiovascular and pulmonary toxic compounds were found in e-cigarettes and, dependently on the patterns of e-cigarette use, their content may increase to the level observed for cigarette smoking. Studies prove that dual use of e-cigarettes and manufactured cigarettes is more risky than cigarette smoking. Therefore, there is an urgent need to regulate e-cigarettes as strictly as tobacco products.

Key words: e-cigarettes, use, harmfulness

There is currently a debate worldwide about whether the increasing consumption of e-cigarettes in many countries may replace the epidemic of traditional cigarette smoking and whether it may reduce the health effects of tobacco smoking.

The e-cigarette consumption and prevalence of e-cigarette use

In the last decade, the global market of e-cigarettes has grown rapidly. According to the World Health Organization (WHO) data, the number of e-cigarette users has increased worldwide from 7 million in 2011 to 68–82 million in 2021 [1]. The fastest increase of e-cigarette consumption has been noticed on the market of so-called disposable e-cigarettes that are no-rechargeable and no-refillable products designed to be used once only. Between 2018 and 2022, the market od disposable cigarettes increased approximately 116%, reaching 22% of the whole global e-cigarette market [2]. In Poland, since e-cigarettes were registered on Polish market, the number of all e-cigarettes consumers rose to 1.5 million and number of disposable e-cigarettes might reach even 100 million sticks in 2023, with over 200% increase since 2022 [3].

Although Poles belong to one of the biggest consumers of e-cigarettes in Europe, the prevalence of e-cigarette use among Polish adults is still much lower than prevalence of cigarette smoking and tends to steadily decline in last years. Results of the 2021 Public Opinion Research Center (Centrum Badania Opinii Społecznej – CBOS) nation-wide survey shows that prevalence of current regular e-cigarette users does not exceed 1% of the total Polish adult population (aged 18 and over) while the proportion of current regular cigarettes smokers among adult Poles reaches 25.1% [4]. However, it should be noted that high proportion of European current e-cigarette

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users (over 50%), including Poles, also simultaneously smoke conventional cigarettes ("dual use") [5, 6].

A much more serious public health problem is the rapid increase in e-cigarette use among adolescents [7], mainly the use of disposable e-cigarettes that are cheaper than other e-cigarettes, aggressively promoted and easily accessible in Internet, and frequently not equipped with any health warnings or information on smoking cessation services [8, 9]. The results of the latest Global Youth Tobacco Survey (GYTS), conducted in Poland in 2022 on nation-wide random sample of 13–15 years old schoolchildren, indicate that 42% of them have ever used e-cigarettes and 22% currently use these products that is over two times bigger proportion when compared with students smoking cigarettes (12%) [10]. Based on results of GYTS and other studies, WHO indicates on high level of dual use of e-cigarettes and smoking of manufactured cigarettes among youth but simultaneously estimates that one third of adolescents who use e-cigarettes have never smoked a conventional cigarette [1, 11, 12]. It shows that e-cigarettes use may serve as a gate to experimentation and, later on, to regular use of tobacco products, including cigarette smoking and contribute to perpetuating the global tobacco epidemic.

The harmfulness of e-cigarette use

Proponents of e-cigarettes argue that e-cigarette vaping, where tobacco burning seems to be eliminated, significantly reduces the number and content of toxic substances when compared to combustible tobacco products [13]. Based on this argument, the 2015 Public Health England report concluded that e-cigarettes are 95% safer than combustible tobacco products, especially cigarettes [14]. The "harm reduction" approach suggests that replacement of the epidemic of cigarette smoking with an epidemic of "smoke-free" e-cigarette use may substantially reduce a number of smoking-attributable diseases, including lung cancer, chronic obstructive pulmonary disease, myocardial infarction or stroke, and, consequently, improve public health [15; see there a debate on the approach].

According to the 2018 US National Academies of Science, Engineering and Medicine's report and recent WHO reports on electronic cigarettes, summarizing the results of the latest reviews of chemical, clinical and epidemiological studies, abovementioned conclusions are inaccurate and based on insufficient evidence [1, 8, 11, 16]. It is pointed out that only a limited range of e-cigarette liquids have been studied so far, and the level of their toxicity varies significantly in individual studies and is dependent on user and device characteristics [11]. It is also emphasized that toxicological monitoring of e-cigarettes is currently very challenging because they are not a subject to as strict regulations in this regard as conventional combustible tobacco products and is too early to fully evaluate the long-term health effects of e-cigarette, in particular for cancer [1, 17].

Nicotine, that is highly psychoactive and addictive substance, is present in e-cigarette liquid in high doses [9, 18]. Prolonged, uninterrupted inhalation of high doses of nicotine may contribute to the risk of poisoning and immediate intoxication [19]. The biggest risk of nicotine intoxication concerns users of disposable e-cigarettes where permitted content of nicotine in e-cigarette liquid (20 mg/ml) is often doubled and the number of puffs (700 to 800) per e-cigarette is the highest [3, 9]. Then an equivalent of nicotine absorbed from e-cigarette equals smoking of 2 to 3 packs of cigarettes per one time unit [11]. High doses of nicotine in e-cigarettes also increase a psychoactive potential of nicotine and impede the effective treatment of nicotine dependence [18]. The higher amount of nicotine in e-cigarettes depends on electrical power generated in the device; increasing the power output of the e-cigarette battery from 3 to 7.5 W may raise the nicotine yield up to five times [8].

According to WHO estimates, e-cigarettes contain the largest number of flavors of all nicotine and tobacco products, especially in disposable e-cigarette devices [8]. Many flavors appeal to young people and some flavors, for example menthol, increase and accelerate nicotine absorption and mask the harshness of nicotine [1, 8, 18]. Flavors contained in e-cigarettes contribute to e-cigarette use initiation, help e-cigarette user switch from experimentation to regular use and from e-cigarette use to cigarette smoking and, finally, make successful quit attempt more difficult [20].

Epidemiological studies show that nicotine may negatively influence on the psychoneurological development of fetus, newborn and small child, especially when woman continue the use of tobacco or nicotine products during pregnancy [1]. It may affect the development of children's and adolescents' brain (changes in so-called nicotine receptors) and increase the risk of nicotine use and dependence during late adolescence or adulthood [19]. There is also an evidence that e-cigarettes are often used as a gate to cigarette and marihuana smoking [11] or are even a vehicle for using soft and heavy drugs such tetrahydrocannabinol (THC), cocaine, heroin or, lastly, fentanyl [21–23].

Results of a number of clinical and epidemiological studies indicate on cardiovascular effects of e-cigarette use. Nicotine may contribute to increased heart rate, blood pressure, increased blood viscosity and the risk of blood clots as well to multiple vasoconstriction and increased risk of blood vessels rupture [18, 19]. It all substantially increases the risk of stroke, pulmonary embolism and heart attack [1, 11].

Although e-cigarette aerosol contains fewer numbers and lower levels of most toxicants that are observed in the smoke of combustible tobacco products, especially in manufactured cigarettes [13], e-cigarettes generate chemical compounds that have carcinogenic properties and are known to cause cancer, even in small, trace doses [11]. Latest investigation indicates that a condensate of disposable e-cigarette aerosol

may enhance the metabolism of benzo(a)pyrene, a strong carcinogen, to genotoxic products in a human oral keratinocyte cell line [24]. Other studies show that prolonged use of e-cigarettes may contribute to overheating the e-cigarette battery and then to the significant increase in the content of some carcinogenic substances such as formaldehyde and benzene even to the level observed in smoked conventional cigarettes [8, 18, 25]. The overheated e-cigarette battery can also explode contributing to serious accidents, injury and burns [1, 19, 26]. Results of the latest clinical studies suggest that e-cigarette use may contribute to the risk of urinary tract cancers since biomarkers of carcinogenic substances responsible for bladder cancer formation were found in the urine of e-cigarette users [27].

A number of clinical and epidemiological studies indicate on pulmonary effects of e-cigarette use [19]. Propylene glycol and glycerin, humectants that are ingredients of e-liquid and effective solvents for nicotine in aerosol, are well known pulmonary irritants when heated in e-cigarettes [28]. Some e-liquid flavors such as diacetyl have also pulmonary toxic properties and when intensively inhaled may lead to bronchiolitis [28]. Intensive puffing of e-cigarette also expose users to higher amounts of carbonyls that contribute to pulmonary disease in smokers [8]. Heating of tetrahydrocannabinol (THC), a marihuana's psychoactive ingredient, when added to e-cigarette liquid (what occurred on broad scale in the United States and in limited extent in Poland), substantially increases the risk of lung injury (defined by the US Food and Drug Administration as EVALI) or even death [28].

The newest analysis of clinical and epidemiological studies, that makes an attempt to summarize previous results of 107 studies and to analyze 124 population-based pooled odds ratios, shows that the odds ratios for cardiovascular disease, stroke and metabolic dysfunction do not differ among e-cigarette users and cigarette smokers, and current dual use of e-cigarettes and conventional cigarettes is associated with 20 to 40% higher odds of almost all health outcomes than for cigarette smoking [29, 30].

Conclusions

The consumption of e-cigarettes has rapidly increased in the last years, both worldwide and in Poland. It especially concerns disposable, one-time use products, and adolescent and youth population. Substantial proportion of e-cigarette users, both among adults and teenagers, also simultaneously smoke cigarettes. For many adolescents, e-cigarettes are a gate to experimentation or regular use of tobacco products or even drug use. And, therefore, tobacco epidemic is rather perpetuating than ending. Despite initial expectations, partly promoted by tobacco industry, partly based on scientific evidence, substitution of tobacco smoking epidemic with the epidemic of e-cigarettes use does not seem to be currently considered as the scientifically justified and the most effective way for reducing the huge health costs of smoking-attributable diseases. The number of studies that prove negative health consequences of e-cigarette use is steadily increasing. Many toxic and carcinogenic compounds were found in e-cigarettes and, although their content is at much lower level than in combustible tobacco products, there is no safe dose for exposure to these chemical agents. In specific conditions such as prolonged, interrupted e-cigarette vaping, overheating the e-cigarette battery or vaping of e-cigarettes from unknown source, their use can be as dangerous as smoking of conventional cigarettes. There is more scientific evidence that dual use of e-cigarettes and manufactured cigarettes is more risky than cigarette smoking.

Therefore, there is an urgent need to regulate e-cigarettes as strictly as cigarettes and other tobacco products in terms of tax and price policy, advertising, promotion and sponsorship, protection from exposure in public places and workplace, labelling and other regulations concerning manufacture, presentation and sale. The complete ban on sale of disposable e-cigarettes that is now considered to be soon enforced in Poland and came already into force or will be enforced in 2024 and 2025 in other countries, including Australia, Belgium, France, Germany, the Netherlands and the United Kingdom, is a next step forward in implementation of comprehensive tobacco control strategy.

Article information and declarations

Author contributions

Krzysztof Przewoźniak – conceptualization, writing – original draft preparation.

Paweł Koczkodaj – conceptualization, writing – review and editing.

Coflict of interest

None declared

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References

1. World Health Organization. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. WHO, Geneva 2021: Geneva.
2. ECigIntelligence. Disposable e-cigarettes: global market overview, May 2022. London 2022. https://ecigintelligence.com/ disposable-e-cigarettes-global-market-overview-may-2022/.
3. Institute of Economic Forecasts and Analyses. A market of disposable e-cigarettes in Poland. Warsaw, February 2024 [in Polish].
4. Center for Research on Social Opinion. Nicotine consumption. A report from quantitative research for the Office of Chemical Substances. Fourth Edition. November 2021 [in Polish].
5. European Commission. Attitudes of Europeans towards tobacco and electronic cigarettes. Report. Special Eurobarometer 506, Brussels 2021.

6. Gallus S, Lugo A, Stival C, et al. TackSHS Project Investigators. Electronic Cigarette Use in 12 European Countries: Results From the TackSHS Survey. J Epidemiol. 2023; 33(6): 276–284, doi: 10.2188/jea.JE20210329, indexed in Pubmed: 34776500.
7. O'Brien D, Long J, Quigley J, et al. Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: a systematic review and meta-analysis. BMC Public Health. 2021; 21(1): 954, doi: 10.1186/s12889-021-10935-1, indexed in Pubmed: 34078351.
8. WHO study group on tobacco product regulation. Report on the scientific basis of tobacco product regulation: ninth report of a WHO study group (WHO Technical Report Series, No. 1047). Geneva: World Health Organization; 2023. https://www.who.int/publications/i/item/9789240079410.
9. Diaz MC, Silver NA, Bertrand A, et al. Bigger, stronger and cheaper: growth in e-cigarette market driven by disposable devices with more e-liquid, higher nicotine concentration and declining prices. Tob Control. 2023 [Epub ahead of print], doi: 10.1136/tc-2023-058033, indexed in Pubmed: 37536928.
10. Centers for Disease Control and Prevention. Global Youth Tobacco Survey. Factsheet. Poland 2022. Office on Smoking and Health, Centers for Disease Control and Prevention 2023.
11. World Health Organization. Call to action to electronic cigarettes. World Health Organization, Geneva 2024.
12. Ollila H, Tarasenko Y, Ciobanu A, et al. Exclusive and dual use of electronic cigarettes among European youth in 32 countries with different regulatory landscapes. Tob Control. 2023 [Epub ahead of print], doi: 10.1136/tc-2022-057749, indexed in Pubmed: 37185883.
13. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014; 23(2): 133–139, doi: 10.1136/tobaccocontrol-2012-050859, indexed in Pubmed: 23467656.
14. McNeill A, Brose L, Calder R, et al. E-cigarettes: an evidence update: a report commissioned by Public Health England. August 2015.
15. Hatsukami DK, Carroll DM. Tobacco harm reduction: Past history, current controversies and a proposed approach for the future. Prev Med. 2020; 140: 106099, doi: 10.1016/j.ypmed.2020.106099, indexed in Pubmed: 32335031.
16. Eaton DL, Kwan LY, Stratton K. (ed.). Public Health Consequences of E--Cigarettes. National Academies of Science, Engineering and Medicine, Washington 2018.
17. Travis N, Knoll M, Cook S, et al. Chemical Profiles and Toxicity of Electronic Cigarettes: An Umbrella Review and Methodological Considerations. Int J Environ Res Public Health. 2023; 20(3), doi: 10.3390/ijerph20031908, indexed in Pubmed: 36767274.
18. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation. 2014; 129(19): 1972–1986, doi: 10.1161/CIRCULATIONAHA.114.007667, indexed in Pubmed: 24821826.
19. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. Med J Aust. 2023; 218(6): 267–275, doi: 10.5694/mja2.51890, indexed in Pubmed: 36939271.
20. Krishnan-Sarin S, O'Malley SS, Green BG, et al. The science of flavour in tobacco products. World Health Organ Tech Rep Ser. 2019; 1015: 125–142, indexed in Pubmed: 36743396.
21. Overbeek DL, Kass AP, Chiel LE, et al. A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults. Crit Rev Toxicol. 2020; 50(6): 531–538, doi: 10.1080/10408444.2020.1794443, indexed in Pubmed: 32715837.
22. Stefaniak AB, LeBouf RF, Ranpara AC, et al. Toxicology of flavoring- and cannabis-containing e-liquids used in electronic delivery systems. Pharmacol Ther. 2021; 224: 107838, doi: 10.1016/j.pharmthera.2021.107838, indexed in Pubmed: 33746051.
23. Jones I. Vapers experimenting with illegal drugs bought on the dark web. New Scientist 2016, December 14. https://www.newscientist.com/article/mg23231045-800-vapers-experimenting-with-illegal-drugs-bought-on-the-dark-web.
24. Sun YW, Kosinska W, Guttenplan JB. E-cigarette Aerosol Condensate Enhances Metabolism of Benzo(a)pyrene to Genotoxic Products, and Induces CYP1A1 and CYP1B1, Likely by Activation of the Aryl Hydrocarbon Receptor. Int J Environ Res Public Health. 2019; 16(14), doi: 10.3390/ijerph16142468, indexed in Pubmed: 31373329.
25. Farsalinos KE, Voudris V, Poulas K. E-cigarettes generate high levels of aldehydes only in ‚dry puff' conditions. Addiction. 2015; 110(8): 1352–1356, doi: 10.1111/add.12942, indexed in Pubmed: 25996087.
26. Brownson EG, Thompson CM, Goldsberry S, et al. Explosion Injuries from E-Cigarettes. N Engl J Med. 2016; 375(14): 1400–1402, doi: 10.1056/NEJMc1608478, indexed in Pubmed: 27705271.
27. Bjurlin MA, Matulewicz RS, Roberts TR, et al. Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer: A Systematic Review. Eur Urol Oncol. 2021; 4(5): 766–783, doi: 10.1016/j.euo.2020.02.004, indexed in Pubmed: 32192941.
28. Cao DJ, Aldy K, Hsu S, et al. Review of Health Consequences of Electronic Cigarettes and the Outbreak of Electronic Cigarette, or Vaping, Product Use-Associated Lung Injury. J Med Toxicol. 2020; 16(3): 295–310, doi: 10.1007/s13181-020-00772-w, indexed in Pubmed: 32301069.
29. Glantz SA, Nguyen N, Oliveira da Silva AL. Population-Based Disease Odds for E-Cigarettes and Dual Use versus Cigarettes. NEJM Evid. 2024; 3(3): EVIDoa2300229, doi: 10.1056/EVIDoa2300229, indexed in Pubmed: 38411454.
30. Pisinger C, Rasmussen SK. The Health Effects of Real-World Dual Use of Electronic and Conventional Cigarettes versus the Health Effects of Exclusive Smoking of Conventional Cigarettes: A Systematic Review. Int J Environ Res Public Health. 2022; 19(20), doi: 10.3390/ijerph192013687, indexed in Pubmed: 36294263.

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Glioblastoma, IDH-wildtype, with oligodendrocyte-like cells – a microscopic challenge

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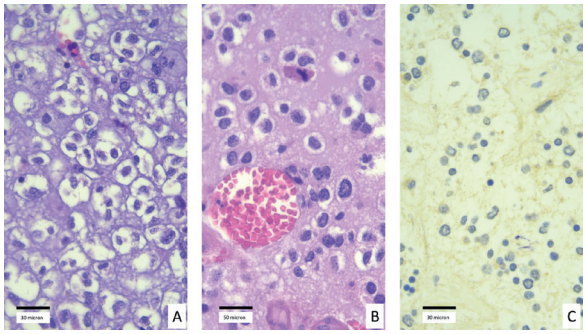

Figure 1. A – photomicrograph (haematoxylin-eosin stain, 40x), showing a neoplasm with oligodendroglioma-like aspects, i.e. round cells with clear perinuclear halos; **B** – photomicrograph (haematoxylin-eosin stain, 60x), where mitosis is evident; **C** – Immunohistochemistry for IDH R132H negative, indicating an IDH-wildtype profile (magnification: 40x)

A 71-year-old woman, who underwent surgery for a meningioma 13 years earlier, presented with an expansive lesion in the left cerebellar hemisphere at her last neuroradiological follow-up check, which was surgically excised. Microscopy showed a glial neoplasm (immunohistochemically positive for GFAP and Olig2) with: increased cellularity, atypia, mitosis and vascular proliferation. Noteworthy, was the presence of numerous round neoplastic cells with a clear perinuclear halo (fig. 1A–B), areas of 'chicken-wire' vascularization and microcalcifications: these constitute the classic histologic features of oligodendroglioma (OG). However, this morphological hypothesis was not supported by the molecular investigations, which instead showed a non-oligodendroglial lineage profile: IDH-wildtype by immunohistochemistry (fig. 1C) and 1p/19q non co-deleted (investigated by FISH method). On the basis of the integration of morpho-molecular data, the definitive diagnosis was therefore that of glioblastoma (GB), IDH-wildtype, with oligodendrocyte-like cells (GBO). GBO is a rare histological pattern of GB, reported in the latest World Health Organization classification of central nervous system tumours of 2021 [1], which should not be misdiagnosed as OG. Although both entities constitute forms of diffuse gliomas, distinguishing GBO from OG is not only a fine histological difference, but also and above all constitutes precise and important clinical-therapeutic information. Indeed, the two neoplasms differ in both their biological behaviour and prognosis, which are worse for GBO [1]. But even more important is the message that increasingly new differences are emerging in the molecular targets of medical therapy of the different types of glioma, some already approved and employed, others still undergoing clinical or laboratory studies [2].

References

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021; 23(8): 1231–1251, doi: 10.1093/neuonc/noab106, indexed in Pubmed: 34185076.
2. Muzyka L, Goff NK, Choudhary N, et al. Systematic Review of Molecular Targeted Therapies for Adult-Type Diffuse Glioma: An Analysis of Clinical and Laboratory Studies. Int J Mol Sci. 2023; 24(13), doi: 10.3390/ijms241310456, indexed in Pubmed: 37445633.

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Cutaneous pseudolymphoma, skin lymphoma or lymphoid papulosis

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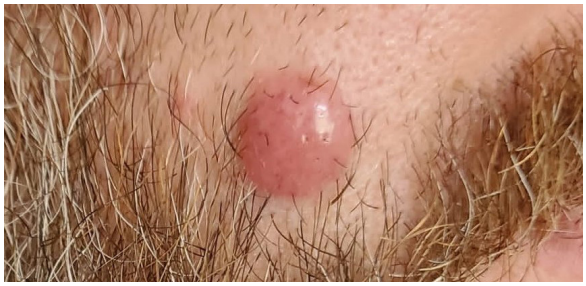

Figure 1. The skin lesion on the right cheek before excision

The terminology and classification of lymphoproliferative skin lesions is complex. It includes multivarious reactive conditions with diversified etiology and clinical picture. The cutaneous pseudolymphoma (PSL) term relates to a group of benign, reactive T- or B-cell lymphocyte-rich infiltrat. It is required to compare clinical presentation with histological findings to reach a correct diagnosis [1]. A wide range of causative agents (e.g. Borrelia, injections, tattoo, scars, arthropod-bite reaction) has been described, but most of the lesions are idiopathic [2]. Lymphomatoid papulosis is a benign, chronic T-cell lymphoma characterized by recurrent, spontaneously regressive papulonodular with tendency to necrotic lesions, often disseminated with histologic features suggestive of a CD30-positive lymphoma [3].

A 34-year-old male with a 12 mm firm lump on the right cheek without any specific signs or symptoms was referred by dermatologist with suspicion of cutaneous lymphoma, sarcoidosis or facial granuloma (fig.1). An incisional skin biopsy was nondiagnostic. The subsequent excisional biopsy indicated an ambiguous picture composed of a mixed population of lymphocytes with a predominance of small cells and the presence of histiocytes. Immunochemistry revealed a mixed population of T (CD3+) and B (CD20+) lymphocytes and a few small CD30+ lymphocytes (activated B and T lymphocytes with some atypic cells). Ki-67 proliferation index was 20–30%. The final pathology report revealed polimorphic lymphoid infiltration of T and B cell lines with the presence of atypical forms with immunoblast and centroblast morphology as well as single cells with multilamellar nuclei. Due to the lack of a granulocytic components, facial granuloma was excluded. A wide local excision of the residual lesion with the surrounding skin was undertaken. Preliminary pathology was suggestive of cutaneous pseudolymphoma, but the profound final pathology report was inconclusive, with a suggestion of either lymphoma or lymphomatoid papulosis, and a recommendation of further immunochemical analyses and incorporation of data from history and clinical picture.

The presented case illustrates the complexity of lymphoproliferative skin lesion diagnostics and the frequent lack of possibility in setting a final diagnosis despite all the available methods used.

References

1. Romero-Pérez D, Blanes Martínez M, Encabo-Durán B. Cutaneous Pseudolymphomas. Actas Dermosifiliogr. 2016; 107(8): 640–651, doi: 10.1016/j.ad.2016.05.003, indexed in Pubmed: 27289134.
2. Ploysangam T, Breneman DL, Mutasim DF. Cutaneous pseudolymphomas. J Am Acad Dermatol. 1998; 38(6 Pt 1): 877–95; quiz 896, doi: 10.1016/s0190-9622(98)70154-9, indexed in Pubmed: 9631994.
3. Toumi A, Fazal S, Litaiem N. Lymphomatoid Papulosis. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL) 2024 Jan. 2023 May 22.

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