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Increased prevalence of pancreatic neuroendocrine microadenomas in patients with intraductal papillary mucinous neoplasms – yet another example of exocrine-neuroendocrine interaction?

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Introduction. Intraductal papillary mucinous neoplasms (IPMN) and neuroendocrine tumours (NET) may develop simultaneously in the pancreas. Neuroendocrine microadenomas (NMA) are precursor lesions for NET. The study aimed to determine the prevalence of NMA/NET in patients with IPMN in a series of resection specimens.

Material and methods. Some 232 prospectively gathered specimens were included and examined histopathologically: 51 IPMN, 114 conventional pancreatic ductal carcinomas (PDAC) and 67 ampullary carcinomas (AMPCA).

Results. NET were rare in the study samples (single cases among IPMN and AMPCA, and two cases among PDAC). In contrast, NMA were frequently found in IPMN specimens when compared to samples of PDAC and AMPCA (27.45%; 7.89%, and 7.46%, respectively, $p < 0.001$). Two NMA in IPMN group were related to ducts, but no case of composite (clonal) IPMN/NMA was found.

Conclusions. IPMN specimens were enriched in NMA but not in NET. IPMN/NMA association may serve as a model of exocrine-neuroendocrine interaction.

Key words: pathology, pancreas, pancreatic neoplasms, pancreatic intraductal neoplasms, islet-cell adenoma

Introduction

Intraductal papillary mucinous neoplasms (IPMN) are macroscopically detectable epithelial proliferations within the pancreatic ductal system, which may progress to invasive ductal carcinomas. Neuroendocrine tumours (NET) of the pancreas are usually slow-growing neoplasms, which are sometimes associated with symptoms of hormone secretion sydromes. Neuroendocrine microadenomas (NMA) are defined as pancreatic non-functioning neuroendocrine neoplasms of less than 5 mm in diameter. NMA are considered precursor lesions for NET [1].

Some investigators hypothesized that pancreatic NET may preferentially develop in patients with IPMN (or *vice versa*), so IPMN and NET may be found simultaneously in the pancreata at higher rate than expected. This suggested that IPMN/NET coexistence could be not necessarily accidental [2]. However, literature data on IPMN/NET association are limited [2–15].

Importantly, IPMN and NET may coexist as independent tumours within the pancreas separated by parenchymal tissue or they may form a single lesion [4]. The latter usually develops as a collision tumour, i.e. it consists of topographically related components of most likely independent origin

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without shared molecular alterations [14]. Recently, several investigators showed that IPMN and NET components within a single IPMN/NET mass may in fact share a molecular profile [13, 14]. This observation served as proof of a common origin of both components in some very rare IPMN/NET cases (so-called composite tumours) [13, 14]. Management of patients with IPMN/NET is not well established. Possibly they should be managed as it is indicated by the nature of each tumour component separately [7].

The purpose of the study was to determine the prevalence of NMA/NET in patients with IPMN in a large single-centre histopathological series of pancreatic resection specimens. For comparative purposes, specimens of patients with conventional pancreatic ductal carcinomas (PDAC) as well as ampullary carcinomas (AMPCA) were taken. The study was designed aiming to exhibit whether IPMN may favour the development of NMA/NET within pancreas. Additionally, the study focused on the microscopical appearance of IPMN/NET lesions/components in the context of potential relatedness of both entities.

Material and methods

Histopathological data on nearly consecutive in-house cases of IPMN of the pancreas diagnosed in resection specimens in the author's institution between July 2015 and March 2021 were retrieved from a prospective database of pancreatic resection samples. Samples of conventional PDAC (i.e. not derived from IPMN) diagnosed between January 2017 and March 2021 as well as samples of AMPCA diagnosed between July 2015 and March 2021 were taken for comparative purposes. Cases were qualified into particular study groups based on histopathological diagnosis of the primary lesion, i.e. a mass which was the main indication for surgery [3].

A small number of cases encountered in the study period were excluded from the study for several reasons (e.g. specimens obtained following neoadjuvant therapy, rare specimens examined using only representative tissue sections due to technical/billing reasons, enucleation/limited resection specimens, specimens obtained in palliative resections, rare cases dissected by other pathologists).

Importantly, the present study was based on a standardized histopathological examination of surgical specimens. All included cases were macroscopically and microscopically examined by a dedicated pathologist (this author) in a standardized fashion, i.e. entire resected pancreatic tissue was taken for microscopical examination irrespective of its gross appearance. Pancreaticoduodenectomy specimens were processed using Leeds Pathology Protocol.

Histopathological diagnoses were established based on the WHO 2019 criteria [1]. Diagnoses established before 2019 were re-assessed for the purpose of the study. In particular, NMA was defined as a clinically-silent neuroendocrine proliferation less than 5 mm in diameter, and additionally:

- demarcated from pancreatic parenchyma by fibrous (pseudo)capsule, and/or
- having trabecular/solid architecture, and/or
- showing abundant stroma, and/or
- presenting with altered distribution of pancreatic hormones in immunohistochemical (IHC) studies [1].

An effort was made to distinguish NMA from its mimickers: islet aggregations and (pseudo)hyperplasia. In brief, islet aggregations are typically found in severely atrophic parenchyma, do not show expansive growth and/or trabecular tissue composition and usually retain topographical distribution of expression of pancreatic hormones (albeit an increase of glucagon-producing cells and a reduction of insulin-producing cells are allowed). Islet hyperplasia is a diffuse enlargement of islets (with or without cytological alterations in endocrine cells), which usually involves the entire pancreas and frequently results in clinical symptoms. Size, shapes as well as hormone distribution patterns of pancreatic islets in hyperplasia are altered. Islet pseudohyperplasia involves typically uncinate process and it is asymptomatic. In selected cases, hormone immunostains were helpful for differential diagnosis of NMA. Lack of expression or overexpression of a particular hormone, or abnormal distribution of pancreatic hormones within a lesion favoured NMA over reactive endocrine proliferations [15–17].

For comparison of continuous variables, Kruskal–Wallis ANOVA or Mann–Whitney U tests were used, as appropriate. Ordinal/nominal variables were compared using Chi^2 tests. Statistical significance was set up at $p \leq 0.05$.

The Institutional Review Board permitted to perform the present observational study without full review, which is necessary for interventional studies on humans, according to national regulations.

Results

Study groups

Some 232 resection specimens were included in the study: 51 cases of IPMN (with or without coexistent invasive carcinomas), 114 cases of PDAC and 67 cases of AMPCA. Invasive adenocarcinomas were found in 51% of samples with IPMN. Gastric and intestinal IPMN subtypes were most prevalent. Conventional tubular adenocarcinoma was the most common histological type among invasive carcinomas associated with IPMN (58%), PDAC (91%), and AMPCA (91%), as expected. All but one invasive cancers coexistent with IPMN were interpreted as derived from IPMN, a single sample was considered equivocal (i.e. it was not clear if invasive cancer was related pathogenetically to IPMN, as described below). Invasive cancers associated with IPMN as well as AMPCA were significantly smaller than conventional PDAC (median 17 mm *vs.* 15 mm *vs.* 31.5 mm, respectively, $p < 0.001$). Not surprisingly, the primary tumour stage and frequency of metastases in regional lymph nodes were lower in carcinomas derived from IPMN in comparison to PDAC. IPMN-related cancers were also enriched in G1 tumours.

There were also some differences related to types of specimens examined within study groups: the majority of conventional PDAC were found in pancreaticoduodenectomy specimens, and total pancreatectomies were performed mainly due to IPMN, as expected. Importantly, median numbers of tissue blocks examined per specimen were similar across study groups ($p = 0.199$). Details on demographical and histopathological characteristics of study populations were described in table I.

NMA/NET in the study groups

A single case of NET was found in the IPMN group (prevalence of 1.96%). This was a 7-mm incidentally detected, non-functional and presumably sporadic G1 tumour in a 61-year-old man treated with total pancreatectomy due to diffuse low-grade gastric mixed-duct type IPMN of the pancreatic head (formerly IPMN with moderate grade dysplasia). Additionally, a 3-mm focus of invasive G1 adenocarcinoma in close association with non-dilated duct of the pancreatic tail with high-grade pancreatic intraepithelial neoplasia was found. It was not clear if invasive cancer was pathogenetically related to IPMN, as dysplastic lesions of various grades were found in many dilated/non-dilated ducts within the pancreas. NET was seen in the pancreatic head, and it was composed of trabeculae in sclerotic stroma. NET extended focally to the peripancreatic adipose tissue, but perineural/vascular invasion was absent. NET was not associated topographically with IPMN (not shown). Additionally, three IPMN-independent NMA were found in the pancreatic head.

Two NET cases and a single NET case were found in patients with PDAC (2/114; 1.75%) and AMPCA (1/67; 1.49%), respectively. The frequencies of NET did not differ across all three study groups (IPMN *vs.* PDAC *vs.* AMPCA; $p = 0.981$).

These numbers contrasted with a prevalence of NMA, which were found in a larger proportion of IPMN cases (14/51; 27.45%), in comparison to PDAC cases (9/114; 7.89%) and AMPCA cases (5/67; 7.46%). That difference was statistically significant ($p < 0.001$) and the odds ratio for NMA in IPMN *versus* NMA in PDAC was 4.41 (95% CI; 1.61–12.49), whereas the odds ratio for NMA in IPMN *versus* NMA in AMPCA was 3.85 (95% CI; 1.24–13.17).

Enrichment of the IPMN group in NMA also resulted in larger proportion of NMA/NET counted in aggregate in specimens with IPMN (27.45%) in comparison to PDAC (8.77%) and AMPCA samples (8.96%, $p = 0.002$). Frequencies of NMA/NET across the study populations were summarized in table II.

IPMN with and without coexisting NMA/NET

Patients treated with pancreatic resections due to IPMN with and without NMA/NET (i.e. in essence: with/without NMA) did not differ in terms of their age and sex. Interestingly, NMA/NET in the IPMN group were somewhat frequent in distal pancreatecomy samples (5/16) and total pancreatecomy samples (8/19) in comparison to pancreaticoduodenectomy specimens (1/14 samples), but that difference did not reach statistical significance ($p = 0.086$). Coexistent NMA/NET was a rare finding when IPMN was localized in the pancreatic head (1/22), but frequent when IPMN diffusely involved the entire pancreas (8/12) ($p < 0.001$). The histological type of IPMN, the grade of dysplasia, or the presence of invasive cancer did not affect the prevalence of NET/NMA in patients with IPMN. However, NMA/NET were more likely to be found in IPMN samples with limited invasion ($p = 0.007$). The prevalence of NMA/NET in IPMN samples was not biased by the volume of resected pancreatic tissue ($p = 0.527$). Histopathological characteristics of IPMN with and without NMA/NET were compared in table III.

NMA in the IPMN group – histopathological characteristics

NMA were found in 14 specimens showing all grades and histological types of IPMN. The number of NMA per specimen ranged from 1 to 6 (median 1). Diameter of NMA ranged from 0.5 mm to 3.8 mm. In 8/14 cases NMA were found in the distal pancreas, in 5/14 – in the pancreatic head, in a single case NMA were found in both segments of the pancreas. NMA were localized within atrophic lobules in a half of IPMN samples. Direct connection of NMA and ducts was found in only two NMA across all the 14 IPMN samples with NMA:

- in a single case (sample no. 10), 3.8 mm NMA did not have a connection with IPMN (fig. 1A), but encircled a small duct and showed partial intraductal spread (fig. 1B). The lesion was synaptophysin-positive (fig. 1C and fig. 1D), chromogranin-A-positive (not shown), but did not express serotonin (not shown). Ki-67 was weakly positive in just several tumour cells (not shown),
- in another case (sample no. 13) 2.5 mm NMA was localized in atrophic lobule surrounded by IPMN lesion (fig. 2A and 2B). NMA was chromogranin-A-positive (not shown), synaptophysin-positive (not shown), glucagon-positive (fig. 2C), and insulin-negative (fig. 2D). The Ki-67 proliferative index was 1% (not shown).

Other NMA did not develop within IPMN (as reported previously in composite IPMN/NET tumours [13, 14]), and did not have a direct connection with ductal epithelium. Representative examples of some NMA are depicted in fig. 3. Histopathological details of NMA/NET in samples with IPMN are presented in table IV.

Type of resection specimens as a potential confounding factor

As described above, NMA/NET in IPMN specimens were found mainly in distal pancreatectomy and total pancreatectomy samples rather than in pancreaticoduodenectomy samples. This may suggest a systematic bias, as distal pancreas was infrequently resected in patients with PDAC/AMPCA (tab. I). However, distal pancreatectomy specimens with IPMN were

Table I. Clinico-pathological characteristics of the study cases

Characteristic	IPMN	Ductal carcinoma	Ampullary carcinoma	p value
no. of cases	51	114	67	NA
age in years – median (interquartile range)	66.5 (62–72)	66 (61–72)	67 (60–71)	0.756[a]
sex (male : female)	19 : 32	55 : 59	35 : 32	0.252[b]
surgery (PD : DP : TP : other)	14 : 16 : 19 : 2	83 : 30 : 1 : 0	65 : 0 : 2 : 0	<0.001[b]
tumor localization (head : distal pancreas : diffuse involvement)	22 : 17 : 12	84 : 30 : 0	67 : 0 : 0	<.001[b]
grade of dysplasia / presence of invasion: low-grade high-grade[c] invasive carcinoma[d]	 8 17 26	only invasive tumors	only invasive tumors	NA
histological type of IPMN (based on predominant pattern): gastric intestinal pancreato-biliary oncocytic ITPN	 27 12 7 4 1	NA	NA	NA
diameter of invasive tumor in mm – median (interquartile range)	17 (3–35)	31.5 (25–38)	15 (12–25)	<0.001[a]
grade of invasive tumor: G1 G2 G3 G4	 17 5 4 0	 16 73 21 4	 11 37 19 0	<0.001[b]
histological type of invasive tumor: tubular colloid adenosquamous MINEN[e] mixed	 15 9 0 0 2[f]	 104 0 5 1 4[g]	 61 1 3 2 0	<0.001[b]
primary tumor stage:[h] pT1a pT1b pT1c pT2 pT3 pT3a pT3b pT4	 9 1 4 7 5 NA NA 0	 0 1 9 76 23 NA NA 5	 4 13 NA 9 NA 8 33 0	<0.001[b, i]
regional nodal status:[h] pN0 pN1 pN2	 20 3 3	 14 28 72	 24 23 20	<0.001[b]
distant metastases:[h] cM0 cM1/pM1	 26 0	 105 9	 67 0	0.022[b]
overall number of tissue block – miedian (interquartile range)	48 (34–69)	50 (43–61)	54 (47–61)	p = 0.199[a]
overall number of tissue block containing pancreas – median (interquartile range)	40 (30–61)	39 (33–45)	43 (37–50)	p = 0.072[a]

DP – distal pancreatectomy; IPMN – intraductal papillary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; NA – not applicable; PD – pancreatoduodenectomy; TP – total pancreatectomy; [a] Kruskal–Wallis ANOVA test; [b] chi² test; [c] including cases of IPMN with concomitant high-grade pancreatic intraepithelial neoplasia (in the same specimen); [d] invasive carcinoma associated with IPMN or invasive carcinoma concomitant with IPMN (in the same specimen); [e] mixed neuroendocrine-nonneuroendocrine neoplasm; adenocarcinoma and large cell neuroendocrine carcinoma; [f] invasive carcinoma with both tubular and colloid differentiation; [g] adenocarcinoma/adenosquamous carcinoma with a component of undifferentiated carcinoma; [h] for invasive tumors only; according to American Joint Committee on Cancer 8th edition staging criteria (2017); [i] for statistical analysis, cases pT1a + pT1b + pT1c were grouped as pT1 category, and cases pT3a + pT3b were grouped as pT3 category

Table II. Neuroendocrine tumors / neuroendocrine microadenomas found in the study specimens

Number of cases	IPMN	Ductal carcinoma	Ampullary carcinoma	p value (chi^2 tests)
with neuroendocrine tumors	1/51 (1.96%)	2/114 (1.75%)	1/67 (1.49%)	p = 0.981
with neuroendocrine microadenomas	14/51 (27.45%)	9/114 (7.89%)	5/67 (7.46%)	p < 0.001
overall number of cases with neuroendocrine tumors and/or neuroendocrine microadenomas	14/51 (27.45%)	10/114 (8.77%)	6/67 (8.96%)	p = 0.002

IPMN – intraductal papillary mucinous neoplasm

Table III. Comparison of IPMN with and without coexisting NMA/NET

Characteristic	IPMN with NET/NMA	IPMN without NET/NMA	p value
no. of cases	14	37	
age in years – median (interquartile range)	65.5 (62–70)	68 (62–72)	0.619[a]
sex (male : female)	4 : 10	15 : 22	p = 0.430[b]
surgery (PD : DP : TP : other)	1 : 5 : 8 : 0	13 : 11 : 11 : 2	p = 0.121[b]
localization of IPMN (head : distal pancreas : diffuse involvement)	1 : 5 : 8	21 : 12 : 4	p < 0.001[b]
grade of dysplasia / presence of invasion: low-grade high-grade[c] invasive carcinoma[d]	 3 5 6	 5 12 20	p = 0.709[b]
histological type of IPMN (based on predominant pattern): gastric intestinal pancreato-biliary oncocytic ITPN	 10 1 1 1 1	 17 11 6 3 0	p = 0.152[b]
diameter of invasive tumor in mm – median (interquartile range)	3 (3–4)	25 (8.5–38.5)	0.007[a]
grade of invasive tumour: G1 G2 G3 G4	 5 1 0 0	 12 4 4 0	0.447[b]
histological type of invasive tumor: tubular colloid adenosquamous mixed	 5 1 0 0	 10 8 0 2[e]	0.330[b]
primary tumor stage:[f] pT1a pT1b pT1c pT2 pT3 pT4	 5 0 1 0 0 0	 4 1 3 7 5 0	0.055[b]
regional nodal status:[f] pN0 pN1 pN2	 6 0 0	 14 3 3	0.310[b]
distant metastases:[f] cM0 cM1	 6 0	 20 0	NA
overall number of tissue block – miedian (interquartile range)	55.5 (34–71)	48 (34–66)	0.627[a]
overall number of tissue blocks containing pancreas – median (interquartile range)	46.5 (33–66)	40 (30–59)	0.527[a]

DP – distal pancreatectomy; IPMN – intraductal papiallary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; NA – not applicable; NET – neuroendocrine tumor; NMA – neuroendocrine micoradenoma; PD – pancreatoduodenectomy; TP – total pancreatectomy; [a] Mann–Whitney U test; [b] chi^2 test; [c] including cases of IPMN with concomitant high-grade pancreatic intraepithelial neoplasia (in the same specimen); [d] invasive carcinoma associated with IPMN or invasive carcinoma concomitant with IPMN (in the same specimen); [e] invasive carcinoma with both tubular and colloid differentiation; [f] for invasive tumours only; according to American Joint Committee on Cancer 8th edition staging criteria (2017)

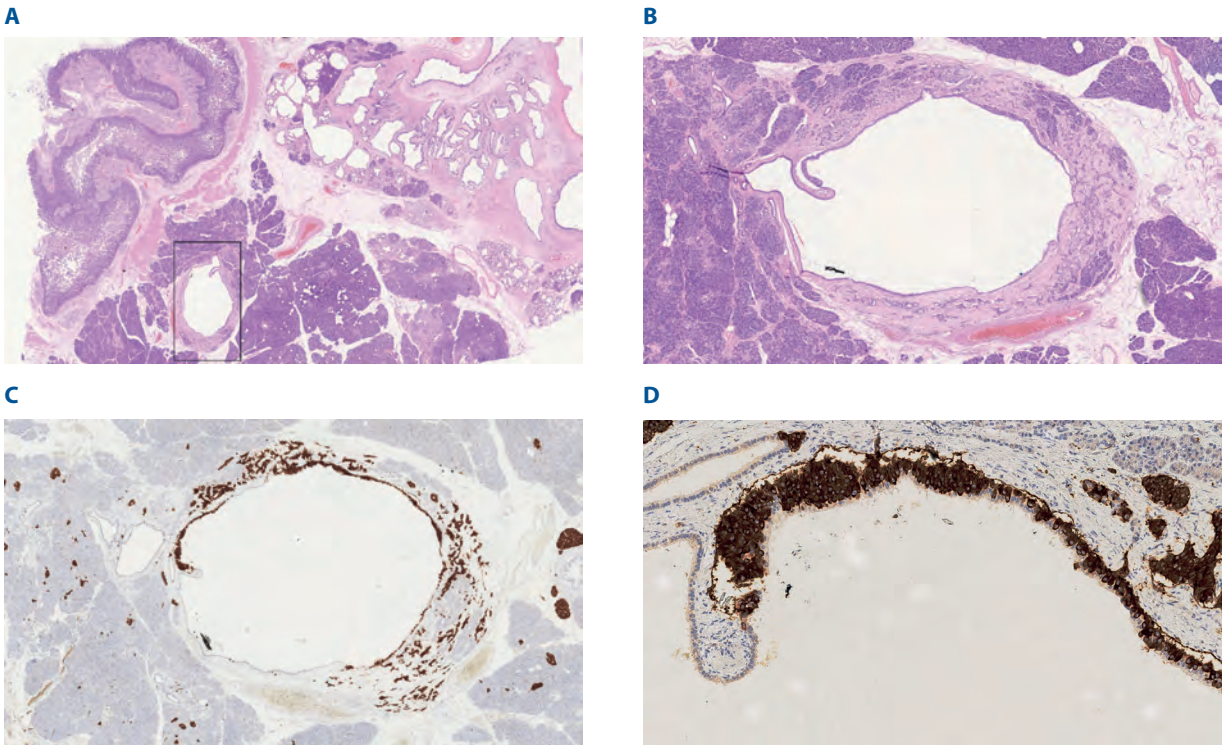

Figure 1. Neuroendocrine microadenoma (NMA) of the pancreas with partial intraductal spread but without direct contact with intraductal papillary mucinous neoplasm (IPMN) (sample no. 10). **A** – NMA surrounding small duct (lower left of the image, lesion indicated by a rectangle) without direct relationship with IPMN (upper right of the image); **B** – partial intraductal spread of the NMA is seen at higher magnification; **C** and **D** – NMA showed chromogranin-A (not shown) and synaptophysin expression; **D** – note synaptophysin-negative ductal cells above intraductal spread of neuroendocrine cells. Magnifications: fig. 1A (1.25×), 1B (5×), 1C (5×), 1D (30×)

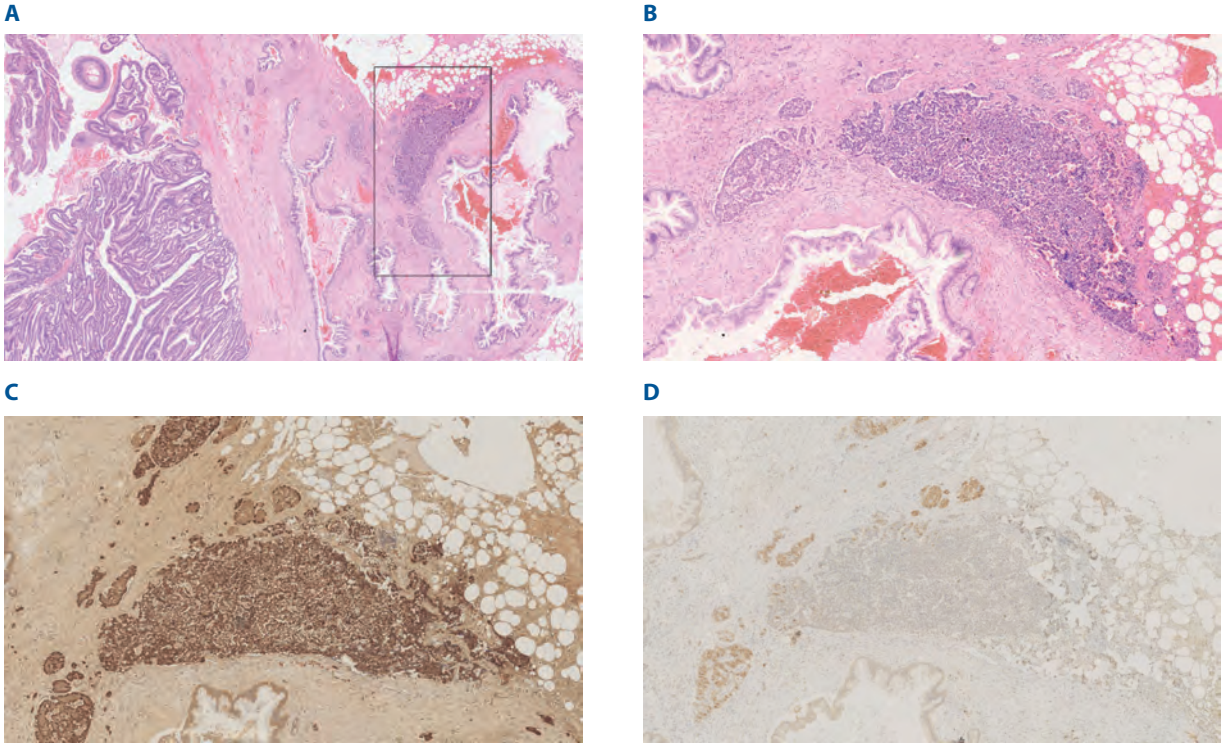

Figure 2. Neuroendocrine microadenoma (NMA) in the atrophic pancreatic lobule surrounded by intraductal papillary mucinous neoplasm (IPMN) (sample no. 13). **A** and **B** – lesion indicated b a rectangle – NMA was found in an atrophic lobule surrounded by gastric-type IPMN with partial intraductal tubular adenoma growth (not shown); **C** – NMA was glucagon-positive; **D** – NMA was insulin-negative, and such hormone expression pattern excluded diagnosis of islet aggregation; note insulin-positive cells in residual islets of the atrophic lobule. Magnifications: fig. 2A (3.5×), 2B (10×), 2C (10×), 2D (10×)

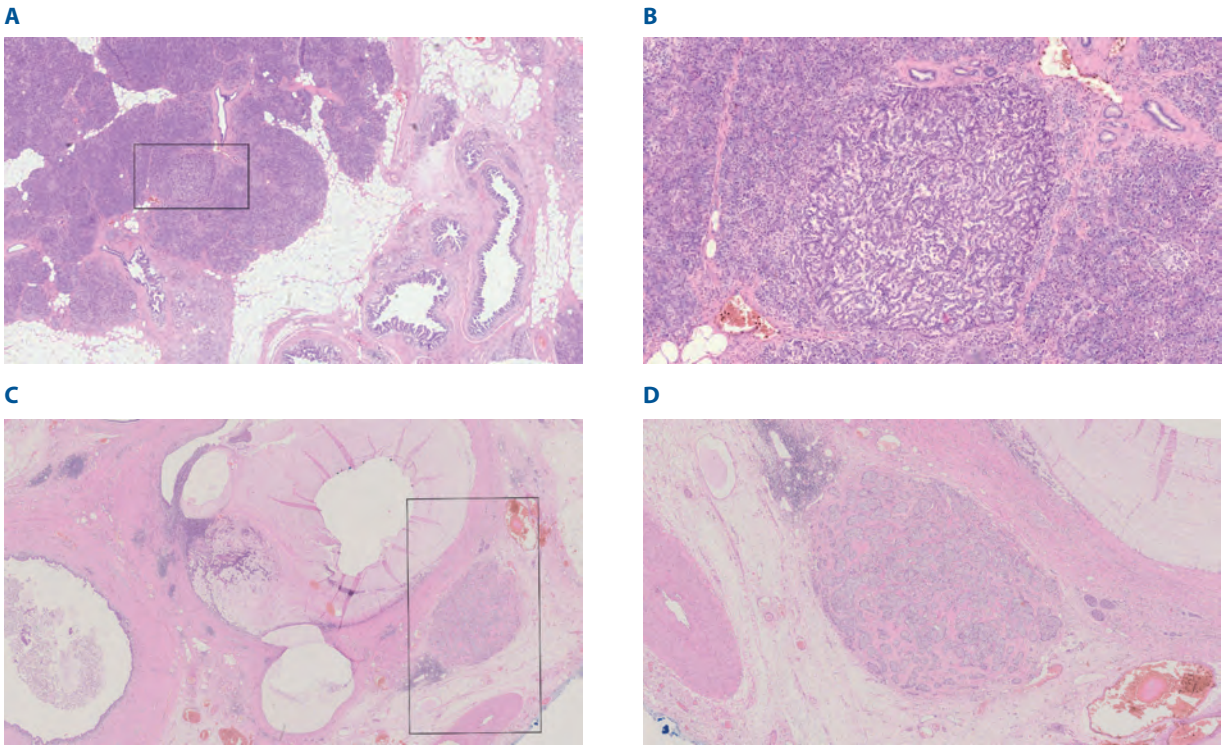

Figure 3. Neuroendocrine microadenomas (NMA) in other pancreatic specimens with intraductal papillary mucinous neoplasm (IPMN). **A** and **B** – conventional NMA (indicated by a rectangle) in pancreatic parenchyma without relationship to IPMN; another NMA (indicated by a rectangle) in pancreas with extensive atrophy. **C** and **D** – NMA was next to a duct with mucin leakage. NMA was chromogranin A-positive (not shown) and synaptophysin-positive (not shown). Magnifications: fig. 3A (3×), 3B (15×), 3C (2×), 3D (5×)

enriched in NMA (5/16; 31.25%) in comparison to distal pancreatectomy specimens with PDAC (3/30; 10%). The difference was not significant (p = 0.070), possibly due to the limited number of distal pancreatectomy samples. Prevalence of NMA/NET in pancreaticoduodenectomy specimens did not differ across the three study groups (p = 0.964).

Discussion

The present study has shown that pancreata with IPMN may be enriched in neuroendocrine neoplasms. In particular, NMA were found in 27% of IPMN specimens. The majority of NMA were found in distal pancreas, and distal pancreatectomies performed due to IPMN were specifically enriched in NMA in comparison with PDAC specimens. However, NMA in IPMN specimens were usually solitary lesions. Microadenomatosis (i.e. multiple, usually uncountable NMA [1]) was not found in any case. No case showed a histopathological picture suggestive of composite IPMN/NET(NMA), as NMA/NET tissue was not in direct contact with IPMN.

NMA/NET prevalence

The results of the study should be interpreted in the context of "baseline" prevalence of NMA/NET in the population. The real incidence of NMA/NET is difficult to estimate, since only a fraction of them come to clinical attention due to symptoms or as asymptomatic "incidentalomas" found during diagnostic/radiologic examinations performed for other reasons. Incidence of clinically-detected pancreatic NET has increased substantially during the last decades [18], but it is still below rates based on autopsy studies [16]. In their autopsy study, Kimura et al. found NMA/NET in 6/60 (10%) totally embedded pancreata and in 12/738 (1.6%) pancreata examined by representative tissue sections [16]. In other autopsy studies, the frequency of pancreatic NET ranged from 0 to 1.4% (as reviewed in [16] and [19]). The prevalence of NMA/NET in retrospective clinical-histopathological studies ranged from 1.4% [15] to 4% [3].

In the present study, the prevalence of NMA/NET in the "control" groups (i.e. PDAC and AMPCA) was between 7 and 9%. These numbers were close to the autopsy-based results in totally embedded pancreata (10%) [16]. Therefore, it can be assumed that the baseline frequency of NET/NMA under the chosen diagnostic approach is probably somewhere around 7–10%. It should be emphasized that the majority of NMA/NET are self-limiting lesions of little clinical significance [3]. However, some rare NMA may have the potential for malignant behaviour [15]. In 2023, the WHO classification of NMA will be renamed as neuroendocrine microtumours as they may very rarely metastasize to the lymph nodes [20].

It should also be kept in mind that the prevalence of NMA in surgical specimens is strongly related to numerous laboratory factors:

- volume of pancreatic tissue available for analysis,

Table IV. Histopathological characteristics of IPMN coexisting with NMA/NET neoplasms

IPMN											Neuroendocrine microadenoma							Neuroendocrine tumor				
no.	procedure	localization	diameter [mm]	histological type	dysplasia in IPMN	invasion	size of invasive carcinoma [mm]	type of invasive carcinoma	grade of invasive carcinoma	staging	number	localization	diameter [mm]	contact with duct or IPMN	localization in atrophic lobule	number	localization	diameter [mm]	grading	staging	connection with duct or IPMN
1.	TP	diffuse	diffuse	G	L	Y [1]	3	T	1	T1aN0M0	3	head	1 [2]	N	Y [3]	1	head	7	1	T1N0M0	N
2.	DP	distal	25	G	H	Y	3	T	1	T1aN0M0	1	distal	1.2	N	N	–	–	–	–	–	–
3.	DP	distal	10	G	L	N	–	–	–	–	1	distal	0.5	N	N	–	–	–	–	–	–
4.	DP	distal	20	G	L	N	–	–	–	–	1	distal	0.7	N	N	–	–	–	–	–	–
5.	TP	diffuse	diffuse	G	L	N	–	–	–	–	1	distal	0.5	N	N	–	–	–	–	–	–
6.	TP	diffuse	diffuse	O	H	N	–	–	–	TisN0M0	1	distal	0.6	N	Y	–	–	–	–	–	–
7.	PD	head	18	ITPN	H	Y	4	T	1	T1aN0M0	2	head	2 [2]	N	N	–	–	–	–	–	–
8.	TP	diffuse	diffuse	I	H	N	–	–	–	TisN0M0	6	head and distal	0.5–3	N	Y [3]	–	–	–	–	–	–
9.	TP	diffuse	diffuse	G	L	N	–	–	–	TisN0M0 [4]	5	distal	0.5–1	N	N	–	–	–	–	–	–
10.	TP	diffuse	diffuse	G	H	Y	3	T	2	T1aN0M0	1	head	3.8	Y[5]	Y	–	–	–	–	–	–
11.	TP	diffuse	diffuse	G	H	Y	1	C	1	T1aN0M0	1	head	0.6	N	N	–	–	–	–	–	–
12.	TP	diffuse	diffuse	G	H	N	–	–	–	TisN0M0	1	head	0.6	N	Y	–	–	–	–	–	–
13.	DP	distal	25	G	H	N	–	–	–	TisN0M0	1	distal	2.5	Y	Y	–	–	–	–	–	–
14.	DP	distal	80	PB	H	Y	12	T	1	T1cN0M0	1	distal	2	N	Y	–	–	–	–	–	–

C – colloid carcinoma; DP – distal pancreatectomy, distal – distal pancreas; G – gastric; H – high-grade IPMN; I – intestinal; IPMN – intraductal papillary mucinous neoplasm; ITPN – intraductal tubulopapillary neoplasm; L – low-grade IPMN; N – no; NET – neuroendocrine tumor; NMA – neuroendocrine microadenoma; O – oncocytic; PB – pancreatobiliary; PD – pancreatoduodenectomy; T – tubular adenocarcinoma; TP – total pancreatectomy; Y – yes; [1] invasive adenocarcinoma associated with non-dilated duct with high-grade pancreatic intraepithelial neoplasia; [2]each; [3]a single microadenoma in atrophic lobule; [4] concomitant high-grade pancreatic intraepithelial neoplasia; [5]partial intraductal spread - duct without IPMN; [6]NMA localized in atrophic lobule surrounded by IPMN lesion

- extensiveness of tissue sampling for histology,
- thickness of tissue sections,
- careful exclusion of NMA mimickers, and
- diligence during microscopical examination.

NMA/NET in patients with IPMN

NMA/NET coexisting with IPMN are rare, with less than 50 reported cases [7]. Currently, it is not fully clear whether IPMN and NMA/NET coexist more frequently than expected, And whether there is a causal relationship between IPMN and NMA/NET [2, 4]. The only exception are recent reports which have proven that both IPMN and NET components within a single composite IPMN/NET lesion may be clonally related [13, 14]. On the contrary, other investigators did not find any evident molecular relationship between topographically related IPMN and NET [5]. These observations indicate that clonally related IPMN/NET is possible, but remains an exceedingly rare lesion.

Results of the previous studies on IPMN/NET association gave inconsistent results. Sahora et al. noticed that the prevalence of NET in patients with IPMN is similar to the general population; the frequency of NET in specimens with IPMN is similar to the frequencies of other incidental pancreatic neoplasms [8]. In contrast, Marrache et al. [2] and Goh et al. [10] found that the frequency of coexistent IPMN/NET was higher than expected. According to the literature data, IPMN was seen in 2.9% (1/35) to 6.5% (3/46) of NET specimens [2, 7, 10], and NET was found in 1.1% (5/441) to 13.6% (3/22) of IPMN specimens [2, 3, 7, 8, 10, 12, 15]. In this study, the prevalence of NMA/NET among IPMN cases was higher than in previous reports (27%), and this number was related not only to the exact NMA/NET prevalence in the study population, but also to the preconceived diagnostic/screening approach.

Pathogenesis of NMA/NET in patients with IPMN

Little is known about pathogenesis of IPMN/NET coexistence. Some risk factors may be involved in the development of both NET and IPMN. Diabetes, a family history of cancer and chronic pancreatitis increase the risk of both NET [21–23] and IPMN [24].

Molecular profiles of IPMN and NET are different [2], with the exception of composite IPMN/NET [13, 14]. It was hypothesized that IPMN/NET forming a single lesion may develop from a common progenitor, or in transdifferentiation of a single cell type into another cell type [2, 7]. It was also speculated that NET may appear as a result of endocrine differentiation/hyperplasia within IPMN [10], but this hypothesis was not convincingly confirmed [2, 6]. Endocrine/paracrine stimulation of exocrine cells by NET-generated hormones may also play a role [11].

At the moment, it is not possible to indicate the exact reason(s) which can lead to increased prevalence of NMA/NET in patients with IPMN. One may speculate that exocrine-endocrine cross-talk [25] is involved in the pathogenesis of IPMN/NET coexistence, but this requires further study. Another hypothesis which could explain increased prevalence of NET/NMA in pancreata with IPMN is related to tissue remodelling, as seen in obstructive chronic pancreatitis/pancreatic atrophy. The histopathological features of obstructive pancreatitis are frequently seen in pancreata with IPMN (personal observation). Histopathological alterations of neuroendocrine cells have been recognized in pancreatic atrophy for decades [16, 17]. Chronic pancreatitis is considered a risk factor for NET development [22]. In the present study, half of NMA in IPMN specimens was found within atrophic lobules. It is possible that diffuse obstructive atrophy in pancreata with IPMN could promote NET/NMA development (the issue under study).

In summary, IPMN and NET/NMA coexisting in the pancreas may be considered as:

- a single lesion with laboratory-confirmed common molecular alterations (composite tumour, common pathogenesis very likely),
- a single lesion in which laboratory tests excluded common molecular alterations (collision tumour, common pathogenesis unlikely),
- distinct lesions isolated by the uninvolved "normal" parenchyma (common pathogenesis highly unlikely),
- distinct lesions (sometimes diffuse and/or multiple) within severely altered pancreatic parenchyma, e.g. in obstructive pancreatitis/atrophy (yet no data on common pathogenesis).

Study strength and limitations

The strength of the study was its design, based on the prospective inclusion of totally embedded pancreatic specimens which were examined histopathologically in a uniform fashion. To the best of our knowledge, this was the first report on IPMN/NET association based on prospectively examined, totally embedded pancreatic resection specimens.

The limitations of the study were the following:

- referral bias related to the examination of surgical specimens (i.e. inclusion of relatively less advanced, potentially resectable PDAC cases as well as more advanced, suspected for cancer and/or symptomatic IPMN cases) [26],
- sampling bias related to anatomical distribution of IPMN/PDAC/AMPCA within pancreata,
- examination of only a portion of the pancreas in the majority of cases, as they were treated with partial pancreatecomy,
- setting-up of "control" groups using PDAC/AMPCA samples, rather than normal pancreata,
- diagnostic bias, as the identification of one tumour (and subsequent pancreatic resection) resulted in extensive examination of the specimen towards identification of other lesions,
- lack of clinical data on IPMN/NET risk factors in the study population.

Conclusions

The prevalence of NMA in pancreatic specimens with IPMN was 27% and it was significantly increased when compared to specimens with PDAC/AMPCA. The majority of NMA in IPMN specimens were solitary and localized within the distal portion of the pancreas. Topographical association of IPMN and NMA was rare and no case in the present series showed features suggestive of composite (clonal) IPMN/NMA. IPMN/NMA association may serve as a model for investigation of exocrine-neuroendocrine interaction. The reasons for IPMN/NET coexistence are largely unknown and require further study.

Article information and declarations

Ethics statement

The Institutional Review Board was permitted to perform the present observational study without full review, which is necessary for interventional studies on humans, according to national regulations.

Author contributions

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Conflicts of Interest

None declared

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Comparison of EPID portal dosimetry verification and RadCalc dose verification for VMAT treatment plans

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Introduction. Dosimetry verification is required before starting each treatment. The legal regulations do not clearly define one method of plan verification. Therefore, it is allowed to perform measurements (electronic portal imaging device [EPID]) or calculations using an independent system. Portal dosimetry using EPID matrices was compared with the RadCalcTM system v. 7.1.4.1, performing independent dose distribution calculations.

Materials and methods. Treatment plans were made for 150 patients treated with the photon 6MV VMAT technique. Three groups of patients were studied: those treated for breast cancer, those treated for prostate cancer, and those irradiated to the prostate area with nodes. Then, the dosimetry verification was carried out on the accelerator using the EPID portal and compared with the independent RadCalc software calculation results.

Results. Comparison of tumor proportion score (TPS) *vs.* EPID and *vs.* RC calculations for breast, prostate, and prostate with nodes showed no significant statistical differences. Regardless of the size (volume) of the clinical target volume (CTV) area, no significant difference was observed, although there was a greater agreement for large CTVs compared to small ones. Similarly, there was no significant difference in the compared methods based on depth, but there was a better agreement for small depths than large ones.

Conclusions. Verification methods in the study groups showed compliance of the measured (EPID) and calculated (RadCalc) doses with the values planned in the TPS. This confirms that verification for patients treated with radiotherapy can be performed with any of these methods. However, for radiosurgical techniques, it is better to use the EPID method because the RadCalc method may give false negative results.

Key words: verification, electronic portal imaging device, RadCalc

Introduction

Cancer radiotherapy techniques have made significant progress in recent years. Conformal stationary techniques have been replaced by dynamic techniques like intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT). These dynamic techniques are now a daily standard in many oncology centers in Poland. Before starting treatment, dosimetry verification is necessary. The legal regulations do not specify a single method of plan verification, so measurements or calculations can be done through various methods.

So far, the most commonly used at the Maria Sklodowska-Curie National Research Institute, Gliwice Branch, was portal dosimetry using electronic portal imaging device (EPID) matrices. In Varian Medical Systems accelerators, the portal matrix is a part of the therapeutic apparatus located perpendicularly to the axis of the beam (fig. 1). It is also used to verify the correct positioning of the patient during treatment.

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Figure 1. TrueBeam therapy accelerator (Varian Medical Systems, Palo Alto, USA) with: 1 – kV lamp; 2 – kV radiation detector; 3 – accelerator head; 4 – MV radiation detector (EPID); 5 – therapeutic table

The treatment planning system performs a verification plan by calculating the fluence map for each irradiation field. Such a plan allows for irradiation of the EPID matrix without the patient before the first therapeutic session. Modern EPID devices are matrices of semiconductor detectors that record the radiation generated by the accelerator, measured in a plane perpendicular to the beam axis of this radiation (measurement of the so-called fluence maps) [1–7]. The signal is collected and saved from all detectors from the active measurement area. Each field of treatment is checked separately. The next step is to compare the measured fluence map with the calculated one. The assessment is based on the gamma index, which verifies compliance with the measurement in the specified range of dose and location [1–9].

The gamma index calculates the difference between the dose calculated and measured at the same point (dose difference [DD]) and the distance (distance to agreement [DTA]) between points with the same dose. By determining the acceptable difference (DD) in the dose and the distance (DTA), we define the sphere within which the points located meet the compliance criterion: TPS calculations – measurement; then the value of the coefficient is less than 1 [1–7]. The advantage of this method is that it does not require any phantom, and the assessment of treatment plans is quick. It only requires access to the accelerator, which may be difficult in the case of a large number of patients. An additional disadvantage of this method is that the measurements are dependent because the calculations, measurements, and comparisons are made using software from the same manufacturer [10, 11].

RadCalc™ v. 7.1.4.1 (LifeLine Software, S. Broadway Ave. Suite, USA) performs independent dose distribution, monitor units (MU) or point dose calculations for 2D and 3D treatment plans. It provides the ability to verify dynamic plans, including IMRT and VMAT. The vendor ensures that the algorithms used ensure quick, easy, and accurate verification of the dose distribution. Verification of plans in the RadCalc program allows one to disqualify plans that do not meet the adopted criteria. The use of the software does not "block" the operation of the accelerator. You should ask yourself in what situations you can abandon the measurement method on the device and use the RadCalc program. The answer would significantly improve the organization of physicists' work related to treatment planning [12].

The aim of the study was to compare two methods for assessing the compliance of dose distribution calculations with the actual dose. These methods include comparison of fluence maps measured with the EPID matrix and independent RadCalc calculations. The EPID matrix performs measurements in the 2D plane, and we have several measurement points at our disposal. Meanwhile, the RadCalc method is based on measurement at one point, and basically calculates the dose at that point. Of course, the RadCalc software has the option to compare fluence maps that were measured using the EPID matrix, but the measurement would also have to be performed on the accelerator. The purpose of introducing RadCalc software for use as an independent verification system was to reduce the load on the accelerator with verification measurements.

You should be aware that these are two different methods of verifying the calculations performed, but in clinical practice, both methods are used independently of each other to assess compliance. Therefore, the question arises whether a positive verification result in one method can be confirmed in the other. Will the obtained matches be the same? In other words, if accepting the approval of the plan for implementation on the basis of the EPID measurement, is there any certainty that by performing the measurement using the RadCalc method, and *vice versa*, this plan will also be approved for implementation.

Therefore, the question is whether these two methods of verifying calculations, EPID *vs.* RadCalc, are equivalent in assessing treatment plans.

Materials and methods

The analyzed group included 150 patients divided into 3 equal groups according to the treated location:

- 50 patients aged 38 to 82 (mean age 60) were diagnosed with left breast cancer. The area of planning target volume (PTV) drawn by the physician, covering the left breast with the margin determined according to the treatment protocol, was irradiated. Each patient had a VMAT treatment plan with a maximum accelerating potential of 6 MV, consisting of 4 therapeutic fields. The total dose for PTV irradiation is 50 Gy, in fractional doses of 2 Gy. The critical structures were: the left lung, the right lung, the heart, and the spinal canal.

- 50 patients aged 63 to 88 (mean age 74) were diagnosed with prostate cancer and lymph nodes. The treatment plan was divided into two stages. In the first stage, the prostate gland with nodes was irradiated to a total dose of 44 Gy in fractional doses of 2 Gy, and in the second stage, the prostate itself was irradiated to a total dose of 78 Gy, also in fractional doses of 2 Gy. The study included the first stage of treatment. The area of PTV drawn by the clinician, including the prostate and lymph nodes, was irradiated with a margin determined according to the treatment protocol. Each patient had a VMAT treatment plan with a maximum accelerating potential of 6 MV, consisting of 4 therapeutic fields. The critical structures were: the bladder, the rectum, the penile bulb, the femoral heads and the bowels.
- 50 patients aged 56 to 89 (mean 73) were diagnosed with prostate cancer (without lymph nodes). The area of PTV drawn by the physician, covering the prostate with the margin determined according to the treatment protocol, was irradiated. Each patient had a VMAT treatment plan with a maximum accelerating potential of 6 MV consisting of 2 or 3 therapeutic fields. The total dose for PTV irradiation is 76 Gy in fractional doses of 2 Gy. The critical structures were: the femoral heads, the bladder, the bowels, the rectum and the penile bulb.

Above treatment locations were selected due to the size of the irradiated field and the depth of the therapeutic dose definition point. Accordingly: mammary gland – a large fields, small depth; prostate gland with nodes – large field and great depth; prostate – a small field of great depth.

The clinical target volume (CTV), drawn by a clinician, was determined for each case. In the case of the prostates, the volumes of the close-fitting critical organs, i.e. the bladder and rectum, were additionally determined to investigate whether this affected the final results. An additional parameter was to determine the depth (distance from the contour of the body to the point) at which the reference point is located and the distance equivalent to water (water-equivalent distance). The calculation of the water-equivalent distance is based on two principles:

- the calculation uses the linear attenuation curves,
- the water-equivalent distance of a single point is calculated along that fanline of the treatment field that goes through the selected point, measured from the point where the fanline crosses the body outline or bolus to the selected point [13].

Treatment plans were made in the Eclipse™ v. 16.1 (Varian Medical Systems, Palo Alto, USA). After the attending physician approved the plan, a verification of the plan was prepared using two methods: EPID portal measurements and the independent RadCalc™ software (LifeLine Software, S. Broadway Ave. Suite, USA). Then the obtained verification results were compared with each other.

For measurements made on the accelerator, the criteria for assessing the gamma plan were adopted: DD = 3% and DTA = 2 mm (dose and its location). The plan must meet the accepted criteria for accepting the plan of compliance with the plan generated in the treatment planning system: 95% of the analyzed area, a threshold of 5%, margin around the field designated by the MLC 1 cm. Otherwise, the plan is rejected as not meeting the acceptable difference between calculation and measurement. An example of the EPID measurement result with the determined gamma index is shown in figure 2.

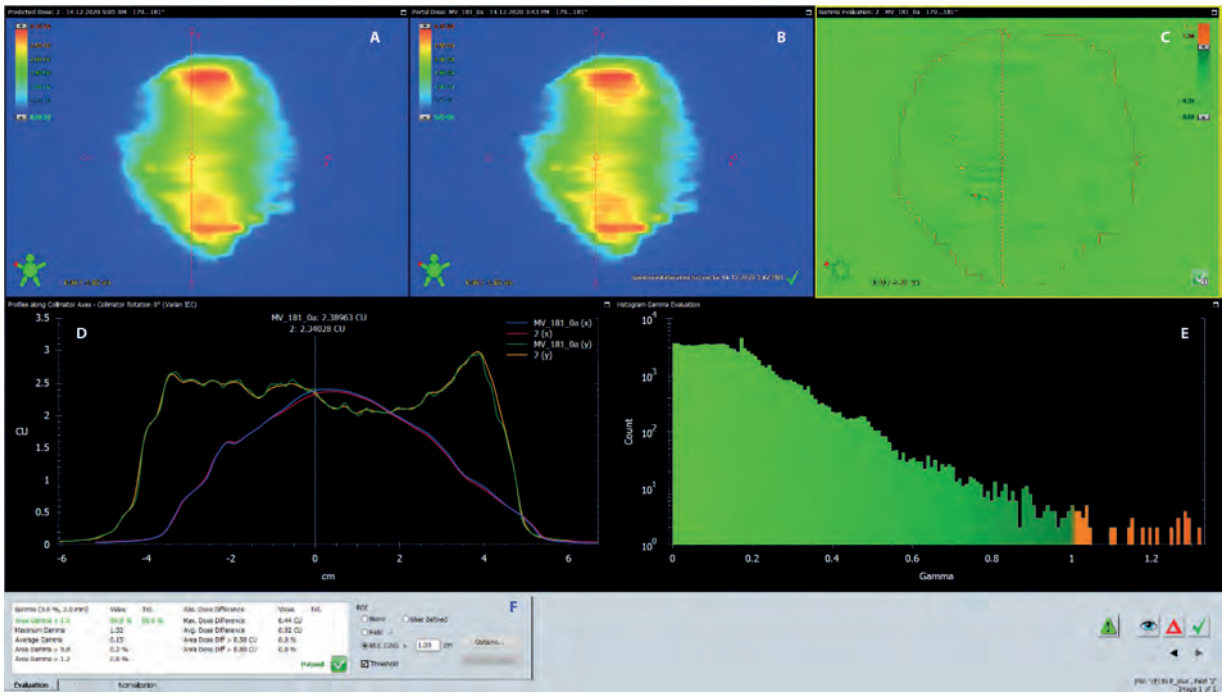

Figure 2. Graphical analysis of measured (**A**) and calculated (**B**) fluence maps based on gamma index (**E**); **C** – differences between measured and calculated fluence maps; **D** – fluence distribution along the axis; **F** – parameters of statistical analysis

The gamma-local index was analyzed with a threshold level of 5% and a 1 cm margin around the MLC. Such values of DD and DTA were selected because the criterion of 4% and 4 mm in 97% [13] of the analyzed field is met by all analyzed cases.

The RadCalc software uses a modified Clarkson integration technique to calculate the contribution of the diffuse dose for individual fields to the isocenter. The input data required by the algorithm is the treatment plan data, i.e. Dynamic multileaf colimator (DMLC) files, jaw settings, monitor units (MUs) for each field, depth to isocentre for each field, and location of each measurement point. The RadCalc software uses independently measured beam data (Sc – in-air output ratio), phantom scatter factor (Sp), tissue phantom ratio (TPR), dose per monitor unit $(D/MU)_{ref}$ and includes the effects of multileaf collimator transmission and radiation field shift (difference in magnitude between the light field and the radiation field caused by transmission through the multileaf collimator leaves). RadCalc allows you to verify dose distributions based on point values. Checking the plan involves selecting a point in the PTV area in the planning system. For the purposes of the study, points were placed in three different locations (cranial, central, and caudal). In the case of the breast, the points were cranial and caudal to the isocenter by approx. 6.5 cm, in the case of prostate irradiation without lymph nodes approx. 3 cm, and in the case of the prostate with lymph nodes – approx. 7 cm. The central point was separated from the isocentre by a maximum of 2 cm. (fig. 3) [11].

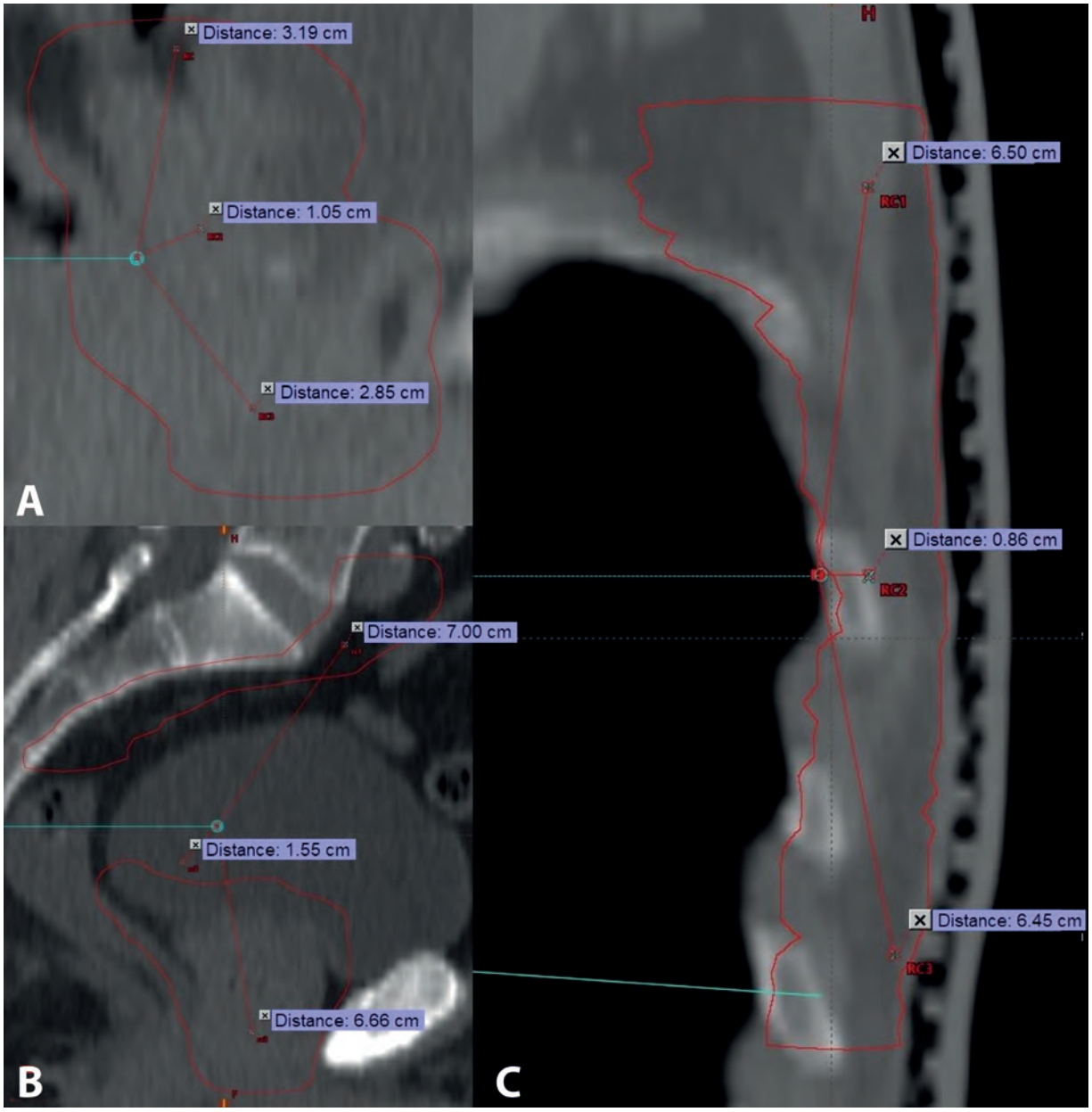

Figure 3. Arrangement of reference points in the sagittal plane in the PTV areas along with the distance from the isocentre; **A** – prostate; **B** – prostate with nodes; **C** – breast

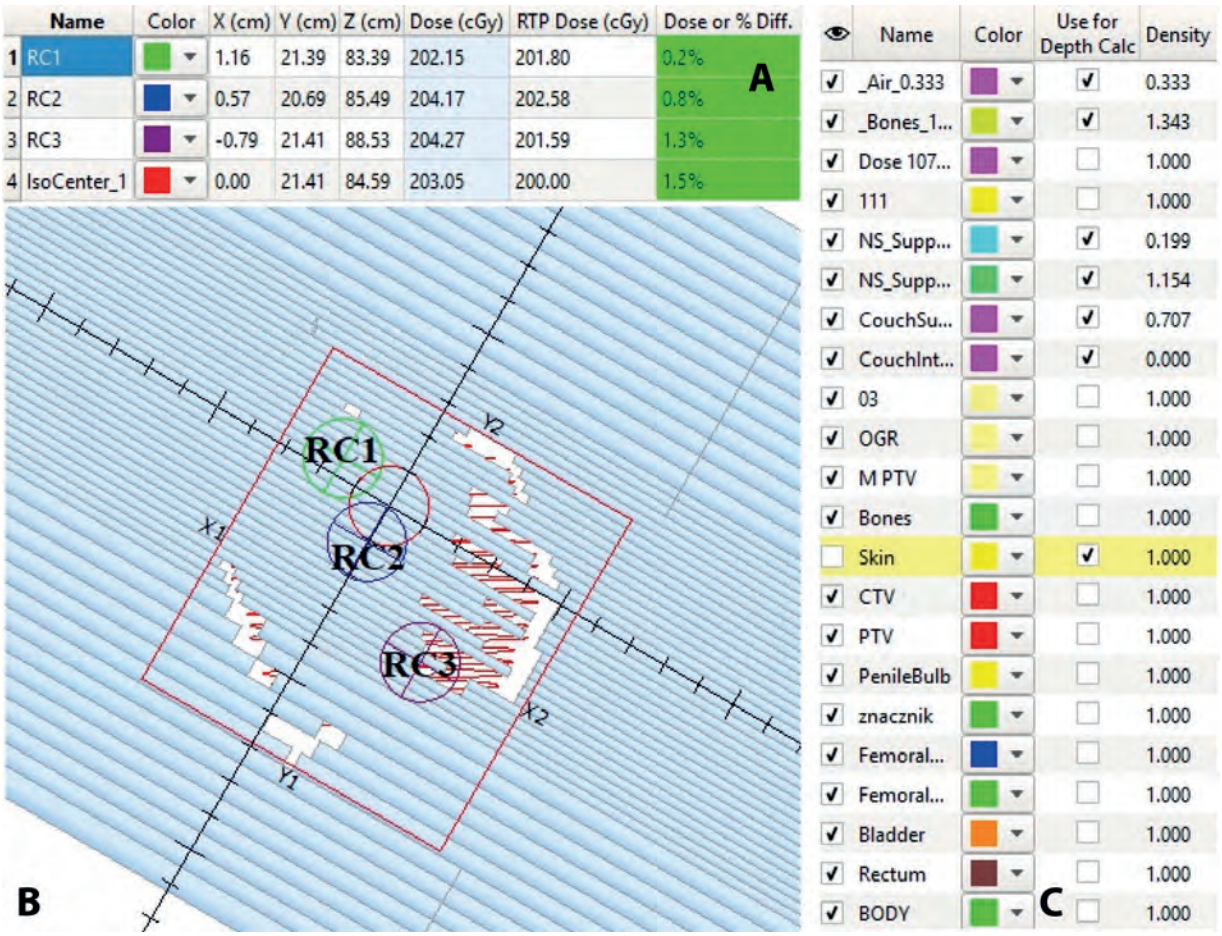

Figure 4. Screenshot from the RadCalc system; **A** – presentation of differences in doses at individual points and isocenter; **B** – distribution of points in the treatment area; **C** – determination of the average density of the drawn structures

The prepared plan is exported to RadCalc, which treats the patient's body as a homogenous medium with the same density as water. Structures with densities different than water, such as air, bone, and other components, require an assigned average density. After recalculating the plan, the dose at reference points should not differ by more than 5%, indicating a 95% agreement level (fig. 4) [8].

In summary:

- for EPID verification, the measured fluence map will be considered consistent with the calculations if, in 95% of the analyzed field, the dose differences are not greater than 3% and the dose shifts are smaller than 2 mm (local gamma analysis),
- for RadCalc verification, if the average difference between the calculated and measured dose is less than 5%, indicating a 95% agreement level.

If the verification plans meet these two conditions, we consider that these methods can be used alternately. The Mann-Whitney U statistical test was used to compare the two groups with a significance level of $p = 0.05$. The null hypothesis assumed that the compared sets were different. Rejection of this hypothesis requires that $p > 0.05$.

Results

Two analyzes were performed for selected treatment plans (portal verification and RadCalc calculations). The averaged results are presented in tables I–III.

Breasts

Both techniques in selected patients showed agreement between the measured (EPID) and calculated (RadCalc) doses with the values planned in the TPS. For EPID measurements, the average value was 98.93% of the analyzed field, which met the criteria of 3% and 2 mm. For point dose calculations made with RadCalc software, the average agreement was 98.90%. Comparing the compliance of the dose distributions / doses planned and measured / calculated, it can be concluded that both methods showed very similar compliance and met the accepted compliance criteria. In the case of EPID measurements, the compliance criterion is 95% of the analyzed field. The chart below (fig. 5) shows that the average results of measurements and calculations, along with the uncertainty, coincide with each other. Statistical tests performed do not show a statistically significant difference between these groups. This means that treatment plan compliance assessment methods can be used interchangeably.

Table I. Average results of measurement and calculation agreement for the breast treatment area

Measurements EPID 3% 2 mm					Calculations RadCalc				
avg. field dimensions (cm)		avg. measurement (%)	std. deviation	avg. diff. (%)	compliance (%)	std. deviation	avg. depth (cm)	avg. eq. path length (cm)	vol. CTV (cm^3)
X	Y								
15.80	21.10	98.93	0.87	0.64	98.90	0.74	7.22	5.64	936.17

Table II. Average results of the measurement and calculation agreement for the prostate treatment area

Measurements EPID 3% 2 mm					Calculations RadCalc						
avg. field dimensions (cm)		avg. measurement (%)	std. deviation	avg. diff. (%)	compliance (%)	std. deviation	avg. depth (cm)	avg. eq. path length (cm)	vol. CTV (cm^3)	vol. bladder (cm^3)	vol. rectum (cm^3)
X	Y										
10.20	10.00	99.58	0.55	2.85	96.89	1.05	16.65	15.88	74.07	307.52	65.50

Table III. The average results of the agreement of measurements and calculations for the prostate treatment area with nodes

Measurements EPID 3% 2 mm					Calculations RadCalc						
avg. field dimensions (cm)		avg. measurement (%)	std. deviation	avg. diff. (%)	compliance (%)	std. deviation	avg. depth (cm)	avg. eq. path length (cm)	vol. CTV (cm^3)	vol. bladder (cm^3)	vol. rectum (cm^3)
X	Y										
17.20	20.40	99.31	1.13	1.41	98.34	1.01	16.72	15.80	378.50	331.13	72.50

Prostate

As in the previous case, both techniques in selected patients showed compliance with the measured and calculated doses with the planned values. For EPID measurements, the average value was 99.58% of the analyzed field, which met the criteria of 3% and 2 mm. For point dose calculations performed with RadCalc software, the average agreement was 96.89%. Comparing the correspondence between dose distributions/doses planned and measured/calculated dose distributions, it can be concluded that both methods showed a similar agreement and met the accepted compliance criteria. In the chart below (fig. 6), it can be seen that in this case a better average result was obtained for the EPID measurement, while the dispersion of the average values of measurements and calculations coincides. The performed statistical tests do not show a statistically significant difference between the results obtained for different methods.

Prostate with lymph nodes

Again, both techniques showed agreement between the measured and calculated doses and the planned values. For EPID measurements, the average value was 99.31% of the analyzed field, which met the criteria of 3% and 2 mm. For point dose calculations performed with the RadCalc software, the average agreement was 98.34%. Comparing the compliance of the dose distributions / doses planned and measured / calculated, it can be concluded that both methods showed very similar compliance and met

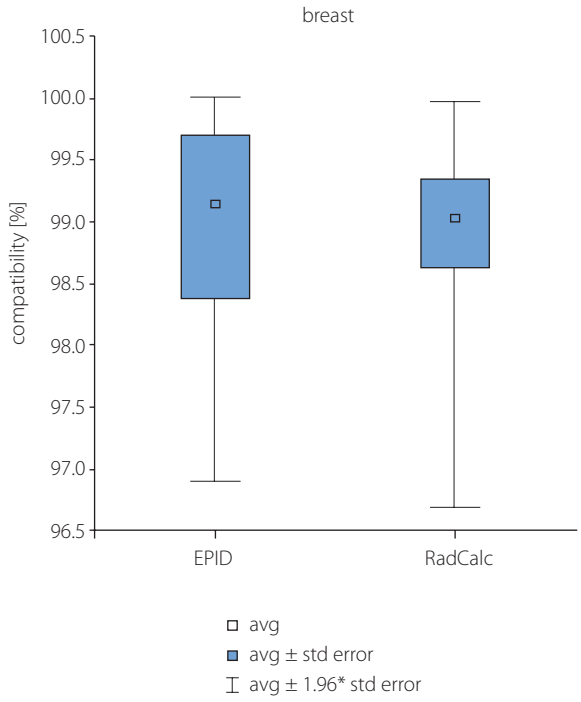

Figure 5. Box-plot chart showing the average results of measurements and calculations for the breast area

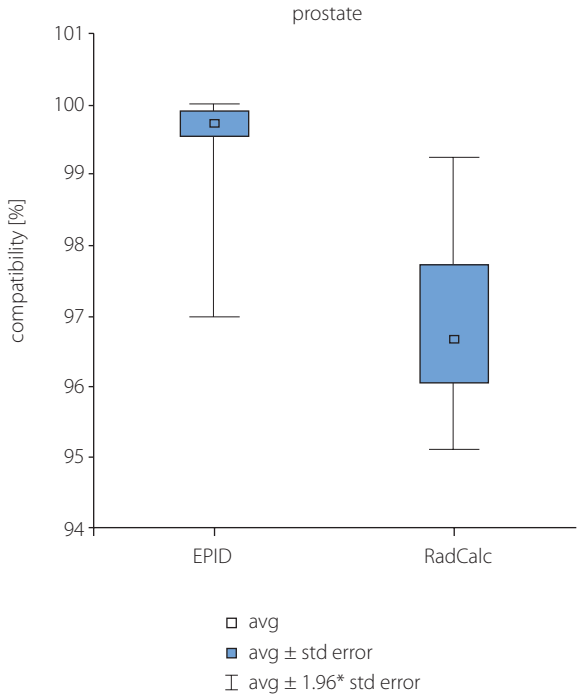

Figure 6. Box-plot chart showing average measurement and calculation results for the prostate area

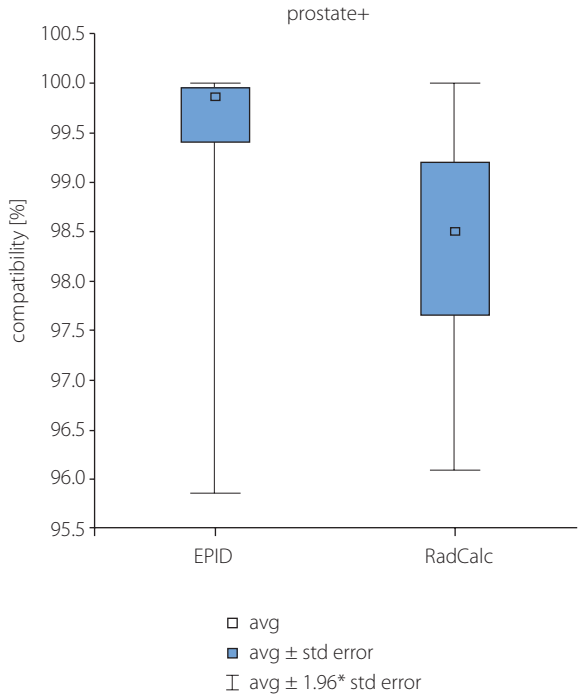

Figure 7. Box-plot showing average measurement and calculation results for the noded prostate area

the accepted compliance criteria. In the chart above (fig. 7), it is evident that in this case the EPID measurement achieved a slightly better average result, and the dispersion of the average values of measurements and calculations also coincides.

Discussion

The paper compares two treatment plan verification methods to assess whether they can be used interchangeably in the treatment quality assurance process. The EPID measurement method is performed on the accelerator, which means that it is excluded from clinical use, while RadCalc allows for independent calculations without switching off the accelerator, which allows patients to be irradiated at the same time. Both methods for all 150 patients showed agreement at the level above 95%, which allows the implementation of the plan on the accelerator.

All results were statistically analyzed using Statistica™ v. 13.3 (TIBCO Software Inc., Hillview Avenue, Palo Alto, USA). The non-parametric U Mann–Whitney test for independent samples allowed us to observe that:

1. comparison of the EPID *vs.* RC method for breast, prostate, and prostate with nodes does not show statistical significance,
2. there is no statistically significant difference between EPID *vs.* RC depending on the size (volume) of the CTV area. However, a greater agreement was observed for large CTVs than for small ones,
3. there is no statistically significant difference between EPID *vs.* RC as a function of depth. However, for small depths, there is better agreement than for large ones.

Table IV shows the differences in the obtained results depending on the volume of the CTV area and the depth of the reference point.

The smallest difference between EPID and RC is in the breast area with a large CTV area and small depth, and the largest in the case of large depth and small field, i.e. the prostate area without lymph nodes.

For small CTV volumes, it is more difficult to select a point "around" where there is a small dose gradient. The dose is inhomogeneous, which means that each shift of the point can cause "large" differences in the read dose. Greater depths

Table IV. Differences in EPID *vs.* RC results depend on the volume of the CTV area and the depth of the reference point

	Min. path length (cm)	Max. path length (cm)	Avg. path length (cm)	Min. CTV (cm^3)	Max. CTV (cm^3)	Avg. CTV (cm^3)	EPID *vs.* RadCalc (%)
breast	3.4	8.3	5.6	279.5	2847.4	936.2	0.9
prostate	13.5	18.9	15.9	10.4	186.4	74.1	2.8
prostate+	13.4	21.0	15.8	215.5	561.3	378.5	1.5

may result in an imprecise calculation of the water equivalent depth, so there may be larger differences than in the case of small depths, for which the difference between physical and equivalent depth is smaller.

Conclusions

The work confirmed that the verification techniques used in the study groups showed compliance with the measured (EPID) and calculated (RadCalc) doses with the values planned in the TPS. This allows us to state that the verification of compliance of the calculations (TPS) with the measurement (EPID) / calculations made by an independent software (RadCalc) for patients treated with external beams can be performed by each of these methods. However, for radiosurgical techniques, when the dimensions of the treated volume are small, it is better to use the EPID method because the RadCalc method may give false negative results. Thus, when using RadCalc calculations, the best "set" will be a large irradiation volume at a shallow depth, while for EPID measurements, it will be a small irradiation volume and a large depth.

Article information and declarations

Data availability statement

Raw data were generated at Maria Sklodowska-Curie National Research Institute, Gliwice Branch. Derived data supporting the findings of this study are available from the corresponding author on request.

Ethics statement

This material is the authors' own original work, which has not been previously published elsewhere. The paper is not currently being considered for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

Author contributions

Adam Gądek – collecting data, measurement data analysis, RadCalc calculation data analysis, compiling and comparing data, comparison of results, writing a paper.
Dominika Plaza – collecting data.
Łukasz Sroka – collecting data.
Marta Reudelsdorf-Ullmann – collecting data.
Krzysztof Ślosarek – statistical analysis of data, substantive correction of the article, work approval.

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Conflict of interest

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Pancreatic cancer concomitant with other malignancies – a single centre experience

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Introduction. Pancreatic cancer (PC) remains one of the most deadly tumours. The study aimed to describe a single-centre experience of PC concomitant with other malignancies.

Material and methods. Fifteen cases of PC associated with other primary malignancies were selected from the studied cohort. Statistical analysis with the usage of appropriate tests was conducted.

Results. Patients were presented with PC and other malignancies, encompassing breast, ovarian, colorectal, prostate, hepatocellular carcinomas, and thymoma. The median survival time was 75.0 months from the diagnosis of the first primary cancer and 14.0 months from the second primary cancer diagnosis. There was no significant difference in progression-free survival ($p = 0.44$) and overall survival ($p = 0.28$) between patients with and without a history of other malignancies.

Conclusions. The long-term follow-up examinations for oncological patients may allow the early diagnosis of concomitant malignancies. Nevertheless, results suggest that second primary tumours do not affect patients overall survival.

Key words: pancreatic cancer, oncology, survival

Introduction

Pancreatic cancer (PC) remains one of the most deadly tumours [1]. It accounts for approximately 2% of all malignancies and is associated with 5% of cancer-related deaths [2]. Incidence increases with age: it is rarely observed in the population under 25 years of age and is still relatively uncommon for those under 40, while 80% of the cases are diagnosed in people between 60 and 80 [3]. Effective screening is unavailable; thus, most patients present with a locally advanced (30–35%) or metastatic (50–55%) stage of the disease at diagnosis. Tumour cells are highly invasive, leading to further disease development and progression [4–6].

Metachronous cancers are defined as multiple primary tumours developing at intervals. Patients with various previous cancers have been shown to have a higher risk of developing a subsequent second primary malignancy [7]. According to recent statistics, metachronous malignancies will occur more frequently due to higher survival rates and demographic changes observed in developed countries [8]. It seems unclear whether metachronous malignancies present a specific correlation to

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previous tumours or if we can distinguish any particular pattern of metachronous spread [9]. Analyses of second malignant neoplasms might provide clues about the aetiologic factors of both primary and second cancer and contribute to identifying groups of patients who would require enhanced surveillance. Multiple primary cancers may be associated with a genetic predisposition, environmental risk factors, iatrogenic effects of prior oncological treatment, or a combination of all the above factors [10]. On the other hand, an excess of a second primary neoplasm compared with an expected occurrence may arise from intensive medical surveillance after the first oncological diagnosis [11]. Pancreatic cancers with metachronous neoplasms are rare, their incidence was reported to vary from 0.75% do 20% [12]. According to the best of our knowledge, little is known about the significance of pancreatic cancer as second malignancy.

The aim of the study was to describe a single-centre experience of pancreatic cancer concomitant with other malignancies.

Materials and methods

Patients and data collection

We conducted a single-centre retrospective analysis of the medical histories of 285 patients with a diagnosis of pancreatic cancer (C25 according to the International Statistical Classification of Diseases and Related Health Problems [ICD-10]) who were treated in the Clinic of Oncology and Haematology at the Central Clinical Hospital (CSK) of the Ministry of Interior (MSW) in Warsaw between February 2012 and March 2021. From this cohort, we selected 15 cases of PC associated with primary malignancies in other organs. Out of the 15 patients, 12 had a history of non-pancreatic primary tumours diagnosed between 1994 and 2020, while three patients were diagnosed with a second primary tumour during PC treatment. Analysed data encompassed sex, age, ECOG status, other diseases, pathological variables (tumour site, tumour size, histological grading, nodal involvement, tumour stage, resection margin), treatment data (type of the operation, vascular reconstruction, postoperative complications, adjuvant and palliative chemotherapy, with side effects), survival and progression time. The period between both carcinomas measured by the first clinical diagnosis was established by analysing medical records. Exclusion criteria encompassed less than two courses of chemotherapy for PC and previous non-malignant tumours or carcinoma *in situ*.

Histopathology

The material came from the patients who underwent surgery (Whipple procedure or distal pancreatectomy with or without splenectomy) and biopsies/excisional biopsies. Both macroscopic and microscopic evaluations of the tumours were performed. After routine initial processing with 10% formaldehyde and embedding in paraffin, 5-µm-thin tissue sections were obtained.

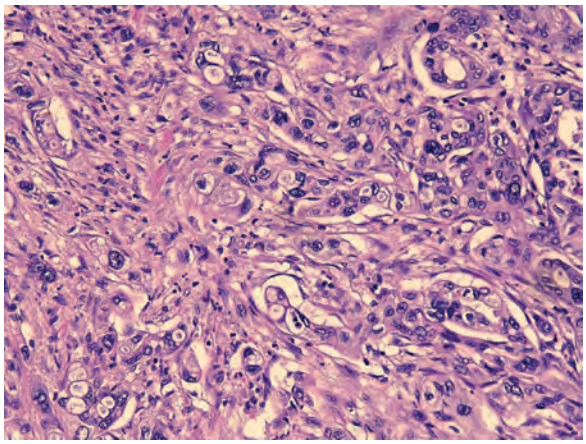

Figure 1. Histopathological image of pancreatic ductal adenocarcinoma (H&E, original magnification, 200×)

Subsequently, the samples were stained with haematoxylin and eosin following the commonly used protocol (fig. 1). Two independent pathologists evaluated tumour slides and prepared pathomorphological reports. To exclude metastatic cancers between the pancreas and other organs, histopathologic features of the cases were precisely examined. Available immunohistochemical staining slides were reviewed for cases with similar histopathologic features, and additional immunohistochemical labelling was performed to define the diagnosis conclusively.

Statistical analysis

Survival (presented as median value) was calculated from the time of primary cancer diagnosis to the time of death. Patients who were alive were censored at their last follow-up. Survival was estimated using the Kaplan–Meier method and compared using the Cox's F test. Results were regarded as significant with a p-value of ≤ 0.05. All statistical analysis was conducted using IBM SPSS Statistics 27.

Ethics approval and consent to participate

The study followed the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, the ethical principles defined in the Farmington Consensus 1997. The study was acknowledged by the Bioethics Committee of the Medical University of Warsaw (AKBE/144/2022).

Results

The fifteen patients enrolled in this work accounted for 5.3% of all analysed cases. In this group, there were 11 females (73.3%) and 4 males (26.7%) aged between 54 and 86, with a mean age of 68 ± 9.6 years at the time of PC diagnosis. All were presented with PC and other primary malignancy, encompassing breast – 5, ovarian – 3, colorectal – 3, prostate – 2, hepatocellular (HCC) – 1, carcinomas and thymoma – 1 (fig. 2).

Concerning non-oncological diseases, 5 patients had an autoimmune disease (hypothyroidism – 4, rheumatoid

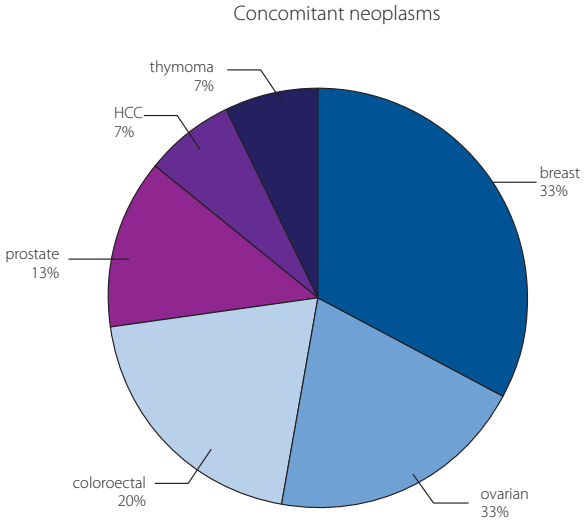

Figure 2. Distribution of neoplasms concomitant with pancreatic cancer

arthritis – 1), 8 diabetes mellitus – either type 2 or new-onset diabetes after the surgery, and 8 had hypertension. Most of the patients were diagnosed with PC in the head of the pancreas (80.0%), grading 2 (60.0%), TNM stage IIB (50.0%), and without distant metastases (62.5%). Nodal involvement was confirmed in all analysed samples. Histologically, 13 cases (86.7%) were confirmed as pancreatic ductal adenocarcinoma, one as mixed adenocarcinoma and pleomorphic sarcomatoid carcinoma of the pancreas, and one as pancreatic ductal adenocarcinoma, partially mucinous.

Most patients (60.0%) underwent Whipple procedure without any further postoperative complications; however, 55.6% required vascular reconstruction during the surgery. 72.7% of operated patients received adjuvant chemotherapy and developed neutropenia as the most prevalent adverse effect. Thirteen out of fifteen (86.7%) eventually received palliative chemotherapy. Most of them (61.5%) were treated with gemcitabine and nab-paclitaxel. The most common adverse effect was neutropenia (46.7%); however, they also developed thrombocytopenia, anaemia, and fatigue. Concerning progression, it was observed in the liver – 5, lungs – 3, peritoneum – 1, and subcutaneous tissue – 1. Non-pancreatic primary tumours were mainly treated with surgery and adjuvant chemotherapy. The patients detailed clinical and pathological characteristics are presented in tables I and II.

The median survival time was 75.0 months (range: 10–326 months) from the first primary cancer diagnosis and 14.0 months (range: 2–26 months) from the second primary cancer diagnosis. The median survival time from the PC diagnosis (irrespectively – as a first or second tumour) was 19 months (range 3–26 months). The median interval between diagnosing the first and second primary tumours was 56 months (range: 7–305 months) (tab. III). There was no significant difference in progression-free survival ($p = 0.44$) and overall survival ($p = 0.28$) between patients with and without a history of other malignancies (fig. 3, 4).

Table I. The summary of clinicodemographic variables

Age	Sex	Other malignancy	Diabetes mellitus	Autoimmune	Hypertension	ECOG
67	F	ovarian cancer	t.2	hypothyroidism	yes	1
67	F	breast cancer	t.2	no	no	1
68	F	breast cancer	t.2	no	yes	1
54	F	thymoma	no	no	no	1
57	F	breast cancer	no	hypothyroidism	no	1
54	F	breast cancer	no	hypothyroidism	no	1
67	M	colorectal cancer	t.2	no	no	1
82	F	ovarian cancer	no	no	yes	1
71	F	ovarian cancer	NODM	no	yes	1
58	F	breast cancer	no	no	no	1
86	M	prostate cancer	no	no	yes	1
70	F	hepatocellular carcinoma	no	hypothyroidism	no	1
82	M	colorectal cancer	t.2	no	yes	1
70	F	colorectal cancer	t.2	rheumatoid arthritis	yes	1
72	M	prostate cancer	t.2	no	yes	1

F – female; M – male; t.2 – type 2 diabetes mellitus; NODM – new-onset diabetes mellitus; ECOG – The Eastern Cooperative Oncology Group performance score

Table II. The summary of the clinicopathological variables

Tumor site	Histopatho-logic	TNM	R	G	Angio--inva-sion	Neuro-invasion	Type of the operation	Vascular recon-struction	Adjuvant chemothe-rapy	Palliative chemothe-rapy	Progres-sion
head	mixed adenocarci-noma and pleomorphic sarcomatoid carcinoma of the pancreas	T2N1M0	0	3	no	yes	Whipple procedure	yes	GemCap	–	–
head	PDAC, partially mucinous	T2N1M0	0	2	no	yes	Whipple procedure	yes	GemCap	gemcitabine, nab--paclitaxel	perito-neum
head	PDAC	T2N2M0	1	2	yes	–	Whipple procedure	no	FOLFIRI-NOX	gemcitabine, nab--paclitaxel	liver, lung, subcu-taneous tissue
head	PDAC	TxNxM1	–	x	–	–	–	–	–	gemcitabine, nab--paclitaxel	–
head	PDAC	T3N2M0	0	2	yes	no	Whipple procedure	yes	–	gemcitabine, nab--paclitaxel	liver
head	PDAC	TxNxM1	–	x	–	–	–	–	–	gemcitabine, nab--paclitaxel	–
head	PDAC	T3N1M0	1	3	yes	–	Whipple procedure	no	gemcita-bine	FOLFIRINOX	liver and lung
head	PDAC	T3N1M0	1	2	yes	yes	Whipple procedure	no	gemcita-bine	FOLFIRINOX	lung
head	PDAC	T3N1M0	1	2	–	–	Whipple procedure	no	gemcita-bine	–	–
undeter-mined	PDAC	TxNxM1	–	x	–	–	–	–	–	gemcitabine, nab--paclitaxel	–
head	PDAC	TxNxM1	–	x	–	–	–	–	–	gemcitabine, nab--paclitaxel	–
head and body	PDAC	T2N2M0	0	2	yes	yes	distal resec-tion with splenectomy	no	gemcita-bine	gemcitabine, nab--paclitaxel	liver
head and body	PDAC	T3N1M1	0	2	yes	no	distal resec-tion with splenectomy	no	gemcita-bine	FOLFOX6	liver
head	PDAC	T3N1M0	0	2	yes	yes	Whipple procedure	yes	–	FOLIRINOX	–
head	PDAC	T3N1M0	1	2	yes	yes	Whipple procedure	yes	–	gemcitabine	–

PDAC – pancreatic ductal adenocarcinoma; T – tumor size; N – nodal status; M – metastasis; R – residual tumour classification; G – grading; GemCap – gemcitabine + capecitabine

Table III. The summary of overall survival time and interval time between the diagnoses of the first and second malignancies

First primary tumour	Interval (months)	OS* (months)	Second primary tumour	OS** (months)
pancreatic cancer	19	21 censored	ovarian cancer	2 censored
breast cancer	56	79	pancreatic cancer	22
breast cancer	305	326	pancreatic cancer	20
pancreatic cancer	13	18	thymoma	18
breast cancer	103	118	pancreatic cancer	15
breast cancer	38	52 censored	pancreatic cancer	14 censored
colorectal cancer	206	217	pancreatic cancer	10

→

Table III cont. The summary of overall survival time and interval time between the diagnoses of the first and second malignancies

First primary tumour	Interval (months)	OS* (months)	Second primary tumour	OS** (months)
ovarian cancer	48	75	pancreatic cancer	26
pancreatic cancer	7	10	ovarian cancer	3
breast cancer	49	56	pancreatic cancer	7
prostate cancer	99	103	pancreatic cancer	3
hepatocellular carcinoma	84	104	pancreatic cancer	20
colorectal cancer	60	73	pancreatic cancer	13
colorectal cancer	32	45	pancreatic cancer	13
prostate cancer	82	108	pancreatic cancer	26
	median: 56	median: 75		median: 14

OS – overall survival; * OS from the time of first primary tumour diagnosis; ** OS from the time of the second primary tumour diagnosis

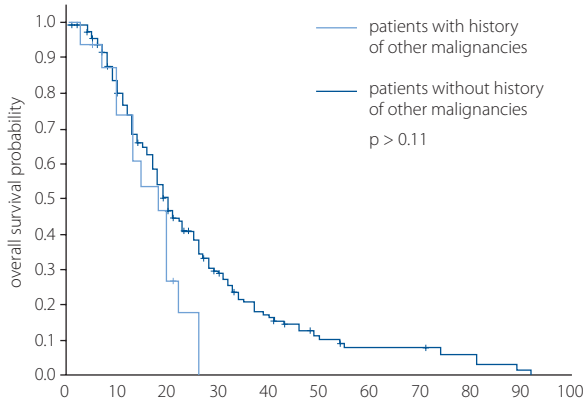

Figure 3. The Kaplan–Meier curve for overall survival in the two studied groups

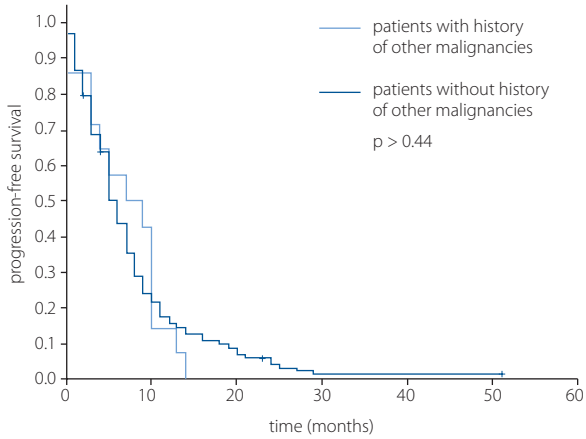

Figure 4. The Kaplan–Meier curve for progression-free survival in the two studied groups

Discussion

So far, single studies have tried to establish the incidence of PC as a second primary malignancy and risk factors for its occurrence. For example, in research from 1995, an elevated incidence of PC was observed after tobacco-related malignancies, most notably after lung cancer, especially in females [13]. The subsequent analysis also suggested a higher prevalence of concomitant PC and lung cancer among the female population [11]. Furthermore, the association between pancreatic adenocarcinoma and other tobacco-related malignancies was also confirmed in other studies [14]. The analysis of The National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) data revealed that patients diagnosed with a primary malignancy had an increased risk of subsequent pancreatic adenocarcinoma after several malignancies: colorectal cancer (ascending colon, hepatic flexure), stomach, hepatobiliary, pharynx, lung, breast, uterine, cervix, bladder, and hematopoietic malignancies [14]. Shen et al. (2005), who also analysed SEER data, suggested that the elevated risk of PC after stomach, gallbladder, lung, female and male breast, cervical, ovarian, kidney, and eye cancers, as well as Hodgkin's disease, was more evident among young individuals [11].

Some studies suggest that cancer survivors for certain gastrointestinal malignancies with long overall survival time, such as colorectal cancer (CRC), are especially at a higher risk of a second primary cancer; nevertheless, results are inconsistent [15]. In a study by Chung et al. (2017), among almost 5,000 CRC patients, 13 cases of PC were observed; however, no risk factors for developing PC were established [16]. The authors suggested that they presented with resectable or locally advanced PC due to regular follow-ups and a higher awareness of cancer risk among oncological survivors. The most pronounced risk associated with a subsequent PC among individuals with CRC diagnosis is suggested to be in the case of neoplasms located at the ascending colon and hepatic flexure [14]. This phenomenon cannot be fully explained; nevertheless, various studies confirm that CRC is a molecularly heterogeneous disease with significantly different molecular and clinical characteristics between right- and left-sided localisation [17, 18].

It is well-established that germline mutations in breast cancer susceptibility proteins (BRCA) genes are correlated with

an enhanced risk of PC and can be found in approximately 8% of individuals with sporadic PC [19]. In the study evaluating *BRCA* mutation status among PC patients, a history of other malignancies approached statistical significance as a predictor of the presence of a *BRCA* mutation – 3 patients were diagnosed with a neoplasm not specific to hereditary breast or ovarian cancers: Hodgkin lymphoma, thymoma, and transitional cell carcinoma of the bladder. Moreover, family history for one or more first-degree relatives with breast/ovarian carcinoma was also trending toward significance [20]. The study by Mocci et al. (2013) revealed that members of families with a history of breast cancer but without *BRCA* mutations might also be at increased risk of developing PC; nevertheless, the number of relatives with breast cancer did not affect this risk [21]. It is consistent with previous reports suggesting that clustering early PC in families with two cases of breast cancer under 50 might be associated with effects unrelated to *BRCA* mutations [22].

Considering lymphomas, up-to-date analyses provided modest evidence for familial aggregation of non-Hodgkin lymphomas with PC [23]. After ten or more years of follow-up, the standardised incidence ratio of PC was proven to be elevated significantly after both Hodgkin and non-Hodgkin lymphomas [11]. Subsequently, several studies reported significantly increased risks of PC among long-term Hodgkin lymphoma (HL) survivors; however, no direct relation to specific radiation dose or chemotherapeutic agents was established [24, 25]. The cumulative incidence of PC as a second malignancy among HL survivors seems not to change over time [26].

Some reports suggest that a family history of selected cancers, observed in our study as concomitant malignancies (ovarian, breast, colorectal, prostate), is associated with an increased risk of PC [27–29]. A family history of cancer was generally proven to correlate with PC, both for first- and second-degree relatives [29]. That said, further studies are required to detect this phenomenon's biological or genetic origin. On the other hand, analysis of Wang et al. (2009) highlighted that relatives of PC patients – both sporadic and familial – are at higher risk of developing cancers at other sites [30]. They proved that individuals with a family history of PC not only have an increased risk of dying from PC but also from breast, ovarian, colon, prostate, liver and bile duct cancers. Moreover, PC patients with a family history of breast, ovarian and colon cancers were, on average, younger than patients without a family history of these cancers [31].

Our study indicated no significant difference in PFS or OS between those patients with second primary carcinoma and those without, which is consistent with some previous case series [32]. Also, the analysis by Shin et al**.** (2018) conducted on 1,352 primary PCs suggested that pancreatic cancer patients diagnosed with metachronous primary tumours had survival times similar to those diagnosed with pancreatic cancer only [12].

This study has limitations due to its small sample size and retrospective design. Moreover, there may be some ambiguity concerning the review of medical history.

Conclusions

The results from the current study suggest that pancreatic cancer might be associated with certain primary neoplasms. Long-term follow-up examinations for oncological patients may allow for the early diagnosis of concomitant malignancies. Further studies are required to identify the risk factors for developing second neoplasms and generate proper screening strategies for cancer survivors. Nevertheless, results suggest that second primary tumours do not affect patients' overall survival.

Article information and declarations

Data availability statement

Correspondence and material requests should be addressed to Marta Fudalej, Anna Badowska-Kozakiewicz or Daria Kwaśniewska.

Ethics statement

The study followed the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, the ethical principles defined in the Farmington Consensus 1997. The study was acknowledged by the Bioethics Committee of the Medical University of Warsaw (AKBE/144/2022).

Authors contribution

Marta Fudalej – conception and study design, literature search and study selection, collection and assembly of data, interpretation of results (all authors), writing the first draft of the manuscript.
Anna Badowska-Kozakiewicz – conception and study design, quality assessment, interpretation of results (all authors), writing the first draft of the manuscript.
Daria Kwaśniewska – conception and study design, literature search and study selection, collection and assembly of data.
Izabella Cichowska – quality assessment.
Andrzej Deptała – quality assessment.
All authors – interpretation of results, revising draft manuscript, approval of the final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work.

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Conflict of interest

None declared

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Artykuł przeglądowy / Review article

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Management of cervical cancer during pregnancy – a systematic review

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Diagnosis of neoplasms during pregnancy and establishing a treatment schedule that is safe for both mother and fetus is problematic. This review summarizes knowledge about the problems associated with cervical cancer during pregnancy and current recommendations for diagnosis and treatment. The systematic review was performed according to PRISMA guidelines. The search was performed using PubMed, Scopus, Web of Science, and Google Scholar. Seven articles on 317 pregnant women with cervical cancer were included. Stage of disease, gestational age at diagnosis, treatment in pregnancy, type of delivery, gestational age of delivery, treatment after delivery, follow-up and main conclusion were analysed. The rare phenomenon of neoplasms during pregnancy, as well as a limited research, do not allow for the development of clear guidelines for the treatment of cervical cancer in pregnant women. It is warrant to address discussed problems in future clinical research to provide the best care for pregnant cancer patients.

Key words: pregnancy, cervical cancer, chemotherapy, radiotherapy, surgery

Introduction

The prevalence of cancer during pregnancy is relatively low and accounts for about 0.1% of all pregnancies [1, 2]. The most commonly diagnosed malignancies are breast cancer (BC), cervical cancer, melanoma, lymphoma, and leukemia [1]. Moreover, the management of cervical cancer during pregnancy is highly challenging in the context of reproductive organ involvement and the occurrence of hormonal changes affecting the anatomy of the female pelvis [3]. Additionally, during pregnancy, an increase in vascular permeability and vascularization is observed with simultaneous immune system suppression, which can contribute to the delay in cancer detection and rapid tumor progression [1]. Thus, it is warranted to establish a relevant treatment strategy that will be safe for both mother and fetus. In this review, we summarized current knowledge about cervical cancer management during pregnancy in the context of different oncological treatment modalities.

Material and methods

Search strategy

The systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol [4] and the PICO (Population, Intervention, Comparison, Outcome) search tool [5].

Evidence acquisition

To find studies reporting information about management of cervical cancer during pregnancy, on the 4th of April 2023 a data searching using PubMed, Scopus, Web of Science, and Google Scholar was performed. The following search queries were used: "cancer during pregnancy", "chemotherapy

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during pregnancy" and "gynecologic cancer during pregnancy", "cervical cancer during pregnancy". We selected 28 articles for full-text analysis, and 7 of them were further analysed.

Inclusion and exclusion criteria

We included original articles, reviews, cohort studies, case reports, case studies and guidelines. The included articles covered the diagnosis, treatment, pregnancy termination, and delivery of cervical cancer in pregnant women. Studies in languages other than English were excluded from this review. Studies published as abstracts or letters were excluded. We also excluded articles that focused only on gynecological cancers in pregnancy without considering cervical cancer.

Evidence synthesis

Table I includes the following information: name of the first author, year of the study, number of patients, stage of disease, gestational age at diagnosis, treatment in pregnancy, type of delivery, gestational age of delivery, treatment after delivery, follow-up, and main conclusion.

Results

We included and analysed 7 original articles. There were 317 pregnant women with cervical cancer, including 1 patient with carcinoma *in situ*, 213 patients with stage I, 46 patients with stage II, 2 patients with stage III, 1 patient with stage IV, 26 patients with stage II–IV, 7 patients with stage III–IV, and 21 with unknown stages.

Gestational age at diagnosis and delivery

The diagnosis was usually made in the 2nd trimester of pregnancy (5 studies). Then in the 1st trimester (2 studies), the 3rd trimester (2 studies), and postpartum (1 study). The 35th week of pregnancy was the most common time for delivery, according to the analysed articles (2 studies). In 4 articles these data were not provided.

Treatment in pregnancy

We summarized various treatments before delivery. In the case of as many as 71 patients, pregnancy termination was performed. 50 patients underwent surgery. Combination therapy was used in 68 women. 51 patients received chemotherapy, 2 patients received concurrent chemoradiotherapy, and 2 patients received radiotherapy. One dilatation and curettage were performed. One patient refused treatment. The data for 3 patients was not provided.

Type of delivery

The most common type of delivery was caesarean section (156 patients, including 29 with additional procedures); 29 patients ended their pregnancies by vaginal delivery. In 2 articles these data were not provided.

Treatment after delivery

Across the included studies, 6 patients received radiotherapy alone, 20 patients received radiochemotherapy, and 6 patients received concurrent chemoradiotherapy; 24 women underwent post-delivery surgery; 23 patients received combination therapy. In the case of 9 women, no treatment or unclear treatment was declared. The data for 41 patients was not provided.

Discussion

Overall incidence of cancer in pregnant women is relatively uncommon. The strictly established guidelines for management are lacking. Hence, it is important to discuss diagnostic and treatment strategies, especially for less common and difficult-to-manage tumors, such as cervical cancer.

Diagnosis

Although symptoms of cervical cancer may often be masked by hormonal changes, due to routine prenatal screening, the detection rate is above 70% [6]. However, there is still a risk of assigning the symptoms of cervical cancer to normal pregnancy and benign conditions, which ultimately delays the diagnosis [1, 7]. Therefore, pregnant and postpartum women should be cautious about irregular vaginal bleeding or abnormal vaginal discharge (bloody, purulent, or smelly) [7, 8]. Therefore, it should be remembered that a clinical examination and histological verification of cervical cancer in a pregnant patient are obligatory [9].

Cytology and pelvic examinations are useful for the detection of asymptomatic cervical cancer. Therefore, the first visit during pregnancy is crucial, especially for patients who have not participated in screening programs [6, 10]. Cytology is a safe procedure for pregnant women and the fetus. Its specificity and sensitivity are comparable to the results of non-pregnant women [7]. In the case of abnormal cytology results, a colposcopy-directed biopsy should be performed, preferentially during the first two trimesters before the periods of the highest hormonal secretion and increased revascularization [7, 10]. Colposcopy provides high sensitivity and safety, with a complication rate up to 0.6%. The most frequent complications are hemorrhage, premature birth, or miscarriage [2]. Even if the colposcopy results are abnormal, endocervical curettage is contraindicated as it increases the risk of miscarriage and premature delivery [2, 7, 9].

In general, diagnosis and staging should be performed similarly as in non-pregnant women, with the exception of imaging procedures emitting ionizing radiation (e.g., positron emission tomography [PET-CT], computed tomography [CT], and X-ray) [11]. Therefore, ultrasound and MRI are the first-choice diagnostic methods [2, 12]. However, in exceptional circumstances, CT or X-ray may be considered. For instance, for patients with invasive cervical cancer in stage IB1 and higher, a chest X-ray to assess lung metastases should be done [13]. A chest CT scan with abdominal shielding can also be used

Table I. Summary of analyzed studies

First author, year [ref.]	Stage (n)	Gestational age at diagnosis in weeks – median (range)	Treatment in pregnancy (n)	Type of delivery	Gestational age at delivery in weeks – median (range)	Treatment after delivery	Follow-up – median (range)	Main conclusion
Fukushima, 2009 [10]	IA1 (6) IB1 (13) IB2 (2) IIA (1) IIIB (1) IVB (1)	16 (6–33)*	TAH (1) TOP + sRAH (1) TOP + RAH (9) TOP + ExL + CCRT (1) TOP + RAH + RT (1) DC (1) denied (1)	CD (1) VD (10)	35.4 (22–42)	Cone + TAH (2) RAH (3) ExL + CT (1) CCRT (1) Cone + ExL + CCRT (1)	50.5 (9–150)	treatment delay during pregnancy should be discussed due to the risk of underestimated disease severity in pregnant patients (p = 0.016)
Halaska, 2019 [17]	IA (19) IB1 (62) IB2 (25) II–IV (26)	18.4 (7–39)	S (23) TOP (35) NACT (28)	CD (84) VD (12) ND (1)	ND	CT + RT (18) S (17)	67 (2–269)	the prognosis of pregnant patients with cervical cancer is similar to non-pregnant women the hazard ratio for progression-free survival was 1.17 (95% CI: 0.64–2.12, p = 0.62)
Li, 2020 [19]	IA (7) IB1 (30) IB2 (33) II (28) III–IV (7)	TOP: 14.8 (5–31) COP: 30.8 (6–41)	RH (23) abortion + RH (20) abortion + CCRT (2) HT + RH (19) ND (3)	CD (34) VD (1) CD + RH (3)	ND	RH + CT (11) RH + CCRT (8) RH (3) CCRT (4) NT/UT (9)	61 ± 6 (1–173)	the hazard ratio for overall survival was 1.063 (95% CI: 0.24–4.71, p = 0.964)
Köhler, 2015 [22]	ND (21)	17 (13–23)	NACT (21)	CD (2) CD + RH (16) CD + SH (1) CD + TMMR (1) CD + pelvic LND (1)	33 (30–36)	ND	33 (7–88)	the overall survival rate was 95.3%
Ustaalioglu, 2010 [23]	IB2 (1)	1st trimester	therapeutic abortion	ND	ND	RT + CT	19.7 (2–122)	the prognosis was poor due to the early diagnosis
Zhang, 2015 [26]	*in situ* (1) IA1 (1) IB1 (5) IB2 (1) IIA (8) IIB (3) IIIB (1)	2nd trimester (4) 1st trimester (8) 3rd trimester (2) PP (6)	S (3) S + RT (3) S + CCRT (5) NACT + S + CCRT (1) S + CCRT + CT (2) NACT + S + CT (1) NACT + CCRT (1) CCRT (2) RT (1) CCRT + CT (1)	CD (4) VD (3)	ND	ND	68 (14–142)	women with cervical cancer during pregnancy require personalized treatment

→

Table I cont. Summary of analyzed studies

First author, year [ref.]	Stage (n)	Gestational age at diagnosis in weeks – median (range)	Treatment in pregnancy (n)	Type of delivery	Gestational age at delivery in weeks – median (range)	Treatment after delivery	Follow-up – median (range)	Main conclusion
Bo, 2021 [29]	IA1 (4) IA2 (2) IB1 (1) IB3 (1) IIA1 (1) IIA2 (3) IIB (2)	18 (7–36) *	CKC + NSD (2) CT (2) TOP + RH (1) NSD (1)	VD (3) CD + RH (7) miscarriage (1) CD (2)	35 (9–39)	RT (6) RT + CT (1) CCRT (1) RH (1)	NA	early diagnosis and effective treatment improve the survival rate of pregnant women

*– hard to estimate; CCRT – concurrent chemoradiotherapy; CD – cesarean delivery; CKC – cold knife conization; COP – continuation of pregnancy; CT – chemotherapy; DC – dilation and curettage; DL – delay; DV – delivery; ExL – exploratory laparotomy; HT – hysterotomy; LND – lymphadenectomy; NA – not applicable; NACT – neoadjuvant chemotherapy; ND – no data; NSD – nominal standard dose; NT/UT – no treatment/unclear treatment; PP – postpartum; PTD – pre-term delivery; RAH – radical abdominal hysterectomy; RH – radical hysterectomy; RT – radiotherapy; S – surgery; SH – simple hysterectomy; TAH – total abdominal hysterectomy; TMMR – total mesometrial resection; TOP – termination of pregnancy; VD – vaginal delivery

as an alternative to diffusion-dependent magnetic resonance imaging (whole-body diffusion-weighted MRI [WB-DWI/MRI]) to evaluate nodal and distant metastases [9], although it should be remembered that any exposure of the fetus to ionizing radiation may be associated with negative effects. If performed in the first trimester, the risk of fetal impairment, childhood cancer, and leukemia is significantly increased [1, 14]. Gadolinium, which is commonly used for MRI as a contrast, is not recommended during pregnancy due to an increased risk of stillbirth, neonatal death, rheumatologic and skin diseases [12, 15].

To establish the clinical stage of disease, a lymph node assessment is done, preferably by the 24th week of pregnancy. This is particularly important due to the prognostic significance and determination of further management [9]. PET-CT, which is commonly used for this purpose, is not recommended during pregnancy. Unfortunately, standard MRI scanning is not specific enough to assess the lymph nodes. Thus, the best approach is to perform a laparoscopic lymphadenectomy and histopathological examination afterward, as it has been proven to be a safe and effective method in women before the 22nd week of pregnancy [2, 12]. That said, in the advanced stages of pregnancy, lymphadenectomy should be avoided [12]. An acceptable alternative to PET-CT and lymphadenectomy in these circumstances can be a WB-DWI / MRI, which has no negative effects on the fetus and has higher specificity than standard MRI scanning [6, 15].

Each patient should be consulted by a multidisciplinary team to establish a treatment plan, considering not only the tumor stage and gestational age at diagnosis but also patient preferences. Further treatment should only be carried out in gynecology and oncology centers affiliated with perinatal centers [9].

Treatment

Treatment of cervical cancer in pregnant patients can be challenging due to balancing between positive oncological effects on the mother, the protection of the fetus, and the preservation of fertility [7, 16]. After fertility-sparing treatment, any pregnancy should be considered a high-risk pregnancy [9]. Moreover, the choice of treatment regimen is highly dependent on the gestational age at the time of diagnosis. Hence, during the first trimester, a standard of care adequate to the FIGO stage and pregnancy termination is preferred [17, 18]. During the second or third trimester, neoadjuvant chemotherapy or definitive treatment delay and induction of delivery are used, respectively. Importantly, the tumor size and local extension International Federation of Gynecology and Obstetrics (FIGO) influence cancer management. Small tumors are more often treated surgically, whereas neoadjuvant chemotherapy is used to treat tumors bigger than 2–4 cm [17]. Nevertheless, in the case of lymph node involvement, neoadjuvant chemotherapy should be administered as

soon as possible [8]. On the other hand, it has been stated that a treatment delay during pregnancy should be discouraged due to the risk of underdiagnosis, which occurs more frequently in pregnant than non-pregnant women [12]. According to the latest guidelines, delaying oncological treatment until fetal maturity should be considered if the term of delivery or fetal maturity is approaching (>34 weeks of age). Then, immediately after the caesarean section, treatment can be started [9]. In conclusion, due to limited and conflicting data, a safe delay time for treatment cannot be determined. Due to the difficulties associated with the treatment of cervical cancer in pregnant women, it is important to have access to several therapeutic methods and discuss them with the patient [9].

Surgery

In women with early-stage cancer (IA2–IB2 and IIA1), a hysterectomy or trachelectomy is performed, whereas chemoradiotherapy is administered for locally advanced tumors [19, 20]. Conization or simple trachelectomy can remove the tumor if the patient wants to preserve the pregnancy [9]. Radical trachelectomy is not recommended during pregnancy due to the high prevalence of surgical and obstetric complications [15, 21]. After a simple or radical trachelectomy, delivery is possible only by caesarean section [9]. If surgery is decided upon, the best time is between the 15th and 20th week of pregnancy [2, 15]. If there is a residual tumor after surgery that cannot be completely removed, chemotherapy may be started [9]. All in all, surgical treatment seems to be the safest option during pregnancy. However, the condition of the fetus should be checked with ultrasonography before and after the induction of general anesthesia [11]. Interestingly, the negative effects of anesthesia on the fetus are related to complications on the mother's side rather than the direct influence of administered drugs [1, 14, 21]. The condition of the fetus should be constantly monitored and consulted with an obstetrician during the whole treatment period.

Chemotherapy

Neoadjuvant chemotherapy provides the opportunity for regression of not only the primary tumor but also the site of nodal and distant metastases if present. However, the main drawback is the loss of ovarian reserve [19, 22]. Hence, pregnancy preservation should be considered before the administration of chemotherapy [16]. Teratogenicity is highly associated with exposure time, applied dose, type of drug, and placental transfer. Thus, most standard regimens are implemented after the 14th week of pregnancy.

The most common neoadjuvant chemotherapy regimen is a combination of cisplatin and paclitaxel as both provide the lowest risk of adverse effects [11, 23]. In the case of preeclampsia or renal failure, carboplatin may be considered instead of cisplatin as it is less nephrotoxic, but more hematotoxic [14, 16]. Furthermore, it is possible to combine platinum derivatives with taxanes. It is noteworthy that the use of bevacizumab and immune checkpoint inhibitors is contraindicated [9].

Currently, the main challenge to overcome is the placental transfer of maternally administered drugs. In comparison to taxanes, cisplatin and carboplatin penetrate this barrier more easily and increase fetal side effects [8, 23]. For instance, children whose mothers have received cisplatin may have impaired hearing [7, 15]. Further research in this field is needed to find ways of decreasing the placental transfer of teratogenic drugs.

A rarely addressed issue is drug pharmacokinetics, which may significantly vary from the 4th week of pregnancy [8]. Specifically, an increase of plasma volume, glomerular filtration rate, and enterohepatic circulation, reduce the concentration of the drug in the body [1, 16]. Additionally, the amniotic fluid serves as a "third space", extending drug exposure [21, 23]. The standard dosing schedule is based on height and current weight, the same as for non-pregnant women. Thus, it is important to take into account the patient's weight during pregnancy when calculating the dose of chemotherapy in each cycle [8, 14].

The administration of chemotherapy in each trimester increases the prevalence of different complications. As such, in the first trimester, there is an increased risk of malformations and spontaneous miscarriage [2, 11, 24]. On the other hand, in the second and third trimesters there is an increased chance of stillbirth, premature birth, intrauterine growth restriction (IUGR), and low birth weight [1, 2]. To decrease the occurrence of congenital abnormalities, chemotherapy should be delayed until the second trimester, but the consequences of this approach should be considered in the light of maternal health [15]. Despite some negative effects in the second and third trimesters, which need to be monitored, chemotherapy is considered to be quite safe during this period [1, 2].

Each cycle of chemotherapy should be preceded by a clinical examination and transvaginal or transrectal ultrasound to assess the patient's response to treatment. If there is no response after 2 cycles of chemotherapy, treatment should be evaluated [9].

Importantly, chemotherapy should be stopped 3 weeks before delivery or before the 37th week of pregnancy to regenerate the bone marrow of the mother and the fetus [1, 15]. Intriguingly, there is a lack of consensus about the long-term side effects of children whose mothers have received chemotherapy during pregnancy. However, there are studies reporting negative results [17, 19], including associations with a higher risk of growth restriction, cognitive impairment, ototoxicity and cardiotoxicity [8].

Radiotherapy

Due to the emission of high doses of ionizing radiation, radiotherapy is generally forbidden in pregnant women as it induces

spontaneous abortion within one month of completion [21]. Hence, postponing the radiotherapy until delivery is the only option when pregnancy preservation is the primary goal.

Concomitant radiochemotherapy and brachytherapy are applied when the disease stage is defined as FIGO IB and above [25]. When the patient chooses to preserve pregnancy, radiotherapy with chemotherapy is postponed until after delivery [6].

Interestingly, postpartum radiotherapy planning might be challenging. The uterus returns to its original shape and size within 6 weeks of delivery [26]. Due to these dynamic changes and organ motion, monitoring and eventual modification of the irradiated area during radiotherapy should be applied.

Delivery and breastfeeding

Cancer progression may enforce premature delivery. If possible, delivery after the 37th week of pregnancy is preferred. If early delivery is unavoidable, steroids should be administered to induce fetal lung maturation [7, 15]. Spontaneous delivery is associated with a negative prognosis [9]. Therefore, in the management of invasive cervical cancer, caesarean section is the preferred method of delivery, followed by definitive treatment [7, 14, 18, 27]. This type of schedule may decrease the risk of neoplastic cell implantation in the episiotomy scar as well as reduce metastasis spreading during vaginal delivery [14, 15]. Finally, as chemotherapy passes into breast milk, breastfeeding is forbidden during treatment. However, it can be reintroduced at least 3 weeks after the last cycle [2, 15, 21].

Pregnancy termination

If the patient wishes to preserve the pregnancy, neoadjuvant chemotherapy should be considered for locally advanced cervical cancer. However, if the woman decides not to preserve the pregnancy, the standard of care adapted to the FIGO stage should be the same as for non-pregnant women [2, 6]. In general, pregnancy termination is offered to patients diagnosed with cervical cancer before the 20th week of pregnancy [14]. However, at different stages of pregnancy, the use of specific treatments may carry different risks of complications. Thus, in stages IB3 and higher, the patient may undergo chemoradiotherapy with the fetus present in the uterus in the first trimester. However, in the second trimester, a hysterectomy followed by chemoradiotherapy should be performed, as it reduces the risk of obstetric complications [15].

Future directions

Due to the low incidence of cervical cancer among pregnant women, there are no specific treatment guidelines established [28]. Thus, the current recommendations are based on limited data derived from a small number of retrospective trials [17]. There is a definite need for true evidence-based data that would define the cancer treatment schedule with adequate and safe drug doses. However, such data may only be obtained from prospective clinical trials, which obviously cannot succeed due to ethical considerations [29]. Moreover, due to the rising rate of cervical cancer in young women, it is necessary to establish fertility-sparing management and guidelines [10]. Furthermore, there is no relevant data assessing the impact of pregnancy on the course of gynecological neoplasms [15]. Recently, Li et al. observed no survival differences between women who preserved their pregnancy and those who terminated it [20]. However, this observation should be further confirmed by others, as physiological changes during pregnancy may accelerate the development of cancer [1, 7, 30].

Conclusions

The treatment of pregnant women with cancer unequivocally presents a serious challenge. The lack of experience in the diagnosis and treatment of neoplasms in pregnant women may lead to delayed and inappropriate management. As such, it can harm both maternal and fetal health. The analyzed literature does not define uniform treatment methods, as it is based on general recommendations and small sample case studies. Therefore, the pregnant patient with cervical cancer should be cared for by experienced board of obstetricians, gynecologists, neonatologists, and oncologists. It is worth addressing the discussed problems in future clinical research so as to provide the very best care possible for pregnant cancer patients.

Article information and declarations

Author contributions

Anna Dąbrowska – conceptualization, data curation, formal analysis, investigation, methodology, project administration, validation, visualization, roles/writing – original draft, review and editing.

Adrian Perdyan – data curation, formal analysis, investigation, methodology, resources, validation, visualization, roles/writing – original draft, review and editing.

Bartosz K. Sobocki – investigation, methodology, resources, validation, roles/writing – original draft, review and editing.

Jacek Rutkowski – conceptualization, funding acquisition, investigation, project administration, resources, supervision, validation, roles/writing – original draft, review and editing.

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Conflict of interest

None declared

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Advances in the management of pheochromocytoma – a short review

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Pheochromocytoma is a rare neuroendocrine neoplasm. It is characterized by overproduction of catecholamines, which causes clinical symptoms associated with elevated blood pressure values, and can even lead to life-threatening complications. The tumor can be associated with genetic syndromes such as multiple endocrine neoplasia type 2 (MEN-2) or von Hippel–Lindau syndrome (VHL), and currently available and constantly evolving genetic testing makes it possible to detect the inherited form and plan appropriate therapy. Management of pheochromocytoma is based on initial laboratory diagnosis, confirmation by imaging studies, determination of hormonal activity and resulting therapy. Surgical resection by laparoscopic approach is the most recommended. For unresectable tumors or advanced disease with distant metastases, systemic therapies under development currently allow the cure or inhibition of tumor progression. In this paper, we will review advances in management of pheochromocytoma over the past decade and potential directions for future research.

Key words: pheochromocytoma, management, imaging studies, systemic therapy, advances

Introduction

Pheochromocytoma is a rare neuroendocrine neoplasm occurring in an estimated average of 1 in 200,000 people. It is characterized by the overproduction of catecholamines originating from pathological chromaffin cells of the adrenal medulla. Only a small fraction metastasizes – approximately 10% of cases [1–4]. The classification of adrenal tumors in the group of endocrine tumors was updated by the WHO in 2017. The terms "benign" and "malignant" are currently no longer used for pheochromocytoma, as all of them (pheochromocytoma and paraganglioma – PPGL) present metastatic potential. To avoid confusion due to the former nomenclature, the WHO has replaced the term "malignant" with "metastatic" for pheochromocytoma. The terminology of paraganglioma also required systematization to distinguish between the histological origin and the anatomy of the lesion [5, 6]. Primary non-metastatic pheochromocytoma is most frequently associated with hereditary multiple endocrine neoplasia type 2A (MEN-2A). It is observed in 50% of MEN-2A patients, who have a somatic mutation of the *RET* gene. It also occurs in MEN-2B which is a much rarer syndrome [7–9]. The components of MEN-2 syndromes containing pheochromocytoma are summarized in table I.

Currently, about 30-40% of all pheochromocytoma cases are considered to be hereditary. This neuroendocrine lesion

Table I. Neoplasms and abnormalities included in MEN-2 [17]

MEN-2A (Sipple syndrome)	MEN-2B (Wagenmann-Froboese syndrome)
• medullary thyroid carcinoma • pheochromocytoma • primary hyperparathyroidism • normal physical appearance	• medullary thyroid carcinoma • pheochromocytoma • mucosal and gastrointestinal neuromas • marfanoid body habitus

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must be differentiated from adrenocortical carcinoma, because it is approximately fifty times rarer and presents similar symptoms, but more often turns out to be metastatic [10, 11]. Due to its characteristics, a pheochromocytoma usually releases enormous amounts of catecholamines, metanephrines or methoxytramine that cause typical sympathetic nervous system manifestations. These could be headaches, tachycardia, hyperhidrosis or even episodic palpitations. They are also accompanied by other symptoms, mainly related to elevated blood pressure values. Less common symptoms include anxiety, panic attacks, seizures, abdominal pain, excessive sweating, diarrhea, nausea, polyuria, fever or weight loss. It is worth mentioning that some patients can be asymptomatic and tumors secreting different substances can provide different symptoms. For example, pheochromocytoma that secretes epinephrine may cause orthostatic hypertension, but a dopamine-secreting lesion would present normal blood pressure values [12, 13].

Untreated or inadequately treated pheochromocytoma can lead to a number of dangerous complications, including acute coronary syndrome, myocardial infarction, cardiogenic shock, Takotsubo-like and dilated cardiomyopathy. As can be seen, these are mainly cardiac related complications. Electrocardiographic changes mimicking myocardial ischemia like ST-elevations or T-wave depressions may also be observed in the course of pheochromocytoma. The tumor may also lead to life-threatening arrhythmias, visible in an ECG as prolongation of corrected QT interval or giant inverted T-waves [14]. However, pheochromocytoma, as a tumor secreting enormous amounts of catecholamines, may also cause hemorrhagic stroke, hypertensive crisis or spontaneous bleeding from the renal parenchyma (Wunderlich syndrome) as an extremely rare complication [15, 16]. The aim of this paper is to review the methods of diagnosis and therapy of pheochromocytoma and the progress that has been made over the past decade of research.

Review methods

For the preparation of this review paper, PubMed, PubMed Central and Google Scholar databases were searched. The phrases used for research were various forms and combinations of terms such as "pheochromocytoma", "pheochromocytoma diagnosis", "pheochromocytoma surgery", "pheochromocytoma systemic therapy", "pheochromocytoma genetics", "peptide receptor radionuclide therapy" or "tyrosine kinase inhibitors". Research was focused mainly on articles from the past decade to display developments and advances in the treatment. After reviewing the abstracts, articles that matched the aim of the work and focused on multidisciplinary diagnosis and therapy were selected. The analyzed papers were original articles, review articles and meta-analyses. Out of the articles from the initial research, 40 that comprehensively and adequately described the topic were selected. Finally, the obtained material was divided into groups of diagnosis, surgical treatment and systemic treatment of pheochromocytoma, and comprehensively described.

Diagnostics

Diagnosis of pheochromocytoma nowadays is based primarily on imaging examinations preceded by biochemical tests. Nowadays, thanks to advances in technology, the genes responsible for the formation of the tumor process have been discovered [18]. With suspicion of pheochromocytoma, either plasma-free metanephrines or fractionated urinary metanephrines are measured. Both methods appear to have a similar sensitivity and specificity. In the case of unclear results, a measurement of urinary dopamine, plasma 3-methoxytramine or even chromogranin A (CgA) can also be used. Following evident biochemistry results, imaging studies are performed starting with CT or MRI scans. Finally, methods such as PET-CT or ^{123}I-MIBG scintigraphy are used to confirm the hormonal activity of the tumor and plan the therapy [5].

Biochemical tests

Pheochromocytoma is a tumor that secretes catecholamines. Thus, it would seem logical to measure these compounds in plasma or urine. Previously it was the levels of catecholamines and their metabolites (vanillylmandelic acid, metanephrines, normetanephrines, 3-hydroxytyramine) in urine that were biochemically assessed by 24-hour urine collection. The current evidenced trend is the measurement of plasma-free metanephrines (metanephrine, normetanephrine, 3-MT), and it appears to be more reliable than the other types of tests, with 96.6% sensitivity and 94.9% specificity compared to the measurement of metanephrines in 24-hour urine collection (92.9% and 94.5%, respectively), but guidelines accept both tests for pheochromocytoma screening [19, 20]. Recent results reported that plasma-free metanephrines have a higher specificity than metanephines in 24-hour urine collection (95% *versus* 90%, respectively). A higher probability of pheochromocytoma is suggested by metabolite values exceeding more than twice the upper reference range. Elevated levels of a minimum of two metabolites also raise suspicion of a tumor. Biochemical testing should always be performed before imaging studies [19]. It has also been proven that the liquid chromatography-mass spectrometry (LC-MS) method has the highest testing accuracy and with liquid chromatography electron capture dissociation (LC-ECD), they are the gold standard nowadays that allows avoiding interactions with drugs. High performance liquid chromatography with electrochemical detection (HPLC-ECD) is considered more prone to analytical interference [19, 21]. However, there might be pitfalls in the diagnosis of PPGL. The possibility of false-positives should be remembered, so before measurements from both urine and plasma, the patient should abstain from caffeine, tea, nicotine, alcohol, cheese or bananas, and discontinue medications such as MAO inhibitors, tricyclic

antidepressants or SSRIs. When collecting the samples, it is important for the patient to remain fasting, without intense stress and in the supine position, which greatly increases the sensitivity of the test and reduces the cost of retesting [19, 22]. It has been proven that supine sampling has a higher testing sensitivity than seated sampling (95% to 89%, respectively) [23]. A case study published by Neary et al. shows that even in a patient with a family history of pheochromocytoma and a genetic burden, elevated levels of catecholamines do not automatically indicate a tumor. In a 51-year-old patient, an abnormal test result was caused by taking venlafaxine, a norepinephrine reuptake inhibitor that dramatically increased norepinephrine levels. In addition, α-adrenergic-receptor blockers and β-adrenergic-receptor blockers may reduce catecholamine-related symptoms and mask pheochromocytoma. Paracetamol may interfere with the aforementioned HPLC--ECD method and bias the test results. Thus, it is recommended to discontinue problematic drugs 24 hours before testing metanephrines in plasma or urine collection [24].

For non-functional pheochromocytomas, false-negative results may occur during standard measurements. The use of a CgA marker is helpful in such cases. This acid protein belongs to a group that forms the components of secretory granules of neuroendocrine cells. It shows 90% clinical sensitivity as an additive method to standard plasma-free metanephrine measurements, but the absence of its elevation cannot be used alone to exclude the presence of a tumor. However, it is also important to remember the possibility of CgA false results as in metanephrine tests. False-positive results may be caused by the treatment with proton pump inhibitors, histamine type-2 receptor antagonists, atrophic gastritis, impaired kidney function, inflammatory bowel disease, liver cirrhosis, hypercortisolemia, post-meal or post-exercise status. For this reason, it is recommended to rule out any medical disorders before the test, discontinue the aforementioned medications (at least 10 days for PPIs) and measure CgA after rest and fasting [25, 26].

Imaging techniques

Imaging uses traditional CT and MRI techniques, but diagnosis can be supplemented with scintigraphy using ^{123}I-MIBG (iodine-123-metaiodobenzylguanidine). Pheochromocytoma may be detected incidentally on routine imaging studies like CT or MRI on CT, pheochromocytoma is most often a solid, hypervascular and well-demarcated mass ranging in size from a few to 15 cm in its largest dimension. Larger tumors typically have a tendency for central necrosis. On MRI, tumors are hyperintense on T_2-weighted images and hypointense on T_1-weighted images. The advantages of ^{123}I-MIBG scintigraphy are the relatively low cost of the test, high image quality and low radiation exposure for the patient. The sensitivity of this method ranges from 83–100% and specificity from 95–100% in tumor detection. The method is very useful in planning radiotherapy with ^{131}I-MIBG [19]. Another method is imaging with PET-CT and ^{68}Ga-labeled DOTA peptides (DOTATATE, DOTATOC and DOTANOC). They are captured by somatostatin receptors (SSTRs) contained in each neuroendocrine tumor cell so that the location of lesions can be assessed with the greatest accuracy [27]. SSTR antagonists (^{111}In DOTA-BASS, ^{111}In-DOTA--JR11 or Ga-DOTA-JR11) are also used there. We can also use ^{18}F-fluorodopa in combination with PET-CT imaging. In this way we image L-type amino acid transporters. Data show that this technique has 100% sensitivity and is used in reputable centers to confirm an inconclusive result. A similar method is 18-fluorodeoxyglucose imaging using PET-CT [28–30].

Genetics and immunohistochemistry

According to a paper by Fishbein et al., the genes involved in the pheochromocytoma pathogenesis can be divided into three clusters, depending on their mechanism of action: pseudohypoxia, kinase signaling and Wnt signaling [31]. First cluster associated with pseudohypoxia and reduced oxidative response includes:

- *SDHx* – encoding succinate dehydrogenase complex,
- *vHL* – responsible for coding von Hippel–Lindau tumor suppressor, that is associated with pheochromocytoma, renal and pancreatic lesions,
- *DLST* – encoding the E2 subunit of mitochondrial α-ketoglutarate dehydrogenase,
- *SLC25A11* – determining the proper functioning of the malate-aspartate shuttle,
- *MDH2* – responsible for mitochondrial malate dehydrogenase that converts malate to oxaloacetate,
- *PHD1* – an unmutated gene activates HIF-1α and HIF-2α.

The second cluster, associated with abnormal activation of kinase-signaling pathways, includes:

- *PNMT* – expression is associated with the adrenergic phenotype of specific hereditary pheochromocytoma,
- *HRAS* – associated with increased expression of components of the RAS-MAPK signaling pathway and reduced expression of the DNA damage pathway.

The third cluster, connected with Wnt and Hedgehog signaling, includes genes like: *WNT4*, *DVL3*, *MAML3* and *CHGA*. The pathogenesis of pheochromocytoma also involves the genes *ATRX* and *H3F3A*. These genes are responsible for chromatin remodeling and H3.3 histone but are not classified into the aforementioned clusters. Genetic testing can be used after a diagnosis of pheochromocytoma to exclude an inherited form or to predict the prognosis and hormonal activity of the tumor. 65% of patients with a mutation of the aforementioned *SDHx* gene have high levels of catecholamines, and patients with second cluster gene mutations are more likely to develop epinephrine-producing tumors than norepinephrine-producing ones. Such tests appear to have numerous indications for predicting prognosis, establishing a treatment plan or implementing preimplantation diagnosis.

Table II. Overview of pheochromocytoma diagnostic methods

	Biochemical tests	Imaging techniques	Genetics and IHC methods
examples	• plasma-free catecholamines • urine catecholamines • plasma-free metanephrines • urine metanephrines • CgA	• abdominal CT • abdominal MRI • ^{123}I-MIBG scintigraphy • PET-CT with SSTR-binding DOTA peptides • ^{18}F-FDG PET-CT	• *SDHx*, *vHL*, *DLST* and other gene testing with molecular methods • IHC markers (CgA, synaptophysin) • *SDHx* mutations testing with IHC
notes	plasma-free metaephrines with LC-MS testing method have the highest accuracy, CgA is useful in non-functional pheochromocytoma, beware of false results (caused by drugs or diet)	should be performed after biochemical tests, routine tests as CT can detect the lesion, then nuclear medicine tests are performed allowing radionuclide treatment	mainly used after tumor diagnosis to determine heritability or metastatic potential; in prognosis prediction IHC as a more available method can be helpful in the diagnosis of genetic mutations

Despite the utility of these tests, they are often expensive. For this purpose, the field of immunohistochemistry (IHC) is developing solutions to reduce costs and assess the pathogenicity of genetically uncertain tumors [19]. IHC methods were used to distinguish metastatic pheochromocytoma from a lesion without metastatic potential, because of the difficulty of doing this in histological methods. It was proven that of the tested IHC markers (e.g., CgA, synaptophysin, S-100, Ki-67, melan-A, inhibin), the first two show utility in predicting the neuroendocrine nature of the tumor. Their immunoreactivity was presented as granular cytoplasmic staining with variation in the intensity in different tumor areas. Overall intensity was higher for chromogranin than for synaptophysin. High variability in the architectural patterns of tumor cells in each lesion prevented the effective use of S-100. High levels of Ki-67 proved specific, but insufficient to predict the metastatic potential of pheochromocytoma independently. Melan-A and inhibin did not show immunoreactivity. The study proved that IHC with the use of these markers is not helpful in predicting the clinical behavior of pheochromocytoma but only in confirming the neuroendocrine nature of the examined lesion [32].

Currently, IHC is collaborating with previously described genetic methods in the diagnosis of mutations in patients with pheochromocytoma. It mainly investigates mutation of the *SDHx* gene through loss of expression of SDHA, SDHB, SDHC and SDHD proteins. The sensitivity and specificity of SDHB IHC in the *SDHx* subunit mutation are 95.0% and 81.8%, respectively. Interobserver variation using SDHB/SDHA immunohistochemistry when there is a poor diffuse SDHB interpretation is also being investigated [30]. In a recent study, Su et al. found that patients with SDHB(–) had a significantly worse prognosis and shorter survival time than patients with SDHB(+). The authors emphasize the possible benefits of these findings, as it is possible to predict the prognosis of mutation-laden pheochromocytoma patients on the basis of these results and include them in a more rigorous follow-up.

Without IHC, this would not be possible on a larger scale, due to the cost and low availability of genetic testing. The IHC procedure can be successfully performed in most centers. There is certainly a need for larger clinical trials in this area, however at present, the use of IHC in pheochromocytoma genetics appears to be a future avenue [33]. Information on the diagnosis of pheochromocytoma is summarized in table II.

Therapy

Over the years, pheochromocytoma therapy has been based on several essential principles: surgery, chemotherapy and radiotherapy. Recently, due to the rapid development of molecular biology, we can also include individualized immune agents in the treatment [34, 35]. The choice of the therapy should include factors such as the resectability of the tumor, its infiltration of adjacent structures, the presence of distant metastases, the amount of hormones secreted by the tumor, its growth rate and the patient's comorbidities. The principal treatment of a pheochromocytoma secreting significant amounts of hormones is surgical resection with perioperative adrenergic receptor blockade, as it is necessary to improve the patient's condition as quickly as possible and prevent severe cardiovascular complications. The presence of disseminated inoperable malignancy disqualifies from surgical treatment. In order to improve the patient's condition, slowing tumor progression and reducing the amount of hormone secretion, systemic treatments such as radiation therapy, chemotherapy or pharmacotherapy are used. Unlike in the case of hormonally active or metastatic lesions, for tumors indolent in hormone secretion or non-metastatic, the "watch and wait" strategy is currently accepted [19].

Surgical treatment

Surgical treatment seems to be associated with a relatively low 5-year survival rate (45%). This is justified by the location of the tumor itself, as well as the difficulty of resecting metastases and the formation of postoperative complications. The preferred method is laparoscopy due to the lower invasiveness of the procedure, but the presence and nature of metastatic lesions most often require modification of the procedure to laparotomy. It was indicated that the limiting tumor size for laparoscopic surgery is 6 cm [18, 36, 37].

A different survival rate was reported by De Filpo et al. which described currently surgical resection of a metastasis--free tumor using available imaging technologies at the time of initial advancement results in a 5-year survival rate of more than 90% [38]. In addition, Amar et al. suggest that it is possible to achieve a decreased rate of postoperative complications of pheochromocytoma with a complete and thorough resection [39]. At this point, it is worth mentioning the anesthesia procedure during pheochromocytoma resection, considered one of the most difficult challenges in anesthesiology practice. Procedures such as laryngoscopy, endotracheal intubation or the manipulation of the tumor itself, could be the triggers that cause catecholamine spikes and hemodynamic instability. The standard procedure is to administer a long-acting benzodiazepine (e.g. diazepam) the night before surgery and α-blockade with shorter-acting drugs (e.g. prazosin) or longer-acting drugs (e.g. phenoxybenzamine); however, drugs with longer half-lives should be withheld 12–24 h before surgery. H_2-blockers are also useful. Propofol or etomidate are used for anesthesia induction but ketamine is not recommended due to its sympathicomimetic effects. The key problem of anesthesia induction appears to be the pressor response to laryngoscopy and endotracheal intubation. Agents like fentanyl, lidocaine, esmolol, nitroglycerin or nicardipine are useful in this case. A recommended depolarizing agent is vecuronium, due to its lack of histamine release, unlike pancuronium. The inhalation anesthetics used are most commonly sevoflurane, enflurane and isoflurane, and opiates are long-acting agents (morphine, hydromorphone) [40, 41].

Systemic treatment

Treatment with somatostatin analogs like Yttrium-90-DOTATOC (^{90}Y-DOTATOC) and lutetium-177-DOTA0-Tyr3-octreotate (^{177}Lu-DOTATATE) has become one of the radiotherapeutic approaches. Lowery A. et al. described a phase II clinical trial for the treatment of pheochromocytoma with an already known radionuclide ^{131}I-MIBG, but at a higher dose. Such a therapy yielded a 5-year survival rate of 64%. On the other hand, the use of somatostatin analogs ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE in a group of patients led to at least partial remission in 46% of the subjects [42]. Another treatment method is the use of chemotherapeutics, especially in patients refractory to radiotherapy. A CVD regimen, consisting of cyclophosphamide, vincristine and dacarbazine, was widely used. It provided an average of 5.5 months without recurrence of the neoplastic process. It was also indicated that a better prognosis was provided by the association of CVD with anthracyclines and oral temozolomide. Biological drugs were gradually introduced into treatment as new substances that yielded promising results in therapy. The known molecular pathway responsible for the pathogenesis of pheochromocytoma has allowed the use of inhibitors of its individual substrates. The mTOR inhibitor everolimus was used in therapy with apparent improvement, albeit unfortunately short lived. Sunitinib, a tyrosine kinase inhibitor (TKI), found therapeutic use, while another drug with the same effect, imatinib, did not provide such promising results [43–48].

Zhang et al. published a pheochromocytoma treating method with a novel immune therapy – a combination of the mTORC1 and mTORC2 inhibitor drug called PP242. The study was conducted on mice. The previously known drug rapamycin, an mTOR1 inhibitor, was compared with the newly discovered substance. Clinical studies showed that PP242 significantly inhibited tumor growth due to the molecular inhibition of the activation of the effector protein in the mTOR pathway and caused activation of apoptosis in tumor cells [49]. Antonio K. et al. described a chemotherapeutic BEZ235. Its antitumor effect is based on several important choke-points. It inhibits phosphoinositide 3-kinase (PI3K), the mTOR1 and mTOR2 complexes. Molecularly, there is a decrease in the expression of the norepinephrine transporter by inducing cytotoxic and antiproliferative effects. The result is the induction of cell apoptosis with a significant reduction in proliferation and angiogenesis [30]. Research has also been conducted on the heat shock protein Hsp90.

Giubellino et al. attempted to cure pheochromocytoma by targeting this protein. The experiment was conducted *in vitro* on a human cell line and *in vivo* on mice. Tested cells were infected with human pheochromocytoma cells. After that, the experimental substances were applied: 17-AAG (17-allylamino-17-demethoxygeldanamycin) and ganetespib, a second-generation Hsp90 inhibitor. In both parts of the experiment, apoptosis of certain tumor cells and a definite reduction in the ability to form metastases were observed, with ganetespib showing a stronger effect at a given concentration [50].

Another treatment strategy was tested by Zhang et al. on mice. The therapy was a combination of both mTORC2 and Hsp90 inhibition. The use of only one agent inhibited the proliferation in the majority of cells, but the additive action of both agents resulted in an increased effect. Apoptosis of tumor cells and their metastatic migration occurred in the same manner [51].

Based on previous experience, Mercado-Asis et al. clearly indicated that the future of treatment will be the association of biological drugs with each other. Single-component formulations do not provide sufficient efficacy, since inhibition of a selected pathway results in the upregulation of a collateral pathway. A small-molecule HIF-2α inhibitor was being investigated. It was molecularly designed to block unrestrained tumor cell growth and proliferation, tumor angiogenesis and the suppression of antitumor immune responses. Also at the clinical trial stage at the time was a topoisomerase I inhibitor, thought to reduce tumor growth and metastatic potential [28, 29].

Targeted therapies were also analyzed by Corssmit et al. The substances were: axitinib and pazopanib, a drug from

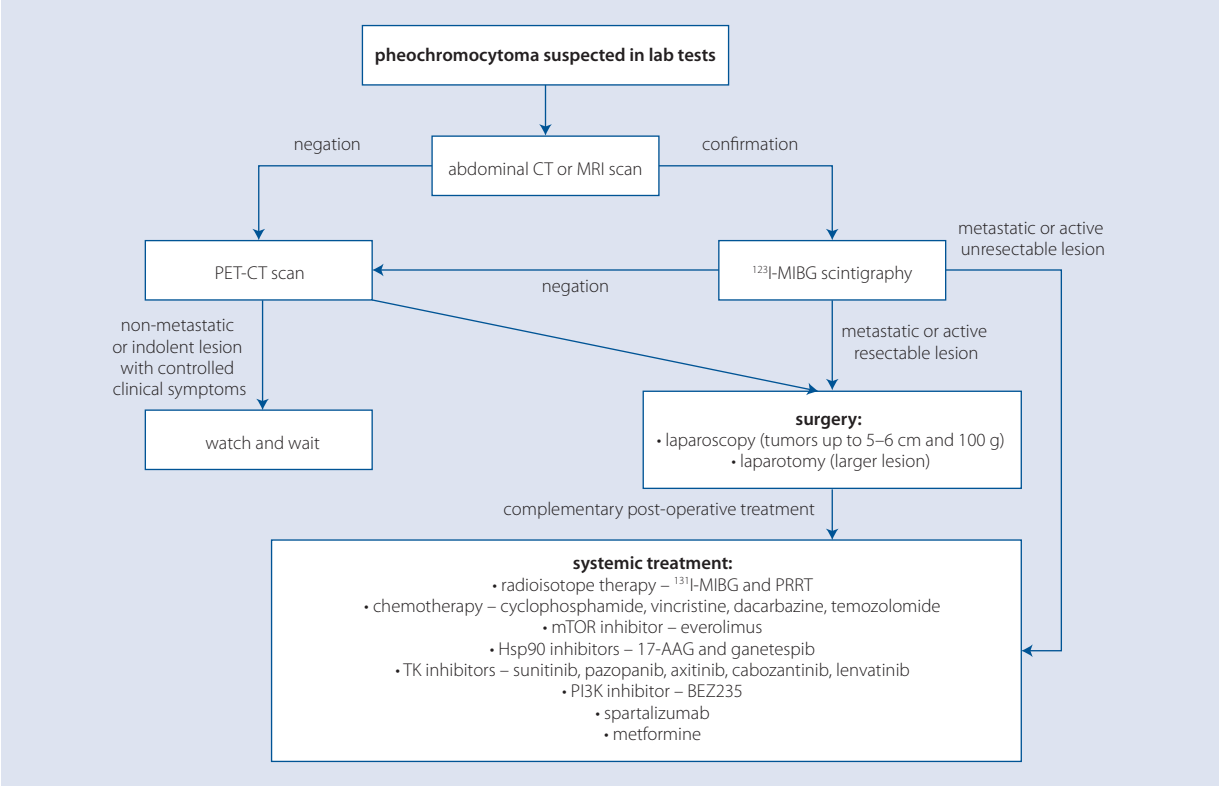

Figure 1. Management algorithm for patients with pheochromocytoma

the long-known group of antiangiogenic receptor TK inhibitors. The initial phases of the study did not show spectacular benefits from their use. In the initial stages of experiments there are two more substances, lenvatinib and cabozantinib. A poly(ADP-ribose) polymerase inhibitor that is responsible for chemotherapy resistance was also discovered. Its inhibitor, olaparib, is showing promising therapeutic activity. A group of immunomodulatory drugs that are also in clinical trials – nivolumab, ipilimumab and pembrolizumab – have also been stopped. These substances are checkpoint inhibitors, allowing for the process of apoptosis to be irreversibly inhibited in neoplastic cells [52, 53]. Spartalizumab, a humanized monoclonal antibody capable of binding to the programmed death checkpoint protein receptor, is also in clinical trials [38].

One of the most recent experimental therapies was described by Meireles et al. and involves the administration of metformin. The study was conducted on rat and human cell lines. The results showed that this substance inhibited PC12-ADH cell proliferation and reduced oxygen consumption, ATP production and proton leakage, as well as loss of mitochondrial membrane potential. In addition, metformin induced AMPK phosphorylation and impaired activation of the AMPK-PI3k-AKT-mTOR pathway [54].

The latest treatment direction for pheochromocytoma was published by Tabebi et al. The target point of the therapy is suggested to be striking the nuclear and mitochondrial genetic material of the neoplasm cells. At the stage of early clinical trials, there are substances that are intended to achieve this goal and represent an optimistic view of the future in pheochromocytoma therapy [55]. The management of patients with pheochromocytoma is reviewed in figure 1.

Conclusions

Pheochromocytoma is a rare neuroendocrine tumor that represents a major therapeutic challenge. Its diagnosis is based on both laboratory and imaging studies, which are being supplemented all the time with new possibilities using the resources of nuclear medicine. Still, the largest number of these tumors are detected incidentally before the onset of alarming clinical symptoms. The great advances that have been made over the past decade now make it possible to detect tumors at an earlier stage, and the gene clusters and carcinogenesis pathways that are being discovered make it possible to predict prognosis and plan the treatment. Surgical resection of the tumor is still the therapy of choice, but when it is not an option, currently existing and developing systemic therapies are able to inhibit or slow tumor growth and limit clinical symptoms. The large range of chemotherapeutics in clinical trials offers hope for the future in pheochromocytoma therapy.

Article information and declarations

Author contributions

Michał Miciak – conceptualization, methodology, writing, review and editing of the manuscript.

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Krzysztof Kaliszewski – conceptualization, methodology, review and editing of the manuscript, supervision.

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Conflict of interest

None declared

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Artykuł przeglądowy / Review article

Nowotwory wątroby / Liver tumors

Stereotactic irradiation of liver tumors – is it worthwhile?

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The standard treatment for metastatic liver lesions as well as primary tumors is surgery. Unfortunately, it is not always possible and other forms of local ablative treatment can be considered: radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemo embolisation (TACE), cryotherapy or stereotactic body radiation therapy (SBRT). SBRT is a highly focused radiation treatment that gives an intense dose of radiation concentrated on a tumor, while limiting the dose to the surrounding organs. SBRT is a non-invasive, short in duration (a few days of therapy) treatment which is feasible also for elderly and fragile patients. This review article presents the role of SBRT in the treatment of liver metastases and primary liver cancers.

Key words: stereotactic body radiation therapy, liver metastases, primary liver tumors, hepatocellular carcinoma, cholangiocarcinoma

Introduction

The role of radiotherapy in the treatment of liver lesions has increased significantly in recent years. For decades, this method was restricted to palliative treatment only [1]. This was due to the risk of damaging the liver parenchyma. The development of irradiation techniques has made it possible to deliver a high dose to the lesion, while reducing the dose to the healthy part of the organ. One of these methods is stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT). It is a highly focused local treatment that gives an intense dose of radiation concentrated on the tumor, while limiting the dose to the surrounding organs, leading to increased local lesion control rates with acceptable levels of toxicity.

This type of radiotherapy can be applied using a traditional linear accelerator, as well as modern devices such as CyberKnife or tomotherapy. It is commonly used for the treatment of lung lesions, brain tumors, or bone metastases. SBRT can also be delivered with a curative intent to primary liver tumors and liver metastases, which happens more often. For patients diagnosed with liver metastases, the best treatment is surgery. The most common metastatic tumor in the liver has a colorectal adenocarcinoma origin [2]. It is due to direct drainage through the portal venous system.

The historical results show that surgical liver metastasectomy improves the overall survival (OS) with 1- and 5-year rates of 90–95% and 30–60%, respectively, with a median overall survival of 40–53 months [3]. Many patients are not candidates for such procedures due to tumor burden, multifocality, comorbidities, or poor general status. For these selected cases, other forms of local ablative treatment can be considered: radiofrequency ablation (RFA), microwave ablation (MWA), transarterial chemo embolisation (TACE), cryotherapy or SBRT [4]. In the case of primary malignancies, the most common tumors are hepatocellular carcinoma (HCC, 75–85%) and intrahepatic cholangiocarcinoma (10–15%) [5]. The problem is patients who are not eligible for hepatectomy with eventual liver transplantation [6]. In this case, other forms including radiotherapy are also to be

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considered. In the following publication, we outline the potential use of SBRT in the treatment of liver lesions.

SBRT for liver metastases

The incidence of liver metastases is increasing of which the most common primary tumor is colorectal cancer. According to Engstrand et al., liver metastases are diagnosed in 26.5% of patients within five years of the diagnosis of this malignancy [7]. Stereotactic radiotherapy is more commonly used for radiotherapy of liver metastases. This is related to the theory of metastatic disease, i.e., the existence of an intermediate form of cancer between localized and generalized forms – oligometastatic disease. This subgroup of patients could be described as patients with a limited number of metastases who could be aggressively treated using local modalities (surgery and/or radiation). That subgroup can be divided into two; one – synchronous metastases diagnosed at the same time and metachronic which occurred after a time interval [8]. It assumes the presence of a group of patients with quantifiable metastatic lesions in the lungs, brain, or liver.

According to the guidelines of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), surgery with/or without perioperative systematic therapy is the first option of local therapy for metastatic liver tumors. All patients should be discussed with the multidisciplinary team (MDT). In patients with favorable factors: fewer metastases (<3 lesions), unilobar disease, no extrahepatic lesions, and metachronous lesions) upfront surgery (or another method of local therapy) should be performed [9–11].

Not all patients are eligible for surgical treatment, and possible induction chemotherapy to downsize the tumor may significantly worsen liver function [12]. Only 20–30% of liver-only metastases patients are potentially resectable. About 30–60% of patients survive 5 years after resection and varies between studies depending mostly on the radicality of the surgery and adjuvant therapy. Disease-free survival after 5 years reported is within the range of 4% and 47% (median 18%) with median postoperative mortality at 2.8% [13]. Rocca et al. in a systematic review showed that robotic surgery postoperative mortality was 0.4% with 3-year overall survival being 55% [14].

The alternative treatment options are the following: stereotactic body radiotherapy (SBRT), radiofrequency ablation, microwave ablation, radiolabeled microspheres, transarterial chemo embolization, cryoablation, and alcohol injection [15]. There are no direct randomized trials comparing SBRT with these other forms of local treatment and all of them have advantages and limits. SBRT, because of its non-invasive nature and short treatment time, is a convenient therapy for elderly and fragile patients.

Stereotactic body radiotherapy and RFA were compared by Jackson et al. in a retrospective study showing 2-year FFLP (freedom from local progression) to be 88.2% and 73.9%, respectively ($p = 0.06$). For bigger tumors (≥2 cm in diameter), SBRT improved FFLP (HR, 0.28; 95% CI: 0.09–0.93) but not OS. On multivariate analysis, treatment with SBRT and a tumor diameter smaller than 2 cm were associated with improved local control. Grade ≥3 treatment-related toxicity was rare, with no difference between SBRT ($n = 4$) and RFA ($n = 3$) [16]. In another systematic review with meta-analyses comparing these two treatment forms, Lee et al. showed improved local control of SBRT compared to RFA (83.6% *vs.* 60%, $p < 0.001$) with no statistically significant difference in overall survival [17].

Patient selection

Imaging studies before a decision on the local treatment form should be based on a CT of the thorax, abdomen, and pelvis. Additionally, FDG-PET could be useful in defining the extent of metastatic disease. An MRI of the liver is also strongly suggested to assess the local extent or to exclude non-typical lesions in the liver [18]. The treatment method for metastatic liver lesions should be made as part of a multidisciplinary team. Only patients with adequate liver function can be candidates for treatment. Unfortunately, only a few patients qualify for surgery. For SBRT the following issues should be considered:

- number of metastases,
- size,
- distance from organs at risk (OARs), and
- laboratory parameters of the liver.

Indications are shown in table I.

Candidates for SBRT are oligometastatic patients with a good performance status (Eastern Cooperative Oncology Group 0–2), extra-hepatic disease should be controlled (absent

Table I. Patient qualification to SBRT according to Comito et al. [19].

Indicated	Borderline	Contra-indicated
number of hepatic lesions ≤3	patients with 4 liver metastases	patients with ≥5 hepatic lesions
size lesions ≤3 cm	diameter >3 and ≤6 cm	diameter >6 cm
OARs distance >8 mm	OARs distance >5 and ≤8 mm	OARs distance ≤5 mm
good liver function (Child-Pugh A)	moderate liver function (Child-Pugh B)	inadequate liver function (Child-Pugh C)
free liver volume >1000 cm^3	free liver ≥700 and <1000 cm^3	free liver volume <700 cm^3

or suitable for local treatment). Histopathology should not be an inclusion nor exclusion factor. The age of the patient is not a selection factor. SBRT is well tolerated by elderly patients who are unsuitable for surgery [19].

SBRT planning

Stereotactic body radiotherapy of metastatic lesions can be performed on conventional linear accelerators and other devices such as CyberKnife or tomotherapy. The treatment involves administering several doses of irradiation precisely to the lesion area while sparing the healthy tissue, which is an excellent alternative for patients who do not qualify for invasive treatment methods.

The recommended doses vary in the available publications. The total dose, the fractional dose, which are planned to be administered depends on the number of lesions, the volume of the healthy liver (total liver volume minus cumulative gross tumor volume [GTV]) and the dose given to the critical organs such as kidneys, stomach, bowel, spinal cord (OARs) [20]. As a result, this technique also has its limitations. This also applies to lesions that are large in size and close to the organs at risk such as the bile ducts or large blood vessels. In the available publications, doses ranged from 14 to 70 Gy given in 1–10 fractions. The respiratory mobility of the liver should be taken into account when planning radiotherapy. It may use a variety of methods such as gating, tumor tracking or abdominal compression. Another important element of treatment planning is the establishment of fiducial markers [21]. Implantation of fiducial markers into the liver metastases or near the leasion helps by patient set-up and online treatment verification (fig. 1).

Results and toxicity

To date, there is a lack of randomized studies comparing SBRT with other forms of local treatment (RFA, MWA) or comparing it with other radiation modalities or fractionation. There are several prospective studies or retrospective case series which have shown promising OS and LC results with mild toxicity. The results of some of them are presented in table II.

One year OS after SBRT in reported studies is higher than 56% in all studies and it reaches a level above 80% in two of them. Among treated patients, local control ranges from 60–95% at 1 year and 45–90% at 2 years. The publications

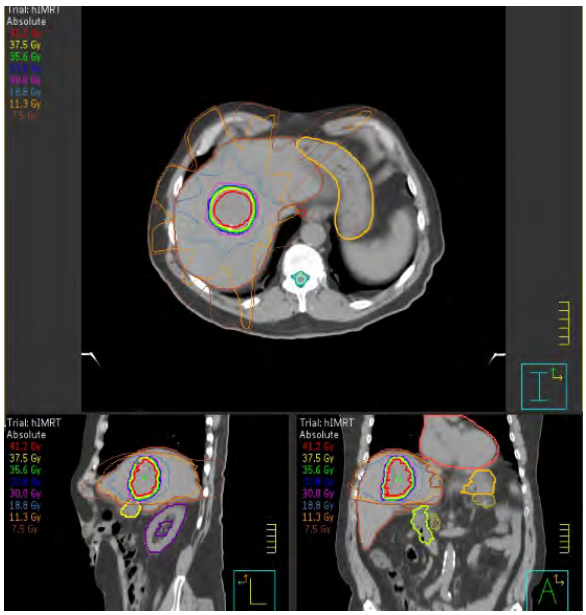

Figure 1. Images from the radiotherapy planning system

Table II. Characteristics of studies

Author, year [ref.]	Type of study	Number of patients	Number of leasions	Dose Gy/fx (fractions)	Follow-up – median (range)	Overal survival	Local control	Toxicity
Scorsetti et al., 2018 [21]	prospective	61	1–3 (<6 cm)	52.5–75 Gy/3 fx	24	1 y – 85.0%; 2 y –31.1%	1 y – 95%; 2 y – 78%	G3 – 1%
Joo et al., 2017 [22]	retrospective	70	1–2 (leasion size – 2.9 cm)	45–60/3–4 fx	34.2	2 y –75%	1 y – 93%; 2 y – 68%	G3 – 0
Hoyer et al., 2006 [23]	prospective	64	leasion size – 3.5 cm	45/3 fx	52	1 y –67%; 2 y – 38%	2 y – 86%	1 patient – liver failure
Chang et al., 2011 [24]	retrospective	65	1–2	22–60/1–6 fx	14	1 y – 72; 2 y – 38%	1 y – 62%, 2 y – 45%	G3 – 3 patients
Berber et al., 2013 (Cyberknife) [25]	retrospective	53	1–6	43/3 fx	17	1 y – 56%	1 y – 60%	1 patient – death
Lee et al., 2009 [26]	retrospective	40	1–8 (mean 2)	27.7–60/6 fx	10.8	18 months – 47%	1 y – 71%	G3 – 9%, G4 – 1%[a]
Bodreau et al., 2023 (stereotactic MR-guided radiotherapy) [27]	prospective	26	1–2	40–60/5 fx	17	1 y – 83.1%; 2 y – 41.6%	1 y – 90%; 2 y – 90%	G1–2 – 34%; G3 – 0

Gy – gray; Fx – fraction; [a] – thrombocytopenia

listed in the table concerned patients with liver metastases from various cancers, while the majority were from colorectal cancer. Several studies have evaluated potential prognostic factors for local control with SBRT for liver metastases.

Smaller tumors and those receiving a higher dose along with motion management methods have been associated with better local control. Mutations of p53 and *KRAS* detected among patients suffering from colon cancer are associated with lower local control [28]. Data regarding the impact of histology on LC are ambiguous [29]. Moreover, the German Society of Radiation Oncology database trial showed that liver metastases from breast cancer are more radioresistant than other histologies [30]. Studies have also shown that a higher dose of radiation therapy is associated with better outcomes. A biological equivalent dose (BED) could be an independent prognostic factor of local control [22].

Joo et al. showed that BED_{10} 80 Gy or less is associated with 2 year LC 52%, BED_{10} 100–112 Gy with 83% and BED_{10} 132 Gy or more with 2 years LC 89% [22]. This means that the higher the dose of radiotherapy given, the better the local control achieved.

Overall, SBRT of metastatic liver lesions is well tolerated. It is a non-invasive treatment form and can be offered to elderly patients [19]. The most common complications (mainly G1–2) are:

- fatigue,
- nausea,
- lack of appetite,
- gastritis, or
- transiently increased levels of hepatic transaminase which normalize within 3 months of treatment.

The most serious complications (G3–4) are:

- perforation of a colonic or duodenal ulceration demanding surgery,
- musculoskeletal discomfort, or
- radiotherapy-induced liver failure.

SBRT as a treatment for primary tumors of the liver

Hepatocellular carcinoma (HCC) is the most common primary pathological diagnosis for liver cancer patients, and is the fourth cause of cancer death globally with a dismal prognosis [31]. The treatment of choice is surgery (hepatic resection or transplantation). According to Japanese data, only 38% of patients qualify for surgery [32]. Depending on the stage of the disease, the patient's general status and liver function, either a resection of the lesion or liver transplantation is the standard of care. Other local methods used for treatment include radiofrequency ablation and transarterial chemoembolisation. According to the guidelines of the American Society of Radiation Oncology (ASTRO) radiotherapy is an option for patients with unresectable and inoperable HCC both as EBRT and SBRT [33]. Stereotactic body radiotherapy can be used as a radical treatment and could be helpful for patients awaiting liver transplantation or be used as a palliative treatment. The continuous development of radiotherapy techniques and imaging methods for liver lesions has enabled more precise radiotherapy treatment. Most publications on SBRT of HCC are retrospective studies of a relatively small group of patients.

Radical treatment of HCC

The results of SBRT treatment were presented in a meta-analysis by Rim et al. in which 32 publications assessing 1950 patients were included [34]. Pooled 1-, 2-, and 3-year OS rates were 72.6%, 57.8%, and 48.3%, respectively. Good LC was also demonstrated: 1-, 2-, and 3-year LC rates were 85.7%, 83.6%, and 83.9%, respectively. The subgroup analysis showed that tumor size was the most important prognostic factor. This prognostic factor has also been proven in similar studies [35, 36]. Additionally, tumor vascular invasion (TVI) was considered a negative prognostic factor. This condition is also associated with an increased risk of developing portal vein trombosis. The meta-analysis also showed that radiation dose escalation does not significantly impact OS and LC [34]. Similar results were obtained by Ohri et al. [37].

Reported SBRT dose is 30–50 Gy in 3–5 fractions [39, 40], according to ASTRO the recommended dose starts from 50–60 Gy in 3–5 fractions, with more scheduled in case of higher burden of the disease [32]. When prescribing the dose of radiotherapy, the number of lesions, their size, distance from the OARs, liver function (e.g. Child-Turcotte-Pugh class) should be taken into account [40, 41]. Guidelines also suggest modern techniques such as SBRT, dynamic techniques such as arc therapy, proton therapy with respiratory motion management with daily imaging. Treatment tolerance is very good and hepatic or gastrointestinal complications >3 grade appeared in <5% of the patients in nearly every publication [42–46]. Rajyaguru et al. in a retrospective study that analyzed 3980 nonsurgically managed patients with stage I or II HCC compared SBRT with radiofrequency ablation (RFA). After propensity matching, 5-year overall survival was 29.8% in the RFA group *versus* 19.3% in the SBRT [45]. Another study comparing SBRT with RFA retrospectively was by Nalee et al., showing similar results [46].

On the other hand, Sapir et al. compared SBRT *versus* TACE showing statistically a significant beneficial effect of SBRT on 1 and 2 year LC (97% and 91% *vs.* 47% and 23%, respectively). The grade 3 toxicity rate was higher with TACE (13%) than SBRT [47].

According to the National Comprehensive Cancer Network (NCCN) guidelines, radiotherapy along with ablation and arterially directed therapies are valid treatment options for nonresectable patients (without recommendation, one treatment over another due to the lack of randomized controlled trials with a comparison between these methods) [48]. Referring to ASTRO guidelines, in patients with liver-only HCC with incomplete response to thermal ablation or catheter-based therapies, EBRT is recommended as a consolidative treatment option [33].

Bridge therapy and downstaging therapy of HCC

Bridge therapy is used in patients qualified for liver transplant. It is used to prevent tumor progression while the patient awaits a liver transplantation. Various methods of local treatment of liver tumors may be used: RFA, MWA, TACE or SBRT [34]. Kulik et al. showed that the forms of local treatment mentioned above do not significantly improve post-transplantation mortality or overall survival, compared to transplants alone [49]. Bridge therapy is mainly used in centers with long waiting times for liver transplantation. Downstaging therapy is used to reduce the size of the tumor so that the patient can fulfil the Milan criteria [50] for surgery with liver transplantation [51].

SBRT for cholangiocarcinoma

The second most common liver tumor is cholangiocarcinoma (CCC). It is highly malignant with an extremely poor diagnosis – 70% of patients have an inoperable tumor [52] and 50% of patients relapse within one year after surgery [53]. Radiotherapy (EBRT) is mainly used as a neoadjuvant, therapy after a successful operation or palliative treatment. The role of SBRT is poorly investigated and is an alternative to surgery or other local treatments. Gkika et al. showed in a retrospective study that SBRT of CCC reached 1 year 0S: 56% with a median OS of 14 months from the start of SBRT and 22 months from diagnosis. Median progression-free survival (PFS) was 9 months [54]. Similar results have been achieved in other studies: Sandler et al. – 1 year LC: 78%, median OS – 15.7 months [55]; Tse et al. – 1 year LC: 65%, median OS – 15 months [56]. The toxicity of the SBRT was acceptable, with the main severe complications being bleeding. It should be mentioned that classical fractionation is recommended in an adjuvant setting and in combination with systemic treatment.

Conclusions

Here we have presented the role of SBRT in the treatment of tumors of the liver – either metastases or primary malignancies. Stereotactic body radiotherapy is increasingly popular for the treatment of all malignancies due to its short treatment time and acceptable level of toxicity. In addition, it is used for patients who are often ineligible for surgery. With the development of radiotherapy, new equipment (e.g. CyberKnife, MRI-guided radiotherapy) is making the treatment more and more precise. However, there are still many concerns about the dose of radiotherapy, patient selection and combination with systemic or immune therapies. Importantly, any decision regarding treatment should be determined by a multi-specialist team.

Article information and declarations

Author contributions

Michał Kurzyński – conceptualization, methodology, writing original draft, resources.
Marta Urbańska-Gąsiorowska – visualization, supervision.
Marcin Hetnał – visualization, supervision, resources.

Conflict of interest

None declared

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Clinical nutrition in oncology

How much can a cancer patient eat and how to calculate it – a dietitian's point of view. Collaboration between doctor and dietitian

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Malnutrition in cancer patients is a severe clinical problem. One of the factors determining nutritional status is nutritional intake. The ability to provide adequate oral nutrition in cancer patients is mainly determined by the location and advancement of the disease, the type of oncological treatment, as well as the severity of the side effects of the therapy. Food intake is often reduced in cancer patients, leading to weight loss. Assessment of the nutritional intake requires a unique approach due to various limitations and conditions that do not occur in healthy people and the frequent deficiencies of multiple nutrients. In the context of preventing and treating malnutrition, cooperation between a doctor and a dietitian is crucial. Dietary counselling is the first step of nutritional intervention and can be offered to most patients. According to The European Society for Clinical Nutrition and Metabolism (ESPEN) recommendations, dietary counselling supported by oral nutritional supplements has a recommendation grade of "A" according to Evidence Based Medicine (EBM). Success in maintaining or improving the patient's nutritional status depends on efficient cooperation between the doctor and dietitian. This publication aims to present the tasks of a dietitian and the principles of collaboration with a doctor in the nutritional care of cancer patients.

Key words: malnutrition, nutritional assessment, clinical nutrition, dietary counselling

Malnutrition in cancer patients

Malnutrition is a severe clinical problem that may affect from 18 to 90% of cancer patients. Weight loss often precedes the diagnosis of the disease and is one of its symptoms. Patients with cancer of the head and neck, upper gastrointestinal tract (esophagus, stomach, pancreas), and lungs are most at risk of developing malnutrition. Patients with these cancers are characterized by moderate to severe malnutrition at the time of diagnosis [1, 2]. Malnutrition has several consequences that influence the course and effect of oncological treatment. The implications of both primary and secondary malnutrition are an increase in the frequency of complications (surgical and infectious), an increase in the duration of hospitalization, treatment costs, and mortality [3].

The development and exacerbation of hospital malnutrition are influenced not only by poor quality hospital diet or numerous diagnostic procedures where the patient must fast but, above all, by not undertaking any nutritional intervention

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in patients who require it or undertaking it too late. Therefore, patients who lose more than 5% of body weight should have their nutritional status assessed when diagnosed with cancer. If malnutrition or its risk is diagnosed, appropriate nutritional intervention should be initiated. The nutritional status assessment should be repeated during active treatment and palliative care [4].

Determining indications for particular types of nutritional intervention and the schedule of follow-up visits are crucial elements of cooperation between a doctor and dietitian.

Assessment of nutritional status

Each patient at high risk of malnutrition (cancer of the head and neck, gastrointestinal tract and lungs) or with a current, unintentional weight loss of >5% at the time of cancer diagnosis should have their nutritional status assessed. Nutritional status should be assessed regularly throughout the entire oncological treatment period. We use screening and in-depth methods to evaluate the nutritional status [1, 4].

The Regulation of the Minister of Health of January 1, 2012, imposes on Polish hospitals the obligation to perform screening assessment of the nutritional status of all hospitalized patients (except for the hospital emergency department, ophthalmology, otolaryngology, allergology, orthopedics and traumatology departments if hospitalization lasts less than three days, as well as in the case of hospitalization <1 day). The nutritional risk screening 2002 (NRS) and subjective global assessment (SGA) scales are used to assess the risk of malnutrition [5]. The NRS 2002 scale is usually used in clinical practice because it is shorter and more accessible to perform. It considers the patient's general condition, treatment and comorbidities, weight loss over the last 3–6 months, and daily coverage of individual energy needs.

In patients whose screening assessment indicates malnutrition or the risk of malnutrition, an in-depth assessment of the nutritional status and initiation of appropriate nutritional intervention are required. Methods used for in-depth assessment of nutritional status are listed below [6]:

- anthropometric measurements (body weight, body height, body mass index [BMI], thickness of the skinfold over the triceps muscle, arm muscle circumference, measurement of muscle strength),
- body composition assessment (including using electrical bioimpedance, computed tomography, magnetic resonance imaging, densitometry),
- biochemical tests (most often determining the concentration of albumin, prealbumin, transferrin, C-reactive protein, nitrogen balance and the total number of lymphocytes),
- assessment of demand for energy, macro- and micronutrients.

Criteria for diagnosing malnutrition

Since 2018, by the Global Leadership Initiative on Malnutrition (GLIM) consensus, we diagnose malnutrition according to the following criteria (at least one phenotypic and etiological criterion must be met) [6]:

1. Phenotypic criteria:
- weight loss >5% in 6 months or >10%, beyond 6 months,
- reduced body mass index BMI < 20 kg/m^2 if <70 years or BMI < 22 kg/m^2 if >70 years of age. For the Asian population: BMI < 18.5 kg/m^2 if <70 years or BMI < 20 kg/m^2 if >70 years of age,
- reduced muscle mass index determined using a validated technique for measuring body composition, e.g. bioelectrical impedance (BIA), dual-energy X-ray absorptiometry (dual energy X-ray absorptiometry [DXA]).

2. Etiological criteria:
- reduced food intake and/or food absorption disorders ≤50% of estimated requirements >1 week, or any reduction for >2 weeks, or any chronic gastrointestinal (GI) condition that adversely impacts food assimilation or absorption,
- inflammation – chronic inflammation associated with chronic disease, trauma, or acute conditions.

The GLIM algorithm is acknowledged as the gold standard for diagnosing malnutrition.

Assessment of nutritional intake in cancer patients

One of the factors determining the nutritional status of cancer patients is the nutritional intake, which should be assessed in both quantitative and qualitative ways. In cancer patients, oral intake is mainly determined by the disease's location and stage, the treatment type, and the severity of the side effects of the therapy used [7]. It is estimated that energy intake lower than 25 kcal/kg/day is associated with a high risk of malnutrition. Therefore, oral intake should be assessed at specified intervals so that it is possible to determine and adapt the optimal diet to the current clinical situation [8, 9].

According to the multi-center study "Nutrition Day", conducted using a one-day assessment of the nutritional status in over 300 European hospitals, hospital meals do not cover the energy needs of hospitalized patients. The study's authors reported that the energy intake of 43% of respondents was less than 1,500 kcal per day [10].

Methods for assessing nutritional intake

Nutritional intake assessment methods are diverse due to the multi-thread nature of this concept and provide information on the qualitative and quantitative value of consumed foods. One of the popular methods of assessing individual oral intake is the 24-hour dietary recall method. The patient is asked what types and quantities of products, dishes and drinks were consumed the previous day or days preceding the examination. When assessing the size of consumed portions, photo albums of products and dishes are used, which present the typical appearance of dishes and products of appropriate weight.

The data obtained are useful for estimating the diet's average energy and nutritional value.

Another method used in dietitian practice to assess nutrition is current dietary records. The method of ongoing recording involves the patient writing down all consumed foods over 1–14 days using home measurements (e.g. a spoon, slice, glass) or using the weight from packaging. When noting, the patient should pay attention to the percentage of fat in the product, e.g. milk – 0.5% or 3.2%, and sugar addition. The diet recording method is easy to conduct and does not require memory, such as a nutritional interview. The most frequently used is a three-day current intake record, but extending it to 7 days makes the average daily intake more realistic.

Crucial to adequately analyzing nutritional intake is to include oral nutritional supplements and single nutrients (liquid formulas, powders, tablets), which are not classified as food but may be an important source of energy and nutrients. The actual (real) energy and protein consumption must be compared to the calculated requirements of the patient and applicable standards. The data obtained from both methods are entered into computer databases, based on which specialized nutritional programs calculate the energy value of daily food rations, the content of total protein, total fat, cholesterol, types of fatty acids, total carbohydrates, dietary fiber, essential vitamins and minerals. Using these same IT devices, the dietitian may compose dietary advice with an adequate menu which is complete regarding nutritional value.

Although the above methods are widely used by dietitians in the individual assessment of patients' nutrition, there still needs to be an indication in the literature of what strategies to use in oncological patients. According to the study authors' many years of experience, the method of 24-hour interview or ongoing recording is used and works well in outpatients under the care of a dietitian. Using the methods described above in hospital care is too time-consuming and challenging to implement on a large scale.

According to Gronowska-Senger et al., in hospitals, it is possible to estimate the size of consumed portions using the so-called plate diagram sheets (fig. 1). The diagram indicates how much from the portion of the dish/product the patient consumed during the meal (0, 25, 50 and 100%). The energy value may be underestimated when the subjects consume less than 50% of the served portion. The method is considered valuable and is recommended in clinical practice to identify people with low caloric intake.

There are also attempts to record consumption by taking photos or filming. An example is the Wellnavi method, which involves taking pictures of meals eaten during the day with a mobile phone and sending the image to a dietitian for further analysis. Because the meals contain invisible added products, subjects complete a short questionnaire about their consumption. For technical reasons, these methods are not yet widely applicable [11, 12].

Analysis of the nutritional intake allows us to identify the subjects who do not consume the recommended amount of energy and protein. The next step is to decide how to increase the supply of macro- and micronutrients. The gap between actual and estimated caloric requirements may be covered with standard or fortified food, food for special medical purposes or artificial nutrition.

Energy, protein and micronutrient requirements in oncological patients

The standard oral diet of an oncological patient should cover the need for energy, protein, micronutrients and water. Depending on the patient's current clinical situation, diets may require modifications to the essential ingredients supply. Any restrictive elimination diets are not recommended. The table below (tab. I) shows the demand for cancer patients by the ESPEN) recommendations [4].

Nutritional support for patients with reduced energy and protein intake

Offering dietary counselling to cancer patients is the easiest option and the cheapest method to improve and maintain proper nutritional status. Patients at nutritional risk or with weight loss that began unintentionally must be referred to a dietitian regardless of their current body weight. It is recommended that counselling be continued during active treatment, as well as for patients treated with palliative intent and for patients after completion of oncological therapy to support healing and as a form of secondary prevention. According to the ESPEN

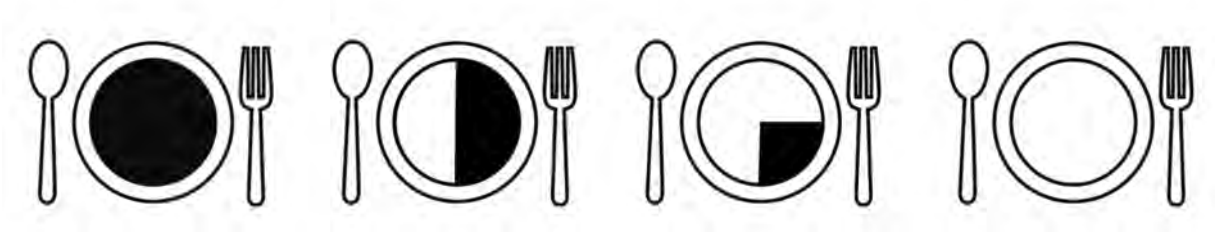

Figure 1. Plate diagram sheets

Table I. Energy demand and essential dietary components

energy	25–30 kcal/kg body weight. In cachectic patients with normal body weight, the requirement is calculated based on the current body weight, and in obese patients, it is the ideal body weight
protein	protein above 1.2 g/kg body weight/day, on average 1.5 g/kg body weight/day, maximum 2.0 g/kg body weight/day
fats	in patients with weight loss and concomitant insulin resistance, it is recommended to increase the amount of energy from fats (up to 50%) by the reduction the amount of energy from carbohydrates
vitamins and trace elements	not exceed the daily requirement RDA – recommended daily allowance and AI – adequate intake
water	30 ml/kg body weight/day

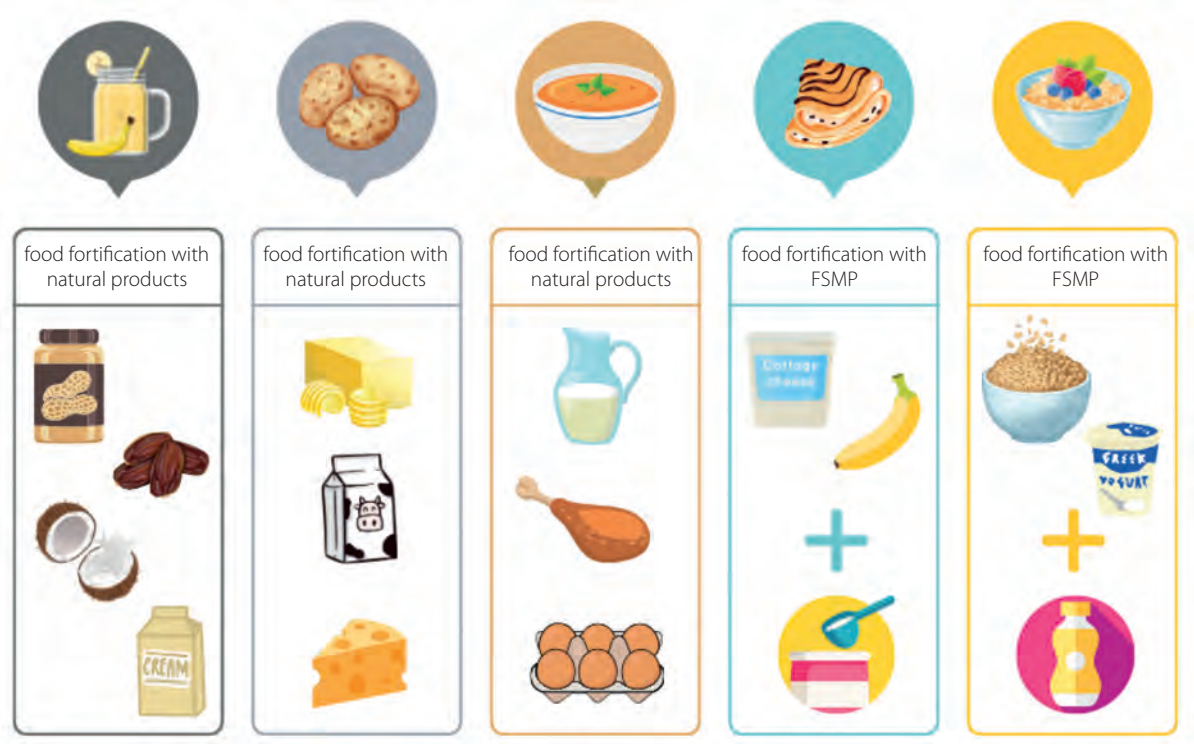

Figure 2. Examples of food fortification

recommendations for oncological patients, dietary counselling supported by oral nutritional supplements has an undeniable recommendation for use (strength of recommendations – strong, level of evidence – moderate) [4].

In patients with reduced energy and protein intake, it is recommended to fortify the diet, i.e. increase its nutritional value by [1] (fig. 2):

- the addition of food products with a natural, high energy density such as butter, vegetable oils, sweet cream, mascarpone cheese, high-fat yoghurts, coconut milk, avocado, egg yolk and egg white, meat, groats, cereals, ground nuts, honey, chocolate,
- addition of complete and incomplete food for special medical purposes (FSMP).

Food fortification should be carried out under the supervision of a dietitian for it to be effective. Incorrect food fortification may disturb the proportions of nutrients in the diet and hinder the absorption of some of them.

Concomitant anorexia, feelings of early satiety, and taste and smell disorders also contribute to reduced food intake. In such a situation, additionally recommended are [13]:

- small-volume meals, served frequently, approximately 6–8 times a day,
- including partially mixed meals in the menu (including cocktails, cream soups, mousses, pastes, jellies, fruit and vegetable purees, soft meatballs in sauce),
- drinks served between meals,
- adding FSMP (chilled, low osmolarity) to the diet,
- seasoning meals according to the patient's preferences: fresh herbs, lemon, lime, balsamic vinegar,
- meat is better tolerated in marinades with fruit (e.g. apple puree, cranberry sauce), as well as in marinades made from cream, coconut milk or lemon juice,
- to stimulate taste, it is recommended to include cold foods between meals: fruit sorbets, ice cream, sucking frozen pineapple cubes or frozen fruit.

Nutritional support – dietary part

An essential element of assessing the patient's nutritional intake is an interview conducted by a clinical dietitian. The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw adopted the following standards for the work of a dietitian in the field of collecting nutritional information:

- what the patient ate that day (breakfast, second breakfast, lunch, dinner, snacks),
- what the patient drank during and between meals,
- type of food products used, fat content (e.g. in dairy products), added sugar and culinary techniques used (e.g. cooking, baking, frying),
- size of portions of meals consumed – using household measures (e.g. spoon, cup, plate) or using plate diagram sheets (the so-called plate system),
- whether and what supplements and food for special medical purposes and in what doses the patient uses.

The conclusions from the interview, i.e. the answer to the question of how much (energy and protein) the patient eats and how it relates to the current demand, are passed on to the attending physician by the dietitian. Based on a comprehensive assessment of the nutritional status, diet, information on accompanying symptoms and the advancement of the disease (cancer type, stage and treatment plan), the doctor-dietitian team decides on the type of nutritional intervention (fig. 3).

The method of choice is constantly feeding through the digestive tract. Dietary counselling and the selection of FSMP are the competencies of a dietitian. If oral nutrition with regular food products and FSMP support fails to cover energy and protein needs, artificial nutrition should be considered. The method of choice is enteral nutrition unless there are contraindications. When enteral nutrition is impossible, insufficient or intolerable, parenteral nutrition should be considered [14].

Nutritional support – the physician's role and cooperation with a dietitian

Collaboration between a doctor and a dietitian is crucial in preventing and treating malnutrition. That said, other specialists may also be necessary: a nurse, a speech therapist, a physiotherapist, a psychologist or a social worker. Multidisciplinary teams aim to improve treatment results and the patient's quality of life [15]. A decision-making algorithm is proposed below to describe a doctor's and dietitian's collaboration in managing nutritional care (fig. 4).

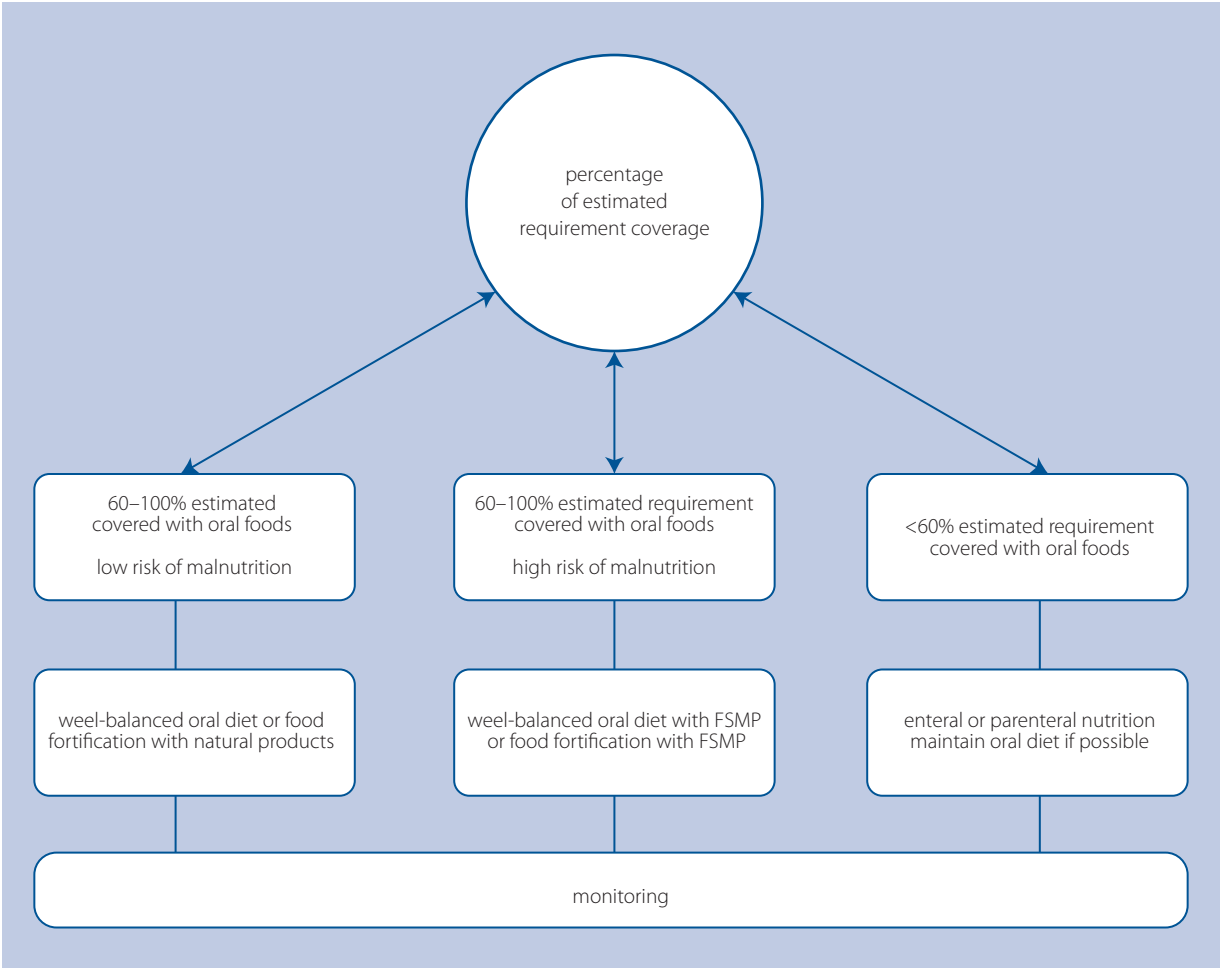

Figure 3. The decision-making flowchart. The type of nutritional intervention depends on the amount of energy, protein and other nutrients taken orally [1, 4, 13]

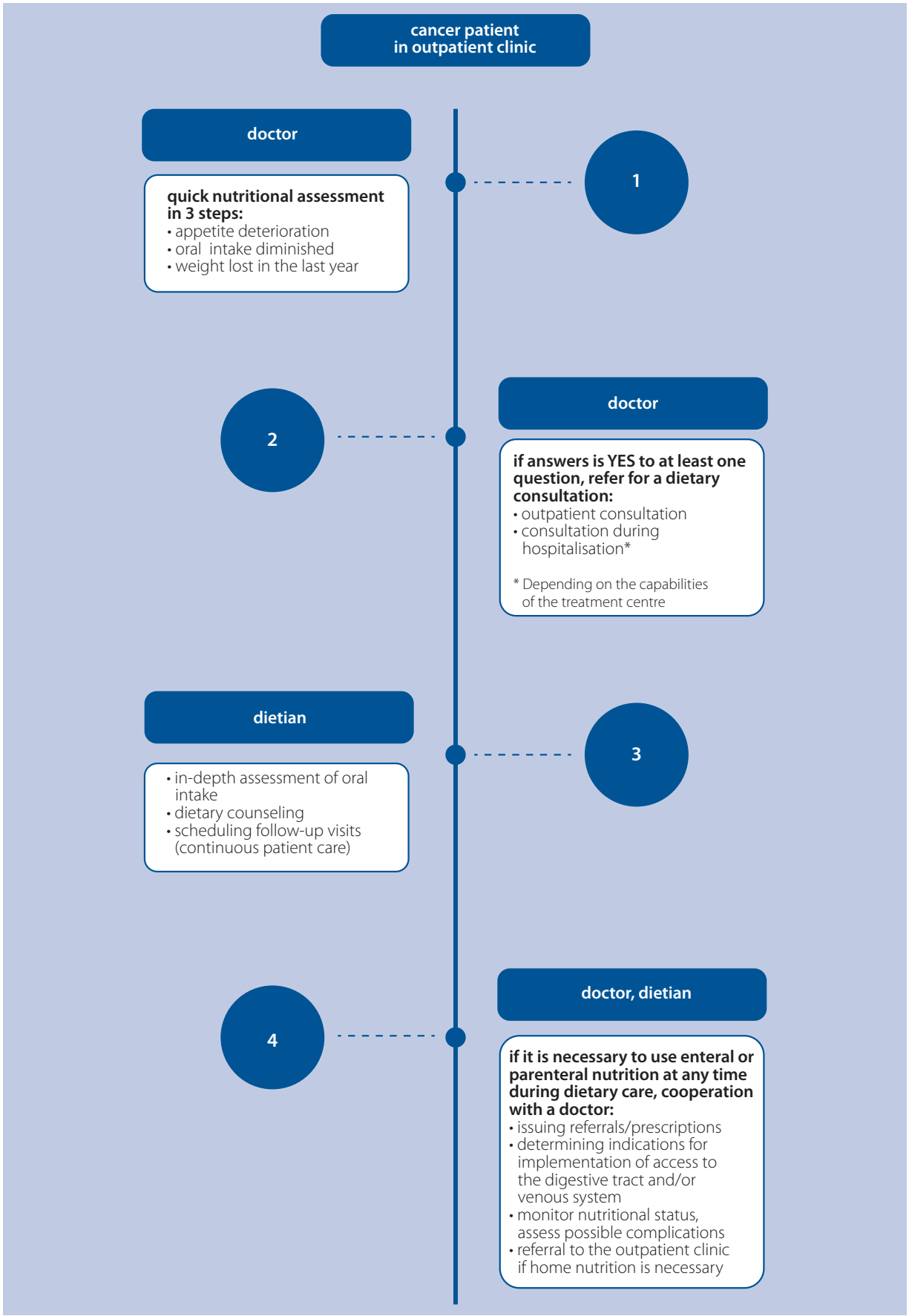

Figure 4. Decision-making algorithm describing cooperation between a doctor and a dietitian

Table II. Competency table of the Polish Society for Parenteral, Enteral Nutrition and Metabolism (POLSPEN) Nutritional Treatment Standards [14]

Specialist	Scope of competence
doctor	• conducting a screening and in-depth assessment of the nutritional status • development of a nutritional treatment plan and responsibility for the correct implementation of the therapy • insertion and replacement of short and long-term artificial access to the gastrointestinal tract • establishment and replacement of central and peripheral, short and long-term venous access • issuing prescriptions, and referrals
dietitian	• dietary and FSMP advice • nutrition education of the patient and/or caregiver of the patient undergoing nutritional treatment • screening and in-depth assessment of nutritional status • establishing assumptions and monitoring the diet for inpatient and outpatient nutritional therapy patients

A constant dialogue between a dietitian and a doctor is necessary for nutritional care to be effective. Both professions are characterized by different professional competencies in malnutrition treatment, which are listed in table II [14].

Plenty of evidence in the literature shows that treatment outcomes can be improved by creating multidisciplinary nutrition teams. The introduction of a screening assessment of nutritional status by a dietitian increased the effectiveness of diagnosing malnutrition by 50–80% and, on average, shortened the hospital's stay by about three days [16, 17]. Moreover, multidisciplinary care reduces hospital admissions, the incidence of infectious complications and treatment costs [18]. A nutritional care program provided in patients with HNC during chemoradiotherapy by a doctor-dietitian team reduced the incidence of infectious complications and prevented drug dose reduction and the deterioration of patients' anthropometric and laboratory parameters [19].

In European medical care, a dietitian should be a part of the team planning oncological treatment. According to the European Food and Safety Association (EFSA's) recommendation, one dietician should care for 50 hospital beds [18, 20].

Article information and declarations

Author contributions

Agnieszka Surwiłło-Snarska – concept, manuscript writing.
Katarzyna Różycka – preparing tables and figures.
Ewelina Grochowska – manuscript writing.
Aleksandra Gazi – manuscript writing.
Emilia Motacka – manuscript writing.
Marta Dąbrowska-Bender – manuscript writing.
Anna Oleksiak – manuscript writing.
Aleksandra Kapała – concept, checking.

Conflict of interest

None declared

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The role of nutrition in oncological prevention

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In the global battle against cancer, the second leading cause of death, research aims to identify preventative measures, with over 40% of worldwide cancer fatalities and disability-adjusted life years linked to modifiable lifestyle aspects. Understanding the multi-stage, long-term process of carcinogenesis is vital, as is the identification of contributing factors. By controlling certain lifestyle factors like diet, exercise, smoking and alcohol consumption, we can mitigate cancer risk. Leading institutions such as the World Cancer Research Fund and American Institute for Cancer Research have formulated guidelines to reduce cancer risk. These tenets include maintaining a healthy weight, engaging in physical activity, adhering to a balanced diet, limiting alcohol, refraining from smoking, avoiding excessive sunlight and taking breastfeeding into account. Many of these principles centre on dietary habits, advocating for a varied intake of fruit, vegetables, whole grains and legumes, while limiting red and processed meats and alcoholic drinks.

Emerging research highlights the considerable influence of diet on cancer risk, leading to the formulation of dietary guidelines to minimize this risk. This paper delves into these recommendations and examines the impact of various dietary components and patterns on cancer development.

Key words: dietary intake, cancer, neoplasms, food intake

Introduction

In Poland, like many regions of the world including Europe, the number of cancer patients is steadily increasing. According to the European Commission's estimates published in the European Cancer Information System (ECIS), the number of new cancer cases in Europe increased by 2.3% in 2022 compared to 2020, reaching 2.74 million. Similarly, the number of deaths due to cancer increased by 2.4% compared to 2020 [1]. The four most common cancer causes of death in the EU are lung (19.5% of all cancer deaths), colorectal (12.3%), breast (7.5%), and pancreatic cancer (7.4%).

In Poland, cancer is the second most common cause of death behind cardiovascular disease, responsible for 24.5% of all deaths [2]. Cancer diseases account for 22.8% of the total disease burden (disability-adjusted life years – DALY) in Poland for men, and 19.6% for women. In Poland, the number of malignant tumour cases has reached more than 164,000 a year. The most common cancers for men are prostate (19.7%), lung (16.8%) and colorectal (12.3%) cancers, whereas for women these are breast (22.5%), colorectal (9.9%) and lung (9.4%) cancers [2].

With cancer being the second most common cause of death worldwide, researchers' attention has been focused on finding ways to prevent these diseases. More than 40% of global cancer deaths and disability-adjusted life years are attributed to modifiable lifestyle factors [3]. It is important to understand that the process of carcinogenesis consists of many stages and can take several to several dozen decades. Undoubtedly, many factors contribute to the development of cancer. Knowledge of these factors, combined with the ability to modify those within our control (such as diet, physical activity, smoking, alcohol consumption, etc.), can help reduce the risk of cancer.

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The European Code Against Cancer (ECAC) promotes raising awareness of health-promoting behaviours among the public, with the goal of reducing exposure to cancer-promoting factors (e.g., smoking, being overweight, physical inactivity, alcohol, sun exposure, carcinogens, unhealthy diet). ECAC also stresses the importance of other measures, such as vaccination programmes and screening [4].

The World Cancer Research Fund/American Institute for Cancer Research are the leading centres that have developed recommendations aimed at reducing cancer risk. According to the AICR, the ten principles of cancer prevention include maintaining a healthy body weight, adequate physical activity, adhering to a healthy diet, limiting alcohol consumption, avoiding smoking and excessive sunlight, and taking breastfeeding into account. Most of these principles apply to diet-related factors. It is recommended to consume a variety of fruit and vegetables, whole grain cereal products and legume seeds, while limiting red meat consumption as well as avoiding processed meat products and alcoholic beverages [5].

A growing body of research indicates that diet has a significant impact on cancer risk, leading to the development of dietary recommendations aimed at reducing this risk. This paper discusses recommendations and research findings on the effects of various dietary elements and patterns on cancer development.

Consumption of animal products and cancer risk

Red meat and processed meats

According to the International Agency for Research on Cancer (IARC), excessive consumption of red meat and especially processed meats such as cold cuts, sausages, frankfurters, snack stick sausages or bacon can increase the risk of certain cancers [5]. In 2015, the International Agency for Research on Cancer (IARC) released a report that included the results of more than 800 studies conducted over the past 20 years examining the relationship between meat consumption and cancer incidence. The report showed that eating pork, beef and other types of red meat regularly may lead to the development of cancer. Red meat has been classified in Group 2A, which includes agents that are potentially carcinogenic to humans and definitely carcinogenic to laboratory animals, including haem iron, heterocyclic amines, etc. Research shows that there is a link between red meat consumption and the incidence of cancer, especially colorectal, pancreatic and prostate cancers. Studies show that the risk of colorectal cancer increases by 17% with every 100 grams of red meat consumed daily [5, 7, 8].

Processed meat that has undergone processes such as prolonged frying, grilling, smoking, salting, curing, marinating or fermentation is even more harmful. Such meat is classified as a Group 1 carcinogen, which also includes alcohol, tobacco, asbestos or aflatoxins [5].

Scientific studies have shown that regular consumption of processed meat promotes the development of colorectal cancer. Furthermore, daily consumption of 50 grams of processed meat raises the risk of colorectal cancer by 18%. The risk of death from cardiovascular diseases also increases with consumption of such meat [5, 7, 8]. According to the comprehensive systematic review and meta-analysis study, high red meat intake was positively associated with the risk of breast cancer, endometrial cancer, colorectal cancer, colon cancer, rectal cancer, lung cancer and hepatocellular carcinoma; high processed meat intake was positively associated with the risk of breast, colorectal, colon, rectal and lung cancers [9]. The European Prospective Investigation into Cancer and Nutrition (EPIC), which is a multicentre prospective study, investigated the relationship between diet-related exposures and incidence or mortality from the four most common cancers in the European population: colorectal, breast, lung and prostate cancer. A higher consumption of fish and lower consumption of red and processed meat were related with a lower risk of colorectal cancer; and a higher consumption of fatty fish with a lower risk of breast cancer [6].

Therefore, it is recommended to limit the consumption of red meat and its products to 350–500 grams per week [5]. These recommendations are not intended to avoid meat consumption completely. Meat can be a valuable source of nutrients, especially protein, iron, zinc and vitamin B_{12}. However, it is strongly recommended to avoid processed meat products. Depending on the processing method, they have a high content of harmful substances such as polycyclic aromatic hydrocarbons and heterocyclic amines, nitrites, N-nitroso compounds, as well as components that, in excess, are harmful to health, such as salt, saturated fats and cholesterol. Eating meat is not an essential part of a healthy diet. For those who eat it, poultry and fish are preferred as valuable substitutes for red meat. Eggs and dairy products are also a valuable source of protein and minerals. It is worth replacing red meat and processed meat with low-fat poultry, fish, legume dishes and nuts, not only for one's own health but also for the health of our planet. People who opt for a meatless diet can get adequate amounts of essential amino acids through careful selection of legume and grain-based foods. Iron is present in many plant foods, although its bioavailability is lower than in meat.

Based on the results of a prospective cohort study, it was found that simultaneous consumption of a small amount of fruit and vegetables and a large amount of processed meat was associated with a higher incidence of 15 cancers (men: HR = 1.85, 1.91; women: HR = 1.44, 1.49) and accelerated time to cancer occurrence (men: 6.5 and 7.1 years respectively, and women 5.6 and 6.3 years), compared to a high consumption of fruit and vegetables combined with a low consumption of processed meat [10]. Low intake of fruit and vegetables was associated with a higher incidence of all cancers and accelerated time to cancer occurrence at every level of processed meat consumption studied, among both men and women. The results show that diet should be looked at comprehensively;

the carcinogenic effects of processed meat can be somewhat mitigated by keeping a healthy diet rich in non-starchy fruit and vegetables, especially with low and moderate levels of processed meat consumption. Less clear and consistent relationships were observed when analysing whole grain cereal and fibre consumption and red meat consumption [10]. The results of these studies provide preliminary evidence for improving existing cancer prevention recommendations to optimize the intake of specific food groups in the general adult population.

A study conducted for more than a decade in the UK found that people who consume little meat and eat fish as well as vegetarians are less likely to develop cancer compared to those who regularly consume meat. The study population was divided into 4 groups: those who regularly consumed meat, including processed meat, red meat (beef, pork, lamb) or poultry, more than five times a week; those who consumed meat less frequently; those who gave up red meat, processed meat and poultry, but continued to eat fish; and vegetarians who did not consume meat, poultry or fish.

A detailed analysis showed that the risk of colorectal cancer was significantly lower in people who consumed little meat compared to those who consumed meat regularly. As regards postmenopausal breast cancer, the risk of developing the disease was slightly lower among those who consumed little meat and fish than among those who regularly ate meat, but only among vegetarians was the lower risk statistically significant. Further analysis showed that lower risk in vegetarians was strongly associated with a lower Body Mass Index (BMI). As for prostate cancer, fewer cases were recorded among men who eat fish and vegetarians than among regular meat eaters. No difference was found in the risk of developing this cancer between those who regularly consume meat and those who consume it in small amounts [11].

It is also worth noting the results of a study published in PLOS Medicine journal that enable us to look at diet more broadly, taking into account the proportions of each product group in the overall diet. The researchers analysed data from already existing databases such as the Global Burden of Diseases to create a model that estimates the effect of dietary changes on life expectancy. The authors of the analysis conclude that at the age of 20, a person can add more than a decade to their life (10.7 years among women and 13 years among men) by switching from a typical Western diet to a healthy diet that includes eating less red or processed meat and more legumes, whole grain cereal products and nuts. Changing the diet to this health-promoting pattern at the age of 60 could increase life expectancy by eight years for women and 8.8 years for men. Even an 80-year-old adult could gain an average of 3.4 years from such dietary changes. According to the authors, looking at diet as an outcome of our choices and understanding the relative health potential of different food groups in the overall diet can enable people to achieve real and significant health benefits [12].

Recommendations to reduce red meat consumption and avoid processed meat are crucial for public health, especially given the high consumption of these products. However, the results of many studies indicate an additional direction for future prevention efforts, which should focus on simultaneously promoting the consumption of non-starchy vegetables and fruit as well as plant-based protein sources such as legume seeds as an overall dietary pattern.

Calcium and dairy products

The WCRF/AICR considers it "probably" that a diet high in calcium and rich in dairy products may reduce the risk of developing colorectal cancer. Evidence suggesting that a diet high in calcium could lower the risk of breast cancer has been considered "limited/suggestive evidence". Similarly "limited/suggestive evidence" suggests that calcium and dairy products may increase the risk of prostate cancer. According to the WCRF/AICR, 400 grams of dairy products consumed daily (which is equivalent to nearly two glasses of milk) increases the risk of prostate cancer but additional studies are needed. A long-term diet high in calcium (more than 2,000 mg per day) is associated with a higher risk of prostate cancer. The recommended daily amount of calcium in an adult's diet is about twice as low, ranging from 1,000 to 1,200 mg, and is often not achieved in the diet. Research results indicate that a diet rich in dairy products with a high content of calcium reduces the risk of breast and colorectal cancer. However, since it has also been shown to increase the risk of prostate cancer, the WCRF has not indicated recommendations for this food group [5].

A possible mechanism of the effect of high amounts of calcium-rich dairy products on increasing prostate cancer risk may involve exposure to the growth factor IGF-1. In the Adventist Health Study-2 cohort study, the researchers focused on dairy products and calcium intake, while paying particular attention to people who are vegans, i.e. those who do not consume dairy, getting their calcium from other sources. The study included 28,737 men affiliated with Seventh-day Adventists in the US and Canada. The observation lasted an average of 7.8 years. The results of this study showed that men who consume 430 g/d of dairy products, compared to those who consume 20.2 g/d, have a 27% higher risk of prostate cancer. Compared to non-dairy eaters, those who consumed the most dairy products had a 60% higher risk. This was mainly related to milk consumption, unrelated to cheese and yoghurt. In contrast, a higher consumption of non-dairy products and calcium supplements did not increase the risk of prostate cancer. According to the authors, the results of this study do not conclusively support a relationship between calcium intake and prostate cancer. However, they indicate that prostate cancer risk is associated with a higher consumption of dairy products or some other causal factor related to dairy consumption [13]. In the EPIC study, calcium and yoghurt intake was found to protect against colorectal and prostate cancer [6].

Plant-based products and cancer risk

Whole grain cereal products, vegetables, fruit and legumes such as beans and lentils, peas and chickpeas, for example, should make up the bulk of our diet. Research indicates that eating mostly plant-based foods, like whole grain products, vegetables, fruit and legumes, plays an important role in cancer prevention and is beneficial to health [14].

Plant-based foods are rich in fibre, having many nutrients and phytochemicals that can reduce the risk of cancer. In addition, plant foods containing high amounts of dietary fibre can be helpful in weight control. Excess body weight is a significant risk factor for cancer.

According to the American Institute for Cancer Research, there is strong scientific evidence that whole grain cereal products and dietary fibre are likely to reduce the risk of colorectal cancer [5, 14, 18, 22]. It has also been shown that a higher intake of vegetables or fruit is likely to show protective effects against many cancers [5, 17, 6]. For example, according to the Nurses' Health Study and Health Professionals Follow-up Study, fruit and vegetable consumption had a protective effect against colorectal, breast and lung cancers, whereas only fruit consumption had a protective effect against prostate cancer [6].

Non-starchy fruit and vegetables contain a large number of potential anticancer components, such as dietary fibre, carotenoids, vitamins C and E, selenium, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors or plant sterols. Whole grain products, on the other hand, are a rich source of various bioactive nutrients and non-nutritional compounds, including vitamin E, selenium, copper, zinc, lignans, phytoestrogens and phenolic compounds, as well as dietary fibre. Many of these compounds, largely found in the bran and germ of grains, have probable anti-carcinogenic properties [14].

Although researchers have identified some plausible biological mechanisms that could explain how various components of these foods might affect cancer risk, the protective effect cannot currently be attributed to any specific single ingredient. According to the 2018 AICR report, there is limited evidence to suggest that eating foods containing carotenoids reduces the risk of developing lung and breast cancer, and that eating foods containing vitamin C reduces the risk of developing lung cancer (in current smokers) and colon cancer. Consuming foods containing isoflavones can probably reduce the risk of developing lung cancer (in people who have never smoked). Single substances or nutrients can have a beneficial effect on maintaining health, however, the research results are inconclusive and show that it is not a matter of providing a single selected ingredient but of changing the entire dietary pattern to one based on products of plant origin [5, 14–21].

The recommendations therefore refer to dietary patterns that reflect the proportion and amount of food consumed altogether on a daily basis. This approach of considering the evidence indicates that most diets that protect against cancer are based on foods of plant origin. It is likely that the combination of all these nutrients and non-nutrients in the diet is responsible for a lower risk of certain cancers.

One of the key anti-cancer components of a plant-based diet is fibre, which is a nutrient that most people do not consume in sufficient amounts. A higher intake of dietary fibre can lower the risk of colorectal cancer by reducing intestinal transit time and increasing faecal volume. This reduces the potential for mutagenic components to affect the mucosa of the large intestine and also reduces the production of secondary bile acids.

Plant-based products such as whole-grain cereals, legumes, vegetables and fruit are sources of dietary fibre, which can also have a beneficial effect on the microflora of the large intestine, reducing the risk of cancer. Dysbiosis, which is caused by dysregulation of the microbiota, can increase chronic inflammation and reduce immune responses, leading to increased cancer incidence [15, 17]. Fibre is fermented or metabolized by the microflora of the large intestine, and this can affect the types and number of bacterial populations found in the colon [20, 22, 23]. Fermentation in the large intestine results in the formation of short-chain fatty acids such as butyrate, which, according to experimental studies, can have an antiproliferative effect on colon cancer cells [16, 17]. Maintaining a healthy gut microbiome supports a healthier immune system and glucose regulation while reducing inflammation.

Findings suggest that daily consumption of legumes may play a role in protecting against cancer development [21, 23]. High antioxidant activity is demonstrated by phenolic compounds, which are present in large amounts in the seed coat of legumes. The study also revealed the presence of flavonoids, anthocyanins and tannins [24, 25]. It has been shown that certain specific types of proteins, such as lectins (carbohydrate-binding proteins), exhibit anti-cancer properties. For instance, it is believed that lectins derived from leguminous plants bind to cancer membranes, inhibit cell proliferation, stimulate the immune system and induce apoptosis [25].

The effect of fibre on colorectal cancer risk is the best documented, but there is little evidence on the effect of fibre on other cancers. The UK Biobank study, with over 8.8 years of follow-up, found that those consuming less dietary fibre compared to the higher intake group (<9.6 *vs.* ≥19.1 g/day) had an overall 10% lower risk of cancer in general. The greatest impact on reducing the risk of disease was observed for cervical cancer (HR: 0.33, 0.14; 0.82), oesophageal cancer (HR: 0.66, 0.52; 0.84), lung cancer (HR: 0.67, 0.59; 0.76), bladder cancer (HR: 0.72, 0.56; 0.91) and kidney cancer (HR: 0.75, 0.61; 0.92). Fibre from cereals, fruit and vegetables showed the greatest impact on risk reduction.

A recent systematic review and meta-analysis has shed new light on the correlation between fibre intake and mortality risk from various causes. This exhaustive study encompassed 64 prospective cohort studies, involving a staggering

3.5 million participants from diverse global regions. Individuals with the highest fibre intake had significantly lower mortality risks compared to those with the least fibre intake – 22% lower for cancer-related death. Higher intakes of fibre derived from cereals, whole grains, vegetables, or legumes corresponded with an 8-16% decrease in all-cause mortality. The consumption of insoluble fibre appears to be more successful in decreasing the overall risk of death, as well as mortality from cardiovascular diseases and cancer, compared to the consumption of soluble fibre. Furthermore, consumption of soluble and insoluble fibre was linked with a 16% and 23% lower risk respectively. Insoluble fibre may bind with carcinogens and other compounds within the gut, which could partially explain the 20% reduction in risk of cancer mortality associated with insoluble fibre intake [26].

The impact of plant-based dietary patterns on cancer risk

A growing number of studies confirm the beneficial effects of a dietary pattern based on products of plant origin and limiting the consumption of meat and other zoonotic products [6, 28–30]. One of these recommended dietary patterns for maintaining health is the traditional Mediterranean diet. The European Prospective Investigation into Cancer and Nutrition (EPIC) is a prospective study conducted at 23 centres in 10 European countries on the relationship between diet and cancer incidence or mortality. Based on the results from this study, it was found that a high consumption of fruit and vegetables showed a protective effect against colorectal, breast and lung cancers, whereas only fruit had a protective effect against prostate cancer. Following the traditional Mediterranean diet pattern, i.e. based on foods of plant origin including vegetables and fruit, legumes, whole grain cereal products, nuts, olive oil and a small amount of fish and dairy products has been shown to be a protective factor for colorectal and breast cancers [5, 6]. In a recent prospective study, it was found that consuming a diet rich in healthy plant-based foods can potentially lower the risk of aggressive forms of prostate cancer. This correlation seems to be particularly strong in men who are under the age of 65. Men with the highest plant-based diet score had a 19% lower risk of fatal prostate cancer, compared to men with the lowest diet score. These discoveries highlight the significant role that dietary intervention could play in the prevention of prostate cancer, especially among younger men [30]. An analysis of the results of two studies of the Adventist Health Study-2 (AHS-2) and the European Prospective Investigation into Cancer and Nutrition-Oxford (EPIC-Oxford), involving a large proportion of people following plant-based diets, showed that in the first study vegans have 16% reduced risk while in the second study vegans, vegetarians and fish-eaters have 11–19% lower risk for all cancers compared to non-vegetarians [31].

A new (recent) meta-analysis involving 49 studies provides solid evidence on the effect of a plant-based diet on gastrointestinal cancer risk. The study evaluated different dietary patterns based on products of plant origin and a plant-based diet while limiting the intake of animal origin food and highly processed foods. Participants included both vegans and semi vegetarians (i.e. people who consume dairy products, eggs and a certain amount of red meat, poultry and fish at least once a month but less than once a week), people who prefer a diet based on a high intake of vegetables, fruit, pasta, potatoes, soy products, mushrooms and seaweed, vegetarians, people who follow a Mediterranean diet and pesco-vegetarians. The results indicate that a plant-based diet has a protective effect on the development of gastrointestinal cancers, reducing their risk by 20–30%. Plant-based diets have been shown to reduce the risk of pancreatic cancer by 29%, colorectal cancer by 24%, rectum cancer by 16%, colon cancer by 12%, stomach cancer by 19%, and liver cancer by 39%. Similar risk reductions were observed in both men and women, regardless of geographic region. The effects of a vegan diet were evaluated in detail and found to be comparable to those of other plant-based dietary patterns. These findings should form the basis for cancer prevention guidelines [32].

However, the findings suggest paying attention to the quality of the plant-based diet [33–36]. Not all plant-based products are beneficial to health, such as white bread, sugary snacks, or plant-based meat substitutes high in salt or fats.

In this cohort study involving 126,394 UK Biobank participants, greater adherence to a healthy plant-based diet (whole grain products, legumes, fruit and vegetables, nuts) was associated with a lower risk of total mortality, cancer and cardiovascular disease. However, similar relationships have not been observed in those who follow a plant-based diet such as processed plant products as meat substitutes and highly processed cereal products, potatoes or sweet drinks and sweets [34]. Reducing the consumption of animal products and consuming more unprocessed plant-based products has health benefits.

The quality of the plant-based diet and the beneficial effect of a properly balanced plant-based diet pattern on reducing cancer risk are also highlighted by the authors of the analysis of data from 3 prospective cohorts: Nurses' Health Study, Nurses' Health Study II and the Health Professionals' Follow-Up Study. A healthy plant-based diet was associated with a reduced risk of digestive system cancers in general, as well as individual cancers of the gastrointestinal tract and accessory organs [35]. Another new study provides evidence that adhering to a healthy plant-based diet can reduce the risk of breast cancer [36].

Experts from Newcastle University analysed data on the link between adherence to the 2018 World Cancer Research Fund/American Institute for Cancer Research Cancer Prevention Recommendations and the incidence of various

cancers. Greater adherence was associated with lower risk of breast, colorectal and lung cancers.

The results of the analyses indicate that among the modifiable cancer risk factor was a healthier lifestyle, including maintaining an appropriate body weight, limiting the consumption of red meat and processed meat, having a diet with plenty of fruit and vegetables as well as legumes; this can help avoid several types of cancer [37].

Highly processed foods high in sugars, salt and fat and cancer risk

Reducing the intake of some ultra-processed foods (UPFs) by replacing them with similar but less processed products may be beneficial in preventing cancer. Limiting the intake of highly processed foods high in fat, sugars and salt helps control caloric intake and keep body weight in check. Consumption of sugar--sweetened beverages is a proven factor leading to weight gain and, consequently, overweight and obesity in both children and adults. A "Western-type" diet, characterized by a high intake of free sugars, meat and fat, can have a similar effect. There is strong evidence that excessive body fat is the cause of many cancers: oral cavity, pharynx and larynx, oesophagus (adenocarcinoma), stomach (heart), pancreas, gall bladder, liver, colorectal, breast (post-menopausal), ovary, endometrium, prostate (advanced) and kidney cancers. There is also strong evidence that glycaemic load (the increase in blood glucose and insulin after eating food) is a cause of endometrial cancer [5, 38–40].

There is a lot of talk about the adverse effects of so-called highly processed products. However, it is worth noting that not all highly processed products have the same effect on health. These discussions relate to NOVA's classification of these products, which does not take all aspects into account. For example, plant-based beverages and plant-based meat alternatives may fall under the definition of highly processed products even if their composition has health-promoting qualities. A prospective cohort study from the EPIC (European Prospective Investigation into Cancer and Nutrition) trial found that UPF intake was associated with an increased risk of cardiometabolic diseases and type 2 diabetes, as well as cancer. Each additional 260 g/d of these products consumed was associated with a 9% higher risk of developing two of these diseases. It is worth emphasizing, however, that increased BMI explained this increase in risk partially but not completely. However, not all ultra-processed foods (UFPs) were associated with similar risks. The highest risk was associated with the consumption of animal-based products and artificially and sugar-sweetened beverages. Other subgroups such as ultra-processed breads and cereals or plant-based alternatives were not associated with risk [41]. Moreover, it was observed that the consumption of bread and cereal was even inversely related to the risk of these chronic conditions.

The authors in the discussion suggest that reasons other than dietary nutritional value may be the source of the adverse health effects of some UPF foods. The potential impact of some UPF components on the endocrine system or the gut microbiome could be the reason for this; e.g., contaminants from packaging materials or others may have an effect on increasing the risk of later diseases [42].

Consuming more ultra-processed foods (UPFs) may be associated with a higher risk of developing head and neck cancers and oesophageal adenocarcinoma (oesophageal cancer), [43]. The authors of this study suggest that excessive weight related to product consumption may be a risk factor. However, they suggest that further research is needed to identify other mechanisms, such as food additives and contaminants, that may explain the observed association.

Another prospective cohort study conducted in the UK showed that people who consumed the highest amounts of ultra-processed foods (UPFs) had a 7% higher risk of developing any type of cancer compared to those who consumed the least. An increase in risk has been shown for lung and brain cancers and one specific type of non-Hodgkin's lymphoma, but not for breast, colorectal or 22 other cancers. In addition, each 10% increase in intake of ultra-processed foods was associated with a 2% increase in overall cancer risk and persisted after taking into account smoking, low physical activity level, BMI and other known risk factors. Each 10% increase in intake was associated with a 19% increase in the risk of ovarian cancer and more deaths from cancer in general and breast or ovarian cancers. However, due to the small number of ovarian cancer cases in the study group, there is a need for further research to confirm the demonstrated relationship [43].

Body weight and cancer risk

One important recommendation for cancer prevention is to maintain a normal body weight and avoid weight gain in adulthood [5, 45, 46]. There is strong compelling evidence that excessive body fat increases the risk of cancers of the oesophagus (adenocarcinoma), pancreas, liver, large intestine, breast (post-menopause) and kidney. Obesity also contributes to an increased risk of endometrial cancer. Greater body fatness is also likely to cause cancers of the mouth, pharynx and larynx, stomach (gullet), gall bladder, ovary and prostate. Weight gain in adulthood is a compelling cause of postmenopausal breast cancer [5]. Each 5 point increase in BMI was associated with a:

- 50% higher risk of endometrial cancer,
- 48% higher risk of oesophageal adenocarcinoma,
- 30% higher risk of kidney cancer,
- 30% higher risk of liver cancer,
- 12% higher risk of postmenopausal breast cancer,
- 10% higher risk of pancreatic cancer, and
- 5% higher risk of colorectal cancer.

Significant weight gain in adulthood is a compelling cause of postmenopausal breast cancer and endometrial cancer.

Each 11-pound weight gain in adulthood was significantly associated with a 16% higher risk of endometrial cancer and a 6% higher risk of postmenopausal breast cancer. The mechanism underlying carcinogenesis is complex and has not yet been fully understood. Altered secretion and metabolism of fatty acids, remodelling of the extracellular matrix, the secretion of anabolic and sex hormones, deregulation of the immune system, chronic inflammation and changes in the gut microbiome have been linked to carcinogenesis, metastasis development and cancer progression in obesity [45].

Conclusions

In recent years, researchers have increasingly emphasized the role of diet in cancer prevention. Proper plant-based nutrition is considered a key element in the prevention of diseases such as cancer. Experts stress the importance of consuming whole grains, non-starchy vegetables, fruit, legumes and nuts for health, noting that they contain significant amounts of dietary fibre and many nutrients, and have low or relatively low energy density, which is key to maintaining a healthy weight. These products, rather than foods of animal origin, should form the basis of a normal daily diet.

According to AICR recommendations, people should consume at least 30 grams of fibre per day. Vegetables and fruit should make up half of what we eat. A total of at least 400 grams of non-starchy vegetables (excluding potatoes) and fruit should be consumed. Examples of non-starchy vegetables include, among others, green leafy vegetables, broccoli, aubergine, zucchini, tomatoes, cabbage, carrots, artichokes, celery, beets but not, for example, potatoes. It is advisable to eat more vegetables than fruit considering as many types and colours as possible (for example, red, green, yellow, white, purple and orange).

Whole grain products include wholemeal bread, graham rolls, wholemeal pasta, brown rice, groats (such as buckwheat, barley), and oatmeal. They should make up ¼ of the plate for our main meals. Products like white bread, rice or pasta should be reduced in favour of whole grain cereal products.

Legumes (such as beans, soybeans, peas and lentils) are an excellent and healthy alternative to animal protein products, while providing a number of nutrients. It is also worth using a range of products made from them, such as high-quality soy-based foods (like tofu or tempeh). When choosing ready-made processed products such as veggie burgers, it is important to pay attention to their composition and choose those with less sodium, and particularly saturated fats, which can come from tropical oils, or other additives that are not good for health.

Red meat consumption should be limited, and consumption of processed meat should be avoided. Processed meat is the one that has been processed by salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation. In addition, there is strong evidence that diets containing large amounts of fast food and other highly processed foods high in unhealthy fats, starch or sugars, as well as eating a "Western-type" diet (characterized by large amounts of added sugar, meat and fat), are the cause of weight gain, being overweight and suffering from obesity, which are risk factors for many cancers. Consumption of diets that largely consist of ultra-processed foods (UPFs) has been linked to decreased nutritional quality. This decrease manifests itself in various ways, such as a lower intake of dietary fibre and essential vitamins. Conversely, these diets often lead to an increased intake of free sugars and saturated fats, further compromising the nutritional value.

There is also strong evidence that consumption of alcoholic beverages causes cancers of the mouth, pharynx and larynx, oesophagus (squamous cell carcinoma), liver, large intestine and breast (especially after menopause). Evidence suggests that alcoholic beverages of all kinds have a similar effect on cancer risk. Therefore, this recommendation covers all types of alcoholic beverages, whether beer, wine, spirits (liquor) or any other alcoholic beverages, as well as other sources of alcohol.

Research in earlier years focused on the isolated effects of individual foods and food components on cancer risk. It is increasingly concluded that foods or individual nutrients are not consumed in isolation, but can interact to generate a combination effect of influences on various pathways involved in carcinogenesis. The pattern of a healthy and balanced diet based on products of plant origin is the one most often cited as recommended for cancer prevention.

Understanding the interactions between nutrients and their impact on the process of carcinogenesis is key to developing effective cancer prevention strategies. A plant-based diet, because of its richness in nutrients that can synergistically act against carcinogenesis, should be a major component of these strategies. Further research in this area is needed to fully understand the mechanisms of these interactions and to be able to use them in preventive measures.

Article information and declarations

Author contributions

Katarzyna Wolnicka – wrote the manuscript, conceived the original idea and supervised the article.

Conflict of interest

None declared

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Digital interventions in smoking cessation – a brief overview of systematic reviews and meta-analyses

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Digital health includes a variety of modern methods that may support smoking cessation. In light of increasing interest in digital health interventions and the widespread digitizaton of the digitalization process in Europe, it seems relevant to assess its efficacy. This review aims to present the current knowledge regarding using digital interventions for tobacco cessation in different population groups. The PubMed and Google Scholar databases were searched for systematic reviews and meta-analyses regarding digital health interventions in smoking cessation. It was found that a wide range of methods have been studied for supporting smoking cessation. Digital interventions offer encouraging tools for the general population in health education but also for smokers and specific groups of patients in smoking cessation. Despite the promising results of some individual studies, most of the systematic reviews emphasized the need for further research and better-quality data to assess the efficacy of this approach.

Key words: digital health, smoking cessation, mobile health, tobacco, cancer prevention

Introduction

Tobacco cessation remains one of the greatest concerns of public health and is responsible for more than 8 million deaths each year [1]. It has been strongly emphasized that there is a need for interventions in smoking cessation and prevention strategies to reduce tobacco-related health and economic burdens on societies. With the proliferation of digital solutions and the incorporation of artificial intelligence, the availability of tools designed to support various health interventions has expanded significantly. It seems that mobile tools, supported by artificial intelligence or not, could become an effective approach to modifying lifestyle, including interventions in smoking cessation [2]. The increasing number of published works on digital intervention for smoking cessation is focused on the efficacy and relevancy of this solution compared to offline support or other available strategies to support smokers. Digital health interventions have proven particularly valuable for smokers during the COVID-19 pandemic, especially as social distancing restrictions limited access to traditional healthcare settings and smoking cessation centers. These digital solutions offered a practical alternative, ensuring individuals could still receive support and guidance in their journey to quit smoking despite the limitations imposed by the pandemic [3].

There is a variety of digital health intervention solutions that can be implemented to support smoking cessation. Digital health is a comprehensive concept that includes different technologies and strategies to improve healthcare. While mobile health (mHealth) utilizes mobile devices, eHealth uses a wider range of electronic technologies. Telemedicine, on the other hand, is specifically concerned with providing healthcare services remotely. These interconnected concepts frequently collaborate to establish a more inclusive and readily accessible

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healthcare environment. The type of digital intervention may differ depending on the need it is supposed to cover. According to the Classification of Digital Health Interventions v 1.0 provided by the World Health Organization, interventions in digital health may include interventions for clients (population groups that require some health intervention), health care providers, health systems, resource managers, or data services [4]. Digital health interventions are designed to tackle specific challenges within the health system, including issues such as inadequate supply of commodities, healthcare professionals' poor adherence to clinical guidelines, limited access to data or information, and a notable percentage of patients disengaging from the treatment plan. Various digital interventions may be employed depending on the unique needs of specific patient groups and the challenges they aim to address. Nevertheless, further research is needed to ascertain their efficacy in smoking cessation.

This review aims to present the current knowledge regarding using digital interventions for tobacco cessation in different population groups.

Material and methods

PubMed and Google Scholar databases were searched between September and October 2023 using the keywords "digital intervention", "smoking", or "tobacco cessation". Results older than five years and those not within systematic reviews and meta-analyses were excluded. The articles must have been fully available in English. Articles were screened for relevance to the topic and compliance with search criteria. The results were categorized into groups based on the type of patients included in the studies, which were as follows: general population, smokers, pregnant women, specific clinical conditions, and others.

Results

The research yielded 59 results in response to the selected keywords and inclusion criteria. This article includes descriptions of 27 papers that met the criteria, while 29 were excluded for not being directly relevant to the topic. Additionally, two papers were excluded as they focused on cannabis use rather than tobacco.

Figure 1 illustrates the scientific interest in digital health interventions. Since 2016, there has been a fourfold increase in research on this topic, indicating a growing trend in scholarly attention to digital health interventions, outlining the growing interest in this field.

General population

Smoking is a problem affecting the whole of society. Therefore, any health intervention should address a wide spectrum of the population. Finding a suitable communication channel for many stakeholders and policymakers to meet people's educational needs in a constantly evolving online environment remains challenging. The following systematic reviews present the current knowledge about digital health interventions for smoking cessation for the general population. One of the systematic reviews by Gold et al. concluded that digital interventions exhibit limited positive impacts on behavior related to health, namely: smoking, alcohol consumption, and interventions addressing both diet and physical activity [5]. The modest effects could stem from the treatment's low efficacy or non-adherence. Based on an analysis of 28 reviews, the authors also concluded that interventions delivered through the Internet, mobile devices, and computers positively affected smokers. However, in a study by Thornton et al., which encompassed various types of smartphone-based approaches to key lifestyle behaviours, the authors asserted that there is some evidence supporting the reliability and validity of using smartphones in addressing tobacco use [6]. Mobile devices can be used to assess and monitor smoking behavior. In this study, the authors referred to several studies where tobacco use was measured with smartphones. Although the results from some individual studies included in the systematic review were promising, the authors concluded that further research is needed to establish the validity and reliability of these objective approaches.

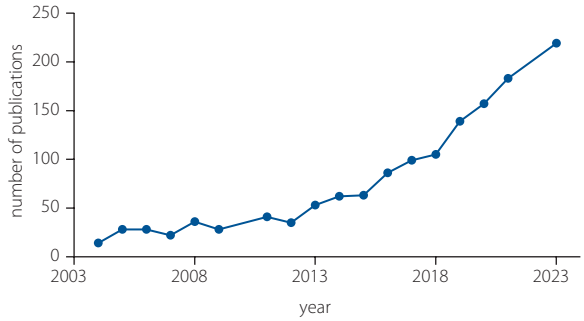

Figure 1. The scientific interest in digital health interventions in smoking cessation

Moreover, the studies typically utilized very small sample sizes. In turn, the review by Katie Newby et al. revealed that some of the automated digital health interventions might strengthen self-efficacy among participants, which is a strong health determinant [7]. Supporting self-efficacy might be useful in strengthening positive health behaviours and encouraging smoking cessation. In a systematic review by Aggarwal et al., the authors summarized evidence for using AI-delivered chatbots to improve types of health behavior in various populations. As mentioned previously, AI-delivered chatbots provide, among others, personalized services and conversation space without judging or scalability to large and varied populations [8]. In general, AI chatbots were described as holding significant promise for integration into existing behavioral services due to their ease of integration, the potential for being cost-effective, accessible, scalable, and sustainable, but also their capability to deliver services to vulnerable populations on

sensitive issues in a non-stigmatizing and engaging manner. Despite the promising results, the authors highlighted limitations and recommended caution regarding implementing this solution into practice due to the need for more high-quality evidence from larger studies.

Regardless of the technology employed, mHealth-driven interventions represent a promising strategy to tackle the issue of non-communicable diseases. A study by Godinho et al. posited that mHealth can transform services from disease-centered to people-centered [9]. However, the authors underscored the necessity for high-quality and well-planned studies to furnish evidence on the efficacy of such a solution.

Digital interventions also emerge as an effective solution for meeting the needs of vulnerable groups. Community--serving organizations can employ various communication strategies to promote health and encourage healthy behavior. One of the reviews included digital health interventions dedicated to vulnerable populations such as low-income pregnant women, parents of young children, and adolescents. In the study by Eppes et al., it was presented that these groups manifested moderate engagement and favorable reception of digital media health campaigns implemented by community-serving agencies [10]. However, the impact of these strategies on enhancing health behaviors remained inconclusive. Using digital interventions in health promotion-focused communication enables reaching a broader and more diverse audience, making it a promising approach for campaigns targeting vulnerable populations. It is particularly noteworthy considering these populations' widespread use of mobile devices.

Noteworthy, digital solutions provide a wide range of information hubs and can become an impactful tool in the health education of society. Social media remains one of the most powerful tools for disseminating information. However, online content is almost impossible to control; therefore, the risk of spreading misinformation on health topics is significant. A study by Suarez-Lledo et al. revealed that the percentage of false health information in social media is very high [11]. The strongest relationship found was on Twitter and referred to tobacco products and drugs.

Smokers

Most of the reviews included in this work stated the positive impact of digital health solutions on smokers. A systematic review by Amri et al. revealed that digital interventions have been effective in promoting smoking cessation, leading to higher rates of abstinence [12]. However, the authors emphasized the need to assess the enduring effects of these digital interventions on smoking cessation outcomes. One of the methods used in smoking cessation is utilizing smartphone apps. In the study by María Barroso-Hurtado et al. the findings suggested that smartphone apps designed for smoking cessation are promising since they can be effective tools to help individuals quit smoking [13]. Mobile health apps can complement established conventional cessation treatments. However, more research with robust methodological quality is needed to accurately determine the impact of mobile apps, either alone or combined with face-to-face contact, on smoking cessation outcomes.

Moreover, future studies should design smoking cessation apps that adhere to standard guidelines and employ rigorous methodologies, including sample size calculations, intention--to-treat analysis, and longer follow-up periods. Due to this field's emerging development, future research is expected to address current limitations to draw clear conclusions. Another recognized approach in digital health interventions for smokers involves using Conversational Agents. However, while this solution appears to be an innovative and modernized approach, its acceptability and efficacy in supporting smoking cessation still need to be determined. Conversational agents can provide a non-judgmental space for supportive conversations tailored to specific populations. However, this approach excludes those without access to mobile devices or the Internet and individuals with cognitive function deterioration who may face challenges in utilizing such a tool. Research by Linwei et al. outlined that the success of Conversational Agents for smoking cessation lies in their effectiveness and acceptability [14]. However, a more thorough evaluation necessitates the standardization of reporting and the design of these agents. While individual interventions have proven effective in smoking cessation, particularly among those with disadvantaged socioeconomic positions, there is a compelling need for additional research on AI-supported solutions to enhance and address these interventions [15].

Smokers with severe mental illnesses

Agulleiro et al. raised a question on the use of digital health interventions for smokers with severe mental illnesses [16]. The study highlighted the potential of digitally delivered health interventions for smoking cessation to improve outcomes for individuals with serious mental illness. However, concerns arise due to limited accessibility. Moreover, according to Agulleiro et al., there is limited evidence comparing bespoke digital interventions with generic interventions, and the authors found no studies comparing them with the usual treatment. In turn, the findings by Goldberg et al. indicated that interventions delivered through mobile phones show the potential for moderately alleviating common psychological symptoms like depression and anxiety [17]. However, the impact is generally modest, and these interventions seldom surpass other therapeutic interventions designed for the same purpose, known as specific active controls. Notably, text message-based interventions demonstrate effectiveness, especially in supporting smoking cessation. Simultaneously, research by Weisel stated that while certain trials indicated the potential of mental health-focused apps, relying on smartphone apps as independent psychological interventions cannot be endorsed, given the current state of the evidence [18].

User experience studies

In delivering any digital health solution, it is crucial to assess the efficacy and user experience to provide the highest possible quality of the intervention. One of the studies aimed at evaluating smokers' experiences related to digital health interventions for smoking cessation. In this study, the authors concluded that, among others, it is important to include simplification, personalization, different content forms, and interactivity, as well as address privacy and security issues while building apps dedicated to smoking cessation [19]. Considering user requirements for app functionality and features is vital during app design. The user needs to play a pivotal role in shaping program theories for smoking cessation interventions. Apps should incorporate a variety of essential functions and characteristics to keep users engaged. One of the systematic reviews, which focused on assessing the consistency in measuring and reporting intervention contents, channels, and dose-response outcomes in digital health interventions for smoking cessation, found that there is a lack of studies evaluating the impact of digital media interventions on smoking-related outcomes [20]. The data synthesis revealed inconsistencies in measurement and reporting across studies, indicating existing challenges in this field. While many studies prioritized reporting outcomes, a notable portion needed more clarity in measuring exposure, including both intended and actual doses. Reporting outcomes and exposures clearly and consistently is crucial to advance evidence in intervention research.

Pregnancy

A systematic review published in 2018 revealed that Text-message or computer-delivered digital interventions, especially those incorporating behavior change techniques centered on goals and planning, such as goal setting, problem-solving, and action planning, can prove effective for smoking cessation during pregnancy [21]. Nevertheless, additional research is needed to determine the potential impact of employing a greater number of behavior change techniques as opposed to fewer on the success of smoking cessation in pregnancy. Interestingly, digital health interventions for pregnant smokers have also been studied concerning continuous abstinence in late pregnancy, alongside counselling from nurses or midwives. The authors asserted that these interventions can attain continuous abstinence in late pregnancy, presenting this approach as a promising and effective tool for supporting smoking cessation interventions in pregnant women [22]. Another study assessed the eHealth intervention on different substance use among pregnant women [23]. Once again, it demonstrated that these interventions might significantly decrease substance use among the studied group of smokers and provide meaningful support for smoking cessation. Considering the complications associated with substance use, especially smoking, given the particular risks involved, it appears worthwhile to contemplate digital interventions for supporting smoking cessation in this group.

One of the studies in the analysis evaluated the cost and cost-effectiveness of mHealth interventions supporting women during pregnancy [24]. The authors presented an analysis indicating that the reported incremental cost--effectiveness ratios were USD 2168 per disability-adjusted life year averted, USD 203.44 per woman ceasing smoking, and USD 3475 per quality-adjusted life year gained. All four full economic evaluation studies, rated as moderate to high quality, concluded that the mHealth intervention was cost-effective. Early evidence suggests that mHealth interventions may be cost-effective and relatively inexpensive. However, additional research is necessary to assess the cost-effectiveness of mHealth interventions concerning positive maternal and child health outcomes and long-term health service utilization.

Specific clinical conditions

A few systematic reviews focused on groups with cardiovascular diseases or other chronic conditions that would benefit from smoking cessation. The assessment of digital health interventions in this recipient group considered the efficacy of the intervention, adherence to medical recommendations, specific health outcomes, and cost-effectiveness in treatment. One of the studies in cardiovascular disease patients presented digital health intervention as effective in improving healthy habits such as physical activity, healthy diet, or medication adherence while lacking effectiveness in unhealthy behavioral factors such as smoking [25]. In contrast, Wongvibulsin et al. stated that the potential of digital technologies to enhance access and engagement in cardiac rehabilitation is evident, addressing challenges linked to conventional facility-based interventions [26]. Due to the common issue of low follow-up rates among cardiovascular disease patients, digital technologies provide more accessible solutions and may enhance adherence rates. Nevertheless, additional studies are required to evaluate the extent to which smoking behaviors have changed within this specific patient group.

Another study assessed the effectiveness of telemedicine--delivered psychoeducational interventions in patients with chronic diseases [27]. The research covered diverse health conditions, including smoking, chronic pain, obesity, and mental illness, employing cognitive-behavioral theory for most interventions. A majority demonstrated positive health outcomes, showing significant reductions in anxiety, pain, and depression, with varying effect sizes. Patients expressed high satisfaction, favoring lectures or self-report writings for recovery over more interactive elements. The conclusion emphasized that telemedicine patient interventions are a secure and effective approach for managing chronic diseases in adults.

Digital intervention also appeared as a potential tool in combating secondary prevention challenges in cardiovascular diseases. However, according to Kavradim et al., compared

to the generic solution, telehealth might have a greater impact on reducing waist circumference, total cholesterol, and triglyceride, improving medication adherence and physical activity while manifesting negligible effects in reducing blood pressure and smoking cessation [28].

Regarding the cost-effectiveness of digital health intervention for smoking cessation in chronic disease, one of the analyses showed that web-based counselling, SMS text messaging, and telephone counselling employed as tools for behavior change seem to be cost-effective interventions [29]. For example, an Australian study determined it was cost-effective, with an incremental cost-effectiveness ratio of USD 6123 per quality-adjusted life year. Similarly, a study in the United States revealed cost-effectiveness, reporting an incremental cost-effectiveness ratio of USD 2973 per QALY when comparing web-based and counsellor-based counselling. Another U.S. study focusing on telephone coaching for behavior change was deemed cost-effective with an incremental cost-effectiveness ratio of USD 42,457 per life-year saved for women and USD 87,300 per life-year saved for men. In contrast, a study conducted across three countries found the intervention cost-effective only in Spain, showing an incremental cost-effectiveness ratio of EUR 18,769 per QALY (USD 21,059 per QALY). At the same time, it was not cost-effective in the Netherlands or Taiwan.

Other

The significant potential of digital health intervention lies in reaching a wide range of patients and educating their caregivers. Some of the available systematic reviews aimed to assess the effectiveness of digital education among healthcare professionals delivering smoking cessation therapy. According to Semwal et al., the available evidence indicates that digital education is, at the very least, as effective as traditional learning methods in enhancing the knowledge and skills of health professionals who provide smoking cessation therapy [30]. Nevertheless, it is important to approach these conclusions cautiously due to certain limitations in the evidence base. Another study evaluated which telehealth and digital technology tools were used by community pharmacists for public health purposes [31]. It was found that telephone calls and automated telephonic prompts were the most commonly used alternative methods of communication to face-to-face discussion. It suggests that more contemporary digital solutions may not be as widespread or adequately studied.

Conclusions

Based on the received results, digital health interventions offer a variety of methods potentially impacting types of health behavior including smoking cessation. Thanks to digitalization, it is possible to reach a broader audience with education and health promotion for the general population or health care providers. It also provides a possible solution with health education, specifically in vulnerable populations or disease-specific groups of patients. Digital health solutions might be helpful in smoking cessation therapy support for current smokers, providing many benefits for its users. However, concerns related to this process include data privacy and security, user experience, lack of high-quality studies evaluating its efficacy, and an inadequate number of studies assessing the cost-effectiveness from a public health perspective. There are potential areas that digital technologies could support in smokers and vulnerable populations. However, the level of evidence seems inadequate to establish specific recommendations.

Article information and declarations

Author contributions

Elwira Gliwska – conceptualization, data curation, methodology, project administration; resources, visualization, writing original draft, review and editing.

Marta Mańczuk – writing original draft, review and editing, conceptualization, data curation, formal analysis, supervision.

Conflict of interest

None declared

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Obrazy w onkologii / Pictures in oncology

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Subependymal giant cell astrocytoma (SEGA), unrelated to tuberous sclerosis, NTRK-positive

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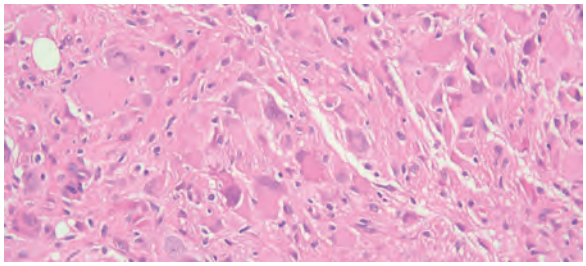

Figure 1. Photomicrograph (haematoxylin-eosin, 40x), showing a neoplasm consisting of epithelioid/ganglioid cells with a large cytoplasm and prominent nucleolus

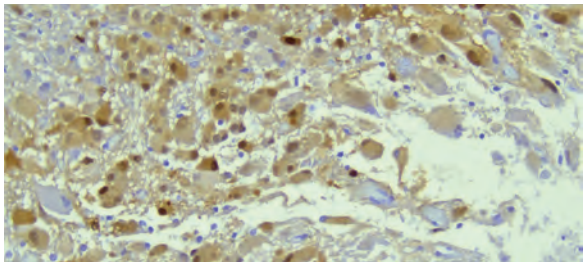

Figure 2. Immunohistochemistry showing positivity in the neoplastic cells for NTRK

An 11-year-old child presented with hydrocephalus-related symptoms. MR demonstrated, in the post T_1-weighted image, an enhancing intraventricular mass in the frontal horn of the right lateral ventricle. The patient underwent neurosurgery, and histology showed it to be a neoplasm with compact architecture, high cellularity, large cells with eosinophilic cytoplasm, in the absence of mitosis and/or vascular proliferation and/or necrosis (fig. 1). Immunohistochemistry revealed positivity for GFAP and S-100. The diagnosis was SEGA – a rare glial neoplasm typically located in the wall of the lateral ventricles and usually associated with tuberous sclerosis (TS), an autosomal dominant syndrome harbouring mutations in the *TSC1* and *TSC2* genes, although cases unrelated to TS are reported. Our case fits into this context of rarity: indeed, the patient was referred for genetic counselling after histological diagnosis, but no alteration in tuberous sclerosis-related genes was found. Although WHO-CNS2016 and WHO-CNS2021 classifications have introduced real "revolutions" in the morpho-molecular aspects of most primary brain neoplasms, SEGA has not substantially changed its classification, always maintaining its features (grade 1 according to WHO-CNS2021), and constituting one of the longest-lived entities of all CNS tumours [1]. Probably because of the rarity of SEGA – compared to neoplasms with extremely higher incidence, prevalence and mortality – histologic expression of predictive targets in SEGAs has not been studied to date. Our immunohistochemistry results were: NTRK+ (fig. 2), ALK–, PDL1–, PD1–, CTLA4–. To date, SEGA therapy is limited to m-TOR inhibitors, such as rapamycin [2], and therefore the immunohistochemical NTRK-positivity could potentially broaden the ever-expanding landscape of tumours that are treatable with TRK-inhibitors, whereas our results suggest no correlation with immunocheckpoint expression.

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The usefulness of nasopharyngoscopy in the diagnostics and treatment planning for patients with early glottic cancer

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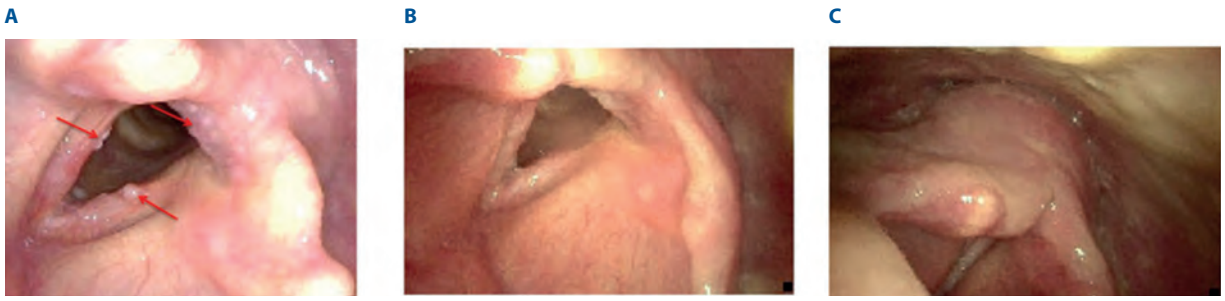

Figure 1. A – pre-treatment examination (red arrows indicate infiltration); **B** – post-treatment examination; **C** – acute mucosal radiation reaction in grade III during the treatment

A 66-year-old female patient with hypertension, obesity and a family history of oral cancer, reported hoarseness for one year. Associated symptoms included resting dyspnea and recurrent laryngitis. After a month of symptomatic treatment, a CT scan of the head and neck was performed, where a thickened vestibular and right vocal fold were found. An abdominal ultrasound as well as a chest X-ray did not reveal any abnormalities. The patient underwent FNP, which showed laryngeal infiltration involving both vocal folds and the posterior commissure region (fig. 1A), while maintaining normal phonation and respiratory mobility. A histopathological examination revealed the presence of SCC. The clinical stage was determined as T_2N0M0, and she was qualified for a definitive RT. The dose prescription was 1.8 Gy in 25 fractions to a total dose of 45 Gy to the lymph nodes area II–IV bilaterally with a simultaneous integrated boost with a fractional dose of 2.5 Gy in 25 fractions. After the 11th fraction of RT, FNP visualized a 50% regression of the infiltration. On the day of completion of RT, FNP revealed complete regression of the lesions in the larynx (fig. 1B). Mucosal radiation reaction in grade III (CTCAE v5) was reported during the treatment (fig. 1C). Imaging of the larynx, particularly in cases of non-advanced tumors can be challenging due to the small size of detected lesions. It may lead to increased difficulties both in appropriate classification and estimating the stage of the disease [1]. FNP provides precise visualization of the glottis area [2]. This case presents a medical history of a patient whose CT scan did not unequivocally confirm the borders of laryngeal cancer and FNP delivers more accurate information about an extension of the infiltration.

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Z kalendarium Zarządu PTO

styczeń–luty 2024 r.

Komitet Naukowy VI Kongresu Onkologii Polskiej ukończył prace nad programem. Więcej informacji na stronie: http://www.kongres.pto.med.pl.

Komunikaty PTO

- Przewodniczący Zarządu Głównego Polskiego Towarzystwa Onkologicznego (PTO), prof. dr hab. Piotr Rutkowski, został uhonorowany Medalem Zasłużony dla Nauki Polskiej *Sapientia et Veritas*.
- 19 grudnia 2023 r. odbyło się posiedzenie Zarządu Głównego Polskiego Towarzystwa Onkologicznego, podczas którego omówiono sprawy organizacyjne związane z VI Kongresem Onkologii Polskiej, kwestie nowego systemu członkowskiego PTO, działalność Sekcji Terapii Spersonalizowanej PTO oraz inne sprawy bieżące.
- 26 stycznia 2024 r. zorganizowano kolejne spotkanie Komitetu Naukowego VI Kongresu Onkologii Polskiej, podczas którego omówiono projekt programu naukowego Kongresu.
- 31 stycznia 2024 r. PTO rozstrzygnęło drugą edycję grantu edukacyjno-naukowego realizowanego we współpracy z firmą Servier Polska pod auspicjami Warsaw Health Innovation Hub. Zwyciężyły projekty: *Platforma testowania nowych kombinacji leków antynowotworowych w hodowlach organoidowych raka trzustki od polskich pacjentów – uzupełnienie o nowe rozwiązania* oraz *Czy krążące komórki nowotworów w raku trzustki mogą stanowić nowy cel terapeutyczny dla CAR-T?* Zostały pozytywnie zaopiniowane pod względem poprawności przez Komisję konkursową w składzie: prof. dr hab. n. med. Piotr Rutkowski, dr hab. n. med. Tomasz Kubiatowski, prof. CMKP, prof. dr hab. n. med. Marta Mańczuk, prof. dr hab. n. med. Lucjan Wyrwicz, oraz uzyskały pozytywne opinie recenzentów – dr hab. n. med. Bożeny Cybulskiej-Stopy, prof. PWr oraz dra n. med. Marcina Ziętka. Środki na realizację projektów zostaną przekazane jednostkom badawczym.
- 6 lutego 2024 r. odbyło się posiedzenie Zarządu Głównego Polskiego Towarzystwa Onkologicznego, podczas którego omówiono sprawy organizacyjne związane z VI Kongresem Onkologii Polskiej, sprawozdanie finansowe PTO za rok 2023, sprawozdania z działalności sekcji PTO za rok 2023. Ponadto przedstawiono koncepcję powołania nowej sekcji – Sekcji Opieki Koordynowanej Polskiego Towarzystwa Onkologicznego, a także wyniki konkursu grantowego i aplikację PTO dotyczącą diagnostyki molekularnej oraz inne sprawy bieżące PTO.

Wywiady i artykuły prasowe

Prof. Rutkowski: Tak zmienia się standardy leczenia raka. W kierunku nauki prowadziła mnie ciekawość

– Badania prowadzone w Polsce mają szansę zmieniać standardy leczenia w niektórych nowotworach, polska onkologia zaczyna liczyć się na świecie – przekonuje prof. Piotr Rutkowski, jeden z najczęściej cytowanych na świecie polskich naukowców, prezes Polskiego Towarzystwa Onkologicznego. Mówi, jak dziś zmienia się leczenie raka, a także o szansach na pierwsze polskie leki onkologiczne.

Polska onkologia coraz bardziej liczy się na świecie, coraz więcej naukowców i klinicystów prowadzi badania kliniczne. Część z nich już doprowadziła do zmian w sposobie leczenia niektórych nowotworów, na wyniki niektórych trzeba jeszcze poczekać. – Mój zespół od lat jest liderem tzw. hipofrakcjonowanej radioterapii u chorych na mięsaki. Mamy już kilka badań własnych na ten temat, które przełożyły się na zmianę standardów leczenia. Jestem przekonany, że już wkrótce na międzynarodowych zjazdach polscy onkolodzy będą chwalić się wynikami prowadzonych przez siebie badań – zaznacza prof. Rutkowski.

Źródło: www.wprost.pl

Przeczytaj cały artykuł:

Rząd przekaże 3 mld zł na zdrowie. Prof. Rutkowski: w onkologii palących potrzeb jest sporo

– Widzimy duże zapotrzebowanie także w kwestii właściwej wyceny procedur w onkologii, ponieważ są procedury, które są wycenione poniżej kosztów – ma to miejsce szczególnie w onkologii zabiegowej czy na przykład w radiologii interwencyjnej. Taki stan rzeczy powoduje duże ograniczenie wykonywania tych procedur w Polsce, co rzecz jasna jest ze szkodą dla naszych pacjentów – ocenia przewodniczący Polskiego Towarzystwa Onkologicznego, prof. Piotr Rutkowski. Konsultanci krajowi ds. onkologii oraz lekarze nie mają wątpliwości, na co powinny zostać wydane środki, które nowy rząd ma przeznaczyć na zdrowie w Polsce.

Źródło: www.medonet.pl

Przeczytaj cały artykuł:

Eksperci u minister zdrowia rozmawiali o wyzwaniach w onkologii

Minister Zdrowia, Izabela Leszczyna, w czwartek spotkała się z ekspertami w dziedzinie onkologii. Rozmawiali o przyszłości m.in. koordynowanej opieki onkologicznej. Jak powiedział politykazdrowotna.com rzecznik prasowy MZ Damian Kuraś, było to pierwsze z serii planowanych spotkań dotyczących onkologii.

Źródło: www.polittkazdrowotna.com

Przeczytaj cały artykuł:

Debata *#45minut dla zdrowia – diagnostyka raka piersi*

Wystartowaliśmy z nowym cyklem redakcyjnym *#45minut dla zdrowia*, w ramach którego w krótkiej formule rozmawiamy z ekspertami o tym, jak usprawnić poszczególne obszary systemu ochrony zdrowia i polepszyć stan zdrowia Polaków bez wielkich reform, nowelizacji ustaw i wielkich pieniędzy. Chcemy wskazywać konkretne rozwiązania organizacyjne, prawne oraz edukacyjne, które mogą zmienić sytuację na lepszą. Zaczęliśmy od tematu: Diagnostyka nowotworów piersi – jak ją usprawnić bez wielkich zmian systemowych i kosztów?

Źródło: www.cowzdrowiu.pl

Przeczytaj cały artykuł:

Aplikacja pomaga zarządzać działaniami niepożądanymi immunoterapii. Korzyści dla pacjenta, lekarza i systemu

Aplikacja *OWPK Bezpieczeństwo immunoterapii* daje lekarzowi, do którego trafia pacjent onkologiczny z działaniami niepożądanymi immunoterapii, możliwość szybkiego sprawdzenia, jak postępować w różnych toksycznościach, tj. jaką diagnostykę wykonać i jakie leczenie zastosować – mówi dr hab. Bożena Cybulska-Stopa.

Źródło: www.rynekzdrowia.pl

Przeczytaj cały artykuł:

Co nowego w opiece onkologicznej dzięki KSO?

W Polsce każdego roku diagnoza: choroba nowotworowa staje się rzeczywistością dla około 200 tysięcy osób. Ta smutna statystyka stanowi przypomnienie o ciągłej potrzebie postępu w medycynie. W najnowszym odcinku programu *Po pierwsze Pacjent*, Monika Rachtan rozmawia z profesorem Piotrem Rutkowskim, specjalistą w dziedzinie chirurgii ogólnej o rozwiązaniach systemowych, które mają wspierać diagnozowanie i leczenie chorób nowotworowych. Krajowa Sieć Onkologiczna i Narodowa Strategia Onkologiczna, to sztandarowe projekty polskiej onkologii, które mają wspierać Pacjenta w systemie opieki zdrowotnej. Dlaczego tak istotne jest pilne wdrożenie wypracowanych założeń? O tym w najnowszym odcinku programu *Po pierwsze Pacjent*.

Źródło: Podcast *Po pierwsze pacjent*

Posłuchaj całej rozmowy:

Konferencje i wydarzenia z udziałem członków Zarządu Głównego PTO

- 15 grudnia 2023 r. odbyło się trzecie spotkanie z cyklu *O przyszłości onkologii. Forum organizacji pacjentów i ekspertów klinicznych* pod hasłem *Profilaktyka onkologiczna – jak możemy ją ulepszyć?*
- 10 stycznia 2024 r. miała miejsce konferencja prasowa na temat aplikacji mobilnej wspomagająca lekarzy *OWPK Bezpieczeństwo immunoterapii* z udziałem prof. Bożeny Cybulskiej-Stopy i prof. Piotra Rutkowskiego.
- 11 stycznia 2024 r. zorganizowano doroczne spotkanie All.Can Polska.

- 16 stycznia 2024 r. odbyła się debata z cyklu *Onkologia – Wspólna Sprawa* (8. debata z cyklu), pt. *Medycyna nuklearna w onkologii – standard diagnostyki i nowe kierunki* organizowana przez Polskie Towarzystwo Onkologiczne.
- 1 lutego 2024 r. miała miejsce konferencja z okazji Światowego Dnia Walki z Rakiem 2024, pt. *Onkologia – dobrze się kojarzy* zorganizowana przez Polskie Towarzystwo Onkologiczne wraz z Fundacją TO SIĘ LECZY oraz partnerami.
- 13 lutego 2024 r zorganizowano debatę z cyklu *Onkologia – Wspólna Sprawa*. Tym razem poświęcona była wyzwaniom w diagnostyce i leczeniu nowotworów prostaty. Uczestniczyli w niej wybitni eksperci z dziedzin onkologii i urologii.
- 16 lutego 2024 r. odbyło się czwarte spotkanie z cyklu *O przyszłości onkologii. Forum organizacji pacjentów i ekspertów klinicznych* pod hasłem *Krajowa Sieć Onkologiczna*.

Beata Jagielska nowym dyrektorem NIO-PIB

Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy w Warszawie ma nowego dyrektora. Na to stanowisko 16 stycznia 2024 roku minister zdrowia Izabela Leszczyna powołała dr hab. n. med. Beatę Jagielską. Poprzedni dyrektor NIO-PIB, prof. dr. hab. n. med. Jan Walewski, kierował tą instytucją przez osiem lat. Beata Jagielska od 2021 roku była prezesem Szpitala Grochowskiego w Warszawie. Wcześniej przez wiele lat była związana z warszawskim Instytutem Onkologii. Pełniła tam funkcję kierownika Kliniki Chorób Wewnętrznych i Kardioonkologii oraz zastępcy dyrektora do spraw lecznictwa, a później do spraw lecznictwa otwartego i rozliczeń świadczeń zdrowotnych. Od 2013 roku jest także mazowieckim konsultantem w dziedzinie onkologii klinicznej. Gdy odbierała nominację na dyrektora NIO-PIB, powiedziała: – Nadrzędnym celem jest poprawa efektywności profilaktyki, wyników leczenia oraz zwiększenie dostępności do świadczeń onkologicznych. Dużym wyzwaniem są działania na rzecz spłacania długu zdrowotnego w onkologii wywołanego przez COVID-19. Kluczowe aspekty to także działania w zakresie rozwoju onkologii.

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Pembrolizumab plus chemotherapy *versus* chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial

Chu Q., Perrone F., Greillier L. i wsp.

Lancet, 2023; 402: 2295–2306

Międzybłoniaka opłucnej zazwyczaj rozpoznaje się w zaawansowanym stadium, gdy jest już nieuleczalny. Standardową metodą leczenia tego nowotworu jest chemioterapia z zastosowaniem pochodnych platyny i pemetreksedu. Postawiono hipotezę, że dołączenie pembrolizumabu do chemioterapii zawierającej pochodną platyny z pemetreksedem wydłuży czas całkowitego przeżycia chorych na międzybłoniaka opłucnej.

Metody. W otwartym międzynarodowym badaniu klinicznym III fazy, prowadzonym w 51 szpitalach w Kanadzie, Włoszech i Francji, wcześniej nieleczonych chorych na międzybłoniaka opłucnej (w wieku powyżej 18 lat), w stanie sprawności 0–1 według kryteriów Eastern Cooperative Oncology Group (ECOG) przydzielano losowo (w stosunku 1:1) do leczenia: 1) przy użyciu chemioterapii (cisplatyna [75 mg/m^2] lub karboplatyna [AUC 5–6 mg/ml/min] z pemetreksedem w dawce 500 mg/m^2, stosowana co 3 tygodnie, dożylnie, do 6 cykli) lub do 2) chemioterapii stosowanej w połączeniu z pembrolizumabem (podawanym dożylnie w dawce 200 mg co 3 tygodnie; do 2 lat). Pierwszorzędowym punktem końcowym była przeżywalność całkowita u wszystkich przydzielonych do leczenia chorych; bezpieczeństwo oceniano u wszystkich, którzy otrzymali co najmniej jedną dawkę badanego leku.

Wyniki. Od 31 stycznia 2017 roku do 4 września 2020 roku włączono do badania 440 chorych, których następnie przydzielono losowo do stosowania wyłącznie chemioterapii (n = 218) lub chemioterapii w połączeniu z leczeniem pembrolizumabem (n = 222). Wśród uczestników badania było 333 mężczyzn (76%), a 347 (79%) chorych należało do rasy białej. Mediana wieku wynosiła 71 lat (IQR 66–75). W ostatniej analizie (zamknięcie bazy danych nastąpiło 15 grudnia 2022 r.) po obserwacji, której mediana wyniosła 16,2 miesiąca (IQR 8,3–27,8), całkowity czas przeżycia był znamiennie dłuższy dla leczonych z użyciem pembrolizumabu. Mediana przeżywalności całkowitej w tej grupie wyniosła 17,3 miesiąca (95% przedział ufności [*confidence interval* – CI] 14,4–21,3) w porównaniu z 16,1 miesiąca (13,1–18,2) w grupie poddanych wyłącznie chemioterapii (współczynnik ryzyka [*hazard ratio* – HR] zgonu 0,79; 95% CI 0,64–0,98, dwustronne p = 0,0324). Odsetek 3-letnich całkowitych przeżyć wyniósł 25% (95% CI 20%–33%) dla leczonych przy użyciu pembrolizumabu i 17% (13%–24%) w grupie poddanych wyłącznie chemioterapii. Działania niepożądane 3. lub 4. stopnia związane z badanym lekiem wystąpiły u 60 spośród 222 chorych (27%) w grupie leczonej pembrolizumabem oraz u 32 spośród 211 chorych (15%) w grupie poddanych wyłącznie chemioterapii. Z powodu poważnych działań niepożądanych związanych z leczeniem do szpitala przyjęto 40 spośród 222 chorych (18%) z grupy leczonej pembrolizumabem i 12 spośród 211 chorych (6%) z grupy poddanej wyłącznie chemioterapii. Działania niepożądane stopnia 5. związane z leczeniem wystąpiły u dwóch chorych z grupy leczonej pembrolizumabem i u jednego chorego z grupy poddanej wyłącznie chemioterapii.

Wnioski. Dołączenie pembrolizumabu do standardowej chemioterapii zawierającej pochodną platyny i pemetreksed było dobrze tolerowane i znamiennie wydłużyło czas całkowitego przeżycia wcześniej nieleczonych chorych na zaawansowanego międzybłoniaka opłucnej. Ten schemat leczenia stanowi nową opcję leczenia dla chorych z tej grupy.

Lenvatinib plus pembrolizumab *versus* lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, phase 3 trial

Llovet J., Kudo M., Merle P. i wsp.

Lancet Oncol., 2023; 24: 1399–1410

Zastosowanie nowych leków poprawiło wyniki leczenia chorych na raka wątrobowokomórkowego, ale nadal poszukuje się możliwości wydłużenia całkowitego czasu przeżycia chorych będących w zaawansowanych stadiach choroby za pomocą pierwszej linii leczenia. Celem omawianego badania była ocena dołączenia pembrolizumabu do lenwatynibu (w porównaniu z użyciem lenwatynibu z placebo) w pierwszej linii leczenia chorych na nieoperacyjnego raka wątrobowokomórkowego.

Metody. W ogólnoświatowym badaniu III fazy LEAP-002, prowadzonym metodą podwójnie ślepej próby w 172 ośrodkach na całym świecie, wcześniej nieleczonych systemowo chorych (w wieku powyżej 18 lat) na nieoperacyjnego raka wątrobowokomórkowego, przydzielono losowo (1:1) do leczenia lenwatynibem (masa ciała <60 kg: 8 mg/d; masa ciała ≥60 kg: 12 mg/d) w połączeniu z pembrolizumabem (200 mg co 3 tygodnie) lub lenwatynibem w połączeniu z placebo. Pod względem niewydolności wątroby uczestnicy badania należeli do klasy A w skali Childa i Pugha i byli w stanie sprawności

0–1 według kryteriów ECOG. W trakcie randomizacji chorzy byli stratyfikowani według regionu geograficznego, zajęcia żyły wrotnej lub rozsiewu pozawątrobowego (albo obu tych cech), stężenia alfafetoproteiny oraz stanu sprawności. Podwójnymi pierwszorzędowymi punktami końcowymi były: czas całkowitego przeżycia (próg wyższości przy końcowej analizie ogólnego przeżycia, jednostronne p = 0,019; analiza końcowa po wystąpieniu 532 zdarzeń) oraz czas wolny od progresji (próg wyższości jednostronne p = 0,002; analiza końcowa po wystąpieniu 571 zdarzeń) w grupie zgodnej z zamiarem leczenia. Przedstawiono wyniki końcowej analizy.

Wyniki. Od 17 stycznia 2019 roku do 28 kwietnia 2020 roku spośród 1309 ocenionych chorych, 794 przydzielono losowo do leczenia: 1) lenwatynibem z pembrolizumabem (n = 395) lub 2) lenwatynibem z placebo (n = 399); wśród przydzielonych było 644 (81%) mężczyzn i 150 (19%) kobiet; 345 chorych (43%) należało do rasy żółtej, 345 (43%) do rasy białej, a 22 (3%) było rasy mieszanej; leczono także 21 (3%) rdzennych mieszkańców Ameryki lub Alaski, 21 (3%) rdzennych mieszkańców Hawajów lub innych wysp Pacyfiku, 13 (2%) chorych rasy czarnej lub Afroamerykanów, a w przypadku 46 osób (6%) nie dysponowano danymi dotyczącymi rasy. Mediana wieku wyniosła 66,0 lat (IQR 57,0–72,0). Mediana czasu obserwacji do chwili odcięcia danych dla analizy końcowej (21 czerwca 2022 r.) wyniosła 32,1 miesiąca (IQR 29,4–35,3). W zakresie całkowitego przeżycia mediana wyniosła 21,2 miesiąca (95% CI 19,0–23,6; zmarło 252 spośród 395 chorych [64%]) wśród leczonych lenwatynibem z pembrolizumabem w porównaniu z 19,0 miesiąca (17,2–21,7; zmarło 282 spośród 399 chorych [71%]) wśród leczonych lenwatynibem z placebo (współczynnik ryzyka [*hazard ratio* – HR] 0,84; 95% CI 0,71–1,00; stratyfikowany test log–rank p = 0,023). W dniu odcięcia danych do końcowej analizy przeżywalności wolnej od progresji (5 kwietnia 2021 r.) mediana czasu wolnego od progresji wyniosła 8,2 miesiąca (95% CI 6,4–8,4; wystąpiło 270 zdarzeń [42 zgony; 228 progresji]) u leczonych lenwatynibem z pembrolizumabem w porównaniu z 8,0 miesiąca (6,3–8,2; wystąpiło 301 zdarzeń [36 zgonów, 265 progresji]) u leczonych lenwatynibem z placebo (HR 0,87; 95% CI 0,73–1,02; stratyfikowany test log–rank p = 0,047). Najczęstszymi związanymi z leczeniem działaniami niepożądanymi 3.–4. stopnia były: nadciśnienie tętnicze (u 69 spośród 395 chorych [17%] w grupie leczonej lenwatynibem z pembrolizumabem w porównaniu z 68 chorymi [17%] w grupie leczonej lenwatynibem z placebo), zwiększone stężenie aminotransferazy asparaginianowej (27 [7%] *vs* 17 [4%]) oraz biegunka (25 [6%] *vs* 15 [4%]). Działania niepożądane związane z leczeniem skutkujące zgonem wystąpiły u czterech chorych (1%) z grupy leczonej lenwatynibem z pembrolizumabem (z powodu krwawienia z przewodu pokarmowego [jedna osoba], zespołu wątrobowo-nerkowego [jedna osoba] oraz encefalopatii wątrobowej [dwie osoby]) oraz u trzech chorych (1%) z grupy leczonej lenwatynibem z placebo (z powodu krwawienia z przewodu pokarmowego [jedna osoba], zespołu wątrobowo-nerkowego [jedna osoba] oraz udaru mózgu [jedna osoba]).

Wnioski. We wcześniejszych badaniach połączenie pembrolizumabu z lenwatynibem w pierwszej linii leczenia chorych na zaawansowanego raka wątrobowokomórkowego wykazywało obiecującą aktywność kliniczną. W niniejszym badaniu lenwatynib z pembrolizumabem nie spełnił wcześniej ustalonej znamienności w zakresie poprawy przeżywalności całkowitej i wolnej od progresji w porównaniu z lenwatynibem z placebo. Wyniki badania nie mogą stanowić przesłanki do zmiany praktyki klinicznej.

Three-year overall survival with tebentafusp in metastatic uveal melanoma

Hassel J.C., Piperno-Neumann S., Rutkowski P. i wsp.
N. Engl. J. Med., 2023; 389: 2256–2266

Tebentafusp, dwuswoista cząsteczka, zawierająca receptor komórek T, ukierunkowana na glikoproteinę 100 i CD3, został zarejestrowany do leczenia dorosłych chorych na nieoperacyjnego lub rozsianego czerniaka błony naczyniowej oka, u których występuje antygen HLA-A*02:01. Podstawowa analiza w niniejszym badaniu III fazy potwierdziła długotrwałą korzyść w zakresie przeżycia.

Metody. Przedstawiono wyniki otwartego badania III fazy uzyskane po 3-letniej obserwacji dotyczące skuteczności i bezpieczeństwa stosowania tebentafuspu. W badaniu przydzielono losowo (w stosunku 2:1) wcześniej nieleczonych chorych na zaawansowanego czerniaka błony naczyniowej oka z potwierdzoną obecnością antygenu HLA-A*02:01, do grupy otrzymującej tebentafusp lub do grupy, w której stosowano wybrane przez badacza leczenie pembrolizumabem, ipilimumabem lub dakarbazyną (grupa kontrolna). Podczas randomizacji chorych stratyfikowano w zależności od stężenia dehydrogenazy mleczanowej. Pierwszorzędowym punktem końcowym była przeżywalność całkowita.

Wyniki. Po obserwacji z najkrótszym okresem wynoszącym 36 miesięcy, mediana całkowitego przeżycia wyniosła 21,6 miesiąca w grupie otrzymującej tebentafusp i 16,9 miesiąca w grupie kontrolnej (HR dla zgonu 0,68; 95% CI 0,54–0,87). Szacunkowy udział 3-letnich przeżyć wyniósł 27% w grupie otrzymującej tebentafusp i 18% w grupie kontrolnej. Najczęstszymi zdarzeniami niepożądanymi dowolnego stopnia były: wysypka (83%), gorączka (76%), świąd (70%) i niedociśnienie (38%) w grupie otrzymującej tebentafusp. Większość działań niepożądanych związanych z tebentafuspem wystąpiła na początku leczenia i nie zaobserwowano żadnych nowych działań niepożądanych podczas długotrwałego podawania. Odsetek chorych, którzy przerwali leczenie z powodu działań niepożądanych był niski w obu grupach (2% w grupie leczonej tebentafuspem i 5% w grupie kontrolnej). Nie odnotowano żadnych zgonów związanych z leczeniem.

Wnioski. W analizie przeprowadzonej po 3-letniej obserwacji potwierdzono długotrwałe korzyści ze stosowania tebentafuspu w zakresie całkowitego przeżycia u dorosłych chorych na

nieoperacyjnego lub rozsianego czerniaka błony naczyniowej oka, u których występuje antygen HLA-A*02:01.

Durvalumab *versus* placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial

Monk B.J., Toita T., Wu X. i wsp.
Lancet Oncol., 2023; 24: 1334–1348

Jednoczesna radiochemioterapia stanowi standard leczenia chorych na miejscowo zaawansowanego raka szyjki macicy, jednakże u 30–40% chorych w ciągu 5 lat od leczenia następuje nawrót lub progresja nowotworu. Hamowanie immunologicznych punktów kontrolnych poprawiło wyniki leczenia u chorych na rozsianego lub nawrotowego raka szyjki macicy z ekspresją PD-L1. Oceniono korzyści z połączenia terapii durwalumabem (przeciwciało anty-PD-L1) z radiochemioterapią oraz podawanego w leczeniu podtrzymującym u chorych na miejscowo zaawansowanego raka szyjki macicy.

Metody. W podwójnie zaślepionym badaniu III fazy CALLA, prowadzonym w 105 szpitalach w 15 krajach, wcześniej nieleczone dorosłe chore na miejscowo zaawansowanego raka szyjki macicy (gruczolakorak, rak płaskonabłonkowy lub rak gruczołowo-płaskonabłonkowy w stopniu IB2–IIB z zajęciem węzłów chłonnych oraz w stopniu ≥III z zajęciem lub bez zajęcia węzłów chłonnych), w stopniu sprawności ECOG 0–1, przydzielano losowo (1:1) do otrzymywania durwalumabu (1500 mg dożylnie raz na 4 tygodnie) lub placebo w trakcie radiochemioterapii i po niej (do 24 cykli). Radiochemioterapia obejmowała radioterapię wiązką zewnętrzną w dawce 45 Gy (5 frakcji tygodniowo) w połączeniu z dożylnie podawaną cisplatyną (40 mg/m^2) lub karboplatyną (AUC2) raz w tygodniu przez 5 tygodni, z następczą brachyterapią pod kontrolą obrazu (HDR 27,5–30 Gy lub LDR/PDR, 35–40 Gy). W trakcie randomizacji chore stratyfikowano według stopnia zaawansowania nowotworu (wg FIGO i zajęcia węzłów chłonnych) oraz regionu geograficznego. Jakość radiochemioterapii podlegała kontroli. Pierwszorzędowym punktem końcowym było przeżycie wolne od progresji, oceniane przez badacza przy użyciu kryteriów RECIST w wersji 1.1, w grupie zgodnej z zamiarem leczenia. Bezpieczeństwo oceniano u tych chorych, które otrzymały co najmniej jedną dawkę badanego leku.

Wyniki. Od 15 lutego 2019 roku do 10 grudnia 2020 roku przydzielono losowo 770 chorych (385 do grupy durwalumabu i 385 do grupy placebo; mediana wieku: 49 lat [IQR 41–57]). Mediana czasu obserwacji wyniosła 18,5 miesiąca (IQR 13,2–21,5) w grupie durwalumabu i 18,4 miesiąca (13,2–23,7) w grupie placebo. W chwili odcięcia danych mediana czasu wolnego od progresji nie została osiągnięta (95% CI nieosiągnięty–nieosiągnięty) w żadnej z grup (HR 0,84; 95% CI 0,65–1,08; p = 0,17); udział 12-miesięcznych przeżyć wolnych od progresji wyniósł 76,0% (71,3–80,0) w grupie leczonych durwalumabem i 73,3% (68,4–77,5) w grupie otrzymujących placebo. Najczęściej zgłaszanymi zdarzeniami niepożądanymi 3. i 4. stopnia w obu grupach były: niedokrwistość (76 spośród 385 [20%] w grupie leczonych durwalumabem w porównaniu z 56 spośród 384 [15%] w grupie otrzymujących placebo) i zmniejszenie liczby białych krwinek (39 [10%] *vs* 49 [13%]). Poważne zdarzenia niepożądane wystąpiły u 106 chorych (28%) leczonych durwalumabem i 89 chorych (23%) otrzymujących placebo. W grupie otrzymującej durwalumab odnotowano pięć zgonów związanych z leczeniem (zakażenie dróg moczowych, niedokrwistość z utraty krwi i zatorowość płucna – związane wyłącznie z radiochemioterapią; zaburzenia endokrynne związane wyłącznie z durwalumabem; posocznica związana z obydwiema metodami leczenia). W grupie placebo wystąpił jeden zgon związany z leczeniem (zapalenie płuc związane z radiochemioterapią).

Wnioski. Durwalumab stosowany w skojarzeniu z radiochemioterapią był dobrze tolerowany przez chore na miejscowo zaawansowanego raka szyjki macicy, jednak nie wydłużył znamiennie czasu wolnego od progresji w grupie wszystkich chorych niewybranych pod kątem biomarkerów. Dalsze badania oceniające durwalumab w skojarzeniu z radiochemioterapią u chorych z wysoką ekspresją PD-L1 wydają się uzasadnione. Rygorystyczne monitorowanie zapewniło wysoką jakość radiochemioterapii przy zastosowaniu zaawansowanej technologii i umożliwiło chorym otrzymanie optymalnej opieki.

Atezolizumab plus bevacizumab *versus* active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial

Qin S., Chen M., Cheng A.-L. i wsp.
Lancet, 2023; 402: 1835–1847

Nie ustalono, jaka terapia uzupełniająca jest optymalna u chorych z grupy wysokiego ryzyka nawrotu raka wątrobowokomórkowego po resekcji lub ablacji. Oceniono skuteczność uzupełniającego leczenia atezolizumabem w skojarzeniu z bewacyzumabem w tej grupie chorych w porównaniu z aktywnym nadzorem.

Metody. W otwartym badaniu III fazy IMbrave050, prowadzonym w 134 szpitalach i ośrodkach medycznych w 26 krajach, w czterech regionach WHO (region europejski, region obu Ameryk, region Azji Południowej i Wschodniej, region Zachodniego Pacyfiku), dorosłych chorych po resekcji lub ablacji raka wątrobowokomórkowego o wysokim ryzyku przydzielano losowo (w stosunku 1:1) do stosowania dożylnie podawanego atezolizumabu w dawce 1200 mg wraz z bewacyzumabem w dawce 15 mg/kg mc. co 3 tygodnie przez 17 cykli (12 miesięcy leczenia) lub do grupy aktywnego nadzoru.

Pierwszorzędowym punktem końcowym była przeżywalność wolna od nawrotu choroby, określona przez niezależną komisję w grupie zgodnej z zamiarem leczenia.

Wyniki. Grupa zgodna z zamiarem leczenia obejmowała 668 chorych przydzielonych losowo, od 31 grudnia 2019 roku do 25 listopada 2021 roku, do leczenia atezolizumabem w skojarzeniu z bewacyzumabem (n = 334) lub do aktywnego nadzoru (n = 334). We wcześniej określonej analizie okresowej (21 października 2022 r.) mediana czasu obserwacji wyniosła 17,4 miesiąca (IQR 13,9–22,1). Leczenie uzupełniające wiązało się ze znamiennym wydłużeniem przeżycia wolnego od nawrotu (mediana nie do oceny [NE]; [95% CI 22,1–NE]) w porównaniu z aktywnym nadzorem (mediana NE [21,4–NE]; HR 0,72 [skorygowany 95% CI 0,53–0,98], p = 0,012). Zdarzenia niepożądane 3. lub 4. stopnia wystąpiły u 136 spośród 332 chorych (41%) leczonych skojarzeniem atezolizumabu z bewacyzumabem oraz u 44 spośród 330 chorych (13%) w grupie aktywnego nadzoru. Zdarzenia niepożądane 5. stopnia wystąpiły u sześciu chorych (2%, w tym dwa związane z leczeniem) z grupy leczenia uzupełniającego i u jednego chorego (<1%) z grupy aktywnego nadzoru. Zarówno podawanie atezolizumabu, jak i bewacyzumabu przerwano z powodu działań niepożądanych u 29 chorych (9%).

Wnioski. Wśród chorych na raka wątrobowokomórkowego z wysokim ryzykiem nawrotu po resekcji lub ablacji uzyskano dłuższe przeżycie wolne od nawrotu u leczonych uzupełniająco atezolizumabem z bewacyzumabem. Badanie IMbrave050 jest pierwszym badaniem III fazy, w którym wykazano korzyść z leczenia uzupełniającego u chorych na raka wątrobowokomórkowego. Aby ocenić pełen profil korzyści i ryzyka, konieczna jest jednak dłuższa obserwacja, zarówno odnośnie do przeżycia wolnego od nawrotu, jak i przeżycia całkowitego.

Perioperative durvalumab for resectable non-small-cell lung cancer

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N. Engl. J. Med., 2023; 389: 1672–1684

Indukcyjna lub uzupełniająca immunoterapia może poprawić wyniki leczenia chorych na operacyjnego niedrobnokomórkowego raka płuca (*non-small-cell lung cancer* – NSCLC). Schematy okołooperacyjne mogą łączyć korzyści obu metod w celu poprawy odległych wyników leczenia.

Metody. Chorych na operacyjnego NSCLC (stopień zaawansowania II–IIIB [z cechą N2]) przydzielono losowo do chemioterapii zawierającej pochodną platyny w skojarzeniu z durwalumabem lub placebo podawanymi dożylnie co 3 tygodnie przez 4 cykle przed zabiegiem operacyjnym; następnie podawano uzupełniająco durwalumab lub placebo (dożylnie, co 4 tygodnie przez 12 cykli). Podczas randomizacji chorych stratyfikowano w zależności od stopnia zaawansowania choroby (II lub III) i ekspresji liganda 1. receptora programowanej śmierci 1 (PD-L1) (≥1% lub <1%). Pierwszorzędowymi punktami końcowymi były: przeżywalność wolna od zdarzeń (określona jako czas do najwcześniejszego wystąpienia progresji choroby, która wykluczyła zabieg operacyjny lub uniemożliwiła jej ukończenie, nawrót choroby lub zgon z jakiejkolwiek przyczyny) oraz całkowita odpowiedź patologiczna (oceniana centralnie).

Wyniki. Łącznie 802 chorych przydzielono losowo do leczenia przy użyciu durwalumabu (400 osób) lub otrzymywania placebo (402 osoby). Czas przeżycia wolnego od zdarzeń był znamiennie dłuższy dla leczonych durwalumabem niż w grupie otrzymujących placebo; stratyfikowany współczynnik ryzyka progresji choroby, nawrotu lub zgonu wyniósł 0,68 (95% CI 0,53–0,88; p = 0,004) w pierwszej analizie okresowej. W planowej analizie przeprowadzonej w trakcie badania udział 12-miesięcznych przeżyć wolnych od zdarzeń wyniósł 73,4% dla otrzymujących durwalumab (95% CI 67,9–78,1) w porównaniu z 64,5% dla otrzymujących placebo (95% CI 58,8–69,6). Całkowitą odpowiedź patologiczną stwierdzano znamiennie częściej u leczonych durwalumabem w porównaniu z otrzymującymi placebo (17,2% w porównaniu do 4,3% w analizie końcowej; różnica 13,0 punktów procentowych; 95% CI 8,7–17,6; p < 0,001 w częściowej analizie danych dotyczących 402 chorych). Chorzy odnosili korzyść w zakresie przeżycia wolnego od zdarzeń i całkowitej odpowiedzi patologicznej niezależnie od stopnia zaawansowania nowotworu i ekspresji PD-L1. Częstość działań niepożądanych 3. lub 4. stopnia wyniosła 42,4% u otrzymujących durwalumab i 43,2% u otrzymujących placebo. Nie stwierdzono niepożądanych zdarzeń 5. stopnia. Dane pochodzące od 62 chorych z udokumentowanymi zaburzeniami w genie *EGFR* lub *ALK* wyłączono z analiz skuteczności w zmodyfikowanej grupie zgodnej z zamiarem leczenia.

Wnioski. Okołooperacyjne podawanie durwalumabu w skojarzeniu z indukcyjną chemioterapią u chorych na operacyjnego NSCLC wiązało się ze znamiennym wydłużeniem przeżywalności wolnej od zdarzeń i większym udziałem całkowitych odpowiedzi patologicznych w porównaniu z wyłączną indukcyjną chemioterapią, przy utrzymaniu opisanego profilu bezpieczeństwa poszczególnych leków.

Phase 3 trial of selpercatinib in advanced *RET*-mutant medullary thyroid cancer

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N. Engl. J. Med., 2023; 389: 1851–1861

Selperkatynib, wysoce wybiórczy, silny inhibitor RET, wykazał skuteczność w leczeniu zaawansowanego raka rdzeniastego tarczycy z mutacją genu *RET* w badaniu I i II fazy, ale jego skuteczność w porównaniu z zarejestrowanymi inhibitorami wielokinazowymi jest niepewna.

Metody. Przeprowadzono badanie III fazy z randomizacją porównujące selperkatynib w leczeniu pierwszej linii z lekiem wybranym przez lekarza (kabozantynib lub wandetanib – grupa kontrolna). U kwalifikujących się chorych udokumentowano progresję choroby w ciągu 14 miesięcy przed włączeniem do

badania. Pierwszorzędowym punktem końcowym w okresowej analizie skuteczności określonej w protokole było przeżycie wolne od progresji, oceniane przez niezależną, zaślepioną centralną komisję, na podstawie przeglądu danych. Zastosowanie selperkatynibu było dozwolone u chorych z grupy kontrolnej po progresji. Przeżycie wolne od niepowodzeń leczenia, oceniane w niezależnym, zaślepionym badaniu centralnym, było wtórnym, kontrolowanym współczynnikiem alfa punktem końcowym, który należało badać tylko wtedy, gdy przeżycie wolne od progresji było znamienne. Innymi drugorzędowymi punktami końcowymi były ogólna odpowiedź na leczenie i bezpieczeństwo.

Wyniki. Randomizacji poddano ogółem 291 chorych. Po obserwacji o medianie wynoszącej 12 miesięcy nie osiągnięto mediany czasu przeżycia wolnego od progresji w grupie selperkatynibu, a w grupie kontrolnej wyniosła ona 16,8 miesiąca (HR progresji lub zgonu 0,28; 95% CI 0,16–0,48; p < 0,001). Odsetek 12-miesięcznych przeżyć wolnych od progresji wyniósł 86,8% (95% CI 79,8–91,6) w grupie selperkatynibu i 65,7% (95% CI 51,9–76,4) w grupie kontrolnej. Mediana czasu wolnego od niepowodzeń leczenia nie została osiągnięta w grupie selperkatynibu, natomiast w grupie kontrolnej wyniosła 13,9 miesiąca (HR progresji, przerwania leczenia z powodu działań niepożądanych związanych z leczeniem lub zgonu 0,25; 95% CI 0,15–0,42; p < 0,001). Udział 12-miesięcznych przeżyć wolnych od niepowodzeń leczenia wyniósł 86,2% (95% CI 79,1–91,0) w grupie selperkatynibu i 62,1% (95% CI 48,9–72,8) w grupie kontrolnej. Odsetek ogólnych odpowiedzi wyniósł 69,4% (95% CI 62,4–75,8) w grupie selperkatynibu i 38,8% (95% CI 29,1–49,2) w grupie kontrolnej. Działania niepożądane doprowadziły do zmniejszenia dawki leku u 38,9% chorych z grupy selperkatynibu w porównaniu z 77,3% w grupie kontrolnej oraz do przerwania leczenia odpowiednio u 4,7% i 26,8% chorych.

Wnioski. Leczenie selperkatynibem wydłużyło czas wolny od progresji i czas wolny od niepowodzeń leczenia u chorych na raka rdzeniastego tarczycy z mutacją *RET* w porównaniu z terapią opartą na kabozantynibie lub wandetanibie.

Tarlatamab for patients with previously treated small-cell lung cancer

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Tarlatamab, dwuswoiste przeciwciało aktywujące limfocyty T, ukierunkowane na ligand podobny do delta 3 (*delta-like* ligand 3) i CD3, wykazał obiecujące działanie przeciwnowotworowe w badaniu I fazy u wcześniej leczonych chorych na drobnokomórkowego raka płuca.

Metody. W badaniu II fazy oceniono działanie przeciwnowotworowe i bezpieczeństwo terapii tarlatamabem podawanym dożylnie co 2 tygodnie w dawce 10 mg lub 100 mg. Pierwszorzędowym punktem końcowym była obiektywna odpowiedź na leczenie (całkowita lub częściowa) oceniana przez niezależną, zaślepioną, centralną komisję na podstawie przeglądu zgodnie z kryteriami RECIST v. 1.1.

Wyniki. Ogółem 220 chorych, wcześniej poddanych średnio dwóm liniom leczenia, otrzymało tarlatamab. W grupie ocenianej pod kątem działania przeciwnowotworowego i czasu przeżycia mediana czasu obserwacji wyniosła 10,6 miesiąca w grupie otrzymującej lek w dawce 10 mg i 10,3 miesiąca w grupie stosującej dawkę 100 mg. Odsetek obiektywnych odpowiedzi wyniósł 40% (97,5% CI 29–52) w grupie leczonej dawką 10 mg i 32% (97,5% CI 21–44) w grupie otrzymującej dawkę 100 mg. Wśród chorych, u których uzyskano obiektywną odpowiedź, czas jej trwania wyniósł co najmniej 6 miesięcy u 59% (40 spośród 68 chorych). Obiektywne odpowiedzi w chwili odcięcia danych utrzymywały się u 22 spośród 40 chorych (55%) w grupie leczonej dawką 10 mg i u 16 spośród 28 chorych (57%) w grupie leczonej dawką 100 mg. Mediana przeżycia wolnego od progresji wyniosła 4,9 miesiąca (95% CI 2,9–6,7) w grupie z dawką 10 mg i 3,9 miesiąca (95% CI 2,6–4,4) w grupie z dawką 100 mg; udziały szacunkowych całkowitych 9-miesięcznych przeżyć wyniosły odpowiednio: 68% i 66%. Najczęstszymi działaniami niepożądanymi były: zespół uwalniania cytokin (u 51% chorych w grupie leczonej mniejszą dawką [10 mg] i u 61% chorych w grupie otrzymujących lek w większej dawce [100 mg]), zmniejszenie apetytu (odpowiednio 29% i 44%) i gorączka (35% oraz 33%). Zespół uwalniania cytokin występował głównie podczas 1. cyklu leczenia, a zdarzenia niepożądane u większości chorych miały niewielkie nasilenie (1. lub 2. stopień). Zespół uwalniania cytokin 3. stopnia występował rzadziej w grupie otrzymującej lek w dawce 10 mg (u 1% chorych) niż w grupie leczonej dawką 100 mg (u 6%). U niewielkiego odsetka chorych (3%) przerwano leczenie tarlatamabem z powodu działań niepożądanych związanych z leczeniem.

Wnioski. Tarlatamab podawany w dawce 10 mg co 2 tygodnie wykazał działanie przeciwnowotworowe z trwałymi obiektywnymi odpowiedziami i obiecującymi wynikami w zakresie przeżycia u wcześniej leczonych chorych na drobnokomórkowego raka płuca. Nie stwierdzono żadnych nowych sygnałów dotyczących bezpieczeństwa.

Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial

Rugo H.S., Aditya Bardia A., Marmé F. i wsp.

Lancet, 2023; 402: 1423–1433

W badaniu III fazy TROPiCS-02 sacytuzumab gowitekan znamiennie wydłużył czas wolny od progresji u chorych na rozsianego hormonozależnego, HER2-ujemnego raka piersi, opornego na leczenie hormonalne, z ograniczonymi możliwościami

leczenia, w porównaniu z chemioterapią. Przedstawiono wyniki określonej w protokole ostatecznej analizy całkowitego przeżycia oraz punktów końcowych na podstawie ekspresji białka Trop-2 i innych zmiennych.

Metody. W otwartym wieloośrodkowym badaniu III fazy z randomizacją, prowadzonym w 91 ośrodkach w Ameryce Północnej (USA i Kanadzie) i Europie (Belgia, Francja, Niemcy, Włochy, Holandia, Hiszpania i Wielka Brytania) chorych przydzielono losowo (1:1) do grupy otrzymującej sacytuzumab gowitekan lub do grupy poddawanej chemioterapii (erybulina, winorelbina, kapecytabina lub gemcytabina). Do badania włączano chore na hormonozależnego, HER2-ujemnego, nieoperacyjnego miejscowo zaawansowanego lub rozsianego raka piersi, które otrzymały co najmniej jedną linię leczenia: hormonoterapię, chemioterapię z zastosowaniem taksanów i inhibitor CDK 4/6 (w dowolnej konfiguracji) oraz od dwóch do czterech linii chemioterapii z powodu rozsiewu. Pierwszorzędowym punktem końcowym był czas wolny od progresji (przedstawiony wcześniej i nieuwzględniony w tej analizie), a drugorzędowymi – przeżywalność całkowita, odsetek obiektywnych odpowiedzi (*objective respons ratio* – ORR) oraz opinie i wyniki zgłaszane przez chorych. Przeżywalność całkowitą oceniano za pomocą stratyfikowanego testu log–rank oraz modelu regresji Coxa. Ekspresję białka Trop-2 oceniano w badaniu immunohistochemicznym. Jeżeli poprawa przeżycia całkowitego była znamienna, sekwencyjnie oceniano udział obiektywnych odpowiedzi (ORR) oraz wyniki zgłaszane przez chorych.

Wyniki. W dniu odcięcia danych do analizy (1 lipca 2022 r.) spośród 776 chorych ocenianych od 30 maja 2019 roku do 5 kwietnia 2021 roku, włączono do badania 543 chore, z których 272 przydzielono do leczenia sacytuzumabem gowitekanem a 271 do grupy poddawanej chemioterapii. Podczas obserwacji o medianie wynoszącej 12,5 miesiąca (IQR 6,4–18,8) wśród 543 chorych odnotowano 390 zgonów. Czas całkowitego przeżycia był znamiennie dłuższy w grupie leczonych sacytuzumabem gowitekanem w porównaniu z poddanymi chemioterapii (mediana 14,4 miesiąca [95% CI 13,0–15,7] w porównaniu z 11,2 miesiąca [10,1–12,7]; HR zgonu 0,79; 95% CI 0,65–0,96; p = 0,020); wydłużenie całkowitej przeżywalności obserwowano we wszystkich podgrupach, niezależnie od ekspresji białka Trop-2. ORR by znamiennie wyższy w grupie leczonej sacytuzumabem gowitekanem w porównaniu z grupą poddawaną chemioterapii (57 chorych [21%] *vs* 38 [14%]; iloraz szans 1,63 [95% CI 1,03–2,56]; p = 0,035), podobnie czas do pogorszenia ogólnego stanu zdrowia i jakości życia (mediana 4,3 *vs* 3 miesiące; HR 0,75, 0,61–0,92; p = 0,0059) oraz nasilenie zmęczenia (mediana 2,2 *vs* 1,4 miesiąca; HR 0,73, 0,60–0,89; p = 0,0021). Profil bezpieczeństwa sacytuzumabu gowitekanu był zgodny z wynikami wcześniejszych badań (w tym pierwotnej analizy TROPiCS-02 i badania ASCENT). Stwierdzono jedno zdarzenie niepożądane prowadzące do zgonu (wstrząs septyczny spowodowany neutropenicznym zapaleniem jelita grubego), które było związane z leczeniem sacytuzumabem gowitekanem.

Wnioski. Wykazano znamienną korzyść ze stosowania sacytuzumabu gowitekanu w porównaniu z chemioterapią. Mediana poprawy przeżywalności całkowitej była o 3,2 miesiąca dłuższa u chorych leczonych sacytuzumabem gowitekanem w porównaniu z chorymi, u których stosowano chemioterapię. Zdarzenia niepożądane związane z sacytuzumabem gowitekanem były możliwe do opanowania. Sacytuzumab gowitekan należy uznać za opcję terapeutyczną dla chorych na hormonozależnego, HER2-ujemnego, opornego na leczenie hormonalne raka piersi.

Adjuvant immunotherapy with nivolumab *versus* observation in completely resected Merkel cell carcinoma (ADMEC-O): disease-free survival results from a randomised, open-label, phase 2 trial

Becker J.C., Ugurel S., Leiter U. i wsp.

Lancet, 2023; 402: 798–808

Rak z komórek Merkla (*Merkel-cell carcinoma* – MCC) to immunogenny, ale agresywny nowotwór skóry. Nawet po całkowitej resekcji i uzupełniającej radioterapii często dochodzi do jego nawrotów. Wykazano kliniczną korzyść ze stosowania inhibitorów punktów kontrolnych PD-1 i PD-L1 u chorych na zaawansowanego MCC. Celem badania była ocena skuteczności i bezpieczeństwa leczenia uzupełniającego niwolumabem u chorych po całkowitej resekcji MCC (tj. grupy, dla której nie ustalono standardowego systemowego leczenia uzupełniającego).

Metody. Wieloośrodkowe badanie II fazy przeprowadzono w 20 akademickich ośrodkach w Niemczech i Holandii. Chorych po całkowitej resekcji MCC, niezależnie od stopnia zaawansowania choroby, w stanie sprawności 0–1 według kryteriów ECOG, przydzielono losowo (w stosunku 2:1), do leczenia niwolumabem (w dawce 480 mg co 4 tygodnie przez rok) lub do obserwacji. Chorych stratyfikowano według stopnia zaawansowania choroby (stopień I–II w porównaniu do stopnia III–IV według AJCC), wieku (<65 w porównaniu do ≥65 lat) oraz płci. Pierwszorzędowym punktem końcowym był udział 12- i 24-miesięcznych przeżyć wolnych od nawrotu (*disease-free survival* – DFS) w grupie zgodnej z intencją leczenia, a drugorzędowymi: czas całkowitego przeżycia oraz bezpieczeństwo leczenia. Analizę okresową wykonano po przynajmniej rocznej obserwacji ostatniego włączonego do badania chorego.

Wyniki. Od 1 października 2014 roku do 31 sierpnia 2020 roku włączono do badania 179 chorych (116 [65%] w stopniu III–IV, w tym122 [68%] w wieku ≥65 lat, 111 [62%] stanowili mężczyźni). Ogólna charakterystyka chorych była zrównoważona pomiędzy grupą leczoną niwolumabem (n = 118) a grupą kontrolną (n = 61). W grupie kontrolnej więcej chorych poddano uzupełniającej radioterapii. Mediana czasu obserwacji wynosiła 24,3 miesiąca (IQR 19,2–33,4). Nie osiągnięto mediany DFS (HR 0,58, 95% CI 0,30–1,12).

Udział DFS w grupie otrzymującej niwolumab wyniósł 85% po 12 miesiącach i 84% po 24 miesiącach, a w grupie kontrolnej 77% po 12 miesiącach i 73% po 24 miesiącach. W chwili przygotowania publikacji wyniki analizy czasu całkowitego przeżycia nie zostały jeszcze ocenione. Zdarzenia niepożądane stopnia 3.–4. wystąpiły u 48 spośród 115 chorych [42%], którzy otrzymali co najmniej jedną dawkę niwolumabu i u 7 spośród 61 chorych [11%] z grupy kontrolnej. Żadne ze zdarzeń niepożądanych nie spowodowało zgonu.

Wnioski. Uzupełniające leczenie niwolumabem wiązało się z bezwzględnym zmniejszeniem ryzyka nawrotu choroby o 9% (roczna DFS) i 10% (2-letnia DFS). Niniejsza okresowa analiza badania ADMEC-O może sugerować kliniczną skuteczność uzupełniającego leczenia niwolumabem u chorych, dla których nie określono standardowej metody leczenia. Wyniki dotyczące przeżywalności całkowitej są niedojrzałe. Konieczne są dalsze badania z losowym doborem chorych dotyczące leczenia uzupełniającego.

Adjuvant everolimus after surgery for renal cell carcinoma (EVEREST): a double-blind, placebo-controlled, randomised, phase 3 trial

Ryan W.C., Tangen C.M., Heath E.I. i wsp.

Lancet, 2023; 402: 1043–1051

U chorych na raka nerkowokomórkowego (*renal-cell carcinoma* – RCC) po radykalnej resekcji chirurgicznej istnieje ryzyko nawrotu choroby. Oceniano skuteczność ewerolimusu w leczeniu uzupełniającym.

Metody. Do podwójnie zaślepionego badania III fazy, prowadzonego w 398 ośrodkach badawczych w USA, włączano dorosłych chorych na histologicznie potwierdzonego RCC, po radykalnej resekcji chirurgicznej, ze średnio-wysokim lub bardzo wysokim ryzykiem nawrotu choroby. Chorych po nefrektomii przydzielono losowo (1:1) do grupy otrzymującej 10 mg ewerolimusu na dobę doustnie lub placebo. Leczenie stosowano przez 54 tygodnie. Charakterystyka chorych w badaniu była zrównoważona. Pierwszorzędowym punktem końcowym był czas wolny od nawrotu choroby (*recurrence-free survival* – RFS). Analizy skuteczności obejmowały wszystkich kwalifikujących się chorych. Analiza profilu bezpieczeństwa obejmowała wszystkich chorych, którzy otrzymali lek lub placebo.

Wyniki. Od 1 kwietnia 2011 roku do 15 września 2016 roku 1545 chorych przydzielono losowo do leczenia ewerolimusem (n = 775) lub do otrzymywania placebo (n = 770). W analizie uwzględniono 755 chorych przydzielonych do grupy otrzymującej ewerolimus i 744 chorych przydzielonych do grupy otrzymującej placebo. Mediana czasu obserwacji wyniosła 76 miesięcy (IQR 61–92). RFS był dłuższy dla leczonych ewerolimusem w porównaniu z otrzymującymi placebo (udział 5-letnich przeżyć bez nawrotu 67% [95% CI 63–70] w porównaniu z 63% [60–67]; stratyfikowany log–rank p = 0,050; stratyfikowany HR 0,85, 95% CI 0,72–1,00; p = 0,051), ale nie spełnił wcześniej założonego progu znamienności (p = 0,044). RFS był dłuższy dla leczonych ewerolimusem w porównaniu z otrzymującymi placebo w grupie o bardzo wysokim ryzyku nawrotu choroby (HR 0,79, 95% CI 0,65–0,97; p = 0,022), ale nie w grupie o średnio-wysokim ryzyku nawrotu choroby (0,99, 0,73–1,35; p = 0,96). Zdarzenia niepożądane stopnia 3. lub wyższego wystąpiły u 343 spośród 740 chorych (46%) otrzymujących ewerolimus i u 79 spośród 723 chorych (11%) otrzymujących placebo.

Wniosek. Ewerolimus nie wydłużył RFS w porównaniu z placebo u chorych z grupy wysokiego ryzyka nawrotu choroby po radykalnym zabiegu chirurgicznym.

Base-edited CAR7 T cells for relapsed T-cell acute lymphoblastic leukemia

Chiesa R., Georgiadis C., Farhatullah Syed F. i wsp.

N. Engl. J. Med., 2023; 389: 899–910

Deaminacja cytydyny za pomocą CRISPR (*clustered regularly interspaced short palindromic repeats*) może pośredniczyć w wysoce precyzyjnej zamianie jednego nukleotydu w inny, w szczególności cytozyny w tyminę, bez powodowania uszkodzeń w DNA. W ten sposób nukleotydy można poddać edycji, co skutkuje ich inaktywowaniem bez wywoływania translokacji lub innych aberracji chromosomowych. Zbadano zastosowanie tej techniki u chorych na nawrotową ostrą białaczkę limfoblastyczną (*acute lymphoblastic leukemia* – ALL) z limfocytów T u dzieci.

Metody. Zastosowano edycję nukleotydów, aby stworzyć uniwersalne chimeryczne limfocyty T (CAR-T). Limfocyty T zdrowego dawcy-ochotnika transdukowano przy użyciu lentiwirusa w celu ekspresji CAR wyposażone w receptor wiążący antygen CD7 (CAR7) białka ulegającego ekspresji w ALL z limfocytów T. Następnie zastosowano edycję nukleotydów, aby inaktywować trzy geny kodujące receptory CD52, CD7 oraz łańcuch β receptora limfocytów Tαβ, aby uniknąć limfodeplecji, bratobójstwa limfocytów CAR7 oraz wystąpienia choroby przeszczep przeciwko gospodarzowi. W badaniu oceniono bezpieczeństwo stosowania edytowanych limfocytów u trójki dzieci chorych na nawrotową ALL z limfocytów T.

Wyniki. Pierwsza chora, 13-letnia dziewczyna, u której wystąpił nawrót ALL z limfocytów T po alogenicznym przeszczepieniu komórek macierzystych, uzyskała remisję molekularną w ciągu 28 dni po otrzymaniu pojedynczej dawki CAR7 o zmodyfikowanych nukleotydach (BE-CAR7). Następnie otrzymała alogeniczny przeszczep komórek macierzystych o zmniejszonej intensywności (niemieloablacyjny) od swojego pierwotnego dawcy, z pomyślną rekonstytucją immunologiczną i utrzymującą się remisją białaczkową. Te same limfocyty BE-CAR7 wykazały aktywność u dwóch innych chorych, ale u jednego chorego nastąpiło zakażenie grzybicze,

prowadzące do zgonu, a u drugiego chorego przeprowadzono alogeniczne przeszczepienie komórek macierzystych w trakcie remisji choroby. Poważne zdarzenia niepożądane obejmowały zespół uwalniania cytokin, pancytopenię oraz zakażenia oportunistyczne.

Wnioski. Częściowe wyniki badania I fazy wskazują na konieczność dalszych badań nad limfocytami T o zmodyfikowanych nukleotydach u chorych na nawrotową ALL z limfocytów T i opisują ryzyko zdarzeń niepożądanych związanych z immunoterapią.

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