ISSN 2543–5248
e-ISSN: 2543–8077

Tom 7 | Numer 1 | Rok 2022

Biuletyn Polskiego Towarzystwa Onkologicznego

Nowotwory

90 lat od otwarcia Instytutu Radowego

Nowotwory. Journal of Oncology – indeksacja:
Scopus, EMBASE, Google Scholar, CrossRef, 100 punktów MEiN

VIA MEDICA

1/2022

X ZIMOWE FORUM ONKOLOGICZNE

11–12 lutego 2022 roku

SPOTKANIE ONKOLOGÓW RÓŻNYCH SPECJALNOŚCI!

POMAGAMY PRZYGOTOWAĆ SIĘ DO EGZAMINÓW SPECJALISTYCZNYCH!

Szczegóły oraz rejestracja na stronie internetowej:
www.zimoweforumonkologiczne.viamedica.pl

PATRONAT

ORGANIZATOR

VIA MEDICA

PATRONAT MEDIALNY

Onkoedu
Serwis dla lekarzy specjalistów

tvmed

PARTNER

ikamed.pl
internetowa księgarnia medyczna

21-0751.001.011

Konferencja jest skierowana do wszystkich osób zainteresowanych tematyką. Sesje satelitarne firm farmaceutycznych, sesje firm farmaceutycznych oraz wystawy firm farmaceutycznych są skierowane tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (Dz.U. z 2017 r. poz. 2211, z późn. zm.).

Biuletyn Polskiego Towarzystwa Onkologicznego

Nowotwory

Biuletyn Polskiego Towarzystwa Onkologicznego

Nowotwory

dwumiesięcznik

oficjalny organ

POLSKIEGO TOWARZYSTWA
ONKOLOGICZNEGO

Narodowy Instytut Onkologii
im. Marii Skłodowskiej-Curie
Państwowy Instytut Badawczy

czasopismo

POLSKIEGO TOWARZYSTWA
CHIRURGII ONKOLOGICZNEJ

Adres Redakcji:
Narodowy Instytut Onkologii im. M. Skłodowskiej-Curie – Państwowy Instytut Badawczy
ul. Roentgena 5
02-781 Warszawa

Adres korespondencyjny:
Krakowska Akademia im. Andrzeja Frycza-Modrzewskiego
ul. Gustawa Herlinga-Grudzińskiego 1
30-705 Kraków
pokój 309
tel. 512 177 774
e-mail: redakcja@nowotwory.edu.pl
www.nowotwory.edu.pl

Adres Wydawcy:
VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80-180 Gdańsk
tel. (48) 58 320 94 94, faks (48) 58 320 94 60
e-mail: viamedica@viamedica.pl, www.viamedica.pl

ISSN 2543–5248
e-ISSN: 2543–8077

21-0502.001.001

Spis treści

VIA MEDICA

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 1

ISSN 2543–5248
www.nowotwory.edu.pl

Edytorial

Zdjęcie: archiwum

Szanowni Państwo,

w ubiegłym roku w piśmie *Nowotwory. Journal of Oncology* wydarzyło się wiele dobrego. Po raz pierwszy odbył się konkurs *Best Original Paper Award*. Nasza redakcja jest jego organizatorem i fundatorem nagrody. W tym roku obędzie się kolejna edycja. Podczas Kongresu Onkologii Polskiej we Wrocławiu zorganizowaliśmy sesję pisma *Nowotwory*. Takie sesje będziemy organizować cyklicznie – także podczas innych konferencji onkologicznych.

Możemy również pochwalić się znaczącym wzrostem liczby punktów przyznanych przez Ministerstwo Edukacji i Nauki – obecnie to 100 punktów. Niemal dwukrotnie wzrosła liczba manuskryptów zgłaszanych do redakcji w porównaniu z rokiem 2020. Z tym związany jest też większy odsetek artykułów odrzucanych (co jest miarą jakości zawartości pisma). *Nowotwory* ukazują się terminowo, a na ich łamach pojawiły się nowe działy (m.in. cykl poświęcony prostemu językowi w nauce). Wprowadziliśmy atrakcyjne, zwięzłe opisy przypadków pod nazwą *Pictures in Oncology* – doskonały sposób na publikację spostrzeżeń klinicznych z zakresu onkologii. Artykuły po pozytywnych recenzjach szybko publikujemy na stronie internetowej w formule *Ahead of Print*. Te artykuły mają już numery DOI, dzięki czemu można je cytować w innych publikacjach bez potrzeby oczekiwania na wersje finalne. Sprawnie działa system elektronicznej obsługi manuskryptów, który pozwala śledzić etapy recenzji i opracowania redakcyjnego. Odświeżyliśmy też wygląd czasopisma – pojawiła się zupełnie nowa okładka i drobne zmiany w szacie graficznej.

To tylko wybrane efekty wspólnej pracy redakcji, patronujących *Nowotworom* stowarzyszeń i instytucji, wydawcy, recenzentów oraz autorów.

A czy Państwo także mogą zrobić coś dla naszego czasopisma? Proszę pamiętać, aby przygotowując nowe artykuły naukowe, sprawdzić zawartości dostępnego online archiwum (www.nowotwory.edu.pl) pod kątem wartościowych, merytorycznie adekwatnych publikacji. I jeśli takie będą, proszę o ich zacytowanie.

Wojciech M. Wysocki
Redaktor Naczelny czasopisma *Nowotwory. Journal of Oncology*

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 2–11

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Serum ROBO4 and CLEC14A: preliminary evaluation as diagnostic and progression biomarkers in colorectal cancer patients

Łukasz Pietrzyk[1, 2], Kamil Torres[1]

[1]*Chair and Department of Didactics and Medical Simulation, Medical University of Lublin, Lublin, Poland*
[2]*Department of General, Oncological, and Minimally Invasive Surgery, 1st Military Clinical Hospital with the Outpatient Clinic, Lublin, Poland*

Introduction. Colorectal cancer (CRC) is an important global burden, and the discovery of biomarkers for screening and monitoring is a current challenge. The present study aimed to determine the serum concentration of ROBO4 and CLEC14A in CRC patients and assess the diagnostic and progression value of these biomarkers in CRC.

Material and methods. Serum samples were collected from 32 patients with CRC and from 16 healthy individuals. Blood serum of CRC patients were tested before and after surgery. Serum concentration of ROBO4 and CLEC14A were measured using ELISA tests.

Results. The serum concentrations of ROBO4 and CLEC14A were significantly higher in CRC patients than non-cancer controls. The sensitivitiy and specificity of ROBO4 and CLEC14A in distiguishing cancer patients from controls ranged from 71.9% to 100% and from 84.5% to 100%, respectively. The serum ROBO4 concentration was associated with the TNM stage, depth of invasion, and lymph node and distant metastases. The level of ROBO4 was statistically lower 3 months after the surgery, compared to the level noted prior to the operation.

Conclusions. Our preliminary study has provided evidence that ROBO4 and CLEC14A seem to be suitable biomarkers for clinical diagnostic purposes in colorectal cancer.

Key words: ROBO4, CLEC14A, biomarker, colorectal cancer, angiogenesis

Introduction

Cancer is an important problem in terms of public health. In developed countries with the western diet and lifestyle, cancer causes nearly a quarter of all deaths [1, 2]. Among cancers, colorectal cancer (CRC) is the fourth malignancy most commonly detected worldwide and represents 9.4% of all cancer incidences in men and 10.1% in women. In 2018, there were approx. 1.9 million new CRC cases diagnosed worldwide and approx. 0.9 million deaths from colorectal cancer were evidenced [3]. An alarming trend is that CRC patients are shifting younger, e.g. the median age in 2001–2002 *vs.* 2015–2016 was 72 *vs.* 66 years at diagnosis [4]. Since colorectal cancer presents clear symptoms only in advanced stages and there are no sensitive and accurate diagnostic methods, the detection of CRC in early stages is problematic and difficult [5]. The main therapies applied for CRC are surgical treatment, chemotherapy, and radiotherapy. Unfortunately, the survival rate is still poor in distant metastatic patients [6]. Even if combined treatments are used, a recurrence occurs in approx. 1/3 of cases, and the median survival after surgery with the best supportive care of chemotherapy is up to 24 months [7]. Therefore, the identification of sensitive, reliable, and noninvasive biomarkers as screening

Jak cytować / How to cite:

Pietrzyk Ł, Torres K. ***Serum ROBO4 and CLEC14A: preliminary evaluation as diagnostic and progression biomarkers in colorectal cancer patients.*** *NOWOTWORY J Oncol* 2022; 72: 1–10.

tests for CRC would be of great advantage, improving patient outcomes and declining the mortality rate [8]. In particular:

- diagnostic biomarkers indicating the early stage of the disease,
- predictive biomarkers that are crucial for the assessment of the risk of cancer development,
- prognostic biomarkers of the risk of cancer progression are required [6]. However, regardless of many efforts, there are still no adequate biomarkers for accurate prediction and diagnosis of CRC [9].

A critical phase for tumor development and further spread is angiogenesis. Angiogenesis supports tumor growth by the influx of essential nutrients and oxygen to the cancer mass [10, 11]. It is widely documented that, without new vasculature formation, the maximum size of 1–2 mm is recognized as the limit for neoplastic expansion [12]. Tumor blood vessels are irregular and differ in their morphology (shape and size) and function from normal vessels. The endothelial cells of tumor blood vessels exhibit overexpression of molecules named tumor endothelial markers (TEMs) [12–14]. Several investigations have indicated that two proteins (ROBO4 and CLEC14A) among TEMs are overexpressed on the surface of tumor endothelial cells in a wide range of solid tumors (ovary, prostate, breast, liver, bladder, kidney, and lung) [15, 16].

The ROBO4 (magic roundabout 4) protein has been extensively expressed in endothelial cells of various cancer cell lines, including breast and colon cancer, but was not identified in such cell lines as fibroblasts and endometrial stromal cells [17]. Moreover, as shown by immunohistochemistry analysis, ROBO4 expression was restricted to sites of active formation of new blood vessels [18]. It was found that the ROBO4 molecule serves a crucial function in tumor neovascularization by initiating vascular endothelial cell migration via specific interaction with ligands (i.e. glycoprotein SLITs) [19, 20]. The involvement of the ROBO4 protein in pathological angiogenesis indicates that this molecule is a mediator of the tumor growth process [21]. Indeed, it has been proved that blocking ROBO activity can cause inhibition of tumor mass [22].

C-type lectin domain family 14 member A (CLEC14A) is considered to be a TEM due to its overexpression in tumor vasculature, compared to adjacent nontumor blood vessels. High expression of CLEC14A was observed in head and neck squamous cell carcinoma, breast cancers, and clear cell renal cell carcinoma [23,24]. Additionally, studies with CLEC14A (–/–) mice proved the promoting role of CLEC14A in tumor growth [24].

Although numerous studies have revealed that activation of ROBO4 and CLEC14A proteins contributes to angiogenesis and plays a decisive role in tumor growth and metastasis, there are limited reports on the expression of these molecules in tissue or blood in colorectal cancer patients [19–24].

The objective of the present research was to determine the serum concentration of ROBO4 and CLEC14A in colorectal cancer patients. Besides, we tried to assess the relationship between the levels of the biomarkers in serum and the clinicopathological features of CRC patients. The clinical value of ROBO4 and CLEC14A in diagnosis and progression of colorectal cancer was also evaluated by comparison with the CEA and CA 19.9 markers commonly used in clinical practice.

Materials and methods

Patients, clinical diagnosis, ethics

The study group comprised 48 patients divided into two groups: 32 patients with colorectal cancer (CRC group) and 16 healthy individuals (control group). All CRC patients were diagnosed and underwent cancer surgery between March 2018 and April 2019. The mean age of the CRC patients was 66.14 ± 9.17 years (range: 47–82) After surgery, all resected tissues underwent histopathological examination, and the pathologist confirmed CRC in all tissue samples. The primary tumour location was the colon in 18 cases (56%) and the rectum in 14 cases (44%). The advancement of the tumour stages was assessed by a highly specialized pathologist according to the staging system (AJCCS) developed by the American Joint Commission on Cancer. Preoperative radiotherapy, chemotherapy, or chemoradiotherapy excluded patients from the examination.

Healthy volunteers (mean age 61 ± 4.59 years, range: 44–79 years) were recruited from the patients of the Outpatient Clinic of our hospital during a routine colonoscopy screening. The control participants did not take any medical treatment during the study period. In addition, the colonoscopy did not reveal any pathological changes. The characteristics of the patients enrolled in the study are presented in table I.

The study was performed according to the Helsinki Declaration 1964 with later amendments and approved by the Ethical Committee (decision no. KE-0254/180/2017). In accordance with the ethical policy, all participants were adequately informed about the aim and methods of the study. As part of the procedure, all patients signed a written consent form before the initiation of the research.

Sample preparation, biomarker assay

Venous blood samples (~10 ml) were collected into commercially available anticoagulant-treated tubes (EDTA). Blood was taken from the CRC patients at two time points: before the surgery (point 0) and postoperatively (point 1), i.e. during the control visit 3 months after the operation. Blood from healthy individuals was sampled only once. The samples were immediately centrifuged at 1000 × g for 10 min at 4°C and the sera were stored at –80°C until further analysis. The concentrations of ROBO4 and CLEC14A in the serum samples were quantified with the use of sandwich ELISA (enzyme-linked immunosorbent assay) according to the manufacturer's instructions (MyBioSource, San Diego, USA).

The CEA and CA 19.9 serum markers were measured routinely in the CRC patients and controls using a Cobas 6000

Table I. Characteristics of the colorectal cancer (CRC) patient group

Colorectal cancer group		Number of patients
gender	male	17
	female	15
tumor location	colon	18
	rectum	14
tumor size	<5.0 cm	16
	≥5.0 cm	16
TNM stage	I + II	18
	III + IV	14
depth of tumor invasion (T-stage)	T1	5
	T2	8
	T3	10
	T4	9
lymph node metastases (N-stage)	N0	24
	N1 + N2	8
distant metastases (M-stage)	M0	26
	M1	5
lymphovascular invasion	absent	20
	present	12

TNM – tumor nodes metastases

analyzer (Roche Diagnostic, North America). CEA and CA 19.9 in the CRC patients were measured at two time points: before and 3 months after the surgery.

Statistical analysis

The data were shown as descriptive statistics (mean ± SD; median with minimum and maximum values). Statistical calculations were performed using SPSS software (SPSS 15.0, Chicago, IL, USA) and XLSTAT 2018; Data Analysis and Statistical Solution for Microsoft Excel (Addinsoft, Paris, France, 2017). Prior to the analyses, the data were tested for normal distribution using the Kolmogorov-Smirnov test. As the data indicated non-normal distributions, non-parametric tests were applied to compare the serum biomarker levels between the studied groups and the serum biomarker levels and clinicopathological paramteres. The Mann-Whitney *U* test was applied to assess the difference between two variable groups, while comparisons among multiple groups were performed using the Kruskal-Wallis test. Receiver-operating characteristic (ROC) curves were used to determine the sensitivity and specificity of serum ROBO4, CLEC14A, CEA, and Ca 19.9. Differences between serum biomarker levels from point 0 to point 1 were evaluated with the Wilcoxon match-pairs signed ranks test. In all analyses, the differences were considered statistically significant when $p < 0.05$.

Results

Serum levels of ROBO4 and CLEC14A in CRC patients

The serum concentration of ROBO4 and CLEC14A was significantly higher in the CRC patients than in the healthy individuals (fig. 1). The mean ROBO4 concentration was approx. 2-fold higher in the CRC group, compared to the control (675.50 ± 275.28 pg/ml *vs.* 339.15 ± 103.27 pg/ml, respectively), while the mean CLEC14A serum level was approx. 4-fold higher in the CRC patients than in the non-cancer individuals (50.91 ± 11.28 ng/ml *vs.* 12.45 ± 5.20 ng/ml, respectively).

Next, the serum levels of ROBO4 and CLEC14A in early-stage (TNM I+II) CRC patients were compared with healthy individuals. The mean serum concentrations of both studied biomarkers were significantly higher in the TNM stage I+II CRC patients than in the controls (fig. 1).

Evaluation of serum ROBO4 and CLEC14A as potential diagnostic biomarkers for CRC

We used ROC analysis to evaluate the ROBO4 and CLEC14A power in discrimination between patients with CRC and healthy controls (tab. II and fig. 2). The ROBO4 protein provided 71.9% sensitivity, 84.5% specificity, and an AUC of 0.873 (95% CI: 0.778–0.968) in diagnosing CRC. The AUC for CLEC14A for discrimination between CRC patients and healthy controls was 1.0; the cutoff value of 23.69 ng/ml contributed to 100% sensitivity and specificity. The cutoff value for CEA was 6.89 ng/ml and provided sensitivity and specificity of 62.5 and 77.0%, respectively (AUC: 0.801; 95 CI: 0.679–0.992). In the case of CA 19.9, the sensitivity and specificity were 81.3% and 91.4%, respectively, at the cutoff point of 11.45 ng/ml (AUC: 0.823; 95 CI: 0.667–0.979).

Relationship between serum levels of ROBO4 and CLEC14A and clinicopathological features in CRC patients

Table III shows the correlation between serum ROBO4 and CLEC14A levels and clinicopathological characteristics in CRC patients. The serum ROBO4 concentration was associated with the TNM stage ($p < 0.001$), depth of invasion (T stage; $p < 0.001$), and lymph node (N stage; $p = 0.015$), distant metastases (M stage; $p = 0.041$) and the presence of the lymphovascular invasion ($p = 0.034$). No significant relationship was observed between the CLEC14A concentration in the serum and the clinopathological features (tumor site, lymph node and distant metastases – N and M stages; in all cases $p > 0.05$). However, the increased CLEC14A levels were associated with the tumor size ($p = 0.015$), TNM stage ($p = 0.001$), and depth of invasion (T stage; $p = 0.002$).

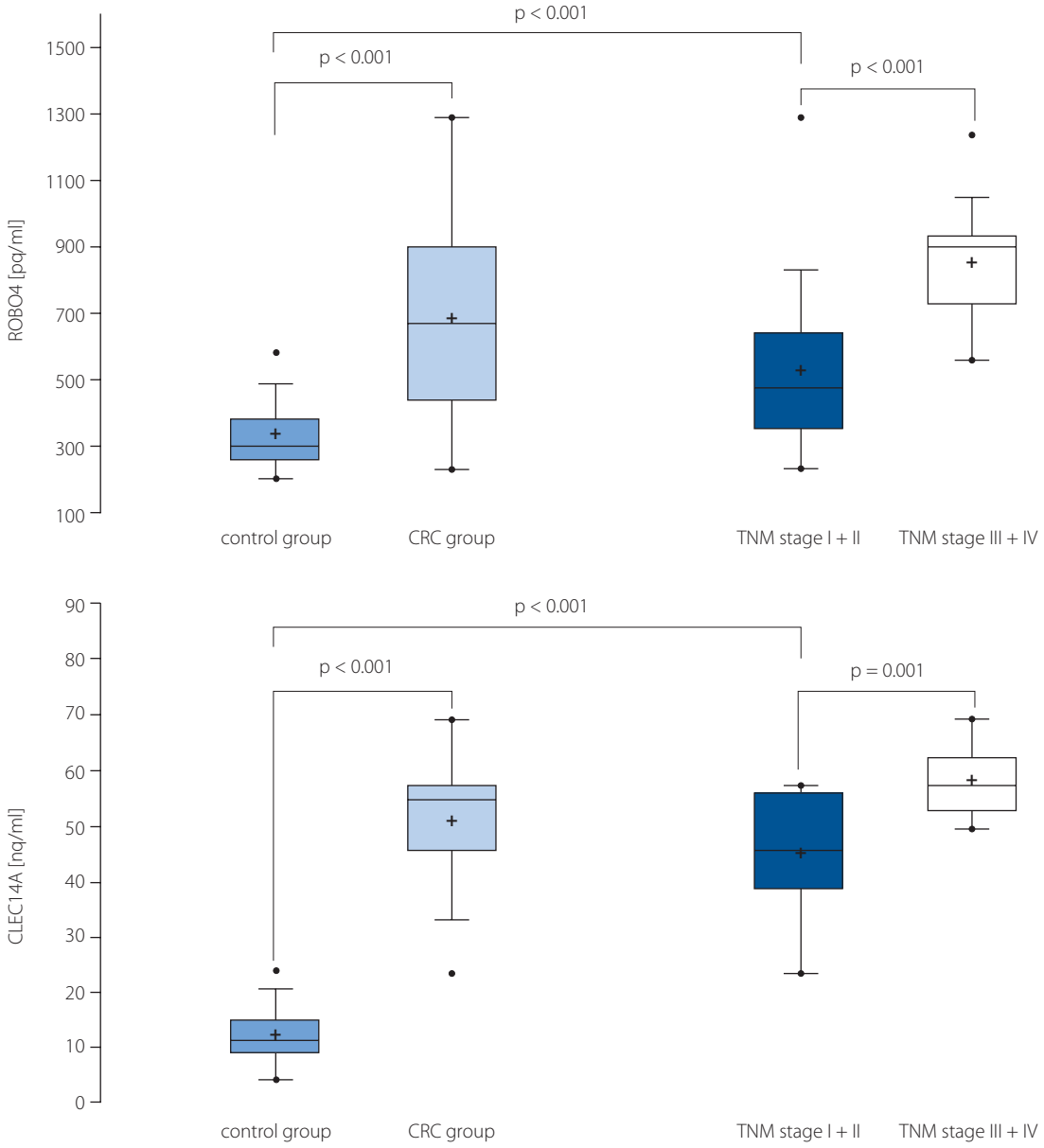

Figure 1. Serum ROBO4 and CLEC14A concentrations in CRC patients and healthy controls

Table II. Diagnostic value of serum ROBO4, CLEC14A, CEA, and CA 19.9 in CRC patients

Factor	Cutoff value	Sensitivity (%)	Specificity (%)	95% CI	AUC
ROBO4	498.76	71.9	84.5	0.778–0.968	0.873
CLEC14A	23.69	100.0	100.0	1.0–1.0	1.0
CEA	6.89	62.5	77.0	0.679–0.992	0.801
CA 19.9	11.45	81.3	91.4	0.667–0.979	0.823

ROBO4 – roundabout4; CLEC14A – C-type lectin family 14 member A; CEA – carcinoembryonic antigen; CA 19.9 – carbohydrate antigen; CI – confidence interval; AUC – area under the curve

Postoperative changes in serum ROBO4, CLEC14A, CEA, and CA 19.9 concentrations in CRC patients

Changes of the serum level of ROBO4, CLEC14A, CEA, and CA 19.9 proteins in the postoperative period were assessed (fig. 3). The serum level of ROBO4 and CEA was statistically lower at point 1 (3 months after the surgery) compared to the level noted at point 0 – prior to the operation (point 0 *vs.* point 1; ROBO4: 675.50 ± 275.28 *vs.* 419.21 ± 166.98 pg/ml, CEA:

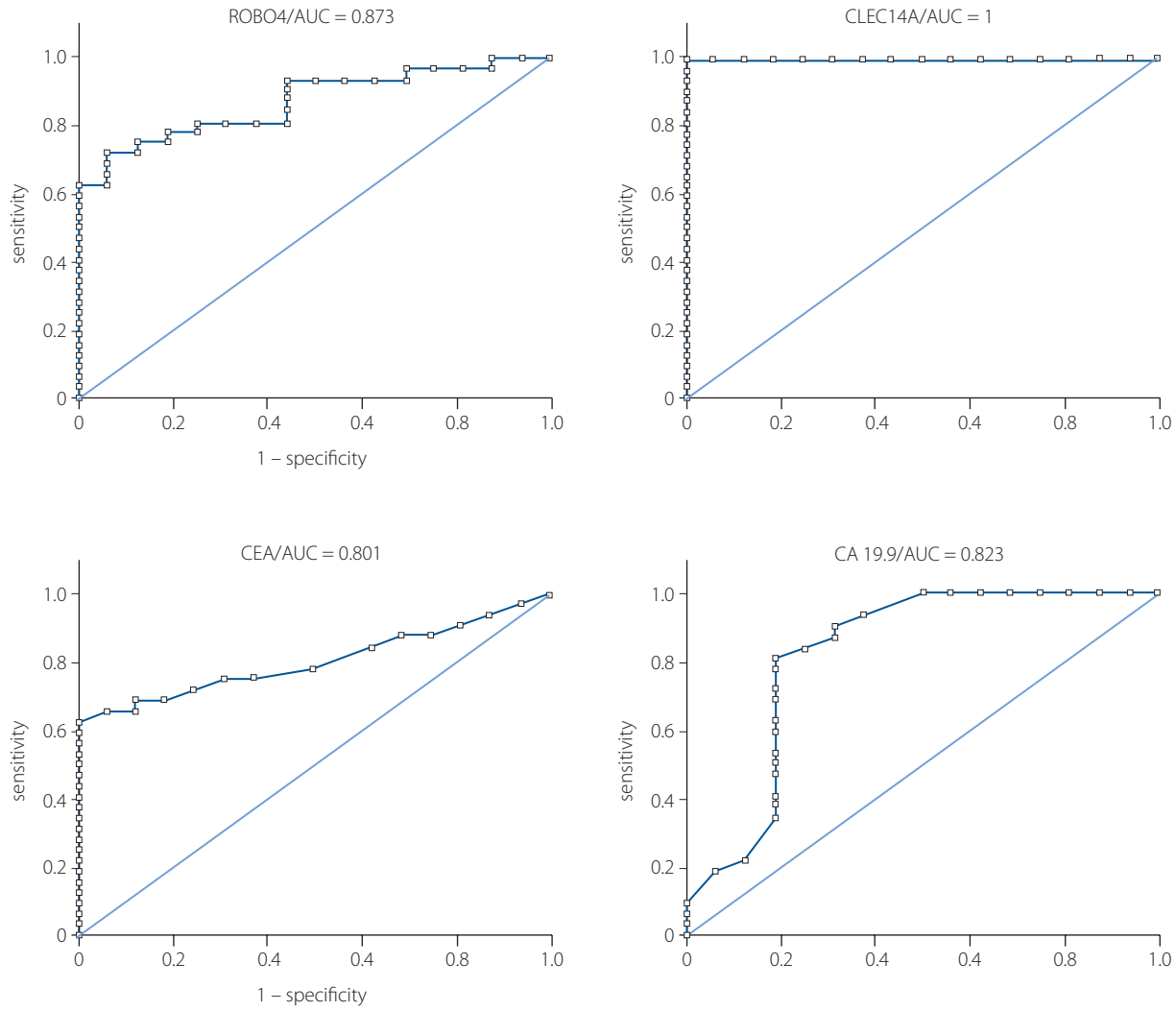

Figure 2. Receiver-operating curve (ROC) for ROBO4, CLEC14A, CEA, and Ca19-9

Table III. Serum concentration of ROBO4 and CLEC14A in relation to the clinicopathological features of CRC patients

Colorectal cancer group			ROBO4	CLEC14A
tumor location	colon n = 18	mean ± SD	678.00 ± 249.05	52.28 ± 10.61
		median	765.72	55.92
		min	234.57	23.69
		max	933.59	69.37
	rectum n = 14	mean±sd	672.27 ± 315.56	49.16 ± 12.25
		median	615.20	52.60
		min	318.65	25.44
		max	1286.69	64.73
	Mann-Whitney *U* test		0.613	0.464
tumor size	<5.0 cm n = 16	mean ± SD	615.73 ± 257.57	45.80 ± 13.07
		median	643.23	45.92
		min	279.14	23.69
		max	10.47.06	69.37

→

Table III. cont. Serum concentration of ROBO4 and CLEC14A in relation to the clinicopathological features of CRC patients

Colorectal cancer group			ROBO4	CLEC14A
tumor size	≥5.0 cm n = 16	mean ± SD	735.26 ± 287.49	56.02 ± 6.02
		median	744.64	56.28
		min	234.57	39.71
		max	1286.69	66.78
	Mann-Whitney *U* test		0.341	0.015
TNM stage	I + II n = 18	mean ± SD	538.92 ± 260.75	45.28 ± 11.20
		median	476.38	45.92
		min	234.57	23.69
		max	1286.69	58.04
	III + IV n = 14	mean ± SD	851.09 ± 181.01	58.16 ± 6.22
		median	904.37	57.60
		min	566.96	49.78
		max	1239.95	69.37
	Mann-Whitney *U* test		<0.001	0.001
depth of tumor invasion (T-stage)	T1 n = 5	mean ± SD	329.16 ± 70.40	32.96 ± 8.35
		median	354.82	33.51
		min	234.57	23.69
		max	406.52	42.47
	T2 n = 8	mean ± SD	513.01 ± 144.74	48.25 ± 10.24
		median	508.28	47.39
		min	318.65	32.67
		max	752.71	62.62
	T3 n = 10	mean ± SD	699.20 ± 163.19	54.25 ± 3.90
		median	727.10	56.01
		min	339.32	46.07
		max	933.59	59.09
	T4 n = 9	mean ± SD	986.00 ± 179.82	59.55 ± 6.56
		median	926.47	58.33
		min	710.54	49.78
		max	1286.69	69.37
	Kruskal-Wallis test		<0.001	0.002
lymph node metastases (N-stage)	N0 n = 24	mean ± SD	606.45 ± 261.68	48.90 ± 12.15
		median	603.46	51.40
		min	234.57	23.69
		max	1286.69	69.37
	N1 + N2 n = 8	mean ± SD	882.65 ± 212.62	56.94 ± 4.82
		median	922.37	56.27
		min	594.44	49.78
		max	1239.95	64.73
	Mann-Whitney *U* test		0.015	0.094

Table III. cont. Serum concentration of ROBO4 and CLEC14A in relation to the clinicopathological features of CRC patients

Colorectal cancer group			ROBO4	CLEC14A
distant metastases (M-stage)	M0 n = 26	mean ± SD	640.51 ± 262.93	50.23 ± 11.78
		median	643.23	54.65
		min	234.57	23.69
		max	1286.69	69.37
	M1 n = 5	mean ± SD	920.38 ± 263.58	55.67 ± 5.54
		median	923.56	55.42
		min	594.44	49.78
		max	1239.95	62.03
	Mann-Whitney *U* test		0.041	0.457
lymphovascular invasion	absent n = 20	mean ± SD	659.75 ± 301.20	47.87 ± 12.46
		median	683.66	50.12
		min	234.57	23.69
		max	1239.95	66.78
	present n = 12	mean ± SD	746.27 ± 264.06	52.99 ± 10.21
		median	696.49	56.23
		min	439.32	25.44
		max	1286.69	69.37
	Mann-Whitney *U* test		0.044	0.195

ROBO4 – roundabout4; CLEC14A – C-type lectin family 14 member A; TNM – tumor nodes metastases; SD – standard deviation; min – minimum; max – maximum

12.07 ± 8.25 *vs.* 7.22 ± 4.70 ng/ml). The serum concentrations of CLEC14A and CA 19.9 decreased in the postoperative time period, compared to the preoperative level; however, the declines were not statistically significant.

Discussion

In the recent years, there has been increasing interest in identification of CRC with the use of noninvasive biomarkers [8]. The expression of ROBO4 and CLEC14A proteins in tumor neovasculature makes these molecules a potential target for use as a diagnostic and prognostic indicators of cancer, including CRC [17, 23, 24].

To the best of our knowladge, the present study investigated the serum level of ROBO4 and CLEC14A in colorectal cancer (CRC) patients for the first time. We found that the mean ROBO4 and CLEC14A concentrations in the serum of CRC patients were significantly higher than in the non-cancer controls. Previous literature reports based on immunohistochemical methods evidenced specific endothelial expression of ROBO4 and CLEC14A in various cell lines, i.e. in MCF-7 breast carcinoma and SY-SH-5Y-neuroblastoma cells [15, 17, 19]. Up-regulation of these biomarkers was also proved in human tissues, i.e. in vessels of colorectal liver metastases, bladder and breast carcinoma, and liver and kidney cancer [15, 19, 26]. Moreover, the expression of ROBO4 and CLEC14A proteins was dominant at sites of active angiogenesis and in regions exposed to hypoxia [19, 27, 28]. In CRC, up-regulation of ROBO4 mRNA was detected in more than 70% of carcinoma tissues and this protein was exclusively present in the endothelium of cancer vessels [29].

In our study, the ROBO4 and CLEC14A serum levels increased already in early-stage CRC, in comparison to the control samples. Moreover, we found that ROBO4 and CLEC14A had high power to discriminate between CRC patients and cancer-free individuals. Interestingly, the diagnostic sensitivity and specificity of serum CLEC14A reached 100% at the level of 23.98 ng/ml, which is higher than values noted for CEA (sensitivity: 62.5% and specificity: 77.0%) and CA 19.9 (sensitivity: 81.3% and specificity: 91.4%), i.e. biomarkers that are currently commonly used in clinical practice. The high predictive ability of CLEC14A was previously described by Robinson et al., who performed ROC curve analysis of CLEC14A staining scores in various tumor tissues and evidenced their high sensitivity (75%) and specificity (85%) in distinguishing between cancer and non-cancer tissue status [30]. The results of our study, together with literature data evidencing that ROBO4 and CLE-

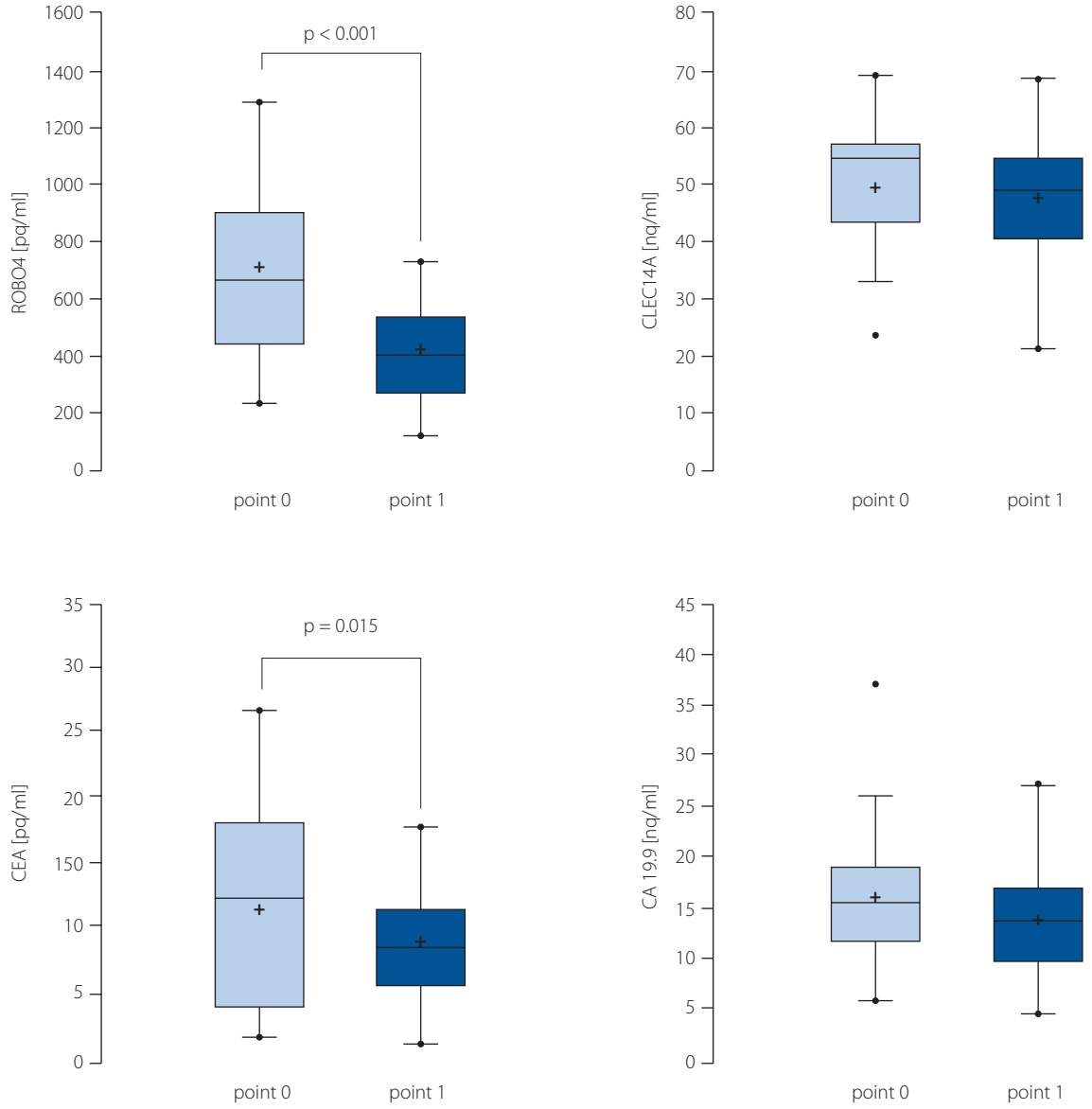

Figure 3. Postoperative changes of serum ROBO4, CLEC14A, CEA, and CA 19.9 concentrations in CRC patients

C14A molecules dominate in tumor endothelial cells, suggest that these biomolecules have diagnostic potential in cancers, presumably including CRC [15, 17, 19, 30, 31].

Further, we analyzed the association between the ROBO4 and CLEC14A serum concentrations and clinicopathological features of the CRC patients. In our study, the increased ROBO4 levels were related to the depth of tumor invasion as well as lymph node and distant metastases. In contrast, the high concentration of CLEC14A was not associated with the presence of lymph node and distant metastases. There is scarce information on the association between ROBO4 or CLEC14A expression and cancer advancement and prognosis. In prostate cancer, a higher histological tumor (Gleason) score was related to overexpression of ROBO4 [32]. In acute myeloid leukemia patients, overexpresion of ROBO4 was a poor prognostic factor and was corelated with shorter disease-free survival and overall survival [33]. Contrasting results were reported by Zhao et al., who evidenced that endothelial overexpression of ROBO4 suppressed breast cancer angiogenesis and reduced the speed of tumor growth [34]. Simmilary, in non-small lung cancer, high ROBO4 tissue expression was related to good prognosis and was connected with normalization of endothelial cells and reduction of cancer spread [16]. Considering CLEC14A, recent reports indicate that elevated levels of this molecule can inhibit carcinogenesis and progression of lung adenocarcinoma [35]. The expression of ROBO4 or CLEC14A molecules in various cancers tissues (up- or down-regulation) suggests that these proteins may act as important modulators of tumorgenesis and tumor progression. Indeed, ROBO4 and CLEC14A are known as angiogenic factors with an essential role in tumor

growth. It was revealed that blocking anti-ROBO4/CLEC14 antibodies induced reduction of the formation of new vessels and led to inhibition of cancer mass [25, 31]. Currently, the pro-angiogenic properties of CLEC14A and its involvement in tumor growth are well documented [24, 25]. For example, the CLEC14A protein promotes filopodia formation and activates cell migration, which is detrimental for tumor cell proliferation [15]. Furthermore, the inhibition of the interaction between CLEC14A and multimerin 2 (MMRN2) by a blocking antibody reduces tumor vessel sprouting and hinders the growth of the tumor mass [25].

As a novel observation, we found that the ROBO4 serum concentrations decreased significantly within 3 months after the surgical removal of CRC. In the case of CLEC14A, we documented a tendency of the serum concentration to decline after the operation. Therefore, we hypothesized that the level of circulating forms of ROBO4 and CLEC14A is associated with the tumor mass. However, we did not find any literatre data to support this hypothesis. We can only speculate that resection of solid tumor mass and removal of existing new vessels that are known to express ROBO4 and CLEC14A proteins result in a decline in the concentrations of these biomarkers in blood. Prevoiusly, Krishna et al. observed reduction of tumor microvessel CLEC14A expresion after preoperative chemotherapy administered to patients with epithelial ovarian cancer [36]. It is accepted that chemotherapy performed prior to surgical cancer excision contributes to reduction of tumor mass, down staging, and a decrease in the expression of cancer-specific molecules, including tumor endothelial markers [37, 38].

Conclusions

In this preliminary study, higher serum levels of ROBO4 and CLEC14A were observed in the CRC patients. Especially, the relationships between ROBO4 and CLEC14A serum levels and TNM stages were assesed and a signinficant post-operative decrease in the serum levels of these biomarkers was demonstrated.

Therefore, ROOB4 and CLEC14A seem to be suitable biomarkers for clinical diagnostic purposes. Nevertheless, due to the preliminary character of our findings, the results have to be taken with caution. In the future, more extensive and prospective studies with a larger CRC patient population seem to be required to validate our results.

Conflict of interest: none declared

Łukasz Pietrzyk
Medical University of Lublin
Chair and Department of Didactics and Medical Simulation
ul. Chodźki 4
20-093 Lublin, Poland
e-mail: lukasz.pietrzyk@wp.pl

Received: 1 Jul 2021
Accepted: 26 Jul 2021

References

1. Brenner H, Chen C. The colorectal cancer epidemic: challenges and opportunities for primary, secondary and tertiary prevention. Br J Cancer. 2018; 119(7): 785–792, doi: 10.1038/s41416-018-0264-x, indexed in Pubmed: 30287914.
2. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017; 67(3): 177–193, doi: 10.3322/caac.21395, indexed in Pubmed: 28248415.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
4. Araghi M, Arnold M, Rutherford MJ, et al. Colon and rectal cancer survival in seven high-income countries 2010-2014: variation by age and stage at diagnosis (the ICBP SURVMARK-2 project). Gut. 2021; 70(1): 114–126, doi: 10.1136/gutjnl-2020-320625, indexed in Pubmed: 32482683.
5. Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. Expert Rev Anticancer Ther. 2017; 17(12): 1131–1146, doi: 10.1080/14737140.2017.1392243, indexed in Pubmed: 29022408.
6. Ogunwobi OO, Mahmood F, Akingboye A. Biomarkers in Colorectal Cancer: Current Research and Future Prospects. Int J Mol Sci. 2020; 21(15), doi: 10.3390/ijms21155311, indexed in Pubmed: 32726923.
7. Scheer A, Auer RA. Surveillance after curative resection of colorectal cancer. Clin Colon Rectal Surg. 2009; 22(4): 242–250, doi: 10.1055/s-0029-1242464, indexed in Pubmed: 21037815.
8. Patel JN, Fong MKa, Jagosky M. Colorectal Cancer Biomarkers in the Era of Personalized Medicine. J Pers Med. 2019; 9(1), doi: 10.3390/jpm9010003, indexed in Pubmed: 30646508.
9. Yiu AJ, Yiu CY. Biomarkers in Colorectal Cancer. Anticancer Res. 2016; 36(3): 1093–1102, indexed in Pubmed: 26977004.
10. Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol. 2002; 29(6 Suppl 16): 15–18, doi: 10.1053/sonc.2002.37263, indexed in Pubmed: 12516034.
11. Naumov GN, Akslen LA, Folkman J. Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. Cell Cycle. 2006; 5(16): 1779–1787, doi: 10.4161/cc.5.16.3018, indexed in Pubmed: 16931911.
12. Pietrzyk Ł. Biomarkers Discovery for Colorectal Cancer: A Review on Tumor Endothelial Markers as Perspective Candidates. Dis Markers. 2016; 2016: 4912405, doi: 10.1155/2016/4912405, indexed in Pubmed: 27965519.
13. Pietrzyk Ł, Wdowiak P. Endosialin (TEM1) as a Diagnostic, Progression, and Prognostic Serum Marker for Patients With Colorectal Cancer-A Preliminary Study. Cancer Control. 2020; 27(1): 1073274820903351, doi: 10.1177/1073274820903351, indexed in Pubmed: 32107922.
14. Pietrzyk Ł, Wdowiak P. Serum TEM5 and TEM7 concentrations correlate with clinicopathologic features and poor prognosis of colorectal cancer patients. Adv Med Sci. 2019; 64(2): 402–408, doi: 10.1016/j.advms.2019.07.001, indexed in Pubmed: 31352222.
15. Mura M, Swain RK, Zhuang X, et al. Identification and angiogenic role of the novel tumor endothelial marker CLEC14A. Oncogene. 2012; 31(3): 293–305, doi: 10.1038/onc.2011.233, indexed in Pubmed: 21706054.
16. Pircher A, Fiegl M, Untergasser G, et al. Favorable prognosis of operable non-small cell lung cancer (NSCLC) patients harboring an increased expression of tumor endothelial markers (TEMs). Lung Cancer. 2013; 81(2): 252–258, doi: 10.1016/j.lungcan.2013.04.014, indexed in Pubmed: 23664449.
17. Seth P, Lin Y, Hanai Ji, et al. Magic roundabout, a tumor endothelial marker: expression and signaling. Biochem Biophys Res Commun. 2005; 332(2): 533–541, doi: 10.1016/j.bbrc.2005.03.250, indexed in Pubmed: 15894287.
18. Pircher A, Schäfer G, Eigentler A, et al. Robo 4 - the double-edged sword in prostate cancer: impact on cancer cell aggressiveness and tumor vasculature. Int J Med Sci. 2019; 16(1): 115–124, doi: 10.7150/ijms.28735, indexed in Pubmed: 30662335.
19. Huminiecki L, Gorn M, Suchting S, et al. Magic roundabout is a new member of the roundabout receptor family that is endothelial specific and expressed at sites of active angiogenesis. Genomics. 2002; 79(4): 547–552, doi: 10.1006/geno.2002.6745, indexed in Pubmed: 11944987.
20. Park KW, Morrison CM, Sorensen LK, et al. Robo4 is a vascular-specific receptor that inhibits endothelial migration. Dev Biol. 2003; 261(1): 251–267, doi: 10.1016/s0012-1606(03)00258-6, indexed in Pubmed: 12941633.
21. Huminiecki L. Magic roundabout is an endothelial-specific ohnolog of ROBO1 which neo-functionalized to an essential new role in an-

giogenesis. PLOS ONE. 2019; 14(2): e0208952, doi: 10.1371/journal.pone.0208952.
22. Wang B, Xiao Y, Ding BB, et al. Induction of tumor angiogenesis by Slit-Robo signaling and inhibition of cancer growth by blocking Robo activity. Cancer Cell. 2003; 4(1): 19–29, doi: 10.1016/s1535-6108(03)00164-8, indexed in Pubmed: 12892710.
23. Masiero M, Simões FC, Han HD, et al. A core human primary tumor angiogenesis signature identifies the endothelial orphan receptor ELTD1 as a key regulator of angiogenesis. Cancer Cell. 2013; 24(2): 229–241, doi: 10.1016/j.ccr.2013.06.004, indexed in Pubmed: 23871637.
24. Borah S, Vasudevan D, Swain RK. C-type lectin family XIV members and angiogenesis. Oncol Lett. 2019; 18(4): 3954–3962, doi: 10.3892/ol.2019.10760, indexed in Pubmed: 31579078.
25. Noy PJ, Lodhia P, Khan K, et al. Blocking CLEC14A-MMRN2 binding inhibits sprouting angiogenesis and tumour growth. Oncogene. 2015; 34(47): 5821–5831, doi: 10.1038/onc.2015.34, indexed in Pubmed: 25745997.
26. Winslow S, Lindquist KE, Edsjö A, et al. The expression pattern of matrix-producing tumor stroma is of prognostic importance in breast cancer. BMC Cancer. 2016; 16(1): 841, doi: 10.1186/s12885-016-2864-2, indexed in Pubmed: 27809802.
27. Jiang Z, Liang G, Xiao Y, et al. Targeting the SLIT/ROBO pathway in tumor progression: molecular mechanisms and therapeutic perspectives. Ther Adv Med Oncol. 2019; 11: 1758835919855238, doi: 10.1177/1758835919855238, indexed in Pubmed: 31217826.
28. Lee S, Rho SS, Park H, et al. Carbohydrate-binding protein CLEC14A regulates VEGFR-2- and VEGFR-3-dependent signals during angiogenesis and lymphangiogenesis. J Clin Invest. 2017; 127(2): 457–471, doi: 10.1172/JCI85145, indexed in Pubmed: 27991863.
29. Gröne J, Doebler O, Loddenkemper C, et al. Robo1/Robo4: differential expression of angiogenic markers in colorectal cancer. Oncol Rep. 2006; 15(6): 1437–1443, indexed in Pubmed: 16685377.
30. Robinson J, Whitworth K, Jinks E, et al. An evaluation of the tumour endothelial marker CLEC14A as a therapeutic target in solid tumours. J Pathol Clin Res. 2020; 6(4): 308–319, doi: 10.1002/cjp2.176, indexed in Pubmed: 32696621.
31. Dai C, Gong Q, Cheng Y, et al. Regulatory mechanisms of Robo4 and their effects on angiogenesis. Biosci Rep. 2019; 39(7), doi: 10.1042/BSR20190513, indexed in Pubmed: 31160487.
32. Pircher A, Schäfer G, Eigentler A, et al. Robo 4 - the double-edged sword in prostate cancer: impact on cancer cell aggressiveness and tumor vasculature. Int J Med Sci. 2019; 16(1): 115–124, doi: 10.7150/ijms.28735, indexed in Pubmed: 30662335.
33. Chen YK, Hou HA, Tang JL, et al. Clinical and prognostic implications of Roundabout 4 (robo4) in adult patients with acute myeloid leukemia. PLoS One. 2015; 10(3): e0119831, doi: 10.1371/journal.pone.0119831, indexed in Pubmed: 25794001.
34. Zhao H, Ahirwar DK, Oghumu S, et al. Endothelial Robo4 suppresses breast cancer growth and metastasis through regulation of tumor angiogenesis. Mol Oncol. 2016; 10(2): 272–281, doi: 10.1016/j.molonc.2015.10.007, indexed in Pubmed: 26778715.
35. Su C, Shi K, Cheng Xu, et al. Methylation of CLEC14A is associated with its expression and lung adenocarcinoma progression. J Cell Physiol. 2019; 234(3): 2954–2962, doi: 10.1002/jcp.27112, indexed in Pubmed: 30191970.
36. Krishna Priya S, Kumar K, Hiran KR, et al. Expression of a novel endothelial marker, C-type lectin 14A, in epithelial ovarian cancer and its prognostic significance. Int J Clin Oncol. 2017; 22(1): 107–117, doi: 10.1007/s10147-016-1033-6, indexed in Pubmed: 27567920.
37. Lone GN, Sheikh AA, Sheikh ZA, et al. Role of preoperative chemotherapy in squamous cell carcinoma of esophagus in kashmir, a cancer belt - a pilot study. Asian Pac J Cancer Prev. 2011; 12(2): 465–470, indexed in Pubmed: 21545214.
38. Ichikawa N, Kamiyama T, Yokoo H, et al. Preoperative chemotherapy in colorectal cancer patients with synchronous liver metastasis. Mol Clin Oncol. 2020; 12(4): 374–383, doi: 10.3892/mco.2020.1992, indexed in Pubmed: 32190322.

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 12–16

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Prognostic significance of sex in patients with primary tracheal tumors – a retrospective, single-center study

Aleksandra Piórek, Adam Płużański, Dariusz Mirosław Kowalski, Maciej Krzakowski

Lung Cancer and Chest Tumor Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Introduction. We aimed to assess the prognostic significance of the sex of patients with primary tracheal tumors based on our own results as well as the literature review.

Material and methods. We carried out a retrospective analysis of 89 patients with primary tracheal tumors treated at the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, between January 2000 and December 2016. Men and women were compared in terms of overall survival, disease-free survival, and progression-free survival.

Results. In the entire study group, the median overall survival was 61.30 months in women and 8.55 months in men ($p < 0.0001$). 5-year overall survival rates were 2.1% in men versus 50.6% in women ($p < 0.0001$). Among those receiving radical treatment, women had improved survival rates compared with men. Sex was an independent prognostic factor in both the total study population and among those undergoing radical treatment.

Conclusions. According to our results, women with primary tracheal tumors have significantly better survival than men. Because female sex is an independent prognostic factor in patients with primary tracheal tumors, the ratio of women to men should be taken into consideration in reports comparing the outcomes of different treatments.

Key words: tracheal tumors, adenoid cystic carcinoma of the trachea, squamous cell carcinoma of the trachea, sex

Introduction

Primary tracheal tumors are rare, and therefore remain poorly understood. They represent 0.2% of all respiratory cancers and 0.02–0.04% of all malignancies [1], with an annual incidence of approximately 0.1 per 100 000 people. The most common types are squamous cell carcinoma (SCC) and adenoid cystic carcinoma (ACC), which together account for more than two-thirds of primary tracheal tumors in adults [2].

Squamous cell carcinoma of the trachea usually presents as multiple and often ulcerative lesions growing into the tracheal lumen, with histology identical to that of SCC of the lung [3]. Squamous cell carcinoma can occupy any part of the trachea, and a third of patients have mediastinal or pulmonary metastases at diagnosis [2]. Of the trachea is 2–4 times more common in men than in women and develops primarily in the sixth and seventh decades of life [2–5]. It is strongly associated with tobacco smoking [3, 4], and 30–40% of patients with SCC of the trachea have concurrent metachronous or synchronous primary smoking-related cancer of the oropharynx, larynx, or lung [2, 3].

Adenoid cystic carcinoma of the trachea occurs with similar frequency in men and women, and is most common in the fourth and fifth decades of life [2–5]. The etiology of ACC is unknown; however, unlike SCC, it is not associated with tobacco smoking [3, 4, 6]. Adenoid cystic carcinoma is characterized by submucosal and perineural spread [7]. It often develops slowly, but can be more aggressive in some cases, with a tendency to local infiltration and, less frequently, lymph node metastases. Moreover, local or systemic recurrences may occur beyond 10 years after primary treatment [2, 3].

Jak cytować / How to cite:

Piórek A, Płużański A, Kowalski DM, Krzakowski M. ***Prognostic significance of sex in patients with primary tracheal tumors – a retrospective, single-center study.*** *NOWOTWORY J Oncol* 2022; 72: 11–15.

The prognosis of patients with primary tracheal tumors is determined by several factors. Histological diagnosis of ACC [4, 8–20], better performance status [14, 16, 21–23], and radical surgery [4, 5, 8, 16, 17, 19, 24–26] have been identified as favorable prognostic factors. Literature on the influence of sex on overall survival (OS) in different tumors has been increasing. An Australian study showed that men had lower 5-year OS than women for all cancers (47.1% [95% confidence interval (CI): 46.9–47.4] versus 52.0% [95% CI: 51.7–52.3]). Specifically, poorer survival for men was observed for 11 cancers (head and neck, esophagus, colon, pancreas, lung, bone, melanoma, mesothelioma, kidney, thyroid, and non-Hodgkin lymphoma) [27]. Several studies on the most common respiratory cancer – non-small cell lung cancer – have shown that women have a lower risk of disease progression and death than men [28–31]. Better prognosis for women with lung cancer has also been shown in Polish studies [32, 33]. In an American study based on the Surveillance, Epidemiology, and End Results (SEER) database, women with ACC of the head and neck had better OS than men in multivariate analyses (HR 0.73; 95% CI: 0.65–0.82) [34]. Data on the influence of sex on the survival of patients with primary tracheal tumors are lacking. In this study we therefore aimed to examine the prognostic significance of sex in patients with primary tracheal tumor.

Material and methods

This retrospective analysis included patients with primary tracheal tumors treated at the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Poland, between January 2000 and December 2016. Patients were identified by searching the institution's cancer registry. We enrolled adults (≥18 years) diagnosed with primary tracheal tumors for whom complete data were available. Patients with tumors that may have originated from the larynx, main bronchus, or other organs (e.g., thyroid or esophagus) were excluded.

Overall, the records of 89 actively treated patients with primary tracheal tumors were included. Data on demographics, clinicopathological variables (symptoms, smoking history, performance status, histological diagnosis, location, and extent of the tumor), and type of treatment were extracted from traditional (paper-based) and electronic medical records. The follow-up ended on December 31, 2019.

Differences in distribution were determined using one-way analysis of variance for normally distributed variables and the Kruskal-Wallis test for other continuous variables. Fisher's exact test was applied to assess the independence between categorical variables.

The Kaplan-Meier estimator, log-rank test, and Cox proportional hazards model were used to analyze survival. For all tests, statistical significance was set at $p < 0.05$. Variables for which the p value was less than 0.10 were included in the multivariate Cox models.

OS was defined as time from diagnosis to death from any cause. Disease-free survival (DFS) was defined as time from initiation of radical treatment to recurrence or death from any cause, and progression-free survival (PFS) as time from initiation of palliative treatment to disease progression or death.

Results

Clinicopathological characteristics

Among the total study population (n = 89), men slightly predominated (48 men and 41 women). The median age at diagnosis was 62 years. SCC was the most common histological type, identified in 50 (56.2%) of 89 patients. 19 patients were diagnosed with ACC (21.3%). The remaining histological findings were classified for statistical purposes as "other". Men were more frequently diagnosed with SCC (66%), whereas ACC predominated among women (73.7%). The majority (78%) of patients with SCC were over 60 years of age and none were under 35 years of age. ACC was diagnosed in all age groups (36.8% of patients were under 35 years of age). Among the 43 patients for whom data on smoking history were available, 100% of those diagnosed with SCC were current or former smokers. Only women were never-smokers. The most commonly reported symptoms were dyspnea (37.1%) and hemoptysis (36%). 68% of women and 56% of men had a WHO performance status of 0–1. Among the patients who underwent radical treatment, 28 (62.2%) were women and 17 (37.8%) were men, compared with 13 (29.5%) women and 31 (70.5%) men among those receiving palliative treatment. 13 (28.9%) of 45 patients receiving radical treatment underwent surgical resection, of whom 11 (85%) were women and two (15%) were men.

Survival analyses

For the entire study group, the median OS was 61.30 months in women and 8.55 months in men ($p < 0.0001$). 5-year OS rates were also significantly higher in women than in men (50.6% *vs.* 2.1%) (fig. 1). Among those who underwent radical treatment, 5-year OS rates were 5.9% in men, compared with 70.6% in women ($p < 0.0001$). Median OS in this group was 16.9 months in men versus 129.4 months in women ($p < 0.0001$) (fig. 2). 5-year DFS rates were 10.9% in men versus 33.6% in women ($p = 0.0023$). Sex was an independent prognostic factor in both the total study population and among those receiving radical treatment. We found no differences in OS and PFS between sexes in patients receiving palliative treatment.

Discussion

Data on the influence of sex on the survival of patients with tracheal tumors are scarce and inconsistent. In a retrospective analysis of 30 patients with ACC of the trachea, 5-year OS rates were 92% in men and 77% in women ($p = 0.345$) [25]. Moreover, the only available meta-analysis did not identify a statistically significant effect of sex on PFS or OS [5]. Another study showed that women had better disease-specific survi-

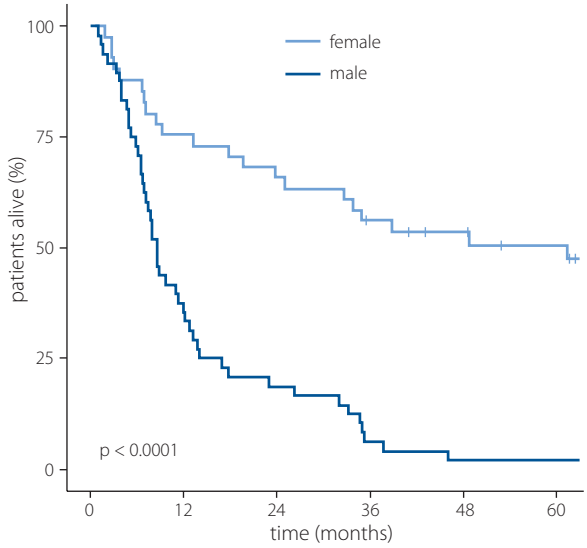

Figure 1. Cumulative probability of overall survival by sex in the total study group

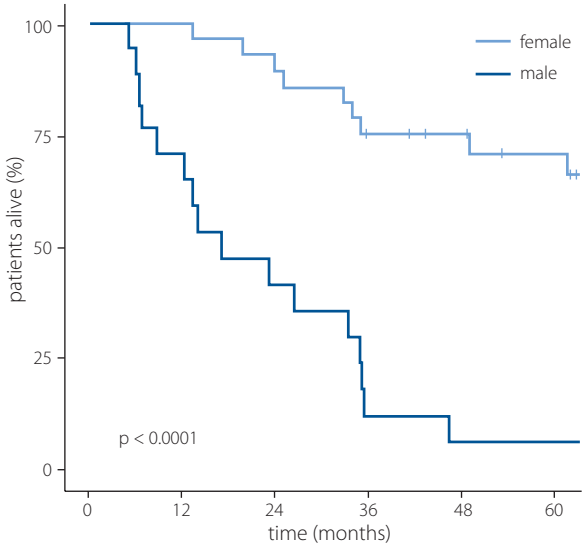

Figure 2. Cumulative probability of overall survival by sex in patients receiving radical treatment

val, defined as time from the initiation of treatment to death from the tracheal tumor (p = 0.044); however, no effect on OS was identified (p = 0.467) [10]. In a study of surgically treated patients with ACC of the trachea, female sex was a favorable prognostic factor for DFS, but not for OS [35]. Only one study, by Hetnał et al. [16] reported a favorable OS for women compared with men (5-year OS rates of 7% in men versus 32% in women, p = 0.04); however, multivariate analysis did not confirm sex to be an independent prognostic factor.

In our study, female sex was associated with favorable OS. OS and DFS benefits were also seen for women among patients who underwent radical treatment. Sex was an independent prognostic factor in both the overall study population and among those who underwent radical treatment. Various factors were considered to identify the underlying causes of such profound differences in survival by sex.

Analysis of other favorable prognostic factors in men and women showed that, in many cases, women predominated among groups with favorable characteristics. We found that:

- the group of never-smokers consisted of only women,
- the proportion of women and men who had a WHO performance status of 0/1, T1, and N0 were as follows: 68% *vs.* 56%, 39% *vs.* 19%, and 61% *vs.* 33%,
- 73.6% of patients with ACC were women,
- 62% of women were eligible for radical treatment compared with 38% of men,
- among those undergoing primary surgical treatment, 11 (85%) were women and two (15%) were men.

Attention was also paid to the difference between male and female life expectancy. Women live longer than men. According to Statistics Poland, the average life expectancy was 73.8 years for men in 2018, compared to 81.7 years for women. Few studies (and none on tracheal tumors) have taken life expectancy into account. A study on surgically treated patients with non-small cell lung cancer that accounted for expected lifetime found that women had better survival than men [36].

Other factors that may be associated with the above relationship include the patient's age at diagnosis of the tumor and comorbidities. A study in small-cell lung cancer indicated that the relationship between the patient's sex and age was important. A favorable prognostic effect of female sex was observed in younger patients, whereas prognosis in men was independent of age. The median OS in patients under 60 years was 13.3 months for women and 10.1 months for men (p = 0.0001); however, no significant difference between sexes was seen in older patients (p = 0.12) [37]. Another study also demonstrated improved prognosis in younger individuals (especially among women) [33]. In our study population, 100% of patients under 35 years of age were women. We found no data in the literature on the correlation between the survival of patients with tracheal tumors and their sex and age.

Sex-specific differences in comorbidities may translate into differences in survival between women and men. Some studies suggest that men have more comorbidities than women at cancer diagnosis and that there is a relationship between comorbidities and poor survival (e.g. in lung cancer) [38]. We did not analyze the presence of comorbidities in our study, nor did we find any data concerning the influence of comorbidities on OS in patients with tracheal tumors in the literature.

Other studies evaluating the effect of female sex on survival highlighted that women seek health care more often and sooner than men, which contributes to earlier diagnosis of cancer [39, 40]. Women may also be more likely than men to take the proposed treatment. Furthermore, women more frequently adhere to the treatment plan and better tolerate treatment [34, 41].

Differences in molecular, endocrine, and metabolic abnormalities may be another factor. In other cancers, men and women were found to vary in terms of genetic disorders. For example, the *EGFR* mutation in non-small cell lung cancer is more common among women than men [42, 43]. Studies on the aforementioned factors could provide relevant information regarding differences in the biological behavior of tracheal cancers and explain disparities in survival.

Conclusions

This study suggests that women with primary tracheal tumors have significantly better survival than men, in both univariate and multivariate analysis. Since female sex is an independent prognostic factor for tracheal tumors, the ratio of women to men should be taken into consideration in reports comparing the outcomes of different treatments. The reasons why women with tracheal tumors live longer than men remain unexplained. Studies on genetic, hormonal, and metabolic factors could help explain sex-specific differences in survival rates.

Conflict of interest: none declared

Aleksandra Piórek
Maria Sklodowska-Curie National Research Institute of Oncology
Lung Cancer and Chest Tumor Department
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: aleksandra.piorek@pib-nio.pl

Received: 29 Jun 2021
Accepted: 26 Jul 2021

References

1. Junker K. Pathology of tracheal tumors. Thorac Surg Clin. 2014; 24(1): 7–11, doi: 10.1016/j.thorsurg.2013.09.008, indexed in Pubmed: 24295655.
2. Macchiarini P. Primary tracheal tumours. Lancet Oncol. 2006; 7(1): 83–91, doi: 10.1016/S1470-2045(05)70541-6, indexed in Pubmed: 16389188.
3. Madariaga ML, Gaissert HA. Overview of malignant tracheal tumors. Ann Cardiothorac Surg. 2018; 7(2): 244–254, doi: 10.21037/acs.2018.03.04, indexed in Pubmed: 29707502.
4. Webb BD, Walsh GL, Roberts DB, et al. Primary tracheal malignant neoplasms: the University of Texas MD Anderson Cancer Center experience. J Am Coll Surg. 2006; 202(2): 237–246, doi: 10.1016/j.jamcollsurg.2005.09.016, indexed in Pubmed: 16427548.
5. Mallick S, Benson R, Giridhar P, et al. Demography, patterns of care and survival outcomes in patients with malignant tumors of trachea: A systematic review and individual patient data analysis of 733 patients. Lung Cancer. 2019; 132: 87–93, doi: 10.1016/j.lungcan.2019.04.017, indexed in Pubmed: 31097099.
6. Albers E, Lawrie T, Harrell JH, et al. Tracheobronchial adenoid cystic carcinoma: a clinicopathologic study of 14 cases. Chest. 2004; 125(3): 1160–1165, doi: 10.1378/chest.125.3.1160, indexed in Pubmed: 15006985.
7. Honings J, Gaissert HA, Weinberg AC, et al. Prognostic value of pathologic characteristics and resection margins in tracheal adenoid cystic carcinoma. Eur J Cardiothorac Surg. 2010; 37(6): 1438–1444, doi: 10.1016/j.ejcts.2010.01.005, indexed in Pubmed: 20356756.
8. Gaissert HA, Grillo HC, Shadmehr MB, et al. Long-term survival after resection of primary adenoid cystic and squamous cell carcinoma of the trachea and carina. Ann Thorac Surg. 2004; 78(6): 1889–96; discussion 1896, doi: 10.1016/j.athoracsur.2004.05.064, indexed in Pubmed: 15560996.
9. Regnard JF, Fourquier P, Levasseur P. Results and prognostic factors in resections of primary tracheal tumors: a multicenter retrospective study. The French Society of Cardiovascular Surgery. J Thorac Cardiovasc Surg. 1996; 111(4): 808–13; discussion 813, doi: 10.1016/s0022-5223(96)70341-0, indexed in Pubmed: 8614141.
10. Wen J, Liu Di, Xu X, et al. Nomograms for predicting survival outcomes in patients with primary tracheal tumors: a large population-based analysis. Cancer Manag Res. 2018; 10: 6843–6856, doi: 10.2147/CMAR.S186546, indexed in Pubmed: 30588090.
11. Bhattacharyya N. Contemporary staging and prognosis for primary tracheal malignancies: a population-based analysis. Otolaryngol Head Neck Surg. 2004; 131(5): 639–642, doi: 10.1016/j.otohns.2004.05.018, indexed in Pubmed: 15523440.
12. Zhengjaiang L, Pingzhang T, Dechao Z, et al. Primary tracheal tumours: 21 years of experience at Peking Union Medical College, Beijing, China. J Laryngol Otol. 2008; 122(11): 1235–1240, doi: 10.1017/S0022215108001710, indexed in Pubmed: 18331654.
13. Urdaneta AI, Yu JB, Wilson LD. Population based cancer registry analysis of primary tracheal carcinoma. Am J Clin Oncol. 2011; 34(1): 32–37, doi: 10.1097/COC.0b013e3181cae8ab, indexed in Pubmed: 20087156.
14. Napieralska A, Miszczyk L, Blamek S. Tracheal cancer - treatment results, prognostic factors and incidence of other neoplasms. Radiol Oncol. 2016; 50(4): 409–417, doi: 10.1515/raon-2016-0046, indexed in Pubmed: 27904449.
15. Makarewicz R, Mross M. Radiation therapy alone in the treatment of tumours of the trachea. Lung Cancer. 1998; 20(3): 169–174, doi: 10.1016/s0169-5002(98)00018-x, indexed in Pubmed: 9733051.
16. Hetnał M, Kielaszek-Ćmiel A, Wolanin M, et al. Tracheal cancer: Role of radiation therapy. Rep Pract Oncol Radiother. 2010; 15(5): 113–118, doi: 10.1016/j.rpor.2010.08.005, indexed in Pubmed: 24376936.
17. Honings J, van Dijck JA, Verhagen AdF, et al. Incidence and treatment of tracheal cancer: a nationwide study in the Netherlands. Ann Surg Oncol. 2007; 14(2): 968–976, doi: 10.1245/s10434-006-9229-z, indexed in Pubmed: 17139460.
18. Manninen MP, Pukander JS, Flander MK, et al. Treatment of primary tracheal carcinoma in Finland in 1967-1985. Acta Oncol. 1993; 32(3): 277–282, doi: 10.3109/02841869309093595, indexed in Pubmed: 8323765.
19. Licht PB, Friis S, Pettersson G. Tracheal cancer in Denmark: a nationwide study. Eur J Cardiothorac Surg. 2001; 19(3): 339–345, doi: 10.1016/s1010-7940(01)00597-8, indexed in Pubmed: 11251276.
20. Yang KY, Chen YM, Huang MH, et al. Revisit of primary malignant neoplasms of the trachea: clinical characteristics and survival analysis. Jpn J Clin Oncol. 1997; 27(5): 305–309, doi: 10.1093/jjco/27.5.305, indexed in Pubmed: 9390206.
21. Chao MW, Smith JG, Laidlaw C, et al. Results of treating primary tumors of the trachea with radiotherapy. Int J Radiat Oncol Biol Phys. 1998; 41(4): 779–785, doi: 10.1016/s0360-3016(98)00120-5, indexed in Pubmed: 9652838.
22. Jeremic B, Shibamoto Y, Acimovic L, et al. Radiotherapy for primary squamous cell carcinoma of the trachea. Radiother Oncol. 1996; 41(2): 135–138, doi: 10.1016/s0167-8140(96)01797-5, indexed in Pubmed: 9004356.
23. Mornex F, Coquard R, Danhier S, et al. Role of radiation therapy in the treatment of primary tracheal carcinoma. Int J Radiat Oncol Biol Phys. 1998; 41(2): 299–305, doi: 10.1016/s0360-3016(98)00073-x, indexed in Pubmed: 9607345.
24. Agulnik M, Cohen EWE, Cohen RB, et al. Phase II study of lapatinib in recurrent or metastatic epidermal growth factor receptor and/or erbB2 expressing adenoid cystic carcinoma and non adenoid cystic carcinoma malignant tumors of the salivary glands. J Clin Oncol. 2007; 25(25): 3978–3984, doi: 10.1200/JCO.2007.11.8612, indexed in Pubmed: 17761983.
25. Lee JH, Jung EJ, Jeon K, et al. Treatment outcomes of patients with adenoid cystic carcinoma of the airway. Lung Cancer. 2011; 72(2): 244–249, doi: 10.1016/j.lungcan.2010.08.011, indexed in Pubmed: 20828861.
26. Molina JR, Aubry MC, Lewis JE, et al. Primary salivary gland-type lung cancer: spectrum of clinical presentation, histopathologic and prognostic factors. Cancer. 2007; 110(10): 2253–2259, doi: 10.1002/cncr.23048, indexed in Pubmed: 17918258.
27. Afshar N, English DR, Blakely T, et al. Differences in cancer survival by sex: a population-based study using cancer registry data. Cancer Causes Control. 2018; 29(11): 1059–1069, doi: 10.1007/s10552-018-1079-z, indexed in Pubmed: 30194549.
28. Barquín M, Calvo V, García-García F, et al. Sex is a strong prognostic factor in stage IV non-small-cell lung cancer patients and should be consi-

dered in survival rate estimation. Cancer Epidemiol. 2020; 67: 101737, doi: 10.1016/j.canep.2020.101737, indexed in Pubmed: 32450544.
29. Hsu LH, Chu NM, Liu CC, et al. Sex-associated differences in non-small cell lung cancer in the new era: is gender an independent prognostic factor? Lung Cancer. 2009; 66(2): 262–267, doi: 10.1016/j.lungcan.2009.01.020, indexed in Pubmed: 19299032.
30. Ferguson M, Wang J, Hoffman P, et al. Sex-associated differences in survival of patients undergoing resection for lung cancer. Ann Thorac Surg. 2000; 69(1): 245–249, doi: 10.1016/s0003-4975(99)01078-4.
31. Minami H, Yoshimura M, Miyamoto Y, et al. Lung cancer in women: sex-associated differences in survival of patients undergoing resection for lung cancer. Chest. 2000; 118(6): 1603–1609, doi: 10.1378/chest.118.6.1603, indexed in Pubmed: 11115446.
32. Radzikowska E, Głaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. Ann Oncol. 2002; 13(7): 1087–1093, doi: 10.1093/annonc/mdf187, indexed in Pubmed: 12176788.
33. Radzikowska E, Głaz P. [The role of sex as a prognostic factor in lung cancer]. Pneumonol Alergol Pol. 2000; 68(9-10): 425–433, indexed in Pubmed: 11276973.
34. Ellington CL, Goodman M, Kono SA, et al. Adenoid cystic carcinoma of the head and neck: Incidence and survival trends based on 1973-2007 Surveillance, Epidemiology, and End Results data. Cancer. 2012; 118(18): 4444–4451, doi: 10.1002/cncr.27408, indexed in Pubmed: 22294420.
35. Yang H, Yao F, Tantai J, et al. Resected Tracheal Adenoid Cystic Carcinoma: Improvements in Outcome at a Single Institution. Ann Thorac Surg. 2016; 101(1): 294–300, doi: 10.1016/j.athoracsur.2015.06.073, indexed in Pubmed: 26431923.
36. Båtevik R, Grong K, Segadal L, et al. The female gender has a positive effect on survival independent of background life expectancy following surgical resection of primary non-small cell lung cancer: a study of absolute and relative survival over 15 years. Lung Cancer. 2005; 47(2): 173–181, doi: 10.1016/j.lungcan.2004.08.014, indexed in Pubmed: 15639716.
37. Wolf M, Holle R, Hans K, et al. Analysis of prognostic factors in 766 patients with small cell lung cancer (SCLC): the role of sex as a predictor for survival. Br J Cancer. 1991; 63(6): 986–992, doi: 10.1038/bjc.1991.215, indexed in Pubmed: 1648949.
38. Asmis TR, Ding K, Seymour L, et al. National Cancer Institute of Canada Clinical Trials Group. Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol. 2008; 26(1): 54–59, doi: 10.1200/JCO.2007.12.8322, indexed in Pubmed: 18165640.
39. Wang Y, Hunt K, Nazareth I, et al. Do men consult less than women? An analysis of routinely collected UK general practice data. BMJ Open. 2013; 3(8): e003320, doi: 10.1136/bmjopen-2013-003320, indexed in Pubmed: 23959757.
40. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005; 49(6): 616–623, doi: 10.1111/j.1365-2648.2004.03331.x, indexed in Pubmed: 15737222.
41. Hamidi M, Moody JS, Kozak KR. Refusal of radiation therapy and its associated impact on survival. Am J Clin Oncol. 2010; 33(6): 629–632, doi: 10.1097/COC.0b013e3181d270ce, indexed in Pubmed: 20216302.
42. Mok T, Wu YL, Thongprasert S, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma. N Engl J Med. 2009; 361(10): 947–957, doi: 10.1056/nejmoa0810699.
43. Radkiewicz C, Dickman PW, Johansson AL, et al. Sex and survival in non-small cell lung cancer: A nationwide cohort study. PLoS One. 2019; 14(6): e0219206, doi: 10.1371/journal.pone.0219206, indexed in Pubmed: 31247015.

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 17–20

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Radiation dose in CT-guided microwave liver tumor ablation

Grzegorz Rosiak[1], Joanna Podgórska[2], Katarzyna Pasicz[3], Krzysztof Milczarek[1], Dariusz Konecki[1], Olgierd Rowiński[1]

[1]*II Radiology Department, Central University Hospital (UCK), Warsaw Medical University, Warsaw, Poland*
[2]*Radiology Department 1, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[3]*Medical Physics Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction. Ablation is one of most important methods of liver tumor treatment. However, radiation is one of disadvantages of CT-guided procedures including ablation. The purpose of this study is to assess the factors that have impact on radiation doses during CT-guided microwave liver tumor ablation.

Material and methods. Radiation doses of CT-guided liver tumor ablations were collected in 127 patients. They were then compared in terms of number of lesions, lesion size and depth, use of additional localization needles and hydrodissection as well as tumor location.

Results. The median radiation doses of ablations of multiple tumors (2348 mGy*cm) were significantly higher (p = 0.03) than those of single tumors (1784 mGy*cm). No statistically significant differences were noted when other factors (lesion size, depth, location, use of localization needles and hydrodissection) were taken into consideration.

Conclusions. The number of lesions is the most important factor in terms of expected radiation doses in CT-guided microwave liver tumor ablations.

Key words: microwave ablation, radiation dose, CT-guided ablation

Introduction

Thermal ablation is an established method of liver tumor treatment [1, 2]. It is frequently performed with CT-guidance due to its high spatial resolution as well as the ability to precisely visualize needles and organs [3]. However this method of guidance is associated with radiation that can potentially increase the risk of malignancy [4, 5]. The risk is low but not negligible and, according to the ALARA concept, the radiation should always be kept as low as reasonably possible. This study is an attempt to estimate those factors affecting radiation doses during CT-guided liver ablation procedures.

Materials and methods

The institutional bioethical committee waived the need for formal consent due to retrospective nature of this study. 127 consecutive patients (85 males, 42 females) underwent liver tumor ablations between 2018 and 2019; 88 of them had single tumor, while 39 patients had multiple (89) tumors. Among the tumors there were 43 hepatocellular carcinomas (HCCs) and 134 metastases: breast cancer (n = 4), neuroendocrine tumors (NET) (n = 4), colorectal cancer (n = 126). The mean age of the patients was 69 years (range 25–91).

Jak cytować / How to cite:
Rosiak G, Podgórska J, Pasicz K, Milczarek K, Konecki D, Rowiński O. ***Radiation dose in CT-guided microwave liver tumor ablation.*** *NOWOTWORY J Oncol* 2022; 72: 16–19.

Table I. Radiation doses (dose length product – DLP) in ablations of single *vs.* multiple tumors

	n total	Mean	Standard deviation	Minimum	Median	Maximum	p value
DLP for single tumors [mGy*cm]	88	2377	1697	450	1784	7518	0.03
DLP for multiple tumors [mGy*cm]	39	2333	746	967	2348	3839	

All procedures were performed percutaneously with a microwave ablation device (Solero, Angiodynamics, Lantham, NY, USA), under general anesthesia. The ablations were done under CT-guidance using 320 slice Toshiba Aquilion One scanner (Toshiba/Canon, Nasu, Japan). Ultrasound was done just before every procedure to make sure no new lesions were visible and the tumor was still ablatable. Non-enhanced CT was performed at the beginning of every procedure to visualize the tumor. Then 3-slice (quick-check) scans were done during the procedure, every time the needle was advanced into the tumor.

After the ablation needle was removed, a 3-phase CT scan was done to estimate the ablation zone size and location, with a special focus on oncological margins of at least 5–10 mm. The following parameters were used for spiral CT scans: 120 kV and 300 mA for spiral scans or 50 mA (quick-check scans). No real-time CT-fluoroscopy was used during the procedures.

In 48 patients who had large tumors (>20 mm), one or two localization needles were used (Chiba, 21G, Cook, Bloomington, IN, USA). Those needles were placed to mark the borders of the tumors that required multiple ablation sessions. Hydrodissection was performed in 5 patients. A thin (22 G) needle was placed under CT guidance in a narrow (1–3 mm) space between the liver and adjacent stomach, colon or kidney. Between 50 and 200 ml of normal saline was then injected to isolate these structures from the heat produced during ablation and to prevent thermal damage to those organs.

Data on radiation doses in terms of dose length product were collected from the dose report generated by the scanner. The effective dose in mSv was calculated by multiplying by a factor of 0.015 [6]. The carcinogenic effect of the procedure, defined as excess risk of malignancy, was calculated at 5% per sievert [7].

The CT images from the procedures were retrospectively reviewed and the following data were collected: number of lesions, lesion size, number of localization needles inserted, hydrodissection application, lesion depth (from the entry point on the skin), location of the lesion (liver segment).

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of distribution of the investigated parameters. Differences were tested by the Wilcoxon rank-sum test and Kruskal-Wallis test. Pearson's correlation was used to analyze the association between DLP versus depth and DLP versus diameter. The values $p < 0.05$ were considered statistically significant. Statistical analysis was done using R environment (version 3.3.2, The R-Foundation, Austria).

Results

Ablations of multiple tumors were associated with higher radiation doses than single tumors in terms of DLP. Median DLP (mGy*cm) for single tumors was 1784 (range: 450–7518) while for multiple tumors it was 2348 (967–3839) and the difference was statistically significant ($p = 0.03$) (tab. I). The median effective doses were calculated at 26.8 mSv and 35.2 mSv respectively.

There was no statistical significance ($p = 0.23$) (fig. 1) in DLP increase in patients in whom localization needles were

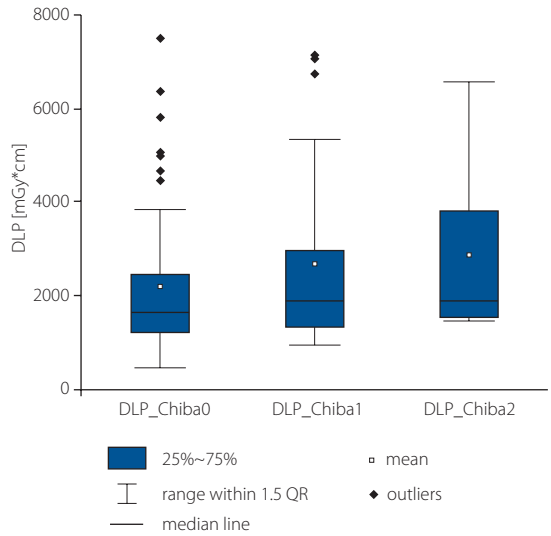

Figure 1. Radiation doses (DLP) by a number of localization needles used

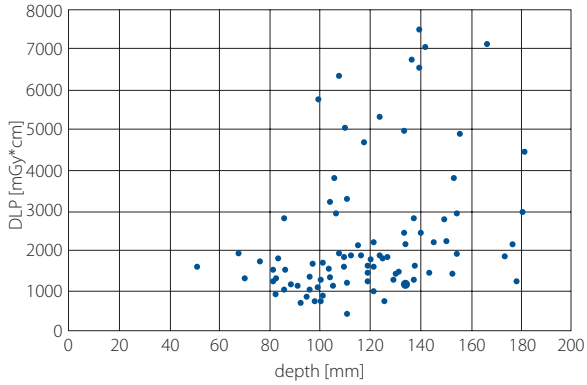

Figure 2. Radiation doses (DLP) by lesion depth

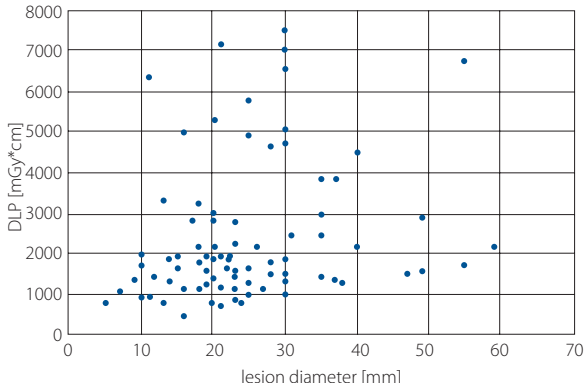

Figure 3. Radiation doses (DLP) by lesion diameter

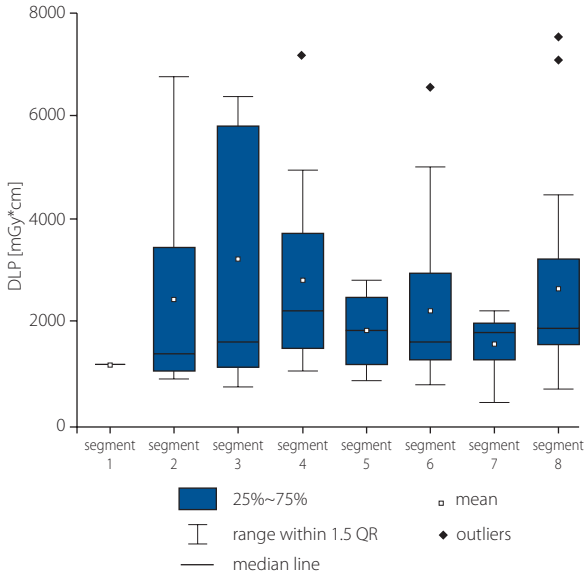

Figure 4. Radiation doses (DLP) in ablations of lesions in particular liver segments

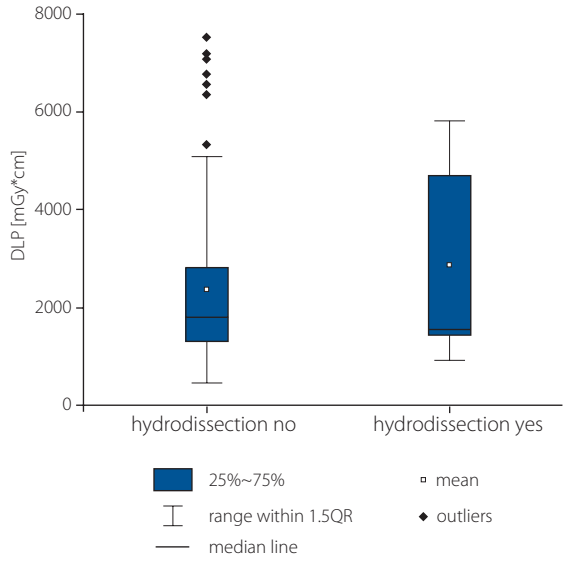

Figure 5. Radiation doses (DLP) during ablation without and with hydrodissection

used. The correlation between DLP and lesion depth or size was very weak and was not statistically significant (fig. 2 and fig. 3). Similarly, the location (by liver segment, fig. 4) of the lesion and the use of hydrodissection (fig. 5) did not have a statistically significant impact on the radiation doses. The estimated lifetime excess risk of malignancy was calculated at 0.10% for ablations of single lesions and 0.14% for ablations of multiple lesions.

Discussion

CT-guidance is frequently used in percutaneous liver tumor ablation due to its excellent spatial resolution and ability to visualize organs and needles with high quality. In many cases ultrasound is not able to show all tumors, especially in a cirrhotic liver or after chemotherapy. Additionally, ultrasound is not a reliable way to show the ablation zone and margin size which is an independent predictor of local tumor progression [8].

Radiation is one of the disadvantages of this method and doses should be kept as low as reasonably achievable (ALARA). The radiation doses in terms of DLP had quite a wide range (450–7518 mGy*cm). Out of several parameters, the number of ablated lesions was a factor that had a significant impact on the radiation dose. Ablation of multiple tumors caused higher radiation than procedures done on single lesions (median 2348 *vs.* 1784 mGy*cm which corresponds to 35 *vs.* 26 mSv).

The results are comparable to other studies. In a publication by Hu et al. [9] the radiation doses acquired during CT-guided ablation were slightly higher and estimated at 41.1 mSv. Similar results were reported by McCarthy et al. [10] where the estimated radiation dose was 30.7 mSv. It is worth noting that the results are similar in many aspects even though the procedures were performed in different centers on different CT scanners.

As opposed to the results of the study by McCarthy et al. [10], hydrodissection was not a factor that would cause a statistically significant increase in radiation dose. The small number of patients that had this additional measure applied in our study could be the reason for such results. However, this result corresponds to other data in our study, especially the application of localization needles as both techniques (hydrodissection and localization needles) require additional punctures and should have a similar impact on the radiation dose.

The lack of statistical significance between radiation doses in the ablation of small and large lesions was somewhat unexpected since large lesions require more needle repositioning and thus more scans. Radiation doses for patients with additional localization needles did not show statistically significant differences. Higher radiation doses in such procedures were expected since they required additional scans to insert the needles precisely into the tumor's border. Moreover, there was a lack of statistical significance when lesion size, depth or location (liver segment) were taken into consideration.

The range of radiation dose values was fairly wide so it remains possible that factors other than the number of lesions have a significant impact. If the effects of lesion size, depth, location (liver segment), hydrodissection and additional needles on radiation doses exist, they seem to have been dominated by other, unknown factors. The effect of "difficulty" of the procedure could be such a factor. Some tumors are more difficult to ablate than others, but no clear parameters have been defined so far. It is possible that the difficulty of the procedure depends on many factors and such complexity makes it hard to clearly define it. That said, the search for such parameters could be a subject of further studies.

This study did not include contrast injections as a factor potentially affecting the radiation dose [10] since all patients had a contrast enhanced CT after needle removal. This step is necessary to assess margin size which predicts the risk of local tumor progression [11]. The majority of radiation doses in CT-guided procedures comes from helical scans [12]. Limiting such scans by replacing some of them with quick-check scans can significantly reduce the radiation dose in CT-guided procedures [13]. However, it can be difficult in such complex procedures as ablations where the operator needs to have high quality visualizations of large volumes of liver tissue. While limiting radiation in CT-guided procedures is important, it should not be done at the cost of reducing the effectiveness of precise needle placement.

The excess risk of malignancy was calculated at 0.10 (single lesions) or 0.14% (multiple lesions) which compares favorably with 0.43% of children and young adults who underwent regular CT scans [14]. The radiation doses acquired by patients who underwent liver tumor ablations correspond to doses acquired during 2–4 multiphase abdominal CT scans.

Liver tumor ablation is a safe procedure with very low major complication rates, from 1.1% [15] to 5% [16], with practically no post-procedural mortality. This compares favorably to liver tumor resection where complications tend to be more frequent, e.g. 27.5% [16]. The results of our study show that excess risk of malignancy in liver tumor ablation is low and in our opinion it should not be a major factor when making decisions on liver tumor treatment. Considering the high efficacy of ablation in liver tumor treatment [17] and its low carcinogenic effect, the potential health gains outweigh the risks of the procedure. The retrospective nature of this study is one of its limitations. Variations in ablation technique between the operators may have also affected the outcomes. Also, the applied conversion factor that was derived from ICRP [7] is designed to estimate the risk to the general population more than individual patients.

Conclusions

The radiation doses and excess risk of malignancy in CT-guided liver ablation are low. The risks are higher in ablations of multiple tumors, however lesion size, depth and location or application of hydrodissection or additional needles do not have a significant impact on radiation dose.

Conflict of interest: none declared

Joanna Podgórska
Maria Sklodowska-Curie National Research Institute of Oncology
Radiology Department 1
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: jpodgo@gmail.com

Received: 7 Sep 2021
Accepted: 30 Nov 2021

References

1. Benson AlB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19(5): 541–565, doi: 10.6004/jnccn.2021.0022, indexed in Pubmed: 34030131.
2. NCCN. Hepatobiliary cancers (Hepatocelluar) v. 2.2021. NCCN. 2021.
3. Baère Tde. Computed Tomography Imaging for Tumor Ablation. Tumor Ablation. 2005: 104–120, doi: 10.1007/0-387-28674-8_9.
4. Brenner DJ, Elliston CD, Hall EJ, et al. Estimated Risks of Radiation. Am Roentgen Ray Soc. 2001; 176: 289–96.
5. Sodickson A, Baeyens PF, Andriole KP, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. Radiology. 2009; 251(1): 175–184, doi: 10.1148/radiol.2511081296, indexed in Pubmed: 19332852.
6. Coakley FV, Gould R, Yeh BM, et al. CT radiation dose: what can you do right now in your practice? AJR Am J Roentgenol. 2011; 196(3): 619–625, doi: 10.2214/AJR.10.5043, indexed in Pubmed: 21343506.
7. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP. 2007; 37(2-4): 1–332, doi: 10.1016/j.icrp.2007.10.003, indexed in Pubmed: 18082557.
8. Wang X, Sofocleous CT, Erinjeri JP, et al. Margin size is an independent predictor of local tumor progression after ablation of colon cancer liver metastases. Cardiovasc Intervent Radiol. 2013; 36(1): 166–175, doi: 10.1007/s00270-012-0377-1, indexed in Pubmed: 22535243.
9. Hu EY, Levesque VM, Bay CP, et al. Liver Tumor Ablation Procedure Duration and Estimated Patient Radiation Dose: Comparing Positron Emission Tomography/CT and CT Guidance. J Vasc Interv Radiol. 2020; 31(7): 1052–1059, doi: 10.1016/j.jvir.2019.11.036, indexed in Pubmed: 32534979.
10. McCarthy CJ, Kilcoyne A, Li X, et al. Radiation Dose and Risk Estimates of CT-Guided Percutaneous Liver Ablations and Factors Associated with Dose Reduction. Cardiovasc Intervent Radiol. 2018; 41(12): 1935–1942, doi: 10.1007/s00270-018-2066-1, indexed in Pubmed: 30132100.
11. Crocetti L, de Baére T, Pereira PL, et al. CIRSE Standards of Practice on Thermal Ablation of Liver Tumours. Cardiovasc Intervent Radiol. 2020; 43(7): 951–962, doi: 10.1007/s00270-020-02471-z, indexed in Pubmed: 32382856.
12. Sarti M, Brehmer WP, Gay SB. Low-dose techniques in CT-guided interventions. Radiographics. 2012; 32(4): 1109–19; discussion 1119, doi: 10.1148/rg.324115072, indexed in Pubmed: 22786997.
13. Rosiak G, Lusakowska A, Milczarek K, et al. Ultra-low radiation dose protocol for CT-guided intrathecal nusinersen injections for patients with spinal muscular atrophy and severe scoliosis. Neuroradiology. 2021; 63(4): 539–545, doi: 10.1007/s00234-021-02643-9, indexed in Pubmed: 33512541.
14. Bosch de Basea M, Moriña D, Figuerola J, et al. Subtle excess in lifetime cancer risk related to CT scanning in Spanish young people. Environ Int. 2018; 120: 1–10, doi: 10.1016/j.envint.2018.07.020, indexed in Pubmed: 30053755.
15. Liu Y, Li S, Wan X, et al. Efficacy and safety of thermal ablation in patients with liver metastases. Eur J Gastroenterol Hepatol. 2013; 25(4): 442–446, doi: 10.1097/MEG.0b013e32835cb566, indexed in Pubmed: 23470267.
16. Fang Y, Chen W, Liang X, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. J Gastroenterol Hepatol. 2014; 29(1): 193–200, doi: 10.1111/jgh.12441, indexed in Pubmed: 24224779.
17. Ruers T, Van Coevorden F, Punt CJA, et al. European Organisation for Research and Treatment of Cancer (EORTC), Gastro-Intestinal Tract Cancer Group, Arbeitsgruppe Lebermetastasen und tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO), National Cancer Research Institute Colorectal Clinical Study Group (NCRI CCSG). Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. J Natl Cancer Inst. 2017; 109(9), doi: 10.1093/jnci/djx015, indexed in Pubmed: 28376151.

VIA MEDICA

Artykuł oryginalny / Original article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 21–26

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Secondary prevention and treatment of cervical cancer – an update from Poland

Patryk Poniewierza[1], Marcin Śniadecki[2], Michał Brzeziński[2], Dagmara Klasa-Mazurkiewicz[2], Grzegorz Panek[3]

[1]*Department of Biology and Medical Genetics, Medical University of Gdansk, Gdansk, Poland*
[2]*Department of Gynecology, Gynecologic Oncology and Gynecologic Endocrinology, Medical University of Gdansk, Gdansk, Poland*
[3]*Department of Oncologic Gynecology and Obstetrics, The Center of Postgraduate Medical Education, Warsaw, Poland*

Introduction. Cervical cancer is the 4th most common cancer in terms of incidence and mortality in women worldwide. The aim of the study was to investigate and analyze the effects of Poland's publicly funded cervical cancer screening and treatment programs.

Material and methods. The study analyzed the financial and epidemiological data provided by the Polish National Health Fund and the Polish National Cancer Registry on the prevention and treatment of cervical cancer in Poland in 2011–2017.

Results. Our study identified a systematic reduction in the number of patients undergoing cervical cytology. Despite high levels of financial expenditure, no correlation was found between the total cost of benefits in PLN million ($W = 0.911$; $p = 0.404$) and mortality expressed by the standardized coefficient ($W = 0.884$; $p = 0.243$).

Conclusions. Despite decreasing mortality rates in cases of cervical cancer in Poland, the organization and delivery of prevention and treatment programs should be considered insufficient.

Key words: cervical cancer, screening, treatment, public health

Introduction

Cervical cancer (CC) is the fourth most common cause of morbidity and mortality among women worldwide. Worldwide, in 2020, incidence and mortality were 604,000 and 342,000, respectively [1]. In Poland in 2018, there were 2360 new cases, representing a world age-standardized rate (ASW) of 7.1 per 100,000 women annually, making it the 8th most common cancer in the female population. The mortality figure was 1593 women, representing an ASW of 4.0 per 100,000. It is worth noting that the mortality rate for CC has recently been decreasing [2].

The Polish cervical screening program consists of a Pap smear (slide cytology) taken every 3 years. When lesions are detected, referred to as either atypical squamous cells of undefined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL), a cytologic evaluation is repeated. A colposcopy with the possibility of a biopsy is performed for the following results: atypical squamous cells, cannot exclude a high-grade lesion (ASCH); high-grade squamous intraepithelial lesions (HSIL); atypical glandular cells (AGH); and in some cases, LSIL. Polymerase chain reaction (PCR) testing for the presence of HPV is not included in the program [3].

In Poland, reduced mortality is due to the introduction of secondary prophylaxis in the 1980s based on Pap smear testing (cervical cytology). In 2006, cervical screening became a national program. The program involves regular Pap smears repeated at three-yearly intervals in women aged 25 to 59. Until 2015, the administration of the screening program included sending personal invitation letters to women [4].

Jak cytować / How to cite:

Poniewierza P, Śniadecki M, Brzeziński M, Klasa-Mazurkiewicz D, Panek G. ***Secondary prevention and treatment of cervical cancer – an update from Poland.*** *NOWOTWORY J Oncol* 2022; 72: 20–25.

Following screening, the program's diagnostic and therapeutic steps include a colposcopy with cervical biopsy, surgical intervention (conization, hysterectomy), chemotherapy, and radiotherapy [5].

Despite a steady decrease in CC mortality, it is alarming that Poland's 5-year survival rate is the lowest (56.4%) of all European countries where the European average is 62.4% [6, 7].

Cervical cancer is an important health and economic issue. Prophylaxis against CC and the treatment of patients with CC are considerable burdens on public health funding. We believe that a systematic evaluation of the effect of screening programs can lead to the improved organization of resources. The aim of the study was to investigate and analyze the costs of Poland's publicly funded CC screening program and treatment for the period of 2011 to 2017, considering the latest data from CC statistics. The intention of the authors is that the results of the data analyses, regardless of the final conclusions, will be useful for future CC screening planning.

Material and methods

Our study used data on the screening program carried out in specialist outpatient clinics (*ambulatoryjna opieka specjalistyczna* – AOS [in Polish]), and CC treatments undertaken in public hospitals in Poland between 2011 and 2017, shared by the Polish National Health Fund (NHF) at the authors' inquiry. The NHF is the primary funder of the Polish healthcare system, and thus it collects extensive data on patient demographics, the number and type of services provided, costs generated, and the duration of hospital stays. In addition, we used epidemiological data on CC mortality rates published by the Polish National Cancer Registry (http://onkologia.org.pl). Among the screening data up to 2015 is a group of women obtained from sending personalized invitations. Treatment data is a separate statistic. It is not limited to the cases screened in 2011–2017.

We analyzed the results of all cervical cytology tests conducted in specialist outpatient clinics in the public healthcare system between 2011 and 2017, including the number of women tested, the percentage of the general population included in the program, the cost of the services provided, and the standardized mortality rate due to CC. We considered each case qualified for further in-depth diagnosis and / or treatment as an abnormal Pap test result (ASCUS, ASCH, LSIL, AGH or HSIL). Similarly, we evaluated the treatment of CC patients in Poland, without analyzing the proportion of the general population. Patients receiving medical services encoded with the C53 (malignant neoplasm of cervix uteri) code according to the ICD-10 classification were enrolled in the study in the treatment analysis.

To test for normality of distribution, we used the Shapiro-Wilk test. The direction and strength of linear correlations between two variables were evaluated using the Pearson correlation coefficient, and the t-test was used to evaluate the statistical significance of correlations. The significance level was set at $\alpha = 0.05$. We conducted our analysis using the R statistical program (v4.01).

Results

Cervical cancer screening

The data on cytological screening between 2011 and 2017 is shown in table I. In 2011, 793,400 women underwent screening in outpatient settings (AOS). Over subsequent years, the numbers decreased. By 2017, 463,000 women presented for screening, 41.6% fewer than in 2011. A similar trend was observed in the annual percentages of the general population included in the screening program. The rate of abnormal screening test results requiring further diagnostic procedures was found to correlate significantly with the percentage of patients included in screening in the general population ($r = 0.961$; $p = 0.019$).

The number of patients with abnormal screening test results and the costs of detecting a single positive case (qualified for further in-depth diagnosis and / or treatment) in the years 2014–2017 are presented in table II. The data of the

Table I. Cervical cytology studies between 2011 and 2017

Criterion	2011	2012	2013	2014	2015	2016	2017	2017/2011 (%)
number of patients tested in outpatient specialty care (AOS)	793,398	726,548	665,520	691,682	652,258	538,273	462,970	58.4
cost of procedures (million PLN)	40.15	39.49	36.03	28.50	27.07	22.69	20.21	50.3
% of general population	24.4	23.75	22.91	22.34	21.72	20.5	18.73	–
mortality rate – ASW	4.84	4.83	4.63	4.46	4.2	4.1	4.2	–

Table II. The number of patients having cervical cytology positive test result and the costs of detecting single positive case (qualified for further in-depth diagnosis and /or treatment) between 2014 and 2017

Criterion	2014	2015	2016	2017	2017/2014 (%)
number of patients with positive test results	19,940	18,521	15,075	13,702	68.7
costs of detecting a single positive case (PLN)	1429.50	1461.79	1505.16	1475.05	103.2

Table III. Costs of cervical cancer treatment between 2011 and 2017

Criterion	2011	2012	2013	2014	2015	2016	2017	2017/2011 (%)
number of patients	22,478	22,829	22,850	22,377	21,730	21,113	20,511	91.2
total costs of procedures (million PLN)	130.85	137.51	140.05	140.05	122.91	123.64	130.89	100.0
average cost of treatment of a single patient (PLN)	5821.33	6023.67	6128.96	6258.63	5656.35	5855.96	6381.57	109.6
total cost of surgery (million PLN)	14.32	15.07	14.86	13.76	14.08	12.91	13.02	90.9
total cost of radiotherapy (million PLN)	56.70	63.24	65.34	66.74	58.79	60.42	61.61	108.7
total cost of chemotherapy (million PLN)	25.83	26.63	26.18	27.46	25.23	24.95	23.40	90.6

NHF register do not contain information from the previous years. In 2014, the number of abnormal cytology tests results reached nearly 20,000. In the following years, this number decreased. In 2017, there were 13,700 abnormal tests, which was 31.3% fewer than in 2014. The cost of detecting one case over that period was similar to previous periods with mean cost M = 1467.86 PLN (SD = 31.37 PLN). Despite fewer women presenting for screening and fewer abnormalities requiring further in-depth diagnosis and / or treatment being detected, there was a systematic decline in the age-standardized mortality rate (ASW) for CC, from 4.84% in 2011 to 4.2% in 2017 (a decrease of 0.64 percentage points).

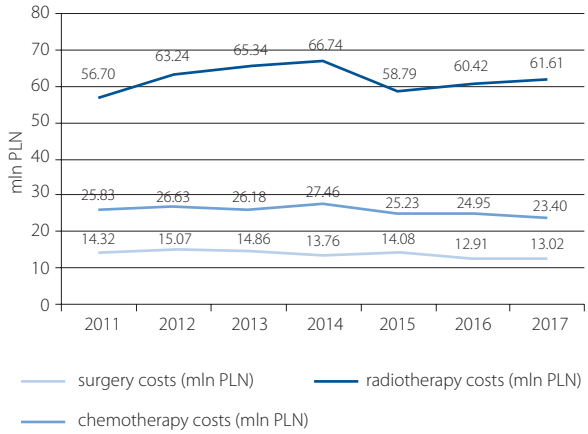

Figure 1. Costs of cervical cancer treatment divided by treatment modalities

Cervical cancer treatment

The costs of treatment of patients with CC between 2011 and 2017, with respect to different types of treatment, are summarized in table III. Between 2011 and 2017, the overall cost of CC treatment was relatively constant, with the average per year cost being 132.3 million PLN (SD = 7.24 million PLN). Relatively minor differences were observed year-by-year with respect to the cost per patient, and also with respect to the costs of different treatment modalities (fig. 1). Despite the average annual cost of treatment (132 million PLN during the analyzed period), no statistically significant correlation has been observed between the overall cost (W = 0.911; p = 0.404) and mortality expressed as the standardized coefficient (W = 0.884; p = 0.243). Also, the correlation between the treatment costs per patient (W = 0.975; p = 0.929) and mortality rates was not significant (tab. IV). The above-listed correlations showed no statistical significance even though there was an increased number of cytology study results and an increased number of services provided (r = 0.886; p = 0.008). For a complete evaluation of hospital treatments over the studied period, we used both mean and maximum durations of the hospital stays (tab. V). In 2014, the mean hospital stay was 4.73 days. Over the following years, this index consistently decreased, reaching 4.38 days of hospital stay in 2017. The maximum hospital

Table IV. Correlation between total cost of procedures and cost of treating one patient with respect to mortality rate

Costs	Mortality rate – ASW			
	N	r	CI	p
cost of procedures (million PLN)	7	0.641	[–0.22–0.94]	0.121
cost of treating one patient (PLN)	7	0.008	[–0.75–0.76]	0.986

Table V. Mean and maximum hospital stay between 2014 and 2017

Criterion	2014	2015	2016	2017	2017/2014 (%)
mean hospital stay (days)	4.73	4.55	4.49	4.38	92.6
maximum hospital stay (days)	104.38	95.88	101.38	96.56	92.5

stay in 2014 was 104.38 days. Over the following years, this parameter's value also declined, reaching 96.56 days in 2017.

Discussion

Cervical cancer is the fourth most common cause of morbidity and mortality among women worldwide. However, its prevalence is inversely proportional to a country's medical resources, with incidence rates being highest in those countries where no cytology screening program is available at all [8]. Cervical cancer has been the focus of public health programs in Poland for the past 15 years. The result of this is that in the last three years alone, approximately 72% of women have undergone cervical cytology, according to the Organization for Economic Co-operation and Development (OECD) data [9]. Notwithstanding these and other countries' efforts, and despite the possibility of primary prophylaxis by vaccination against the human papillomavirus (HPV), it is expected that in the next 15 years, cases of CC worldwide will increase by 42% annually on average, while an 11% increase is expected in developed economies [10]. Poland's recent promotion to the rank of developed country in terms of capital markets does not correlate with its health ranking. One area where this lack of correlation is revealed is in the health outcomes resulting from cervical cancer screening tests.

Our study found a decline in the number and proportion of women enrolled in the national screening program in AOS over the 2011 to 2017 observation period. This is a negative connotation since the number of lesions requiring further diagnostics detected in cervical cytology correlates strongly with numbers of patients tested in outpatient specialty care (AOS) and the percentage of the national population covered by the screening program. In addition, Turkot et al., in their 2018 audit of cytology laboratories in Poland, found there was a significant increase in Pap testing outside the national healthcare program, that is, in the private healthcare sector [11]. Both our results and those of the authors mentioned above may suggest that Pap smear tests are performed in private healthcare. There is an open question about the reasons for the decline in patients' interest in examinations financed by the national screening program. The cessation of sending personalized invitations in 2015 can be considered to be one of the reasons. This action was dictated by low cost-effectiveness considerations [3]. The significantly positive correlation shown between the number of patients tested in outpatient specialty care (AOS) and the value of benefits in PLN million, calls into question the advisability of stopping the sending of personal invitations to cervical screening tests as an activity aimed at cost optimization of the process. Referring to the second argument concerning the ineffectiveness of invitations, it is necessary to cite the studies of independent centers, which say that the use of personalized methods of contact targeted at specific age groups, combined with setting the date of the examination, significantly increases participation in the screening program [12–14]. The increased interest the private healthcare sector has shown in performing screening tests may result, in part, from the availability of improved diagnostic methods, including the possibility of testing for the presence of HPV [15].

The current state of knowledge indicates that almost all CCs are caused or co-caused by persistent high-risk HPV (hrHPV) infection. Two genotypes (16 and 18) are responsible for 70% of CC and 50% of HSIL cases [4]. High-risk HPV tests are characterized by a 20–50% higher sensitivity than routine cervical cytology which means that the risk of overlooking a malignant transformation from precancer to cancer is minimized when compared with a Pap smear slide evaluation (when, in both cases, a negative screening test result is compared) [3].

Our study shows that the declining number of women screened under the national screening program is accompanied by a slight reduction in the national mortality rate from cervical cancer (ASW decreased by 0.64 percentage points over the studied 7-year period). Analysis over a broader time period showed that the annual percentage change (APC 1990–2017) in the mortality rate in Poland accounted –2.3. By comparison, in the countries of the so-called old European Union (EU15), the APC was –2.5, with a low ASW rate of 1.9 [16].

Considering our results and those of other researchers, the slight decrease in mortality observed in Poland should be considered unsatisfactory and indicates the need to make changes in the overall approach of the preventive program. Moreover, the observed decrease in mortality may be partly attributed to the activities of the private healthcare sector in Poland, but we do not have sufficient data to test this hypothesis. We suggest creating a national cervical cancer prevention register that encompasses the combined data of both the NHF and the private sector.

In studies assessing the Standard Expected Years of Life Lost per death (SEYLLd), for every woman's death in Poland from CC in 2011, the SEYLLd was 25.8 years lost, while in 2015 it was 23.7 years. Despite this decrease, when analyzed according to education level, the SEYLLd in women with only primary school education, was 5.8 times greater than in women with higher education [17]. This relationship is another reason to suggest that reintroducing personalized invitations for specific social groups ("Poland says STOP cervical cancer") may be beneficial. Another interesting option especially for young people starting sexual activity can be Instagram influencers spots to encourage vaccination against HPV.

Across the analyzed period, the average annual cost of detecting one lesion requiring further treatment remained at the relatively constant level of 1,467.86 PLN, and the average annual cost of treatments also remained constant at 132.3 million PLN. This funding level places a heavy burden on the public health system. The large number of women treated for CC and the high costs of prophylaxis and treatment constitute a significant challenge for the healthcare budget in Poland

and worldwide as well [18, 19]. Various cost-saving measures undertaken so far, including the inclusion of primary healthcare midwives in the cytology collection process, have not produced the expected results [20]. An effective solution may be the introduction of HPV screening tests [21, 23]. Recent research results suggest that replacing a triennial program of cytology with screening for HPV every 5 years has benefits [24, 25].

The CC mortality rate decreased insignificantly over the period of our study, despite high, though relatively constant, levels of treatment cost. According to OECD data, even though Poland's 5-year survival results (55%) for CC treatment have improved slightly, they are still below the European average of 63% [9, 26]. It should therefore be assumed that if CC treatment in Poland is operating below the average European effectiveness, there is room for improvement.

Apart from the ethical aspect, Poland's relatively low 5-year survival rate of CC has an economic context. In 2012 alone, CC incidence and the consequent mortality caused the loss of approximately 957,678 working days in Poland, and this resulted in production losses of EUR 111.4 million, 66% of which was related to mortality [27].

Our study has shown that in Poland, public sector CC treatment costs and the duration of hospitalization have both remained at constant levels during our study period. In comparison, Western European countries have seen a decrease in the cost of treatment with accompanying reductions in morbidity and mortality [28]. Those countries are seeing the long-term effects of the introduction of the HPV vaccination, which is not yet common in Poland [29, 30]. It is worth emphasizing that for the period we analyzed, our study did not identify any significant statistical relationships between the cost of treatment services provided and the mortality rate expressed by ASW. This may suggest a relationship between the decline in mortality and the level of preventive measures only, and not the quality of treatment services. However, in the context of CC, there are no reports in the current literature that would challenge what our study discovered. In the absence of a relationship between the cost of treatment and mortality rates, the hypothesis that mortality rates are influenced by preventative measures rather than by hospital services remains.

Limitations

This study has several limitations. Actual recommended tools for an analysis of health care systems in the context of cost-effectiveness, including cervical cancer prevention are the Incremental Cost-Effectiveness Ratio (ICER), Quality Adjusted Life Year (QALY), and Quality-Adjusted Life Expectancy (QALE). These parameters were not used in the study due to the lack of current data from Poland in the literature. The results of other scientists refer to years earlier than presented in our study.

Conclusions

We want to draw attention to the systematic decrease in the number of patients undergoing cytological examinations funded by the state, which also translates into a reduction of the percentage of the population covered. The recommended solution is to return to personalized invitations, but instead of using letters as before, we suggest that invitations be made through "new media" – e-mail/SMS under the administration of a primary care physician and midwife. The results of our research suggest that patients may be undergoing cytological testing in private healthcare settings. This situation significantly impedes public access to complete statistical data and a comprehensive assessment of the effectiveness of cervical cancer preventive measures and resourcing in Poland. To enable a full analysis in the future, we propose the creation of a national cervical screening registry to include all National Health Funded providers and private healthcare sector providers.

The issue that our report raises, regarding the falling number of women undergoing Pap smear testing within public healthcare settings, also results from the difficulty of public healthcare providers accessing modern diagnostic methods such as liquid-based cytology or molecular diagnostics for the presence of HPV; these observations also indicate possible avenues for changes. The slow decrease in mortality due to cervical cancer described in our study can be accelerated by introducing mandatory vaccination against HPV. Currently, the limited spread of mandatory vaccination programs, funded by some municipalities, has not had a noticeable effect on population-wide data. Poland's unsatisfactory 5-year cervical cancer survival rates may be a result of the phenomena described above: declining prophylactic examination rates across the whole population, diagnostics primarily based on cytological smears, and the limited availability of vaccination against HPV.

We believe that the current processes of diagnosis and treatment of cervical cancer in Poland require a change of approach in line with the recommendations presented in our study.

Conflict of interest: none declared

Patryk Poniewierza
Medical University of Gdansk
Department of Biology and Medical Genetics
ul. Debinki 1
80-211 Gdańsk, Poland
e-mail: patryk.poniewierza@gumed.edu.pl

Received: 1 Nov 2021
Accepted: 4 Jan 2022

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
2. Wojciechowska U, Didkowska J, Michałek I. Cancer in Poland in 2018. Polish National Cancer Registry, Warsaw 2020.
3. Nowakowski A, Arbyn M, Turkot MH, et al. A roadmap for a comprehensive control of cervical cancer in Poland: integration of available solutions into current practice in primary and secondary prevention. Eur J Cancer

Prev. 2020; 29(2): 157–164, doi: 10.1097/CEJ.0000000000000528, indexed in Pubmed: 31517672.
4. Nowakowski A, Turkot M, Miłosz K. Should we continue population--based cervical cancer screening programme in Poland? A statement in favour. Nowotwory. Journal of Oncology. 2018; 68(2): 108–112, doi: 10.5603/njo.2018.0017.
5. de Rycke Y, Tubach F, Lafourcade A, et al. Cervical cancer screening coverage, management of squamous intraepithelial lesions and related costs in France. PLoS One. 2020; 15(2): e0228660, doi: 10.1371/journal.pone.0228660, indexed in Pubmed: 32053648.
6. Wojciechowska U, Didkowska J. Changes in five-year relative survival rates in Poland in patients diagnosed in the years 1999–2010. Nowotwory. Journal of Oncology. 2018; 67(6): 349–358, doi: 10.5603/njo.2017.0057.
7. Sant M, Lopez MC, Agresti R, et al. Survival of women with cancers of breast and genital organs in Europe 1999–2007: Results of the EUROCARE-5 study. European Journal of Cancer. 2015; 51(15): 2191–2205, doi: 10.1016/j.ejca.2015.07.022.
8. Devarapalli P, Labani S, Nagarjuna N, et al. Barriers affecting uptake of cervical cancer screening in low and middle income countries: A systematic review. Indian J Cancer. 2018; 55(4): 318–326, doi: 10.4103/ijc.IJC_253_18, indexed in Pubmed: 30829264.
9. Screening, survival and mortality for cervical cancer. Health at a Glance: Europe. 2018: 158–159, doi: 10.1787/health_glance_eur-2018-41-en.
10. Arbyn M, Castellsagué X, de Sanjosé S, et al. Worldwide burden of cervical cancer in 2008. Ann Oncol. 2011; 22(12): 2675–2686, doi: 10.1093/annonc/mdr015, indexed in Pubmed: 21471563.
11. Turkot M, Mokwa D, Wieszczy P, et al. External audit of providers of the Cervical Cancer Prevention Programme in Poland in 2016/2017. Nowotwory. Journal of Oncology. 2018; 68(2): 65–78, doi: 10.5603/njo.2018.0011.
12. Bao HL, Wang LH, Wang LM, et al. Zhonghua Liu Xing Bing Xue Za Zhi. 2018; 39(2): 208–212.
13. Acera A, Manresa JM, Rodriguez D, et al. Increasing Cervical Cancer Screening Coverage: A Randomised, Community-Based Clinical Trial. PLoS One. 2017; 12(1): e0170371, doi: 10.1371/journal.pone.0170371, indexed in Pubmed: 28118410.
14. Kurt G, Akyuz A. Evaluating the Effectiveness of Interventions on Increasing Participation in Cervical Cancer Screening. J Nurs Res. 2019; 27(5): e40, doi: 10.1097/jnr.0000000000000317, indexed in Pubmed: 30908429.
15. Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. Cochrane Database Syst Rev. 2017; 8: CD008587, doi: 10.1002/14651858.CD008587.pub2, indexed in Pubmed: 28796882.
16. Wojtyla C, Ciebiera M, Kowalczyk D, et al. Cervical Cancer Mortality in East-Central European Countries. Int J Environ Res Public Health. 2020; 17(13), doi: 10.3390/ijerph17134639, indexed in Pubmed: 32605159.
17. Pikala M, Burzyńska M, Maniecka-Bryła I. Years of Life Lost Due to Cervical Cancer in Poland in 2000 to 2015. Int J Environ Res Public Health. 2019; 16(9), doi: 10.3390/ijerph16091545, indexed in Pubmed: 31052396.
18. Nowakowski A, Śliwczyński A, Seroczyński P, et al. Reimbursed Costs of Management of Uterine Cervical Lesions in Poland--a Descriptive Analysis of Data from the National Health Fund and the Ministry of Health. Cent Eur J Public Health. 2016; 24(2): 163–168, doi: 10.21101/cejph.a4737, indexed in Pubmed: 27178030.
19. Pendrith C, Thind A, Zaric GS, et al. Costs of cervical cancer treatment: population-based estimates from Ontario. Curr Oncol. 2016; 23(2): e109–e115, doi: 10.3747/co.23.2598, indexed in Pubmed: 27122978.
20. Sobczyk K, Woźniak-Holecka J, Holecki T, et al. The organization and financing of cervical cancer prevention carried out by midwives in primary health care. Ginekol Pol. 2016; 87(12): 798–804, doi: 10.5603/GP.2016.0091, indexed in Pubmed: 28098929.
21. Mezei AK, Armstrong HL, Pedersen HN, et al. Cost-effectiveness of cervical cancer screening methods in low- and middle-income countries: A systematic review. Int J Cancer. 2017; 141(3): 437–446, doi: 10.1002/ijc.30695, indexed in Pubmed: 28297074.
22. Campos NG, Maza M, Alfaro K, et al. The cost-effectiveness of implementing HPV testing for cervical cancer screening in El Salvador. Int J Gynaecol Obstet. 2019; 145(1): 40–46, doi: 10.1002/ijgo.12773, indexed in Pubmed: 30702142.
23. Pista A, Costa C, Saldanha C, et al. Budget impact analysis of cervical cancer screening in Portugal: comparison of cytology and primary HPV screening strategies. BMC Public Health. 2019; 19(1): 235, doi: 10.1186/s12889-019-6536-4, indexed in Pubmed: 30808324.
24. Diaz M, Moriña D, Rodríguez-Salés V, et al. Moving towards an organized cervical cancer screening: costs and impact. Eur J Public Health. 2018; 28(6): 1132–1138, doi: 10.1093/eurpub/cky061, indexed in Pubmed: 29684144.
25. Sawaya GF, Sanstead E, Alarid-Escudero F, et al. Estimated Quality of Life and Economic Outcomes Associated With 12 Cervical Cancer Screening Strategies: A Cost-effectiveness Analysis. JAMA Intern Med. 2019; 179(7): 867–878, doi: 10.1001/jamainternmed.2019.0299, indexed in Pubmed: 31081851.
26. Gliniewicz A, Zielińska A, Kwiatkowska K, et al. Survival in women diagnosed with breast and cervical cancer in Poland – compared to European countries, based on CONCORD - 3 Programme. Przegl Epidemiol. 2018; 72(4): 499–508, doi: 10.32394/pe.72.4.25, indexed in Pubmed: 30810005.
27. Dubas-Jakóbczyk K, Kocot E, Seweryn M, et al. Production lost due to cervical cancer in Poland in 2012. Med Pr. 2016; 67(3): 289–299, doi: 10.13075/mp.5893.00378, indexed in Pubmed: 27364103.
28. Bianchi FP, Gallone MS, Fortunato F, et al. Epidemiology and cost of cervical cancer care and prevention in Apulia (Italy), 2007/2016. Ann Ig. 2018; 30(6): 490–501, doi: 10.7416/ai.2018.2249, indexed in Pubmed: 30614498.
29. Chesson HW, Meites E, Ekwueme DU, et al. Updated medical care cost estimates for HPV-associated cancers: implications for cost-effectiveness analyses of HPV vaccination in the United States. Hum Vaccin Immunother. 2019; 15(7-8): 1942–1948, doi: 10.1080/21645515.2019.1603562, indexed in Pubmed: 31107640.
30. Wolff E, Elfström KM, Haugen Cange H, et al. Cost-effectiveness of sex--neutral HPV-vaccination in Sweden, accounting for herd-immunity and sexual behaviour. Vaccine. 2018; 36(34): 5160–5165, doi: 10.1016/j.vaccine.2018.07.018, indexed in Pubmed: 30017146.

VIA MEDICA

Artykuł przeglądowy / Review article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 27–33

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Off-label use of medicinal products in oncology: exercising due diligence or experimental activity?

Justyna Estera Król-Całkowska[1], Janusz Jaroszyński[2]

[1]*Department of European and International Law, Faculty of Law and Administration, Lazarski University, Warsaw, Poland*
[2]*Department of Administrative Procedure, Faculty of Law and Administration, Maria Curie-Sklodowska University of Lublin, Lublin, Poland*

One of the primary responsibilities of a physician is to diagnose and treat diseases with due diligence. Exercising due diligence in treatment process involves, among others, the use of optimal diagnostic, therapeutic and follow-up management in accordance with the current state of medical knowledge. Each medicinal product has the Summary of Product Characteristics which defines, among others, registered indications, the age group for which the product is registered, the dosing scheme, and route of administration of the product. Polish law does not refer directly to the admissibility of products that use off-label nor does it include regulations forbidding such activities. Considering a number of problems associated with products which use off-label and, on the other hand, commonness of such activities, it is necessary to introduce legal regulations defining the legitimacy and admissibility of such methods of proceeding.

Key words: off-label use, oncology treatment, medical experiment, due diligence, reimbursement of drugs

Introduction

According to article 4 of the Act on the Profession of Doctor and Dentist [1], one of the fundamental responsibilities of a physician is to diagnose and treat diseases with due diligence. Within due diligence, a physician is obliged to apply available methods and means of preventing, diagnosing, and treating diseases, including especially, those being optimal procedures in time offering the best chances of treatment success. Often it requires the use of medicinal products discordant with the provisions of the Summary of the Product Characteristics (SPC), for instance, due to the lack of medicinal products registered in a particular indication or in a specified age group. Exercising due diligence in the treatment process involves, among others, applying optimal diagnostic, therapeutic, and follow-up management in line with the current state of medical knowledge. The authors state that current medical knowledge should be understood as reflecting recent guidelines, management schemes, and treatment standards formulated by scientific societies and groups of experts, as well as applying the elements of evidence based medicine (EBM) as a supplementary factor.

The issue of due diligence is directly referred to article 355 of the Civil Code [41] stating that "the debtor is obliged to perform generally required diligence in relationships of a particular type (due diligence)". In the physician-patient relationship, a physician becomes the stipulated debtor and, at the same time, guarantor of the patient's life and health which binds a physician to undertake any actions focused on the intended objective. The ground for these actions is undoubtedly due diligence understood as treatment implementation based on the current medical knowledge supplemented with EBM. The element of due diligence is, among others, the implementation of pharmacological therapy with the use of medicinal products in an optimized manner and adjusted to the individual needs of the patient. According to article 2 item 32 of the Pharmaceutical Law Act [2], a "medicinal product" should be understood "as a substance or a combination of substances presented

Jak cytować / How to cite:

Król-Całkowska JE, Jaroszyński J. ***Off-label use of medicinal products in oncology: exercising due diligence or experimental activity?*** *NOWOTWORY J Oncol* 2022; 72: 26–33.

as owning properties to prevent or treat diseases in humans or animals or administered to diagnose or restore, improve or modify the physiological functions of an organism through pharmacological, immunological or metabolic activities".

Each medicinal product has the Summary of Product Characteristics (SPC) which determines, among others, registered indications, the age group for which the product was registered, dosage regimen, and route of administration of the product. In clinical practice medicinal products are also used beyond SPC provisions (off-label use) which is a result of, among others, constantly developing medical knowledge, a patient's individual needs and strictly formal reasons – i.e. the lack of verification of SPC content which was established several or a dozen or so years earlier. Off-label use of medicinal products implies a number of questions of a legal nature, including the admissibility and legal compliance of such activity, and the responsibility of health care professionals regarding negative effects arising from initiation or continuation of off--label treatment.

Aim

The aim of this paper is to analyze the admissibility of off-label use of medicinal products in oncology and to indicate whether such activity should be identified as exercising due diligence or rather as an experimental activity. The subsidiary aim is to indicate a physician's responsibility to provide information on treatment implemented off-label before its commencement. The paper deliberately omits principles of responsibility associated with the use of medicinal products discordant with the provisions of the Summary of Product Characteristics. Given the extensiveness of the subject associated with physician responsibility due to off-label use of drugs, a separate paper should be dedicated to this issue.

Material and methods

This paper uses analysis of the provisions of the law, the present position of the doctrine, and jurisprudence. The material involves current legal regulations referring to conducting therapeutic experiments, principles of using medicinal products as well as principles of expressing consent to treatment. The fundamental material was complemented by the positions grounded in the doctrine and content of the current Polish Courts' Case Law on the use of medicinal products beyond SPC provisions.

Admissibility of off-label use of medicinal products in oncology

In many fields of medicine, off-label use of medicinal products constitutes a typical and completely acceptable activity in light of current medical knowledge. According to the WHO, half of all drugs available on the worldwide pharmaceutical market is at least incidentally used in a manner not stated in the instructions [3]. In 1997, the FDA defined this method of therapy as "off-label use" referring to the use of drugs in unregistered indications, in a dosage or scheme varying from SPC provisions, or in a population for which the drug was not registered [4].

The Summary of Product Characteristics is created based on the European Parliament and Council Directive 2001/83/WE on community code referring to medicinal products used in humans [5] and the Pharmaceutical Law Act [2]. The information included in SPC is the result of clinical trials conducted for registration of a particular drug. Article 11 section 1 items 1–13 of the Pharmaceutical Law Act [2], includes a list of information necessary to include in the content of the summary of product characteristics. The most important include: clinical data involving indications for use, dosage and route of administration, contraindications, special warnings and precautions for use, interactions with other medicinal products or other forms of interactions, use during pregnancy and breast-feeding, effects on the ability to drive and use machinery, adverse reactions, overdose and antidotes, pharmacological properties, pharmaceutical data on, among others, expiry date, special precautions for storage, name and address of marketing authorization holder. The listing of all SPCs for drugs authorized for use is available on the website of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL) [6].

The literature indicates the following off-label drug use amounts: 7.5–15% in typical outpatient internal indication, 30–50% in oncology patients and even 90% in the case of neonatology and pediatric oncology. Off-label use is especially common in the field of pediatrics, oncology, dermatology, hematology, and palliative care [7]. Review of the literature concerning off-label use of drugs in oncology indicates that it is common practice used with various intensity by oncologists around the world.

The authors M.M. Saiyed, P.S. Ong, and L. Chew indicate that the use of drugs beyond registration indications in hospitalized oncology patients varied between 18% and 41% [8]. Among adult patients with cancer, 13–71% received at least one off-label chemotherapy. Major reasons for off-label drug use was the lack of product registration in the treatment of diseases diagnosed in a patient, or the necessity to retreat from the dosage scheme indicated in the SPC [8]. The scale of needs for off-label treatment in oncology is depicted by research conducted by A.K. Herbrand, A.M. Schmitt, M. Briel, et al. in years 2015–2018. Research conducted in a Swiss population demonstrated that 45% of first line treatment cases in a group of 3046 patients treated for cancer was associated with a decision to implement off-label treatment [9]. In a study published in 2021, Japanese researchers demonstrated that diseases most commonly treated off-label were sarcoma, urologic cancers, and gastrointestinal cancers [10]. Research conducted in Peter MacCallum Cancer Centre in Australia demonstrated that prescribing beyond registered indications is prevalent in patients hospitalized due to acute cancer wherein approximately 22% of all prescriptions concern off-label or unlicensed drugs [11].

Off-label use in oncological treatment is also prevalent in Germany [12] and France [13].

It should be emphasized that, beside oncology, off-label therapy is prevalent in the pediatric and neonatology population. Research conducted in Europe indicates that at least one third of hospitalized children and up to 90% of infants treated in neonatal intensive care units are administered off--label treatment [14].

Polish literature [15] distinguishes four cases of the use of drugs beyond strictly registered indications, involving the use of:

- a medicinal product in a manner or with the route of administration which was not stated in the Summary of Product Characteristics,
- a drug in line with registered indication in patients for whom dosage was not determined,
- a drug in an indication which was not listed in the Summary of Product Characteristics but for which reliable data confirming its safety and efficacy exist,
- a drug in a new indication which is not yet supported by evidence, but for which there are scientific foundations allowing to expect its efficacy and safety.

In the opinion of I. Vrancken, the notion of off-label use should be primarily understood as the use of drugs in the population which was not stated in the SPC as well as discordant with the registered indication [16]. The literature also items out that the use of drugs beyond SPC may stand for the use of a drug in a different age group, other doses or discordant with the purpose [17]. In the opinion of the authors, off-label use of medicinal products should be divided into two categories:

- off-label use of medicinal products in the primary meaning – i.e. the use of products discordant with the registered indications (beyond registered indications), or in an age group for which the drug was not registered,
- off-label use of medicinal products in the secondary meaning – i.e. the use of products in different dosing schemes or route of administration as well as the modification of other SPC provisions.

The literature referring to the legal aspects of the use of medicinal products beyond SPC defines off-label use also as the use of a product discordant with the approved product information, as well as the implementation of treatment in a different manner than that stated in the patient information leaflet (PIL) [18].

Regarding the meaning of the Summary of Product Characteristics, the Court of Appeal in Warsaw in its judgement of 14.02.2014 [19] emphasized that "SPC is one of the crucial documents in marketing authorization procedure for medical products, it contains data of a manufacturer, composition, action, posology and any identified risks associated with the use of a particular product, however it is not of a normative nature, but rather informative one concluding the state of knowledge on this product in a particular moment. Considering continuous development in medical knowledge, a physician must have appropriate license to adjust the use of drugs to current achievements of medicine and the needs of a particular patient".

On the other hand, the Supreme Court in the judgement of 24.11.2011 [20] referred to the relationship of SPC provisions to a physician's decision on drug dosage. The Supreme Court stated that: "a physician's entitlement to prescribe a dosage regimen recognized as appropriate, arises from the fact that he makes therapeutic decisions and is responsible for them, therefore, in any event, he cannot be bound by a dosing regimen determined in the summary of product characteristics. A physician's decision on dosage regimen must consider the individual needs determined by the health state of a particular patient and other professionally assessed circumstances; if it was to be otherwise § 8 section 1 item 2 of the Regulation of the Minister of Health of 17.05.2007 would be completely redundant or would lead to the absurd conclusion that a physician is obliged to automatically duplicate only the dosage regimen determined in the summary of product characteristics".

A similar statement was issued by the Supreme Court in the resolution of 26.10.2011 [21], emphasizing that "article 45 of the Act on the Profession of Doctor and Dentist of 5.12.1996 (…) and article 10 section 1 item 11 and article 11 section 1 item 4 of the Pharmaceutical Law Act of 6.09.2001, do not lay the foundation to assume that a physician is bound by the dosage regimen included in the summary of the product characteristics".

The presented jurisprudence indicates that SPC provisions are only of a formal nature and in each case do not guarantee proceeding in line with the current medical knowledge. The doctrine mentions that the medical knowledge resulting from research must be publicly released in a verifiable form, so as to allow not only control and possible criticism of the accuracy of the applied method, but also the replication of research in line with the proposed method in order to compare the obtained results [22].

At the same time, the literature emphasizes that "no regulation requires that, for valid and efficient execution of a physician's competence to prescribe a drug (in any form), a medical product is prescribed in line with registered indications" and "there are no detailed rules to limit a physician's right to prescribe a medicinal product of his choice, naturally considering the diagnostic and therapeutic findings in a particular case, maintaining the legal and non-legal directives for physician's due diligence. This conclusion also applies to therapies with medicinal products used beyond registered indications" [23].

Although, the law neither excludes nor limits off-label use of drugs, the authors state that SPC provisions should not be subject to arbitrary and unlimited modification, especially in terms of non-adherence to registered indications incorporated in the SPC. It should be considered inherent to distinguish the primary meaning of off-label use, which should be understood

as non-adherence to registered indications or the use of a product in an age group other than that indicated in the SPC, from its secondary meaning which should be identified as a change of dosage regimen, route of administration, or change of other conditions for drug use expressed in the SPC. As far as a change of route of administration or modification of dosage regimen can be justified by the individual specificity of a disease or a patients' individual traits, the use of drugs beyond registered indications should be justified by the need to save life or health. The authors' opinion correlates with the position of American oncologists; they emphasize that in cases when previously used medicinal products registered in oncological treatment do not have the expected outcome, the implementation of off-label treatment is admissible [24]. Moreover, as recent studies have shown, off-label use has not only a positive, but also a negative impact on the health of oncological patients [25]. The authors indicate the following, among others, indications for use of medicinal products beyond the SPC:

- direct threat to the life or health of a patient,
- exhaustion of the available and registered medicinal products and no expected outcome of therapy,
- the lack of medicinal products registered in a particular indication in the specified age group.

Automatic decision-making on the implementation of treatment beyond SPC without consideration. The point was to indicate analysing conditions given in a certain situation can represent the adoption of practice of drug use incompatible with the registration as a rule, as well as an increase of health risks associated with the use of drugs discordant with their formal registration. Admissibility of automatic use of off-label drugs emerges in a situation in which such possibility is foreseen by an announcement of the Minister of Health on the list of reimbursed medicines, foods for medical purposes and medical devices [26]. In specific cases, the refund announcement allows to prescribe a reimbursed medicine, even though the medicine is not registered in the indications concerned. Although it is the exception to the rule, according to which reimbursement corresponds with registered indications, the announcement does not refer to single use of off-label therapy. In the case when column no 13 of the appendix to the reimbursement announcement named "reimbursement indications beyond registration" includes specified units not included in the SPC, a drug can be prescribed with reimbursement in spite of not being registered in these indications [27]. The situation regarding off-label use of medicinal products based on drug programs is similar. Drug programs constitute the appendix to the reimbursement announcement which determines their binding nature. This means that a physician using a medicinal product beyond the SPC, in line with the drug program guidelines, is not subject to liability due to making such a decision and his activity is identified as exercising due diligence and fulfilling his obligations associated with the initiation of treatment of a patient qualified to the drug program [28].

Off-label drug use and regulations for medical experiments

Off-label use of medicinal products in its primary meaning should not be identified with a medical experiment in the true meaning of this concept. According to article 21 section 2 of the Act on the Profession of Doctor and Dentist [1]: "a medical experiment is the implementation of novel or only partially tested diagnostic, medical or prophylactic methods to achieve direct health benefit in a patient. It can be conducted if previously applied methods are not efficient or not sufficiently efficient (…)." The medical experiments category includes also research experiments. According to article 2 section 3 of the Act on the Profession of Doctor and Dentist [1] "a research experiment primarily aims at expanding medical knowledge (…)." Administration of an off-label drug does not have such an aim, however, in practice, it may enrich medical knowledge. Therefore, the use of drugs beyond the SPC in order to achieve optimal therapeutic effect cannot be in principle identified as a research experiment activity.

Regardless of whether a medical experiment is regarded as being of therapeutic or research in nature, eo ipso such activities contribute to the expansion of medical knowledge (especially evident in the case of research experiments). Administrating a particular patient an off-label drug does not have such an aim (although in practice it may enrich medical knowledge).

The fundamental difference between a medical experiment and the use of medicinal products beyond SPC, in the primary meaning, is the fact that activities of an experimental nature are entirely novel or only partially tested. On the other hand, the use of medicinal products discordant with registration indications is, in principle, an activity having its foundations in EBM, medical literature, and guidelines of teams of experts. Due to the safety of use specified by EBM, off-label drug use should be identified with regular medical service which is not a medically experimental. At the same time, it should be remembered that the regular health service, i.e. not experimental in nature, can be associated with an increased risk of a negative impact on a patient's life or health. The literature emphasizes that activity of an experimental nature cannot be identified with regular therapeutic activity [29]. What is more, the literature indicates that: "(…) only research activities conducted in line with generally accepted principles for scientific research, especially in strictly defined, purposefully chosen, precisely controlled conditions allowing for multiple replication, can be called medical experiment. Therefore unplanned, single use of a novel or unconventional treatment method applied by a physician to save a patient's life or health is not a medical experiment" [30]. In the authors' opinion, the medical experiment catalogue, within the meaning of provisions of chapter 4 of the Act on the Profession of Doctor and Dentist [1] (medical experiments) does not include single activities aiming at the protection of a patient's life or health in urgent

cases, understood as all the cases in which the risk of loss of life, severe body injury or severe disorder of health occurs. As literal wording of article 30 of the Act on the Profession of Doctor and Dentist states: "a physician is obliged to provide medical aid in all cases when a delay in its provision could cause a risk of life loss, severe body injury or severe disorder of health" [1]. Therefore, the activities a physician is obliged to undertake in line with article 30 of the Act on the Profession of Doctor and Dentist [1] must not be identified with a medical experiment, which is due to the procedure of their implementation (urgent case), the nature of the activity (prophylactic, medical, and diagnostic activities), and the specifics of risk associated with refraining from the implementation of optimal methods of medical procedure (loss of life, severe disorder of health, severe body injury).

At the same time, urgent cases and measures should not be identified with an experiment carried out in conditions of an urgent cases and measures. In accordance with article 25a item 2 and 5 of the Act on the Profession of Doctor and Dentist [1], a medical experiment can be conducted without the participant's consent if the following conditions are met: "an urgent case occurs and due to the necessity to undertake immediate action, it is impossible to obtain consent for participation in the medical experiment from a legal representative of the participant or judicial authorization within a sufficiently short period of time", and "the experiment's participant […] he and his legal representative will receive all significant information regarding participation in this experiment in the shortest period of time possible." However, it should be emphasized that all actions bearing the marks of a medical experiment in the understanding of the Act on the Profession of Doctor and Dentist can only be conducted after previously obtained positive opinion of the Bioethics Committee – article 29 section 1 of the Act on the Profession of Doctor and Dentist [1]. The above analysis clearly demonstrates that incidental medical activities aiming at saving life or health in urgent cases are not medical experiments, even if their nature is innovative, atypical or uncommon.

Assuming that the use of drugs beyond SPC is not of an experimental nature is crucial, among others, from the perspective of the obligation to conclude liability insurance by the entity conducting the experiment. According to article 23c section 1 of the Act on the Profession of Doctor and Dentist [1], the experimenting entity is obliged to conclude a separate liability insurance agreement covering the experiment's participant and a person who can be directly influenced by the effects of the experiment. Exception from the obligation to conclude liability insurance is defined in article 23c section 2 of the Act on the Profession of Doctor and Dentist [1], stating that conducting a medical experiment in spite of lack of liability insurance is only admissible in the case of a need for the experiment in urgent mode or in the case when the life of the experiment's participant is threatened.

According to § 2 of the Ordinance of the Minister of Finance, Funds and Regional Policy on compulsory civil liability insurance of the body carrying out the medical experiment [31], third party liability insurance is covered by the civil liability of the body carrying out the medical experiment for damage caused by its action or negligence to the participant and the person whose effects may be directly affected by the experiment, in connection with the medical experiment being carried out. As is indicated in the doctrine "both – the Pharmaceutical Law Act (article 37 b section 2 item 6) and the Act on Medical Devices (article 40 section 4 item 6) introduced a requirement to conclude mandatory liability insurance for damages caused due to conducting clinical trials. This resolution can be justified by the protection of participants' rights, for whom in case of a damage due to experimental activities, compensation would be guaranteed. However, application of these regulations is limited to research activities regulated pursuant to current acts. Therefore, it was demanded to unify these solutions and introduce them to chapter 4 of the Act on the Profession of Doctor and Dentist. Such a regulation was placed in the added article 23 c which imposes such an obligation" (…) [32].

The use of medical products incompatible with SPC records does not constitute a medical experiment, if implementation of treatment aims at protecting the life or health of patients, instead of, for example, only observation of drug activity. In case of medical off-label use of medicinal products, provisions of the Act on the Profession of Doctor and Dentist on medical experiments have no appropriate application, therefore no obligation for concluding liability insurance by the entity which initiates and conducts such therapy occurs.

It should be emphasized that the use of medicinal products discordant with SPC represents exercising due diligence, provided that such activity constitutes optimal therapeutic management.

The issue of the lack of due diligence in treatment process was addressed by the Court of Appeal in Krakow in its judgement of 12.10.2007 [33], emphasizing that "it is a physician's fault not to exercise the highest degree of due diligence which is possible at currently used methods of treatment of a particular disease (…)." The use of medicinal products beyond SPC constitutes due diligence, provided that such activity is commonly accepted and applied, as well as being in line with the current state of medical knowledge.

According to P. Kwinta "continuous development in medical sciences (…) leads to the situation in which the information included in SPC, being a primary document required for drug registration, in some circumstances can be out-of-date" [34]. Both doctrine and judicature refer to the issues of the use of medicinal products discordant with registration provisions, however these issues are not treated in a uniform manner. Also, they are not directly regulated by the law.

Obligation to provide information in case of off-label drug use

In case of decision on off-label use of a drug a physician is obliged to inform a patient on possible results and complications of planned procedure, including alternative types of therapeutic management.

The obligation to provide information specified in article 31 section 1 of the Act on the Profession of Doctor and Dentist [1] requires that a physician provides, among others, information on the potential negative effects associated with a proposed treatment, the available alternative methods of proceeding, as well as the possible negative effects resulting from treatment initiation withdrawal. This issue becomes especially significant in cases where a physician proceeds discordant with SPC provisions, for the patient must know that such a method will be used and why a physician has decided to apply it. In the case where a patient accepts the offered nonstandard therapeutic management, they assume the risk associated with off-label drug administration. However, it is crucial to clarify the predictable consequences (favorable and unfavorable for the patient) of such a method of prescribing drugs [42–45]. The current case law states that once a patient is properly informed, he assumes the risk associated with the undertaken activities, under the condition that a "medical error", resulting in negative consequences, is not made by the physician [46, 47].

The literature emphasizes that the obligation to provide information is not limited to the level of information considered important by a physician, but a patient [35]. Due to the specificity and scope of results possibly occurring in treatment beyond the SPC, such activities should be identified as high-risk activities which highlights the importance of the obligation to provide information. In the authors' opinion, the risk of off-label treatment can be identified as typical (average) only in cases, when the use of a product incompatible with SPC is a common and schematic activity.

The doctrine emphasizes that "the lack of due diligence (provided for a professional) in the case of a physician, can involve the use of a drug in a defective way or to an inappropriate patient as well as the lack of possibility to predict adverse reactions of a drug as a result of a physician's insufficient knowledge regarding its properties or side effects when they possessed or should have possessed such knowledge. Responsibility for damage caused this way can be assigned to the physician (…), as lack of due diligence is a physician's fault. A physician (…) will be also responsible in case of prescribing or administering a patient drugs which harm the patient and the physician possessed or should have possessed knowledge on the properties of these drugs" [36]. In terms of the use of medicinal products beyond the SPC, prediction of all and even typical effects of their application is impossible due to the lack of previous drug assessment in terms of the risks associated with its use.

In view of the article 31 section 1 of the Act on the Profession of Doctor and Dentist, prior to off-label treatment initiation, a physician should deliver, among others, any information on effects and complications that may be predictable in light of the current medical knowledge, including these of casuistic occurrence. Case law indicates that an obligation to provide information covers normal, predictable, events even of rare occurrence, but impossible to exclude (…), especially those of a dangerous nature for life or health [37].

The delivery of understandable and comprehensive information on off-label treatment provides grounds for patient's informed consent for treatment [38]. In the judgement of 9.04.2019, the Court of Appeal in Warsaw itemed out that "the right for information – beside the right for consent – is in fact one of the most important elements of the relationship between the health care professional and the patient. Guaranteeing a patient the right to information is condition *sine qua non* of protection of his autonomy. Thereby the right for information should be treated as an instrument of significant importance (…)" [39]. On the other hand, the Court of Appeal in Warsaw, in the judgement of 19.02.2019, adopted a position that "(…) obligation to provide appropriate information is in fact integrally associated with a physician's obligations concerning the treatment process alone. Properly fulfilled obligation to inform is a necessary condition for a patient's expression of legally binding consent (termed as "informed") for determined treatment; the ineffectiveness of consent due to the lack of delivery of appropriate information affirms the unlawful activities of a physician (…)" [40].

Conclusions

Polish law does not refer directly to the admissibility of off-label use of medicinal products, nor includes regulations forbidding to undertake such activities. The physician's obligation to exercise due diligence should be identified with, among others, the necessity to implement optimal pharmacological therapy in accordance with current medical knowledge. In some cases, optimal therapeutic management is associated with the necessary off-label use of medicinal products. However, the use of treatment beyond SPC provisions should not be the rule, but rather it should be justified by strictly defined conditions. The occurrence of conditions in the form of protection of health and life has particular relevance in a case when off-label products use consists of implementation or continuation of treatment with a product which was not registered in an indication in which it is used, or it is used in an age group not listed in the SPC. Off-label use of drugs should not be identified with an experiment in the understanding of the provisions of the Act on the Profession of Doctor and Dentist due to the different specificity of both activities, as well as the criteria to be met to undertake each activity.

Due to the nature of off-label therapy, its initiation or continuation requires particularly careful communication to the patient on the possible consequences of the action of the drug administered against the SPC provisions. Considering

the number of problems associated with off-label use of drugs and, on the other hand, commonplace nature of such activities, the introduction of legal regulations defining the legitimacy and admissibility of such methods of proceeding is necessary. At the same time, it is necessary to initiate education of health professionals regarding the legal possibilities concerning off--label use of drugs, as well as prescribing beyond registration in line with the guidelines of reimbursement announcement.

Conflict of interest: none declared

Janusz Jaroszyński
Maria Curie-Skłodowska University of Lublin
Faculty of Law and Administration
Department of Administrative Procedure
pl. Marii Curie-Skłodowskiej 5
20-031 Lublin, Poland
e-mail: janusz_jaroszynski@tlen.pl

Received: 10 Aug 2021
Accepted: 11 Nov 2021

References

1. The Act on the Profession of Doctor and Dentist of 5.12.1996., ie. DzU 2021 r., pos. 719.
2. The Pharmaceutical Law of 06.09.2001, ie. DzU 2021 r., pos. 974, with changes.
3. Dal Pan GJ. Monitoring the safety of off label medicine use. WHO Drug Information 2009: 21–22.
4. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008; 358(14): 1427–1429, doi: 10.1056/NEJMp0802107, indexed in Pubmed: 18385495.
5. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. OJ L 311/67. https://eur-lex.europa.eu/legal-content/PL/TXT/PDF/?uri=CELEX:32001L0083&from=EN (01.08.2021).
6. https://rejestrymedyczne.ezdrowie.gov.pl/rpl/search/public (01.08.2021).
7. Matusewicz W. Stosowanie leków w onkologii i hematologii w zakresie wskazań do stosowania lub dawkowania, lub sposobu podawania odmiennych niż określone w Charakterystyce Produktu Leczniczego, Warszawa 2012. http://www.korektorzdrowia.pl/wp-content/uploads/prezes-aotm-wojciech-matusewicz-stosowanie-lekow.pdf (01.08.2021).
8. Saiyed MM, Ong PS, Chew L. Off-label drug use in oncology: a systematic review of literature. J Clin Pharm Ther. 2017; 42(3): 251–258, doi: 10.1111/jcpt.12507, indexed in Pubmed: 28164359.
9. Herbrand AK, Schmitt AM, Briel M, et al. Association of Supporting Trial Evidence and Reimbursement for Off-Label Use of Cancer Drugs. JAMA Netw Open. 2021; 4(3): e210380, doi: 10.1001/jamanetworkopen.2021.0380, indexed in Pubmed: 33651108.
10. Bun S, Yonemori K, Sunadoi H, et al. Safety and Evidence of Off-Label Use of Approved Drugs at the National Cancer Center Hospital in Japan. JCO Oncol Pract. 2021; 17(3): e416–e425, doi: 10.1200/OP.20.00131, indexed in Pubmed: 32956004.
11. Poole SG, Dooley MJ. Off-label prescribing in oncology. Support Care Cancer. 2004; 12(5): 302–305, doi: 10.1007/s00520-004-0593-6, indexed in Pubmed: 14986075.
12. Rückeshäuser P. Off label use: the legal problems of drug application beyond the licensed use. , Hamburg 2011: 1–386.
13. Emmerich J, Dumarcet N, Lorence A. France's new framework for regulating off-label drug use. N Engl J Med. 2012; 367(14): 1279–1281, doi: 10.1056/NEJMp1208347, indexed in Pubmed: 23034018.
14. Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. Drug Saf. 2002; 25(1): 1–5, doi: 10.2165/00002018-200225010-00001, indexed in Pubmed: 11820908.
15. Masełbas W, Członkowski A. Stosowanie produktów leczniczych poza wskazaniami rejestracyjnymi. Przewodnik Lekarza. 2008; 3: 81–87.
16. Vrancken I. Off-label Prescription of Medication. European Journal of Health Law. 2015; 22(2): 165–186.
17. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Archives of Internal Medicine. 2006; 9: 1021–1026.
18. Kapko M. In: Zielińska E. ed. Ustawa o zawodach lekarza i lekarza dentysty. Comment. Wolters Kluwer Polska 2008: 528.
19. The Judgment of the Court of Appeal in Warsaw of 14.02.2014, no, VI ACa 1000/13, LEX nr 1469448.
20. The Judgment of the Supreme Court of 24.11.2011, no, I CSK 69/11, OSNC 2012/5/63 2012.
21. The Resolution of the Supreme Court of 26.10.2011, no, III CZP 58/11, OSNC 2012/5, pos. 59.
22. Widłak T. nterpretacja klauzuli „aktualna wiedza medyczna" w polskim prawie — zarys zagadnień epistemologicznych i metodologicznych. Gdańskie Studia Prawnicze. 2017; 38.
23. Luty O. Zaniechanie zlecenia produktu leczniczego poza zarejestrowanym wskazaniem a odpowiedzialność cywilna lekarza. PiM. 2014; 2: 132–150.
24. American Society of Clinical Oncology. Reimbursement for cancer treatment: coverage of off-label drug indications. J Clin Oncol. 2006; 24(19): 3206–3208, doi: 10.1200/JCO.2006.06.8940, indexed in Pubmed: 16717290.
25. Lim M, Shulman DS, Roberts H, et al. Off-label prescribing of targeted anticancer therapy at a large pediatric cancer center. Cancer Med. 2020; 9(18): 6658–6666, doi: 10.1002/cam4.3349, indexed in Pubmed: 32750219.
26. The Announcement of the Minister of Health of 21.06.2021, on the list of reimbursed medicines, foods for special medical purposes and medical devices as of 1st July 2021. https://www.gov.pl/web/zdrowie/obwieszczenia-ministra-zdrowia-lista-lekow-refundowanych.
27. Chromiec Z, Hoffmann E. Stosowanie leków poza wskazaniami — przesłanki oraz refundacja. Folia Cardiologica. 2020; 15(2): 188–191, doi: 10.5603/fc.2020.0024.
28. Zajdel. Dopuszczalność stosowania produktów leczniczych poza ChPL w programie lekowym „Leczenie przetoczeniami immunoglobulin w chorobach neurologicznych". Neuroedu.pl. file:///C:/Users/User/Downloads/neuroedu%202016%20Dopuszczalno%C5%9B%C4%87%20stosowania.pdf (01.08.2021).
29. Safjan M. Prawo i medycyna. Ochrona praw jednostki a dylematy współczesnej medycyny. , Warszawa 1998: 172.
30. Kondrat M. (ed.). Prawo farmaceutyczne. Komentarz, ed. II. WKP 2016.
31. The Regulation of the Minister of Finance, Development Funds and Regional Policy on mandatory liability insurance of the entity conducting medical experiment, DzU 2020, pos. 2412.
32. Kubiak R. Nowe uwarunkowania prawne przeprowadzania eksperymentów medycznych. PS. 2021; 1: 5–26.
33. The Judgment of the Court of Appeal in Kraków of 12.10.2007, no., I ACa 920/07, LEX no 570272.
34. Kwinta P. Stosowanie leków poza rejestracją u dzieci – perspektywa lekarza. Przegląd Lekarski. 2011; 68: 1–3.
35. Aagaard L, Kristensen K. Off-label and Unlicensed Prescribing in Europe: Implications for Patients' Informed Consent and Liability. International Journal of Clinical Pharmacy. 2018; 40(3): 509–512.
36. Gęsicka DK. Odpowiedzialność za szkody wyrządzone przez produkty lecznicze – zagadnienia wybrane. Prawo i Medycyna. 2013(3-4): 189–208.
37. The Judgment of the Supreme Court of 18.01.2013, no, IV CSK 431/12, Lex no 1275006.
38. Zajdel J. Prawo medyczne. PZWL, Warszawa 2019.
39. The Judgment of the Court of Appeal in Warsaw of 9.04.2019, no, akt V ACa 147/18, Lex no 2668829.
40. The Judgment of the Court of Appeal in Warsaw of 19.02.2019, no, V ACa 119/18, Lex no 2631471.
41. The Civil Code of 23.04.1964, ie. DzU 2020, pos. 1740.
42. Kubiak R. Prawo medyczne. C.H.Beck, Warszawa 2017: 291–295.
43. The Judgment of the Supreme Court of 28.08.1972, no akt II CR 296/72, OSNC, No 5/1973, pos. 86.
44. The Judgment of the Court of Appeal in Kraków of 06.09.2012 r., no akt I ACa 723/12, LEX no 1236722.
45. The Judgment of the Supreme Court of 28.09.1999 r., no akt II CKN 511/96, LEX no 453701).
46. The Judgment of the Court of Appeal in Szczecin of 11.05.2017, no akt I Aca 560/15, LEX no 2376937.
47. The Judgement of the Court of Appeal in Katowice of 18.01.2017 r., no akt V ACa 146/16, LEX no 2233014.

VIA MEDICA

Artykuł przeglądowy / Review article

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 34–43

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

The Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer

Katarzyna Zubik[1], Julia Talaśka[1], Dawid Sigorski[2, 3*], Sergiusz Nawrocki[2, 4*]

[1]*Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland*
[2]*Department of Oncology, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland*
[3]*Department of Oncology and Immuno-Oncology, Warmian-Masurian Cancer Center of The Ministry of The Interior and Administration's Hospital, Olsztyn, Poland*
[4]*Department of Radiotherapy, Warmian-Masurian Cancer Center of The Ministry of The Interior and Administration's Hospital, Olsztyn, Poland*
** co senior-authorship*

Genome instability and mutations are the hallmarks of cancer. Mutations within *BRCA* genes increase the risk of pancreatic cancer (PC) development. Poly(ADP-ribose) polymerase inhibitors (PARPi) show the synthetic lethality phenomenon in tumoral cells with *BRCA* mutation and improve outcomes in patients with breast, prostate and ovarian cancer. Olaparib was the first PARPi registered for the patient with metastatic PC with a deleterious or suspected deleterious germline *BRCA*-mutation. The POLO phase III clinical trial shows that olaparib in PC increases progression-free survival, however it does not prolong the overall survival. Currently, many clinical trials are ongoing to determine the clinical utility of PARPi in monotherapy or polytherapy of PC. The role of PARPi in PC has not been well established and many questions remain unanswered. This review aims to summarise the rationales behind the use of PARPi and current clinical data.

Key words: PARP inhibitors, olaparib, pancreatic cancer, *BRCA* mutation

Introduction

It is estimated that 60,430 (31,950 men and 28,480 women) cases of pancreatic cancer (PC) will be diagnosed and 48,220 people (25,270 men and 22,950 women) will die in 2021 in the USA according to the American Cancer Society [1]. PC is the fourth leading cause of cancer death in men as well as women. The prognosis of PC is unfavorable and life expectancy is about 5% at 5 years [2]. The majority of patients at the time of diagnosis present unresectable tumours due to either local extension or distant metastases. The current treatment options for patients with metastatic PC include fibrinolysin, gemcitabine with nab-paclitaxel, or erlotinib regimens which significantly improved the clinical outcomes in comparison to gemcitabine monotherapy that was the standard therapy for many years [3, 4].

Advances in molecular biology and genetics allow designing poly(ADP-ribose) polymerase inhibitors (PARPi), which are a new class of drugs based on molecular profiling, including *BRCA* mutational status assessment. PARP belongs to a group of enzymes involved in DNA repair, which are activated by DNA damage [5, 6]. It includes olaparib, niraparib, talazoparib and rucaparib. PARPi improved treatment outcomes in patients with breast, prostate and ovarian cancer [7–12].

Currently, they are being tested in monotherapy or polytherapy in PC and may potentially improve the therapeutic armamentarium for that population of patients. In December 2019, the Food and Drug Administration (FDA) approved olaparib as a maintenance treatment for patients with deleterious or suspected deleterious germline *BRCA*-mutated metastatic pancreatic adenocarcinoma [13]. Recently, in the phase

Jak cytować / How to cite:
Zubik K, Talaśka J, Sigorski D, Nawrocki S. ***The Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer.*** *NOWOTWORY J Oncol* 2022; 72: 34–43.

III POLO trial, it was shown that olaparib increases the median of progression-free survival (mPFS), however without improving the median of overall survival (mOS) [14]. Nevertheless, PARPi are a promising new class of drugs that need further studies. This review aims to summarise the preclinical and clinical data on PARPi in PC.

The role of *BRCA* genes and BRCAness in PC

One of the hallmarks of cancer is genomic instability which leads to DNA alterations and predisposes to cancer development [15]. Two types of genetic alterations which lead to tumorigenesis can be distinguished – germline mutations and somatic – a somatic acquired mutation that arises spontaneously as a result of environmental factors like smoking [16]. The majority of PC, approximately 80%, do not have any associations with either positive family history, or inherited genetic causes. 5.2% are associated with an inherited component without positive family history and about 8% of patients with PC have a positive family history [17]. The most common mutation is in the *KRAS* (Kirsten rat sarcoma virus) gene whereas germline and somatic mutations in genes *BRCA* (breast cancer) *1/2, ATM* (ataxia–teleangiesctasia mutated) and *PALB2* (partner and localizer of *BRCA2*) occurs less common of cases [15]. The incidence of germline and somatic mutations in PC is presented in table I. BRCA1 and BRCA2 are proteins that are involved in DNA repair and transcriptional regulation in response to DNA damage. They also take part in replication fork protection and are important factors responsible for resistance to the activity of numerous nucleases, including MRE11, DNA2, EXO1 and MUS81 [20, 21]. Importantly, both proteins are involved in the homologous recombination repair (HRR) process, in which a homologous DNA sequence is used to guide repair that results in restoring the DNA sequence to its original form [22, 23]. Cells with dysfunction in *BRCA 1/2* genes have deficits in HRR and must use less accurate mechanisms to repair double-strand breaks, increasing the risk of cancer development [24]. In unselected populations, a pathogenic mutation in *BRCA1* is found in less than 1% and *BRCA2* mutation in up to 2% of PC cases [17]. Identifying the *BRCA* mutation status in patients is clinically relevant because the mutation provides the data on other possible cancer risks associated with the *BRCA* mutation, like breast, ovarian and prostate cancers. Additionally, identifying the *BRCA* mutation status allows for testing at-risk family members for the same mutation with limited cost [25].

The mOS of patients with PC and *BRCA1* and *BRCA2* mutations is approximately 15 and 13 months, respectively [24]. Among approximately 13 hereditary genes associated with PC development, *BRCA1* and *2* mutations are the most frequent genetic alteration responsible for FPC, which are diagnosed in 2.7% of patients with PC [17]. It has been reported that in about 3,9% of unselected patients, somatic *BRCA1/2* mutations drive the PC [28]. The mOS for patients who carry mutations in *HRR* genes (*ATM, BARD1* [*BRCA1-associated RING domain protein 1*], *BRCA1, BRCA2, BRIP1* [*BRCA1 interacting protein 1*], *PALB2, RAD51C, RAD51D*) associated with PC is 14.6 months, whereas mOS for patients without mutations was 11.7 months [26].

Apart from *BRCA1/2* mutations, the other mutations related to PC are alterations within other HRR genes like *ATM, CDKN2A* (cyclin-dependent kinase inhibitor 2a), *MLH1* (mutL homolog 1) [17]. As opposed to breast cancer and prostate cancer, mutations in *CHEK2* (checkpoint kinase 2) and *PALB2* have no significant correlation to pancreatic cancer [17, 29]. The mOS for patients treated with FOLFIRINOX chemotherapy in metastatic PC, who have somatic or germline mutations in *BRCA1*, *BRCA2*, *PALB2*, *MSH2*, *FANC* (the Fanconi anemia) complementation

Table I. The incidence of germline and somatic mutations in PC

Gene – germline mutation	Incidence in PC	Incidence in patients with a positive family history of PC	Gene – somatic mutation	Incidence in PC	Reference
BRCA1 *BRCA2* *PALB2*	2.4% 26.2% 2.4%	– – –	*KRAS* *TP53* *SMAD4* *CDKN2A* *SMARCB1* *RB1*	88.1% 33.3% 16.7% 4.8% 2.4% 2.4%	[73]
ATM *BRCA1* *BRCA2* *PALB2* *RAD51*	2.1% 0.6% 2.2% 0.4% 0.2%	– – – – –	–	–	[26]
ATM *BRCA1* *BRCA2* *CDKN2A* *MSH2* *PALB2*	2.6% 0.7% 3.6% 1.3% 0.3% 0.3%	3.2% 1.1% 4.3% 2.2% 0.5% 0.5%	–	–	[33]

group was 14 months in comparison to 5 months in patients without mutations [30].

BRCAness is a phenomenon referred to as the existence of a HRR defect despite the absence of a germline *BRCA1/2* mutation in tumour, which leads to oversensitivity to DNA damage as a result of increased genomic instability. The most common mutation in the HRR repair gene that contributes to the BRCAness phenotype is a somatic defect in *BRCA1* and *BRCA2*, however, BRCAness is also related to other genes involved in HRR, such as *ATM*, *PALB2*, *ATR* (ataxia teleangiectasia and Rad3 related), *CHEK1/2*, *RAD51*, *NBS1* (Nijmegen breakage syndrome) and *FANC* family of genes [19, 31]. The incidence of HRR mutations in PC is shown in table II.

The data describing the role of genes other than *BRCA* are limited. Among the HRR genes, one of the most relatively known mutations related to inherited and sporadic PC is the *ATM* mutation [32]. The incidence of *ATM* mutations in patients with a positive family history of PC is approximately 3.2% [30]. ATM serine/threonine kinase controls cells' survival, death, cell cycle arrest, apoptosis and DNA repair. Pathogenic germline *ATM* mutation increases the risk of PC [34–37]. However, *ATM* mutational status may be also important in predicting radiation and chemotherapy response [38, 39]. *ATM*-deficient PC cells are more sensitive to fractionated radiation than wild-type pancreatic cancer [38]. *ATM*-mutated PC cells treated with olaparib significantly enhance suppression of the PC proliferation *in vivo* and *in vitro* [40].

Furthermore, it has been demonstrated that tumours with BRCAness have similar therapeutic vulnerability as tumours with germline *BRCA* gene mutations. For that reason, it is considered as a potentially significant factor in PARPi therapy [41, 42].

DNA damage response and PARP involvement in synthetic lethality

DNA damage occurs constantly in cells due to exogenous and endogenous stressors leading to genome instability. DNA damage response (DDR) is a central mechanism responsible for detecting DNA lesions and promoting their swift repair. In the process of DDR, a great amount of different intra- and extracellular signalling pathways and enzyme activities are activated. In suboptimal or lack of activity of DDR, an exaggerated level of genomic instability arises – a characteristic feature of cancers. In human cells, two major forms of DNA damage could occur, either a single-strand break (SSB) or double-strand breaks (DSB), whereby SSB occurs more often. Different forms of DNA damage bring responses by proper signalling pathways and repair mechanisms [43, 44]. There are four known repair pathways involved in SSB: base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR) and trans-lesional synthesis. HRR and non-homologous end joining (NHEJ) are two pathways responsible for repair DSBs. The HRR process involves BRCA1/2, PALB2, ATM, RAD51, CHEK1/2, ATR, p53 proteins and MRN complex composed of Mre11, Rad50 and NBS1/NBN proteins [45–47]. When DSB occurs, it is detected by the MRN complex and the ATM and ATR – the cell cycle regulatory kinases are activated. Subsequently, ATM activates CHK2, which arrests cell cycle progression, contributes to regulating BRCA1 in DNA repair, and interacts with TP53, which is responsible for cell cycle and apoptosis control. The MRN complex also recruits BRCA1/2 and PALB2 to the DNA damage site. These proteins form a new complex, which finally activates RAD51 that is responsible for binding single-stranded DNA segments and invading the homologous sequences in the sister chromatid.

PARP enzymes are known as DNA damage sensors. This nuclear deoxyribonucleic acid-binding protein contains an N-terminal double zinc-finger DNA-binding domain, a nuclear localization signal, a central automodification and a C-terminal catalytic domain. Its basal enzymatic activity is low but the variety of allosteric activators, for example, damaged DNA, nucleosomes and a variety of protein-binding partners, strongly stimulates it. When SSBs occur, the PARP enzymes are activated and binds to the site of single-DNA damage using its zinc-finger DNA-binding domain. It cleaves NAD+ into nicotinamide and ADP-ribose. The latter cleavage product is covalently attached to glutamate or aspartate residues of nuclear acceptor proteins in the form of long branching ADP-ribose polymers. This results in a highly negatively charged polymer and subsequently leads to the unwinding and repair of the damaged DNA through the BER [48–52]. PARPi interfere with base excision repair by binding to the catalytic domain of PARP, which prevents PARylation, traps PARP to the SSB, and prevents repair. Consequently, an accumulation of SSB occurs, which degenerate into DNA DBS. As a result, cancer cells undergo cell cycle arrest and apoptosis when exposed to these agents. Inhibition of PARP-1 in PC cells increases the caspase-3 activity, and by increasing the p53 protein expression suppresses BCL-2 (B-cell lymphoma 2), as a consequence leading to apoptosis and suppression of PC cell proliferation [53]. Except for SSB,

Table II. Frequency of BRCAness mutations among patients with a positive family history of PC [17]

BRCAness	Prevalence in PC
BRCA1	0.6%
BRCA2	2.10%
ATM	3.29%
PALB2	0.6%
ATR	–
CHEK1	–
CHEK2	2.4%
RAD51	0%
NBS1	0.3%
FANC	0.3%

in cells PARP enzymes also take part in HRR-mediated DSB repair [54]. Inhibition of these enzymes in cancer cells could cause cell death which is based on a phenomenon called synthetic lethality (fig. 1). It is defined as the situation when two or more separate genes are simultaneously mutated which lead to cell death. The product of one of these genes is crucial to the survival of the cell, whereas another gene is used as an alternative. In a situation when the gene is mutated, it is replaced by a second one that is involved in an alternative pathway of the same process. In cells with *BRCA* biallelic mutation, cells become incapable to properly perform HRR. In case of DNA damage, these disorders are repaired with PARP and BER repair. The use of olaparib in the presence of the mutation disrupts both repair mechanisms, leading to cell death, because inhibition of PARP activity leads to the accumulation of single-strand breaks, which can lead to double-strand breaks properly repaired by HRR [55–58]. The synthetic lethality in *BRCA*-mutated cancers caused by selective inactivation of PARP enzymes cells are unable to successfully repair DNA damaged, which consequently cause its death [59, 60].

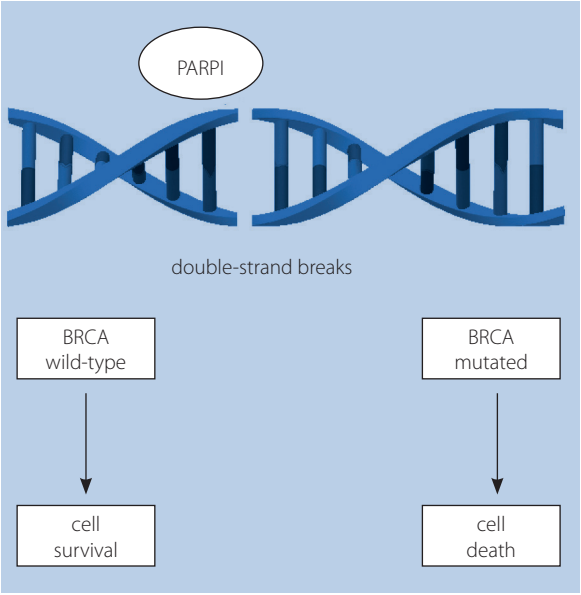

Figure 1. Synthetic lethality and PARPi

Pathobiology of PC

The expression and localization of PARP-1 in the pancreas and PC are different. In the human pancreas, only nuclear PARP-1 (nPARP-1) expression was shown, contrary to nPARP-1 and cytoplasmic PARP-1 (cPARP-1) expression in PC. In the pancreas, the expression of nPARP-1 is enough to maintain the cell's homeostasis by triggering apoptosis in response to DNA damage due to its proapoptotic activity; whereas in PC tissue, the lower expression of nPARP-1 prevents it. PARP-1 takes part in regulating TRAIL (TNF-related apoptosis-inducing ligand) induced apoptosis. Inhibition of PARP-1 may sensitize TRAIL resistant PC cells to TRA-8-induced apoptosis [57]. PARP expression was studied as a new potential prognostic factor in PC. Immunohistochemical analysis of cPARP and nPARP among 178 PC show that high nPARP was associated with a better prognosis (mOS14.5 *vs.* 9.6 months, p = 0.004), however, it did not show a statistically significant correlation with clinicopathological parameters [61]. FeiXu et al. in their studies focused on cPARP-1 and compared the frequency of cPARP-1 in well, moderately and poorly differentiated PC. Initially, they suggest potential relations between cPARP-1 expression on PC pathogenesis and progression, similar to recent breast cancer reports where the correlation between aggressiveness, higher risk of relapse and the death of patients were seen [57, 62]. In their studies, the expression of cPARP-1 was higher in moderately and poorly differentiated than well-differentiated pancreatic tumours. Furthermore, they linked PARP-1 in the cytoplasm to the extrinsic pathway of apoptosis [57].

The results of clinical trials in patients with PC

Currently, the PARPi (olaparib, niraparib, rucaparib and talazoparib) are being tested in monotherapy (tab. III) and polytherapy (tab. IV) on different stages of PC, however, the

Table III. Ongoing trials with PARPi in monotherapy in patients with PC

Name of the study	Phase	Indication/ tumour type	Study drug	Control arm	Mutational status	Primary outcome measure	Secondary outcome measure
NCT04005690	early I	stage I–IV PC	olaparib	cobimetinib	–	proportion of all feasibility – evaluable participants that have a measurable change in post-treatment tumour biology from baseline	• incidence of ≥ grade 3 toxicities for each assigned window treatment • proportion of feasibility – evaluable participants within each study arm that have a measurable change in post-treatment tumour biology from baseline
NCT01078662	II	ovarian, breast, prostate, pancreatic advanced tumours	olaparib	–	*BRCA1/2* mutation	tumour response rate	• ORR* • PFS • OS • duration of response

→

Table III. cont. Ongoing trials with PARPi in monotherapy in patients with PC

Name of the study	Phase	Indication/ tumour type	Study drug	Control arm	Mutational status	Primary outcome measure	Secondary outcome measure
NCT02184195 (POLO)	III	PC	olaparib	placebo	germline *BRCA1/2* mutation	PFS	• OS • time from randomisation to second progression • time from randomisation to first and second subsequent therapy or death • ORR* • quality of life (QoL) • AEs
NCT02677038	II	metastatic PC	olaparib	–	• mutation in germline *BRCA1/2* negative • BRCAness pheno-type	ORR*	• OS • PFS • change in CA19-9 • AEs
NCT04858334 (APOLLO)	II	resectable PC	olaparib	–	*BRCA1/2, PALB2*	improvement in relapse-free survival	• RFS • OS • efficacy after chemotherapy • differences in survival
NCT03601923	II	advanced PC	niraparib	–	• *BRCA1* • *BRCA2* • *PALB2* • *CHEK2* or *ATM* mutation	PFS	• ORR** • OSR • AEs
NCT04171700 (LODESTAR)	II	solid tumours	rucaparib	–	• *BRCA1* • *BRCA2* • *PALB2* • *RAD51* • *RAD51* • *BARD1* • *BRIP1* • *FANC* • *NBN* • *RAD51* or *RAD51B* mutation	best ORR **	• ORR ** • PFS • AEs
NCT03140670	II	metastatic locally advanced PC	rucaparib	–	*BRCA1/2* or *PALB2* mutation	AEs	–
NCT04550494	II	malignant solid neoplasm including PC	talazoparib	–	germline or somatic aberrations in genes involved in DNA damage response	percent of patients who demonstrate simultaneous Rad51 activation	• ORR** • tumour genomic alterations potentially associated with sensitivity to talazoparib
NCT04182516	I	• locally advanced/ metastatic HER2 negative breast cancer • epithelial ovarian cancer • castration-resistant prostate cancer • PC	NMS –03305293	–	–	number of participants with first-cycle dose-limiting toxicity	AEs

AE – adverse events; ORR* – objective response rate; ORR** – overall response rate; OS – overall survival; OSR – overall survival rate; PC – pancreatic cancer; PFS – progression free survival; RFS – relapse-free survival

Table IV. Ongoing clinical trials with PARPi in polytherapy

Name of the study	Phase	Tumour type	Experimental arm	Control arm	Mutational status	Primary outcome measures	Main secondary outcome measures
NCT02498613	II	• PC • lung cancer • breast cancer	olaparib + cediranib	–	–	ORR*	• AEs • PFS
NCT03682289	II	• PC • renal cell carcinoma • urothelial carcinoma • other solid tumours	olaparib + AZD6738	AZD6738	–	• ORR* • composite prostate cancer • patient response • rate ORR for other solid tumours	• DOR • PFS • AEs
NCT04548752	II	metastatic PC	olaparib + pembrolizumab	olaparib	germline mutation in *BRCA 1/2*	PFS	• AEs • OS • ORR**
NCT04493060	II	metastatic PDAC pancreatic cancer	niraparib + dostarlimab	–	• *BRCA1/2* • *PALB2*	DCR – 12 weeks	• ORR* • time to next treatment • OS • PFS and AEs
NCT04673448	I	• PC • breast cancer • ovarian cancer • fallopian tube or primary peritoneal cancer	niraparib + dostarlimab	–	mutation in *BRCA1* or *BRCA2*	best objective response	• Aes • PFS • DOR • DCR • OS
NCT03404960 (Parpvax)	I/II	PC after platinum-based therapy	1 : niraparib + nivolumab	niraparib + ipilimumab	–	PFS	• the proportion of tumours with HRD, ORR*, DOR, OS, AEs • Immune activation prior/ during treatment
NCT03337087	I/II	metastatic PC	rucaparib + irinotecan liposome + leucovorin + fluorouracil	–	selected (*BRCA1* or *BRCA2* or *PALB2* mutation) and unselected	• number of participants with dose-limiting toxicities • objective response • best response rate	• DCR • OS • PFS • AE
NCT02890355	II	metastatic PC	veliparib + mFOLFIRI	FOLFIRI	–	OS	• AEs • PFS • ORR* • DCR
NCT01585805	II	• metastatic PC • recurrent PC • stage III PC	1: veliparib + gemcitabine + cisplatin 2: veliparib	gemcitabine + cisplatin	*BRCA1/2* or *PALB2* mutation	• the optimal dose of drugs • the response rate to gemcitabine hydrochloride and cisplatin with versus without veliparib • response rate of single-agent veliparib	• PFS • Aes • DCR • OS
NCT00576654	I	metastatic tumours or tumours that cannot be removed by surgery	veliparib + irinotecan	–		• optimal biologic dose • maximum administered dose of study drugs • maximally tolerated dose • recommended phase II dose	• AE • tumour response
NCT04228601	Ib/II	advanced PC	fluzoparib + mFOLFIRINOX	placebo + mFOLFIRI-NOX	mutation in germline *BRCA1/2* or *PALB2*	• number of participants with a dose limited toxicity • maximum tolerated dose • ORR*	• AEs • DCR • OS • PFS

→

Table IV. cont. Ongoing clinical trials with PARPi in polytherapy

Name of the study	Phase	Tumour type	Experimental arm	Control arm	Mutational status	Primary outcome measures	Main secondary outcome measures
NCT04644068 (PETRA)	I	PC ovarian cancer breast cancer prostate cancer	AZD5305	AZD5305 + paclitaxel AZD5305 + carboplatin with or without paclitaxel	–	• the number of subjects with adverse events/ serious adverse events • the number of subjects with dose-limiting toxicity	• ORR* • PFS
NCT04503265	I/II	• PC • advanced malignant neoplasm • breast cancer • ovarian cancer • homologous recombination deficiency • prostate cancer	AMXI-5001	–	–	maximum-tolerated dose	recommended phase 2 dose

AE – adverse events; DCR – disease control rate; DOR – duration of response; HRD – homologous recombination deficits; ORR* – objective response rate; ORR** – overall response rate; OS – overall survival; PC – pancreatic cancer; PFS – progression free survival

results of clinical trials are limited. Olaparib remains the most studied drug.

The NCT01078662, phase II trial assessed the efficacy of olaparib in 298 patients with many solid tumours, including PC. 23 patients with PC were enrolled. 74% of them had the *BRCA2* mutation. The primary outcome measure was the tumour response rate. The main secondary outcome measure was the objective response rate, progression-free survival (PFS) and overall survival (OS). Eligible patients had a deleterious or suspected deleterious germline *BRCA* mutation. The tumour response rate in the PC was 21.7% (5–23; 95% CI: 7.5–43.7). Stable disease (≥8 weeks) was observed in 35% (95% CI: 16.4–57.3) of PC patients. The median PFS was 4.6 months. The mOS was 9.8 months. The most common adverse event involved fatigue, nausea and vomiting [63]. Olaparib is also studied in phase II trials in U.S and Israel (NCT02677038, NCT02511223) among 32 patients with metastatic PC and the BRCAness phenotype but without the germline *BRCA1/2* mutation, who received at least one prior therapy. The antitumour activity was seen only in platinum-sensitive patients. The median PFS varies between 14 weeks (range: 5.7–40 weeks) in the Israel part of the study and 24.7 weeks (range: 3.9–41.1 weeks) in the U.S. group [64].

The POLO, a randomized, placebo-controlled phase III trial (NCT02184195), evaluated the role of olaparib as a maintained treatment among 154 enrolled patients with metastatic PC and deleterious/suspected deleterious germline *BRCA1/2* mutation that had not progressed within 16 weeks during the first-line platinum-based chemotherapy (mainly folfirinox). The patients were divided into two groups, the first was given olaparib 300 mg twice a day (n = 92), the second received a placebo (n = 62). The primary endpoint measure was PFS. The main secondary endpoint measure was the OS, time from randomization to the second progression, safety and tolerability. Initially, it was published that olaparib treatment significantly prolonged PFS in comparison to the placebo (7.4 *vs.* 3.8 months; HR = 0.53, p = 0.0038). Recently, on the ASCO Gastrointestinal Cancers Symposium 2021, the newest result data were shown. The OS analysis shows that the OS for the olaparib group was 19 *vs.* 19.2 months for placebo, which failed to be statistically significant (HR: 0.83; p = 0.3487), however, 33.9% of patients who received PARPi survived 3 years *vs.* 17.8% in the placebo group. The most common (≥15%) adverse events in the olaparib group across all grades were nausea, fatigue and diarrhoea. Anemia was the most common AE grade 3 in the study group [14, 65].

The NCT03140670 phase II study is evaluating Rucaparib among patients with metastatic or locally advanced PC and germline, somatic *BRCA1/2*, or *PALB2* mutation. The primary outcome measure is the number of adverse events. The initial results showed that the median PFS was 9.1 months and the ORR of 36.8% [66].

Veliparib was studied, in phase II trials in patients with germline *BRCA1/2* or the *PALB2* mutation and stage III and IV PC. The enrolled patients were treated with 1–2 previous chemotherapy regimen. The response rate was not confirmed. The mPFS was 1.7 ms (95% CI: 1.57–1.83) and mOS was 3.1 ms [67].

The results of clinical studies with drugs other than olaparib are limited. The currently ongoing clinical trials try to determine the biomarkers, the role of genes other than *BRCA* mutated genes and proper sequention of treatment. Among them, one of the most interesting studies is the APOLLO trial (NCT04858334) a phase II, randomized trial that determines the RFS benefit from the maintenance of olaparib therapy following chemotherapy in patients with resected PC and a pathogenic germline or somatic *BRCA1/2, PALB2* mutation.

The LODESTAR, a phase II study (NCT04171700) is evaluating the rucaparib in patients with solid tumours and with deleterious mutations in HRR genes. Patients enrolled to the study had solid tumors with the *BRCA1/2, PALB2, RAD51C, RAD51D,*

BARD1, *BRIP1*, *FANC*, *NBN*, *RAD51*, or *RAD51B* mutation. The primary outcome measure is the best overall response rate. Niraparib is also being studied in a phase II trial (NCT03601923) among patients with the *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, or *ATM* mutation and advanced PC that is not curable with standard approaches. Talazoparib in monotherapy is studied in two clinical trials. The NCT04550494 trial is the II phase trial that evaluates the pharmacodynamic of PARPi in patients with advanced cancers and mutations in DDR genes. The NCT01286987 trials are a phase I study that evaluates the number of participants with objective response among patients with advanced or recurrent tumours.

PARPi are also being tested in polytherapy with other drugs. It has been hypothesized that combined therapy, especially with chemotherapy, may provide a synergistic therapeutic strategy for patients with PC. The rationale of this combination with a platinum is based on e.g. increased DNA damage by chemotherapy [68]. Initial results come from a phase I trial which assessed the combination of veliparib, gemcitabine and cisplatinin patients with *BRCA1/2* mutated and wild-type PC. The response rate within the *BRCA* mutated cohort was 77.8%. The mOS of patients with *BRCA1/2*-mutated PC and patients with wild-type PC was 23,3 months and 11 months respectively [69]. These promising results led to a phase II, randomized trial. Patients with *BRCA1/2* or *PALB2*-mutated PC were treated with gemcitabine and cisplatin chemotherapy with or without veliparib. The authors found non-significant benefit in the response rate between these two groups (74.1% in arm with veliparib *vs.* 65.2% in chemotherapy arm; p = 0.55) [70]. The trials did not show a survival benefit in mPFS (10.1 months for arm with veliparib (95% CI: 6.7–11.5 months) *vs*. 9.7 months for chemotherapy (95% CI: 4.2–13.6 months; p = 0.73). Median OS for veliparib and chemotherapy cohort was 15.5 months (95% CI: 12.2–24.3 months) *vs.* 16.4 months for chemotherapy (95% CI: 11.7–23.4 months; p = 0.6).

Currently, there are more clinical trials testing PARPi with chemotherapy mainly based on irinotecan-based chemotherapy regimens like (NCT03337087, NCT02890355, NCT00576654, NCT04228601) and cisplatin (NCT01585805). The PARPi are being tested with targeted therapy like cediranib (inhibitor of vascular endothelial growth factor receptor tyrosine kinases; NCT02498613), AZD6738 (ATR kinase inhibitor; NCT03682289), immunotherapy: pembrolizumab (anti-PD1 inhibitor; NCT04548752), dostarlimab (anti-PD1 inhibitor; NCT04493060, NCT04673448), nivolumab (anti-PD1 inhibitor; NCT03404960), ipilimumab (anti-CTLA4; NCT03404960). In addition, the new PARPi are being tested like AMXI-5001, an orally available dual PARP and microtubule polymerization inhibitor (NCT04503265), AZD5305 (NCT04644068) or NMS-03305293 (NCT04182516).

Conclusions

Pancreatic cancer remains one of the deadliest neoplasms with poor survival rates. There is a high need for new therapeutic regimens which improve the clinical outcomes of patients. In recent years, thanks to a deeper understanding of the molecular and genetic landscape of PC, PARPi has also emerged as a novel class of targeted therapy for patients with PC.

PARPi is a new class of drugs based on gene profiling that is currently being studied in PC. Many clinical trials are ongoing to determine the role of drugs in monotherapy and polytherapy. Despite that, the POLO trial did not show that olaparib increases the OS, yet many questions remain regarding the genetic status, role of other HRR genes in PC treatment and sequential treatment strategy. The new direction in PC treatment is signalling pathway inhibitors, immunotherapy agents, drugs targeting the metabolism of tumours and drugs targeting the tumour microenvironment, which could be studied as polytherapy with PARPi [71]. A better understanding of the action and responses at the molecular level of PC cells and the implementation of routine genetic testing in patients have the potential to reveal novel treatment opportunities and thus may broaden the treatment for patients with actionable aberrations [71]. NCCN recommends gene profiling for patients with locally advanced/metastatic PC. The testing should be performed to identify fusions (*ALK* [anaplastic lymphoma kinase], *NRG1* [neuregulin1], *NTRK* [neurotrophic receptor tyrosine kinase 1], *ROS1* [c-Ros Oncogene 1]), mutations (*BRAF, BRCA1/2, HER2* [human epidermal growth factor receptor 2], *KRAS, PALB2*), and MMR deficiency [72]. The recommended material for study is the tumour tissue or, if not available, the cell-free DNA. The preferred technique includes immunohistochemistry, polymerase chain reaction, or next-generation sequencing. Molecular tumour profiling is the future of personalized therapy in pancreatic cancer treatment, which may finally improve the survival rates of patients.

Conflict of interest: none declared

Dawid Sigorski
University of Warmia and Mazury in Olsztyn
Collegium Medicum
Department of Oncology
ul. M. Oczapowskiego 2
10-714 Olsztyn, Poland
e-mail: dawid.sigorski@uwm.edu.pl

Received: 18 Aug 2021
Accepted: 21 Dec 2021

References

1. Society. AC. Facts & Figures 2021. American Cancer Society.
2. Ducreux M, Cuhna ASa, Caramella C, et al. ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26 Suppl 5: v56–v68, doi: 10.1093/annonc/mdv295, indexed in Pubmed: 26314780.
3. Springfeld C, Jäger D, Büchler MW, et al. Chemotherapy for pancreatic cancer. Presse Med. 2019; 48(3 Pt 2): e159–e174, doi: 10.1016/j.lpm.2019.02.025, indexed in Pubmed: 30879894.
4. Piątek M, Nawrocki S. Locally advanced pancreatic cancer — new therapeutic challenges. Nowotwory. Journal of Oncology. 2016; 66(4): 312–316, doi: 10.5603/njo.2016.0059.

5. Aguilar-Quesada R, Muñoz-Gámez JA, Martín-Oliva D, et al. Modulation of transcription by PARP-1: consequences in carcinogenesis and inflammation. Curr Med Chem. 2007; 14(11): 1179–1187, doi: 10.2174/092986707780597998, indexed in Pubmed: 17504138.
6. Martínez-Bosch N, Fernández-Zapico ME, Navarro P, et al. Poly(ADP--Ribose) Polymerases: New Players in the Pathogenesis of Exocrine Pancreatic Diseases. Am J Pathol. 2016; 186(2): 234–241, doi: 10.1016/j.ajpath.2015.09.021, indexed in Pubmed: 26687988.
7. Sigorski D, Iżycka-Świeszewska E, Bodnar L. Poly(ADP-Ribose) Polymerase Inhibitors in Prostate Cancer: Molecular Mechanisms, and Preclinical and Clinical Data. Target Oncol. 2020; 15(6): 709–722, doi: 10.1007/s11523-020-00756-4, indexed in Pubmed: 33044685.
8. Pujade-Lauraine E, Ledermann J, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017; 18(9): 1274–1284, doi: 10.1016/s1470-2045(17)30469-2.
9. Coleman RL, Sill MW, Bell-McGuinn K, et al. A phase II evaluation of the potent, highly selective PARP inhibitor veliparib in the treatment of persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who carry a germline BRCA1 or BRCA2 mutation - An NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2015; 137(3): 386–391, doi: 10.1016/j.ygyno.2015.03.042, indexed in Pubmed: 25818403.
10. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018; 379(8): 753–763, doi: 10.1056/NEJMoa1802905, indexed in Pubmed: 30110579.
11. Mateo J, Porta N, Bianchini D, et al. Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): a multicentre, open-label, randomised, phase 2 trial. Lancet Oncol. 2020; 21(1): 162–174, doi: 10.1016/S1470-2045(19)30684-9, indexed in Pubmed: 31806540.
12. Doraczyńska-Kowalik A, Janus-Szymańska G, Matkowski R, et al. Genetyka i onkologia (część 2.). Podstawy medycyny personalizowanej w leczeniu raka piersi i raka jajnika. Nowotwory. Journal of Oncology. 2020; 70(5): 187–202, doi: 10.5603/njo.2020.0040.
13. Food and Drug Administration. FDA approves olaparib for gBRCAm metastatic pancreatic adenocarcinoma. 2020.
14. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline -Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019; 381(4): 317–327, doi: 10.1056/NEJMoa1903387, indexed in Pubmed: 31157963.
15. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674, doi: 10.1016/j.cell.2011.02.013, indexed in Pubmed: 21376230.
16. Goral V. Pancreatic Cancer: Pathogenesis and Diagnosis. Asian Pac J Cancer Prev. 2015; 16(14): 5619–5624, doi: 10.7314/apjcp.2015.16.14.5619, indexed in Pubmed: 26320426.
17. Hu C, Hart SN, Polley EC, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA. 2018; 319(23): 2401–2409, doi: 10.1001/jama.2018.6228, indexed in Pubmed: 29922827.
18. Bailey P, Chang DK, Nones K, et al. Australian Pancreatic Cancer Genome Initiative. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016; 531(7592): 47–52, doi: 10.1038/nature16965, indexed in Pubmed: 26909576.
19. Waddell N, Pajic M, Patch AM, et al. Australian Pancreatic Cancer Genome Initiative. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature. 2015; 518(7540): 495–501, doi: 10.1038/nature14169, indexed in Pubmed: 25719666.
20. Rondinelli B, Gogola E, Yücel H, et al. EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation. Nat Cell Biol. 2017; 19(11): 1371–1378, doi: 10.1038/ncb3626, indexed in Pubmed: 29035360.
21. Chaudhuri AR, Callen E, Ding X, et al. Replication fork stability confers chemoresistance in BRCA-deficient cells. Nature. 2016; 535(7612): 382–387, doi: 10.1038/nature18325.
22. Li X, Heyer WD. Homologous recombination in DNA repair and DNA damage tolerance. Cell Res. 2008; 18(1): 99–113, doi: 10.1038/cr.2008.1, indexed in Pubmed: 18166982.
23. Moynahan ME, Jasin M. Mitotic homologous recombination maintains genomic stability and suppresses tumorigenesis. Nat Rev Mol Cell Biol. 2010; 11(3): 196–207, doi: 10.1038/nrm2851, indexed in Pubmed: 20177395.
24. Lohse I, Kumareswaran R, Cao P, et al. Effects of Combined Treatment with Ionizing Radiation and the PARP Inhibitor Olaparib in BRCA Mutant and Wild Type Patient-Derived Pancreatic Cancer Xenografts. PLoS One. 2016; 11(12): e0167272, doi: 10.1371/journal.pone.0167272, indexed in Pubmed: 28033382.
25. Pilarski R. The Role of Testing in Hereditary Pancreatic and Prostate Cancer Families. Am Soc Clin Oncol Educ Book. 2019; 39: 79–86, doi: 10.1200/EDBK_238977, indexed in Pubmed: 31099688.
26. Yadav S, Kasi PM, Bamlet WR, et al. Effect of Germline Mutations in Homologous Recombination Repair Genes on Overall Survival of Patients with Pancreatic Adenocarcinoma. Clin Cancer Res. 2020; 26(24): 6505–6512, doi: 10.1158/1078-0432.CCR-20-1788, indexed in Pubmed: 33028596.
27. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer. 2014; 111(6): 1132–1138, doi: 10.1038/bjc.2014.418, indexed in Pubmed: 25072261.
28. Lowery MA, Jordan EJ, Basturk O, et al. Real-Time Genomic Profiling of Pancreatic Ductal Adenocarcinoma: Potential Actionability and Correlation with Clinical Phenotype. Clin Cancer Res. 2017; 23(20): 6094–6100, doi: 10.1158/1078-0432.CCR-17-0899, indexed in Pubmed: 28754816.
29. Southey MC, Goldgar DE, Winqvist R, et al. Australian Ovarian Cancer Study Group. PALB2, CHEK2 and ATM rare variants and cancer risk: data from COGS. J Med Genet. 2016; 53(12): 800–811, doi: 10.1136/jmedgenet-2016-103839, indexed in Pubmed: 27595995.
30. Sehdev A, Gbolahan O, Hancock BA, et al. Germline and Somatic DNA Damage Repair Gene Mutations and Overall Survival in Metastatic Pancreatic Adenocarcinoma Patients Treated with FOLFIRINOX. Clin Cancer Res. 2018; 24(24): 6204–6211, doi: 10.1158/1078-0432.CCR-18-1472, indexed in Pubmed: 30131383.
31. Lord C, Ashworth A. BRCAness revisited. Nature Reviews Cancer. 2016; 16(2): 110–120, doi: 10.1038/nrc.2015.21.
32. Holter S, Borgida A, Dodd A, et al. Germline BRCA Mutations in a Large Clinic-Based Cohort of Patients With Pancreatic Adenocarcinoma. J Clin Oncol. 2015; 33(28): 3124–3129, doi: 10.1200/JCO.2014.59.7401, indexed in Pubmed: 25940717.
33. Chaffee KG, Oberg AL, McWilliams RR, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. Genet Med. 2018; 20(1): 119–127, doi: 10.1038/gim.2017.85, indexed in Pubmed: 28726808.
34. Nanda N, Roberts NJ. Serine/Threonine Kinase and its Role in Pancreatic Risk. Genes (Basel). 2020; 11(1), doi: 10.3390/genes11010108, indexed in Pubmed: 31963441.
35. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov. 2012; 2(1): 41–46, doi: 10.1158/2159-8290.CD-11-0194, indexed in Pubmed: 22585167.
36. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology. 2015; 148(3): 556–564, doi: 10.1053/j.gastro.2014.11.042, indexed in Pubmed: 25479140.
37. Mandelker D, Zhang L, Kemel Y, et al. Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing. JAMA. 2017; 318(9): 825–835, doi: 10.1001/jama.2017.11137, indexed in Pubmed: 28873162.
38. Ayars M, Eshleman J, Goggins M. Susceptibility of ATM-deficient pancreatic cancer cells to radiation. Cell Cycle. 2017; 16(10): 991–998, doi: 10.1080/15384101.2017.1312236, indexed in Pubmed: 28453388.
39. Wang Y, Kuramitsu Y, Tokuda K, et al. Gemcitabine induces poly (ADP--ribose) polymerase-1 (PARP-1) degradation through autophagy in pancreatic cancer. PLoS One. 2014; 9(10): e109076, doi: 10.1371/journal.pone.0109076, indexed in Pubmed: 25271986.
40. Perkhofer L, Schmitt A, Romero Carrasco MC, et al. ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage. Cancer Res. 2017; 77(20): 5576–5590, doi: 10.1158/0008-5472.CAN-17-0634, indexed in Pubmed: 28790064.
41. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017; 355(6330): 1152–1158, doi: 10.1126/science.aam7344, indexed in Pubmed: 28302823.
42. McCabe N, Turner NC, Lord CJ, et al. Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP--ribose) polymerase inhibition. Cancer Res. 2006; 66(16): 8109–8115, doi: 10.1158/0008-5472.CAN-06-0140, indexed in Pubmed: 16912188.
43. Marteijn JA, Lans H, Vermeulen W, et al. Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol. 2014; 15(7): 465–481, doi: 10.1038/nrm3822, indexed in Pubmed: 24954209.

44. Li GM. DNA Mismatch Repair and the DNA Damage Response. Encyclopedia of Biological Chemistry. 2013: 51–53, doi: 10.1016/b978-0-12-378630-2.00238-3.
45. Wong W, Raufi AG, Safyan RA, et al. BRCA Mutations in Pancreas Cancer: Spectrum, Current Management, Challenges and Future Prospects. Cancer Manag Res. 2020; 12: 2731–2742, doi: 10.2147/CMAR.S211151, indexed in Pubmed: 32368150.
46. Plummer R. Perspective on the pipeline of drugs being developed with modulation of DNA damage as a target. Clin Cancer Res. 2010; 16(18): 4527–4531, doi: 10.1158/1078-0432.CCR-10-0984, indexed in Pubmed: 20823148.
47. Lee MV, Katabathina VS, Bowerson ML, et al. BRCA-associated Cancers: Role of Imaging in Screening, Diagnosis, and Management. Radiographics. 2017; 37(4): 1005–1023, doi: 10.1148/rg.2017160144, indexed in Pubmed: 28548905.
48. Peralta-Leal A, Rodríguez MI, Oliver FJ. Poly(ADP-ribose)polymerase-1 (PARP-1) in carcinogenesis: potential role of PARP inhibitors in cancer treatment. Clin Transl Oncol. 2008; 10(6): 318–323, doi: 10.1007/s12094-008-0207-8, indexed in Pubmed: 18558578.
49. Virág L. Structure and function of poly(ADP-ribose) polymerase-1: role in oxidative stress-related pathologies. Curr Vasc Pharmacol. 2005; 3(3): 209–214, doi: 10.2174/1570161054368625, indexed in Pubmed: 16026317.
50. Otto H, Reche PA, Bazan F, et al. In silico characterization of the family of PARP-like poly(ADP-ribosyl)transferases (pARTs). BMC Genomics. 2005; 6: 139, doi: 10.1186/1471-2164-6-139, indexed in Pubmed: 16202152.
51. de Murcia JM, Niedergang C, Trucco C, et al. Requirement of poly(ADP--ribose) polymerase in recovery from DNA damage in mice and in cells. Proc Natl Acad Sci U S A. 1997; 94(14): 7303–7307, doi: 10.1073/pnas.94.14.7303, indexed in Pubmed: 9207086.
52. Martínez-Bosch N, Iglesias M, Munné-Collado J, et al. Parp-1 genetic ablation in Ela-myc mice unveils novel roles for Parp-1 in pancreatic cancer. J Pathol. 2014; 234(2): 214–227, doi: 10.1002/path.4384, indexed in Pubmed: 24889936.
53. Hou Z, Cui Y, Xing H, et al. Down-expression of poly(ADP-ribose) polymerase in p53-regulated pancreatic cancer cells. Oncol Lett. 2018; 15(2): 1943–1948, doi: 10.3892/ol.2017.7500, indexed in Pubmed: 29434894.
54. Wang M, Wu W, Wu W, et al. PARP-1 and Ku compete for repair of DNA double strand breaks by distinct NHEJ pathways. Nucleic Acids Res. 2006; 34(21): 6170–6182, doi: 10.1093/nar/gkl840, indexed in Pubmed: 17088286.
55. Pilié PG, Tang C, Mills GB, et al. State-of-the-art strategies for targeting the DNA damage response in cancer. Nat Rev Clin Oncol. 2019; 16(2): 81–104, doi: 10.1038/s41571-018-0114-z, indexed in Pubmed: 30356138.
56. Dedes KJ, Wilkerson PM, Wetterskog D, et al. Synthetic lethality of PARP inhibition in cancers lacking BRCA1 and BRCA2 mutations. Cell Cycle. 2011; 10(8): 1192–1199, doi: 10.4161/cc.10.8.15273, indexed in Pubmed: 21487248.
57. Xu F, Sun Y, Yang SZ, et al. Cytoplasmic PARP-1 promotes pancreatic cancer tumorigenesis and resistance. Int J Cancer. 2019; 145(2): 474–483, doi: 10.1002/ijc.32108, indexed in Pubmed: 30614530.
58. Toma M, Skorski T, Śliwiński T. Synthetic lethality as a functional tool in basic research and in anticancer therapy. Postepy Hig Med Dosw. 2014; 68: 1091–1103, doi: 10.5604/17322693.1119792.
59. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2--deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005; 434(7035): 913–917, doi: 10.1038/nature03443, indexed in Pubmed: 15829966.
60. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005; 434(7035): 917–921, doi: 10.1038/nature03445, indexed in Pubmed: 15829967.
61. Klauschen F, von Winterfeld M, Stenzinger A, et al. High nuclear poly-(ADP-ribose)-polymerase expression is prognostic of improved survival in pancreatic cancer. Histopathology. 2012; 61(3): 409–416, doi: 10.1111/j.1365-2559.2012.04225.x, indexed in Pubmed: 22384823.
62. Gonçalves A, Finetti P, Sabatier R, et al. Poly(ADP-ribose) polymerase-1 mRNA expression in human breast cancer: a meta-analysis. Breast Cancer Res Treat. 2011; 127(1): 273–281, doi: 10.1007/s10549-010-1199-y, indexed in Pubmed: 21069454.
63. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015; 33(3): 244–250, doi: 10.1200/JCO.2014.56.2728, indexed in Pubmed: 25366685.
64. Golan T, Varadhachary G, Sela T, et al. Phase II study of olaparib for BRCA-ness phenotype in pancreatic cancer. J Clin Oncol. 2018; 36(4_suppl): 297–297, doi: 10.1200/jco.2018.36.4_suppl.297.
65. Golan T, Hammel P, Reni M, et al. Overall survival from the phase 3 POLO trial: Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. J Clin Oncol. 2021; 39(3_suppl): 378–378, doi: 10.1200/jco.2021.39.3_suppl.378.
66. Reiss KA, Mick R, O'Hara MH, et al. Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in , , or . J Clin Oncol. 2021; 39(22): 2497–2505, doi: 10.1200/JCO.21.00003, indexed in Pubmed: 33970687.
67. Lowery MA, Kelsen DP, Capanu M, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. Eur J Cancer. 2018; 89: 19–26, doi: 10.1016/j.ejca.2017.11.004, indexed in Pubmed: 29223478.
68. Matulonis UA, Monk BJ. PARP inhibitor and chemotherapy combination trials for the treatment of advanced malignancies: does a development pathway forward exist? Ann Oncol. 2017; 28(3): 443–447, doi: 10.1093/annonc/mdw697, indexed in Pubmed: 28057663.
69. O'Reilly EM, Lee JW, Lowery MA, et al. Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. Cancer. 2018; 124(7): 1374–1382, doi: 10.1002/cncr.31218, indexed in Pubmed: 29338080.
70. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, Multicenter, Phase II Trial of Gemcitabine and Cisplatin With or Without Veliparib in Patients With Pancreas Adenocarcinoma and a Germline Mutation. J Clin Oncol. 2020; 38(13): 1378–1388, doi: 10.1200/JCO.19.02931, indexed in Pubmed: 31976786.
71. Nevala-Plagemann C, Hidalgo M, Garrido-Laguna I. From state-of--the-art treatments to novel therapies for advanced-stage pancreatic cancer. Nat Rev Clin Oncol. 2020; 17(2): 108–123, doi: 10.1038/s41571-019-0281-6, indexed in Pubmed: 31705130.
72. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic Adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2021; 19(4): 439–457, doi: 10.6004/jnccn.2021.0017, indexed in Pubmed: 33845462.
73. Takeuchi S, Doi M, Ikari N, et al. Mutations in BRCA1, BRCA2, and PALB2, and a panel of 50 cancer-associated genes in pancreatic ductal adenocarcinoma. Sci Rep. 2018; 8(1): 8105, doi: 10.1038/s41598-018-26526-x, indexed in Pubmed: 29802286.

VIA MEDICA

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 44–50

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Wytyczne i rekomendacje /
Guidelines and recommendations

Consensus on methods of development of clinical practice guidelines in oncology under the auspices of Maria Sklodowska-Curie National Research Institute of Oncology and the Agency for Health Technology Assessment and Tariff System

Jan Walewski[1*], Dominik Dziurda[2*], Mariusz Bidziński[3], Barbara Bobek-Bilewicz[4], Marek Dedecjus[5], Iwona Hus[6], Beata Jagielska[7], Jacek Jassem[8], Andrzej Kawecki[9], Dariusz Kowalski[10], Magdalena Krasztel[2], Maciej Krzakowski[11], Tomasz Kubiatowski[12], Piotr Potemski[13, 14], Radosław Mądry[15], Piotr Rutkowski[16], Anna Rychert[2], Janusz Ryś[17], Krzysztof Składowski[18], Rafał Tarnawski[4], Hanna Tchórzewska-Korba[19], Andrzej Tysarowski[20], Piotr J. Wysocki[21], Roman Topór-Mądry[2]

[1]Department of Lymphoid Malignancies, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]The Agency for Health Technology Assessment and Tariff System (AOTMiT), Warsaw, Poland
[3]Department of Gynecologic Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[4]Department of Radiology and Imaging Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland
[5]Department of Oncological Endocrinology and Nuclear Medicine, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[6]Institute of Hematology and Transfusion Medicine, Warsaw, Poland
[7]Grochowski Hospital, Warsaw, Poland
[8]Department and Clinic of Oncology and Radiotherapy, Medical University, Gdańsk, Poland
[9]Department of Head and Neck Cancer, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[10]Department of Oncological Radiotherapy and Clinical Oncology, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[11]Department of Lung Cancer and Chest Tumors, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[12] Department of Oncology and Immunooncology, Warmian-Masurian Cancer Center of the Ministry of the Interior and Administration's Hospital, Olsztyn, Poland
[13]Chemotherapy Clinic, Oncology Department, Medical University, Lodz, Poland
[14]Nicolaus Copernicus Multidisciplinary Centre of Oncology and Traumatology, Lodz, Poland
[15]Department of Gynecological Oncology, Poznan University of Medical Sciences, Poznan, Poland
[16]Department of Soft Tissue-Bone Sarcoma and Melanoma, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[17]Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland
[18]Department of Radiology and Imaging Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland
[19]Department of Rehabilitation, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[20]Independent Laboratory of Genetic and Molecular Diagnostics of Cancer, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[21]Department and Clinic of Oncology, Jagiellonian University Medical College, Krakow, Poland
***** *Equal contribution*

Jak cytować / How to cite:

Walewski J, Dziurda D, Bidziński M, Bobek-Bilewicz B, Dedecjus M, Hus I, Jagielska B, Jassem J, Kawecki A, Kowalski D, Krasztel M, Krzakowski M, Kubiatowski T, Potemski P, Mądry R, Rutkowski P, Rychert A, Ryś J, Składowski K, Tarnawski R, Tchórzewska-Korba H, Tysarowski A, Wysocki PJ, Topór-Mądry R. ***Consensus on methods of development of clinical practice guidelines in oncology under the auspices of Maria Sklodowska-Curie National Research Institute of Oncology and the Agency for Health Technology Assessment and Tariff System.*** *NOWOTWORY J Oncol* 2022; 72: 44–50.

Introduction. As the changes leading to improvement of cancer care in Poland have shown the need to introduce clinical practice guidelines into the health care system, it has become clear that no methodological standard of the process for guidelines preparation has been established so far. The following process aims to present a unified and comprehensive clinical practice guidelines (CPGs) development methodology.

Materials and methods. A review of globally recognised methods used by guideline development groups was prepared, informing the discussion during three plenary meetings and extensive consultations in writing. The resulting document was unanimously approved by a group of 24 methodologists and clinical experts, and has been formally recognized as a standard for CPGs development by the management of the National Institute of Oncology and the Agency for Health Technology Assessment and Tariff System.

Results. Within the process, 43 recommendations were formulated to create unified and comprehensive rules for guideline development within the Polish healthcare system.

Conclusions. The presented methods are consistent with the globally recognized tools and methods of guideline development, such as GRADE and ADAPTE, and follow quality criteria described by AGREE II. The process supports the development of high-quality guidelines within a resource-constrained setting by allowing to choose between adoption, adaptation, or *de novo* development of either the whole document of guidelines or particular recommendations.

Key words: practice guidelines, oncology, guidelines development, consensus

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide, with an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths in 2020 [1]. In Europe, the total economic toll from cancer was €199 billion in 2018 [2]. Thus, it is crucial to provide sufficient expert guidance and resources to address this burden, especially in resource-constrained settings. Worldwide, attempts have been made to help improve access to cancer control, inter alia, by developing clinical practice guidelines (CPGs).

In modern medicine, CPGs play a decisive role in both facilitating the decisions made in specific clinical situations, and influencing the effectiveness and quality of diagnosis and therapy. They constitute a synthesis of the most current, well-founded research that is aimed at identifying the most efficient and safest modes of operating in clinical situations. The CPGs are usually developed by scientific societies, non-governmental organizations as well as governmental institutions.

High-quality guidelines should be based on a transparent process of development and assessment of recommendations, as well as hold the logical connection between alternative therapeutic options and health results, and an appraisal of quality of evidence and strength of recommendations [3, 4]. Thus ensuring the process is systematized, consistent with specific quality criteria, and based on a systematic review of scientific literature, as well as on an assessment of quality and selection of evidence as a basis for the development of recommendations [5].

At the same time, the multitude of organisations that are engaged in guideline production in Poland make it difficult to compare the quality and rigour of CPGs development, as so far no methodological standard of the process has been established. Taking that into consideration and the necessity to introduce a system of quality management into Polish healthcare, the need arose to create a unified and comprehensive guideline development methodology.

Materials and methods

The process was initiated to support the Maria Sklodowska-Curie National Research Institute of Oncology (MSCI) in its statutory activities regarding developing oncology guidelines. It aims to propose the recommended pathway for CPGs development and their effective incorporation into the Polish healthcare system. The process itself is based on the expertise of the clinicians experienced in CPG development, and a review prepared by the Agency for Health Technology Assessment and Tariff System (AOTMiT).

In light of this and in order to propose the best methods, a review of the key solutions for guideline development was prepared by the AOTMiT [6]. The analysis allowed to indicate key areas in the guideline development process, as well as the methods most frequently used by guideline development groups. This served as a basis for further discussion which comprised three on-line meetings and several series of consultations via e-mail. During the meetings, methods for addressing key areas of CPGs development were discussed – both those employed globally by societies producing oncology guidelines, and those recommended by recognized methodological tools and documents (i.e. GRADE, ADAPTE). These allowed the experts to choose – in a series of unanimous votes – solutions in each area best suited to the target conditions.

These decisions allowed for a formulation of the following methodology, which will serve as the basis for the future development of clinical practice guidelines by the National Institute of Oncology. The results of this process were unanimously approved by experts and were formally recognized as a standard by the management of both the National Institute of Oncology and the Agency for Health Technology Assessment and Tariff

System. The presented methods of guideline development respect the principles of evidence-based medicine for guideline development and take into consideration the available resources and organisational context to ensure relevance for local practice. It is designed to transparently communicate the means and solutions used to produce clinical practice guidelines, their adoptions or adaptations. Topic selection within the process is based on health priorities indicated by the Polish Ministry of Health, scientific societies or other institutions depending on the circumstances.

Methods of guideline development

Topic selection

The objective of the guideline should be described in detail including:

- clinical state or health problem,
- population,
- intent (i.e., prevention, screening, diagnosis, treatment, etc.),
- expected benefit or outcome,
- target users.

Guideline development group

Guidelines are developed by an expert group.

- The group is led by a chair appointed by the institution initiating the guideline development process.
- The expert group consists of clinical experts representing fields of medicine relevant to the topic of the guidelines. The chair is responsible for ensuring that all relevant medical specialisations and professions are included.
- The expert group identifies all appropriate stakeholders. If justified, the stakeholders, especially patient representatives, are invited to participate in the work.
- If necessary, EBM analysts are to participate in the process.
- The chair or a designated editor is responsible for editing the document.
- Developed recommendations are subject to approval by the expert group proceeding in full composition of guidelines.
- For each member of the guideline development group, the following information has to be published:
  - discipline/content expertise,
  - institutional affiliation(s),
  - role in the development process, especially the tasks described below.

Conflict of interest

- Conflicting interests are defined as financial or personal involvement, relationship, affiliation or any other activity that could potentially influence the wording of the guidelines. Group members are obliged to disclose all relationships that may constitute a factual or potential conflict of interest.
- Declaration of Interest is to be submitted to the chair using the form provided in the attachment to this document.
- Each group member is obliged to inform other members of any potential or factual conflict of interests that has a bearing upon the developed recommendation.
- The group member suggests how to manage the conflict of interest described above. The possible actions include exclusion from the discussion, exclusion from the consensus or voting or no restrictions at all. The proposed method is submitted for acceptance from other members.
- In case of a substantial conflict of interest, the member is excluded from the process of recommendation development. A substantial conflict of interest is defined as relationships that amount to 20,000 USD (based on NCCN standards) per year in value, not including participation in clinical trials as a research assistant/investigator.
- Information disclosed in the DOI current for the date of finalizing the development process is published as a part of the guidelines and should include the area and institution of conflict.

Criteria for authorship recognition

- The authorship should be ascribed only to persons who fulfil all of the following criteria:
  - substantial contribution in collection, analysis and interpretation of data serving as the basis for the formulation of recommendations;
  - participation in formulation of recommendations or their critical review;
  - final acceptance of the document.

Methods of guideline development

- Guidelines are developed through adoption, adaptation, *de novo* development or a combination of these methods.
- Choice of the method depends on: guideline topic, availability of current high quality guidelines and available resources.
- The choice of the method is made by the expert group.
- The key health question(s) serving as the basis for the recommendations should be specific, preferably in PICO format.
- If either the whole guideline or particular recommendations are developed *de novo*, the relevant body of evidence should be gathered in a systematic review of literature.
- In case of adoption or adaptation of the whole guideline or particular recommendations, the process should be held in compliance with ADAPTE [7] or GRADE-ADOLOPMENT [8] tools, or the methods designated by the authors of the source document.

Formulating and accepting recommendations

- Recommendations are formulated based on the available evidence, taking into account health benefits, side effects and the risk of the intervention.

- The strengths and limitations of the body of evidence should be clearly described in the context of the recommendation it refers to.
- The process aims to achieve unanimous acceptance of the wording of the recommendations.
- If available evidence is limited, inconsistent, of low quality, does not directly concern the target population, or in other justified situations, the recommendation is formulated through formal consensus.
- The modified Delphi method is the preferred consensus technique, involving the following steps:
  - systematic review of evidence for the given health problem,
  - formulation of draft recommendation,
  - collection and summary of group members' appraisal and opinions,
  - a meeting to discuss the results and establish the final wording of the recommendation and level of consensus.
- High level of consensus is considered to have been reached at 85% agreement, and a moderate level of at least 50% (but less than 85%) agreement. Agreement lower than 50% is recognised as a lack of consensus and the recommendation is not to be published.

Quality of evidence and strength of recommendation

- The quality of evidence describes the quality of the overall evidence gathered on the clinical profile of the intervention in relation to the PICO question serving as the basis of the recommendation. It defines the level of certainty that the available scientific evidence reflects the true dimensions and direction of effects.
- The quality of evidence is ascribed to every recommendation in accordance with the grading system presented in table I.
- The strength of recommendation defines the degree of conviction that the content of the recommendation should be considered in clinical practice taken into account the conditions of the target healthcare system. The strength of recommendations is a derivative of i.a. quality of evidence, absolute and relative strength of intervention and the level of consensus with regard to implementation in clinical practice.
- The strength of recommendation is ascribed to every recommendation in accordance with the grading system presented in table II.

Presentation of recommendations

- In order to ensure their unambiguous interpretation, each recommendation should provide a clear and precise description of the population group, clinical description, intervention being recommended, alternative approach(es), and context for which they are intended.

Table I. Quality of evidence

Quality of evidence	
I	evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses well-constructed randomised trials without significant heterogeneity
II	small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or trials with demonstrated significant heterogeneity
III	prospective cohort studies
IV	retrospective cohort studies or case-control studies
V	studies without a control group, case reports, expert opinions

Source: The ESMO Guidelines Committee. (2021). *Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores* [9]

Table II. Strength of recommendation

Strength of recommendation	
1	recommendation based on high-quality evidence and a uniform or high-level consensus among the expert group
2A	recommendation based on lower-level evidence and a uniform or high-level consensus among the expert group
2B	recommendation based on lower-level evidence and a moderate-level consensus among the expert group
3[1]	recommendation based on any level of evidence to which the expert group could not reach consensus

[1] Category 3 was introduced to ensure compliance with NCCN guidelines and should be used only in case of NCCN guidelines adoption/adaptation

Source: Own compilation based on The National Comprehensive Cancer Network [10]

- The recommendations should use standardized wording to maintain consistency throughout the guideline.
- Remarks that describe the context, feasibility and applicability of the recommendation should hold an explicit link to the recommendation it refers to.
- Recommendations are presented in a clear form that is easy to follow. For example, they can be numbered, gathered in thematic sections or a summary section, or, optionally, presented as flow charts (preferably using BPMN2).

Review and quality assessment

- The final draft of guidelines is to be reviewed by all stakeholders mentioned in point: the expert group identifies all appropriate stakeholders. If justified, the stakeholders, especially patient representatives, are invited to participate in the works.
- Quality assessment of guidelines is held using the AGREE II (Appraisal of Guidelines for Research and Evaluation) [4].
- Guidelines should undergo an external peer review by at least two independent reviewers. If the document is to be published in a peer-reviewed journal, this review can substitute for the external peer review.

- The results of reviews and quality assessment are discussed by the guideline development group. The authors should examine every point and indicate any changes in the document that arise from the process, or if no changes are made, they justify the decision.

Updating the guidelines

- The expert group is responsible for constant monitoring whether the guideline needs to be updated.
- If justified, particular recommendations are updated, especially when new significant evidence is available, changes in the health care context take place, or a justified motion from the stakeholders is submitted.
- Formal assessment of guideline validity is held every two years.

Glossary of key terms

- **The quality of evidence for a single study** refers to the impact of methodological structure of a clinical trial upon uncertainty of estimation of intervention results for a specific endpoint in a specific population in a single study [11].
- **The quality of evidence** describes the quality of the overall evidence gathered on the clinical profile of the intervention in relation to the defined endpoint. It defines the level of certainty that the available scientific evidence reflects the true dimensions and direction of effects in the context of the conditions of the target healthcare system. It is also referred to as strength of evidence, trust in estimations, certainty of evidence, or level of evidence, as well as level of strength of evidence [11].
- **The strength of intervention** refers to the effectiveness of the intervention; it illustrates the magnitude of achievable effect of the new intervention in comparison to other available options in the population subject to the recommendation [11].
- **The strength of recommendation** defines the degree of conviction that the content of the recommendation should be considered in clinical practice taking into account the conditions of the target healthcare system. It is a derivative of quality of evidence, absolute and relative strength of intervention and the degree of consensus [11].

Discussion

The approach established within the process allows the development of high-quality guidelines considering the available resources and target healthcare settings, by allowing to choose between adoption, adaptation, as well as *de novo* development of either the whole guidelines document or particular recommendations.

The suggested process has a number of strengths:

1. It is consistent with recognized tools and methods of guideline development.
2. It is flexible in allowing for the use of different guideline development frameworks depending on the subject and available resources. Thus, existing evidence syntheses can be used, if available, avoiding the necessity of conducting full systematic reviews. At the same time, it helps to identify gaps in knowledge, which might necessitate a systematic review.
3. It allows to build locally contextualized recommendations by involving local experts and stakeholders to ensure that the recommendations address local needs and health care system structure.

While developing the presented approach, the authors sought to ensure that the methods comply with international standards as far as possible within the resources. While there are a number of published standards for guideline development methodology, AGREE II [4] is the most recognized and evidence-based of these [12]. Although the presented Guideline Methodology aims to be consistent with AGREE II, it needs to be noted that not all AGREE II items lie within the scope of NIO's statutory activities; that said, these items (or the reasons for not providing the appropriate data) should still be addressed in the clinical practice guidelines developed within the process (tab. III).

Conclusions

The presented Methods of Guideline Development were produced in an attempt to introduce a unified and transparent set of methods of guideline development across each branch of medicine (at least) and, hence, to tackle the uncertainties that arise with regard to the diversity of published standards for guideline development methodology. The suggested approach allows to develop high-quality guidelines within a resource-constrained setting, by allowing to choose between adoption, adaptation, or *de novo* development of either the whole document of guidelines or particular recommendations. At the same time, it is consistent with the recognized tools and methods of guideline development, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) [13] and ADAPTE [7], and follows key quality criteria described by GIN-McMaster [14] and AGREE II [4].

Conflict of interest: none declared

Piotr Rutkowski
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Soft Tissue-Bone Sarcoma and Melanoma
ul. Roentgena 5
02-093 Warszawa, Poland
e-mail: piotr.rutkowski@pib-nio.pl

Received: 21 Oct 2021
Accepted: 26 Oct 2021

Table III. The sections in presented guideline methodology that address AGREE II items

AGREE II items		NIO guideline methodology
Scope and purpose		
1	the overall objective(s) of the guideline is (are) specifically described	1. topic selection
2	the health question(s) covered by the guideline is (are) specifically described	4. methods of guideline development
3	the population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	1. topic selection
Stakeholder involvement		
4	the guideline development group includes individuals from all relevant professional groups	1. guideline development group
5	the views and preferences of the target population (patients, public, etc.) have been sought	1. guideline development group 8. review and quality assessment
6	the target users of the guideline are clearly defined	1. topic selection
Rigour of development		
7	systematic methods were used to search for evidence	4. methods of guideline development
8	the criteria for selecting the evidence are clearly described	4. methods of guideline development
9	the strengths and limitations of the body of evidence are clearly described	5. formulating and accepting recommendations
10	the methods for formulating the recommendations are clearly described	5. formulating and accepting recommendations
11	the health benefits, side effects and risks have been considered in formulating the recommendations	5. formulating and accepting recommendations
12	there is an explicit link between the recommendations and the supporting evidence	5. formulating and accepting recommendations
13	the guideline has been externally reviewed by experts prior to its publication	8. review and quality assessment
14	a procedure for updating the guideline is provided	9. updating the guidelines
Clarity of presentation		
15	the recommendations are specific and unambiguous	7. presentation of recommendations
16	the different options for management of the condition or health issue are clearly presented	7. presentation of recommendations
17	key recommendations are easily identifiable	7. presentation of recommendations
Applicability		
18	the guideline describes facilitators and barriers to its application	5. formulating and accepting recommendations
19	the guideline provides advice and/or tools on how the recommendations can be put into practice	not applicable
20	the potential resource implications of applying the recommendations have been considered	5. formulating and accepting recommendations
21	the guideline presents monitoring and/or auditing criteria	not applicable
Editorial independence		
22	the views of the funding body have not influenced the content of the guideline	not applicable
23	competing interests of guideline development group members have been recorded and addressed	2. conflict of interest

Note: Wherever "not applicable" is used, it is understood as not within the scope of NIO's statutory activities. Particular tasks associated with these quality items are held by other institutions within the Polish healthcare system

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021; 71(3): 209–249, doi: 10.3322/caac.21660, indexed in Pubmed: 33538338.
2. Hofmarcher T, Lindgren P, Wilking N, et al. The cost of cancer in Europe 2018. Eur J Cancer. 2020; 129: 41–49, doi: 10.1016/j.ejca.2020.01.011, indexed in Pubmed: 32120274.
3. Graham R. Institute of Medicine (U.S.), Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. National Academies Press, Washington 2011: xxxiv, 266.
4. Brouwers MC, Kho ME, Browman GP, et al. AGREE Next Steps Consortium. The Global Rating Scale complements the AGREE II in advancing the quality of practice guidelines. J Clin Epidemiol. 2012; 65(5): 526–534, doi: 10.1016/j.jclinepi.2011.10.008, indexed in Pubmed: 22189163.

5. Leśniak W, Bała M, Jaeschke R, et al. Od danych naukowych do praktycznych zaleceń – tworzenie wytycznych według metodologii GRADE. Polish Archives of Internal Medicine. 2015; 125(Special Issue): 26–41, doi: 10.20452/pamw.3232.
6. Agencja Oceny Technologii Medycznych i Taryfikacji. Metodyka opracowywania wytycznych praktyki klinicznej w onkologii. Opracowanie przygotowane w ramach projektu „Wsparcie procesu poprawy jakości w leczeniu onkologicznym oraz zmiana organizacji systemu opieki zdrowotnej w zakresie onkologii. Material not published 2020.
7. The ADAPTE Collaboration. The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.02009.
8. Schünemann HJ, Wiercioch W, Brozek J, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017; 81: 101–110, doi: 10.1016/j.jclinepi.2016.09.009, indexed in Pubmed: 27713072.
9. European Society for Medical Oncology. Standard Operating Procedures (SOPs) for Authors and templates for ESMO Clinical Practice Guidelines (CPGs) and ESMO-MCBS Scores 2021. https://www.esmo.org/content/download/77789/1426712/file/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf.
10. The National Comprehensive Cancer Network. About the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 2020. https://www.nccn.org/professionals/default.aspx.
11. Rychert A, Dziurda D, Koperny M, et al. Systems for grading the strength of recommendations in clinical practice guidelines in oncology. Material not published.
12. Yao X, Ma J, Wang Qi, et al. A Comparison of AGREE and RIGHT: which Clinical Practice Guideline Reporting Checklist Should Be Followed by Guideline Developers? J Gen Intern Med. 2020; 35(3): 894–898, doi: 10.1007/s11606-019-05508-3, indexed in Pubmed: 31713037.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008; 336(7650): 924–926, doi: 10.1136/bmj.39489.470347.AD, indexed in Pubmed: 18436948.
14. Schünemann HJ, Wiercioch W, Etxeandia I, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. CMAJ. 2014; 186(3): E123–E142, doi: 10.1503/cmaj.131237, indexed in Pubmed: 24344144.

VIA MEDICA

Obrazy w onkologii / Pictures in oncology

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 51

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Melanoma metastases to the intestines – presentation and management

Michał Aporowicz[1], Adam Maciejczyk[1, 2], Rafał Matkowski[1, 2], Marcin Ziętek[1, 2]

[1]*Wroclaw Medical University, Wroclaw, Poland*
[2]*Wroclaw Comprehensive Cancer Centre, Wroclaw, Poland*

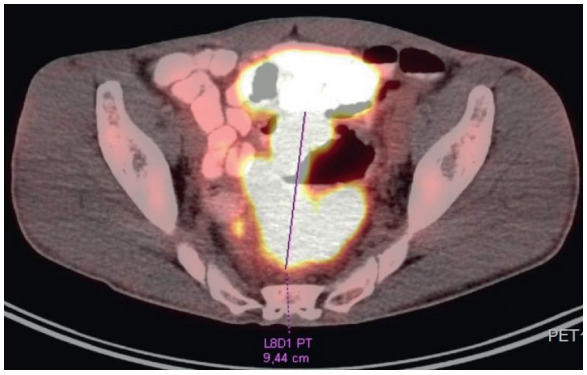

Figure 1. A 49-year-old male with melanoma (pT1N0M1c); a PET scan, a transverse view – a rectosigmoid tumor involving the rectovesical space, 94 × 71 × 67 mm (AP × TR × CC), standardized uptake value (SUV): 11.1

A 49-year-old male, in follow-up due to melanoma on the back (Clark III, Breslow 0.8 mm – pT1N0), 4.5 years after a re-excision with a sentinel lymph node biopsy, presented with a cramping, epigastric pain, nausea, vomiting, and 10 kg weight loss. A PET scan revealed a mass in pelvis (fig. 1). The patient underwent sigmoidectomy and resection of infiltrated loops of the small bowel with adjacent mesentery, followed by a stapled side-to-side ileo-ileal and end-to-end colorectal anastomosis. The pathological report confirmed a metastatic melanoma of the small intestine, infiltrating the sigmoid colon and involving mesenteric lymph nodes (8/20; 0/20 mesorectal LN); *BRAF*(+). The patient received BRAF/MEK inhibitors and anti-PD-L1 immunotherapy (vemurafemib+cobimetinib±atezolizumab). Patient has no sign of disease (9 years after first diagnosis, 4 years after laparotomy). Melanoma may metastasize to the lymph nodes, skin, lungs and pleura, brain, liver, bones, adrenal glands, and gastrointestinal tract. Metastases to the small bowel are rare (1–5%), yet melanoma is the malignancy that most frequently metastasizes to the small intestine (1/3 of all cases). Patients with a newly diagnosed locally advanced melanoma (T4) should undergo an abdominal/pelvic CT to exclude metastases. Melanoma patients who experience abdominal pain and/or distension, nausea/vomiting, hematochezia/melena should be reevaluated with CT/MRI/PET. Patients with isolated bowel metastases or presenting with bowel obstruction, severe bleeding, perforation should be reffered to surgery with metastasectomy (including regional lymph nodes). Adjuvant systemic therapy is advised, with a regimen depending on a *BRAF* gene mutation. Despite intestinal metastases, a prolonged survival is possible with appropriate management [1, 2].

This research was financed through statutory subsidies by the Minister of Science and Higher Education as part of the Wrocław Medical University Department of Oncology research grant: SUB. C280.21.023 (record number in the Simple System).

References

1. Wiśniewski P, Szumera-Ciećkiewicz A, Nasierowska-Guttmejer A. New pathomorphological classification of melanomas. Nowotwory. Journal of Oncology. 2019; 69(3-4): 103–107, doi: 10.5603/njo.2019.0020.
2. Rutkowski P, Wysocki PJ, Nasierowska-Guttmejer A, et al. Cutaneous melanomas. Oncol Clin Pract. 2019; 15(1): 1–19, doi: 10.5603/OCP.2018.0055.

Jak cytować / How to cite:
Aporowicz M, Maciejczyk A, Matkowski R, Ziętek M. ***Melanoma metastases to the intestines – presentation and management.*** *NOWOTWORY J Oncol* 2022; 72: 51.

VIA MEDICA

Onkogeriatria / Oncogeriatrics

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 52–57

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Hepatocellular cancer and colorectal liver metastasis treatment in the older population

Jakub Kenig

Department of General, Gastrointestinal, Oncologic Surgery and Transplantology, I Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

More than 60% of patients with primary and secondary liver tumors are older than 65 years. Thanks to improvements in radiological staging, anesthesia, surgical technique, and perioperative care it is possible to offer complex liver surgery to older patients. However, chronological age or functional status alone should not be a contraindication for multimodal radical treatment in older patients. Fit patients, according to the Comprehensive Geriatric Assessment, should be qualified for the same treatment as younger patients to ensure the same outcomes. Prefrail patients should undergo prehabilitation, and be reevaluated. Frail patients should be discussed in an oncogeriatric meeting. All patients with liver malignant tumors must be operated on in high-volume hospitals by an experienced surgeon. The introduction of parenchymal sparing surgery (instead of a major resection) in combination with other treatment tools, minimal invasive techniques, and enhanced postoperative recovery demonstrated being beneficial for older patients. In particular, frail, older patients can benefit from the wide variety of treatment options.

Key words: hepatocellular cancer, colorectal liver metastasis, older population, liver resection

The key components of successful oncologic liver surgery are: the ability to achieve an R0 resection, to maintain an appropriate vasculature and biliary system and to leave a sufficient functional liver parenchyma [1]. Thanks to improvements in radiological staging, anesthesia, surgical technique (understanding of segmental liver anatomy, parenchymal preserving surgery, bleeding control), and perioperative care it was possible to offer complex liver surgery to older patients. This is particularly important because, more than 60% of patients with primary and secondary liver tumors are older than 65 years at the moment of diagnosis [2].

At present, there are no treatment guidelines dedicated to older patients. The main reason for this situation is still the underrepresentation of older patients in trials regarding liver resection. In the majority of the published studies, only 15–20% of patients were older than 70 years [2]. Therefore, the extrapolation of such results on the geriatric population can lead to inappropriate treatment decisions.

Normal aging of the liver

Several age-related changes can be observed in liver physiology. The most important are: a decrease in liver weight and volume (up to 25%), decrease in the hepatic blood flow (up to 40%), an increase in the hepatic dense body compartment, shifts in the expression of a variety of proteins, and a decrease in bile flow and bile acid secretion [3–8]. These changes influence the liver's metabolic function, regeneration capacity, and immunity [3–8], which, in turn, may result in an increased risk of postoperative liver failure, drug-induced liver damage, and sepsis [3–10]. 25–30% of a total healthy liver volume needs to be preserved after the resection. However, in the case of patients with liver cirrhosis, steatosis or fibrosis, a larger remnant of the organ

Jak cytować / How to cite:
Kenig J. ***Hepatocellular cancer and colorectal liver metastasis treatment in the older population.*** *NOWOTWORY J Oncol* 2022; 72: 52–57.

needs to be intact. Despite preoperative evaluations, liver failure occurs in up to 5% patients in the postoperative period, particularly often in older patients [11]. Tzend et al. did not observe a significant difference in the preoperative LiMAx liver function between young and older patients. However, liver regeneration is significantly different in older population in the early period. Age was inversely correlated with liver regeneration potential during the first postoperative week, without any difference between young and older patients after one month [12]. None of the studies analyzed the biologic age.

Preoperative assessment and treatment decisions

As was mentioned in our previous publications, the population of older patients is very heterogeneous in terms of co-morbidity, physical reserve, cognitive function, and social support. Chronological age alone is a poor predictor of cancer treatment outcomes and toxicities [13]. Current routine pre-operative assessments cannot adequately identify patients at risk. Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with poorer outcomes. As a result, the Comprehensive Geriatric Assessment (CGA) was introduced to help determine the primary status of the older patient, to diagnose frailty syndrome, and to identify how to optimize the patient's condition before the start of treatment [14–16]. Therefore, more and more organisations, including the International Society of Geriatric Oncology, the National Comprehensive Network, the European Organisation for the Research and Treatment of Cancer, the American College of Surgeons National Surgical Quality Improvement Program, and the American Geriatric Society have called for the routine use of the Geriatric Assessment.

Rostoft et al. analyzed the literature regarding the role of the CGA in predicting the outcome in hepatobiliary and pancreatic surgery among older patients with cancer. It was concluded that although there are not many studies, frailty and elements from the CGA are significantly associated with negative short- and long-term treatment outcomes in older patients with hepatobiliary and pancreatic cancers [17].

Clinical characteristics of older HCC patients

Hepatocellular carcinoma (HCC) is the primary tumor of the liver with the greatest incidence worldwide. It is the fifth most common neoplasm and the third highest cause of cancer-related mortality [18]. The risk of developing HCC increases with age, reaching the highest incidence in the geriatric population during the seventh decade of life. Moreover, improvements in the treatment of chronic liver disease have caused an increase in the number of potential patients who may develop HCC [19]. In Europe, HCC older patients are more likely to be women and to be infected with HCV, less common with HBV. Moreover, in older patients, HCC develops more commonly in healthy livers [19]

Liver surgery in older patients with HCC

The Barcelona Clinic Liver Cancer (BCLC) stage system is the most used tool for treatment planning in patients with HCC. Based on the characteristics of the tumor, the degree of liver failure and physical condition, patients are stratified into five categories:

- very early (BCLC 0),
- early (BCLC A),
- intermediate (BCLC B),
- advanced (BCLC C),
- terminal (BCLC D).

For the two first stages (BCLC stage 0 and A), there is a wide range of treatment options including liver resection, liver transplantation, and local ablation. In the BCLC B stage, transarterial chemoembolization is usually proposed. In turn, in the BCLC C stage patients are qualified for treatment with Sorafenib. In the terminal stage (BCLC D), the best supportive treatment seems the optimal option [20]. There are also other staging systems. However, none of them is using the comprehensive geriatric assessment caps earlier or any other geriatric scale that allows determining frailty.

Concluding recently published studies on older populations undergoing various liver resections due to HCC, the morbidity and mortality rates ranged from 9% to 51% and from 0% to 7.5%, respectively. In high volume hospitals, there was no difference between younger and older patients in short-term morbidity, mortality, and length of hospital stay [21–23]. The 5-year overall survival rate ranged between 26% and even 75.9% in well-selected older patients. However, surgical treatment was only possible in up to 14% of older patients, compared with the younger group (12–28%) [24–27].

The introduction of parenchymal sparing surgery resulted in a decrease in mortality in older patients compared with older patients undergoing major hepatectomy [28]. In experienced hands, laparoscopic and robotic techniques further reduce surgical stress and improve the outcomes. Reported morbidity ranges were 10–15% and mortality was around 1%, respectively [29]. However, when analyzing the outcomes, various selection bias must be considered. A systematic review and meta-analysis, published in 2019, showed no significant difference in terms of blood loss, transfusions, liver failure, Clavien-Dindo III/IV complications, postoperative mortality, hospital stay, R0 resection, and operative time between younger and older patients undergoing laparoscopic hepatectomy [29]. Moreover, the minimal invasive approach in HCC cirrhotic patients has also the potential to reduce risk of post-operative liver decompensation and morbidities [30, 31]. However, most of the studied patients were evaluated based on chronological age, comorbidities, and physical function – not on the comprehensive geriatric assessment.

Liver transplant in older patients

Data from the United Network for Organ Sharing and the European Liver Transplant Registry show a significant increase

in the number of patients over 70 years with end-stage liver disease who qualified for a liver transplant in the last decade; it was also one of the fastest-growing patient populations [32]. In the 2019 systematic review and meta-analysis, Gavara et al. did observe acceptable short- and long-term results. They also did not find any difference in the risk of complications between young and older patients [33]. Although long-term liver transplant results are very good, older patients are rarely qualified because of their low priority on the list of available organs [32, 33].

Radiofrequency ablation for older HCC patients

The European Association for the Study of the Liver (EASL) guidelines recommends RFA as a standard of care for patients with BCLC stage 0–A, in the case of tumors not suitable for surgical resection [34, 35]. However, in the case of older patients, the results of published studies are inconsistent. Some of them report comparable outcomes between young and older population [36–38]. In turn, others reveal higher complication rates due to patients' comorbidities, use of antiplatelet or anticoagulant drugs, and preoperative low functional levels. The overall survival rates in the older group were significantly lower than those in the younger population and the recurrence-free survival rates were comparable [39].

Transarterial chemoembolization for older HCC patients

The transarterial chemoembolisation (TACE) is a procedure combing the transcatheter delivery of an anticancer drug into the hepatic artery followed by vascular obstruction with embolic agents [40]. Current guidelines recommend TACE as the standard of care for patients with multinodular, asymptomatic tumors without vascular invasion or extrahepatic spread (BCLC stage B tumors). Recent studies showed that the TACE is a safe and effective treatment in older HCC patients. The morbidity rate ranged from 4.5% to 27%, without any significant difference between older and younger patients, including also contrast medium-induced renal dysfunctions [41]. The 3-year and 5-year OS ranged between 14.9–48% and 8.4–33.8%, respectively [42–44].

Immunotherapy for older HCC patients

Sorafenib has shown efficacy in two randomized trials, resulting in a significant 30% improvement in survival of HCC patients [45]. The European Association for the Study of the Liver recommends sorafenib as the preferred treatment for patients with HCC who cannot tolerate potentially more effective therapies, particularly in the case of preserved liver function (Child––Pugh grade A) and advanced tumor stages (BCLC stage C) [46]. In the case of the older population, it turned out to be equally safe among older and younger patients with similar toxicity-related discontinuation rates between these groups [47]. There was also no difference between these groups regarding overall survival and time to treatment failure [48]. After 10 years, another multikinase inhibitor, Lenvatinib, was approved in first-line treatment [49]. Studies have proven its non-inferiority compared with sorafenib in cases of overall survival. Moreover, lenvatinib may have some potential benefits over sorafenib for patients with HBV chronic infection [49]. Atezolizumab plus bevacizumab as first-line treatment is the next treatment possibility in the treatment of advanced HCC [50]. However, we have to wait for further studies including those on the geriatric population.

Concluding, we need well-designed studies on a larger group of older patients using various advances of geriatric oncology. The Comprehensive Geriatric Assessment, evaluation of life expectancy, and analysis of patients' goals should become routine preoperative instruments allowing for better selection of older patients for a tailored treatment. They are proven to correlate much more with the short- and long-term outcomes in comparison to the currently evaluated factors. Therefore, Suda et al. proposed the percent life expectancy (%LE). It is the survival time for each patient divided by the life expectancy. This parameter may evaluate the benefits of a given treatment for older HCC patients. The authors showed that patients aged 80 years or older had the best survival benefit according to the %LE [52].

Moreover, there are currently many unintentional selections bias in most of the studies. The physicians tend to qualify older patients for surgical treatment with a good performance status and preserved liver function. This might favor similar outcomes to those of younger patients. In turn, the chronologically oldest patients are often qualified for non-curative treatment, which might favor poorer prognosis compared with younger patients [51].

Colorectal liver metastasis in older patients

Recent studies have shown that patients aged 70 and more who undergo liver resection for colorectal liver metastases have the possibility to achieve a 5-year survival of 21–44%, with postoperative morbidity and mortality rates of approximately 20–40% and 0–7%, respectively. This is despite patients undergoing more complex treatment for more extensive disease [53–62]. The main reason for the outcome improvement is the introduction of parenchymal sparing liver surgery. It has been shown to be associated with less surgical stress, fewer postoperative complications, non-inferior cancer-related outcomes, and higher feasibility of future resections [63]. There is also a higher rate of R1 resection. However, it is not associated with poorer disease free survival [64, 65]. Therefore, major resection should be limited only to patients where it is the only curative option.

More and more older patients are getting neoadjuvant chemotherapy with intend to downstage the disease and to converse the disease into resectable. It has been proven that chemotherapy in combination with surgical techniques was

not associated with poorer postoperative outcomes in older patients in comparison to younger groups [66]. So, excellent perioperative outcomes can be achieved with morbidity and mortality of 38.2% and 0.3%, respectively, using parenchymal sparing liver surgery, chemotherapy, and ablation. That combination should be used to avoid unnecessary major liver resection [67–71]. Implementation of the ERAS program in the postoperative period may further improve outcomes. A 2015 meta-analysis of randomized controlled trials on the efficacy of the ERAS program in liver surgery showed that this approach significantly reduces post-operative morbidity, length of stay, and accelerates functional recovery [72].

For older patients with unresectable CRLM who meet the eligibility criteria for radioembolization, 90Y-radioembolisation microspheres appear to be effective and well-tolerated, regardless of age. Therefore, the selection of patients for radioembolization should not include chronological age as an exclusion factor [73].

Conflict of interest: none declared

Jakub Kenig
Jagiellonian University Medical College
Department of General, Oncologic, Gastrointestinal Surgery and Transplantology
I Chair of General Surgery
ul. Jakubowskiego 2
30-688 Kraków, Poland
e-mail: jkenig@cm-uj.krakow.pl

Received: 30 Nov 2021
Accepted: 24 Dec 2021

References

1. Orcutt ST, Anaya DA. Liver Resection and Surgical Strategies for Management of Primary Liver Cancer. Cancer Control. 2018; 25(1): 1073274817744621, doi: 10.1177/1073274817744621, indexed in Pubmed: 29327594.
2. Federico P, Giunta EF, Pappalardo A, et al. How to Treat Hepatocellular Carcinoma in Elderly Patients. Pharmaceuticals (Basel). 2021; 14(3), doi: 10.3390/ph14030233, indexed in Pubmed: 33800217.
3. Marchesini G, Bua V, Brunori A, et al. Galactose elimination capacity and liver volume in aging man. Hepatology. 1988; 8(5): 1079–1083, doi: 10.1002/hep.1840080516, indexed in Pubmed: 3417228.
4. Jansen PLM. Liver disease in the elderly. Best Pract Res Clin Gastroenterol. 2002; 16(1): 149–158, doi: 10.1053/bega.2002.0271, indexed in Pubmed: 11977934.
5. Frith J, Jones D, Newton JL. Chronic liver disease in an ageing population. Age Ageing. 2009; 38(1): 11–18, doi: 10.1093/ageing/afn242, indexed in Pubmed: 19029099.
6. Gan L, Chitturi S, Farrell GC. Mechanisms and implications of age-related changes in the liver: nonalcoholic Fatty liver disease in the elderly. Curr Gerontol Geriatr Res. 2011; 2011: 831536, doi: 10.1155/2011/831536, indexed in Pubmed: 21918648.
7. Wynne HA, Cope LH, Mutch E, et al. The effect of age upon liver volume and apparent liver blood flow in healthy man. Hepatology. 1989; 9(2): 297–301, doi: 10.1002/hep.1840090222, indexed in Pubmed: 2643548.
8. Zoli M, Magalotti D, Bianchi G, et al. Total and functional hepatic blood flow decrease in parallel with ageing. Age Ageing. 1999; 28(1): 29–33, doi: 10.1093/ageing/28.1.29, indexed in Pubmed: 10203201.
9. Schmucker DL, Gilbert R, Jones AL, et al. Effect of aging on the hepatobiliary transport of dimeric immunoglobulin A in the male Fischer rat. Gastroenterology. 1985; 88(2): 436–443, doi: 10.1016/0016-5085(85)90504-9, indexed in Pubmed: 3965333.
10. Brouwer A, Barelds RJ, Knook DL, et al. Maintenance cultures of Kupffer cells isolated from rats of various ages: ultrastructure, enzyme cytochemistry, and endocytosis. Hepatology. 1983; 3(4): 497–506, doi: 10.1002/hep.1840030405, indexed in Pubmed: 6345331.
11. Farges O, Goutte N, Bendersky N, et al. ACHBT-French Hepatectomy Study Group. Incidence and risks of liver resection: an all-inclusive French nationwide study. Ann Surg. 2012; 256(5): 697–704; discussion 704, doi: 10.1097/SLA.0b013e31827241d5, indexed in Pubmed: 23095612.
12. Tzeng CWD, Cooper AB, Vauthey JN, et al. Predictors of morbidity and mortality after hepatectomy in elderly patients: analysis of 7621 NSQIP patients. HPB (Oxford). 2014; 16(5): 459–468, doi: 10.1111/hpb.12155, indexed in Pubmed: 24033514.
13. Kenig J. Oncogeriatrics (part 1.). Frailty in older adults with cancer. Nowotwory. Journal of Oncology. 2019; 69(2): 55–57, doi: 10.5603/njo.2019.0010.
14. Loh KP, Soto-Perez-de-Celis E, Hsu T, et al. What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper. J Oncol Pract. 2018; 14(2): 85–94, doi: 10.1200/JOP.2017.026435, indexed in Pubmed: 29436306.
15. Grodzicki T, Kenig J. Problemy okołooperacyjne u osób w wieku podeszłym. PZWL Wydawnictwo Lekarskie, Warszawa 2018.
16. Kenig J, Szabat K. Oncogeriatrics (part 7.). Geriatric assessment for older patients with cancer. Nowotwory. Journal of Oncology. 2020; 70(4): 153–157, doi: 10.5603/njo.2020.0031.
17. Rostoft S, van Leeuwen B. Frailty assessment tools and geriatric assessment in older patients with hepatobiliary and pancreatic malignancies. Eur J Surg Oncol. 2021; 47(3 Pt A): 514–518, doi: 10.1016/j.ejso.2020.08.024, indexed in Pubmed: 32933803.
18. Forner A, Llovet J, Bruix J. Hepatocellular carcinoma. The Lancet. 2012; 379(9822): 1245–1255, doi: 10.1016/s0140-6736(11)61347-0.
19. Bruix J, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. Gut. 2014; 63(5): 844–855, doi: 10.1136/gutjnl-2013-306627, indexed in Pubmed: 24531850.
20. Oishi K, Itamoto T, Kohashi T, et al. Safety of hepatectomy for elderly patients with hepatocellular carcinoma. World J Gastroenterol. 2014; 20(41): 15028–15036, doi: 10.3748/wjg.v20.i41.15028, indexed in Pubmed: 25386051.
21. Wu CC, Chen JT, Ho WL, et al. Liver resection for hepatocellular carcinoma in octogenarians. Surgery. 1999; 125(3): 332–338, doi: 10.1016/s0039-6060(99)70245-x.
22. Hazama H, Omagari K, Matsuo I, et al. Clinical features and treatment of hepatocellular carcinoma in eight patients older than eighty years of age. Hepatogastroenterology. 2001; 48(42): 1692–1696, indexed in Pubmed: 11813602.
23. Shirabe K, Kajiyama K, Harimoto N, et al. Early outcome following hepatic resection in patients older than 80 years of age. World J Surg. 2009; 33(9): 1927–1932, doi: 10.1007/s00268-009-0122-3, indexed in Pubmed: 19603226.
24. Nanashima A, Abo T, Nonaka T, et al. Prognosis of patients with hepatocellular carcinoma after hepatic resection: are elderly patients suitable for surgery? J Surg Oncol. 2011; 104(3): 284–291, doi: 10.1002/jso.21932, indexed in Pubmed: 21462192.
25. Yamada S, Shimada M, Miyake H, et al. Outcome of hepatectomy in super-elderly patients with hepatocellular carcinoma. Hepatol Res. 2012; 42(5): 454–458, doi: 10.1111/j.1872-034X.2011.00952.x, indexed in Pubmed: 22295877.
26. Tsujita E, Utsunomiya T, Yamashita Y, et al. Outcome of hepatectomy in hepatocellular carcinoma patients aged 80 years and older. Hepatogastroenterology. 2012; 59: 1553.
27. Katsuta E, Tanaka S, Mogushi K, et al. Age-related clinicopathologic and molecular features of patients receiving curative hepatectomy for hepatocellular carcinoma. Am J Surg. 2014; 208(3): 450–456, doi: 10.1016/j.amjsurg.2014.01.015, indexed in Pubmed: 24972857.
28. Nozawa A, Kubo S, Takemura S, et al. Hepatic resection for hepatocellular carcinoma in super-elderly patients aged 80 years and older in the first decade of the 21st century. Surg Today. 2015; 45(7): 851–857, doi: 10.1007/s00595-014-0994-1, indexed in Pubmed: 25113072.
29. Notarnicola M, Felli E, Roselli S, et al. Laparoscopic liver resection in elderly patients: systematic review and meta-analysis. Surg Endosc. 2019; 33(9): 2763–2773, doi: 10.1007/s00464-019-06840-9, indexed in Pubmed: 31139986.
30. Sahara K, Paredes AZ, Tsilimigras DI, et al. Impact of Liver Cirrhosis on Perioperative Outcomes Among Elderly Patients Undergoing Hepatectomy: the Effect of Minimally Invasive Surgery. J Gastrointest Surg. 2019; 23(12): 2346–2353, doi: 10.1007/s11605-019-04117-z, indexed in Pubmed: 30719676.

31. Federico P, Giunta EF, Pappalardo A, et al. How to Treat Hepatocellular Carcinoma in Elderly Patients. Pharmaceuticals (Basel). 2021; 14(3), doi: 10.3390/ph14030233, indexed in Pubmed: 33800217.
32. Dolnikov S, Adam R, Cherqui D, et al. Liver transplantation in elderly patients: what do we know at the beginning of 2020? Surg Today. 2020; 50(6): 533–539, doi: 10.1007/s00595-020-01996-7, indexed in Pubmed: 32279191.
33. Gómez Gavara C, Esposito F, Gurusamy K, et al. Liver transplantation in elderly patients: a systematic review and first meta-analysis. HPB (Oxford). 2019; 21(1): 14–25, doi: 10.1016/j.hpb.2018.07.025, indexed in Pubmed: 30146227.
34. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53(3): 1020–1022, doi: 10.1002/hep.24199, indexed in Pubmed: 21374666.
35. Cucchetti A, Piscaglia F, Cescon M, et al. Systematic review of surgical resection vs radiofrequency ablation for hepatocellular carcinoma. World J Gastroenterol. 2013; 19(26): 4106–4118, doi: 10.3748/wjg.v19.i26.4106, indexed in Pubmed: 23864773.
36. Hiraoka A, Michitaka K, Horiike N, et al. Radiofrequency ablation therapy for hepatocellular carcinoma in elderly patients. J Gastroenterol Hepatol. 2010; 25(2): 403–407, doi: 10.1111/j.1440-1746.2009.06037.x, indexed in Pubmed: 19929922.
37. Takahashi H, Mizuta T, Kawazoe S, et al. Efficacy and safety of radiofrequency ablation for elderly hepatocellular carcinoma patients. Hepatol Res. 2010; 40(10): 997–1005, doi: 10.1111/j.1872-034X.2010.00713.x, indexed in Pubmed: 20887335.
38. Yamazaki H, Tsuji K, Nagai K, et al. Efficacy and long-term outcomes of radiofrequency ablation in the elderly with hepatocellular carcinoma. Hepatol Res. 2014; 44(11): 1095–1101, doi: 10.1111/hepr.12233, indexed in Pubmed: 24033930.
39. Zhang F, Wu G, Sun H, et al. Radiofrequency ablation of hepatocellular carcinoma in elderly patients fitting the Milan criteria: a single centre with 13 years experience. Int J Hyperthermia. 2014; 30(7): 471–479, doi: 10.3109/02656736.2014.961042, indexed in Pubmed: 25314335.
40. Yau T, Yao TJ, Chan P, et al. The outcomes of elderly patients with hepatocellular carcinoma treated with transarterial chemoembolization. Cancer. 2009; 115(23): 5507–5515, doi: 10.1002/cncr.24636, indexed in Pubmed: 19701904.
41. Cohen MJ, Levy I, Barak O, et al. Trans-arterial chemo-embolization is safe and effective for very elderly patients with hepatocellular carcinoma. World J Gastroenterol. 2013; 19(16): 2521–2528, doi: 10.3748/wjg.v19.i16.2521, indexed in Pubmed: 23674854.
42. Cohen MJ, Levy I, Barak O, et al. Trans-arterial chemo-embolization is safe and effective for elderly advanced hepatocellular carcinoma patients: results from an international database. Liver Int. 2014; 34(7): 1109–1117, doi: 10.1111/liv.12486, indexed in Pubmed: 24512125.
43. Nishikawa H, Kita R, Kimura T, et al. Transcatheter arterial chemoembolization for intermediate-stage hepatocellular carcinoma: clinical outcome and safety in elderly patients. J Cancer. 2014; 5(7): 590–597, doi: 10.7150/jca.9413, indexed in Pubmed: 25057310.
44. Golfieri R, Bilbao JI, Carpanese L, et al. European Network on Radioembolization with Yttrium-90 Microspheres (ENRY) study collaborators. Comparison of the survival and tolerability of radioembolization in elderly vs. younger patients with unresectable hepatocellular carcinoma. J Hepatol. 2013; 59(4): 753–761, doi: 10.1016/j.jhep.2013.05.025, indexed in Pubmed: 23707371.
45. Guilherme NM, da Fonseca LG, Braghiroli MG, et al. Efficacy and safety of sorafenib in elderly patients with advanced hepatocellular carcinoma. Clinics. 2021; 76: 123–130.
46. Wong H, Tang YF, Yao TJ, et al. The outcomes and safety of single--agent sorafenib in the treatment of elderly patients with advanced hepatocellular carcinoma (HCC). Oncologist. 2011; 16(12): 1721–1728, doi: 10.1634/theoncologist.2011-0192, indexed in Pubmed: 22135121.
47. Di Costanzo GG, Tortora R, De Luca M, et al. Impact of age on toxicity and efficacy of sorafenib-targeted therapy in cirrhotic patients with hepatocellular carcinoma. Med Oncol. 2013; 30(1): 446, doi: 10.1007/s12032-012-0446-y, indexed in Pubmed: 23307255.
48. Jo M, Yasui K, Kirishima T, et al. Efficacy and safety of sorafenib in very elderly patients aged 80 years and older with advanced hepatocellular carcinoma. Hepatol Res. 2014; 44(13): 1329–1338, doi: 10.1111/hepr.12308, indexed in Pubmed: 24528772.
49. Morimoto M, Numata K, Kondo M, et al. Higher discontinuation and lower survival rates are likely in elderly Japanese patients with advanced hepatocellular carcinoma receiving sorafenib. Hepatol Res. 2011; 41(4): 296–302, doi: 10.1111/j.1872-034X.2011.00778.x, indexed in Pubmed: 21348907.
50. Edeline J, Crouzet L, Le Sourd S, et al. Sorafenib use in elderly patients with hepatocellular carcinoma: caution about use of platelet aggregation inhibitors. Cancer Chemother Pharmacol. 2015; 75(1): 215–219, doi: 10.1007/s00280-014-2645-z, indexed in Pubmed: 25477009.
51. Kinoshita A, Koike K, Nishino H. Clinical features and prognosis of elderly patients with hepatocellular carcinoma not indicated for surgical resection. Geriatr Gerontol Int. 2017; 17(2): 189–201, doi: 10.1111/ggi.12747, indexed in Pubmed: 26847184.
52. Suda T, Nagashima A, Takahashi S, et al. Active treatments are a rational approach for hepatocellular carcinoma in elderly patients. World J Gastroenterol. 2013; 19(24): 3831–3840, doi: 10.3748/wjg.v19.i24.3831, indexed in Pubmed: 23840122.
53. Cho SW, Steel J, Tsung A, et al. Safety of liver resection in the elderly: how important is age? Ann Surg Oncol. 2011; 18(4): 1088–1095, doi: 10.1245/s10434-010-1404-6, indexed in Pubmed: 21046265.
54. de Liguori Carino N, van Leeuwen BL, Ghaneh P, et al. Liver resection for colorectal liver metastases in older patients. Crit Rev Oncol Hematol. 2008; 67(3): 273–278, doi: 10.1016/j.critrevonc.2008.05.003, indexed in Pubmed: 18595728.
55. Figueras J, Ramos E, López-Ben S, et al. Surgical treatment of liver metastases from colorectal carcinoma in elderly patients. When is it worthwhile? Clin Transl Oncol. 2007; 9(6): 392–400, doi: 10.1007/s12094-007-0072-x, indexed in Pubmed: 17594954.
56. Menon KV, Al-Mukhtar A, Aldouri A, et al. Outcomes after major hepatectomy in elderly patients. J Am Coll Surg. 2006; 203(5): 677–683, doi: 10.1016/j.jamcollsurg.2006.07.025, indexed in Pubmed: 17084329.
57. Adam R, Frilling A, Elias D, et al. LiverMetSurvey Centres. Liver resection of colorectal metastases in elderly patients. Br J Surg. 2010; 97(3): 366–376, doi: 10.1002/bjs.6889, indexed in Pubmed: 20101645.
58. Cannon RM, Martin RCG, Callender GG, et al. Safety and efficacy of hepatectomy for colorectal metastases in the elderly. J Surg Oncol. 2011; 104(7): 804–808, doi: 10.1002/jso.22042, indexed in Pubmed: 21792943.
59. Orcutt ST, Artinyan A, Li LT, et al. Postoperative mortality and need for transitional care following liver resection for metastatic disease in elderly patients: a population-level analysis of 4026 patients. HPB (Oxford). 2012; 14(12): 863–870, doi: 10.1111/j.1477-2574.2012.00577.x, indexed in Pubmed: 23134189.
60. Mann CD, Neal CP, Pattenden CJ, et al. Major resection of hepatic colorectal liver metastases in elderly patients - an aggressive approach is justified. Eur J Surg Oncol. 2008; 34(4): 428–432, doi: 10.1016/j.ejso.2007.03.013, indexed in Pubmed: 17466484.
61. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999; 341(27): 2061–2067, doi: 10.1056/NEJM199912303412706, indexed in Pubmed: 10615079.
62. Song W, Wang K, Zhang RJ, et al. The enhanced recovery after surgery (ERAS) program in liver surgery: a meta-analysis of randomized controlled trials. Springerplus. 2016; 5: 207, doi: 10.1186/s40064-016-1793-5, indexed in Pubmed: 27026903.
63. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016; 27(8): 1386–1422, doi: 10.1093/annonc/mdw235, indexed in Pubmed: 27380959.
64. Rinaldi F, George E, Adler AI. NICE guidance on cetuximab, bevacizumab, and panitumumab for treatment of metastatic colorectal cancer after first-line chemotherapy. Lancet Oncol. 2012; 13(3): 233–234, doi: 10.1016/s1470-2045(12)70044-x, indexed in Pubmed: 22489288.
65. Tufo A, Dunne DFj, Manu N, et al. Changing outlook for colorectal liver metastasis resection in the elderly. Eur J Surg Oncol. 2019; 45(4): 635–643, doi: 10.1016/j.ejso.2018.11.024, indexed in Pubmed: 30553630.
66. Kanas GP, Taylor A, Primrose JN, et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. Clin Epidemiol. 2012; 4: 283–301, doi: 10.2147/CLEP.S34285, indexed in Pubmed: 23152705.
67. Kopetz S, Chang GJ, Overman MJ, et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol. 2009; 27(22): 3677–3683, doi: 10.1200/JCO.2008.20.5278, indexed in Pubmed: 19470929.
68. Taner T, Atwell TD, Zhang L, et al. Adjunctive radiofrequency ablation of metastatic neuroendocrine cancer to the liver complements surgical resection. HPB (Oxford). 2013; 15(3): 190–195, doi: 10.1111/j.1477--2574.2012.00528.x, indexed in Pubmed: 23374359.
69. Mohan H, Nicholson P, Winter DC, et al. Radiofrequency ablation for neuroendocrine liver metastases: a systematic review. J Vasc Interv Radiol. 2015; 26(7): 935–942.e1, doi: 10.1016/j.jvir.2014.12.009, indexed in Pubmed: 25840836.

70. Baere Tde, Deschamps F, Tselikas L, et al. GEP-NETS UPDATE: Interventional radiology: role in the treatment of liver metastases from GEP--NETs. European Journal of Endocrinology. 2015; 172(4): R151–R166, doi: 10.1530/eje-14-0630.
71. Song W, Wang K, Zhang RJ, et al. The enhanced recovery after surgery (ERAS) program in liver surgery: a meta-analysis of randomized controlled trials. Springerplus. 2016; 5: 207, doi: 10.1186/s40064-016-1793-5, indexed in Pubmed: 27026903.
72. Kennedy AS, Ball DS, Cohen SJ, et al. Metastatic Colorectal Cancer Liver Metastases Outcomes After Radioembolization (MORE) Study Investigators. Safety and Efficacy of Radioembolization in Elderly (≥ 70 Years) and Younger Patients With Unresectable Liver-Dominant Colorectal Cancer. Clin Colorectal Cancer. 2016; 15(2): 141–151.e6, doi: 10.1016/j.clcc.2015.09.001, indexed in Pubmed: 26541321.

VIA MEDICA

Genetyka i onkologia / Genetics and oncology

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 58–65

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Fakomatozy – znaczenie badań genetycznych dla personalizacji postępowania klinicznego (część 2)

Anna Kofla-Dłubacz[1], Andrzej Stawarski[1], Tomasz Pytrus[1], Justyna Gil[2]

[1]*II Katedra i Klinika Pediatrii, Gastroenterologii i Żywienia, Wydział Lekarski, Uniwersytet Medyczny we Wrocławiu*
[2]*Katedra i Zakład Genetyki, Wydział Lekarski, Uniwersytet Medyczny we Wrocławiu*

Choroba von Hippla i Lindaua (VHL) oraz stwardnienie guzowate są rzadko występującymi schorzeniami uwarunkowanymi genetycznie, należącymi do grupy fakomatoz. W ich przebiegu występuje zwiększone ryzyko rozwoju mnogich nowotworów, głównie o charakterze łagodnym, które mogą ulegać transformacji do formy złośliwej. Diagnostyka genetyczna obejmująca identyfikację wariantu patogennego genów *VHL* i *TSC1* oraz *TSC2* umożliwia optymalizację opieki nad pacjentami oraz typowanie krewnych obciążonych mutacją.

Słowa kluczowe: choroba von Hippla i Lindaua, VHL, stwardnienie guzowate, *sclerosis tuberosa complex*, *TSC*, fakomatozy

Choroba von Hippla i Lindaua

Choroba von Hippla i Lindaua (*Von Hippel-Lindau disease* – VHL, OMIM 193300) zawdzięcza nazwę niemieckiemu okuliście Eugenowi von Hippel oraz szwedzkiemu patologowi Arvidowi Lindau, którzy w latach 1904 i 1926 niezależnie od siebie opisali zespoły kliniczne charakteryzujące się występowaniem guzów siatkówki i ośrodkowego układu nerwowego (OUN) [1]. VHL jest zespołem uwarunkowanym genetycznie, predysponującym do rozwoju nowotworów, który dziedziczony jest w sposób autosomalny dominujący z niemal pełną penetracją. U około 20% chorych mutacja powstaje *de novo*, ale nosiciel przekazuje zmiany potomstwu (50% ryzyka przekazania mutacji). W kolejnych pokoleniach obserwowany jest cięższy przebieg choroby oraz jej wcześniejsze wystąpienie, tzw. antycypacja genetyczna [2]. Schorzenie rozpoznawane jest u 1 osoby na 38–91 000, a zapadalność wynosi 1 na 36–45 000 urodzeń [1]. Pierwsze objawy pojawiają się już w drugiej dekadzie życia, kryteria rozpoznania spełnione są u wszystkich pacjentów przed ukończeniem 70. roku życia [1]. Po rozpoznaniu zespołu VHL konieczny jest stały nadzór nad pacjentem. Dzięki temu można wcześnie wykryć nowotwory i podjąć właściwe leczenie. Pomimo to spodziewana długość życia osób obciążonych VHL jest najkrótsza wśród obciążonych innymi dziedzicznymi zespołami zwiększonego ryzyka zachorowania na chorobę nowotworową [3].

W przebiegu tego zespołu dochodzi do tworzenia mnogich guzów o charakterze łagodnym i złośliwym w obrębie ośrodkowego układu nerwowego, oka, narządów wewnętrznych – ze szczególnym uwzględnieniem nerek, trzustki i nadnerczy [4].

Hemangioblastoma (naczyniaki zarodkowe) OUN są często pierwszym objawem choroby i występują u 72–75% pacjentów [1]. Mogą lokalizować się w móżdżku (*hemangioblastoma cerebelli*), w rdzeniu przedłużonym (*hemangioblastoma medullae oblongatae*) lub w rdzeniu kręgowym (*hematoblastoma medullae spinalis*). W zależności od lokalizacji i wielkości prowadzą do różnorodnych objawów klinicznych. Efekt masy guzów zlokalizowanych wewnątrzczaszkowo może prowadzić do wzrostu ciśnienia śródczaszkowego objawiającego się nudnościami, wymiotami, przemieszczeniem struktur mózgowia z wklinowa-

Jak cytować / How to cite:
Kofla-Dłubacz A, Stawarski A, Pytrus T, Gil J. ***Phacomatoses, genetic testing for personalisation of clinical management (part 2).*** *NOWOTWORY J Oncol* 2022; 72: 58–64.

niem prowadzącym do zgonu. W przypadku guzów o mniejszych rozmiarach mogą występować objawy ogniskowe, bóle głowy, bądź objawy asymptomatyczne. Lokalizacja móżdżkowa powoduje wystąpienie zaburzeń równowagi, które spotykane są również w przypadku guza worka endolimfatycznego (*endolymphatic sac tumors* – ELST), obserwowanego u ok. 15% chorych z VHL. Guz ten charakteryzuje się miejscową złośliwością. Gdy się powiększa, niszczy struktury ucha wewnętrznego, piramidę kości skroniowej, może naciekać również nerwy czaszkowe (twarzowy i przedsionkowo-ślimakowy). Rozrastając się w kierunku móżdżku, prowadzi do zespołu kąta mostkowo-móżdżkowego. Wśród objawów typowych wymienić należy całkowitą lub częściową utratę słuchu występującą u 95–100% pacjentów, szumy uszne u 77% pacjentów, zaburzenia równowagi pochodzenia przedsionkowego – u 62% pacjentów i porażenie nerwu twarzowego – u 8% pacjentów [1, 5]. Leczenie hemangioblastoma OUN, jak również ELST ,jest głównie chirurgiczne i zależy od lokalizacji oraz rozmiarów guza i ewentualnego naciekania sąsiednich struktur anatomicznych.

Hemangioblastoma siatkówki (naczyniak włośniczkowy siatkówki, naczyniak krwionośny zarodkowy) opisywane są u 50–60% chorych z VHL [6]. W badaniu okulistycznym stwierdza się ostro odgraniczoną pomarańczowo-czerwoną zmianę bogato unaczynioną, z wysiękiem śród- i podsiatkówkowym. Zmiany lokalizują się w części okołotarczowej lub na obwodzie siatkówki (obszar górno- lub dolnoskroniowy). U około 25% chorych dochodzi do trwałej utraty widzenia, a wystąpienie zmian mnogich predysponuje do tworzenia kolejnych ognisk [7].

Pacjenci z rozpoznaniem VHL wymagają stałego nadzoru okulistycznego z uwzględnieniem angiografii fluoresceinowej (odróżnienie tętniczek odżywczych od żyłek odprowadzających), badania ultrasonograficznego (określenie średnicy guza, uwidocznienie płynu), optycznej tomografii koherentnej (*optical coherent tomography* – OCT) (ustalenie miejsca gromadzenia płynu podsiatkówkowego). W ramach leczenia stosuje się fotokoagulację laserową, krioterapię, terapię fotodynamiczną, techniki chirurgii witroretinalnej. W ramach farmakoterapii podejmowane są próby podawania antagonistów czynnika wzrostu śródbłonka naczyń (*vascular endothelial growth factor* – VEGF) – w przypadku naczyniaków tylnego bieguna [1, 7].

Rak nerkowokomórkowy (*renal-cell carcinoma* – RCC) występuje u ok. 30% chorych z VHL, wywodzi się z nabłonka kanalików nerkowych. Histologicznie ma najczęściej postać raka jasnokomórkowego, różni się od postaci występującej sporadycznie wieloogniskową manifestacją oraz współwystępowaniem torbieli (cyst) nerkowych. Może tworzyć się obustronnie [1, 8]. Objawy kliniczne w postaci wyczuwalnej masy guza, bólu okolicy lędźwiowej oraz krwiomoczu występują w przypadku guzów dużych (triada Virchowa). Nowotwory mniejszych rozmiarów pozostają bezobjawowe i wykrywane są w trakcie przesiewowych badań obrazowych. Możliwe jest także wystąpienie tzw. objawów paranowotworowych z hiperkalcemią związaną z wydzielaniem peptydu PTH-podobnego (PThrP), nadciśnieniem tętniczym, spowodowanym produkcją reniny przez komórki guza czy poliglobulią – występującą w efekcie uwalniania z nich erytropoetyny [9].

Podstawowymi metodami diagnostycznymi są tomografia komputerowa oraz rezonans magnetyczny. Rozpoznania histologicznego dokonuje się po pobraniu fragmentu guza drogą biopsji nerki lub w trakcie nefrektomii, która należy do podstawowych metod terapeutycznych RCC. Leczenie chirurgiczne w przypadku guzów małych (poniżej 3 cm) polega na usunięciu masy guza z marginesem zdrowej nerki. W ramach farmakoterapii, w stadium zaawansowanym nowotworu, podejmowane są próby leczenia inhibitorami kinazy tyrozynowej, które blokują angiogenezę i kinazę mTOR. Stosowana jest także immunoterapia interferonem alfa.

Guz chromochłonny (*pheochromocytoma*) występuje u ok. 16% pacjentów [1]. Jest to guz wydzielający katecholaminy, zazwyczaj łagodny, lokalizujący się w przebiegu VHL głównie w nadnerczach, często obustronnie, może przyjmować postać wieloogniskową. Podobnie jak w postaci sporadycznej, głównym objawem klinicznym jest nadciśnienie tętnicze (napadowe bądź utrwalone), któremu mogą towarzyszyć bóle głowy, wzmożona potliwość. Obserwowane jest napadowe blednięcie powłok skórnych, uczucie niepokoju, drżenia, zaburzenia rytmu serca w postaci tachykardii, migotania przedsionków czy dodatkowych pobudzeń komorowych, które mogą być przyczyną nagłego zgonu sercowego lub przewlekłej choroby serca – kardiomiopatii z rozwojem zastoju w krążeniu płucnym.

W ramach diagnostyki oznacza się wolne katecholaminy lub ich metabolity (kwas wanilinomigdałowy – VMA, metoksykatecholaminy) w dobowej zbiórce moczu. Metoksykatecholamina może być również oznaczona w surowicy. W celu określenia lokalizacji guza wykonywane jest badanie tomografii komputerowej lub rezonans magnetyczny, ewentualnie scyntygrafia z użyciem m-jodobenzyloguanidyny znakowanej jodem (MIBG), która jest szczególnie przydatna w rozpoznawaniu zmian małych i przerzutów [1]. Metodą przesiewową stosowaną do wykrywania guzów o typie *pheochromocytoma* jest również USG jamy brzusznej.

Leczenie guzów chromochłonnych obejmuje resekcję chirurgiczną (adrenalektomia całkowita bądź oszczędzająca) po przygotowaniu farmakologicznym, w ramach którego należy znormalizować ciśnienie tętnicze krwi oraz akcję serca. W tym celu stosowane są alfa blokery – lekiem podstawowym jest fenoksybenzamina stosowana przez 2 tygodnie przed planowanym zabiegiem operacyjnym. Terapię alfa blokerami można uzupełnić lekami blokującymi receptory beta, szczególnie u osób ze współistniejącą tachykardią. Beta blokery nie mogą być stosowane w monoterapii [1]. Pacjenci po zabiegu usunięcia guza chromochłonnego wymagają stałego nadzoru w celu wczesnego wykrycia ewentualnej wznowy nowotworu.

Z kolei zmiany w obrębie trzustki mają charakter torbieli (cyst) lub łagodnych nowotworów torbielowatych (*cystadenomas*) i występują u dużej części pacjentów z chorobą VHL

– 72% [1]. Mogą pozostawać bezobjawowe lub – powodując ucisk – wpływać na wydolność edno- i egzokrynną trzustki. W przebiegu VHL wystąpić mogą również guzy neuroendokrynne trzustki (*pancreatic neuroendocrine tumor* – PNET).

Wielonarządowa manifestacja choroby VHL i związana z tym mnogość możliwych objawów klinicznych wymagają wielospecjalistycznego nadzoru oraz doboru leczenia zgodnego z typem zmian u pacjenta. Zasadniczo wyróżnić można dwa typy podstawowe schorzenia: 1 i 2. W typie 2 wyróżnia się podtypy a, b, c [10]. Kryteria diagnostyczne obejmują analizę kliniczną u pacjenta ze stwierdzonym współwystępowaniem mnogich ognisk nowotworowych [1]. Do ustalenia rozpoznania wymagane jest wykrycie:

- przynajmniej dwóch guzów o typie naczyniaka zarodkowego centralnego układu nerwowego (*central nervous system hemangioblastomas*),
- przynajmniej jednego naczyniaka zarodkowego ośrodkowego układu nerwowego i jednego z guzów nowotworowych opisanych poniżej,
- przynajmniej jednego z guzów opisanych poniżej oraz wykrycie mutacji typowej dla VHL lub obecność krewnego pierwszego stopnia z rozpoznanym VHL.

Typowe objawy VHL ujęte w kryteriach diagnostycznych obejmują:

- nerwiaka zarodkowego OUN (w tym stwierdzenie hemangioblastomy siatkówki), (*hemangioblastoma of central nervous system, including retinal hemangioblastoma*),
- guza worka endolimfatycznego (*endolymphatic sac tumors*),
- raka nerkowokomórkowego (*renal-cell carcinoma*),
- guza chromochłonnego (*pheochromocytoma*),
- przyzwojaka (*paraganglioma, glomus tumor*),
- guzy neuroendokrynne i/lub liczne cysty trzustki.

Podczas badań okresowych u pacjentów z rozpoznaniem VHL potwierdzonym wynikiem testu genetycznego należy wykonywać:

- w wieku 0–2 lata – coroczne badanie fizykalne i okulistyczne,
- w wieku od 2 lat – badanie MR mózgowia i rdzenia kręgowego – 2 razy w roku; badanie USG jamy brzusznej – co roku; jeżeli zostaną stwierdzone torbiele lub guzy – badanie tomografii komputerowej (TK) – co 6 miesięcy,
- w wieku od 20 lat – coroczne badanie TK zamiast corocznego badania USG,
- w wieku od 60 lat – tomografia komputerowa w każdym roku, w którym nie było MRI; w przypadku braku objawów badanie MRI – co 3–5 lat [11].

Podłoże genetyczne, diagnostyka i poradnictwo genetyczne

Mutacje w genie supresorowym *VHL* stanowią podstawę molekularną rozwoju zespołu von Hippla i Lindaua. Gen *VHL* położony jest na krótkim ramieniu chromosomu 3 (locus p25.3, MIM*608537), składa się z trzech egzonów (642 nukleotydy) i koduje wysoce konserwatywne białko. Obecność transkryptu genu jest obserwowana w różnych typach komórek w wielu tkankach (zarówno w życiu płodowym jak i postnatalnie) [12]. W zależności od miejsca rozpoczęcia translacji, zdeterminowanego obecnością dwóch kodonów metioninowych (startowych), powstają dwie izoformy białka (pVHL). Jedna składa się z 213 aminokwasów ($VHLp_{30}$, ekspresja w cytoplazmie), druga – ze 160 reszt aminokwasowych ($VHLp_{19}$, ekspresja w jądrze komórkowym) [13].

Białko VHL działa w kompleksach z różnymi białkami. Przede wszystkim tworzy kompleks VBC z elonginą C oraz kompleksem elonginy B z kulliną-2 i Rbx (wiązanie przez domenę α) [14]. W warunkach fizjologicznych (prawidłowe stężenie tlenu) kompleks VBC, który posiada aktywność ligazy E3 ubikwityny, odpowiedzialny jest za ubikwitynację podjednostki alfa czynnika indukowanego hipoksją 1 (*hypoxia-inducible factor 1* – HIF1-α), która prowadzi do jego proteolizy w proteasomie i w konsekwencji hamuje transkrypcję genów indukowanych hipoksją [15]. Domeną odpowiedzialną za wiązanie substratu z kompleksem VBC jest domena β pVHL, która wiąże HIF1-α poprzez hydroksylowane reszty proliny. W warunkach hipoksji nie dochodzi do hydroksylacji reszt prolinowych HIF1-α i wiązania z pVHL [16]. Skutkuje to akumulacją HIF1-α, w rezultacie indukowana zostaje transkrypcja genów regulowanych przez białko HIF1 (heterodimer HIF1-α i HIF1-β). Są to m.in. geny kodujące czynniki wzrostu, takie jak: naczyniowo-śródbłonkowy czynnik wzrostu (*vascular endothelial growth factor* – VEGF), płytkopochodny czynnik wzrostu (*pellet-derived growth factor* – PDGF) i transformujący czynnik wzrostu alfa (*transforming growth factor alpha* – TGF-α) oraz gen *EPO* kodujący erytropoetynę. Ponadto kompleks VBC reguluje HIF2-α, HIF3-α oraz atypową kinazę białkową λ [10, 17, 18].

Dysfunkcja białka VHL powoduje rozregulowanie kontroli nad degradacją HIF1-α i wiąże się ze stałym wysokim poziomem HIF (niezależnie od poziomu tlenu), który prowadzi do nadprodukcji VEGF, PDGF i TGF-α. Jest to najbardziej prawdopodobny mechanizm molekularny wyjaśniający nadmierną nieprawidłową proliferację i angiogenezę w bogato unaczynionych guzach ze spektrum VHL. Wykazano również, że dysfunkcja kompleksu VBC przyczynia się do rozwoju guzów chromochłonnych jako rezultat akumulacji atypowej kinazy białkowej λ. Akumulacja ta prowadzi do nadmiernej ekspresji czynnika transkrypcyjnego B-jun, który hamuje apoptozę w komórkach grzebienia nerwowego w rdzeniu nadnerczy [10, 19].

Zespół VHL jest dziedziczony w sposób autosomalnie dominujący i w około 80% przypadków mutacja jest odziedziczona po jednym z rodziców (dziedziczenie Mendlowskie, 50% ryzyko przekazania zmiany). W pozostałych 20% przypadków zmiana powstaje de novo a w wywiadzie rodzinnym nie ma osób, z rozpoznaniem lub z podejrzeniem VHL [13]. Badanie genetyczne, które pozwala określić status mutacyjny probanda, jest niezwykle istotne w aspekcie opracowania programu opieki profilaktycznej nad nosicielem mutacji (z uwzględnieniem

ryzyka występowania nowotworów ze spektrum tego zespołu) oraz objęcia poradnictwem genetycznym całej rodziny. Testy genetyczne mogą być ukierunkowane na analizę jednego genu lub panelu genów związanych z fakomatozami, a w przypadku niejednoznacznego fenotypu można rozważyć badania całoegzomowe lub całogenomowe. Najczęstszym typem mutacji genu *VHL* są mutacje typu zmiany sensu (*missense*, około 30–60%), wewnątrzgenowe insercje/delecje, mutacje typu zmiany ramki odczytu i mutacje miejsc splicingowych. Wszystkie prowadzą do skrócenia białka stanowią około 20–30%. Około 20–40% mutacji to duże delecje obejmujące niekiedy cały gen [20].

Dotychczas zidentyfikowano ponad 300 wariantów patogennych w genie *VHL* [17]. Obecność wariantów patogennych stwierdzono we wszystkich 3 egzonach. Kodon 167 kodujący argininę jest uważany za tzw. gorący punkt mutacyjny [21]. Choroba charakteryzuje się zależną od wieku, pełną penetracją oraz zmienną ekspresją (przyjmuje się że około 65. roku życia penetracja przekracza 90%) [13]. Teoria dwóch uderzeń Knudsona, tłumaczy rozwój VHL. Jeden uszkodzony allel obecny jest we wszystkich komórkach (mutacja konstytucyjna), a utrata drugiej kopii (delecja, mutacja punktowa, hipermetylacja sekwencji promotorowej) genu jest czynnikiem rozpoczynającym proces transformacji nowotworowej [22].

Dobrze poznane są korelacje genotyp–fenotyp. Duże zmiany typu delecji całych egzonów oraz mutacje prowadzące do skrócenia białka najczęściej wiążą się z fenotypem VHL typu 1, w którym występują naczyniaki zarodkowe siatkówki i ośrodkowego układu nerwowego, rak nerki, torbiele trzustki, natomiast nie występuje guz chromochłonny. Zmiany patogenne typu *missense* są związane z VHL typu 2, w którym obserwuje się występowanie guza chromochłonnego. Typ 2 w zależności od współwystępowania innych manifestacji narządowych dzieli się na typy:

- 2A (guz chromochłonny, naczyniaki zarodkowe, brak raka nerki),
- 2B (guz chromochłonny, naczyniaki zarodkowe, rak nerki),
- 2C (guz chromochłonny) [13].

Sugerowany jest również typ 1B, charakteryzujący się podobnie jak typ 1 brakiem guza chromochłonnego a ponadto małym ryzykiem rozwoju raka nerki. Typ 1B jest charakterystyczny dla pacjentów, u których poza delecją genu *VHL* stwierdza się delecję genu *BRK1* [13].

Identyfikacja wariantu patogennego genu *VHL* pozwala na zastosowanie diagnostyki molekularnej u członków rodziny w celu wytypowania osób z grupy ryzyka. Pozwala to wprowadzić odpowiedni algorytm badań diagnostyczno-profilaktycznych oraz zmniejszyć potrzebę wykonywania procedur przesiewowych u tych osób, które nie odziedziczyły wariantów patogennych [23]. W poradnictwie genetycznym należy również wziąć pod uwagę ryzyko występowania mozaicyzmu komórek germinalnych rodzica, którego dziecko jest chore i ma potwierdzoną mutację genową, natomiast takiej samej zmiany nie stwierdzono w badaniu rodziców. Ponadto możliwe jest również istnienie mozaicyzmu somatycznego. Wtedy tylko w części komórek obecny jest wariant patogenny. Przebieg choroby w takim przypadku będzie łagodniejszy i o ile wariant patogenny jest nieobecny w komórkach rozrodczych, ryzyko choroby u potomstwa jest na poziomie ryzyka populacyjnego [24].

W Polsce pacjenci z VHL są objęci programem opieki nad rodzinami wysokiego, dziedzicznie uwarunkowanego ryzyka zachorowania na nowotwory złośliwe – Moduł III – „Profilaktyka oraz wczesne wykrywanie nowotworów złośliwych w rodzinach z rzadkimi zespołami dziedzicznej predyspozycji do nowotworów – siatkówczak, choroba Von Hippel-Lindau (VHL)". W ramach programu gwarantowane świadczenia zapewniają identyfikację pacjentów z VHL na podstawie rozpoznania klinicznego, analizę molekularną – badanie genetyczne, oraz prowadzenie opieki nad pacjentem. Opieka ta obejmuje:

- coroczną konsultację lekarską,
- MRI głowy i rdzenia kręgowego od 11. roku życia (co 1–3 lata, w zależności od zmian obecności OUN),
- USG jamy brzusznej (corocznie),
- TK (lub MRI) jamy brzusznej (co 2–3 lata),
- konsultację okulistyczną od 1. roku życia; badanie dna oka w lustrze Goldmana od 6. roku życia.

W związku z powyższym kluczowa jest identyfikacja osób z grupy ryzyka i jak najwcześniejsze wprowadzenie badań przesiewowych u bezobjawowych nosicieli patogennej zmiany. Dlatego też uzasadnione jest wykonywanie u dzieci z rodzin obarczonych krytyczną mutacją, testów genetycznych w kierunku mutacji genu *VHL*. Ponadto, u rodzin ze zidentyfikowaną mutacją możliwe jest również wykonanie badań prenatalnych oraz preimplantacyjnych [21].

Stwardnienie guzowate

Stwardnienie guzowate (*sclerosis tuberosa complex* – TSC), zwane również chorobą Bourneville'a-Pringle'a, jest schorzeniem dziedziczonym autosomalnie dominująco, z pełną penetracją i różnorodnym stopniem ekspresji. W około 75% przypadków TSC mutacja powstaje *de novo*. Częstość występowania choroby w populacji ogólnej wynosi 1:6800–1:17 300 [25, 26].

Cechą charakterystyczną stwardnienia guzowatego jest tworzenie guzów hamartomatycznych w obrębie skóry, centralnego układu nerwowego, nerek, płuc i serca. Charakterystyczna triada objawów obejmuje opóźnienie umysłowe, padaczkę oraz naczyniakowłókniaki skóry typu Pringle'a (angiofibroma), które pojawiają się już we wczesnym dzieciństwie i mają postać żółtoróżowych grudek na powierzchniach łojotokowych twarzy (nos, przyśrodkowe części policzków, czoło). Występują one niemal u 90% chorych, ich liczba zwiększa się w okresie dojrzewania. Dają niepożądany efekt kosmetyczny, mogą samoistnie krwawić [26].

Innymi zmianami skórnym obserwowanymi w przebiegu TSC są plamy odbarwieniowe w kształcie liścia (*leaf-shaped*

leukoderma), lokalizujące się często na owłosionej skórze głowy. Dają obraz charakterystycznego odbarwionego pasma włosów wyrastającego ze zmiany. Spotyka się ponadto plamy typu confetti w postaci bezbarwnych znamion na wyprostnych powierzchniach kończyn, plamy szagrynowe na tułowiu w okolicy krzyżowej czy włókniaki płaskie w okolicy czołowej – u 25% chorych [27]. Włókniaki dziąseł, podobnie jak włókniaki wałów paznokciowych, zwane guzkami Koenena, pojawiają się głównie u osób dorosłych [26].

Objawy nerkowe

Angiomiolipoma jest guzem hamartomatycznym występującym u 80% pacjentów. Jest nowotworem łagodnym, jednak powiększając się, może spowodować samoistny krwotok do torebki nerki (zespół Wunderlicha) lub jej niewydolność, będąc przyczyną zwiększonej śmiertelności wśród pacjentów [26]. Rokowniczo niekorzystne jest również wystąpienie raka jasnokomórkowego nerki, na którego chorzy na TSC zapadają częściej w porównaniu z populacją ogólną. Ponadto mutacje obecne w genie *TSC2* zwiększają ryzyko wystąpienia wielotorbielowatości nerek [28].

Objawy neurologiczne

Padaczka rozpoznana w wieku wczesnodziecięcym, często niemowlęcym, jest objawem charakterystycznym TSC i występuje u 79–90% pacjentów [26]. Obserwowane są ponadto zaburzenia zachowania ze spektrum autyzmu, ADHD, opóźnienie umysłowe – u ok. 40% chorych [29]. Część z tych zaburzeń ma związek ze zmianami strukturalnymi mózgu, które wynikają z tworzenia hamartomatycznych guzów korowo-podkorowych (*cortial--subcortial tubers*) czy podwyściółkowych guzków okołokomorowych (*subependymal heterotopic nodules*). Podwyściółkowe guzki okołokomorowe mogą być punktem wyjścia dla złośliwego guza zwanego gwiaździakiem podwyściółkowym olbrzymiokomórkowym (*subependymal gigant cell astrocytoma*), który rozrastając się w komorach bocznych mózgu, może powodować niedrożność otworów Monro, powiększenie komór, wodogłowie i zgon pacjenta.

Podstawą diagnostyki są badania obrazowe mózgowia uwzględniające tomografię komputerową, rezonans magnetyczny, w którym widoczne są również heterotypie istoty białej (*white matter linear migration lines*) występujące u 20–30% pacjentów [30].

Objawy płucne

Limfangiolejomiomatoza (*lymphangioleiomyomatosis*) jest jednym z objawów płucnych TSC, i jest spowodowana rozplemem komórek mięśniowych gładkich wokół oskrzeli i drobnych naczyń, czego skutkiem jest przebudowa tkanki płucnej i tworzenie torbieli. Charakterystyczne objawy to: kaszel, duszność, krwioplucie. Limfangiolejomiomatoza występuje głównie u dorosłych kobiet [25]. U chorych z TSC może wystąpić również wieloogniskowa mikroguzkowa hiperplazja pneumocytów, która daje obraz drobnych guzków widocznych w badaniu radiologicznym [31].

Objawy sercowe

Zmianami ulegającymi samoistnej inwolucji są mięśniaki prążkowanokomórkowe (*rhabdomyomata*), które występują u najmłodszych dzieci i w większości zanikają w okresie przedszkolnym. U części pacjentów mogą powodować zaburzenia rytmu serca, a niekiedy prowadzić do jego niewydolność [32].

Objawy oczne

Zmiany oczne występujące w przebiegu TSC to guzki hamartomatyczne siatkówki, które pomimo wieloognskowej manifestacji najczęściej nie powodują pogorszenia widzenia. Wyróżnia się guzki płaskie (*flat lesions*), typu owoca morwy (*mulberry leasions*) i mieszane (*transitional lesions*) [33].

Wielorakość objawów klinicznych oraz zróżnicowana ekspresja mogą stwarzać trudności diagnostyczne. Pomocne w ustaleniu rozpoznania, jak również dalszego postępowania z pacjentem, są aktualnie obowiązujące kryteria, które zostały zaproponowane w 2021 roku na konferencji w Waszyngtonie [34].

Do rozpoznania choroby wymagane jest spełnienie kryteriów wymienionych poniżej (dwóch dużych lub jednego dużego i dwóch małych).

Kryteria duże:

- plamy odbarwieniowe: >3 plam, >5 mm średnicy,
- naczyniakowłókniaki twarzy (*angiofibromas*): >3 lub włókniaki płaskie okolicy czołowej (*angiofibromas or fibrous cephalic plaque*): >3,
- włókniaki okołopaznokciowe, niepourazowe (*ungula fibromas*): >2,
- plamy szagrynowe (*shagreen patch*),
- mnogie hamartoma siatkówki (*multiple retinal hamartomas*),
- guzy korowe mózgu (*cortical dysplasia*),
- guzki podwyściółkowe mózgu (*subependymal nodules*),
- podwyściółkowy gwiaździak olbrzymiokomórkowy (*subependymal gigant cell astrocytoma*),
- mięśniaki prążkowanokomórkowe serca (*rhabdomyomata*),
- limfangiolejomiomatoza (*lymphangioleiomyomatosis*),
- naczyniomięśniakotłuszczak (*angiomyolipoma*) [2].

Kryteria małe:

- zmiany skórne typu konfetti,
- mnogie ubytki szkliwa (*dental enemal pits*): >3,
- włókniaki jamy ustnej (*intraoral fibroma*): >2,
- zmiany achromatyczne w siatkówce (*retinal achromic patch*),
- mnogie torbiele nerek (*multiple renal cysts*),
- hamartoma w lokalizacji pozanerkowej (*nonrenal hamartomas*).

Podłoże genetyczne, diagnostyka i poradnictwo genetyczne

Podstawę genetyczną stwardnienia guzowatego stanowią warianty patogenne obecne w genach supresorowych *TSC1*

lub *TSC2*. Gen *TSC1* zlokalizowany jest na długim ramieniu chromosomu 9 (*locus* q34.13), najdłuższy transkrypt genu składa się z 23 egzonów (2 pierwsze są niekodujące, a egzon 5 i 12 ulegają alternatywnemu splicingowi), koduje białko hamartynę. Gen *TSC2* koduje tuberynę, położony jest na krótkim ramieniu chromosomu 16 (*locus* p13.3), najdłuższy transkrypt składa się z 42 egzonów (egzon 1 niekodujący, a egzony 25 i 31 ulegają alternatywnemu splicingowi) [35].

Hamartyna z tuberyną tworzą kompleks w którym hamartyna odpowiada za jego stabilizację poprzez superhelikalną domenę (*colied-coil*), dodatkowo wchodząc w interakcje z innymi białkami. Natomiast tuberyna pełni m.in. funkcję białka aktywującego GTPazę (*GTPase activating protein* – GAP) małego białka G Rheb, który reguluje/hamuje mTORC1 (kompleks 1 kinazy mTOR, ssaczy cel rapamycyny [*mammalian target of rapamycin kinase*]), kontrolujący translację białek, wzrost i proliferację komórek. Aktywność kompleksu hamartyna-tuberyna jest hamowana przez kinazy białkowe Akt i p38 MAPK [36].

Dysfunkcja kompleksu hamartyna-tuberyna przyczynia się do braku kontroli nad wieloma ścieżkami sygnałowymi, w tym nad ścieżką mTOR. Prowadzi to do jej stałej aktywności, co za tym idzie do niekontrolowanych podziałów komórkowych i proliferacji, a tym samym do rozwoju łagodnych guzów hamartomatycznych w wielu narządach [37].

Dotychczas poznano około 650 wariantów patogennych obecnych w *TSC1*, najczęściej są to zmiany prowadzące do skrócenia białka. Zmiany rozproszone są po całym genie i nie znaleziono miejsc *hot spot* z wyjątkiem egzonu 15, w którym odnotowano kilka powtarzających się mutacji. Warianty *missense* są rzadkie i występują głównie w miejscu kodującym koniec N białka, przez co wpływają na jego destabilizację [38]. W genie *TSC2* znanych jest około 1900 wariantów patogennych. Rozmieszczone są w całym genie, a ponad 30% zlokalizowanych jest w egzonach od 32 do 41, kodujących domenę karboksylową zawierającą ważne domeny funkcjonalne, w tym GAP [39].

Nie znaleziono korelacji między typem mutacji w *TSC1* a fenotypem, ponadto u chorych obserwuje się lżejszy przebieg choroby w porównaniu z pacjentami z mutacjami w *TSC2*. Kobiety, u których stwierdza się mutacje w domenie karboksylowej genu *TSC2* (egzony 40 i 41), są bardziej narażone na rozwój limfangiolejomiomatozy [40]. Ponadto pacjenci z TSC i wielotorbielowatością nerek mają wyższe ryzyko cięższego przebiegu choroby, jeśli obecne są patogenne warianty genu *TSC2*. W przypadku delecji genu *TSC2* dochodzi do delecji genu kodującego policystynę-1 *PKD1* (końce 3' tych genów zachodzą na siebie), powodując zespół genów przyległych związany z wczesnym wystąpieniem oraz ciężkim przebiegiem wielotorbielowatości nerek [41]. Co ciekawe, opisywane są również przypadki osób/rodzin z mutacjami w *TSC2*, które miały łagodniejszy przebieg choroby, były skąpoobjawowe lub asymptomatyczne [42, 43].

Stwardnienie guzowate dziedziczone jest w sposób autosomalnie dominujący ze znaczą przewagą przypadków choroby z mutacją *de novo*. Szacuje się, że około 70% pacjentów nie ma w rodzinie nikogo chorego, natomiast pozostałe 30% to przypadki rodzinne [35]. Mutacje w genie *TSC1* są prawie dwukrotnie częstsze w rodzinach w porównaniu z formą sporadyczną. Penetracja mutacji *TSC1* i *TSC2* jest całkowita, obserwuje się natomiast zmienną ekspresję choroby [42]. Jej objawy występują u osób, u których druga kopia genu ulega wyciszeniu na skutek zmian w obrębie sekwencji DNA (mutacji) lub zmian epigenetycznych – teoria dwóch uderzeń Knudsona [35].

Identyfikacja patogennej zmiany jest niezbędna dla opracowania optymalnego dla pacjenta postępowania profilaktycznego oraz poradnictwa genetycznego obejmującego jego rodzinę. Ryzyko przekazania przez nosiciela mutacji krytycznej zmiany potomstwu wynosi 50%. Obecnie w badaniu genetycznym analizowane są sekwencje obu kluczowych genów oraz zmiany typu delecji/duplikacji. Metodą, która pozwala na szybką analizę sekwencji, jest sekwencjonowanie następnej generacji (*next generation sequencing* – NGS), natomiast do analizy delecji/duplikacji rekomendowane są metody oparte m.in. na technice MLPA (amplifikacja sond zależna od ligacji [*multiplex ligation-depend probe amplification*]), FISH (*fluorescent in situ hybrydization*) i aCGH (*array comparative genomic hybridization*) [35, 39]. W przypadku niepewnej diagnozy klinicznej można rozważyć użycie testu opartego o wybrany panel genów (diagnostyka różnicowa). Około 70% mutacji stwierdzanych jest w genie *TSC2*, a pozostałe 25% w genie *TSC1*. Niestwierdzenie obecności wariantu patogennego u osoby z rozpoznaniem klinicznym często wiąże się z istnieniem mozaicyzmu. W związku z tym do rozważenia pozostaje badanie innych tkanek chorego. Ponadto możliwy jest również mozaicyzm germinalny u zdrowych rodziców (bez mutacji), którzy mają chore dziecko [35]. W przypadku identyfikacji mutacji germinalnej możliwe jest również przeprowadzenie testów prenatalnych i preimplantacyjnych [39].

Podsumowanie

Choroba von Hippla i Lindaua oraz stwardnienie guzowate należą do grupy fakomatoz – schorzeń uwarunkowanych genetycznie predysponujących do rozwoju nowotworów mnogich. Z uwagi na podobieństwo zmian skórnych występujących w przebiegu omawianych jednostek chorobowych, konieczne jest różnicowanie z nerwiakowłókniakowatością 1 i 2 oraz schwannomatozą. Wczesne wykrycie i w konsekwencji objęcie pacjentów wielospecjalistycznym nadzorem poprawia rokowanie, umożliwiając wdrożenie leczenia nowotworów w początkowym stadium zaawansowania choroby. Poszerzająca się wciąż wiedza genetyczna pozwala coraz lepiej poznać obie choroby od strony molekularnej. A to prawdopodobnie pozwoli w przyszłości na wprowadzenie

leczenia personalizowanego, które znacznie podniesie komfort życia pacjentów.

Konflikt interesów: nie zgłoszono

Anna Kofla-Dłubacz
Uniwersytet Medyczny we Wrocławiu
Wydział Lekarski
II Katedra i Klinika Pediatrii, Gastroenterologii i Żywienia
ul. M. Curie-Skłodowskiej 50/52
55-369 Wrocław
e-mail: anna.kofla-dlubacz@umed.wroc.pl

Otrzymano: 7 czerwca 2021
Zaakceptowano: 18 października 2021

Piśmiennictwo

1. Chittiboina P, Lonser RR. Von Hippel-Lindau disease. Handb Clin Neurol. 2015; 132: 139–156, doi: 10.1016/B978-0-444-62702-5.00010-X, indexed in Pubmed: 26564077.
2. Ning XH, Zhang N, Li T, et al. Telomere shortening is associated with genetic anticipation in Chinese Von Hippel-Lindau disease families. Cancer Res. 2014; 74(14): 3802–3809, doi: 10.1158/0008-5472.CAN-14-0024, indexed in Pubmed: 24986515.
3. Wilding A, Ingham SL, Lalloo F, et al. Life expectancy in hereditary cancer predisposing diseases: an observational study. J Med Genet. 2012; 49(4): 264–269, doi: 10.1136/jmedgenet-2011-100562, indexed in Pubmed: 22362873.
4. Neumann H, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome: evidence for a complex genetic locus. Lancet. 1991; 337(8749): 1052–1054, doi: 10.1016/0140-6736(91)91705-y, indexed in Pubmed: 1673491.
5. Manski TJ. Endolymphatic sac tumors. A source of morbid hearing loss in von Hippel-Lindau disease. JAMA. 1997; 277(18): 1461–1466, doi: 10.1001/jama.277.18.1461, indexed in Pubmed: 9145719.
6. Poulsen MLM, Budtz-Jørgensen E, Bisgaard ML. Surveillance in von Hippel-Lindau disease (vHL). Clin Genet. 2010; 77(1): 49–59, doi: 10.1111/j.1399-0004.2009.01281.x , indexed in Pubmed: 19863552.
7. Knutsson KA, De Benedetto U, Querques G, et al. Primitive retinal vascular abnormalities: tumors and telangiectasias. Ophthalmologica. 2012; 228(2): 67–77, doi: 10.1159/000338230, indexed in Pubmed: 22738997.
8. Renal Cell Carcinoma EAU Guidelines on. 2018.
9. Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. Rev Urol. 2002; 4(4): 163–170, indexed in Pubmed: 16985675.
10. Shuin T, Yamasaki I, Tamura K, et al. Von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment. Jpn J Clin Oncol. 2006; 36(6): 337–343, doi: 10.1093/jjco/hyl052, indexed in Pubmed: 16818478.
11. Choyke PL, Glenn GM, Walther MM, et al. von Hippel-Lindau disease: genetic, clinical, and imaging features. Radiology. 1995; 194(3): 629–642, doi: 10.1148/radiology.194.3.7862955, indexed in Pubmed: 7862955.
12. Clark PE, Cookson MS. The von Hippel-Lindau gene: turning discovery into therapy. Cancer. 2008; 113(7 Suppl): 1768–1778, doi: 10.1002/cncr.23645, indexed in Pubmed: 18800388.
13. Maher E, Sandford R. von Hippel-Lindau Disease: an Update. Current Genetic Medicine Reports. 2019; 7(4): 227–235, doi: 10.1007/s40142-019-00180-9.
14. Lonser R, Glenn G, Walther M, et al. von Hippel-Lindau disease. The Lancet. 2003; 361(9374): 2059–2067, doi: 10.1016/s0140-6736(03)13643-4.
15. Groulx I, Lee S. Oxygen-dependent ubiquitination and degradation of hypoxia-inducible factor requires nuclear-cytoplasmic trafficking of the von Hippel-Lindau tumor suppressor protein. Mol Cell Biol. 2002; 22(15): 5319–5336, doi: 10.1128/MCB.22.15.5319-5336.2002, indexed in Pubmed: 12101228.
16. Strowitzki MJ, Cummins EP, Taylor CT. Protein Hydroxylation by Hypoxia-Inducible Factor (HIF) Hydroxylases: Unique or Ubiquitous? Cells. 2019; 8(5), doi: 10.3390/cells8050384, indexed in Pubmed: 31035491.
17. Aronow M, Wiley H, Gaudric A, et al. VON HIPPEL–LINDAU DISEASE. Retina. 2019; 39(12): 2243–2253, doi: 10.1097/iae.0000000000002555.
18. Haase VH. The VHL tumor suppressor: master regulator of HIF. Curr Pharm Des. 2009; 15(33): 3895–3903, doi: 10.2174/138161209789649394, indexed in Pubmed: 19671042.
19. Ben-Skowronek I, Kozaczuk S. Von Hippel-Lindau Syndrome. Horm Res Paediatr. 2015; 84(3): 145–152, doi: 10.1159/000431323, indexed in Pubmed: 26279462.
20. Decker J, Neuhaus C, Macdonald F, et al. Clinical utility gene card for: von Hippel-Lindau (VHL). Eur J Hum Genet. 2014; 22(4), doi: 10.1038/ejhg.2013.180, indexed in Pubmed: 23982691.
21. Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al. ed. GeneReviews®. University of Washington, Seattle 2018: 1–32.
22. Kondo K, Kaelin WG. The von Hippel-Lindau tumor suppressor gene. Exp Cell Res. 2001; 264(1): 117–125, doi: 10.1006/excr.2000.5139, indexed in Pubmed: 11237528.
23. Priesemann M, Davies KM, Perry LA, et al. Benefits of screening in von Hippel-Lindau disease--comparison of morbidity associated with initial tumours in affected parents and children. Horm Res. 2006; 66(1): 1–5, doi: 10.1159/000093008, indexed in Pubmed: 16651847.
24. Santarpia L, Sarlis NJ, Santarpia M, et al. Mosaicism in von Hippel-Lindau disease: an event important to recognize. J Cell Mol Med. 2007; 11(6): 1408–1415, doi: 10.1111/j.1582-4934.2007.00122.x, indexed in Pubmed: 18205710.
25. Yates J. Tuberous sclerosis. European Journal of Human Genetics. 2006; 14(10): 1065–1073, doi: 10.1038/sj.ejhg.5201625.
26. Portocarrero LK, Quental KN, Samorano LP, et al. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018; 93(3): 323–331, doi: 10.1590/abd1806-4841.20186972, indexed in Pubmed: 29924239.
27. Roach ES, Sparagana SP. Diagnosis of tuberous sclerosis complex. J Child Neurol. 2004; 19(9): 643–649, doi: 10.1177/08830738040190090301, indexed in Pubmed: 15563009.
28. Kandt RS, Haines JL, Smith M, et al. Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease. Nat Genet. 1992; 2(1): 37–41, doi: 10.1038/ng0992-37, indexed in Pubmed: 1303246.
29. Joinson C, O'Callaghan FJ, Osborne JP, et al. Learning disability and epilepsy in an epidemiological sample of individuals with tuberous sclerosis complex. Psychol Med. 2003; 33(2): 335–344, doi: 10.1017/s0033291702007092, indexed in Pubmed: 12622312.
30. DiMario F. Brain Abnormalities in Tuberous Sclerosis Complex. J Child Neurol. 2016; 19(9): 650–657, doi: 10.1177/08830738040190090401, indexed in Pubmed: 15563010.
31. McClintock W. Neurologic manifestations of tuberous sclerosis complex. J Child Neurol. 2002; 2(2): 158–163, doi: 10.1007/s11910-002-0025-2, indexed in Pubmed: 15563016.
32. Rodrigues DA, Gomes CM, Costa IM. Tuberous sclerosis complex. An Bras Dermatol. 2012; 87(2): 184–196, doi: 10.1590/s0365-05962012000200001, indexed in Pubmed: 22570021.
33. Rowley SA, O'Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001; 85(4): 420–423, doi: 10.1136/bjo.85.4.420, indexed in Pubmed: 11264130.
34. Krueger D, Northrup H, Northrup H, et al. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurology. 2013; 49(4): 255–265, doi: 10.1016/j.pediatrneurol.2013.08.002.
35. Rosset C, Netto CB, Ashton-Prolla P. TSC1 and TSC2 gene mutations and their implications for treatment in Tuberous Sclerosis Complex: a review. Genet Mol Biol. 2017; 40(1): 69–79, doi: 10.1590/1678-4685-GMB-2015-0321, indexed in Pubmed: 28222202.
36. Tee A, Manning B, Roux P, et al. Tuberous Sclerosis Complex Gene Products, Tuberin and Hamartin, Control mTOR Signaling by Acting as a GTPase-Activating Protein Complex toward Rheb. Curr Biol. 2003; 13(15): 1259–1268, doi: 10.1016/s0960-9822(03)00506-2, indexed in Pubmed: 12906785.
37. Huang J, Manning BD. The TSC1-TSC2 complex: a molecular switchboard controlling cell growth. Biochem J. 2008; 412(2): 179–190, doi: 10.1042/BJ20080281, indexed in Pubmed: 18466115.
38. Hoogeveen-Westerveld M, Ekong R, Povey S, et al. Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. Hum Mutat. 2012; 33(3): 476–479, doi: 10.1002/humu.22007, indexed in Pubmed: 22161988.

39. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous Sclerosis Complex-GeneReviews®. GeneReviews®. University of Washington, Seattle 1993.
40. Strizheva GD, Carsillo T, Kruger WD, et al. The spectrum of mutations in TSC1 and TSC2 in women with tuberous sclerosis and lymphangiomyomatosis. Am J Respir Crit Care Med. 2001; 163(1): 253–258, doi: 10.1164/ajrccm.163.1.2005004, indexed in Pubmed: 11208653.
41. Woerner AC, Au KS, Williams AT, et al. Tuberous sclerosis complex and polycystic kidney disease together: an exception to the contiguous gene syndrome. Genet Med. 2006; 8(3): 197–198, doi: 10.1097/01.gim.0000204466.34876.d5, indexed in Pubmed: 16540757.
42. Fox J, Ben-Shachar S, Uliel S, et al. Rare familial TSC2 gene mutation associated with atypical phenotype presentation of Tuberous Sclerosis Complex. Am J Med Genet A. 2017; 173(3): 744–748, doi: 10.1002/ajmg.a.38027, indexed in Pubmed: 28127866.
43. Farach LS, Gibson WT, Sparagana SP, et al. TSC2 c.1864C>T variant associated with mild cases of tuberous sclerosis complex. Am J Med Genet A. 2017; 173(3): 771–775, doi: 10.1002/ajmg.a.38083, indexed in Pubmed: 28211972.

VIA MEDICA

List do Redakcji / Letter to the Editor

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 66–67

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Is the elimination of cervical cancer now 3 times easier? One-dose vaccine efficacy has far-reaching implications

Paweł Koczkodaj[1], Joakim Dillner[2], Marta Mańczuk[1]

[1]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Karolinska Institute, Stockholm, Sweden*

More and more studies have proven that low trust in vaccines has become a universal phenomenon, regardless of the region of the world and type of vaccine [1–3]. Particularly intense public debate on vaccines efficacy and safety has been (and still is) visible during the COVID-19 pandemic. A plethora of misconceptions, myths and fake news on vaccines has come to the fore recently, causing a lack of trust, not only in COVID-19 vaccines. Searching for new paths to cope with this public health challenge should be one of the key points of current international and national health policy agendas. In this context, recent research results look very promising, i.e. a single dose of vaccination against HPV has a similar efficacy to two and three doses [4]. These results may have far-reaching implications – primarily in a public health context, as it may enable a much faster eradication of HPV regionally and worldwide, moreover, those reluctant to get the HPV vaccine will be more likely to take just one dose, rather than three.

Europe's Beating Cancer Plan launched by the European Commission at the beginning of 2021 assumes vaccinations of target population of girls will be at the level of 90% by 2030 as well as acceleration of vaccinations among boys. However, the document describes a "fully vaccinated" target population, implying having completed a 3-dose scheme which can be much more difficult taking into consideration high social HPV vaccine hesitancy. Moreover, in the coming years (at least 4-5 years), due to rapidly growing demand, there are predictions of further HPV-vaccine shortages on the world market. Furthermore, despite the plans of new manufacturers to enter the market, it will take some time to begin efficient production (even 4 years are needed for manufacturing the final product). Moreover, legal difficulties impede shifting HPV vaccinations supplies from one country to another [5]. Discussing all of these obstacles, it is crucial to significantly increase social trust in HPV vaccinations. Implementation of the one-dose vaccination scheme seems to be one of the easiest and most beneficial ways to achieve this goal. Additionally, faster HPV eradication can be obtained by combining vaccination and screening in organised programs [6, 7] and this strategy would be greatly facilitated if both screening and vaccination could be completed in a single visit.

The WHO has specifically called for further research on innovative ways to achieve the elimination goal faster. The fact that it has also now been shown for the quadrivalent vaccine (that a single-dose HPV vaccination is as effective as a 3-doses full scheme), means the results could help to overcome one of the most important barriers to broad vaccine coverage – low social trust.

Conflict of interest: none declared

Paweł Koczkodaj
Maria Sklodowska-Curie National Research Institute of Oncology
Cancer Epidemiology and Primary Prevention Department
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: pawel.koczkodaj@pib-nio.pl

Received: 16 Nov 2021
Accepted: 21 Nov 2021

Jak cytować / How to cite:

Koczkodaj P, Dillner J, Mańczuk M. ***Is the elimination of cervical cancer now 3 times easier? One-dose vaccine efficacy has far-reaching implications.*** *NOWOTWORY J Oncol* 2022; 72: 65–66.

References

1. Kunitoki K, Funato M, Mitsunami M, et al. Access to HPV vaccination in Japan: Increasing social trust to regain vaccine confidence. Vaccine. 2021; 39(41): 6104–6110, doi: 10.1016/j.vaccine.2021.08.085, indexed in Pubmed: 34507858.
2. Karafillakis E, Simas C, Jarrett C, et al. HPV vaccination in a context of public mistrust and uncertainty: a systematic literature review of determinants of HPV vaccine hesitancy in Europe. Hum Vaccin Immunother. 2019; 15(7-8): 1615–1627, doi: 10.1080/21645515.2018.1564436, indexed in Pubmed: 30633623.
3. Troiano G, Nardi A. Vaccine hesitancy in the era of COVID-19. Public Health. 2021; 194: 245–251, doi: 10.1016/j.puhe.2021.02.025, indexed in Pubmed: 33965796.
4. Basu P, Malvi S, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. The Lancet Oncology. 2021; 22(11): 1518–1529, doi: 10.1016/s1470-2045(21)00453-8.
5. Garland SM, Stanley MA, Giuliano AR, et al. IPVS Policy Committee. IPVS statement on "Temporary HPV vaccine shortage: Implications globally to achieve equity". Papillomavirus Res. 2020; 9: 100195, doi: 10.1016/j.pvr.2020.100195, indexed in Pubmed: 32205196.
6. Bosch FX, Robles C, Díaz M, et al. HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nat Rev Clin Oncol. 2016; 13(2): 119–132, doi: 10.1038/nrclinonc.2015.146, indexed in Pubmed: 26323382.
7. Dillner J, Elfström KM, Baussano I. Prospects for accelerated elimination of cervical cancer. Prev Med. 2021; 153: 106827, doi: 10.1016/j.ypmed.2021.106827, indexed in Pubmed: 34599922.

Z kalendarium Zarządu PTO

listopad – grudzień 2021

Wszystkie wykłady z V Kongresu Onkologii Polskiej dostępne online

Wszystkie osoby, które opłaciły udział w V Kongresie Onkologii Polskiej, otrzymują bezpłatny dostęp do nagrań z kongresu.

1. Aby uzyskać dostęp do nagrań, należy wejść na stronę: www.kongres.pto.med.pl.
2. Następnie prosimy o zalogowanie się loginem i hasłem użytymi podczas rejestracji na kongres.
3. Po zalogowaniu na górze strony pojawi się zakładka: „Sesje nagrane".
4. Poszczególne nagrania można odtworzyć, klikając w wybraną grafikę.

Stanowisko Polskiego Towarzystwa Onkologicznego w sprawie projektu Ustawy o Krajowej Sieci Onkologicznej

Wdrożenie Krajowej Sieci Onkologicznej jest jednym z kluczowych elementów przewidzianych w ramach Narodowej Strategii Onkologicznej przyjętej zgodnie z regulacjami ustawy o Narodowej Strategii Onkologicznej. Podstawowym celem w tym obszarze jest utworzenie podmiotów wyspecjalizowanych w diagnostyce i leczeniu wybranych nowotworów oraz zapewnienie wszystkim pacjentom onkologicznym najwyższej jakości standardów diagnostyki i leczenia.

Ustawa ma uporządkować strukturę organizacyjną i wprowadzić nowy model zarządzania opieką onkologiczną, które mają przyczynić się do usprawnienia organizacji systemu udzielania świadczeń opieki zdrowotnej w zakresie onkologii. Projekt ustawy, ze względu na swą strategiczną i systemową rolę, ma kluczowe znaczenie dla polskiej onkologii. Zaproponowane w nim rozwiązania organizacyjne i finansowe mogą w kolejnych latach w istotny sposób wpłynąć na dostępność i jakość diagnostyki oraz leczenia w tym obszarze – przy zastrzeżeniu, że powinno to odbywać się zgodnie z „Mapami potrzeb zdrowotnych w zakresie onkologii".

Szczegóły na stronie www.pto.med.pl

Powstała pierwsza polska edycja wytycznych NCCN

W ramach międzynarodowej współpracy pomiędzy National Comprehensive Cancer Network (NCCN), a Narodowym Instytutem Onkologii – Państwowym Instytutem Badawczym (NIO–PIB) i Fundacją Alliance for Innovation opublikowano pierwsze z kilku wytycznych dla ośrodków onkologicznych. Opracowane w wyniku współpracy ekspertów wytyczne zostały oparte na dowodach naukowych i konsensusie ekspertów. Zawierają najnowsze zalecenia dotyczące leczenia nowotworów raka szyjki macicy. Opracowywane standardy mają na celu usprawnienie ogólnoświatowej opieki nad chorymi na raka, tak by pacjenci onkologiczni mieli dostęp do leczenia na zbliżonym poziomie w swoich krajach. Edycja polska wytycznych jest jedną z pierwszych, jakie udało się opracować w gronie międzynarodowych ekspertów, i które będą miały zastosowanie poza Stanami Zjednoczonymi.

Szczegóły na stronie www.pib-nio.pl

Wywiady i artykuły

Prof. Piotr Rutkowski w gronie najczęściej cytowanych naukowców 2021

Prof. dr hab. n. med. Piotr Rutkowski znalazł się w tegorocznym światowym gronie najczęściej cytowanych naukowców – na liście ekspertów Institute for Scientific Information™. Od 2001 roku lista Highly Cited Researchers™ zawiera nazwiska naukowców i socjologów, którzy wykazali wyjątkowy wpływ (w skali globalnej) – odzwierciedlony w publikacjach wielu artykułów często w ciągu ostatniej dekady cytowanych przez ich kolegów.

Źródło: www.pib-nio.pl

Polskie życzenia onkologiczne na 2022 rok

Każdy coś sobie życzy na Nowy Rok, również pacjenci i lekarze, chyba nawet szczególnie oni w dobie pandemii. Prof. Maciej Krzakowski z Narodowego Instytutu Onkologii nie ma wątpliwości: ważne jest, żeby wreszcie w Polsce powstał system koordynowanego i kompleksowego postępowania w Lung Cancer Unitach. „Tego sobie życzę na 2022 r. i oczywiście chorym również" – dodał.

Prof. Piotr Rutkowski, zastępca dyrektora Narodowego Instytutu Onkologii ds. Narodowej Strategii Onkologicznej i badań klinicznych, twierdzi, że mimo pandemii wiele się zmienia w polskiej onkologii. Bez perturbacji postępują badania nad terapiami onkologicznymi, jedynie na początku pandemii były zakłócenia w badaniach klinicznych, zarówno w Polsce, jak i na

świecie. Również jedynie na początku były u nas opóźnienia w rejestracji nowych leków onkologicznych. Na nowej liście refundacyjnej mamy nowe leki onkologiczne.

Źródło: mZdrowie

Dr hab. Adam Maciejczyk: uprządkowanie organizacji opieki onkologicznej to duże wyzwanie

Pandemia trwa już drugi rok i nadal wywiera negatywny wpływ na dostęp do opieki onkologicznej w Polsce. Pozytywne jest to, że organizacja pracy szpitali onkologicznych w obecnej fazie pandemii znacząco się poprawiła – mówi dr hab. n. med. Adam Maciejczyk, dyrektor Dolnośląskiego Centrum Onkologii, prezes Polskiego Towarzystwa Onkologicznego, kierownik Kliniki Radioterapii Katedry Onkologii Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu.

Przede wszystkim należy zwrócić uwagę na potrzebę zwiększenia wykrywalności nowotworów we wczesnych stadiach oraz obniżenia umieralności, w tym również poprzez zwiększenie efektywności leczenia. Nowe rozwiązania organizacyjne (Krajowa Sieć Onkologiczna – KSO) mają przyczynić się do ograniczania negatywnych zjawisk w polskiej onkologii, takich jak: fragmentacja opieki, rozproszenie świadczeń i ośrodków onkologicznych, które dotychczas wpływały bardzo negatywnie na jakość leczenia onkologicznego, a co za tym idzie, na szanse pacjentów na efektywną opiekę.

Uporządkowanie obowiązującego systemu, wprowadzenie KSO i konsekwentna realizacja zadań, których celem jest zapewnienie wszystkim pacjentom, bez względu na miejsce zamieszkania, dostępu do dobrej jakościowo opieki onkologicznej to duże wyzwanie dla naszego całego środowiska.

Źródło: Puls Medycyny

Dr hab. Adam Maciejczyk: karta DiLO powinna być specyficzna dla nowotworu

System DiLO i pilotaż Krajowej Sieci Onkologicznej to wzajemnie przenikające się i uzupełniające systemy. Konieczne jest ich scalenie. Niezbędna jest też modyfikacja karty DiLO, tak aby stała się kartą narządową – wskazuje dr hab. n. med. Adam Maciejczyk, prezes Polskiego Towarzystwa Onkologicznego.

Pilotaż KSO pozwala na kontrolę czasu wykonania procedur, kompletności poszczególnych etapów diagnostyki, a także na ocenę wpływu tych elementów na los chorych. Stanowi podstawę do oceny aktualnej sytuacji i umożliwia monitorowanie efektu wprowadzania zmian.

– System prowadzenia karty DiLO nie uwzględnia bardzo wielu elementów. Przede wszystkim nadzoru nad pacjentem po leczeniu, szczególnie w nowotworach trudnych do takiej kontroli, np. w raku pęcherza moczowego. W uroonkologii jest to konieczne. Nie obejmuje także leczenia ambulatoryjnego, np. BCG w terapii dopęcherzowej – z tym mamy poważny problem rozliczeniowy. Ponadto nie wyodrębnia chorych z wznową procesu nowotworowego.

– W tej chwili łączymy kartę DiLO z danymi medycznymi i widzimy różnice w możliwości wnioskowania na podstawie samych informacji z karty DiLO oraz na podstawie informacji z karty uzupełnionych o nasze dane medyczne. Karta DiLO nie jest odpowiednim narzędziem do monitorowania efektywności diagnostyki i leczenia pacjentów onkologicznych – tylko wyróżnia takiego pacjenta w systemie. Pokazuje, że chory może pójść na badanie i poprosić, aby było ono wcześniej wykonane, aczkolwiek nielimitowane badania obrazowe są już dostępne dla wszystkich – wyjaśnia dyrektor DCO.

Źródło: Puls Medycyny

Konferencje i wydarzenia

- 16 listopada 2021 r. PTO współorganizowało webinar na temat raportu „Standardy obsługi pacjentów w ramach leczenia raka piersi". Raport dostępny jest na stronie www.pto.med.pl.
- 24 listopada 2021 r. odbyła się Konferencja Fundacji Kulskich pt. „Recepta na przyszłość Europy w obliczu wyzwań społecznych, ekonomicznych i zdrowotnych po COVID-19. Unia Europejska, państwa członkowskie, społeczeństwo obywatelskie". Wziął w niej udział prezes PTO, dr hab. Adam Maciejczyk.
- 25 listopada 2021 r. zorganizowano 5. Ogólnopolskie Forum Kierowników Medycznych Laboratoriów Diagnostycznych. Dr hab. Adam Maciejczyk wygłosił wykład „Jakość diagnostyki molekularnej warunkiem skuteczności procesu leczenia w onkologii".
- 26 listopada 2021 r. miała miejsce V Konferencja Naukowo-Szkoleniowa „4R – Radioterapeuci Radioterapeutom mówią o radioterapii i radiobiologii" z udziałem członków Zarządu Głównego PTO.
- 1 grudnia 2021 r. w Senacie RP odbyło się spotkanie poświęcone podsumowaniu efektów pracy Europejskiej Specjalnej Komisji do spraw Walki z Rakiem. Uczestniczyli w nim członkowie ZG PTO – prof. Maciej Krzakowski, prof. Piotr Rutkowski oraz dr hab. Adam Maciejczyk.
- 9 grudnia 2021 r. w formie hybrydowej odbyła się konferencja „Warsaw Summit of European Cancer Strategies". Wydarzenie zorganizowali: Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy oraz Ministerstwo Zdrowia. W spotkaniu wzięli udział przedstawiciele Instytutów Onkologicznych ze Słowacji, Słowenii, Niemiec, Wielkiej Brytanii, Francji, Holandii, Brukseli, Litwy, Węgier i Łotwy.

VIA MEDICA

Journal Club

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 70–75

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

Pembrolizumab for persistent, recurrent or metastatic cervical cancer

Colombo N., Dubot C., Lorusso D. i wsp.
N. Engl. J. Med., 2021; 385: 1856–1867

Pembrolizumab jest skuteczny w leczeniu chorych na rozsianego lub nieoperacyjnego raka szyjki macicy z ekspresją 1. liganda programowanej śmierci (PD-L1), u których doszło do progresji po chemioterapii. Oceniono korzyść z dołączenia pembrolizumabu do chemioterapii podawanej z bewacyzumabem lub bez niego.

Metody. W podwójnie zaślepionym badaniu III fazy chore na przetrwałego, nawrotowego lub rozsianego raka szyjki macicy przydzielano losowo w stosunku 1:1 do leczenia pembrolizumabem (200 mg) lub placebo (co 3 tygodnie do 35 cykli) w połączeniu z chemioterapią zawierającą pochodną platyny, z bewacyzumabem do decyzji badacza. Pierwszorzędowym punktem końcowym był czas wolny od progresji oraz całkowity czas przeżycia oceniany u chorych z łącznym dodatnim wynikiem (*combined positive score* – CPS) PD-L1 co najmniej 1 w grupie zgodnej z intencją leczenia oraz u chorych z łącznym dodatnim wynikiem PD-L1 co najmniej 10; CPS PD-L1 oznacza liczbę komórek z ekspresją PD-L1 podzieloną przez całkowitą liczbę żywych komórek nowotworowych pomnożoną przez 100. Wszystkie wyniki pochodzą z pierwszej analizy pośredniej określonej w protokole.

Wyniki. U 548 chorych z CPS PD-L1 co najmniej 1 mediana czasu wolnego od progresji wyniosła 10,4 miesiąca w grupie leczonych z użyciem pembrolizumabu i 8,2 miesiąca w grupie otrzymującej placebo (współczynnik ryzyka progresji lub zgonu 0,62; 95% przedział ufności [*confidence interval* – CI] 0,50–0,77; p < 0,001). U 617 chorych w grupie zgodnej z intencją leczenia czas wolny od progresji wyniósł odpowiednio 10,4 i 8,2 miesiąca (współczynnik ryzyka [*hazard ratio* – HR] 0,65; 95% CI 0,53–0,79; p < 0,001). Z kolei dla 317 chorych z CPS PD-L1 co najmniej 10 czas wolny od progresji wyniósł odpowiednio 10,4 i 8,1 miesiąca (współczynnik ryzyka 0,58; 95% CI 0,44–0,77; p < 0,001). Udział całkowitych 24-miesięcznych przeżyć w grupie leczonej z użyciem pembrolizumabu wyniósł 53%, a w grupie otrzymujących placebo 41,7% (współczynnik ryzyka zgonu 0,64; 95% CI 0,50–0,81; p < 0,001) oraz odpowiednio 50,4% i 40,4% (współczynnik ryzyka 0,67; 95% CI 0,54–0,84; p < 0,001) i odpowiednio 54,4% i 44,6% (współczynnik ryzyka 0,61; 95% CI 0,44–0,84; p = 0,001). Najczęstszym działaniem niepożądanym w stopniu 3.–5. była niedokrwistość (30,3% w grupie leczonych pembrolizumabem i 26,9% w grupie otrzymujących placebo) oraz neutropenia (odpowiednio: 12,4% i 9,7%).

Wnioski. Czas wolny od progresji i całkowity czas przeżycia chorych na przetrwałego, nawrotowego lub rozsianego raka szyjki macicy poddawanych chemioterapii, z lub bez bewacyzumabu, były znacząco dłuższe dla otrzymujących równocześnie z chemioterapią pembrolizumab niż w grupie stosujących placebo.

The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study

Falcaro M., Castañon A., Ndlela B. i wsp.
Lancet, 2021; 398: 2084–2092

Szczepienie przeciwko wirusowi brodawczaka ludzkiego (*human papilloma virus* – HPV) szczepionką dwuwalentną (Cervarix) zostało wprowadzone w Anglii 1 września 2008 roku. Powszechne szczepienie było proponowane dziewczynkom w wieku 12–13 lat z programem wyrównawczym dla dziewcząt w wieku 14–18 lat w latach 2008–2010. W badaniu oceniono wczesne skutki programu szczepienia przeciwko rakowi szyjki macicy i przeciwko przedinwazyjnemu rakowi szyjki macicy, nazywanemu wewnątrznabłonkowym nowotworzeniem (*cervical intraepithelial neoplasia* – CIN) szyjki macicy 3. stopnia (CIN3).

Metody. W badaniu obserwacyjnym zastosowano rozszerzony rozkład Poissona dla grupy wiekowej w celu oszacowania względnego ryzyka zachorowania na raka szyjki macicy w trzech zaszczepionych grupach w porównaniu z wcześniejszymi kohortami, które nie kwalifikowały się do szczepienia przeciwko HPV. Dane z powszechnego rejestru nowotworów pobrane 26 stycznia 2021 roku oceniono pod kątem rozpoznania raka szyjki macicy i CIN3 od 1 stycznia 2006 roku do 30 czerwca 2019 roku u mieszkających w Anglii kobiet w wieku 20–64 lat. Wykorzystano trzy zaszczepione grupy, aby uwzględnić różnice w roku szkolnym, w którym zaoferowano szczepionkę oraz jej ogólnokrajowy zasięg. Analizy dokonano, uwzględniając zmiany w polityce badań przesiewowych w kierunku raka szyjki macicy i wydarzenia historyczne, które wpłynęły na zachorowalność na raka szyjki macicy. Wyniki porównano pomiędzy modelami z uwzględnieniem czynników zakłócających.

Wyniki. Wykorzystano dane z 13,7 miliona lat obserwacji kobiet w wieku od 20 do mniej niż 30 lat. Szacowane względne

zmniejszenie zachorowalności na raka szyjki macicy według wieku w chwili podania szczepionki wyniosło 34% (95% CI 25–41) dla wieku 16–18 lat (12. –13. rok szkolny), 62% (52–71) dla wieku 14–16 lat (10. –11. rok szkolny) i 87% (72–94) dla wieku 12–13 lat (8. rok szkolny) w porównaniu z dobraną grupą niezaszczepionych. Zmniejszenie ryzyka rozwoju CIN3 wyniosło 39% (95% CI 36–41) dla wieku 16–18 lat, 75% (72–77) dla wieku 14–16 lat i 97% (96–98) dla wieku 12-–13 lat. Wyniki te były podobne we wszystkich modelach. Oszacowano, że do 30 czerwca 2019 roku w zaszczepionych grupach w Anglii zachorowań na raka szyjki macicy było o 448 (339–556) mniej niż oczekiwano. Odnotowano także o 17 235 (15 919–18 552) mniej rozpoznań CIN3.

Wnioski. Po wprowadzeniu programu szczepień przeciw HPV w Anglii zaobserwowano znaczne zmniejszenie liczby zachorowań na raka szyjki macicy i CIN3, zwłaszcza wśród dziewcząt zaszczepionych w wieku 12–13 lat. Program szczepień przeciwko HPV prawie całkowicie wyeliminował raka szyjki macicy u kobiet urodzonych po 1 września 1995 roku.

21-gene assay to inform chemotherapy benefit in node-positive breast cancer

Kalinsky K., Barlow W., Gralow J. i wsp.
N. Engl. J. Med., 2021; 385: 2336–2347

Ocena ryzyka nawrotu raka piersi oparta na badaniu 21 genów jest klinicznie użyteczna w przewidywaniu korzyści z chemioterapii u chorych na hormonozależnego, HER2-ujemnego raka piersi bez zajęcia pachowych węzłów chłonnych. U kobiet z zajętymi pachowymi węzłami chłonnymi rola tej oceny ryzyka nawrotu raka piersi oraz określenia korzyści z zastosowania uzupełniającej chemioterapii jest niejasna.

Metody. W prospektywnym badaniu chore na hormonozależnego, HER2-ujemnego raka piersi z zajęciem 1–3 pachowych węzłów chłonnych i wskaźnikiem nawrotu 25 lub niższym (zakres wyniku 0–100; im wyższy wynik, tym gorsze rokowanie) przydzielano losowo do wyłącznej hormonoterapii lub do chemioterapii z hormonoterapią. Pierwszorzędowym punktem końcowym było określenie wpływu chemioterapii na czas wolny od choroby i wynik oceny wskaźnika nawrotu. Drugorzędowym punktem końcowym był czas wolny od rozsiewu.

Wyniki. Spośród 5083 chorych (33,2% przed menopauzą i 66,8% po menopauzie) przydzielonych losowo do leczenia, w badaniu wzięło udział 5018. W określonej wcześniej, trzeciej analizie śródokresowej stwierdzono różnice w korzyści z zastosowania chemioterapii w zakresie wydłużenia czasu wolnego od choroby w zależności od występowania menopauzy (p = 0,008 dla porównania korzyści z chemioterapii u kobiet przed menopauzą i po menopauzie) i przeprowadzono oddzielne, z góry określone analizy. Wśród kobiet po menopauzie udział 5-letnich przeżyć wolnych od choroby wyniósł 91,9% wśród poddanych hormonoterapii oraz 91,3% wśród poddanych chemioterapii i hormonoterapii, bez korzyści z zastosowania chemioterapii (współczynnik ryzyka nawrotu choroby lub wystąpienia nowego nowotworu pierwotnego [rak piersi lub inny nowotwór pierwotny] oraz zgonu 1,02; 95% CI 0,82–1,26; p = 0,89). Wśród kobiet przed menopauzą udział 5-letnich przeżyć wolnych od choroby wyniósł 89% w grupie poddanej wyłącznie hormonoterapii oraz 93,9% w grupie poddanej hormonoterapii i chemioterapii (współczynnik ryzyka 0,60; 95% CI 0,43–0,83; p = 0,002) z podobną korzyścią w zakresie przeżycia bez rozsiewu (współczynnik ryzyka 0,58; 95% CI 0,39–0,87; p = 0,009). Względna korzyść z chemioterapii nie wzrosła wraz z wyższym wskaźnikiem ryzyka nawrotu.

Wnioski. Wśród kobiet przed menopauzą, z zajęciem od jednego do trzech pachowych węzłów chłonnych i wskaźnikiem ryzyka nawrotu wynoszącym 25 lub mniej, poddanych chemioterapii z hormonoterapią, czas wolny od choroby i wolny od rozsiewu był dłuższy w porównaniu z kobietami poddanymi wyłącznie hormonoterapii. U kobiet po menopauzie z podobnymi cechami uzupełniająca chemioterapia nie przyniosła korzyści.

Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study

Mohile S.G., Mohamed M.R., Xu H. i wsp.
Lancet, 2021; 398: 1894–1904

U starszych chorych na zaawansowane nowotwory ryzyko toksycznych powikłań związanych z leczeniem onkologicznym jest duże. Ocena geriatryczna określa cechy związane ze starzeniem się oraz jest źródłem wytycznych prawidłowego postępowania w tej grupie chorych. Zbadano, czy stosowanie oceny geriatrycznej może zmniejszyć częstość poważnych działań niepożądanych u starszych chorych na zaawansowane nowotwory poddawanych leczeniu wysokiego ryzyka (np. chemioterapii).

Metody. Do badania klastrowego z randomizacją włączano chorych na nieuleczalne guzy lite lub chłoniaki, w wieku 70 lat i starszych, z co najmniej jedną nieprawidłową domeną oceny geriatrycznej, którzy rozpoczynali nowy schemat leczenia. W 40 ośrodkach onkologicznych w Stanach Zjednoczonych losowo przydzielono (1:1) obserwowanych do interwencji (onkolodzy otrzymali dostosowane do potrzeb podsumowanie oceny geriatrycznej i zalecenia dotyczące postępowania) lub do zwykłej opieki (onkologom nie przekazano podsumowania oceny geriatrycznej ani zaleceń). Pierwszorzędowym punktem końcowym był udział chorych, u których wystąpiło jakiekolwiek działanie niepożądane stopnia 3.–5. (wg CTCAE wersja 4.0) w ciągu 3 miesięcy. Działania niepożądane były odnotowywane prospektywnie przez personel medyczny. Niezależna grupa onkologów analizowała dokumentację medyczną w celu weryfikacji danych.

Wyniki. Od 29 lipca 2014 roku do 13 marca 2019 roku włączono do badania 718 chorych. Średni wiek chorych wynosił 77,2 roku (SD 5,4), a 311 spośród 718 chorych (43%) stanowiły kobiety. Średnia liczba nieprawidłowych domen oceny geriatrycznej wyniosła 4,5 (SD 1,6) i pod tym względem nie było znamiennej różnicy pomiędzy grupami. Większa liczba chorych w grupie interwencyjnej w porównaniu z grupą kontrolną była rasy czarnej w porównaniu z innymi rasami (40 spośród 349 chorych [11%] w porównaniu z 12 spośród 369 chorych [3%]; p < 0,0001) i była wcześniej poddana chemioterapii (104 spośród 349 chorych [30%] *vs* 81 spośród 369 chorych [22%]; p = 0,016). Mniejsza liczba chorych w grupie interwencyjnej doświadczyła toksyczności leczenia w stopniu 3.–5. (177 spośród 349 chorych [51%]) w porównaniu z grupą kontrolną (263 spośród 369 chorych [71%]; ryzyko względne [*relative rsk* – RR] 0,74 (95% CI 0,64–0,86; p = 0,0001). Chorzy w grupie interwencyjnej doznali mniejszej ilości upadków w ciągu 3 miesięcy (35 spośród 298 chorych [12%] *vs* 68 spośród 329 chorych [21%]; skorygowane RR 0,58, 95% CI 0,40–0,84; p = 0,035) oraz możliwe było u nich odstawienie większej liczby przyjmowanych leków (średnia skorygowana różnica 0,14, 95% CI 0,03–0,25; p = 0,015).

Wnioski. Ocena geriatryczna u starszych chorych na zaawansowane nowotwory zmniejszyła częstość poważnych działań niepożądanych związanych z leczeniem nowotworu. Ocena geriatryczna wraz z opartym na niej właściwym postępowaniem powinna stanowić zintegrowany element opieki klinicznej w tej grupie chorych.

Belzutifan for renal cell carcinoma in von Hippel-Lindau disease

Jonasch E., Donskov F., Iliopoulos O. i wsp.
N. Engl. J. Med., 2021; 385: 2036–2046

U chorych z zespołem von Hippla i Lindaua (VHL) ryzyko zachorowania na raka nerkowokomórkowego jest duże z powodu inaktywacji genu VHL i konstytutywnej aktywacji czynnika transkrypcyjnego indukowanego hipoksją 2α (HIF-2α).

Metody. W otwartym jednogrupowym badaniu II fazy zbadano skuteczność i bezpieczeństwo stosowania belzutifanu – inhibitora HIF-2α – podawanego doustnie (w dawce 120 mg na dobę) u chorych na raka nerkowokomórkowego związanego z chorobą VHL. Pierwszorzędowym punktem końcowym była obiektywna odpowiedź na leczenie (CR lub PR) mierzona zgodnie z kryteriami RECIST (wersja 1.1). Oceniono również odpowiedź na belzutifan u chorych na nowotwory nie-nerkowokomórkowe oraz bezpieczeństwo stosowania tego leku.

Wyniki. Po obserwacji o medianie wynoszącej 21,8 miesiąca (zakres 20,2–30,1), udział chorych z obiektywną odpowiedzią wyniósł 49% (95% CI 36–62). Odpowiedzi obserwowano również u chorych ze zmianami w trzustce (47 spośród 61 chorych [77%]) i zarodkowymi naczyniakami krwionośnymi ośrodkowego układu nerwowego (15 spośród 50 chorych [30%)]. Dodatkowo wykazano poprawę u wszystkich chorych z zarodkowymi naczyniakami siatkówki (12 chorych [100%]). Najczęstszymi zdarzeniami niepożądanymi były niedokrwistość (u 90% chorych) i zmęczenie (u 66%). Siedmiu chorych przerwało leczenie: czterech z własnej woli, jeden z powodu zdarzenia niepożądanego związanego z leczeniem (zawroty głowy stopnia 1.), jeden z powodu progresji choroby w ocenie badacza, jeden zmarł (z powodu toksycznego działania fentanylu).

Wnioski. Belzutifan wykazywał aktywność u chorych na raka nerkowokomórkowego i nowotwory nie-nerkowokomórkowe związane z chorobą VHL. Stosowanie tego leku było związane ze zdarzeniami niepożądanymi głównie stopnia 1. i 2.

Randomized trial of cytoreductive surgery for relapsed ovarian cancer

Harter P., Sehouli J., Vergote I. i wsp.
N. Engl. J. Med., 2021; 385: 2123–2131

Leczenie chorych z wznową raka jajnika opiera się głównie na leczeniu systemowym. Rola zabiegu cytoredukcyjnego w tej grupie chorych jest niejasna.

Metody. Chore z pierwszym nawrotem raka jajnika, który wystąpił po 6 lub więcej miesiącach po zakończeniu chemioterapii z zastosowaniem pochodnej platyny, przydzielano losowo do zabiegu cytoredukcyjnego i uzupełniającej chemioterapii zawierającej pochodną platyny lub wyłącznie do chemioterapii. Kryteriami włączenia do badania był dodatni wynik AGO (Arbeitsgemeinschaft Gynäkologische Onkologie), określany jako: stopień sprawności 0 w skali Eastern Cooperative Oncology Group (ECOG), brak wodobrzusza lub wodobrzusze mniejsze niż 500 ml oraz całkowita cytoredukcja w pierwszym zabiegu operacyjnym. Dodatni wynik AGO pozwala wskazać chore, u których można uzyskać całkowitą resekcję. Pierwszorzędowym punktem końcowym był czas całkowitego przeżycia. Oceniono również jakość życia i czynniki rokownicze przeżycia.

Wyniki. Do leczenia przydzielono losowo 407 chorych, w tym 206 do operacji cytoredukcyjnej i chemioterapii a 201 do wyłącznej chemioterapii. Udział całkowitych resekcji wyniósł 75,5%. Mediana przeżycia całkowitego wyniosła 53,7 miesiąca w grupie operowanej i 46,0 miesięcy w grupie poddanej wyłącznie chemioterapii (współczynnik ryzyka zgonu 0,75; 95% CI 0,59–0,96; p = 0,02). Chore po całkowitej resekcji miały najlepsze wyniki leczenia, z medianą całkowitego przeżycia 61,9 miesiąca. We wszystkich analizach zaobserwowano korzyść z zabiegu operacyjnego. Jakość życia w ciągu pierwszego roku obserwacji nie różniła się między obiema grupami. Dodatkowo nie odnotowano zgonów w ciągu 30 dni po zabiegu.

Wnioski. U chorych z wznową raka jajnika operacja cytoredukcyjna poprzedzająca chemioterapię wiązała się z dłuższym

całkowitym przeżyciem w porównaniu z wyłączną chemioterapią.

Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial

Yau T., Park J., Finn R. i wsp.
Lancet Oncol., 2022; 23: 77–90

W badaniu I/II fazy CheckMate 040 zastosowanie niwolumabu u chorych na zaawansowanego raka wątrobowokomórkowego wiązało się z długotrwałymi odpowiedziami, obiecującym przeżyciem oraz akceptowalnym bezpieczeństwem. Porównano niwolumab i sorafenib w pierwszej linii leczenia chorych na zaawansowanego raka wątrobowokomórkowego.

Metody. W otwartym badaniu III fazy przeprowadzonym w ośrodkach medycznych 22 krajów na terenie Azji, Australii, Europy i Ameryki Północnej, chorzy (powyżej 18. r.ż.) na potwierdzonego histopatologicznie zaawansowanego raka wątrobowokomórkowego, niekwalifikujący się do zabiegu operacyjnego lub ze stwierdzoną progresją po zabiegu operacyjnym albo po leczeniu miejscowym, bez uprzedniego leczenia systemowego, z wynikiem oceny w skali Child–Pugh A, w stanie ogólnym 0–1 według kryteriów ECOG, niezależnie od stwierdzenia wirusowego zapalenia wątroby, zostali losowo przydzieleni w stosunku 1:1 do leczenia niwolumabem (240 mg dożylnie co 2 tygodnie) lub sorafenibem (400 mg doustnie dwa razy dziennie), podawanych do progresji lub wystąpienia nieakceptowalnej toksyczności leczenia. Pierwszorzędowym punktem końcowym było całkowite przeżycie oceniane w grupie zgodnej z intencją leczenia. Bezpieczeństwo leczenia oceniano u wszystkich chorych, którzy otrzymali przynajmniej jedną dawkę leku.

Wyniki. Od 11 stycznia 2016 do 24 maja 2017 roku 743 chorych przydzielono losowo do leczenia (niwolumabem n = 371; sorafenibem n = 372). W pierwszej analizie mediana obserwacji dla całkowitego przeżycia wynosiła 15,2 miesiąca (IQR 5,7–28,0) wśród leczonych niwolumabem i 13,4 miesiąca (5,7–25,9) wśród leczonych sorafenibem. Mediana całkowitego przeżycia wyniosła 16,4 miesiąca (95% CI 13,9–18,4) dla leczonych niwolumabem i 14,7 miesiąca (11,9–17,2) dla leczonych sorafenibem (współczynnik ryzyka 0,85 [95% CI 0,72–1,02]; p = 0,075; minimalny czas obserwacji 22,8 miesiąca); poziom znamienności określony w protokole (p = 0,0419) nie został osiągnięty. Najczęstszymi działaniami niepożądanymi związanym z leczeniem w stopniu co najmniej 3. były zespół ręka–stopa (1 spośród 367 chorych [<1%] w grupie leczonej niwolumabem *vs* 52 [14%] w grupie leczonej sorafenibem), wzrost stężenia aminotransferazy asparaginianowej (22 [6%] *vs* 13 [4%]) i nadciśnienie tętnicze (0 *vs* 26 [7%]). Poważne działania niepożądane stwierdzono u 43 chorych (12%) wśród leczonych niwolumabem i 39 (11%) wśród leczonych sorafenibem. W grupie leczonej niwolumabem stwierdzono 4 zgony związane z leczeniem zaś wśród leczonych sorafenibem odnotowano 1 zgon.

Wnioski. Niwolumab zastosowany w pierwszej linii leczenia nie wydłużył znamiennie całkowitego czasu przeżycia chorych na zaawansowanego raka wątrobowokomórkowego w porównaniu z leczeniem sorafenibem, ale zaobserwowano aktywność kliniczną i korzystny profil bezpieczeństwa. Niwolumab może być rozważany jako opcja leczenia u chorych, u których inhibitory kinazy tyrozynowej i leki antyangiogenne są przeciwwskazane lub ich użycie wiąże się ze znacznym ryzykiem.

Adjuvant palbocyklib for early breast cancer: the PALLAS trial results (ABCSG-42/AFT-05/BIG-14-03)

Gnant M., Dueck A.C., Frantal S. i wsp.
J. Clin. Oncol., 2022; 40: 282–293

Palbocyklib jest inhibitorem kinazy zależnej od cyklin 4 i 6 zatwierdzonym do leczenia zaawansowanego raka piersi. Nie potwierdzono potencjalnej wartości dodania palbocyklibu do leczenia hormonalnego w leczeniu uzupełniającym chorych na raka piersi z obecnością receptorów hormonalnych.

Metody. W prospektywnym badaniu III fazy PALLAS chore na wczesnego raka piersi z dodatnimi receptorami hormonalnymi, bez receptora ludzkiego naskórkowego czynnika wzrostu typu 2, przydzielano losowo do grupy otrzymującej przez 2 lata palbocyklib (125 mg doustnie raz na dobę w dniach 1.–21. 28-dniowego cyklu) z uzupełniającym leczeniem hormonalnym lub do wyłącznej uzupełniającej hormonoterapii (przez co najmniej 5 lat). Pierwszorzędowym punktem końcowym badania był czas wolny od choroby inwazyjnej (iDFS), a drugorzędowymi: czas wolny od inwazyjnego raka piersi, czas wolny od rozsiewu, czas wolny od miejscowo-regionalnego nawrotu i czas całkowitego przeżycia.

Wyniki. Spośród 5796 chorych włączonych do badania w 406 ośrodkach w 21 krajach na całym świecie w ciągu 3 lat, 5761 włączono do grupy leczonej zgodnie z intencją. W końcowej analizie określonej w protokole, przy medianie okresu obserwacji wynoszącej 31 miesięcy, zdarzenia związane z iDFS wystąpiły u 253 spośród 2884 chorych (8,8%) leczonych palbocyklibem w skojarzeniu z hormonoterapią oraz u 263 spośród 2877 chorych (9,1%) poddanych wyłącznie hormonoterapii, z podobnymi wynikami w obu grupach (iDFS po 4 latach 84,2% *vs* 84,5%; HR 0,96; CI 0,81–1,14; p = 0,65). Nie zaobserwowano znamiennych różnic w zakresie drugorzędowych punktów końcowych, a analizy podgrup nie wykazały żadnych różnic w poszczególnych podgrupach. Nie stwierdzono nowych sygnałów dotyczących bezpieczeństwa stosowania palbocyklibu.

Wnioski. W końcowej analizie badania PALLAS dodanie palbocyklibu do standardowej uzupełniającej hormonoterapii

nie poprawiło wyników leczenia chorych na wczesnego raka piersi z dodatnimi receptorami hormonalnym w porównaniu z zastosowaniem wyłącznie hormonoterapii.

Nivolumab versus placebo in patients with relapsed malignant mesothelioma (CONFIRM): a multicentre, double-blind, randomised, phase 3 trial

Fennell D.A., Ewings S., Ottensmeier C. i wsp.
Lancet Oncol., 2021; 22: 1530–1540

W żadnym badaniu III fazy nie wykazano poprawy przeżycia chorych na międzybłoniaka opłucnej lub otrzewnej, z progresją choroby po chemioterapii zawierającej pochodne platyny. Celem badania była ocena skuteczności i bezpieczeństwa stosowania niwolumabu, przeciwciała anty-PD-1, w tej grupie chorych.
Metody. W wieloośrodkowym podwójnie zaślepionym badaniu III fazy z grupą kontrolną stosującą placebo, przeprowadzonym w 24 szpitalach w Wielkiej Brytanii dorosłych chorych (w wieku ≥18 lat) w stanie sprawności 0–1 według ECOG, z histologicznie potwierdzonym międzybłoniakiem opłucnej lub otrzewnej i radiologiczną progresją po chemioterapii pierwszej linii zawierającej pochodne platyny, przydzielano losowo (2:1) do leczenia niwolumabem w stałej dawce (240 mg co 2 tygodnie przez 30 minut dożylnie) lub do przyjmowania placebo, podawanych do progresji choroby lub do 12 miesięcy. Chorych stratyfikowano według histologii nowotworu (nabłonkowa *vs.* nienabłonkowa). Chorzy i prowadzący leczenie klinicyści nie znali przydziału do grup leczenia. Równorzędnymi pierwszorzędowymi punktami końcowymi były: oceniany przez badacza czas wolny od progresji i czas całkowitego przeżycia oceniany zgodnie z intencją leczenia. Wszyscy chorzy przydzieleni losowo do leczenia zostali włączeni do grupy bezpieczeństwa, ocenianej zgodnie z przydziałem do grupy.
Wyniki. Od 10 maja 2017 roku do 30 marca 2020 roku do badania włączono 332 chorych, spośród których 221 (67%) przydzielono losowo do leczenia niwolumabem, a 111 (33%) do grupy otrzymującej placebo. Mediana czasu obserwacji wyniosła 11,6 miesiąca (IQR 7,2–16,8). Mediana przeżycia wolnego od progresji wyniosła 3,0 miesiąca (95% CI 2,8–4,1) wśród leczonych niwolumabem w porównaniu z 1,8 miesiąca (1,4–2,6) w grupie placebo (skorygowany HR 0,67 [95% CI 0,53–0,85; p = 0,0012), a mediana czasu całkowitego przeżycia – odpowiednio 10,2 miesiąca (95% CI 8,5–12,1) i 6,9 miesiąca (5,0–8,0; skorygowany HR 0,69 [95 % CI 0,52–0,91]; p = 0,0090). Najczęściej zgłaszanymi zdarzeniami niepożądanymi stopnia 3. lub wyższego związanymi z leczeniem były biegunka (u 6 spośród 221 chorych [3%] wśród leczonych niwolumabem *vs* u 2 spośród 111 [2%] w grupie placebo) i reakcje związane z wlewem (6 [3%] w porównaniu z 0). Poważne zdarzenia niepożądane wystąpiły u 90 chorych (41%) wśród leczonych niwolumabem i u 49 (44%) w grupie placebo. W żadnej z grup nie stwierdzono zgonów związanych z leczeniem.
Wnioski. Niwolumab może stanowić korzystną opcję leczenia chorych na złośliwego międzybłoniaka, u których doszło do progresji podczas leczenia pierwszej linii.

Apalutamide plus abiraterone acetate and prednisone versus placebo plus abiraterone and prednisone in metastatic, castration-resistant prostate cancer (ACIS): a randomised, placebo--controlled, double-blind, multinational, phase 3 study

Saad F., Efstathiou E., Attard G. i wsp.
Lancet Oncol., 2021; 22: 1541–1559

U większości chorych na rozsianego raka gruczołu krokowego opornego na kastrację (mCRPC) wystąpi progresja choroby prowadząca do zgonu. Progresja mCRPC jest związana zarówno z aktywacją receptorów androgenowych, jak i podwyższonym stężenie androgenów w guzie, jednak obecnie standardem opieki jest leczenie ukierunkowane na pojedynczy mechanizm sygnalizacji androgenowej. Celem badania było porównanie leczenia skojarzonego z użyciem apalutamidu i octanu abirateronu, z których każdy w inny sposób hamuje oś sygnalizacji androgenów, ze standardowym leczeniem mCRPC.
Metody. Podwójnie zaślepione badanie III fazy z grupą kontrolną otrzymującą placebo (ACIS) przeprowadzono w 167 szpitalach w 17 krajach w USA, Kanadzie, Meksyku, Europie, regionie Azji i Pacyfiku, Afryce i Ameryce Południowej. Do badania włączono chorych na mCRPC (w wieku ≥18 lat), niepoddanych wcześniej chemioterapii ani leczeniu inhibitorami sygnalizacji biosyntezy androgenów, w trakcie leczenia blokującego wydzielanie androgenów, w stanie sprawności 0–1 według ECOG, z wynikiem 3 lub niższym w odpowiedzi na pytanie 3. w Krótkim Kwestionariuszu Bólu (dotyczącym odczuwania najgorszego bólu w ciągu ostatnich 24 godzin). Chorych przydzielano losowo (1:1) do przyjmownia apalutamidu 240 mg raz na dobę w połączeniu z octanem abirateronu 1000 mg raz na dobę i prednizonem 5 mg dwa razy na dobę lub do grupy otrzymującej placebo w połączeniu z octanem abirateronu i prednizonem, podawanych doustnie w 28-dniowych cyklach. Randomizacja była stratyfikowana według obecności lub braku przerzutów w narządach trzewnych, stanu sprawności według ECOG i regionu geograficznego. Chorzy, badacze, zespół badawczy i sponsor nie znali przydziału do leczenia. Niezależny komitet monitorujący dane kontrolował dane w celu zapewnienia stałego bezpieczeństwa chorych oraz przeglądał dane dotyczące skuteczności. Pierwszorzędowym punktem końcowym było przeżycie bez progresji radiologicznej oceniane w grupie zgodnej z zamiarem leczenia. Bezpieczeństwo oceniano u wszystkich chorych, którzy otrzymali co najmniej

jedną dawkę badanego leku. Badanie zostało zakończone i nie prowadzi się już rekrutacji.

Wyniki. Od 10 grudnia 2014 roku do 30 sierpnia 2016 roku przydzielono losowo do leczenia 982 chorych, w tym 492 do stosowania apalutamidu w połączeniu z abirateronem i prednizonem oraz 490 do abirateronu z prednizonem. W pierwotnej analizie (mediana czasu obserwacji 25,7 miesiąca [IQR 23,0–28,9]) mediana przeżycia bez progresji radiologicznej wyniosła 22,6 miesiąca (95% CI 19,4–27,4) wśród leczonych z użyciem apalutamidu w porównaniu z 16,6 miesiąca (13,9–19,3) w grupie leczonej wyłącznie abirateronem z prednizonem (HR 0,69, 95% CI 0,58–0,83; p < 0,0001). W zaktualizowanej analizie (analiza końcowa dla przeżycia całkowitego; mediana czasu obserwacji 54,8 miesiąca [IQR 51,5–58,4]) mediana czasu wolnego od progresji radiologicznej wyniosła 24,0 miesiące (95% CI 19,7–27,5) w porównaniu z 16,6 miesiąca (13,9–19,3; HR 0,70, 95% CI 0,60–0,83; p < 0,0001). Najczęstszym zdarzeniem niepożądanym stopnia 3.–4., pojawiającym się podczas leczenia, było nadciśnienie tętnicze (82 spośród 490 chorych [17%] otrzymujących apalutamid w połączeniu z abirateronem i prednizonem i 49 spośród 489 [10%] otrzymujących abirateron z prednizonem). Poważne zdarzenia niepożądane związane z leczeniem wystąpiły u 195 chorych (40%) otrzymujących apalutamid w połączeniu z abirateronem i prednizonem oraz u 181 (37%) otrzymujących wyłącznie abirateron z prednizonem. Zdarzenia niepożądane związane z leczeniem, które zakończyły się zgonem, wystąpiły u trzech chorych (1%) wśród leczonych z udziałem apalutamidu (u 2 zatorowość płucna, u 1 niewydolność serca) i pięciu (1%) w grupie leczone wyłącznie abirateronem i prednizonem (1 niewydolność serca, 1 zatrzymanie akcji serca, 1 niedrożność tętnicy krezkowej, 1 napad padaczkowy i 1 nagły zgon).

Wnioski. Pomimo zastosowania aktywnego i ustalonego leczenia w grupie kontrolnej, apalutamid w połączeniu z abirateronem i prednizonem wydłużył czas wolny od progresji radiologicznej. Potrzebne są dodatkowe badania w celu określenia podgrup chorych, którzy mogą odnieść największe korzyści z leczenia skojarzonego, aby poprawić wyniki leczenia chorych na rozsianego raka gruczołu krokowego opornego na kastrację.

Magdalena Dróżka
Anna Kaczmarczyk
Anna Kowalczyk
Ewa Szutowicz-Zielińska

VIA MEDICA

Komunikaty

Biuletyn Polskiego
Towarzystwa Onkologicznego
NOWOTWORY
2022, tom 7, nr 1, 76

ISSN 2543–5248, e-ISSN: 2543–8077
www.nowotwory.edu.pl

X Zimowe Forum Onkologiczne

11–12 lutego 2022 roku

Tomaszowice

Przewodniczący Komitetu Naukowego:
Wojciech M. Wysocki

Komitet Naukowy:
Andrzej Stelmach
Aleksandra Grela-Wojewoda
Barbara Radecka
Joanna Wysocka

Więcej informacji na stronie: **www.zimoweforumonkologiczne.viamedica.pl**

XXVIII Zjazd Polskiego Towarzystwa Chirurgii Onkologicznej

1–3 września 2022 roku

Gdańsk

Zjazdowi towarzyszyć będzie XXXIX Konferencja Naukowo-Szkoleniowa PTChO.

Więcej szczegółów na stronach: **https://zjazdptcho.pl oraz https://ptcho.pl**

Nowotwory. Journal of Oncology – Best Original Paper Award

Przypominamy o konkursie czasopisma *Nowotwory*. *Journal of Oncology* na najlepszą pracę oryginalną opublikowaną w danym roczniku. Ogłoszenie wyników za 2021 r. nastąpi w pierwszym kwartale 2022 r.

Zapraszamy do składania manuskryptów przez nasz system elektroniczny.

Szczegóły na stronie **www.nowotwory.edu.pl**

Akademia Młodego Onkologa

VIRTUAL MEETING

24 marca 2022 roku

Przewodniczący Komitetu Naukowego:

prof. dr hab. n. med. Piotr Wysocki
prof. dr hab. n. med. Maciej Krzakowski

www.akademiaonkologa.viamedica.pl

ORGANIZATOR

VIA MEDICA

PARTNER

ikamed.pl
internetowa księgarnia medyczna

PATRONAT MEDIALNY

Onkoedu
Serwis dla lekarzy specjalistów

tvmed

Virtual Meeting jest skierowany tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).

21-0724.001.002

VIRTUAL MEETING

NOWOTWORY SKÓRY 2022
UPDATE DLA CHIRURGÓW

Przewodniczący Komitetu Naukowego:
prof. dr hab. n. med. Piotr Rutkowski

- **18 marca 2022 roku**
- **22 kwietnia 2022 roku**
- **27 maja 2022 roku**
- **16 września 2022 roku**

Szczegółowe informacje i rejestracja na stronie internetowej:

www.nowotworyskory.viamedica.pl

ORGANIZATOR VIA MEDICA

PATRONAT

PATRONAT MEDIALNY tvmed

PARTNER ikamed.pl

21-0771.001.002

Virtual Meeting jest skierowany tylko do osób uprawnionych do wystawiania recept lub osób prowadzących obrót produktami leczniczymi — podstawa prawna: Ustawa z dnia 6 września 2001 r. Prawo farmaceutyczne (t. j. Dz.U. z 2019 r. poz. 499).