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Lung cancer and breast cancer mortality trends among 45–74-year-old European women

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Introduction. We aimed to analyze and compare the most up-to-date breast and lung cancer mortality rates in European women aged 45–74.

Material and methods. The data on breast and lung cancer mortality in 1960–2017 were obtained from the World Health Organization Mortality Data Base and Eurostat. To determine the mortality trends and generate annual percent change, with 95% confidence intervals, joinpoint regression was applied.

Results. In most European Union (EU) member states (15 out of 28), lung cancer mortality was higher than breast cancer mortality, with either increasing or stable lung cancer mortality rates. In four other EU countries, breast and lung cancer mortality rates in the last reported year were almost equal or equal.

Conclusions. Lung cancer is becoming the leading cause of cancer deaths among European women. There is a need for ensuring women-targeted smoking cessation services to decrease tobacco-attributable lung cancer mortality.

Key words: lung cancer, breast cancer, women, mortality, tobacco, cancer prevention, Europe

Introduction

Breast cancer is the most prevalent female neoplasm worldwide. According to the International Agency for Research on Cancer (IARC), in 2018, globally, 2,261,419 women were diagnosed with breast cancer. Moreover, breast cancer is a leading cause of cancer deaths among women (684,996 deceases in 2018). According to the same global cancer statistics, lung cancer is the third-most-common female neoplasm and the second-most-common cause of female cancer deaths globally, with the number of incident cases at 770,828 and the number of deaths at 607,465 in 2018 [1]. In the European Union (EU; state of 2018 with 28 EU member states), breast cancer is still the most prevalent female neoplasm, however, lung cancer is now the leading cause of female cancer deaths [2].

While a systematic understanding of breast cancer risk factors is still unsatisfactory, it is already known that about 70–80% of female lung cancer cases are associated exclusively to tobacco smoking [3, 4]. Hence, cancer mortality trends are affected by changes in European tobacco consumption patterns. At the end of the 20th century, tobacco-related mortality decreased among men, and was stable or increased among women [5]. This phenomenon is evident in lung cancer, considered a good proxy for smoking prevalence estimations.

Although mechanisms underpinning cancer prevalence and mortality rates are not fully understood, their changes can be a valuable indicator for policymakers and stakeholders, enabling more tailored and efficient actions aimed at decreasing tobacco consumption in the EU and its suitable member states. This study aimed to analyze and compare the most recent female breast and lung cancer mortality rates in 31 European countries.

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Material and methods

The presented analysis is an update of the data published in the article by Sulkowska et al. in Nowotwory. Journal of Oncology 2015; 65 (5): 395–403, entitled *Lung cancer, the leading cause of cancer deaths among women in Europe* [5]. We followed previously applied methodology (including the same age group: 45–74 years old) to enable comparability of the data.

Source of the data

The analyzed data were obtained in a hybrid manner. First, we obtained data from the World Health Organization (WHO) Mortality Data Base (MDB) (data available as of 15th December 2019). The MDB contains the number of deaths by country, year, sex, age group, and cause of death. The cause of death is coded according to the International Classification of Diseases (ICD). We identified all female deaths due to breast and lung cancer registered in the MDB since 1960 in 28 EU member states and three non-member states, namely Norway, Russia, and Switzerland. The included diagnosis codes encompassed lung cancer (162–163 – ICD 7th revision; 162 – ICD 8th and 9th revisions; and C33 and C34 – ICD 10th revision) and breast cancer (170 – 7th revision; 174 – 8th and 9th revisions; and C50 – 10th revision). In cases where the data for additional (following) years were available in Eurostat, these were also included in our analysis (detailed data sources, by country, by year in table I). The mid-year population estimates were obtained from WHO MDB and Eurostat.

Statistical analysis

Crude annual mortality rates were defined as the number of new deaths per 100,000 person-years. In the denominator, we applied the mid-year population, defined as the population's size on the 31st of June. In all calculations, both the numerator and denominator came from the same data source, WHO MDB or Eurostat. To enable a comparison with other populations, we performed direct age-standardization for the Segi's World Standard Population [6]. For Luxembourg and Malta, the mortality rates were calculated as three-year moving averages (deploying the preceding and following year).

To determine mortality trends and to generate the annual percent change (APC), with 95% confidence intervals (CI), joinpoint regression was applied [7]. The best-fitting model was selected with permutations tests, with an overall significance level at 0.05 and the number of randomly permutated data sets for permutation set at 4499. Rates were considered to decrease if APC < 0 and 95% CI does not contain zero, and to increase if APC > 0 and 95% CI do not contain zero; otherwise, rates were considered stable.

Joinpoint analysis was performed using the Joinpoint Regression Program (version 4.3.1.0, National Cancer Institute, Bethesda, MD, USA).

Compliance with ethical standards

According to the WHO and Eurostat policies, the analyzed data can be freely used for scientific purposes. This study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [8].

Results

Breast and lung cancer mortality rates in 1960–2017, analyzed by EU member states, manifested four different patterns:

- Group 1 – higher mortality from lung cancer than from breast cancer with increasing mortality rates of lung cancer;
- Group 2 – higher mortality from lung cancer than from breast cancer with stable or decreasing lung cancer mortality rates;
- Group 3 – almost equal or equal breast and lung cancer mortality rates in the last reported year;
- Group 4 – other EU countries (tab. I).

Non-EU countries were analyzed separately, as Group 5.

In the vast majority of countries in group 1, lung and breast cancer mortality rates intersected around 2010. In Poland the intersection occurred in 2004, and in Spain in 2016 (fig. 1 A). In Austria, Croatia, Germany, and Slovenia, the increase in lung cancer mortality rates was constant. In Poland, a very short period of trend stabilization was observed between 1968–1972, and in Luxembourg, lung cancer mortality rates decreased between 1971–1974. In Czechia, the trend began stabilizing in 2000. In Spain, in 1990, after years of a plateau, lung cancer mortality rates started increasing.

In group 2, time of the lung and breast mortality trends intersection varied widely, e.g., in Denmark it took place in 1991, in Sweden in 2001, and in Ireland in 2012 (fig. 1 B). Lung cancer mortality rates were sharply dropping in Belgium, Denmark, Sweden, and the United Kingdom. In Hungary, Ireland, and the Netherlands, the decrease was more gradual. The onset of decreasing rates for lung cancer mortality ranged from 1980 in Ireland to 2015 in Belgium.

In group 3, the breast and lung cancer mortality rates were almost equal or equal (fig. 1 C). In all countries in the group, lung cancer mortality increased; however, only in Italy was the increase constant. The trend plateaued in Finland and France in 1962–1974 and in 1960–1977, respectively.

In every country in group 4, lung cancer mortality has always been lower than breast cancer mortality (fig. 1 D). However, in some countries (Bulgaria, Cyprus, Estonia, Lithuania, Malta, Portugal, and Romania), the breast cancer mortality rate has been decreasing substantially and/or the lung cancer mortality rate has been sharply increasing, which might point toward future intersection of the rates.

Group 5 represents three non-EU countries (fig. 1 E). In Norway and Switzerland the rates intersected in 1998 and 2012, respectively. In Russia, such a phenomenon has never occurred.

Table I. Age-standardized mortality rates † (ASR) of breast and lung cancer, and the annual percentage change (APC) with a 95% confidence interval (95% CI), by joinpoint analysis segment

Country	Location	ASR 2010‡	ASR 018‡	Segment 1			Segment 2			Segment 3			Segment 4		
				Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI	Period	APC	95% CI
Group 1															
Austria	beast	41.9	37.2	1960–1965	3.9*	1.6; 6.1	1965–1991	0.9*	0.7; 1.1	1991–2018	–2.4*	–2.5; –2.2			
	lung	45.8	51.4	1960–1978	1.2*	0.7 ;1.7	1978–2018	2.3*	2.1; 2.4						
Croatia	breast	53.8	42.2	1985–1999	2.4*	2.1; 2.7	1999–2003	–5.7*	–8.7; –2.5	2003–2015	–0.2	–0.7; 0.2	2015–2018	–5.5*	–8.5; –2.3
	lung	43.4	60.3	1985–2018	2.7*	2.5; 3.0									
Czechia	breast	40.7	34.1	1986–1994	0.1	–0.9; 1.2	1994–2005	–2.1*	–2.8; –1.4	2005–2008	–7.7	–15.9; 1.3	2008–2018	–1.9*	–2.6; –1.2
	lung	44.1	44.4	1986–2000	2.9*	2.3; 3.4	2000–2018	0.5*	0.1; 0.8						
Germany	breast	49.2	44.6	1973–1992	1.0*	0.8; 1.1	1992–2017	–1.8*	–1.9; –1.7						
	lung	45.8	52.4	1973–1980	2.0*	1.4; 2.5	1980–1991	3.8*	3.4; 4.1	1991–2013	3.0*	2.9; 3.1	2013–2017	1.1	–0.2; 2.5
Luxembourg	beast	49.0	45.1	1968–1986	1.7*	0.9; 2.5	1986–2004	–3.2*	–4.0; –2.3	2004–2016	–0.5	–2.0; 0.9			
	lung	41.2	46.4	1968–1971	20.3*	0.1; 44.6	1971–1974	–14.1	–40.5; 24.0	1974–1985	8.5*	5.5; 11.7	1985–2016	1.6*	1.0; 2.1
Poland	beast	43.5	45.4	1960–1964	14.9*	12.3; 17.4	1964–1981	2.2*	1.9; 2.4	1981–1992	0.4	–0.1; 1.0	1992–2018	–0.4*	–0.6; –0.3
	lung	58.4	64.4	1960–1968	4.6*	3.4; 5.9	1968–1972	–0.1	–5.3; 5.3	1972–1988	4.0*	3.5; 4.5	1988–2018	2.7*	2.6; 2.9
Slovenia	beast	46.4	39.9	1971–1993	1.5*	1.0; 2.0	1993–2018	–2.5*	–2.9; –2.1						
	lung	42.4	61.3	1971–2018	2.6*	2.4; 2.8									
Spain	beast	35.1	31.9	1960–1991	2.6*	2.4; 2.7	1991–2018	–2.2*	–2.4; –2.0						
	lung	25.2	32.9	1960–1973	0.9*	0.3; 1.5	1973–1989	–1.6*	–2.1; –1.2	1989–1996	2.0*	0.1; 3.9	1996–2018	5.4*	5.2; 5.7
Group 2															
Belgium	beast	56.6	44.7	1960–1986	1.1*	1.0; 1.3	1986–1997	–0.7	–1.4; 0.1	1997–2017	–2.7*	–2.9; –2.4			
	lung	51.5	48.2	1960–1966	–0.1	–2.6; 2.5	1966–2015	3.1*	3.0; 3.2	2015–2017	–7.6	–20.5; 7.4			
Denmark	beast	58.1	39.8	1960–1997	0.5*	0.4; 0.7	1997–2017	–3.8*	–4.1; –3.4						
	lung	89.6	73.8	1960–1973	5.0*	4.0; 6.0	1973–1984	7.6*	6.2; 9.1	1984–1997	2.9*	1.9; 4.0	1997–2017	–1.4*	–1.9; –0.9
Hungary	beast	53.3	49.6	1960–1976	2.9*	2.4; 3.3	1976–1995	1.1*	0.8; 1.5	1995–2018	–1.6*	–1.9; –1.4			
	lung	96.7	100.7	1960–1975	1.1*	0.6; 1.6	1975–1996	4.3*	4.0; 4.7	1996–2013	3.2*	2.7; 3.7	2013–2018	–0.4	–3.1; 2.5

Ireland	beast	55.0	46.9	1960–1975	1.9*	1.2; 2.6	1975–1994	0.3	−0.3; 0.8	1994–2017	−2.4*	−2.8; −2.1			
	lung	53.3	52.6	1960–1980	5.1*	4.5; 5.7	1980–2017	−0.2	−0.4; 0.1						
Netherlands	beast	56.1	43.2	1960–1967	1.5*	0.4; 2.5	1967–1994	0.0	−0.1; 0.2	1994–2018	−2.4*	−2.6; −2.3			
	lung	73.4	73.6	1960–1973	1.3*	0.7; 2.0	1973–1989	7.1*	6.6; 7.6	1989–2007	4.4*	4.0; 4.9	2007–2018	−0.2	−1.0; 0.6
Sweden	beast	40.6	32.7	1960–1988	-0.3*	−0.5; −0.2	1988–2005	−1.1*	−1.5; −0.7	2005–2017	−2.9*	−3.4; −2.3			
	lung	50.2	44.6	1960–1964	−1.0	−5.4; 3.5	1964–1991	4.3*	4.0; 4.6	1991–2005	2.8*	2.0; 3.5	2005–2017	−1.4*	−2.2; −0.6
United Kingdom	beast	48.2	42.3	1960–1976	1.1*	1.0; 1.3	1976–1989	0.4*	0.1; 0.6	1989–2001	−3.0*	−3.3; −2.7	2001–2017	−2.6*	−2.7; −2.4
	lung	63.1	56.9	1960–1975	4.8*	4.5; 5.0	1975–1988	2.4*	2.0; 2.8	1988–2001	−1.2*	−1.5; −0.8	2001–2017	−0.3*	−0.5; −0.1
Group 3															
Finland	beast	44.9	36.3	1960–1995	0.6*	0.4; 0.8	1995–2018	−1.6*	−1.9; −1.2						
	lung	31.2	30.8	1960–1962	19.9	−2.6; 47.4	1962–1974	−0.0	−1.4; 1.4	1974–1977	10.7	−10.0; 36.2	1977–2018	1.7*	1.5; 1.9
France	beast	48.4	44.4	1960–1974	1.5*	1.2; 1.8	1974–1997	0.3*	0.2; 0.5	1997–2016	−1.9*	−2.1; −1.8			
	lung	37.0	42.1	1960–1977	−0.1	−0.5; 0.3	1977–1996	3.2*	2.8; 3.5	1996–2008	5.3*	4.5; 6.1	2008–2016	2.4*	1.1; 3.6
Greece	beastt	41.3	38.2	1961–1963	24.5*	8.3; 43.1	1963–1980	4.4*	3.9; 5.0	1980–1993	0.4	−0.5; 1.2	1993–2017	−1.1*	−1.4; −0.8
	lung	28.1	33.6	1961–1965	6.9*	1.1; 12.9	1965–2005	0.4*	0.2; 0.6	2005–2017	4.4*	3.3; 5.5			
Italy	beast	45.7	42.5	1960–1970	2.1*	1.7; 2.5	1970–1990	0.9*	0.8; 1.1	1990–2017	−1.7*	−1.8; −1.6			
	lung	30.3	35.1	1960–1972	1.7*	1.2; 2.2	1972–1988	2.4*	2.1; 2.7	1988–1999	0.6*	0.0; 1.2	1999–2017	2.0*	1.8; 2.3
Group 4															
Bulgaria	beast	44.0	42.6	1964–1986	2.7*	2.3; 3.1	1986–2018	−0.2	−0.4; 0.0						
	lung	23.1	33.1	1964–2001	−0.1	−0.3; 0.2	2001–2018	2.7*	1.9; 3.5						
Cyprus	beast	36.4	44.6	2004–2018	−1.2	−2.4; 0.0									
	lung	14.0	22.6	2004–2018	1.6	−1.1; 4.4									
Estonia	beast	42.7	43.1	1981–1999	1.9*	1.1; 2.6	1999–2017	−2.4*	−3.0; −1.7						
	lung	24.1	26.4	1981–1983	−14.4	−33.4; 9.9	1983–1989	6.2*	0.5; 12.3	1989–2000	−1.5	−3.4; 0.4	2000–2017	1.3*	0.4; 2.2
Latvia	beast	56.4	47.3	1980–1994	2.2*	1.4; 3.1	1994–2017	−0.5*	−0.9; −0.1						
	lung	20.6	22.2	1980–2017	−0.1	−0.3; 0.2									

Lithuania	beast	53.1	43.0	1981–1994	2.8*	1.9; 3.7	1994–2011	–0.8*	–1.5; –0.2	2011–2018	–3.8*	–5.9; –1.6			
	lung	15.5	17.7	1981–2002	–0.9*	–1.7; –0.1	2002–2018	1.5*	0.3; 2.8						
Malta	beast	62.3	42.1	1968–1975	5.0*	2.0; 8.2	1975–1994	0.1	–0.6; 0.8	1994–2016	–3.3*	–3.8; –2.8			
	lung	22.4	32.6	1968–1973	–23.0*	–31.7; –13.3	1973–1976	56.9	–7.8; 166.9	1976–1992	–0.1	–2.3; 2.2	1992–2016	2.8*	1.7; 3.9
Portugal	beast	40.2	38.3	1960–1991	1.5*	1.3; 1.7	1991–2017	–1.6*	–1.9; –1.4						
	lung	17.3	21.8	1960–1982	2.4*	1.8; 2.9	1982–1997	0.6	–0.4; 1.7	1997–2017	2.7*	2.1; 3.4			
Romania	beast	47.5	47.8	1969–1988	2.2*	1.9; 2.4	1988–2000	1.1*	0.5; 1.7	2000–2018	–0.4*	–0.7; –0.2			
	lung	29.6	37.1	1969–1989	0.8*	0.5; 1.1	1989–2018	1.8*	1.7; 2.0						
Slovakia	beast	45.6	49.6	1992–2001	1.0	–0.1; 2.2	2001–2006	–3.9*	–7.6; –0.1	2006–2018	0.5	–0.2; 1.3			
	lung	32.9	31.4	1992–1995	–5.0	–13.6; 4.5	1995–2018	2.5*	2.1; 3.0						
Group 5															
Norway	beast	39.6	32.1	1960–1996	0.1	–0.0; 0.3	1996–2017	–2.9*	–3.2; –2.5						
	lung	59.4	50.4	1960–1965	0.2	–4.2; 4.9	1965–1997	6.0*	5.7; 6.3	1997–2017	0.2	–0.3; 0.8			
Switzerland	beast	45.5	37.6	1960–1988	0.4*	0.2; 0.5	1988–2017	–2.4*	–2.6; –2.2						
	lung	43.1	42.7	1960–2006	3.7*	3.5; 3.9	2006–2017	–0.1	–1.7; 1.5						
Russia	beast	54.6	48.4	1980–1994	3.1*	2.9; 3.3	1994–1999	2.0*	0.9; 3.1	1999–2009	0.0	–0.3; 0.3	2009–2015	–2.4*	–3.0; –1.9
	lung	17.3	17.8	1980–1988	1.6*	1.0; 2.3	1988–1993	–0.7	–2.6; 1.2	1993–2003	–3.0*	–3.5; –2.5	2003–2015	0.1	–0.2; 0.5

† New cases diagnosed per 100,000 person-years, age-adjusted to the Segi's World Standard Population

‡ For Luxembourg and Malta, the mortality rates were calculated as three-year moving averages (deploying the preceding and following year)

* APC statistically significant

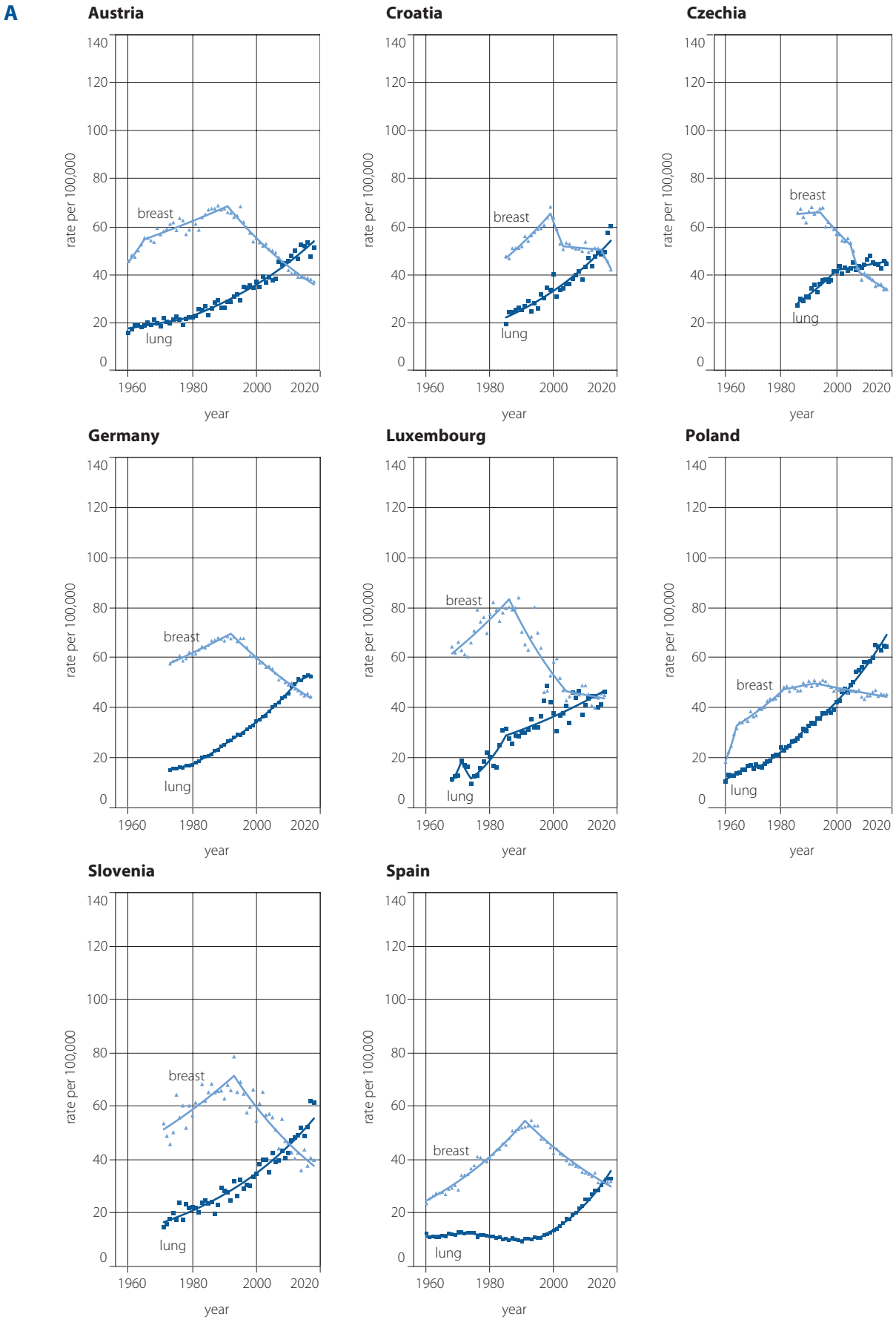

Figure 1. A. Breast and lung cancer mortality rates among women aged 45–74-years-old. Group 1 – EU countries with higher mortality from lung cancer than from breast cancer with increasing lung cancer mortality rates

B

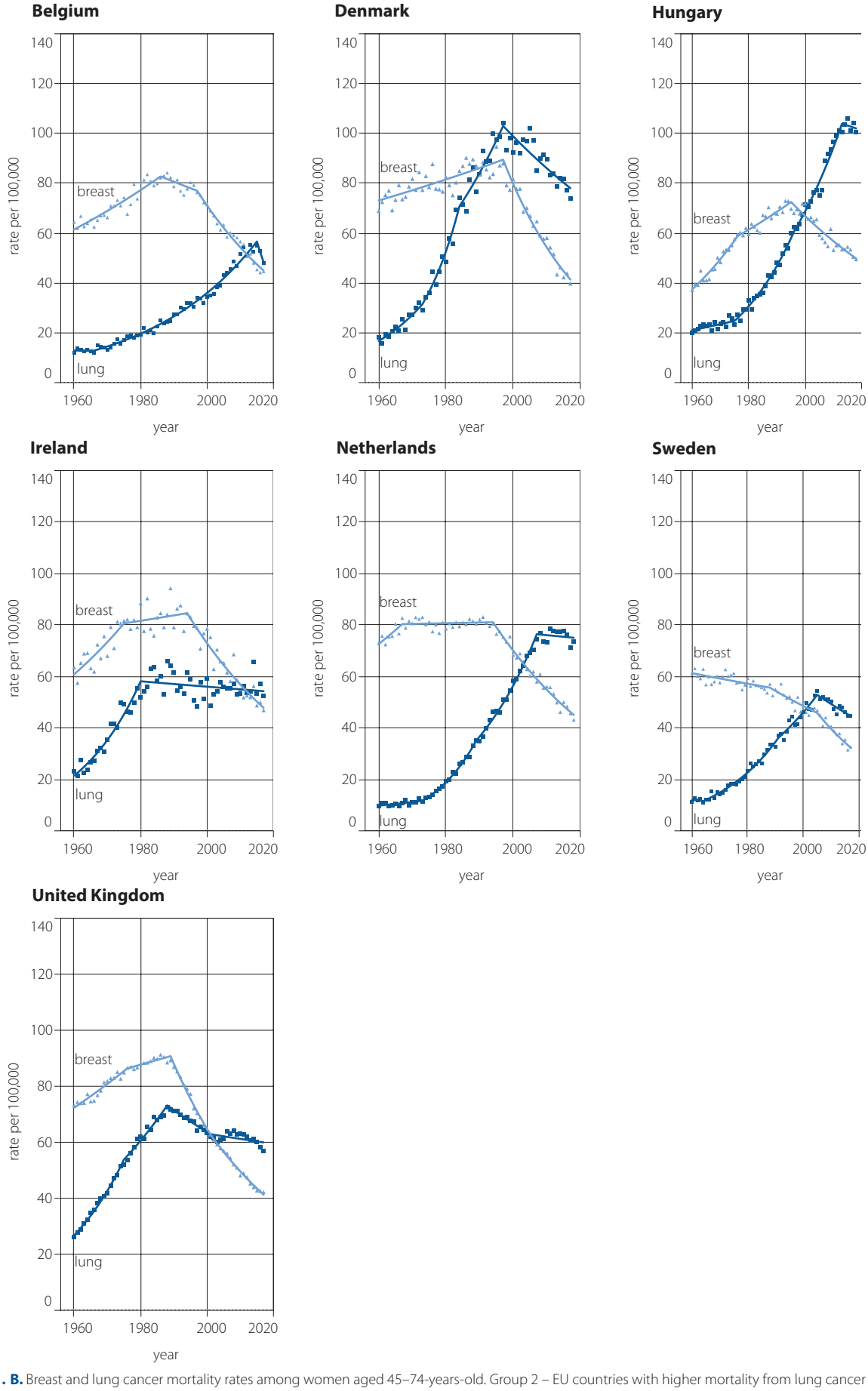

Figure 1. B. Breast and lung cancer mortality rates among women aged 45–74-years-old. Group 2 – EU countries with higher mortality from lung cancer than from breast cancer with stable or decreasing lung cancer mortality rates

C

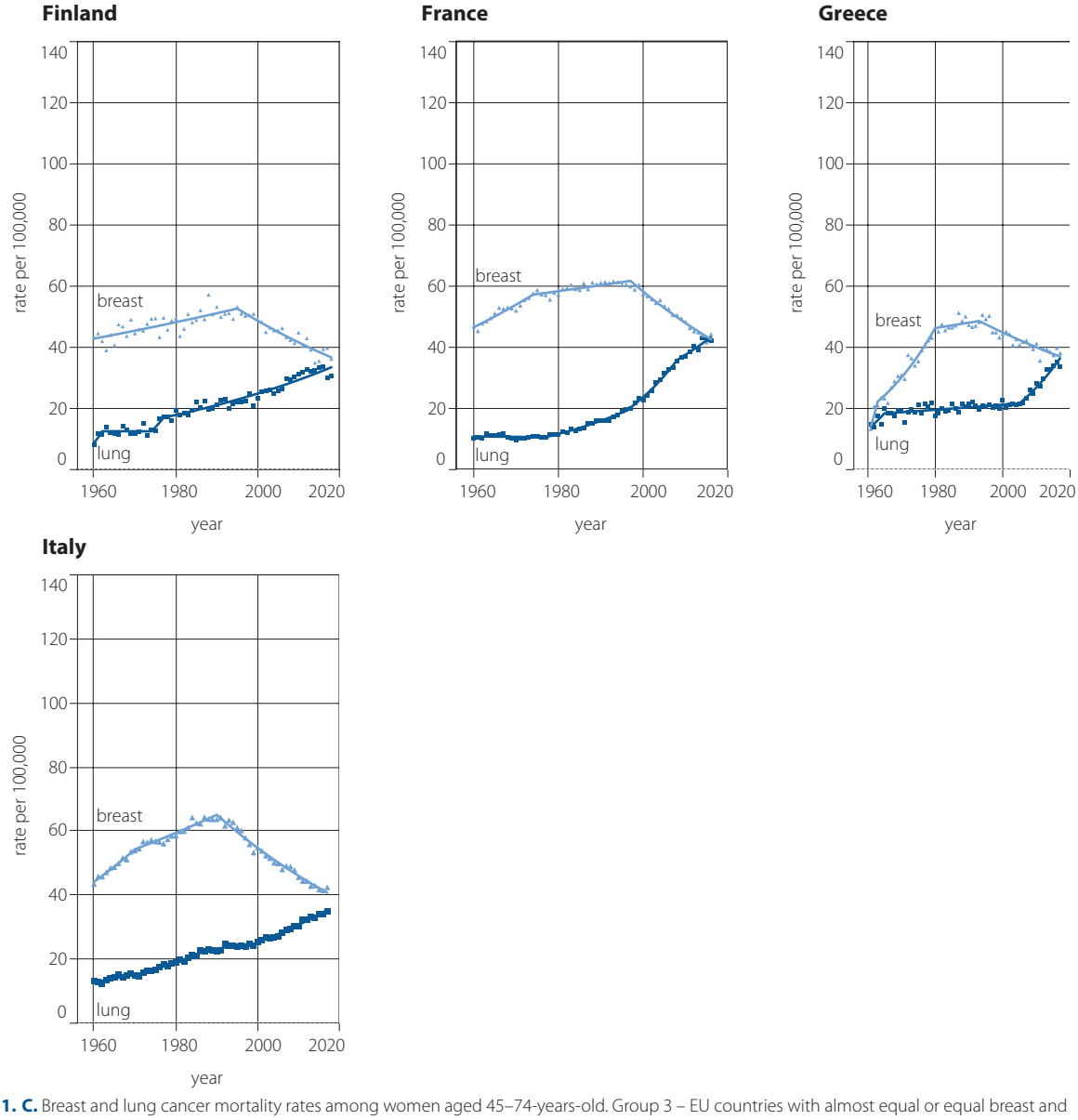

Figure 1. C. Breast and lung cancer mortality rates among women aged 45–74-years-old. Group 3 – EU countries with almost equal or equal breast and lung cancer mortality rates in the last reported year

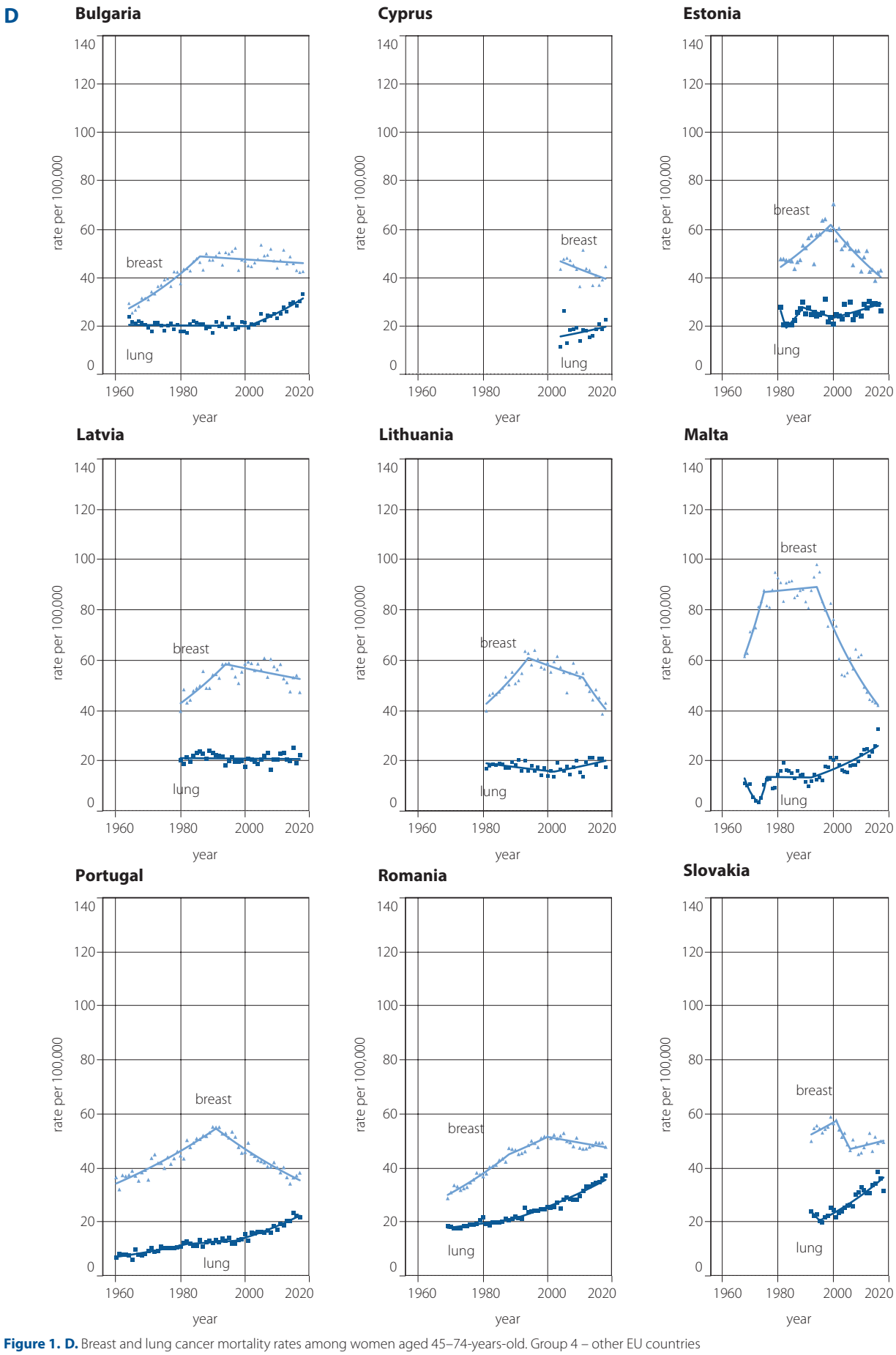

Figure 1. D. Breast and lung cancer mortality rates among women aged 45–74-years-old. Group 4 – other EU countries

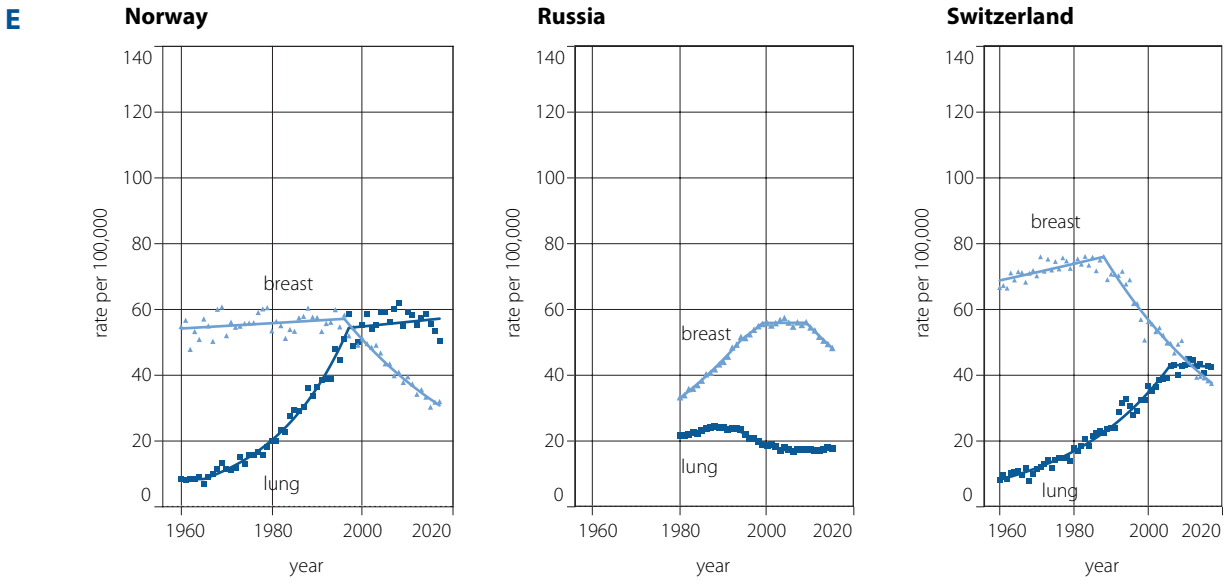

Figure 1. E. Breast and lung cancer mortality rates among women aged 45–74-years-old. Group 5 – non-EU countries

Discussion

The presented analysis depicts a substantial increase in female lung cancer mortality across the vast majority of European countries (tab. II). In comparison with our previous analysis on female lung and breast cancer mortality in the EU [5] (the last reported year was 2010), we noticed progressive cancer mortality changes. Previously we had forecasted further increases in lung cancer mortality and the intersection of both analyzed trends for 12 EU countries. This forecast proved to be true for Belgium, Croatia, Spain, Ireland, Germany, and Slovenia, in our current analysis. However, in Finland, France, Greece, and Italy, the trends have not intersected yet. Contrary to our earlier predictions, the current analysis shows that in Estonia and Slovakia breast cancer mortality is still higher than lung cancer mortality.

Considering the most up-to-date data on tobacco use, we know that at present in the EU about 47 million women currently smoke. Moreover, the advanced stage of tobacco epidemic was observed in 12 UE member states, where smoking prevalence among women is higher than 15% [9]. According to the Institute for Health Metrics and Evaluation (IHME), an exceptionally high smoking-attributable disease burden is observed in Bulgaria, Croatia, Greece, Hungary, and Poland, with the disability-adjusted life years index ranging between 17.5% and 20% [10]. Trends reported in our analysis are following the IHME data. Noteworthy, in Poland and Croatia, the increase is very sharp, and Hungary is characterized by the highest lung cancer mortality rate among all 31 analyzed countries (>100 per 100,000).

The presented analysis implies that greater efforts are needed to ensure a decline in lung cancer mortality rates. Several possible courses of action are mainly related to more restrictive anti-tobacco policies. Raising the excise tax for tobacco products is one of the most effective tools to achieve this goal [11], particularly among women who are more responsive to such measures than men [12]. Another solution is banning menthol and slim cigarettes, perceived as being more feminine tobacco products, targeted primarily at this group of users [13, 14]. Some of these solutions have already been introduced under the Tobacco Products Directive (2014/40/EU) [15]. However, the decline in lung cancer mortality observed in our analysis should not yet be connected with the enforcement of this particular law, since it has been in force too short to impact the mortality statistics. Notwithstanding, effective implementation of the Directive should be a priority for European policymakers, since it may further reduce lung cancer mortality among EU women.

The strength of the analysis is in the completeness of the analyzed cause-of-death data, which was close to 100%, except for Cyprus, where it was 68% [16]. The most important limitation of the study results from the possible cross-national differences in coding practices, particularly in codes for ill-defined and unknown causes. This should be taken into account when comparing mortality rates for specific causes across countries. However, since we assessed time trends of mortality rates within the countries in this study, the presented results' generalizability should not be limited.

Table II. Completeness † of cause-of-death data and their source by years included

Country	WHO MDB		Eurostat
	Years included	Completeness	Years included
Austria	1960–2017	100%	2018
Belgium	1960–2016	100%	2017
Bulgaria	1964–2015	100%	2016–2018
Croatia	1985–2016	100%	2017–2018
Cyprus	2004–2016	68%	2017–2018
Czechia	1986–2017	100%	2018
Denmark	1960–2015	100%	2016–2017
Estonia	1981–2016	100%	2017
Finland	1960–2016	100%	2017–2018
France	1960–2015	100%	2016
Germany	1973–2016	100%	2017
Greece	1961–2016	100%	2017
Hungary	1960–2017	100%	2018
Ireland	1960–2015	100%	2016–2017
Italy	1960–2015	100%	2016–2017
Latvia	1980–2015	100%	2016–2017
Lithuania	1981–2017	99%	2018
Luxembourg	1968–2016	100%	2017
Malta	1968–2015	100%	2016–2017
Netherlands	1960–2016	100%	2017–2018
Norway	1960–2016	100%	2017
Poland	1960–2016	100%	2017–2018
Portugal	1960–2016	100%	2017
Romania	1969–2017	100%	2018
Russia	1980–2015	100%	–
Slovakia	1992–2014	100%	2015–2018
Slovenia	1971–2015	100%	2016–2018
Spain	1960–2016	100%	2017–2018
Sweden	1960–2016	100%	2017
Switzerland	1960–2016	100%	2017
United Kingdom	1960–2016	100%	2017

†– available for the WHO MDB only; WHO MDB – the World Health Organization Mortality Data Base

Conclusions

In many European countries during the last decades, lung cancer has become the leading cause of cancer deaths among women. Ensuring the implementation of gender-tailored evidence-based smoking cessation services and primary smoking prevention actions should be a priority for European healthcare policymakers to decrease tobacco-attributable lung cancer mortality.

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MRI utility in predicting extraprostatic extension of prostate cancer and biochemical recurrence after radical prostatectomy

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Introduction. The study aimed to evaluate the performance of multiparametric magnetic resonance imaging (mpMRI) and the Martini model to predict extraprostatic extension (EPE) and biochemical recurrence (BCR) of prostate cancer (PCa).
Materials and methods. 61 patients underwent a radical laparoscopic prostatectomy. The preoperative risk of EPE was determined using mpMRI and the Martini model.
Results. MpMRI predicts the presence of EPE of PCa with a sensitivity and specificity of 47.4% and 85.7%, respectively (AUC 0.66, 95% CI: 0.51–0.82, p = 0.046). The Martini model's sensitivity was higher, but the specificity was lower than that of mpMRI and was 84.2% and 66.7%, respectively (AUC 0.78, 95% CI: 0.66–0.89, p < 0.001). Univariate and multivariate Cox analysis indicated that EPE in mpMRI (HR 6.6, 95% CI: 1.8–24.1), and the presence of positive surgical margins (PSM) (HR 7.1, 95% CI: 1.9–26.7) are independent factors increasing the probability of BCR.
Conclusions. MpMRI and Martini model are valuable tools in local staging of PCa, managing and predicting the oncological treatment outcomes of patients with PCa.

Key words: prostate cancer, multiparametric magnetic resonance imaging, radical prostatectomy, biochemical recurrence, extraprostatic extension

Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignant neoplasm in men in the world [1]. A radical prostatectomy (RP), next to radiotherapy (RT), is the treatment of choice in patients with non-metastatic PCa [2]. Biochemical recurrence (BCR) after RP affects 30% of patients and is one of the risk factors for disease progression and death [3, 4]. The confirmed risk factors for the occurrence of BCR in the postoperative report are: positive surgical margins (PSM) and extraprostatic extension (EPE)/locally advanced disease (stage T3–T4) [5]. The presence of the above parameters determines adjuvant treatment, i.e. local RT, aimed at reducing the risk of disease recurrence.

Precise local staging is an essential clinical issue due to its significance in treating patients with non-metastatic PCa. According to the current standards, the local staging is based on clinical examination (digital rectal exam – DRE) or a transrectal ultrasound (TRUS) [2]. Apart from the clinical examina-

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tion and TRUS, local staging can also be performed based on mpMRI. MpMRI provides valuable information about the clinical significance and localization of the lesion [6]. This information is used to qualify the patient for a prostate biopsy. According to the current guidelines, it is recommended to perform mpMRI in suspected PCa before the first prostate biopsy [2]. Moreover, mpMRI, in the case of PCa, allows for a characterization of such clinical parameters as lesion size, possible EPE or seminal vesicle invasion (SVI) [6]. The above information allows for an estimation of the appropriate risk group of disease progression, choose the treatment method (RP *vs.* RT), or plan the extension of the RP. Nevertheless, mpMRI is still not validated as a diagnostic tool for local staging and treatment planning [2, 7, 8].

The study aimed to evaluate the utility of mpMRI in the prediction of EPE and the impact of EPE on the occurrence of BCR in patients qualified for RP.

Material and methods

The study group consisted of 61 patients diagnosed with PCa who underwent laparoscopic RP. RP was performed either by the trans- or retroperitoneal approach. An extended lymphadenectomy was performed in the case of high-risk and intermediate-risk cancer with a predicted probability of lymph node involvement above 7%, according to the Briganti 2017 model [9]. The operation was performed with bilateral or unilateral NVB preservation or without NVB preservation. The NVB preserving technique involved inter- or intra-fascial dissection of the bundles, according to Walz [10]. The procedures without NVB preservation involved a wide extra-fascial prostatectomy [10]. The decision to preserve NVB was made depending on the EAU risk group. The preoperative risk of EPE was determined according to the Martini et al. model [11]. The decision to preserve NVB was also influenced by comorbidities, erectile dysfunction present before the planned procedure, age, and the patient's preferences.

The biopsy material and specimen acquired during RP underwent histopathological assessment conducted by three pathologists in accordance with the guidelines of the International Society of Urological Pathology (ISUP) 2014 in the field of pathomorphological diagnosis of PCa [12].

The study used mpMRI obtained when qualifying the patients for the first biopsy due to suspected PCa 1.5T (GE Healthcare Medical System Optima MR360, Chicago, IL, USA) and 3T equipment (Siemens HealthCare Magnetom Skyra, Erlangen, Germany) were utilized using 12- or 18-channel Body Matrix coils. The mpMRI scheme followed the PIRADS v. 2.0 guidelines of the American College of Radiology (ACR) [6]. It included a multiplanar assessment of the prostate in T1- and T2-weighted images, diffusion weighted imaging (DWI) and a dynamic contrast-enhanced (DCE) MRI. Apparent diffusion coefficient (ADC) maps were developed automatically. The mpMRI was evaluated by four radiologists experienced in prostate imaging who knew the PSA levels and rectal examination (DRE).

Based on mpMRI, a targeted cognitive biopsy of the prostate combined with a systematic biopsy was performed, guided with transrectal ultrasound using a biplane transducer with simultaneous imaging of both planes (BK Medical Flex 400, Herlev, Denmark).

The biopsy was performed according to the scheme recommended by the European Society of Urology (EAU) [2], 6–8 specimens were collected from each lobe, plus additionally 2–4 specimens from the suspicious lesion depending on its size [2, 13, 14]. The biopsy was performed by four urologists.

BCR was diagnosed when two PSA levels above 0.2 ng/ml were obtained. PSA was monitored every three months during the first year and every six months in consecutive years.

Statistical analysis

The analyzed parameters were described using an arithmetic mean, standard deviation, and median. The normality of distribution was verified using the Shapiro-Wilk test in each of the analyzed groups. In a normal distribution, the t-Student test for independent variables was used to compare the two groups. In the case of non-normal distribution, the non-parametric Mann-Whitney test was applied. Categorical variables in individual groups were described using percentage values; they were compared using the Chi^2 test with the Yates correction and with Fisher's exact test. Receiver operating characteristic (ROC) curves were determined for the analyzed parameters (Martini model and mpMRI). AUC (area under curve) was subsequently calculated, and their significance was analyzed. Cut-off points for which sensitivity and specificity reach optimal values were determined for parameters with significant AUC (Youden point).

Kaplan-Meier analysis and the log-rank test were used to compare BCR-free survival for patients with EPE in mpMRI. For BCR risk factors, hazard ratios (HRs) with 95% confidence intervals (CIs) were determined using the Cox model. The univariate and multivariate model was established. The assumed p-value was <0.05. The IBM SPSS Statistics statistical package was used for the calculations.

Results

Table I presents the clinical characteristics of 61 patients undergoing RP (n = 61). 19 patients (n = 19) were diagnosed with EPE(+) and 42 (n = 42) without EPE (–) in the final histopathological report post RP. Patients with EPE(+) differed statistically significantly from patients without EPE(–), in terms of the following clinical parameters: ISUP grade in the preoperative biopsy, maximum index lesion (IL) dimension in mpMRI, EPE diagnosis in mpMRI, ISUP grade in the postoperative report, the incidence of PSM, and the incidence of BCR in follow-up.

Analysis using the ROC curve showed that preoperative mpMRI might predict the presence of EPE of PCa with a sensitivity and specificity of 47.4% and 85.7%, respectively (AUC 0.66, 95% CI: 0.51–0.82, p = 0.046). Taking into account

Table I. Clinical characteristics of patients. Comparison of clinical data between pEPE(–) and pEPE(+) patients

Total n (%) or median	Overall (n = 61)	pEPE(–) (n = 42)	pEPE(+) (n = 19)	pEPE(+) *vs.* pEPE(–) p value
age (median)	65	65.7	63.4	NS
PSA (ng/ml)	8.46	8.01	9.47	NS
PSAD (ng/ml/ml)	0.24	0.22	0.29	NS
DRE: • normal • abnormal	 22 (36.1) 39 (63.9)	 18 (42.9) 24 (57.1)	 4 (21) 15 (79)	NS
biopsy ISUP grade: • 1 • >1	 35(57.4) 26 (42.6)	 29 (69) 13 (31)	 6 (31.6) 13 (68.4)	*
prostate volume (ml) (median)	38.9	39.32	37.86	NS
PIRADS: • 1–3 • 4–5	 21 (34.4) 40 (65.6)	 15 (35.7) 27 (64.3)	 6 (31.6) 13 (68.4)	NS
max diameter of IL in mpMRI (mm)	13.8	12.26	17.32	*
mpMRI EPE: • EPE(–) • EPE(+)	 46 (75.4) 15 (24.6)	 36 (85.7) 6 (14.3)	 10 (52.6) 9 (47.4)	*
mpMRI zone location: • PZ • non-PZ	 45 (73.8) 16 (26.2)	 29 (69) 13 (31)	 16 (84.2) 3 (15.8)	NS
BCR(+)	11 (18)	3 (7.1)	8 (42.1)	*
pathologic ISUP grade: • 1 • >1	 25 (41) 36 (59)	 22 (52.4) 20 (47.6)	 3 (15.8) 16 (84.2)	*
PSM	18 (29.5)	8 (19)	10 (52.6)	*

PSA – prostate specific antigen; PSAD – PSA density; DRE – digital rectal exam; ISUP grade – 2014 International Society of Urological Pathology Grade; PIRADS – Prostate Imaging Reporting and Data System; mpMRI – multiparametric magnetic resonance imaging; EPE – extraprostatic extension ("–"absent, "+" present); pEPE – pathological extraprostatic extension ("–" absent, "+" present); PZ – peripheral zone; non-PZ – zone other than peripheral; BCR – biochemical recurrence; PSM – positive surgical margin; IL – index lesion; NS – not significant; * – $p < 0.05$

the results of the first statistical analysis, which indicate that EPE may also be dependent on other clinical parameters, we examined the sensitivity and specificity of the Martini model, which uses the following data: PSA level, EPE status in mpMRI, ISUP Gleason grade, and the percentage of the biopsy specimen involvement. The Martini model's sensitivity was higher, but the specificity was lower than that of mpMRI and was 84.2% and 66.7%, respectively (AUC 0.78, 95% CI: 0.66–0.89, $p < 0.001$) (fig. 1).

All patients in the study were subject to follow-up. The mean follow-up was 38 months (95% CI: 34.0–42.5 months). Patients with pEPE(+) more frequently experienced BCR 42% (n = 8) *vs.* pEPE(–) 7% (n = 3) (HR 6.4, 95% CI: 1.7–24). Using univariate and multivariate Cox analysis, it was examined whether other clinical factors may also influence the occurrence of BCR. Previous prognostic factors influencing the patient's prognosis (PSA, ISUP grade, DRE, prostate volume, SM) were analyzed, taking into account mpMRI (PIRADS of IL, EPE status, largest IL dimension) (tab. II). The final Cox model showed that EPE in mpMRI was an independent factor that increased the likelihood of BCR – HR 6.6 (95% CI: 1.8–24.1). Another important factor, also significantly increasing the risk of BCR, was the presence of PSM in the postoperative report – HR 7.1 (95% CI: 1.9–26.7). Based on the above analysis, the Kaplan-Meier curve was determined for EPE assessment in mpMRI (fig. 2).

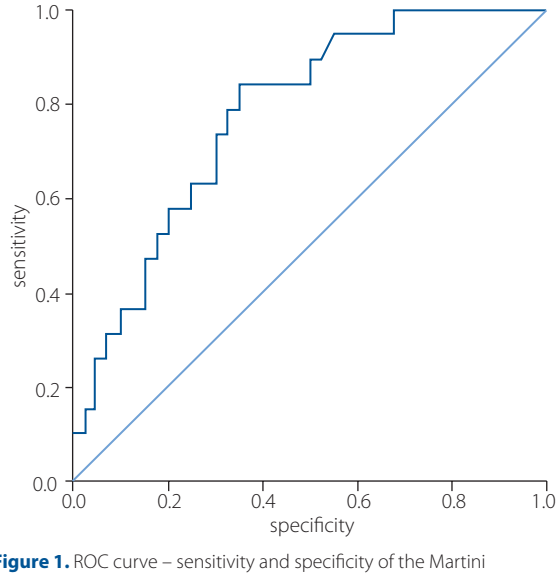

Figure 1. ROC curve – sensitivity and specificity of the Martini nomogram for EPE prediction before RP

Table II. Univariate and multivariate Cox regression analysis of clinical factors for BCR in patients with localized PCa after RP

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
DRE, ref. normal	0.96 (0.28–3.3)	0.94	NA	
PSA	0.95 (0.81-1.1)	0.4		
biopsy ISUP grade, ref. grade 1	1.76 (0.56–5.8)	0.35		
prostate volume	0.97 (0.92–1.0)	0.33		
max diameter of IL in mpMRI (mm)	1.04 (0.97–1.1)	0.26		
PIRADS, ref. ≤3	1.025 (0.3–3.6)	0.97		
mpMRI – EPE, ref. EPE(–)	3.9 (1.2–12.9)	0.02	6.6 (1.8–24.1)	0.005
SM, ref. negative	4.7 (1.4–16.1)	0.01	7.1 (1.9–26.7)	0.004

DRE – digital rectal exam; PSA – prostate specific antigen; ISUP grade – 2014 International Society of Urological Pathology Grade; PIRADS – Prostate Imaging Reporting and Data System; mpMRI – multiparametric magnetic resonance imaging; EPE – extraprostatic extension; BCR – biochemical recurrence; SM – surgical margins; IL – index lesion; NA – not applicable in final model; CI – confidence interval; ref – reference

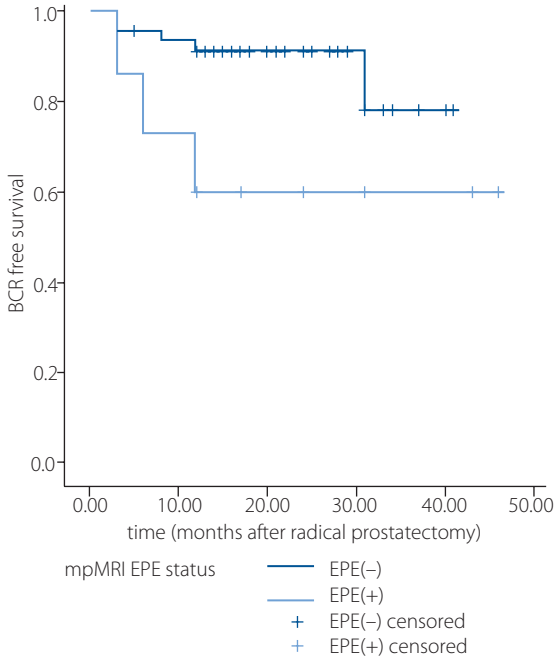

Figure 2. Kaplan-Meier survival curves for biochemical-free survival in patients with positive (+) and negative (–) mpMRI EPE

Discussion

The results obtained indicate that preoperative mpMRI may be a useful tool in local staging of PCa and for the prediction of recurrence; they are to a large extent consistent with the results of other similar studies [7, 8, 15, 16]. The mpMRI parameters analyzed by other researchers included: PIRADS score, volume and location of index lesions, presence of EPE, and/or SVI. Moreover, taking into account mpMRI parameters in conjunction with other clinical data, such as PSA levels and prostate biopsy reports, may contribute to a significant improvement in local staging. An example of this strategy is the model according to Martini et al., which takes into account mpMRI, PSA levels, and a report of the targeted biopsy based on MRI [11].

This retrospective study is one of the few studies available in the literature, which indicates that mpMRI and the Martini model may be tools that are helpful in determining the presence of EPE before surgical treatment [8, 11]. The sensitivity and specificity of mpMRI in assessing EPE in our study were 47.4% and 85.7%, respectively, while for the Martini model – 84.2% and 66.7%, respectively. The meta-analysis conducted by de Rooij, assessing the diagnostic utility of mpMRI in the prediction of stage T3a (EPE), indicated a sensitivity of 0.57 (95% CI: 0.49–0.64) and a specificity of 0.91 (95% CI: 0.88–0.93) [8]. When creating this predictive model for the presence of EPE, Martini estimated the sensitivity of mpMRI alone at 40.7%. [11]. Then, considering the mpMRI and clinical variables, the created model resulted in a higher diagnostic value than mpMRI alone (AUC for mpMRI 0.68 *vs*. AUC for the model 0.82) [11]. We obtained similar results in our research.

Our study also confirmed the relationship between the presence of EPE in the postoperative histopathological report and an increased risk of BCR. Moreover, we demonstrated that EPE in preoperative mpMRI might also be an essential pre-surgical factor increasing the risk of BCR after RP. Therefore, the results obtained in our study indicate that mpMRI may improve the prediction of possible disease recurrence by improving local disease staging. In a study with a similar methodology, conducted on a large group of respondents (n = 804), Gandalgia et al. proved that preoperative information obtained from mpMRI and the report of systematic biopsy combined with a targeted biopsy based on mpMRI allows stratification of PCa recurrence after RP [15]. When assessing the influence of preoperative factors on BCR, Manceau et al. also proved that patients with EPE(+) diagnosed in mpMRI at the treatment planning stage more frequently experience BCR after RP [16]. Moreover, they showed a correlation between the occurrence of BCR and higher PIRADS scores, the greater maximum dimension of MRI lesions, and a higher ISUP Gleason grade in fusion biopsy [16].

From a clinical perspective, the presence of EPE in mpMRI may be a predictive factor for the risk of adjuvant RT implementation after RP. This knowledge at the treatment planning stage can help in the choice of a treatment method, i.e., RP

vs. RT. If surgical treatment is chosen, the information about the presence of EPE in mpMRI and its location can be used to plan the procedure's technique and make decisions, for example, regarding the preservation of nerve bundles. It has been proven that planning RP based on mpMRI changes the operator's decision to preserve NVB in 35% (95% CI: 29–41%) of cases; this strategy is correct in 77% (95% CI: 72–81%) of cases and does not worsen oncological outcomes [17].

Our study has several limitations. The first significant limitation is that it was conducted on a small group studied in one center. The second limitation is the lack of assessment of the extent of EPE and its detailed location, which, according to available knowledge, may also be a significant factor influencing the risk of BCR.

Conclusions

MpMRI and the Martini model are helpful tools in the local staging of patients with PCa. Preoperative use of mpMRI can predict oncological treatment outcomes in patients with PCa after RP.

Conflict of interest: none declared

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Does epidural analgesia modify the risk of complications after gastrectomy?

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Introduction. The surgical treatment of gastric cancer is associated with overall complication rates as high as 50%. The intent of this study was to assess the impact of epidural analgesia (EA) on postoperative complication rates among patients undergoing gastric resections.

Materials and methods. Of the 617 gastric cancer patients who between 2002 and 2010 had undergone stomach resection, 246 (39.8%) were administered EA. Groups with and without EA were compared.

Results. The general rate of complications was lower in the EA group in the univariable analysis – 38.5% *vs.* 54.2% (odds ratio [OR]: 0.47, 95% confidence interval [CI]: 0.34–0.66, p < 0.001), intra-abdominal abscess (OR 0,28, 95% CI: 0.14–0.59, p = 0.001), pneumonia (OR 0,39, 95% CI: 0.24–0.63, p < 0.001), temperature >38°C (OR 0.53, 95% CI: 0.37–0.74, p < 0.001) and re-operation (OR 0.53, 95% CI: 0.28–1.00, p = 0.049). These relationships were confirmed in a multivariable analysis for the general number of complications (OR 0.53, 95% CI: 0.37–0.75, p < 0.001), intra-abdominal abscess (OR 0.36, 95% CI: 0.16–0.77, p = 0.009), temperature >38°C (OR 0.56, 95% CI: 0.39–0.82, p = 0.009), pneumonia (OR 0.42, 95% CI: 0.25–0.71, p = 0.001).

Conclusions. Our findings indicate that postoperative treatment with EA for patients undergoing stomach resection is safe and contributes to a reduction in the number of postoperative complications.

Key words: gastric cancer, GEJ cancer, epidural analgesia, postoperative complications, gastrectomy, postoperative pain

Introduction

For the past 100 years, cases of stomach cancer (gastric cancer – GC) amongst developed countries have been systemically in decline. Possible contributing factors for this decline may be attributed to the increased use of refrigeration for food storage, dietary changes, and decreased incidents of infections with Helicobacter pylori [1]. Despite progress, stomach cancer remains the fourth most frequently diagnosed cancer worldwide. In 2008, there were 980,000 new cases, of which, 83,000 were reported in the European Union and over 5000 in Poland alone [1, 2]. In Poland, the 5-year survival rate post stomach cancer diagnosis is about 18%, in Europe is about 25%, while in Japan about 70% [2–4].

Surgical resection of gastric cancer has produced suboptimal survival rates despite multidisciplinary treatment approaches and improvements in surgical techniques. The European Society for Medical Oncology (ESMO) guidelines of treatment for patients diagnosed with an advanced GC include perio-

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perative chemotherapy [5]. However, a total or subtotal gastrectomy with removal of the surrounding lymph nodes, (D2 resection) remains the only curative method of treatment [5–8]. The vast extent of surgical intervention is one of the main contributing factors to the high risk of complications associated with the procedure. The estimated number of complications varies between 17 and 48%. Additionally, gastric resection in conjunction with splenectomy or spleno-pancreatectomy significantly increases the potential for complications [9–14]. The management of quality care in postsurgical settings that include administration of regional analgesia contributes to better treatment outcomes [15, 16]. Due to the limitations in the use of opioids, resulting from the recommendations of the ERAS protocol, the effectiveness of epidural analgesia (EA) is very important. Currently, EA is a standard procedure in our team and for this reason historical data were compared. On the other hand, surgical procedures did not undergo significant modification during the period under review.

Objective

To assess the impact of EA on postoperative complication rates in patients undergoing subtotal or total gastrectomy for gastric cancer.

Materials and methods

This study was conducted in a single institution using its administrative database. All patients were treated between 2002 and 2010 at The Maria Sklodowska-Curie Institute, Oncology Center in Warsaw. No neoadjuvant therapy was administered in the analyzed period. Of 723 GC resections performed, 617 cases had complete medical documentation that was adequate for retrospective review (study flow – fig. 1).

The data of 617 patients diagnosed with gastric cancer that underwent resection of the stomach was retrospectively reviewed and analyzed by univariable and multivariable methods. Patients were divided into two study groups based on the use of epidural analgesia and other methods. The group of patients treated without EA included patients who underwent treatment during a period of time when epidural catheterization use was not the treatment of choice (until the end of 2006); these cases primarily occurred historically earlier than those who were treated with EA. Another reason for non EA administration was the lack of patient consent. Our study included 413 males (66.9%) and 204 females (33.1%) with a median age of 63 (53–71). Epidural analgesia was administered in 246 patients (39.8%). The patients' demographic and clinical characteristics are illustrated in table I and table II.

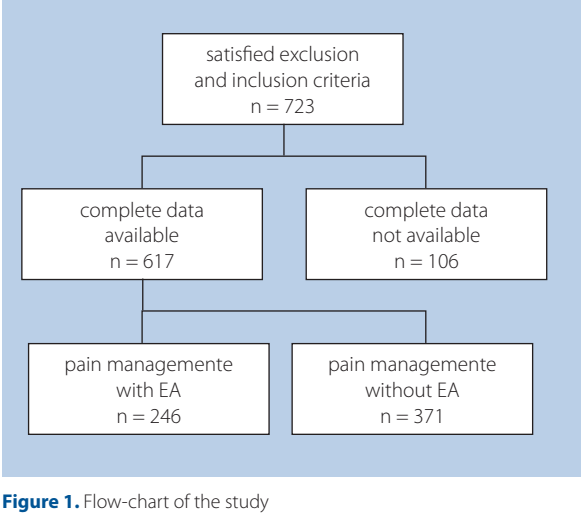

Figure 1. Flow-chart of the study

Table I. Baseline characteristics – demographic data, nutrition status, and comorbidities

Characteristic	Epidural analgesia (EA)		p value
	No n = 371 (%)	Yes n = 246 (%)	
gender: • female • male	 119 (58.3) 252 (61)	 85 (41.7) 161 (39)	0.522
age: (median) (IQR)	64 (53–71)	61 (54–72)	0.144
BMI • <19 • 19–25 • >25	 31 (70.5) 164 (63.8) 176 (55.7)	 13 (29.5) 93 (36.2) 140 (44.3)	0.050
comorbidities	296 (61.0)	189 (39.0)	0.381
diabetes	28 (54.9)	23 (45.1)	0.426
coronary disease	107 (60.1)	71 (39.9)	0.996
hypertension	125 (53.6)	108 (46.4)	0.010
peptic ulcer	93 (64.1)	52 (35.9)	0.260
anemia	304 (58.6)	215 (41.4)	0.069

EA – epidural analgesia; IQR – interquartile range

Analysis of the two group of patients indicated differences in the location of the gastric tumor, the extent of the gastric resection, and spleen removal. Patients treated without EA more frequently experienced malnutrition (BMI < 19). We did not observe statistically significant differences among both studied groups in respect to demographic characteristics, pre-operative risk factors (excluding hypertension), and the length of the procedure. The statistical univariable and multivariable analysis of the factors contributing to postsurgical complications included:

- administered EA,
- gender,
- age,
- pre-surgical BMI,
- diabetes,
- hypertension,
- coronary disease,
- and peptic ulcers.

Additionally, in our analysis we included perioperative transfusions, the length of the surgery, and the extent of the multi-organ resection.

Table II. Type and extent of surgical intervention

	Epidural analgesia (EA)		p value
	No n = 371 (%)	Yes n = 371 (%)	
operative approach:			
• laparotomy	270 (72.7)	164 (66.7)	0.104
• thoracolaparotomy	101 (27.3)	82 (33.3)	
type of surgery:			
• gastrectomy (TG)	216 (58.3)	105 (42.7)	
• TG + distal esophagostomy	97 (26.1)	77 (31.3)	
• distal resection (SG)	55 (14.8)	55 (22.4)	<0.001
• proximal gastrectomy (PG)	2 (0.5)	4 (1.6)	
• antrectomy	1 (0.2)	5 (2.0)	
length of surgery (min.):			
• <140	63 (16.9)	62 (25.2)	
• 140–169	93 (25.2)	55 (22.4)	0.102
• 170–209	101 (27.2)	61 (24.8)	
• 210–570	114 (30.7)	68 (27.6)	
perioperative blood transfusion	147 (39.6)	72 (29.3)	0.008
neighboring organ resection	178 (48.0)	110 (44.7)	0.426
splenectomy	138 (37.2)	65 (26.4)	0.005
distal pancreatectomy	15 (4.0)	6 (2.4)	0.282
large bowel resection	6 (1.6)	7 (2.8)	0.298
cholecystectomy	29 (7.8)	14 (5.7)	0.310

Operative treatment

All cases included in this study contained patients who were operated on by the same experienced (over 30 operations per surgeon) surgical team. Post-operative care and management was provided using consistent post-surgical protocols that included enteral and parenteral nutrition for a period of 7 to 10 days. Total gastrectomy (TG) was performed on 321 patients (52%), 174 (28.2%) patients were treated with TG expanded by resection of the lower section of the esophagus, 110 (17.85%) patients underwent distal subtotal gastrectomy (SG), and in 6 (1%) of these cases proximal gastrectomy (PG) was performed. In 434 (70.3%) of these cases, surgery was performed by laparotomy, in 183 (29.7%) patient's a laparotomy was performed *via* the thoraco-abdominal approach. We performed curative gastrectomies and dissections of the lymph nodes expanded by removal of the additional organs in cases rendering more extensive surgical interventions. The range of surgical resections in both groups of patients is presented in table II.

Postoperative pain management

All patients (from 2007) were preoperatively evaluated for the postoperative use of epidural analgesia. Additionally, patients that were administered epidural analgesia consented to the procedure in a separate preoperative assessment. We administered EA in all suitable cases, except in patients with clinical contraindications to the procedure, and in cases where the patient did not consent. Contraindications included:

- coagulation disorders or perioperative use of blood clotting medications,
- inflammation at the catheter placemat area,
- neurological conditions.

Prior to administering general anesthesia, in the operating room, the epidural catheter was placed into the epidural space between Th6 and Th7 (when the patient's anatomy dictated, exact vertebral space varied by one up/down segments). The area designated for catheter placement was prepared according to surgical protocols, with the insertion site disinfected and surgical dressing administered. The skin and the subcutaneous tissue in the puncture site was anesthetized with a 2% solution of lidocaine and kept sterile. After the catheter was inserted into the epidural space, it was secured on the skin surface with clearly marked transparent dressing tape. Our postoperative pain management regimen of choice was epidural analgesia, administered *via* continuous infusion of Breivik's mixture into the epidural space using a syringe pump [17]. The mixture was composed of low concentrations of medications (22 µg/ml adrenaline, 2 µg/ml fentanyl and 1.25 mg/ml bupivacaine – which deviates slightly from the standard regimen) in a 0.9% solution of sodium chloride. The epidural infusion delivery rate was about 3:9 ml/h. Patients in both studied groups were intravenously administered coanalgesics (metamizol and paracetamol). Patients that were not postoperatively administered EA received a subcutaneously delivered morphine sulfate in fractionated doses (5–10 mg/dose) in 4–6 hour intervals, accompanied with coanalgesics.

Statistical analysis

Information collected throughout our research was recorded, analyzed, and presented in tables with a cross-tabulation of data. The operative time and age are divided into four categories based on quartiles. The Chi^2 test and Wilcoxon test were used to compare the groups. The relationship between postoperative complications (outcomes) and the use of epidural analgesia is analyzed in a univariable logistic regression model and in a multivariable logistic regression model that controls for confounders. Multi-step forward regression was used to select significant disturbing variables in multivariate models, including significant variables at <0.1 (the multiple variables describing the EA was included in each model regardless of its significance level). The results of the models are presented in the form of odds ratios (OR) and 95% confidence intervals (CI). Variables for which $p < 0.05$ were considered significant. This analysis is performed with Stata software, version 13.1 (Stata Corporation, College Station, Texas, USA).

Bioethics

The study was conducted in compliance with the Declaration of Helsinki for medical research and was approved by the Local Bioethics Committee at The Maria Sklodowska-Curie Institute, Oncology Center in Warsaw (permit No. 20/2017 from 09.02.2017). As a retrospective study, according to the approval of the bioethical committee, the informed consent of the patient was not required.

Results

There were no EA-related complications (neurological deficits, postdural puncture headache), although not every patient managed to insert an epidural catheter. Patients who did not have an epidural catheter inserted for technical reasons were analyzed in the group without EA. Administration of epidural catheters or epidural analgesia is not associated with increased risk for postoperative complications. The postoperative mortality rate was 1%, (6 patients of 617). No thromboembolic or pulmonary complications were present amongst postoperative patients who had received EA. Due to an insignificant occurrence rate, we did not review incidents of hemoperitoneum (intra-abdominal leak), postoperative eventration, or cases of anastomotic strictures (tab. III).

Additionally, the univariable analysis of patients that were administered EA displayed a lower frequency of postoperative complications compared to the group treated with other methods (OR 0.47, 95% CI: 0.34–0.66, $p < 0.001$), intra-abdominal abscesses (OR 0.28, 95% CI: 0.14–0.59, $p = 0.001$), pneumonia (OR 0.39, 95% CI: 0.24–0.63, $p < 0.001$), temperature >38°C (OR 0.53, 95% CI: 0.37–0.74, $p < 0.001$) and reoperations (OR 0.53, 95% CI: 0.28–1.00, $p = 0.049$) (fig. 2).

These relationships were confirmed in a multivariable analysis for the general number of complications (OR 0.53, 95% CI: 0.37–0.75, $p < 0.001$), intra-abdominal abscess (OR 0.36, 95% CI: 0.16–0.77, $p = 0.009$), temperature >38°C (OR 0.56, 95% CI: 0.39–0.82, $p = 0.009$), pneumonia (OR 0.42, 95% CI: 0.25–0.71, $p = 0.001$) – tables: IV, V and VI. The relationship between administering EA and reoperation in a multivariable analysis was not confirmed. Diagnosis of pneumonia was based on the correlation of clinical symptoms and radiological determinations. There were no significant statistical differences in univariable and multivariable analysis of wound infections, infection of the central line, or the anastomotic stricture, (table VI and table VII).

Table III. Postoperative complications

Complication type	Epidural analgesia (EA)	
	No n = 371 (%)	Yes n = 246 (%)
overall complications (total)	201 (54.2)	88 (35.8)
temperature >38°C	158 (42.6)	69 (28)
pneumonia	81 (21.8)	24 (9.8)
intra-abdominal abscess	44 (11.9)	9 (3.7)
anastomotic leak	40 (10.8)	20 (8.1)
re-operation	38 (10.2)	14 (5.7)
wound infections	28 (7.5)	13 (5.3)
catheter related sepsis	28 (7.5)	17 (6.9)
anatomic stricture	6 (1.6)	1 (0,4)
intra-abdominal bleeding	4 (1.1)	4 (1.6)
eventration	2 (0.5)	1 (0.4)

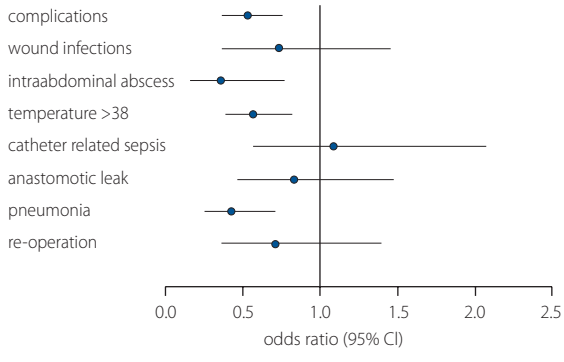

Figure 2. Risk of complications according to EA administration

Discussion

Complications associated with gastrectomy with D2 lymphadenectomy for the treatment of gastric cancer presents multiple clinical considerations against extensive lymphadenectomy [10, 13, 14]. The overall rate of complications is between 17 to 48%. The most frequent postoperative complications in gastric resection surgeries for curative gastric cancer interventions are pneumonia, surgical site infections, (incision infections, intra-abdominal abscesses) and leaking anastomosis [9–14, 18]. Despite the potential for postoperative complications, extensive surgical resection with lymph nodes dissection remains the only curative therapy for gastric cancer

Table IV. Analysis of complications (total complications and temperature >38°C) based on the administration of epidural analgesia

	Total complications						Temperature >38°C					
	Univariable			Multivariable			Univariable			Multivariable		
variable	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
EA	0.47	0.34–0.66	<0.001	0.53	0.37–0.75	<0.001	0.53	0.37–0.74	<0.001	0.56	0.39–0.82	0.003
BMI:												
• 19–25	1.49	0.77–2.88	0.241	1.67	0.81–3.44	0.162	1.41	0.69–2.88	0.341	1.61	0.75–3.45	0.225
• >25	1.68	0.88–3.24	0.117	2.25	1.09–4.65	0.029	1.77	0.88–3.56	0.111	2.38	1.11–5.10	0.026
diabetes	1.31	0.74–2.32	0.363				1.59	0.89–2.83	0.115			
CD	1.16	0.82–1.64	0.410				1.02	0.71–1.46	0.925			
hypertension	0.67	0.49–0.94	0.019	0.64	0.44–0.94	0.023	0.75	0.53–1.05	0.094			
peptic ulcer	1.29	0.89–1.88	0.178				1.68	1.15–2.44	0.007	1.88	1.25–2.81	0.002
OT (ref. <140):												
• 140–169	1.81	1.10–3.00	0.021	1.43	0.83–2.47	0.194	1.82	1.06–3.13	0.030			
• 170–209	2.38	1.45–3.89	0.001	1.58	0.92–2.69	0.096	2.51	1.48–4.23	0.001			
• 210–570	3.39	2.09–5.51	0.000	2.18	1.28–3.70	0.004	2.72	1.63–4.54	<0.001			
BT	1.69	1.21–2.36	0.002	1.58	1.10–2.28	0.014	1.50	1.07–2.10	0.019	1.45	1.00–2.10	0.047
Spl	2.77	1.95–3.92	<0.001	2.17	1.49–3.18	<0.001	2.73	1.93–3.87	<0.001	2.57	1.77–3.72	0.000
SP	2.33	0.93–5.87	0.071				1.59	0.66–3.80	0.299			
gender (male)	1.85	1.31v2.61	<0.001	1.60	1.09–2.33	0.016	1.63	1.14–2.33	0.008	1.59	1.08–2.35	0.020
age (ref. <53):												
• 54–62	1.23	0.78–1.95	0.367	1.39	0.84–2.32	0.203	1.02	0.64–1.64	0.921	0.96	0.58–1.61	0.885
• 63–70	1.89	1.18–3.03	0.008	2.05	1.21–3.48	0.007	1.60	0.99–2.58	0.053	1.49	0.89–2.49	0.131
• 71–87	1.00	0.64–1.58	0.995	1.21	0.71–2.05	0.483	0.81	0.50–1.30	0.385	0.75	0.45–1.28	0.293

EA – epidural analgesia; CD – coronary disease; BT – blood transfusion; OT – operation time (minutes); Spl – splenectomy; SP – splenopancreatectomy

Table V. Analysis of complications (pneumonia and intra-abdominal abscess) based on the administration of epidural analgesia

	Pneumonia						Intra-abdominal abscess					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
EA	0.39	0.24–0.63	<0.001	0.42	0.25–0.71	0.001	0.28	0.14–0.59	0.001	0.36	0.16–0.77	0.009
BMI:												
• 19–25	1.03	0.41–2.62	0.948	1.28	0.48–3.46	0.621	1.28	0.37–4.47	0.699			
• >25	1.58	0.64–3.90	0.323	2.74	1.03–7.30	0.044	1.33	0.39–4.57	0.652			
diabetes	1.56	0.79–3.10	0.199	1.91	0.90–4.03	0.092	0.90	0.31–2.60	0.843			
CD	1.16	0.74–1.83	0.522				0.97	0.52–1.81	0.927			
hypertension	0.64	0.41–1.01	0.057	0.58	0.35–0.96	0.036	0.57	0.30–1.07	0.078			
peptic ulcer	1.64	1.03–2.60	0.037	1.82	1.11–3.01	0.018	1.19	0.62–2.25	0.601			
OT (ref. <140):												
• 140–169	1.59	0.16–16.02	0.694				2.91	0.92–9.17	0.068			
• 170–209	1.86	0.21–16.47	0.578				2.42	0.76–7.69	0.134			
• 210–570	2.27	0.27–19.38	0.453				4.59	1.55–13.59	0.006			
BT	2.30	1.16–4.55	0.017	2.34	1.13–4.85	0.023	2.82	1.59–5.00	<0.001	2.55	1.37–4.73	0.003
SpI	2.27	1.04–4.92	0.038	2.10	0.93–4.74	0.075	6.79	3.59–12.85	<0.001	5.61	2.91–10.82	<0.001
SP	1.68	0.55–5.12	0.363			1.47	4.67	1.73–12.61	0.002			
gender (male)	2.56	1.51–4.34	<0.001	2.39	1.37–4.17	0.002	3.00	1.38–6.48	0.005	2.93	1.27–6.75	0.012
age (ref. <53):												
• 54–62	0.68	0.37–1.27	0.228	0.68	0.37–1.27	0.228	0.99	0.45–2.16	0.978			
• 63–70	1.08	0.60–1.94	0.804	1.08	0.60–1.94	0.804	1.11	0.51–2.43	0.794			
• 71–87	0.86	0.48–1.54	0.607	0.86	0.48–1.54	0.607	0.61	0.26–1.43	0.252			

EA – epidural analgesia; CD – coronary disease; BT – blond transfusion; OT – operation time (minutes); SpI – splenectomy; SP – splenopancreatectomy

Table VI. Analysis of complications (anastomotic leak and reoperation) based on administration of epidural analgesia

	Anastomotic leak						Re-operation					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
EA	0.73	0.42–1.29	0.278	0.83	0.46–1.48	0.523	0.53	0.28–1.00	0.049	0.72	0.37–1.40	0.328
BMI:												
• 19–25	0.53	0.20–1.42	0.208				0.62	0.22–1.76	0.373			
• >25	0.76	0.30–1.94	0.570				0.76	0.28–2.08	0.591			
diabetes	2.16	1.00–4.70	0.051	2.35	1.07–5.19	0.034	1.20	0.45–3.17	0.712			
CD	1.06	0.59–1.90	0.836				1.11	0.60–2.05	0.750			
hypertension	0.81	0.46–1.42	0.457				0.78	0.43–1.44	0.431			
peptic ulcer	1.59	0.89–2.83	0.119				0.76	0.37–1.55	0.449			
OT (ref. <140):												
• 140–169	1.09	0.39–3.02	0.866				0.96	0.34–2.73	0.944			
• 170–209	2.37	0.97–5.81	0.058				1.59	0.62–4.08	0.330			
• 210–570	2.56	1.07–6.14	0.035				2.44	1.01–5.87	0.047			
BT	2.10	1.23–3.59	0.007	2.06	1.19–3.56	0.009	4.70	2.54–8.68	<0.001	4.77	2.53–9.01	<0.001
Spl	1.91	1.12–3.27	0.018	1.78	1.03–3.09	0.039	3.37	1.88–6.04	<0.001	2.90	1.58–5.33	0.001
SP	0.98	0.22–4.30	0.975				3.65	1.28–10.40	0.015			
gender (male)	1.70	0.91–3.17	0.095				3.44	1.52–7.77	0.003	3.51	1.51–8.14	0.003
age (ref. <53):												
• 54–62	0.92	0.42–2.02	0.830				1.02	0.44–2.34	0.972			
• 63–70	1.36	0.64–2.90	0.421				1.64	0.74–3.60	0.221			
• 71–87	0.94	0.43–2.04	0.872				0.73	0.30–1.77	0.482			

EA – epidural analgesia; CD – coronary disease; BT – blond transfusion; OT – operation time (minutes); Spl – splenectomy; SP – splenopancreatectomy

Table VII. Analysis of complications (wound infections and catheter related sepsis) based on the administration of epidural analgesia

	Wound infections						Catheter related sepsis					
	Univariable			Multivariable			Univariable			Multivariable		
Variable	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
EA	0.68	0.35–1.35	0.272	0.73	0.37–1.45	0.368	0.91	0.49–1.70	0.766	1.08	0.57–2.08	0.808
BMI:												
• 19–25	3.05	0.39–23.49	0.285				0.79	0.22–2.86	0.716			
• >25	3.38	0.44–25.64	0.240				1.33	0.39–4.57	0.652			
diabetes	0.87	0.26–2.92	0.820				2.21	0.93–5.24	0.072			
CD	1.02	0.51–2.05	0.951				1.72	0.92–3.20	0.089	1.78	0.92–3.42	0.085
hypertension	0.58	0.29–1.19	0.139				1.11	0.60–2.06	0.748			
peptic ulcer	0.91	0.42–1.95	0.809				1.52	0.79–2.94	0.214			
OT (ref. <140):												
• 140–169	1.50	0.43–5.25	0.524				1.50	0.43–5.25	0.524			
• 170–209	2.64	0.84–8.30	0.097				3.55	1.16–10.82	0.026			
• 210–570	3.12	1.02–9.50	0.046				3.12	1.02–9.50	0.046			
BT	1.62	0.86–3.07	0.136				1.50	0.81–2.77	0.195			
Spl	1.65	0.87–3.14	0.124				2.28	1.24–4.19	0.008	2.52	1.32–4.80	0.005
SP	3.55	1.14–11.10	0.029	2.85	0.90–9.02	0.075	0.63	0.08–4.78	0.653			
gender (male)	2.52	1.10–5.80	0.029	2.38	1.03–5.50	0.042	0.54	0.29–0.99	0.047	0.50	0.26–0.94	0.032
age (ref. <53):												
• 54–62	1.08	0.41–2.81	0.879				0.96	0.36–2.57	0.940	0.98	0.36–2.66	0.961
• 63–70	1.74	0.70–4.28	0.230				2.45	1.04–5.80	0.041	2.32	0.96–5.60	0.062
• 71–87	0.92	0.34–2.44	0.860				0.92	0.34–2.44	0.860	0.94	0.34–2.61	0.902

EA – epidural analgesia; CD – coronary disease; BT – blond transfusion; OT – operation time (minutes); Spl – splenectomy; SP – splenopancreatectomy

worldwide. Experienced medical institutions specializing in surgical oncology routinely perform extensive curative resections for gastric cancer [9, 10, 14, 19].

Effective analgesia is an essential part of postsurgical management and provides statistically and clinically significant improvements in treatment outcomes. Most published clinical studies have demonstrated that the administration of epidural analgesia in gastric surgery patients is a safe practice as a means to improve perioperative outcomes [16, 20–24]. Effective postoperative pain management, as well as the reduction of stress response to surgery along with management of the cardiovascular system and microcirculation significantly reduces complications. Furthermore, studies suggest that administering EA contributes to the reduction of perioperative blood loss. The recommended technique requires continuous infusion of pain medications assisted by intermitted bolus injections [25, 26].

A comprehensive literature review of the effect of postoperative analgesia on surgical outcomes [24] showed the impact of administering epidural analgesia on complications rates following major abdominal surgery. Throughout this study, authors established that the administration of epidural analgesia significantly reduces the risk of pulmonary and cardiovascular complications, as well as thromboembolism, postoperative occlusions, and hastens the return of bowel function. Our study was performed retrospectively and is therefore subject to associated biases. During the extensive research period in which the review of this data occurred, our standards of postoperative care and surgical experience have improved; possibly affecting our findings had this data included newer cases. Therefore, based on this study alone, we cannot definitively conclude that administering EA decreases the risk of complications after gastrectomy. There is, however increasing evidence of the overall positive impact that EA has on treatment outcomes. When considering the retrospective review of 84 patients that underwent laparoscopic SG [27], all data suggests that administering EA has no significant impact on treatment outcomes, except for patients treated with EA who experienced urinary retention.

In a prospective study of 1021 patients, the analysis confirmed more effective pain management, a lower need for analgesics, and a shorter stay in the intensive care unit [28]. No statistically significant differences were reported for mortality and the postoperative complication rate. Further analysis demonstrated a reduction of postoperative complications in the group of patients administered EA that underwent vascular surgical interventions. In the relatively smaller groups of patients that underwent gastrectomy (77 patients), large intestine or bile duct operation, the difference between the number of postoperative complications remains insignificant. The results of the Cochrane Database analysis [29] in which 94 studies were evaluated, (total of 5864 patients) suggests effective pain management and an accelerated return of gastrointestinal transit in patients treated with EA. With the use of the open surgery technique, EA reduces the length of the hospital stay. There was no difference in vomiting incidence or anastomotic leak. Complications of epidural analgesia are rare, but additional studies to examine the impact of administering epidural analgesia in extensive surgical interventions for gastric cancer are needed.

A recently publish retrospective review of the American College of Surgeons National Surgical Quality Improvement Program [30] performed for patients undergoing open elective esophagectomies and gastrectomies for nonmetastatic cancer, analyzed a group of 2599 gastrectomies, among which 18% received EA. The only conclusion from the analysis is that EA was associated with a longer length of stay (EA median [IQR] 8 [7, 11] *vs.* no EA 7 [6, 11], $p = 0.0002$). No other differences between the groups were noted.

Of the retrospective review of 723 gastric cancer resections performed at our institution, 617 cases had complete medical documentation that was adequate for review (85.3%). Data not included in this study amounting to the remaining 14.7% of cases was excluded due to random issues such as incomplete medical records and other associated factors. The analyzed group of patients was treated with comparable surgical techniques, postoperative care, and perioperative management protocols. Patients administered EA did not experience a higher number of complications than the group of patients treated with other methods. Thus, administering EA has proven to be safe in the perioperative care of patients undergoing gastric resection. Research indicates that the frequency of wound infections (fever >38°C, intra-abdominal abscess) pneumonia and reoperations is reduced in the group of patients with EA. Metaanalysis [26] as well as our assessments confirm that effective postoperative pain management decreases the incidence of pulmonary complications. We observed a decreased number of other complications, (except for frequency of anastomotic leak), however in conclusion, they offer no statistical significance.

Conclusions

Our findings indicate that administering EA to patients undergoing major stomach resection for gastric cancer is safe. Furthermore, postoperative treatment with epidural analgesia following stomach resection contributes to a reduction in the number of postoperative complications; this is most notable in the reduced number of cases of pneumonia, sepsis, and the need for additional surgical interventions.

Conflict of interest: none declared

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The quality of life of patients with head neoplasms and incidence of depression treated with radiotherapy. A preliminary research report

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Introduction. The diagnosis of a primary tumor of the central nervous system is a source of huge fear and anxiety for a patient, because the prognosis is usually unfavorable. Very often, the cancer is accompanied by depression, which reduces the effectiveness of treatment and worsens the patient's functioning in everyday life.

The aim. The aim of the study is to determine the cause-and-effect relationship between quality of life and incidence of depression, as well as the side effects of treatment in people treated with radiation for head cancer.

Material and methods. The study group consisted of 103 patients during treatment in the Radiotherapy Ward of the Specialist Hospital in Nowy Sącz. The research tools were: the WHO QOL-Bref questionnaire, the Beck Depression Scale and a questionnaire of the author's own design regarding patients treated with radiation therapy for head cancer.

Results. The general perception of the quality of life in the studied group was 2.88 points, the general perception of the patient's own health was 1.88 points. The average quality of life was the highest in the environmental field: 62.50 ± 23.21, while the lowest in the physical field: 44.24 ± 28.65.

Conclusions. Both the overall assessment of the quality of life in the assessed areas and the perception of health by patients treated with radiation therapy for head cancer are low.

Key words: head cancer, depression, quality of life

Introduction

Radiation therapy is a very effective and one of the most commonly used methods of cancer treatment; at the same time it is one of the factors that cause increased stress in the oncological patient. This is associated with anxiety and the occurrence of side effects that can significantly affect the quality of life [1]. Treatment methods used in oncology are usually very aggressive, which causes anxiety in patients. As Walden-Gałuszko emphasizes, not knowing about the side effects and their consequences as well as the method of treatment is the most common reason for a patient's anxiety. The quality of life in patients treated with radiation therapy depends on multiple factors. The patient's ability to quickly adapt mentally to the situation has a significant impact. Moreover, the ability to deal with the side effects of early and late treatment is also of crucial importance during the treatment [2].

Radiotherapy is usually a kind of treatment that requires the patient to stay in an oncological center for several weeks, which can lead to anxiety for the patient. For a long time during the treatment, the patient can experience discomfort in life

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caused by various undesirable symptoms brought on by the radiation therapy [3]. Irradiation treatment is associated with a reduced intensity of side effects when compared to chemotherapy [4]. A diagnosis of cancer heightens the patient's fear, elevates anxiety, a sense of danger and the uncertainty of life. The image of this disease, which is common in society, evokes negative emotions [2]. On the one hand, the quality of life of a cancer patient is determined through the prism of the ailments or fears that accompany the disease, on the other hand, there is faith in treatment and a reduction of discomfort [5]. When diagnosing cancer, it seems necessary to start treatment as soon as possible.

For most patients, even staying in hospital is a big psychological problem and experience. A patient's value system is often radically changed. The onset of illness means that the person is at a level of basic needs, such as health, life and psychosomatic comfort. Safety and physical comfort are usually provided by the hospital, but the need for peace of mind is often not met. This is usually caused by a lack of communication between the patient and the medical staff. Providing information on the state of health, the course of the disease, the treatment and side effects, as well as establishing and maintaining vital emotional contact are all factors that are responsible for a patient's mental comfort. Another factor that reduces the quality of life of a hospitalized patient is the feeling of helplessness and passivity [2]. In scientific research, the basic and very often only criteria for assessing the effectiveness of oncological treatment was the survival time and remission period. Currently, more attention is paid to the impact of the disease and its treatment than on the patient's functional and psychological condition and their place in society [5].

The assessment of the quality of life of patients treated oncologically is of great interest in recent years. Cancer and depression are causes of a patient's suffering [6]. The concept of depression in the aspect of cancer is very important in many aspects. One of them is the occurrence of depression and mood disorders as a cause or factor of cancer [7, 8]. In such patients, there are disturbances and obstacles regarding cooperation in the treatment process [6]. Incidence of depression in patients with cancer is 3.5 times higher than in patients with diabetes, hypertension, heart disease, rheumatic arthritis, chronic lung disease or stroke [9].

The aim of the study was to determine the cause-and-effect relationship between the quality of life and the frequency and severity of depression and the side effects of radiation therapy in people treated for head cancer.

In order to achieve the aim of the work, the following research questions were asked:

1. How do patients treated with radiation for head cancer assess their quality of life?
2. What is the relationship between the assessment of the quality of life and the occurrence of depression in patients treated with radiation therapy for head cancer?
3. What is the relationship between the quality of life and the occurrence of side effects in the course of radiation therapy in patients treated for head cancer?
4. What is the relationship between the quality of life and the patient's attitude to the disease?

Material and methods

The research was conducted in the Radiotherapy Ward of the Specialist Hospital J. Śniadeckiego in Nowy Sącz. The diagnostic survey method was used. To assess the quality of life, the Polish version of the standardized WHO QOL-Bref questionnaire developed by Laura Wołowicka and Krystyna Jaracz, containing 26 questions, was used [10]. To assess the severity of depression, the Beck Depression Scale was used, consisting of 21 questions considering the most common symptoms of depression, whose translation and initial adaptation was undertaken by Parnowski and Jernajczyk [11]. The third tool was the author's own questionnaire focused on a group of patients treated with radiation for head cancers. The study group consisted of 103 adults, over 18 years of age, in whom radiotherapy was performed using an accelerator emitting photon radiation with the following energies: X6MV, X15MV, and electrons: E6MeV, E9MeV, E12MeV, E15MeV, E18MeV, E22MeV. The accelerator was equipped with multileaf colimators enabling conformal therapies in any location and IMRT (intensity modulated radiotherapy) therapies in the *step and shot* and *sliding window* technique [12]. In the case of multifocal metastases to the brain, the whole brain was irradiated. In primary lesions or single brain metastases, the area of the lesion was irradiated with a margin along with edema or the tumor bed. In the case of irradiation of the whole brain (palliative treatment), the hypothalamus was not protected. By contrast, in the case of irradiation of the primary tumor area (if possible), the minimum dose per hypothalamus was used.

Participation in the study was voluntary, the patients were informed about the purpose of the study, and they verbally agreed to take part in it.

The Chi^2 independence test, the Mann-Whitney test and the Kruskel-Wallis test were used in the statistical analysis of the results. The choice of nonparametric tests was dictated by the lack of normality of variables (verified with the Kolmogorov-Smirnov and Shapiro-Wilk tests) or by the lack of group equivalence (verified with the Chi^2 compliance test). A significance level of $p < 0.05$ was adopted. The calculations were carried out using the IBM SPSS Statistics 20 program.

Results

One hundred three people aged 20–70 were examined (53.4% men; 46.6% women). The largest group among all the respondents were patients between 41 and 50 years of age (34.0%). Over half of the respondents (55.3%) declared having secondary education. Few respondents (8.7%) had higher education. Analyzing the marital status of the respondents,

it was found that 68.9% of them were married. Single people accounted for only 18.4% of the respondents, and widowed patients constituted 12.6% of the respondents. Most frequently, respondents were diagnosed with glioblastoma multiforme (ICD-094) (34.0%) or a metastatic tumor (ICD-094) (31.1%) of the central nervous system. Less frequent was anaplastic astrocytoma (ICD-094) (14.6%), anaplastic oligospermia (ICD-094) (10.7%), germinal spinal cord (ICD-094) (6.8%) or meningioma (ICD-095) (2.9%).

Radiotherapy at a dose of 20 Gy in fractions of 4 Gy was used in 29.1% of patients and lasted 1 week. The most numerous group of 37.9% were patients treated for 2–3 weeks with 30 Gy of irradiation in 3 Gy fractions; 24.3% of patients diagnosed with meningioma and/or patients who did not complete the treatment were treated for 4 to 5 weeks. Treatment with a dose of 60 Gy was used in 8.7% of the patients, in fractions of 2.0 Gy, which lasted 6 weeks.

The most common effects of radiation were headaches (68.0%). Slightly less often, the subjects suffered from nausea (44.7%) or hair loss (42.7%). Vomiting occurred in 25.2% of the respondents, and 16.5% of the respondents did not experience radiation side effects. Some patients experienced balance disorders (14.6%) or blurred vision (5.8%). Only a few of the respondents (13.6%) used the help of a psychologist from the moment of diagnosis to the present. Most respondents (86.4%) did not benefit from such assistance.

Analysis of the research showed that the respondents rated their quality of life higher (2.88) than their quality of health (1.88). In both cases, the self-assessment of the quality of life and health was very low (1–5 points scale) (tab. I).

The highest quality of life was observed in the environment field (62.50 ± 23.21), a lower one in the social field (50.16 ± 31.35). The lowest indicator of the quality of life was observed in the psychological field (46.93 ± 31.73) and the physical field (44.24 ± 28.65) (tab. II).

Table I. Individual overall perception of the quality of life and health

	Individual overall perception of the quality of life	Individual overall perception of the quality of health
mean	2.88	1.88
median	3.00	2.00
SD	1.41	0.97

On the basis of the Beck scale, it was found that 32.0% of people did not have symptoms of depression. Mild depression was observed in the group of 20.4% of respondents. Moderately severe depression was found in 34.0% of respondents, and very severe depression occurred in 13.6% of the respondents. It was shown that the lack of depression in 44.2% of the respondents or mild depression in 27.9% of the respondents was significantly more common in patients aged 20–40 years. In 48.6% of people aged 41–50 and 40.0% of people over 51 years of age, moderate depression was more frequent than in the rest of the respondents.

Analysis of the author's research shows that respondents without depression rated their overall quality of life the highest (4.30), slightly lower than the respondents with mild depression (3.67), the lowest quality of life rating was respondents with moderately severe (1.57) or very severe depression (1.64). The respondents rated their quality of health in a similar way. The respondents without depression rated their quality of life the highest (2.88), lower (1.81) – the respondents with mild depression, and those with moderately severe (1.34) or severe depression (1.00) rated their quality of health the lowest. Statistical analysis showed a relationship between depression and satisfaction with one's life and health ($p < 0.0001$). In this respect, people without depression showed a statistically significantly higher level of overall perception of quality of life and health than people with depression (tab. III).

It was shown that the lower the severity of depression, the higher the quality of life in individual subscales. The author's research shows that the quality of life in each of the assessed fields was significantly better in people without depression than in those with depression. As a result of the analysis, the differences found were statistically significant ($p < 0.0001$) (tab. IV).

Analysis of the research showed that respondents who had headaches as a side effect of radiation therapy rated their overall quality of life (3.10) and quality of health (2.10) higher than respondents who did not have headaches, who rated their overall quality of life (2.42) and quality of health (1.42) lower. Relationships were observed in each of the fields of the quality of life. People with headaches obtained average values of the quality of life in individual subscales at the level: in the physical field – 47.50, in the psychological field – 50.24, in the social field – 55.24, in the environmental field – 65.67; and these values were higher than in people who did not have

Table II. The quality of life of patients treated for head cancer with radiation therapy

	Physical field	Psychological field	Social field	Environment
mean	44.24	46.93	50.16	62.50
median	39.29	41.67	41.67	59.38
SD	28.65	31.73	31.35	23.21
min.	0	4	0	16
max.	89	96	100	94

Table III. Individual perception of the quality of life and health

Depression (Beck Depression Scale)		Individual overall perception of the quality of life	Individual overall perception of the quality of health
without depression	mean	4.30	2.88
	SD	0.47	0.86
mild depression	mean	3.67	1.81
	SD	0.86	0.40
moderately severe depression	mean	1.57	1.34
	SD	0.70	0.68
very severe depression	mean	1.64	1.00
	SD	0.50	0.00
in total	mean	2.88	1.88
	SD	1.41	0.97
p		<0.0001	<0.0001

headaches. In the case of other side effects: vomiting, nausea, hair loss, and vision and balance disorders in patients treated with radiation for head tumors, similar relationships were observed as in the case of the headache. Both the respondents who did not have side effects of radiation therapy and those who did, assessed their overall quality of life and health in a similar way. A statistically significant dependence on all analyzed side effects of radiotherapy was found in the general perception of the quality of life and health, as well as in the social and environmental field. The obtained results concerning the most statistically significant relationships between variables at the significance level of $p < 0.0001$ revealed a relationship between hair loss and balance disorders and a subjective assessment of quality of life and health, and the quality of life for individual subscales (tab. V).

Table IV. The quality of life and depression in patients treated for head cancer

Depression (Beck scale)		Physical field	Psychological field	Social field	Environment
without depression	mean	78.03	84.97	87.37	88.45
	SD	7.37	8.59	7.55	6.42
mild depression	mean	52.21	54.56	58.73	69.35
	SD	10.13	14.90	11.92	9.04
moderately severe depression	mean	21.22	21.79	23.81	43.21
	SD	12.49	10.98	11.81	10.21
very severe depression	mean	10.20	8.63	15.48	39.29
	SD	8.03	3.45	13.81	19.02
in total	mean	44.24	46.93	50.16	62.50
	SD	28.65	31.73	31.35	23.21
p		<0.0001	<0.0001	<0.0001	<0.0001

Table V. The relationship between the quality of life and the side effects of radiation treatment

Side effects	Occrence		Individual overall perception of the quality of life	Individual overall perception of the quality of health	Physical field	Psychological field	Social field	Environment
headache	no	mean	2.42	1.42	37.34	39.90	39.39	55.78
		SD	1.56	0.50	28.19	29.57	30.64	26.68
	yes	mean	3.10	2.10	47.50	50.24	55.24	65.67
		SD	1.29	1.07	28.48	32.38	30.60	20.85
p			0.0208	0.0027	0.0877	0.0714	0.0168	0.0422
vomiting	no	mean	3.19	1.99	51.02	52.44	57.03	68.63
		SD	1.21	0.87	24.17	29.52	28.20	18.77
	yes	mean	1.96	1.58	24.18	30.61	29.81	44.35
		SD	1.56	1.21	31.82	33.00	31.90	25.88
p			0.0001	0.0022	<0.0001	0.0039	0.0001	<0.0001
nausea	no	mean	3.33	2.05	56.39	58.85	62.43	71.44
		SD	1.31	0.89	25.43	30.40	29.26	20.96
	yes	mean	2.33	1.67	29.19	32.16	34.96	51.43
		SD	1.33	1.03	25.23	27.01	27.14	21.17
p			0.0003	0.0070	<0.0001	0.0001	<0.0001	0.0001

Side effects	Occurence		Individual overall perception of the quality of life	Individual overall perception of the quality of health	Physical field	Psychological field	Social field	Environment
vision disorders	no	mean	3.00	1.94	45.66	48.28	51.72	63.66
		SD	1.37	0.98	28.94	32.22	31.66	23.43
	yes	mean	1.00	1.00	21.43	25.00	25.00	43.75
		SD	0.00	0.00	0.00	0.00	0.00	0.00
p			0.0006	0.0088	0.0686	0.2520	0.0460	0.0157
balance disorders	no	mean	3.20	2.03	49.84	51.94	55.30	67.05
		SD	1.27	0.98	27.03	31.61	31.08	21.84
	yes	mean	1.00	1.00	11.43	17.50	20.00	35.83
		SD	0.00	0.00	9.47	6.34	4.23	8.34
p			<0.0001	<0.0001	<0.0001	0.0006	<0.0001	<0.0001
hair loss	no	mean	2.24	1.47	29.72	31.78	34.04	51.64
		SD	1.43	0.88	26.00	28.80	26.23	21.80
	yes	mean	3.75	2.43	63.72	67.23	71.78	77.06
		SD	0.78	0.82	18.90	23.08	23.86	16.08
p			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
no side effects	no	mean	2.88	1.95	44.73	47.72	51.55	62.86
		SD	1.38	1.03	29.80	32.28	32.20	23.93
	yes	mean	2.88	1.53	41.81	42.89	43.14	60.66
		SD	1.58	0.51	22.51	29.38	26.39	19.74
p			1.0000	0.2064	0.5808	0.4589	0.3348	0.3585

It was shown that respondents who accepted their illness perceived their quality of life the highest (4.33), which was higher than in respondents who somehow got used to it (2.85) or did not accept it (1.39). When analyzing the results of the research, the overall perception of the quality of health was similar. Those who had accepted their disease had a higher score (2.64) than those who had become used to the disease (1.85). The overall perception of the quality of health was rated the lowest by respondents who had not accepted their disease (1.13). The differences were statistically significant (tab. VI).

Table VI. Individual perception of the quality of life and the acceptance of the disease

The acceptance of the disease		Individual overall perception of the quality of life	Individual overall perception of the quality of health
I accept the disease.	mean	4.33	2.64
	SD	0.69	1.06
I do not accept the disease.	mean	1.39	1.13
	SD	0.50	0.34
I feel accustomed to the disease.	mean	2.85	1.85
	SD	1.04	0.74
in total	mean	2.88	1.88
	SD	1.41	0.97
p		<0.0001	<0.0001

It was found that the patients who had fully accepted their illness had the highest quality of life in each of the fields, the respondents who *had got used to* the disease had a lower quality of life, and the lowest were the patients who had not accepted their disease. A higher quality of life in particular fields was demonstrated by people accepting their illness: in the physical field: 72.75, in the psychological field: 80.18, in the social field: 79.55, and in the environmental field: 84.28. The respondents who had not accepted their disease had the lowest quality of life in all fields: in the physical field: 17.51, in the psychological field: 15.86, in the social field: 20.97, and in the environmental field: 40.83. In terms of acceptance of the disease, the compared groups are the most diverse in the psychological field. While analyzing the obtained test results, there was a statistically significant relationship between the acceptance of the disease and the individual fields, which was $p < 0001$ (tab. VII).

Discussion

The Scientific Council of the National Cancer Registry states that in 2016 there was an increase in cancer incidence by about one thousand cases compared to 2015. This number also systematically increases in relation to cases of cancers of the central nervous system [13]. One of the methods of treating cancers of the central nervous system is the use of radiation therapy [14]. Very often, along with the occurrence of cancer, patients at various stages of the disease are accompanied by

Table VII. The quality of life and the acceptance of the disease

The acceptance of the disease		Physical field	Psychological field	Social field	Environment
I accept the disease.	mean	72.51	80.18	79.55	84.28
	SD	14.87	16.24	17.32	9.49
I do not accept the disease.	mean	17.51	15.86	20.97	40.83
	SD	10.65	8.96	15.35	13.33
I feel accustomed to the disease.	mean	41.58	43.48	48.50	61.30
	SD	25.35	25.65	27.43	20.82
in total	mean	44.24	46.93	50.16	62.50
	SD	28.65	31.73	31.35	23.21
p		<0.0001	<0.0001	<0.0001	<0.0001

anxiety, anger and depression, which negatively affects the healing process and affects the quality of life [15].

Cancers of the central nervous system are not very common. However, the most common ones have a poor prognosis. According to the Scientific Council of the National Cancer Registry in Warsaw, cancer occurrence is estimated at 2% per annum [16]. Dziadziuszko and Fijuth indicate that the incidence of glioblastoma multiforme is as much as 40%, while metastatic tumors account for 15–20% in patients with all cancers [15]. The research conducted in the radiotherapy ward confirms the fact that the most common cancers of the central nervous system are glioblastoma multiforme 34.0% and metastatic tumors to the central nervous system 31.1%.

Kowalska and Szemik's research conducted among 225 people aged 25–44, using the WHO QOL-BREF questionnaire, showed that the average values of the quality of life for individual subscales were at these levels: for the physical field – 53.5, for the psychological field – 62.8, for social relations – 70.0, and for the environmental field – 57.3 [17]. Kowalska et al. also assessed the quality of life of 746 healthy, professionally active people aged 45–60. The average of the individual fields was: somatic – 54.4, psychological – 60.8, social – 68.3 and environmental – 57.6 [18]. Patients' quality of life deteriorates after the start of radiation and this condition persists for up to three months after the end of the treatment, as reported by Kozak et al. [19].

The analysis of the results of research showed that cancer and the treatment that is used significantly affect the quality of life of respondents in the physical, psychological and social field. The quality of life in the individual fields was as follows: the best results were obtained in the field of social relations – the average: 62.50; in the social field – the average: 50.16; in the environmental field – the average: 46.93; in the physical field – the average: 44.24.

The occurrence of depression during cancer is a fairly common phenomenon. Studies by Mitchell et al. on the occurrence of depression during cancer show that the co-occurrence of cancer and depression exceeds 50% in many cases [20]. Onitilo et al. note in their publication that regardless of the etiology, the occurrence of depression in cancer patients has an additional impact on the results of the treatment. Patients with depression who are diagnosed with cancer experience a lower quality of life, their cooperation with medical staff is negatively affected and the patients are hospitalized longer [6]. The incidence of depression in patients treated with irradiation of the central nervous system is confirmed by the author's research. Based on the Beck Depression Scale, it was found that 32.0% of the respondents had no symptoms of depression. One in five patients – 20.4% – had mild depression. Moderately severe depression was found in 34.0% of the people, and 13.6% of the respondents had very severe depression. The results of research by Mitchell et al. conducted in a group of 279 oncological patients revealed the occurrence of major depression in 12.7%, and depressive disorders in 29.6% of the subjects [21]. According to the authors, the diagnosis of depression in cancer patients should be more frequently analyzed, as depression in cancer patients can undoubtedly have a negative impact on the treatment process as well as on their cooperation with the medical staff.

Treating the central nervous system with irradiation is very often associated with the occurrence of various types of side effects. Ionizing radiation affects both cancerous and healthy tissues. The author's research carried out in the radiotherapy ward indicates that the most common effects of radiation were headaches – 68.0%. Slightly less frequently, the respondents had nausea 44.7% or hair loss 42.7%. In the study of Kapela et al., 20.7% of respondents experienced pain during chemotherapy [22]. A cancer patient undergoing ionizing radiation treatment is a person who is suffering. Nowak et al. show that pain management results in better coping with its side effects, and in looking at the future – dealing with changes in the quality of life [23]. The author's research has shown that the side effects of radiation therapy: headache, vomiting, nausea,

hair loss, vision and balance disorders significantly affect the overall perception of the quality of life and health.

Assessing the quality of life, especially its psychological sphere, it is crucial to adapt to the disease, i.e. the level of its acceptance, which is emphasized by Kurpas et al. [24]. In the studies by Smoleń et al., adapting to the disease in the studied group of cancer patients was at a medium level, however, people who did not experience pain and assessed their health well adapted better [25]. Szczepańska-Gieracha et al. indicate that among 71 patients with malignant neoplasms, strategies of coping with neoplastic disease may change with the time that elapses since the start of the treatment [26]. Research on the acceptance of cancer was carried out by Smoleń et al. on a group of 229 randomly selected respondents. It was demonstrated that the higher the degree of cancer acceptance, the lower the severity of the helplessness-hopelessness relationship [27]. Ślusarska et al. assessed the level of acceptance of the disease and quality of life during treatment of patients with lymphoma using the WHO QOL-Bref questionnaire. Among 105 respondents, 7.6% of them showed a very low level of acceptance, and 15.2% – a high level. The higher the level of acceptance, the better the quality of life of patients [28].

In the author's research, correlations were found between the level of the acceptance of the disease and the individual general perception of the quality of life and health in its individual areas.

Cancer puts people in a difficult position. Our physicality, mentality, community and human spirituality are all burdened. The reason for this can be any changes that occur in the patient's body, as well as various social factors. Very often, oncological diseases are accompanied by depression and anxiety, which significantly reduce the patient's quality of life and may affect the course of their treatment. Having the necessary knowledge about all stages of treatment and recovery, in both the physical and mental context, as well as the active participation in the process of treating of the patient and the family, can significantly affect the patient's self-esteem. The state of health of a patient treated with head irradiation for metastatic tumors often deteriorates rapidly, which is why J. Zapała et al. drew attention to the importance of health education; this is not only the transfer of knowledge and skills, but also instilling motivation to change one's behavior in order to have more effective treatment [29]. At present, there are few publications regarding the quality of life of patients undergoing radiation therapy for cancers of the central nervous system.

Conclusions

1. Respondents treated with radiation for head cancers rated their quality of life higher than their quality of health. In both cases, the self-assessment of the quality of life and health was very low.
2. Patients who did not have symptoms of depression rated their quality of life higher. Similarly, the higher the assessment of the quality of health, the lower the level of depression. It was shown that the higher the quality of life in specific fields, the lower the severity of depression in patients.
3. The intensity of side effects of radiation therapy for head tumors affects the assessment of the quality of life in specific fields. The greater the intensity of side effects of radiation therapy, the lower the quality of life in all fields. Patient education, carried out by a radiotherapy nurse that refers to how to deal with radiation reactions may significantly affect the patient's assessment of their quality of life.
4. The acceptance of the disease affects the perception of the quality of life. Patients who accepted their disease assessed their quality of life and health the highest, and those who did not accept the disease – rated it the lowest. It was shown that patients who fully accepted their disease had the highest quality of life in every field, a lower quality of life had those who got used to the disease, and the lowest the quality of life had patients who did not accept the disease.

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Chronic obstructive pulmonary disease assessment test predicts postoperative complications in patients with lung cancer qualified for lobectomy

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Introduction. Patients considered for radical surgery for lung cancer need a functional evaluation to identify those at increased risk of postoperative complications.

Material and methods. We performed an analysis of clinical data of 1214 patients who underwent a single lobectomy for lung cancer. To assess the risk of complications, we used the chronic obstructive pulmonary disease assessment test (CAT).

Results. 254 pulmonary and 51 cardiovascular complications occurred in 216 (17.8%) patients. In 204 patients with a CAT score ≥12 complications occurred more often than in patients with a lower score (26.5% *vs.* 16.0%; $p < 0.001$).

Conclusions. In patients undergoing lobectomy for lung cancer, pulmonary complications occurred much more frequently than cardiovascular complications. Patients with a CAT score ≥12 had a higher rate of postoperative complications as compared to those with a lower score.

Key words: lung cancer, lung resection, preoperative evaluation, CAT

Introduction

The goal of preoperative decision making is to minimise postoperative complications. Knowing which clinical factors are associated with complications permits oncologists, pulmonologists or surgeons to assess which candidates are appropriate for major thoracic surgery. Patients with lung cancer qualified for curative lung resection need an assessment of their health status, as they frequently suffer from comorbidities, mainly chronic obstructive pulmonary disease (COPD) and cardiovascular disease [1, 2], which are considered significant prognostic factors [3, 4].

The joint European Respiratory Society/European Society of Thoracic Surgeons and the American College of Chest Physicians [5, 6] recommend a stepwise functional workup of lung resection candidates. The assessment begins with a cardiovascular evaluation using the thoracic revised cardiac risk index (ThRCRI), then pulmonary function tests are performed with the calculation of predicted postoperative lung function. Patients with reduced predictive postoperative lung function are referred for exercise tests.

Current guidelines endorse the thoracic revised cardiac risk index (ThRCRI), as a first-line screening tool assessing the cardiac risk before lung resection [7]. The ThRCRI includes cardiac ischaemia, cerebrovascular disease, renal disease and the extent of resection (pneumonectomy). However, simple registration of comorbidities does not provide information

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on the impact of comorbidities on patients' health. Besides, an assessment of the risk of pulmonary complications is not included at this stage of the preoperative evaluation. The chronic obstructive pulmonary disease assessment test (CAT) was introduced in 2009 as a tool to measure health status impairment in patients with COPD [8]. The CAT is a simple, patient-completed questionnaire, that covers a broad range of effects of COPD on patients' health. It is a standardised assessment tool consisting of only 8 items, that provides reliable and valid information on symptoms, activity limitation and other manifestations of COPD. We assumed that the CAT could also measure the symptomatic effect of other comorbidities and be useful in assessing the risk of complications in all patients qualified for lung resection, regardless of whether they have COPD or not.

The current study aimed to:

- rate the incidence of pulmonary complications and evaluate the need to include these type of complications at an early stage of preoperative evaluation;
- determine the utility of incorporating the CAT in the initial stage of the overall risk assessment of perioperative pulmonary and cardiovascular complications in patients with lung cancer qualified for lobectomy.

Materials and methods

The study was accepted by the local ethics committee. The participating subjects were patients who had undergone a single lobectomy for lung cancer at the Department of Thoracic Surgery, Institute of Tuberculosis and Lung Diseases in Warsaw, between March 2014 and March 2019. Preoperative staging included a complete medical history and physical examination, blood and urine examinations, a 12-lead resting electrocardiogram, pulmonary functional tests (PFT), computed tomography of the chest, and a fibrobronchoscopy. In the presence of symptomatic or previously documented cardiovascular disease, echocardiography, neck or lower limb ultrasound studies were performed. PFT included spirometry with measurements of forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) and a lung transfer factor for carbon monoxide (TL_{CO}) measurements using the single breath method.

Tests were performed using a MasterScreen system (software version 4.65; Jaeger, Würzburg, Germany). We used reference values from the 2012 Global Lung Function Initiative for spirometry [9] and from the 1993 ERS/European Community for Coal and Steel for TL_{CO} [10]. The spirometric criterion of COPD diagnosis was FEV_1/FVC ratio < 0.7 in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [11]. The classification of airflow limitation severity was also taken from the GOLD, mild – FEV_1 ≥80% predicted, moderate – FEV_1 <80% and ≥50% predicted, severe – FEV_1 <50% and ≥30% predicted. The ThRCRI score was calculated according to Brunelli et al. [8].

In our study, the ThRCRI included only three classes, as patients undergoing pneumonectomy were not included in the analysis. The Polish version of the CAT, obtained from the website www.catestonline.org, was administered to patients while they were waiting for PFT. The patients were briefly informed on how to complete the questionnaire and then filled it in independently. The CAT consists of eight items assessing cough, phlegm, chest tightness, breathlessness going up a hill/stairs, activity limitations at home, confidence in leaving home, sleep and energy, with 6-point ordinal scales (scored 0–5) of severity for each item, that provides a scoring range of 0–40.

Lobectomies were performed by either thoracotomy or video-assisted thoracoscopic surgery. Stage I tumours were removed using a minimally invasive technique. The surgical approach was decided by experienced thoracic surgeons. Extended lobectomies (e.g. chest wall resections) were excluded from the analysis. Complications and deaths were those occurring within 30 days postoperatively or later if the patient was still in the hospital. The following pulmonary and cardiovascular complications were included: prolonged air leak, respiratory failure requiring mechanical ventilation for more than 48 hours, atelectasis or retention of secretions in the airways requiring bronchoscopy, pneumonia, myocardial infarction, cardiac failure, pulmonary embolism and death of the patient. The degree of severity of complications was assigned according to the Clavien-Dindo classification [12]. Only life-threatening complications or those requiring surgical or endoscopic intervention (category >2) were included in the analysis.

Statistical analysis

Categorical data were tested by the Chi^2 test. Tests for complications for CAT score ≥12 *vs.* CAT score <12 and two more such tests included separately COPD and non-COPD patients (fig. 1) were adjusted using the Holm-Bonferroni method for

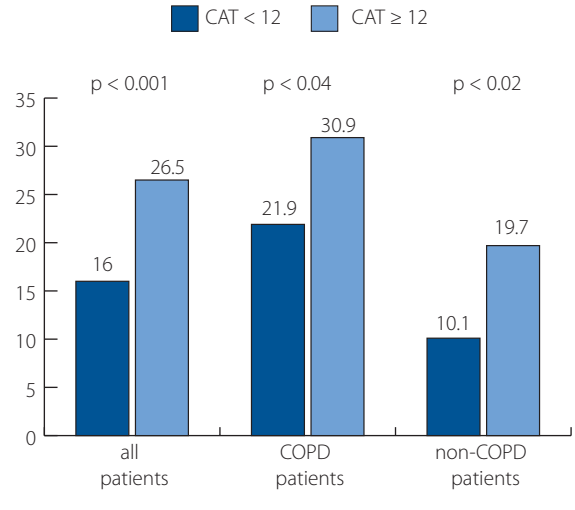

Figure 1. The incidence of complications by CAT score and COPD diagnosis

Table I. Demographic and clinical characteristics of the study patients (n = 1214)

	All patients	COPD patients n = 630	Non-COPD patients n = 584	p value
age in years, mean (SD)	65.2 (8.6)	66.4 (7.6)	63.9 (9.3)	<0.0001*
male, n (%)	647 (53)	388 (61.6)	259 (44.3)	<0.0001**
FEV_1, % predicted (SD)	84.0 (19.1)	73.3 (15.7)	95.4 (15.5)	<0.0001*
FVC, % predicted (SD)	96.0 (15.4)	94.1 (15.5)	98.1 (15.1)	<0.0001*
FEV_1/FVC, mean (SD)	0.67 (0.10)	0.60 (0.07)	0.76 (0.04)	<0.001*
TL_{CO} % predicted (SD)	72.8 (17.6)	68.0 (16.7)	78.0 (17.1)	<0.0001*
CAT, mean (SD)	6.4 (5.7)	6.8 (6.0)	5.9 (5.5)	0.006*
ThRCRI^, mean (SD)	0.32 (0.66)	0.35 (0.68)	0.28 (0.63)	0.08*
comorbidity				
COPD, n (%)	630 (51.9)			
IHD, n (%)	223 (18)	123 (20%)	100 (17)	0.28**
CVD, n (%)	29 (2.4)	19 (3)	10 (2)	0.21**
renal insufficiency, n (%)	5 (0.4)	3 (0.5)	2 (0.4)	0.72**

Tests for COPD *vs.* non-COPD patients – * T-Test for means; ** Chi^2 test; FEV_1 – forced expiratory volume in the first second; FVC – forced vital capacity; TL_{CO} – lung transfer factor for carbon monoxide; IHD – ischemic heart disease; CVD – cerebrovascular disease; SD – standard deviation; ^ – ThRCRI included only three items, without pneumonectomy (score range 0–4.5).

multiple comparisons with p value thresholds adjusted to be respectively: 0.017, 0.025 and 0.05. Lower test p-values were met in testing.

Numerical data statistics were presented in the form of means with standard deviations (SD). Examining table I, means of numerical variables for COPD and non-COPD groups were tested using the independent-samples T-Test. P values below 0.05 for 2-tailed tests were considered statistically significant to reject the hypothesis for equality. Analyses were performed using scientific computation libraries, SciPy (ver. 1.3) and Numpy (ver. 1.16.2), in the Python programming language (ver. 3.8).

Results

The demographic and clinical characteristics of the study subjects are shown in table I. Among 1214 subjects, 630 (52%) patients met the spirometric criteria of the COPD diagnosis ($FEV_1/FVC < 0.7$), of whom 95% were smokers, with mean pack-years 35.9 (SD: 21.9). There were 206 (33%) cases with mild, 384 (61%) moderate and 40 (6%) with severe airway limitation. COPD was the most common comorbidity, followed by ischaemic heart disease. Cerebrovascular disease and renal insufficiency were rare, found in less than 3% of patients. The incidence of ischaemic heart disease, cerebrovascular disease and renal insufficiency was similar in COPD patients and non-COPD patients. The mean CAT score was 6.4 (SD: 5.7, range 0–32) and was higher in patients with COPD 6.8 (SD: 5.9) than in non-COPD patients 5.9 (SD: 5.5; p = 0.005). Surgical interventions comprised 434 (36%) right upper, 288 (24%) left upper, 210 (17%) left lower, 193 (16%) right lower, and 89 (7%) middle lobe lobectomies.

From the entire group of 1214 patients, 235 pulmonary and 51 cardiovascular complications were registered, which occurred in 216 (17.8%) patients. Grade 3a complications (surgical or endoscopic intervention not under general anaesthesia) occurred in 168 (13.8%), grade 3b complications (surgical or endoscopic intervention under general anaesthesia) in 4 (0.3%), grade 4a (life-threatening single organ dysfunction) in 23 (1.9%), grade 4b (life-threatening multi organ dysfunction) in 12 (1.0%), and grade 5 (the death of the patient) complications in 9 (0.7%) patients.

Table II. The distribution of patients in each class of the ThRCRI and the CAT

	Number of cases n (%)	Number of cases with pulmonary and cardiovascular complications n (%)
ThRCRI*		
0	972 (80)	164 (16.9)
1–1.5	224 (18.5)	50 (22.2)
2–2.5	5 (0.5)	0
>2.5	12 (1)	2 (16)
CAT		
<12	1010 (83)	162 (16.0)
≥12	204 (17)	54 (26.5)

* – ThRCRI included only three items, without pneumonectomy (score range 0–4.5).

Based on the analysis of the discrimination of CAT scores in relation to complications, patients were divided into two groups, CAT score <12 and ≥12. At this CAT bound, the variable was more precise in terms of assessing complications, compared to other tested thresholds, and at the same time included a fairly large number of patients with complications. The distribution of patients in classes of the ThRCRI and the CAT, and the number of cardiovascular and pulmonary complications in each class are shown in table II.

In the analysed group, the maximum value of the ThRCRI could be 4.5, not 5.5, because pneumonectomy was an exclusion criterion. 20% of patients had ThRCRI greater than zero, mainly due to comorbid ischaemic heart disease. The rate of pulmonary and cardiovascular complications increased in patients with a ThRCRI score ≥1, 21.5% *vs.* 16.9% (Chi^2 test; $p = 0.048$). The incidence of complications by CAT score in the whole group, in COPD and non-COPD patients, is shown in figure 1.

There were 204 (16.8% of the whole group) patients with a CAT score ≥12, and in these patients, complications occurred more often than in patients with a lower score (26.5% *vs*. 16.0%, Chi^2 test; $p < 0.001$). This difference was true both in COPD patients (30,9% *vs*. 21,9%, $p < 0.04$) and in non-COPD patients (19.7% *vs*. 10.1%, $p < 0.02$). In COPD patients, the rate of complications increased with the severity of airway limitation, 16%, 27% and 30% in patients with mild, moderate and severe airway obstruction respectively.

Conclusions

Thoracic surgery is considered high-risk surgery but remains the best therapeutic option for a cure in patients with resectable non-small cell lung cancer. Patients with lung cancer who are considered for radical surgery should be assessed to identify subjects at increased risk of perioperative complications. The initial step in the current algorithm of functional qualification focused on cardiovascular complications has limitations. The incidence of major cardiac complications is low – 3.3% in the series by Brunelli et al. [8], 4.1% in the series by Ferguson et al. [13] and in our group.

We found major pulmonary complications more than four times more common than cardiovascular complications, so the risk of this type of complication should be assessed from the beginning of the functional workup. Pulmonary function tests, which are the second step of the functional workup, allow for the calculation of predictive postoperative lung function, but they are not a good tool for health status assessment. Several studies have indicated that the relationship between lung function and health status scores is weak [14, 15]. We used the CAT, a simple instrument to assess the symptomatic impact on patients' health. The CAT was developed as an instrument to measure the health status of patients with COPD in an easy way [9]. The CAT covers all the important symptomatic areas of COPD and consists of only 8 items that provides a quantified measure of health status.

The item selection process followed a vigorous methodology and created a questionnaire with very good measurement properties. It requires only 2–3 minutes to complete and score, which enables rapid and reliable assessment of a patient's health status that can be readily incorporated into routine care [16, 17]. The CAT was extensively evaluated in COPD patients with varying severity of the disease across Europe [18]. In our opinion, symptoms assessed by CAT are not limited to COPD and many of them, e.g. breathlessness going up a hill/stairs, activity limitation at home, confidence in leaving home, sleep and energy levels, are common to lung and cardiovascular diseases. That was the reason we decided to use the CAT as a tool to assess the risk of pulmonary and cardiovascular complications in all patients qualified for lung resection. We found that patients with a CAT score ≥12 had more complications than patients with a lower CAT score and the higher incidence of complications was independent of the COPD diagnosis. The CAT identified the high-risk group at a very early stage of functional workup before PFT or exercise tests were performed. It is difficult to compare the results of our study with other series because we have found only one study aimed at verifying the usefulness of symptoms or quality of life-based scores, including the CAT, in predicting the risk of pulmonary postoperative complications in patients with early-stage COPD [19].

Our study is the first in which the CAT was used in a large group of patients qualified for thoracic surgery regardless of COPD diagnosis. It is worth mentioning that the analysis in the current study differs from those by Brunelli et al. [7] and Ferguson et al. [13]. The series by Brunelli and Ferguson included patients who underwent lung resection for benign and malignant diagnoses, and our study group included only patients with lung cancer undergoing a single lobectomy – the most common type of resection (89% of resection surgeries for lung cancer in our hospital). In this way, we got a large and homogeneous group of patients in terms of the extent of surgery, something we consider a strength of our study. Patients undergoing elective pneumonectomy were excluded from the analysis because we think these patients should undergo a separate functional workup, since such an extensive procedure is a very strong risk factor – independent of the accompanying diseases and the patient's state of health. In practice, in patients undergoing lobectomy, only ischaemic heart disease was a prevalent ThRCRI criterion, since renal insufficiency and cerebrovascular disease were rare, and found in less than 3% of patients. Moreover, our analysis embraced not only cardiovascular, but also pulmonary perioperative complications, which were much more common. In this context, the CAT, which turned out to be more effective, could replace the THRCRI in the pre-operative functional assessment algorithm.

In conclusion, pulmonary complications, occurring much more frequently than cardiovascular complications, should be included in the risk assessment scheme for lung resection. The CAT turned out to be an effective and easy to apply in practice instrument for initial risk assessment in patients with lung cancer qualified for lobectomy. Patients with a CAT score ≥12 had a higher rate of pulmonary and cardiovascular complications as compared to those with a lower score. The CAT has enabled simple early identification of patients in the high-risk group who require the most thorough further functional assessment.

Conflict of interest: none declared

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A review of methods of intraoperative margin assessment in breast conserving surgery

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Breast conserving therapy is the primary treatment modality in early-stage breast cancer patients. Despite the development of methods for the intraoperative assessment of tumor margins, 20–30% of patients still require re-resection due to postoperative tumor infiltration at the surgery margins. In recent years, many methods have been developed to reduce the number of re-resections due to margin infiltration. Here we review the current methods together with several more techniques under investigation.

Key words: breast conserving surgery, surgical margin, re-resection

Introduction

Breast conserving surgery (BCS) is the standard of care in patients with early-stage breast cancer (BC) [1]. In stage I and II, BCS is at least as effective as a mastectomy [2]. It includes resection of the primary breast tumor as well as diagnostic and therapeutic axillary procedures. Then the remaining mammary gland is irradiated. Most patients receive additional systemic (adjuvant) therapies depending on the pathological stage of the cancer and the biological subtype. One of the conditions for effective breast conserving therapy is obtaining clean margins, e.g. a site free of cancer cells, after surgical tumor resection [3]. The current definition of free surgical margins for invasive cancer is the absence of tumor cells in the surgical incision line (no ink on tumor) [4, 5]. In ductal carcinoma *in situ* (DCIS), it is recommended to maintain a margin of not less than 2 mm from the surgical incision line [5].

Due to increasingly common screening tests and progress in imaging diagnostics, more and more breast cancers are detected during the preclinical phase. The early stage at diagnosis enables the widespread use of breast conserving therapy. Progress in adjuvant treatment – both systemic and radiotherapy – has significantly reduced the risk of local recurrence after BCS. Currently, the ten-year recurrence risk ranges between 4 and 7% [6]. In patients without tumor-free margins, the local recurrence risk increases two- to three-fold; therefore radical breast tumor resection is the main goal of conserving therapy [4, 7].

The intraoperative assessment of surgical margins remains a challenge for conserving therapy. Despite significant progress in this area, in 20–30% of cases the final histopathological examination still indicates the presence of cancer cells in the surgical incision line [3, 7]. This results in reoperation – a local scar excision or mastectomy, which in turn extends the treatment duration, adversely affect the aesthetic effect, increasing the patient's stress and anxiety levels, and exacerbating the total treatment costs. Reoperation rates are higher for DCIS and breast invasive ductal carcinoma coexisting with ductal carcinoma *in situ* (IDC-DCIS), accounting for 46% and 45%, respectively [8, 9]. Therefore, the use of sufficiently sensitive and specific methods of intraoperative assessment of resection margins is very important. None of the methods currently used

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are ideal, and research is ongoing to evaluate the different approaches. In the following sections we will present the available methods that increase the effectiveness of conserving therapy by reducing the rate of microscopic irradicality resulting in the need for reoperation.

Surgical methods

Intraoperative gross clinical evaluation of the lumpectomy specimen

This technique consists of an intraoperative clinical evaluation of the removed specimen and the resection bed to establish possible indications for extended resection. During the operation, the surgeon palpates the resected part of the breast and assesses the margins macroscopically. The surgeon assesses the tissue of the tumor bed and feels around for any suspicious lumps. The advantages of this procedure include its simplicity and relatively short duration; however, the sensitivity and specificity is low (<70%), which significantly limits its usefulness in reducing the need for reoperation [3, 10].

Routine resection of cavity shave margins (CSM)

During the operation, the surgeon, after tumor resection, collects four, and if the preparation does not reach the skin and pectoral fascia, even six additional samples corresponding to the upper, lateral, medial and lower margins, and possibly the anterior (on the skin side) and the posterior (on the pectoral fascia side) [11]. Each of these tissue samples should be about 1 cm thick. Two meta-analyzes, comparing wide excision alone versus tumor excision with CSM, showed that routine use of the CSM significantly reduced the reoperation rate for margins infiltrations from 32% to 16% and from 31% to 12%, respectively [12, 13]. The size of the total part of breast removed in the CSM group is greater than in the group without CSM; however, according to the cited meta-analyzes, this does not affect the postoperative aesthetic effect [12, 13]. On the contrary, there are single analyzes available that negate the beneficial effect of routinely used CSM in reducing reoperation rates [14].

Microscopic method

Frozen section analysis (FSA)

After processing, freezing and staining, the removed specimen is subjected to an intraoperative histopathological evaluation. This method requires transport of preparation to the histopathological laboratory and its preparation while the patient remains under anesthesia. This increases surgery duration by an average of 15–30 minutes [15, 16]. *Ad hoc* margin assessment does not completely eliminate the reoperations due to non-clean margins, although it can significantly reduce their rates even from 35% to 10% [15–17]. The sensitivity of this method ranges from 65% to 83% and the specificity exceeds 90% [15, 16]. Sensitivity decreases in DCIS, as well as when surgery is preceded by systemic treatment [17]. In some cases, tissue freezing may cause its damage and artifacts that hinder or prevent post-operative histopathological margin assessment.

Ad hoc *macroscopic margin assessment (MMA)*

In this method, the margin of the specimen removed is assessed macroscopically and intraoperatively by a pathologist, after marking the edges with ink. If any of the margins is smaller than 10 mm, then it is simultaneously excised as an additional, extended margin. This procedure allows a reduction in the re-excision rate compared to surgery alone, from 34% to 26% [7].

Touch imprint cytology/preparation

This can be an alternative to the intraoperative margin assessment using FSA. This method is based on the increased ability of cancer cells to adhere to glass surfaces as opposed to fat cells [15]. During surgery, each margin of the removed specimen is pressed against a glass plate. The obtained cytological preparations are assessed by a pathologist. The advantage of this method compared to FSA is no consumption of tissue material and shorter evaluation time [15]. Additionally, the assessed impression captures the entire surface of the specimen (the entire margin), and not only selected areas [15, 18]. The sensitivity and specificity of this method is comparable to FSA and account for up to 72% and 97%, respectively [15]. However, cauterization (thermal damage) or drying of the margins can lead to false results in the cytological evaluation. For this reason, it is necessary to cooperate with a pathologist who has extensive experience in cytological assessment. It is worth noting that there are attempts to automate this assessment method [18].

Radiological methods

Two-dimensional 2D mammography specimen

After resection of part of the breast, an X-ray of the removed preparation is made. It allows to determine whether the target lesion has been removed and to assess the width of the radiological resection margins. Two images should be taken in perpendicular planes. This procedure is considered the gold standard in most cancer centers, and is also in line with the Polish Society of Oncological Surgery recommendations [19].

The advantages of this method include the relatively low complexity, and the availability and existing experience of radiologists. Thanks to standard mammography performed as part of preoperative diagnosis, it is possible to compare the images of the removed preparation with the preoperative ones. Thanks to the appropriate mammographic chambers, the intraoperative mammographic evaluation of removed tissue can also be performed directly in the operating room. This not only significantly reduces the rate of reoperations due to infiltrated margins, but also shortens the total procedure duration [20]. There is some criticism of specimen mammography

usefulness as an ineffective method of margins assessment, while emphasizing its high value in confirming the removal of the target lesion [21, 22]. The method allows for a reduction in the volume of the resected breast in the case of palpable lesions, which results in a better aesthetic effect [20]. It should be added that the accuracy of the mammographic margin assessment is significantly lower in the case of pre-invasive and lobular carcinomas [23].

Digital breast tomosynthesis (DBT)

DBT consists of taking a series of digital X-ray images of the preparation at different angles; from these photos a three-dimensional (3D) image is reconstructed (synthesized). Tomosynthesis improves assessment sensitivity by about 8% compared to conventional 2D imaging [24]. Assessment with this method is quick and requires little contribution of the support staff. The images obtained can be assessed in the operating room by the operating surgeon or sent for radiological evaluation. Using this imaging method, it is possible to verify the positive resection margins with a sensitivity of 77% and a specificity of 98% [25]. In traditional mammography, the spatial image of the removed specimen is compressed into one flat image, which can result in a misassessment of the margins. Tomosynthesis enables evaluation of the entire resected specimen in 1 mm slices, which significantly reduces the risk of error [24, 26].

Ultrasound of the removed part of breast

An intraoperative ultrasound examination enables the localization and precise resection of palpable and nonpalpable breast masses. In the case of palpable lesions, an ultrasound allows better margin control compared to removal only under palpation, reducing the re-resection rate from 17% to 6% [27]. The volume of the removed preparation is also smaller, which may translate into better aesthetic effects [28]. In the case of nonpalpable lesions, the use of an intraoperative ultrasound with a high-frequency linear probe in combination with gross clinical evaluation in 223 patients allowed to obtain a precise lesion visualization in 99.6% of cases and to reduce the need for reoperation due to infiltrated margins to levels as low as 4% [28].

The challenges in using this method include invisible or poorly visible lesions on the ultrasonography (microcalcifications, small lesions in adipose tissue), as well as difficulties in visualizing pre-invasive cancer, or pre-invasive components around invasive cancer. In contrast, the assessment of lesions in breast glandular tissue may be better than using X-ray methods [29]. However, this requires the surgeon to be skilled in using ultrasound and the availability of high-class ultrasound machines in the operating theater.

Micro CT

The principle of operation is the same as in the case of conventional computed tomography, however, higher resolution is necessary. CT enables a spatial analysis of the removed specimen to be performed in order to assess resection margins, which eliminates the limitations of conventional 2D mammography. The studies conducted so far in a small group of patients show the possibility of reducing the need for reoperation from 31% to 14%, however, they do not allow for an unequivocal assessment of the usefulness of this method in reducing the positive margins after conserving surgeries [30]. Furthermore, despite the higher resolution and high contrast between soft tissues, it is still difficult to distinguish between fibroglandular breast tissue and a tumor, which results in a low sensitivity of 56–60% [30, 31].

Magnetic resonance imaging (MRI)

The advantage of MRI in the intraoperative assessment of a resected breast is the high possibility of differentiating soft tissues on the obtained images. The sensitivity of the cancer extent assessment in the resected specimen may reach up to 93% [32]. Due to the high spatial resolution, attempts are made to assess the lesions by a pathologist based on magnetic resonance images, which would eliminate the need to process and fix histopathological preparations. So far, the accuracy of this assessment is unsatisfactory (distinguishing a malignant from a benign lesion in 57% of cases) [33]. Until recently, the time needed to obtain images, the need for pre-operative contrast administration and the size of the entire system were a serious limitation in the intraoperative use of this method. Lately, mobile MRI scanners have become available that do not require additional covers and enable developing satisfactory images without enhancing contrast. In a study involving 22 patients, a sensitivity of 91% and a specificity of 93% were achieved in distinguishing malignant from healthy tissues in the resected breast [32].

Electromagnetic methods

Radiofrequency spectroscopy

Radio waves emitted by the probe are absorbed, scattered and reflected differently by healthy and cancerous tissues. This is due to the lower electric potential of the tumor cell membrane compared to a normal cell, less mutual adhesion of tumor cells, greater vascularization of tumor tissues and the different morphology of the tumor cell nucleus. Due to these phenomena, the device emitting radiofrequency waves can distinguish between neoplastic and normal tissues. The transducer should be placed on the surface of the removed specimen. A positive reading indicates the presence of cancer cells to a depth of 1 mm from the edge of the specimen and obliges the surgeon to extent resection margin [34]. It is recommended to use the device in conjunction with standard techniques for imaging the removed tissue (mammography). Device sensitivity in the studies was estimated at 75–76% with a specificity of 46%. The researchers emphasize that the device is not an ideal solution

to the margins issue in BSC, but it is a considerable help, significantly reducing reoperation rates [35].

Bioimpedance spectroscopy

In a clinical setting, mobile, handheld devices are used; their principle of operation in margin assessment is based on the spectroscopic analysis of tissue impedance (the phenomenon of different dielectric properties of normal and neoplastic tissues is used). Due to different cell morphology, increased vascularization and mutual adherence of cells, neoplastic tissue has a lower impedance as well as higher conductivity and electrical permeability compared to healthy tissues. The technique is fast (the turnaround time is about 5 minutes) and does not require tissue damage (e.g. cutting and fixing). Limitations include the possibility of false results in inflammatory tissues, which bioimpedance may be similar to neoplastic tissues. In the analysis performed by Dixon et al., the need for reoperation due to infiltrated margins was reduced from 37% to 17%, and after gaining more experience in using the device, even up to 9% of patients undergoing surgery compared to intraoperative margin assessment using a 2D radiograph [36]. One of the advantages of this device is its usefulness in assessing resection margins for both invasive and DCIS cancer and other atypical proliferative lesions [36].

It should be mentioned that a device operating on a similar principle was developed in 2017 in Wroclaw by M. Rząca et al. and is currently under study [37].

Optical methods

Optical coherence tomography (OCT)

This method uses infrared radiation and the phenomenon that cancer cells scatter waves differently. Cancer cells, due to the larger nucleus, higher cytosol density, and lower nuclear to cytoplasmic ratio, have greater capacity to scatter and reflect of electromagnetic waves compared to normal cells. The emitted and reflected radiation is captured by the detector and based on this the image is formed [38]. Since infrared permeability into the tissues reaches about 2 mm, this method is very promising in the margin assessment of the resected breast. In the first studies comparing this method with postoperative histopathological assessment, the sensitivity and specificity of optical tomography was 91.7% and 92.1%, respectively [39]. However, in subsequent clinical trials, much lower sensitivity and specificity was obtained, e.g. 55–65% and 68–70%, respectively [40].

Photoacoustic tomography

The method, currently being evaluated in preclinical studies, consists of treating the examined tissue with laser pulses. The laser energy is partially reflected and radiated in the form of ultrasound waves detected by a suitable detector. The laser pulses penetrate into the tissue up to 3 mm deep. The difference in ultrasound wave frequency depends on the hemoglobin level and fat content in the tissues. So far, attempts to use this method concern only very small tissue surfaces and it performs well in fatty fragments, and much worse in glandular tissue [41].

Fluorescence imaging

There have been some attempts to use fluorescence for imaging and assessment of resection margins. These methods require dye administration (e.g., methylene blue or indocyanine green) prior to surgery. Thanks to the faster "washing out" of the dye from healthy cells and its longer retention in cancer cells, it is possible to assess (in infrared) whether there is dye accumulation in the resection margin [42]. Attempts are also being made to combine a dye (fluorophore) with a targeted antibody, such as an antibody binding to a vascular endothelial growth factor (VEGF), to increase the dye concentration in the tumor [43]. The limitation of this method, which is still under investigation, is the need to administer the substance before surgery and the fact that the currently used fluorophores are not selectively retained in breast tissues.

Microscopy with ultraviolet surface excitation (MUSE)

This method, currently being evaluated in preclinical studies, is based on stimulation of fluorophores by ultraviolet radiation falling on the surface. Ultraviolet radiation does not penetrate deeply and therefore has limited utility for assessing deeper layers of tissues. Assessing resection margins in DCIS can be problematic, but in the case of margins in invasive cancer, it is sufficient, according to the accepted consensus no ink on the tumor. MUSE seems to be a promising technique. An additional advantage of this method is that it does not damage tissues [44].

Hybrid methods

The combination of different methods of assessing the resected breast would make it possible to use the advantages of each of them, while partially compensating for their disadvantages. For example, radiological methods are very accurate when it comes to confirming complete resection, while spectroscopic or optical methods assess the surface of the resected breast with high accuracy, i.e. an infiltration-free resection margin. An example of such a hybrid system is mammography of a resected breast combined with a spectroscopy using electromagnetic waves. Mammography confirms the removal of a neoplastic lesion with high accuracy, while a spectroscopy assesses whether the margins of a resected specimen are free of cancer cells. The combination of these two assessments reduces the need for reoperation by up to 50% [45, 46]. Another hybrid approach is a device combining photoacoustic tomography with ultrasonography. The study on a small group of patients showed very high (100%) sensitivity and high specificity in margin assessment [45].

Other methods

Intelligent knife

This technique analyzes the smoke produced by the electrocoagulation used to resect the specimen. Cell damage during the use of surgical diathermy results in the evaporation of their contents and transformation into an aerosol state. Using smoke spectrometric analysis and having established smoke models when cutting normal tissue and neoplastic tissue, it is possible to assess whether the cut is performed within normal or neoplastic tissues. Preliminary studies show a sensitivity of 77% with a very low number of false positive results [46, 47].

Nuclear medicine

The use of positron emission tomography (PET) to assess the margins of a resected breast in clinical practice is currently not possible, taking into account the availability and complexity of the apparatus. However, there have been attempts involving preoperative administration of 18-fluorodeoxyglucose for the intraoperative evaluation of sentinel node and the margins of the resected breast. The unique evaluation which was carried out in two patients showed the high sensitivity and specificity of this method, however, the small number of patients makes it impossible to draw definitive conclusions regarding the effectiveness in resection margin assessment [48].

Conclusions

Numerous techniques have been developed for the intraoperative assessment of resection margins, which can significantly reduce reoperation rates. Some of these methods, however, are time and labor-intensive as well as expensive and with difficult access, which prevents their use in daily clinical practice in most centers. At the same time, intraoperative margin assessment according to the standard of care is necessary in every center specializing in the management of BC patients. The procedure still in force in Poland is the intraoperative mammographic evaluation of the resected part of the breast. Intraoperative ultrasound, tomosynthesis and microtomography are increasingly used. Some centers use *ad hoc* histopathological margin assessment, although this is associated with a significant extension of the total procedure duration. Spectroscopic techniques are noteworthy due to their short evaluation time and simple operation. In combination with standard imaging techniques – mammography, ultrasound – they can be a significant help in margin assessment in the future. Other methods, as promising as they are, are not yet developed enough to be used as a standard of care.

However, it is important that each breast cancer center monitors the rate of re-resections due to margin infiltration, ensuring every effort is made to reduce it. A standard of care in the intraoperative evaluation of the preparation should be developed based on the Polish Society of Oncological Surgery recommendations and, depending on the availability of additional methods, should be systematically improved. The key to success is an accurate preoperative diagnosis, precise marking of malignant lesion and a refined method of intraoperative margin assessment [49].

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Sexual well being of breast cancer patients

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Introduction. Breast cancer is the most common cancer in women – both in Poland and around the world. In terms of the mortality rate, it subsides brest cancer with lung cancer. In 2018, almost 2 million new cases were reported worldwide, and almost 44 million women have been diagnosed with breast cancer in the last 5 years.
Material. The aim of this paper is to present ways to improve the sexual well being of breast cancer patients.
Methods. Analysis of the literature by oncologists, gynecologists, and psychologists was used for theoretical discussion.
Results. Sexuality is an extremely important part of every woman's life, including those suffering from breast cancer. Surgery of the breast, a symbol of a woman's sexuality, and the negative effects of cancer therapy can alter a woman's perception of her own body and lower her libido. Sexual therapy which should be based on multi-faceted activities, is an extremely important part of breast cancer treatment.
Conclusions. Therapeutic possibilities may be based on psychological and sexual therapies as well as pharmacological support (moisturizers, silicone lubricants, tampons inserted for several minutes with 4% vaginal lidocaine before intercourse, topical gels with estrogens, ospemifen, DHEA, testosterone).

Key words: sexuality well being, breast cancer, sexual satisfaction, sexual therapy, treatment, surgery

Introduction

Breast cancer is the most common cancer in women in Poland and around the world. In terms of the mortality rate, it subsides breast cancer with lung cancer. In 2018, almost 2 million new cases were reported worldwide, and almost 44 million women have been diagnosed with breast cancer in the last 5 years [1].

Early and modern diagnostics as well as effective treatments have improved the prognosis of women with breast cancer, i.e. increasing the time of total survival and improving the overall quality of life. The majority (about 70–80%) of breast cancers show expression of hormonal (estrogen and/or progesterone) receptors, about 15–20% are cancers showing an overexpression of the HER2 receptor or amplification of its gene, about 15% are the worst case prognoses – the so-called triple negative (without expression of hormonal receptors and an overexpression of the HER2 receptor). The expression of hormonal receptors has a predictive meaning, conditioning treatment that inhibits or significantly reduces the level of sexual hormones. The treatment is usually applied by patients for 5–10 years.

Chemotherapy is used in most patients with triple negative and HER2-positive breast cancer, also occasionally in

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patients with hormone dependent breast cancer. Side effects of chemotherapy appear early in the course of treatment, such as nausea, vomiting, diarrhea, alopecia; some, after weeks, months or years of therapy – cardiomyopathy, myelodysplastic syndrome, or secondary malignancies.

Sexuality is an extremely important part of every woman's life, including those suffering from breast cancer. Surgery of the breast, a symbol of a woman's sexuality, and the negative effects of cancer treatment alter a woman's perception of her own body and lower her libido. The aim of this paper is to present ways to improve the sexual well being of breast cancer patients.

Influence of systemic treatment on premature cessation of ovarian function

Up to ⅓ of women with recently diagnosed breast cancer, menstruate when the cancer is diagnosed. Chemotherapy causes premature cessation of ovarian function in about 30–40% of women under 40 years of age, and even in 90% of women over 40 years of age. In 90% of women under 35 years of age, menstruation only returns up to 2 years after the end of chemotherapy [2].

Approximately 64% of premenopausal women complain of hot flashes or night sweats during or after treatment, 42% of them have vaginal atrophy, 29% of them have osteoporosis, 28% even think about discontinuing breast cancer hormonal treatment because of the accompanying symptoms. Studies show that almost ⅓ of these women have never been asked by their physician about the possible presence of vasomotor symptoms (hot flashes, sweats, increased blood pressure) [3].

The symptoms caused by menopause induced by cancer treatment are usually exacerbated. Physiological menopause is a long-term process, which is slow for many months, while menopause induced by cancer therapy often affects young patients experiencing a decrease in sexual hormone levels within a short time, even overnight. The changes in the body can be rapid and the symptoms rather troublesome.

Influence of systemic treatment on fertility

Extra attention is also being paid to reproductive issues. Women want to be mothers and enjoy motherhood, despite their cancer. Current anticancer treatments have a significant impact on a woman's reproductive abilities.

Over the years, women have been deciding to have offspring later. Now the average age of a European woman at the birth of her first child is 39 years. Subsequently, a breast cancer diagnosis can appear before or during a woman's procreation plans. Systemic treatment can not precipitate the cessation of ovarian function, but also postpone the moment when it is possible and safe to become pregnant. Pregnancy after breast cancer treatment is possible and safe.

Every woman of childbearing age should be informed about the side effects of treatment as well as the possibility of using fertility preservation techniques; they can also be referred to a reproductive medicine specialist before starting cancer treatment. The most commonly used techniques with proven effectiveness include: the collection and freezing of oocytes or embryos. The choice of an appropriate method depends on age, a woman's ovarian reserve, and the planned oncological treatment.

It is worth taking care to maintain fertility before cancer treatment, which will make a woman's life more comfortable. Sex need not only be a way to get pregnant, but can also be a source of pleasure.

Reproduction after breast cancer

Indeed, for many young women, the possibility of having children after completing cancer treatment is significant. Of course, a decision about pregnancy may be challenging and problematic due to prevailing myths and distortions regarding the safety of the future mother's pregnancy, the impact of chemotherapy on the fetus and the child, and breastfeeding issues.

A breast cancer diagnosis is usually accompanied by shock, fear, disbelief, anxiety, and high-stress levels. Hence, patients accumulate all their thoughts around treatment, rejecting decisions related to functioning, fertility, and motherhood after treatment. After undergoing anticancer treatment, the possibility of becoming pregnant may be significantly limited or completely unavailable. This is caused by the toxic effects of drugs on the gonads [4–6].

Young female patients, premenopausal, who became sterile due to anticancer treatment, may experience many psychological difficulties, including depression. In addition, some patients may experience intense fear and the fear of a recurrence of the disease and related problems or e.g. the inability to raise a child. This fear can be so overwhelming that some women stop trying to get pregnant. Therefore, it is worth emphasizing the role of psychological counseling therapy, and the benefit of support from a psycho-oncologist or sexologist who can help women and their partners make the right decisions, and choose the best solutions during diagnosis and post-treatment [7–9].

Unfortunately, it still happens all too often that physicians do not sufficiently and adequately inform patients at the time of diagnosis about the possibility of preserving fertility. Such inconsistent and hard communication with the patient causes frustration and anger and is associated with increased stress. Therefore, it should be remembered how vital motherhood is, for it can be a significant element in aiding women's psychological rehabilitation after breast cancer treatment.

The influence of surgical treatment on the perception of one's body

Breast cancer and the methods involved in its treatment have a very important impact, not only on somatic health or the patients' quality of life, but above all on the extremely im-

portant psychological and sexual sphere, as well as on the attitude to one's body. This is particularly evident in the case of a one-sided or two-sided mastectomy, which changes the way patients perceive, feel, and experience emotional, social, and family life. Surgical treatment of cancer causes a woman to start perceiving their body differently. In addition, the sense of aesthetics deteriorates and there is increased restraint of women body, which undoubtedly has a significant impact on one's awareness of beauty and self-esteem, causing a disparity between the idealized, sexually attractive image of a woman ubiquitous in popular media, and the body of a cancer patient after treatment [10–12].

The process of cancer treatment has a significant impact on the patient's quality of life, as well as on the satisfaction level of sexual well being. Unfortunately, the sexual aspect is still often neglected, without due diligence. Sexuality is one of the important components of general health and quality of life.

The Declaration of Human Sexual Rights established by the World Sexual Health Organization (2014) [13] assumes that: "Sexuality is a key aspect of a person's life throughout its entire duration and includes gender, roles and sexual identities (socio-cultural gender-related), sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in the form of thoughts, fantasies, desires, beliefs, attitudes, values, behaviors, practices, roles and relationships. Sexuality can include all of the above, but not all of its dimensions must be experienced or expressed. Human sexuality is influenced by complex biological, psychological, social, economic, political, cultural, legal, historical, religious and spiritual factors".

Of course, the psychological aspect, emotional sphere, or sense of attraction for the patient's partner should not be omitted here; this undoubtedly affects the quality of one's sexual life, as it is associated with self-esteem, a sense of self-respect, and an acceptance of the body that was changed by the cancer. According to Zdończyk S.A. [14], women after cancer surgery show a worryingly low self-esteem as sexual partners. Therefore, it seems appropriate to rationally approach this type of disorder.

The psychophysical condition and psychological well-being of a breast cancer patient are often very unsatisfactory. Their reduced level of self-esteem and the presence of the disease are often the main factors that cause sexual disorders. The patient's approach to their own body, sexuality, well-being, sense of attraction, and relationship with their partner are all extremely important. If before surgery, the patient had a low opinion of their attractiveness, and exhibited low self-esteem, these feelings will be all the more exacerbated after treatment. Many women struggle with the so-called half-woman complex – the loss of one breast, the resulting asymmetry of the body, scarring; these are all reasons for a serious reduction in the level of one's visual self confidence regarding appearance [15].

In addition to the patient's lack of self confidence, their mood or depression, which may develop during the cancer and cancer treatment process, is also worth noting. In such a case, the therapy to combat depression should be undertaken with the appropriate diagnosis. The socio-cultural standards of beauty, ubiquitous sexuality, and the perfect ideal of woman's body present in the mass media are also important factors that may speed up the development of these disorders.

Patients often feel that sex is unnatural, forced, and often involves internal compulsion. The woman feels guilty of her indisposition, her attitude begins to become more restrictive, until she finally gives up on sexual activity completely.

Sexual satisfaction

It is safe to say that sexual satisfaction is largely related to the quality of relationship in which the woman realizes herself sexually. Furthermore, the satisfaction that results from sexual intercourse should be considered a vital element of any successful original meaning [16]. There is no doubt that sexual satisfaction is a very important element of sexual activity. It is recognized as an important indicator of health in the sexual sphere, as well as an exponent of well being and quality of life; a satisfying sex life determines both the quality and endurance of a partnership [17, 18].

The frequency of initiated behaviors and sexual activities is associated with sexual satisfaction and, consequently, the satisfaction of a partnership or marriage [19, 20]. The forms of breast cancer treatment, and the methods used are often very aggressive, subsequently causing a number of inconveniences and side effects. These include, among others, sexual disorders, which significantly reduce the state of one's sexual health. The patient feels a recurring problem of a sexual nature, and discomfort and dissatisfaction with sexual activity [21]. There are four basic categories of sexual disorders in women:

- reduced desire – a reduction or loss of interest in sexual issues, images related to sexual activity, a reduction of feelings of desire and thoughts regarding sex-related matters,
- sexual arousal disorders – the genital response is insufficient in terms of lack of vaginal lubrication and inadequate swelling of the lips of the vulva,
- orgasm disorders – associated with an orgasm dysfunction, its delay or complete absence,
- dyspareunia – permanent or recurring pain of the genitals occurring during the course of penis penetration into the vagina throughout intercourse (including during a gynecological examination).

Sexual dysfunctions resulting from cancer treatment may have serious consequences and significantly affect the patient's quality of life, their relationship with a partner, psychological difficulties. They may cause the patient to avoid sexual intercourse, in addition, there may be unpleasant associations with sexual activity, or shifting the blame to the partner, which,

in turn may lead to a complete breakdown of their intimate relationship.

It should be clearly emphasized that patients treated for breast cancer experience a decrease in physical activity and satisfaction with their sexual life. In addition, desire disorders, orgasm problems, breast sensation disorders, vulvovaginal atrophy, menopausal symptoms appear (hot flashes, sweating, fatigue, joint and muscle pains, irregular menstruation, irritability, intimate infections, weight loss), or lubrication disorders [13, 22].

Pain associated with sexual activity results in a negative attitude towards sexuality, and thus increases the impairment of sexual function. Patients with dyspareunia are accompanied by reduced frequency of sexual intercourse and are less enthusiastic about initiating this type of behavior. They also have a reduced desire level, excitement is diminished, with less intense feelings of orgasm during intercourse [23].

Sexual therapy

The issue of women's sexuality after breast cancer treatment still seems taboo. It is possible to observe an increased number of publications devoted to this subject, but this is still insufficient. Patients, their families, and even medical staff often feel too much embarrassment and shame to report problems, with regards to the prospect of discussing the diagnosis and analyzing the sexual concerns that arise. There is still an inner conviction that compared to the grave severity of cancer, which is a real threat to life, the subject of possible sexual dysfunction is trivialized.

Sexual therapy, which should be based on multi-faceted activities, is an extremely important process that has a key role:

- first stage – conversation with the patient about the problem in the sexual sphere related to the disease or its treatment,
- second stage – gathering as much knowledge as possible about the problem, its origin, details and aspects of the patient's sexual life by the physician,
- third stage – detailed suggestions, i.e. conversation/consultation with specialists in the field of sexology, psychology or oncology based on an individual approach to the problem,
- fourth stage – intensive care for patients who require it or who have been recommended, which may include psychotherapy, pharmacological therapy or surgery [24].

Pharmacological treatment

Problems during intercourse can be permanent or recurring. They may appear during penetration or intercourse. They may even arise earlier as a fear of penetration or intercourse, and the associated tension and tightening of the pelvic floor muscles.

Treatment must first start with awareness and discussion of the problem. If there is openness in the relationship, the partner should also be involved in the treatment. The patient should be listened to but also be aware that the range of standards and expectations of sexuality are very different, not only between people, but even during the individual process of puberty, maturity, and aging. The disease, and especially the treatment of the disease, will have a significant impact on the leap in sexual stimulation and excitement curve that is appropriate for the patient. Expectations about the necessity of intercourse may also be relative. However, if penetration is expected, additional measures to increase comfort and facilitate sexual activity are desirable. The definition of expected sexual satisfaction is a reference point for proposing further treatment. Based on the diagnosed problems and expectations, individualized treatment should be chosen.

Therapeutic possibilities may be based on psychological and sexual therapies as well as pharmacological support. Treatment of physical problems during intercourse can be based on an algorithm of gradually increasing the invasiveness of treatment, depending on the difficulty of obtaining the expected effect [25]. In the first stage, moisturizers are proposed, while opinions about lubricants are more ambiguous. Using the former in doses larger than standard, achieves good vaginal lubrication and a transient positive effect during intercourse [26]. If a positive effect is obtained, its stability should be verified and the treatment in case of its loss should be modified. In case of further problems with the use of maximum amounts of silicone lubricants, it is proposed to use tampons for several minutes before intercourse with 4% vaginal lidocaine.

In the next stage, the use of topical gels with estrogens in minimal doses may be considered. As both opinions and published data on the potential risk of steroid use in patients treated for breast cancer are divided [27], a decision on hormone treatment should be made together with the patient. Approximately 30–50% of women opt for estrogen treatment under medical supervision [28]. Some of them would also accept an increase of ⅓ of the risk of relapse, if the treatment resulted in cessation of symptoms [29]. It is assumed that doubling the level of estradiol in the blood increases the risk of relapse by about ⅓ [30]. Therefore, estradiol levels should oscillate within this range.

There is no direct correlation between serum estrogen levels and the resolution of symptoms associated with vaginal atrophy, thus the dose should be adjusted to the quality of vaginal mucosa and function required. The period of epithelial regeneration under the influence of hormones takes about 4 weeks. During this period, estrogens more easily penetrate the atrophic vaginal mucosa into the bloodstream. Therefore, minimum doses should be used to rebuild the vaginal epithelium at the expense of prolonging its regeneration time.

It is also worth noting that most breast cancer patients with hormone receptor expressions use tamoxifen or aromatase inhibitor based therapy for 5–10 years. Tamoxifen is an estrogen receptor modulator (selective estrogen receptor modulator – SERD), it stimulates or blocks its activity, depen-

ding on its location in the body. Aromatase inhibitors inhibit the aromatization of androgens to estrogen primarily in the fat tissue, inhibiting their production, but without affecting the effects of estrogen on the receptor. Due to their mechanism of action (aromatase inhibitors), it seems that for those patients who use tamoxifen, the vaginal estrogen effect will be mainly limited to topical effects.

Among the possible estrogens to use, the selective estrogen receptor modulator ospemifen should be mentioned. It is recommended in post-menopausal women with severe symptoms: dryness and vaginal atrophy. Due to its beneficial effect profile, it is not contraindicated in women with breast cancer after the completion of adjuvant therapy [31].

The use of DHEA is also considered both orally and vaginally. In both cases, this treatment seems to reduce the symptoms of vaginal atrophy and improve sexual function without increasing estrogen levels above the expected levels [32]. The use of testosterone is more controversial. It improves satisfaction from intercourse, increases libido, improves mood and general well-being, but there are no clear data on the safety of its use in women who are being treated for breast cancer [33].

It is extremely important to educate patients to be open to conversations related to sexuality in order for them to enjoy life to the fullest, despite the disease, and to feel satisfaction and contentment. It is worthwhile informing patients about available methods and strategies for dealing with sexual dysfunction. Providing basic knowledge on how to properly lubricate vaginal walls before sexual intercourse with the use of water or silicone based lubricants, as well as the systematic use of vaginal globules or gel applications with hyaluronic acid can significantly contribute to improving the sex life of women.

It is also worth referring the patient to a urogynelogical physiotherapist, in order to stimulate the blood supply to the genitals through the use of appropriate relaxation exercises for vaginal muscles.

Conclusions

Sexual activity and performance are extremely important in human life. Treatment of breast cancer certainly has a negative impact on a patient's emotional state, their mental state, but also on the sexual satisfaction and intimate relations with a partner [34]. Patients treated with breast-conserving therapy are still relatively few in Poland [35]. Proper breast oncology surveillance during pregnancy, using safe and inexpensive methods including ultrasonography and biopsy of suspicious masses, can ensure the prevention of cancer development and progression [36]. The stage of the disease at diagnosis is also a major prognostic factor in pregnancy-related cervical cancer [37].

Sexual dysfunctions may also occur after treatment is completed, which is undoubtedly associated with a decrease in satisfaction and contentment resulting from a decrease in the quality of intimate relationships. Unfortunately, in most cases, women are not informed about the possibilities of dealing with this problem. The diagnosis and consequences of treatment affect intimate relationships [38]. Relationship with one's partner is a very important factor that determines the psychosocial health of patients.

Unfortunately, women's knowledge of changes in their body during the disease and their knowledge of solutions to sexual disorders is still inadequate. Patients are ashamed to talk to an oncologist about sexuality or dysfunctions that have arisen as a result of oncological treatment. Zdończyk (2015) points out that there is still a big taboo evident; a barrier is created by shame, lack of trust from the patient, ignorance of proper terminology, and a basic lack of openness or empathy from the physician. All this is further exacerbated by the lack of sufficient time and knowledge of physicians or other health care representatives.

It is worth noting that the subject of sexuality of patients treated for breast cancer is becoming more discussed. This paper does not exhaust the entire subject, and the area of issues could be more detailed with regard to the psychophysical difficulties associated with the disease, as well as the various approaches to the subject of the disease and the disorders resulting from it, along with the communication problems between the patient and the health service.

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Lung volume irradiation procedures in patients with pneumonia during COVID-19 infection – physical aspects of treatment planning and dosimetry

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Introduction. The paper presents an original, used in our Institute, method of lung volume irradiation in patients with pneumonia during COVID-19 infection.

Material and methods. Procedures such as the simulation of treatment and radiotherapy are performed in a treatment room. Real time radiation treatment planning is realized as 2D planning (Irreg Planning VMS) in a separate room, and the 3D (eclipse VMS) dose distribution is calculated after the treatment. During radiation exposure, a fluence map is measured.

Results. A method of irradiating the lungs of patients with COVID-19 was developed, which allows to shorten the time the patient is on the treatment table and minimize contacts between the patient and staff.

Conclusions. The presented procedure made it possible to minimize the time of patient's stay in the radiotherapy department and at the same time, it retains all the required quality assurance procedures in radiotherapy treatment.

Key words: COVID-19, cone beam computed tomography, 2D and 3D treatment planning, a fluence map

Introduction

The use of ionizing radiation in the treatment of pneumonia and other inflammatory conditions has a long tradition [1–3]. In contemporary literature [4–7], information can be found on the use of low-dose rate radiotherapy in the treatment of inflammation, including pneumonia. The current pandemic situation is characterized by the dramatic course of pneumonia among certain COVID-19 patients and the relatively high percentage of deaths due to lung failure in this group. Therefore, the question should be raised as to whether low-dose radiotherapy can become a treatment method that gives a chance to improve the quality of life and reduce the risk of death for such patients. Such a treatment protocol should determine a radiation dose per lung volume area [8–10] and be positively assessed by the Bioethics Committee.

Objective

The aim of this paper is to present a unique and proprietary procedure of lung radiotherapy in pneumonia patients during the course of COVID-19 infection with particular emphasis on the physical aspects of treatment planning and dosimetry. The duration of the procedure (planning and treatment) should be as short as possible.

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1. The place of the procedure should be limited to a minimum number of rooms. The irradiation session should be image guided.
2. The target area refers to the irradiated volume, namely the patient's lungs. The only organ shielded is the spinal canal.
3. The dose distribution should be presented in 3D.

Based on pre-clinical and clinical studies [8–10], a dose in the range: 0.5–1.5 Gy is considered to have anti-inflammatory properties. Given this, the mean dose in this procedure was set at 1 Gy in whole lungs volume.

Material and methods

Considering the epidemic risk, it was assumed that the patients should be admitted to the Radiotherapy Department through a separate entrance, so as not to cross communication routes dedicated to oncological patients and medical staff. Additionally, both radiotherapy preparation and treatment should take place in a combined complex of rooms isolated from other patients and staff.

One of the TrueBeam Varian Medical Systems (VMS) accelerators was installed near the service entrance to the RT Department. It is equipped with an OBI (On-Board Imager): CBCT and kV/MV imaging. Software Irreg Planning, is an integrated part of the Aria System (16.1.0) VMS, which makes it possible to calculate the treatment time (MU – monitor units) based on the size of the irradiation field (beam), source skin distance (SSD) and the depth of the planning dose definition. Therefore, the MUs is calculated for a density of 1 g/cm^3. When this software (Irreg Planning) is used in the irradiation of the chest volume, the calculated treatment time is overstated. This software (2D planning) is used for clinical purposes during simulation in cases where it is particularly important to shorten the preparation time of patients to radiotherapy e.g., analgesic therapy. In the case of a single irradiation session, a CT scan is not required to be performed.

It was assumed that the calculated dose distribution would be three-dimensional, in order to assess the statistical dose in the lungs and critical organs: the heart and the spinal cord. The TrueBeam accelerator is equipped with both kV and MV (on board imager – OBI) imaging systems; CBCT is a routine procedure to verify the patient's position before a therapeutic session. Until now, this study has not been used to plan dose distributions. In this case, however, in order to shorten the overall duration of the treatment procedure, CBCT was used to calculate the dose distribution.

With regard to the clear reduction of the procedure time, it was decided that treatment would be carried out using the TrueBeam VMS. The following procedure stages were developed (fig. 1):

1. The patient is placed in a therapeutic position on the table of the therapeutic apparatus.
2. With the use of kV (X-ray) imaging, the irradiation conditions are simulated by defining the maximum dimensions of the therapeutic beam. The AP (anterior-posterior) dimension is defined in the transverse largest dimension at lung level. Based on this measurement, the depth (half AP dimension) of prescribed dose is determined.
3. Based on the simulation image (one, at an angle of 0°) in the Irreg Planning software, MLC is introduced – limiting the irradiation area to the contour of the lungs with the spinal canal being shielded (the MLC collimator should be

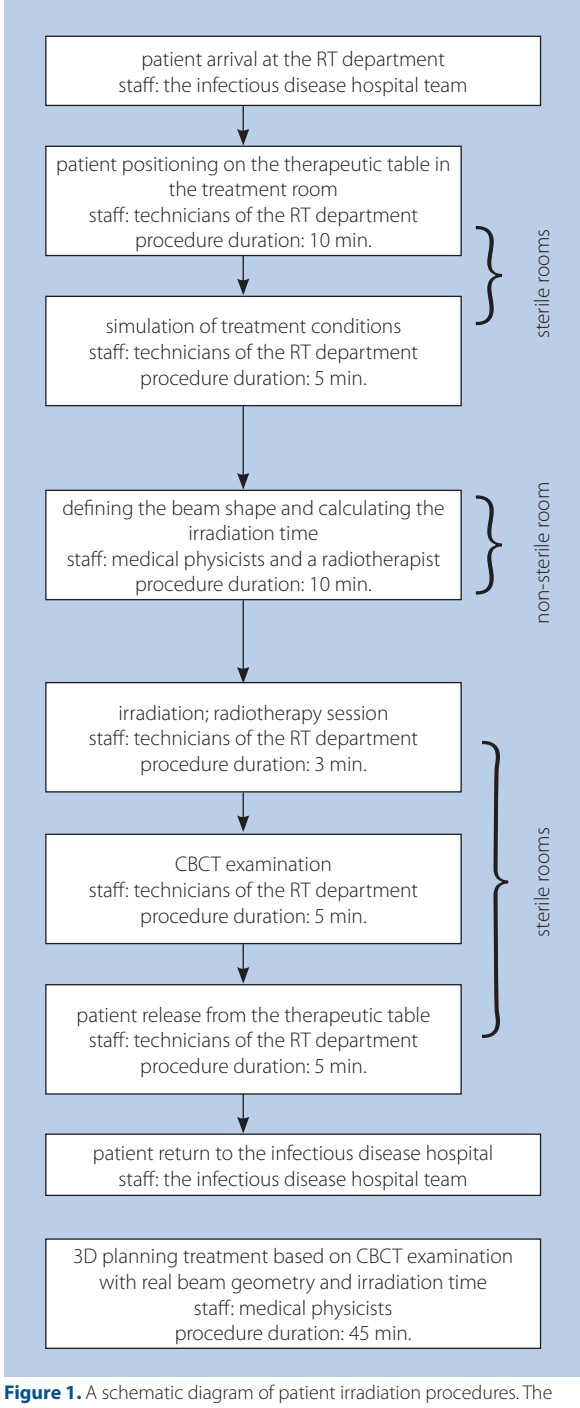

Figure 1. A schematic diagram of patient irradiation procedures. The time the patient stays in the therapeutic position on the table is 30 minutes. The total stay in the RT Department is limited to 45 minutes

set at 90°). After copying the field shape defined in this way to the opposite beam, at an angle of 180°, the software adjusts the position of the collimator leaves to the new irradiation angle. The irradiation time is calculated.

4. The treatment planning (2D) process is completed by entering the beam parameters (i.e. MU, MLC, table, gantry, collimator position) into the patient management system (ARIA).
5. The patient is irradiated and the fluence map is measured by EPID., and at the end of exposure, a CBCT scan is performed.
6. The patient completes the treatment and is taken back to their hospital base.
7. Dose distribution calculations (3D) are performed for the implemented radiation conditions, i.e., the shape of the radiation beam and exposure time. This stage is designed to accurately determine the dose received by the patient in the volume of each defined area.

Dosimetric preparation

The Irreg Planning software does not consider the heterogeneity of the irradiated medium, and thus the actual radiation dose in this volume can be expected to be higher, since the lung density is less than the water density – 1 g/cm^3. That is why it should be verified by calculations based on CT scans. The precise calculation of dose distributions requires the introduction of the calibration curve of the device used for imaging into the treatment planning system (TPS-Eclipse VMS 16.01.03). In this case, it was the OBI-CBCT device of the TrueBeam accelerator. Unfortunately, this proved to be difficult to implement, and thus the differences were checked between the dose distribution calculations made with CT scans for routine treatment planning and CBCT, using the reference calibration curve (fig. 2). For this purpose, phantoms were utilized to calibrate the CT scanner (CIRS-Norfolk, Virginia, USA). Due to the slight differences between the calculations: maximum dose, the examination performed with a calibrated CT scanner – 2.173 Gy, and for CBCT, with a reference calibration curve – 2.176 Gy, it was found that it was possible to perform dose calculations for the patient using the CBCT scanner.

Before the first treatment procedure, all the steps described above were taught to the staff (RT technicians, medical physicists). It was established that in order to optimize the duration of the treatment, the patient's irradiation procedure should be carried out first; only at the end of exposure should a conical CT scan be performed. The width of the area that can be examined during one CT scan is 20 cm. Since the examined lung volume is a much larger area, two CBCT scans need to be performed so that they can be later combined to determine the entire lung volume needed for calculation. This requires changing the centering points, which involves moving the therapy table. The CBCT scan is performed in the SAD technique and the patient is treated in the SSD technique. This requires changing the position of the therapy table.

The first patient

The patient was admitted to the RT Department on December 15th, 2020 at 5:12 pm. A 50-year-old woman with COVID-19 (based on a real time polymerase chain reaction of SARS-CoV-2 RNA) has been admitted to the hospital with symptoms and radiographic pneumonic consolidations of COVID-related pneumonia. 96 hours after admission, an RT procedure was carried out. Oxygen saturation level [SpO_2] with O_2 supplementation via facial mask with reservoir bag was 88% prior to RT.

The first procedure involved placing the patient on a therapeutic table in the treatment position – on their back with their hands along their body and head supported (part of the AiO system – ORFIT company). No immobilization systems were used. A simulation image was produced using the MV beam. Then, the shape of the irradiation field was defined by determining the lung area by placing the collimator leaves on the image obtained in the MV examination. Finally, the irradiation field determined at an angle of 0° was copied to the opposite beam at an angle of 180° by adjusting the shape of MLC (fig. 3).

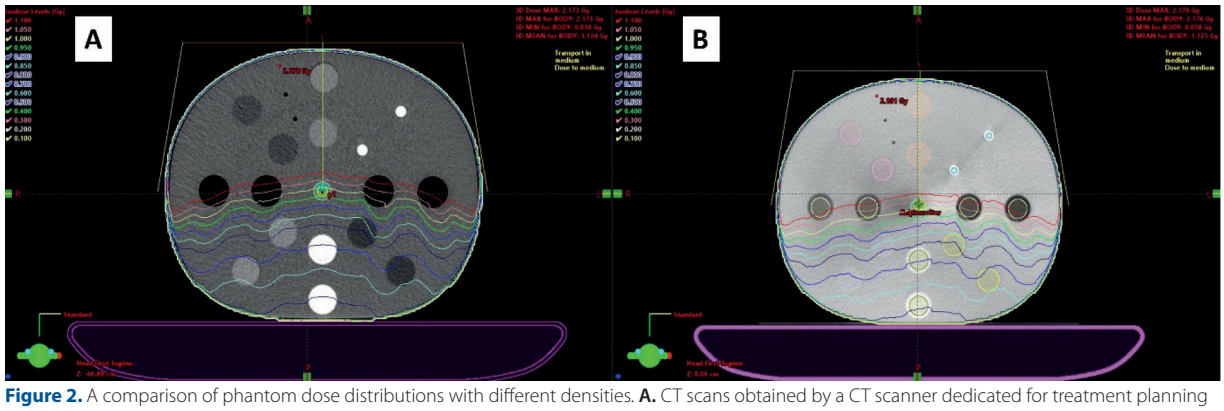

Figure 2. A comparison of phantom dose distributions with different densities. **A.** CT scans obtained by a CT scanner dedicated for treatment planning (AS-Siemens), a calibration curve introduced into the treatment planning system; **B.** scans obtained by a therapeutic device, with CBCT. Dose distribution calculations were made with the use of the treatment planning system Eclipse v 16.1.0 by Varian Medical Systems based on the reference calibration curve

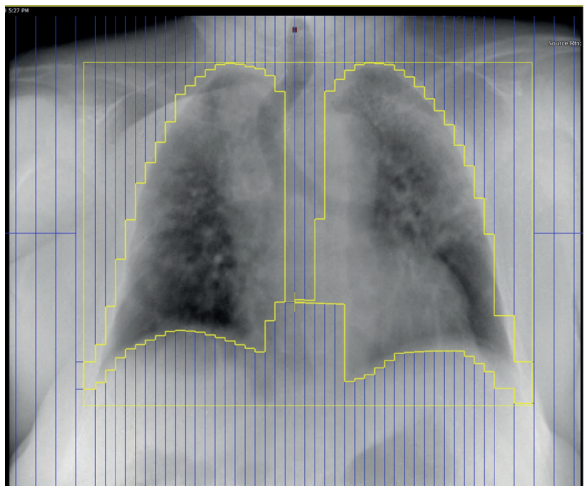

Figure 3. A simulation image with a prepared beam shape – MLC, beam entry at an angle of 0°. One should remember to set the collimator angle to 90°; to use the collimator leaves to shield the spinal canal (the direction of the collimator leaves' movement). The position of the collimator leaves is copied to the opposite beam at an angle of 180°

The next stage involved calculating the irradiation time, for a dose of 1 Gy, at a depth equal to ½ of the AP (anterior – posterior; in this case, it was 13.7 cm). The X-ray beam of 6 MV was applied and the SSD technique (100 cm) was used. The calculations were performed using the Irreg Planning 16.1.0 software by Varian Medical Systems [11], which is dedicated to calculations in 2D planning.

The patient was irradiated and a CBCT scan was performed at the end of the exposure. Due to the maximum volume that can be obtained in one CBCT rotation, two scans had to be performed, moving them relative to each other to cover the entire lungs.

During radiation exposure, a fluence map was measured on the extended EPID (Electronic Portal Imaging Devices) using the integrated dose option of the Varian Medical Systems' ARIA 16.1.0 software for both 0° and 180° radiation beams. The patient left the Radiotherapy Department at 5:50 pm. The whole described procedure lasted 38 minutes in total. However, the patient was on the therapeutic table, in the treatment position for only 20 minutes.

The 3D dose distribution planning, based on CBCT, is performed without the patient's presence in the RT Department. The dose distribution (3D) is calculated in the Eclipse v 16.1.0 VMS planning system, for irradiation time and beam geometry predefined in the Irreg Planning – ARIA VMS software (fig. 4). It is worth emphasizing at this point once again that this procedure is performed without the presence of the patient in the RT Department. It aims to precisely determine the dose received by the patient as the dosage calculation algorithm (Acuros 16.1.0-VMS) considers the actual tissue density obtained from CBCT.

The calculated dose distributions (Acuros algorithm 16.1.0--VMS), considering heterogeneity in density, indicate that the patient received an average dose of 1.091 Gy in the lungs. The average dose in the lungs was found to be higher than assumed, since the time calculated in the Irreg Planning option was for a medium with a density of 1g/cm^3, while, in fact, lung tissue has a lower density. This makes the actual doses slightly higher. The modal dose in the spinal cord was 0.016 Gy. These differences do not exceed the therapeutic assumptions and significantly shorten the duration of the entire treatment procedure.

24 hours after the RT procedure, an increase in $SatO_2$ was noticed and continued over the next days. 24 hours after RT, there was also significant decrease in CRP, IL6 and ferritin level (tab. I). Clinically, improvement started 24 hours after RT and continued to the state that the patient was discharged from the hospital 14 days later with their overall status being very good.

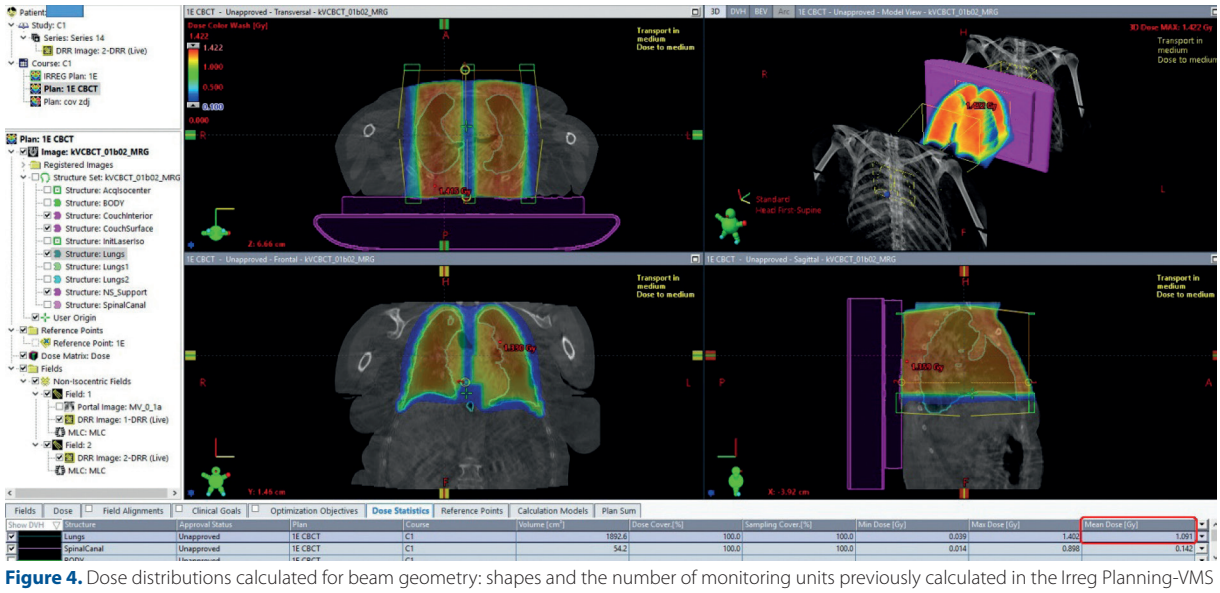

Figure 4. Dose distributions calculated for beam geometry: shapes and the number of monitoring units previously calculated in the Irreg Planning-VMS software 16.1.0

Table I. The change of biochemical parameters in the selected days after RT

Marker/day	0	1	5	7	14
Sat	88%	90%	94%	97%	92%
CRP	166.73	7.68	2.47	1.58	1.58
Ferrytyna	2453	685.52	783.95	601.95	556.76
IL6	23.38	2.04	3.06	2.19	

Sat – oxygen saturation; CRP – C-reactive protein; IL6 – interleukin 6

Conclusions

The presented procedure of lung irradiation in patients with pneumonia during the course of COVID-19 infection made it possible to minimize the patient's stay in the Radiotherapy Department. At the same time, it ensures all the required radiotherapy treatment quality assurance procedures are adhered to. The dose received by the patient was consistent with the therapeutic requirements. The irradiation process was controlled from both a dosimetric (a fluence map) and an imaging (real-time MV imaging) perspective. The procedure also involved the calculation of three-dimensional dose distribution, which allows for the presentation of full statistics of dose distribution to the critical organs (spinal cord, heart).

Conflict of interest: none declared

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32 lata obserwacji po odtworzeniu obu piersi protezami silikonowymi po podskórnej mastektomii

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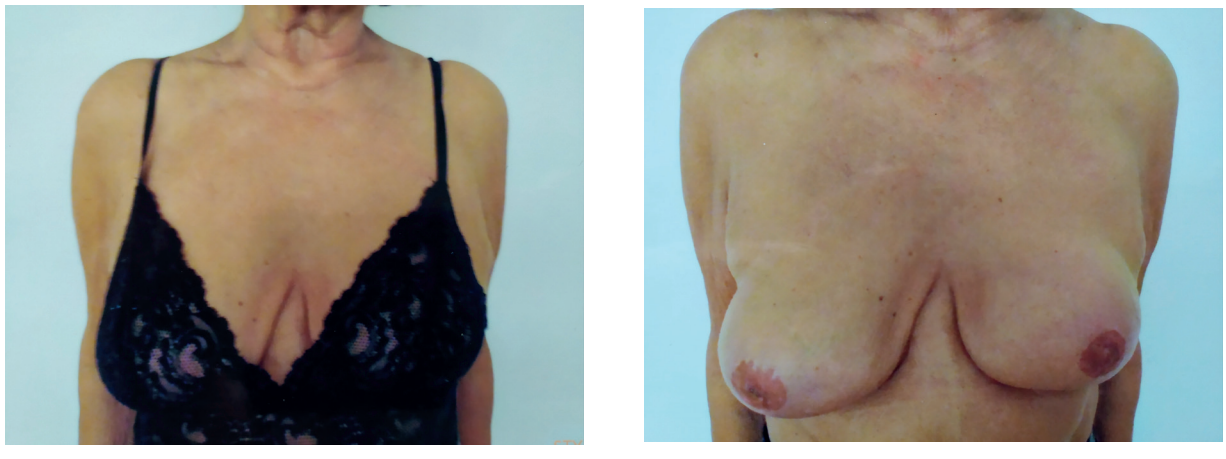

Rycina 1. Stan 32 lata po wszczepieniu w 1988 roku silikonowych protez demonstracyjnych wyjałowionych z użyciem bomby kobaltowej

W 1988 roku zgłosiła się do mnie kobieta (ur. 1947 roku) z obustronnymi zmianami włóknisto-torbielowatymi piersi. Badania obrazowe i wielokrotna ocena cytologiczna płynu z torbieli nie wykazywały zmian nowotworowych. Bardzo nasilone i przewlekłe dolegliwości bólowe oraz wielokrotnie powtarzane punkcje torbieli skłoniły chorą do poszukiwania definitywnego leczenia.

Przedstawiłem jej możliwość obustronnej, podskórnej mastektomii z jednoczesną implantacją protez. W 1988 roku w Polsce jedyną drogą pozyskania protez był ich walutowy zakup za granicą, co przekraczało możliwości pacjentki, a rekonstrukcje piersi inicjowano dopiero w latach 80. [1, 2]. Dlatego zwróciłem się do producenta ze Stanów Zjednoczonych (Dow Corning Corporation) z prośbą o pomoc. W odpowiedzi otrzymałem paczkę z cennikiem oraz 4 pełnowartościowe, choć niewyjałowione, protezy demonstracyjne (opisane „*Do not implant*"). Uznałem, że po wysterylizowaniu można je wszczepić. Wspólnie z radioterapeutami rozważyliśmy dostępne możliwości i wyjałowiliśmy protezy z wykorzystaniem bomby kobaltowej, która od niedawna była zainstalowana w Zakładzie Radioterapii warszawskiego Centrum Onkologii.

29 grudnia 1988 roku z cięcia w fałdzie podsutkowym wykonałem obustronną podskórną mastektomię z jednoczesną implantacją obu protez. W badaniu histopatologicznym potwierdzono zmiany włóknisto-torbielowate znacznego stopnia. Chora pozostawała w mojej wieloletniej obserwacji, wyrażając zadowolenie z efektu estetycznego. Protezy przez 32 lata nie uległy uszkodzeniu – mimo upływu czasu oraz urazów narciarskich przedniej powierzchni klatki piersiowej pacjentki.

Zgodnie z moją wiedzą to jedna z najdłuższych w Polsce obserwacji niepowikłanego wszczepienia silikonowych implantów, które wyjałowiono z użyciem bomby kobaltowej.

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Treatment of gastric cancer in the older population

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Gastric cancer (GC) is predominantly a disease of the elderly as approximately 60% of all patients are 70 years of age or older. At present, there are no guidelines dedicated to this group, and current treatment strategies are mainly based on evidence from clinical trials often carried out on younger patients.

The GC in older patients is typically located in the distal third of the stomach and it is well/moderately differentiated, having mainly an intestinal type of tumor by Lauren's criteria. Lymph nodes and peritoneal metastases have been reported less frequently in comparison to younger patients.

Older patients are a very heterogeneous population in terms of co-morbidity, physical reserve, cognitive function, and social support. Treatment side effects can cause more serious problems than cancer itself, so the comprehensive geriatric assessment (CGA) is as important as the cancer staging. Chronological age alone is not a contraindication for treatment. Surgery is the preferred standard treatment option for resectable GC. However, the prognostic significance of surgery and other treatment options is unknown in the frail group. Fitter patients, according to the CGA, should qualify for the same treatment as younger patients. Frail patients should be discussed during oncogeriatric meetings. Surgery, the benefits of limitation of the surgical resection, and no or non-selective lymphadenectomy should all be analyzed. In experienced hands, minimal invasive surgery is favorable in the short- and long-term. In cases of severe frailty, the best supportive care can often be the best option.

Key words: older patients, gastric cancer, frailty

The prevalence of gastric cancer (GC) has gradually decreased over the last decades, nevertheless, it remains a major cause of cancer-related death and remains the fifth most common cancer in the world. GC is also predominantly a disease of the elderly as approximately 60% of all patients are 70 years and older. Subsequently, an aging population means that the number of older patients with GC is increasing continuously [1].

Surgery is the preferred standard treatment option for resectable GC. However, the prognostic significance of surgery and other treatment modalities is still unknown in frail patients. At present, there are also no guidelines dedicated to older patients and current treatment strategies are mainly based on evidence from clinical trials frequently carried out on younger patients [2]. Therefore, surgeons and oncologists experience many difficulties when making decision in this age group. Very often these decisions are taken based on comorbidity burden, subjective assessments or are age driven.

The clinical and pathological characteristics of GC in older patients

There is a male predominance among older patient with GC, which contrasts with younger patients where the gender ratio is typically closer to 1:1. There is usually no family history. The GC is typically located in the distal third of the stomach and it is well/moderately differentiated. Moreover, histologically, older patients present mainly with an intestinal type of tumor by

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Lauren's criteria. It frequently metastasizes to the liver. Lymph nodes and peritoneal metastases have been reported less frequently in comparison to younger patients [3].

According to the Japanese classification of GC, the predominant type of early gastric cancer (EGC) in older patients is the superficial depressed type IIc, followed by the superficial elevated type IIa, and the polypoid type I [4]. Genetically, older patients have more frequent TP-53 and HER2 overexpression, and more microsatellite instability-high tumors [5].

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 [6]. Current routine pre-operative assessment also cannot adequately identify patients at risk. Therefore, the comprehensive geriatric assessment (CGA) was introduced to help determine the primary status of the older patient, to diagnose frailty syndrome (surrogate of the biological age), and to identify how to optimize the patient's condition before the start of the treatment. Many older adults have unidentified, uncommunicated, and therefore unaddressed aging-related conditions that are associated with morbidity and early mortality [7, 8]. The natural life expectancy of older people is surely shorter than that of younger people. Considering their limited remaining lifetime, their postoperative quality of life is as valuable as the need to cure or remove the cancer. Therefore, the International Society of Geriatric Oncology (SIOG) and The European Society for Medical Oncology (ESMO) recommends the use of the CGA to determine biological age before the beginning of the treatment.

In general, based on the CGA, we can differentiate three groups of older patients:

1. Fit: patients without any deficits in the CGA domains and less than 80 years old. In this group, standard oncologic treatment can be offered and the postoperative outcomes are comparable with younger patients.
2. Pre-frail: patients with one or two deficits in the CGA domains or more than 80 years old. In these patients, rehabilitation should be recommended to improve resilience to surgical stress by, at least, augmenting functional capacity and nutritional status before surgery.
3. Frail patients: patients with three or more impaired domains in the CGA or 80 years old with two deficits in the CGA. A tailored approach should be discussed in a geriatric multidisciplinary team meeting [9].

It is also possible to determine the severity of the frailty using a cumulative deficit model for the CGA [10].

Treatment of gastric cancer in older patients

The therapeutic options for GC depending on the cancer stage [11, 12] including options for frailer, older patients, are presented in table I.

Patients with early GC (T1) can undergo endoscopic resection using an endoscopic submucosal dissection (ESD) technique. The ESD, in experienced hands, is an effective and safe procedure for older patients, with clinical and oncological outcomes comparable to younger population. A higher prevalence of cardiopulmonary problems was reported during the procedure when compared to the younger group. However, they were managed effectively during the procedure without further clinical sequelae. Therefore, the ESD should be the standard treatment for management of early GC fulfilling the Japanese criteria of a negligible risk of lymph node metastasis for both fit and frail patients [13, 14].

At present, surgical resection is the main curative treatment option for patients with gastric cancer GC stage T1b and higher. However, it can cause high morbidity and mortality, particularly in the older population. Improvement in anesthesiology, standardization of the surgical technique, and perioperative care improve the 30-day outcomes significantly in comparison to previously reported data. Katai et al. and Zhou et al. reported that surgery can be safely performed with an excellent prognosis in older patients with GC [15, 16]. In contrast, Fujisaki et al. observed that after gastrectomy there was as higher rate of postoperative non-surgical complications (pneumonia, heart failure, and liver dysfunction) in comparison to younger patients [17]. In turn, Wakahara et al. observed a 10% increase in the overall postoperative morbidity, including the rate of anastomotic leakage that was significantly elevated in the older group [18]. Mengardo et al. concluded that ≥80 years of age is

Table I. Therapeutic options for gastric cancer depending on the cancer stage [11, 12], including options for frail, older patients

Stage factors	Fit patients	Frail patients
T1N0	• endoscopic resection • limited resection	• endoscopic resection • best supportive care in severe frailty
T2–4 N0–2	• preoperative chemotherapy, followed by total/subtotal gastrectomy and postoperative chemotherapy • surgery followed by adjuvant chemotherapy	• subtotal/partial gastrectomy with no or selected lymphadenectomy • palliative treatment • best supportive care in severe frailty
not-resectable metastatic	• palliative treatment • clinical trials	• best supportive care

a negative independent factor impacting overall survival (OS), thus, these patients should be carefully selected for surgery [19]. Endo et al. reported on a heterogeneous population of patients aged 85 years who underwent surgery for gastric cancer. This group had a better prognosis than those who did not undergo surgery. Females, patients aged 85–89 years, and patients with stage IB–IIIC cancer had significantly better OS with surgery than without. For males, patients aged 90 years of age, or stage IA patients, the decision to perform surgery should be carefully discussed, and best support care may be an optimal strategy [20]. Most of the postoperative deaths in these patients were due to pneumonia and not due to GC. However, the most important limitation of the study is that the authors divided the patients based on their chronological age alone and not on the presence of frailty factors (a surrogate of biological age). Therefore, I would view the group of 90-year-old patients in this study as being equivalent to a severe frailty group.

To conclude, it appears that fit and mildly frail patients can and should be operated on with acceptable short-term outcomes. In the case of severe frailty, surgery might not be the optimal option. However, currently studied patients were fit older patients mostly defined based on their chronological age and/or comorbidity burden and not on the biological age. We are still lacking good data on the long-term outcomes of frail patients, because their risk of mortality after hospitalization remains particularly high during the first 6 months. Moreover, surgery is a well-known trigger for postoperative institutionalization and dependency on other people in older patients. Therefore, quality of life as an end point is even more important than OS or disease-free survival (DFS).

The next question is the extent of the surgery. Total/subtotal gastrectomy with a D2 lymphadenectomy is recommended for most fit patients with resectable advanced GC as a standard surgical procedure. In the case of older patients, the essential clinical question is whether perioperative trauma can be limited which, in turn, may reduce the risk of postoperative morbidity/mortality and increase the quality of life. Therefore, there is a trend among surgeons to perform a subtotal gastrectomy, since a total gastrectomy in this age group had been associated with higher rates of postoperative morbidity and mortality. A Dutch study reported that older patients qualified to total gastrectomy had a relative risk of 2.15 for in-hospital mortality and 3.25 for morbidity, as compared to those who had undergone a partial gastrectomy [21]. Similarly, Katai et al. demonstrated that total gastrectomy in octogenarian patients was associated with higher operative and 90-day mortality [22]. Moreover, the 5-year overall survival was better in older patients in partial as opposed to total gastrectomy (86% *vs.* 67%). There are also studies showing the benefit to limit the resection to specific margins in the case of cancers with beneficial histology [23].

To conclude, the extent of the resection, if there is any possibility, should be limited in older patients. However, similarly as above, we do not have good studies using biological age as opposed to chronological.

Limited data are also available to clarify the survival benefit of D2 lymphadenectomy for older patients. Shinozuka et al. analyzed 3484 patients from many centers who received surgical resection for GC. The authors selected patients aged ≥80 years with T2–4 GC. Their performed propensity score matching to balance the essential variables (stage of disease and gastrectomy type). The D2 group had significantly longer operative times, more blood loss, and more retrieved lymph nodes than the non-D2 group. The D2 group had a greater incidence of intra-abdominal abscesses (grade ≥II in the Clavien–Dindo classification) than the non-D2 group. The overall, disease-specific and relapse-free survival rates of the D2 group tended to be worse than those of the non-D2 group (hazard ratios: 1.49, 1.70 and 1.14, respectively). The non-D2 group had a slightly longer relapse-free survival compared with that of the D2 group, indicating that limited lymphadenectomy did not increase the risk of disease recurrence [24].

Also essential, is that postoperative complications after gastrectomy influence the prognosis. Wang et al. and Kanda et al. showed that morbidity following gastrectomy shortens the long-term survival of older patients with GC; D2 lymphadenectomy was an independent risk factor of postoperative complications [25–27]. In turn, Takeda et al. recommend that standard radical lymph node dissection should be used for tumors extending through the serosa (T3) and/or involving extragastric lymph nodes (N2), even in patients aged 80 years or more [28].

To conclude, it seems that in fit (based on the CGA) older patients a standard D2 lymphadenctomy can be carried out. However, the more severe the frailty, the more selective the lymphadenectomy should be. Larger prospective studies are required to clarify the necessity of D2 lymph node dissection to treat older, frail patients.

Most of the studies on minimal invasive surgery in older patients with the GC report have comparable oncological results and good short-/long-term outcomes both in unmatched and propensity-matched patients aged 80 years and older [29]. Total gastrectomy, a Charlson comorbidity index ≥4, and pathological N stage were identified as independent prognostic factors for overall survival in patients undergoing a laparoscopic gastrectonmy [30]. The first Western experience in laparoscopic distal gastrectomy was published by Rausei S. et al. this year, including 46 patients aged 80 years and older. The authors concluded that the laparoscopic approach reduces the effect of surgical trauma without compromising the oncological results [31]. There are also the first studies analyzing frailty as a prognostic factor in the laparoscopic group of older patients with GC. Tanaka et al. reported that operative complications (especially systemic complications) were positively associated with an increase in clinical frailty scores. Moreover, the overall 5-year survival rate and the 5-year survival rates

for those with a clinical frailty score of 1–2, 3–4, and 5–7 were respectively 70.9%, 59.8%, and 35.1%. Therefore, the authors conclude that frailty has a great impact on operative morbidity and prognosis in the elderly, and the CFS score could be a promising prognostic predictor, especially for frail patients with advanced gastric cancer [32].

To conclude, minimal invasive gastrectomy has the potential to provide a balance between oncological clearance and quality of life issues that remain crucially important in the older population. However, full a comprehensive geriatric assessment was not performed in any of the studies. The legal point of view is also interesting. Older cancer patients are offered a standardized treatment model geared toward younger adults by their physicians, due to the fear of being accused of undertaking the incorrect oncological treatment. In this context, it may be useful to surgeons to highlight the Polish Supreme Court verdict from September 24, 2015 (V CSK 738/14 – the extent of obligation to provide information by physicians), discussed in the article by dr. Radosław Drozda from the Department of Forensic Medicine at the Wroclaw Medical University. It concluded that "the choice between alternative treatment methods belongs to the patient, and the clinician should present the patient with all available treatment options that are possible in their physical condition – at most with an indication as to which of these options is the most beneficial according to the doctor…" and "…it is the patient – despite a lack of medical training – who should make the ultimate decision on the surgical method that they will be subjected to. The role of the physician is to convince the patient why (and for what medical reasons) it might be worth undergoing a riskier procedure. The patient however has the right (driven by personal reasons or even superstition) to pick a method that would be less invasive and is likely to have a lower efficacy than the method proposed by the clinician" [33].

Perioperative chemotherapy

Due to high recurrence rates, multimodal treatment is a standard for GC in stage IB disease and higher. However, concerns remain regarding chemotherapy in older patients due to the risks of perioperative morbidity from toxicity. Therefore, to determine the feasibility of treating patients over the age of 65, a predefined exploratory subgroup analysis of patients within the randomized phase II FLOT 65+ trial compared patients treated with perioperative FLOT (5-fluorouracil, oxaliplatin and docetaxel) or FLO (without docetaxel). In the study, a high level of adherence among older patients was observed: 85% of patients received all 4 preoperative cycles of FLOT, and there was no clinically significant increase in grade 3–4 toxicity postoperatively. Mortality and morbidity rates were comparable to other trials, including patients across all ages. The authors concluded that neoadjuvant FLO or FLOT chemotherapy is therefore a reasonable option in older patients with locally advanced resectable gastric cancer [34–36]. It must be stressed that, although, there was no upper age limits included in the study, the patients were generally fit. In turn, Slagter et al. evaluated treatment-related toxicity, treatment compliance, surgical complications, and event-free survival in older (>70 years) versus younger (<70 years) patients who underwent perioperative treatment for GC. 788 patients with resectable gastric cancer were randomized before the start of any treatment, and received preoperative chemotherapy (3 cycles of epirubicin, cisplatin or oxaliplatin and capecitabine), followed by surgery, followed by either postoperative chemotherapy or chemoradiotherapy (45 Gy, cisplatin, capecitabine). During preoperative chemotherapy, 77% of older adults versus 62% of younger adults experienced severe toxicity ($p < 0.001$) and older adults received significantly lower relative dose intensities for all chemotherapeutic drugs. Equal proportions of older and younger adults underwent curative surgery (80% *vs.* 81%), with comparable postoperative complications and postoperative mortality; 64% of older patients and 78% of young patients started adjuvant chemotherapy ($p < 0.001$). There was no difference in the severe toxicity rate between the groups; however, older adults received significantly lower relative dose intensities for all chemotherapeutic drugs [37]. The question as to whether this kind of treatment can be proposed to frail patients with good short- and long-term outcomes still remains unanswered.

In the case of patients with resected gastric cancer who have not received preoperative chemotherapy, adjuvant chemotherapy is recommended [38]. However, adjuvant chemotherapy is, generally, less well tolerated than preoperative chemotherapy. Therefore, the latter may be the preferential option. An interesting study was published this year by Schendel et al. including 75-year and older patients with GC from Canada. The 5 year DFS for the surgery only group was 67.3% and for the multimodality group was 52.9% ($p = 0.25$). The 5 year OS for the surgery only group was 38.9% and for the multimodality group was 47.1% ($p = 0.52$). The authors concluded that even with surgery alone, selected older patients with non-metastatic gastric cancer can obtain prolonged survival, despite not receiving standard of care multimodality therapy [39].

Concluding, limited data on these topics are available from the Western world. Most of the studies were conducted in Asia and the applicability of these results in Europe remains uncertain, not to mention the evaluation of frailty based on the comprehensive geriatric assessment.

Palliative treatment

Currently, there is little evidence of the role of palliative resection in GC in older patients. The REGATTA trial including patients with incurable gastric cancer, randomizing them to palliative chemotherapy alone or to gastrectomy with chemotherapy, showed no survival advantage of surgery, with the median OS at 16.6 months (95% CI: 13.7–19.8) with chemotherapy versus 14.3 months (95% CI: 11.8–16.3) with surgery and chemotherapy.

The included patients were young, between 49 and 67 years old. It seems that palliative gastrectomy should not be considered in patients with advanced gastric cancer, unless there are other indications (bleeding or obstruction) [40].

As far as palliative chemotherapy is concerned, in patients over 70, it is recommended to consider tailored treatment based on biological age with two/three-drug chemotherapy regimens and dose reduced therapy.

Conclusions

Chronological age should not be a contraindication for multimodal radical treatment in older patients. The frailty (surrogate of the biological age) evaluation should be the basis for the discussion on treatment planning. At present, it is one of the most reliable factors predicting functional decline in different organs, making it more difficult for older patients to overcome surgical stress. Moreover, the potential benefits of surgery for frail patients with GC must be explored in the context of their shorter life expectancy compared to younger patients.

Therefore, before treatment begins, the following questions should be discussed:

- Is the currently planned treatment strategy correct? Are there alternative treatment options?
- What is the result of the comprehensive geriatric assessment? Can frailty syndrome be diagnosed in the patient?
- What is the risk of complications?
- What would the patient's lifespan be without treatment?
- What are the goals, preferences, and expectations of the patient? What effect might the treatment have on these goals?
- Is it possible to improve the patient's state prior to the surgical procedure?

Fit patients, according to the comprehensive geriatric assessment, should be qualified for the same treatment as younger patients. Prefrail patients should undergo pre rehabilitation and be reevaluated. Frail patients should be discussed in the oncogeriatric meeting. In the case of surgical treatment, the limitation of the resection's extent, no or selective lymphadenectomy should be considered. In experienced hands, minimal invasive surgery may be beneficial regarding the short- and long-term outcome. In the case of severe frailty, best supportive treatment can be the optimal option. The goal of the modifications is to reduce surgical stress. In older patients (aged 75 years or older), the pathological outcome and postoperative complications are predictors of survival, whereas pathological outcome and chemotherapy are predictors of survival in the younger population (aged 74 years or less). Thus, the prevention of postoperative morbidity may contribute to improved prognosis for older patients with gastric cancer [41].

However, we still need better designed studies on a larger group of patients using frailty evaluation. Existing studies on this topic are limited, too small, and lack important details with satisfactory statistical clout. In clinical observational studies, overall survival is usually considered the gold standard endpoint because it is simple and reliable to measure. Overall survival could be diluted by non-cancer-related deaths, especially in the older population. Therefore, cancer-specific survival and relative survival should be used in this group [42, 43]. Moreover, novel endpoints should be explored such as patients reported outcomes to establish appropriate treatment guidelines for frail, older patients.

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Personalizowane postępowanie medyczne u pacjentów z czerniakiem (część 2.)

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W ostatnich latach obserwuje się dynamiczny wzrost zachorowań na czerniaki, szczególnie u osób młodych oraz w wieku średnim. Dlatego wyleczalność chorych staje się priorytetem również w odniesieniu do czynników ekonomicznych. Czerniaki pod względem zmian genetycznych należą do grupy nowotworów o bardzo dużej heterogenności. Najczęściej stwierdzane zmiany genetyczne dotyczą dwóch ścieżek przekazywania sygnałów, są to: ścieżka aktywowana mitogenami (MAPK) oraz ścieżka sygnałowa kinazy 3-fosfatydyloinozytolu (PI3K). Identyfikacja charakterystycznych zmian molekularnych w tkance nowotworowej pozwala zoptymalizować i zindywidualizować terapię. Tym samym przyczynia się do ograniczenia skutków ubocznych leczenia oraz poprawy jakości życia chorych. Obecnie standardem postępowania w leczeniu pacjentów z czerniakiem skóry, obok postępowania chirurgicznego i klasycznej – coraz rzadziej stosowanej chemio-/radioterapii – jest wdrażanie leczenia ukierunkowanego na zmiany molekularne w tkance guza oraz immunoterapia, która polega na aktywowaniu układu immunologicznego.

Słowa kluczowe: czerniak, *BRAF*, *NRAS*, terapia celowana

Podstawową metodą leczenia czerniaka jest zabieg chirurgiczny, podczas którego usuwa się guz pierwotny wraz z odpowiednim marginesem tkanek niezmienionych chorobowo. Wielkość marginesu zależy od głębokości nacieku czerniaka. Aby wykryć mikroprzerzuty do układu chłonnego, często dodatkowo wykonuje się biopsję węzła wartowniczego (*sentinel lymph node biopsy* – SLNB). Rutynowo do SLNB kwalifikowani są pacjenci z czerniakiem skóry o zaawansowaniu pT1b–T4b (po wykluczeniu rozsiewu choroby). Jeśli stwierdzi się obecność komórek nowotworowych w węźle chłonnym, do rozważenia pozostaje radykalna limfadenektomia [1]. Ponadto, aby zmniejszyć ryzyko nawrotu choroby, w zaawansowanych przypadkach (stopień III i IV resekcyjny) wdrażane jest leczenie uzupełniające ukierunkowane na zmiany molekularne lub immunoterapia. Chorzy z chorobą rozsianą leczeni są w podobnym zakresie, ale już paliatywnie.

Leczenie ukierunkowane na zmiany molekularne

BRAF

Przerzutowego czerniaka, w którym stwierdza się mutacje genu *BRAF* V600, leczy się w sposób ukierunkowany inhibitorami BRAF kompetycyjnymi wobec ATP (BRAFi): wemurafenibem (rekomendacje FDA od 2011 roku) lub dabrafenibem (rekomendacje FDA od 2013 roku) [2, 3]. Inhibitory BRAF prowadzą do regresji nowotworu w około 90% przypadków u chorych z przerzutami i mutacją *BRAF* V600. Czas odpowiedzi jest zróżnicowany i trwa od kilku miesięcy do ponad 1,5 roku [4].

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Skuteczniejsze od monoterapii BRAFi jest leczenie skojarzone – w raz z selektywnymi inhibitorami MEK. Wyniki badań klinicznych pierwszej linii leczenia trametynibem (Mekinist) w skojarzeniu z dabrafenibem (Tafinlar) (COMBI-v i COMBI-d) wykazały 5-letni okres przeżycia u około 30% pacjentów z przerzutowym lub nieresekcyjnym czerniakiem [5]. Również badania kliniczne pacjentów leczonych w sposób skojarzony, czyli kobimetynibem (Cotellic) z wemurafenibem (Zelboraf) (coBRIM, BRIM-2, BRIM-3, BRIM-7), wykazały wyższą medianę całkowitego przeżycia (*overall survival* – OS) i czasu wolnego od progresji choroby (*progression-free survival* – PFS) w porównaniu z monoterapią BRAFi [6, 7]. Jednak obie te terapie mają skutki uboczne w postaci gorączki czy fotowrażliwości. Natomiast przy kombinacji inhibitorów BRAF/MEK (enkorafenib + binimetynib) odnotowuje się mniej działań niepożądanych i wysoką skuteczność leczenia (badanie COLUMBUS) [4].

Według polskich rekomendacji u pacjentów z potwierdzoną mutacją *BRAF* zalecana jest – zgodnie z wytycznymi ESMO oraz NCCN – w określonych sytuacjach klinicznych terapia skojarzona inhibitorami BRAF i MEK [1]. Od września 2020 roku w ramach programu lekowego „Leczenie czerniaka skóry lub błon śluzowych" u pacjentów z mutacją, która aktywuje *BRAF* V600, i z przerzutowym lub nieresekcyjnym czerniakiem refundowana jest terapia ukierunkowana molekularnie: enkorafenib (Braftovi) + binimetynib (Mektovi). Dodatkowo zapisy dotyczące innych połączeń BRAFi z MEKi zostały ujednolicone, co ułatwia lekarzom kwalifikację chorych do odpowiednich terapii.

Pomimo stosowania leczenia kombinowanego dwoma przeciwciałami często u chorych obserwuje się powstawanie mechanizmu oporności, a część z nich w ogóle nie odnosi korzyści z leczenia. Oznacza to, że konieczne są kolejne badania, które mogłyby pomóc w ustaleniu mechanizmów oporności [8].

NRAS

Pomimo wieloletnich badań terapia celowana w postaci bezpośrednich inhibitorów białka NRAS wciąż stanowi poważne wyzwanie, gdyż drobnocząsteczkowa GTPaza jest bardzo trudnym celem dla konwencjonalnych leków [9]. W związku z tym skupiono się na terapii ukierunkowanej na szlaki efektorowe (leżące poniżej) aktywowane przez *NRAS*: MAPK i PI3K jako najlepiej poznane w etiopatogenezie czerniaków. U pacjentów z zaawansowanym czerniakiem i mutacją *NRAS* dotychczas obiecujące wyniki uzyskano dla inhibitora MEK (MEK-162) [10]. Takich wyników nie otrzymano jeszcze dla ścieżki PI3K. Chociaż badania kliniczne nadal trwają (np. NCT03932253), wstępne dane sugerują, że terapie ukierunkowane molekularnie (inhibitory MEK1/2) staną się wkrótce dostępne dla tej podgrupy pacjentów.

KIT

Na razie przeprowadzono kilkanaście badań klinicznych dotyczących podawania różnych drobnocząsteczkowych inhibitorów KIT. Imatynib (Glivec) – początkowo stosowany przeciw fuzji BCR-ABL w przewlekłej białaczce szpikowej – okazał się także skutecznym inhibitorem KIT. Najlepszą odpowiedź obserwowano u pacjentów z mutacjami w eksonach 11 i 13 oraz amplifikacją genu.

Kolejnym inhibitorem KIT jest nilotynib (Tasigna), który ma porównywalną lub większą siłę niż imatynib. Dazatynib również wykazuje działanie przeciw mutacjom/amplifikacjom *KIT* i dodatkowo celuje w kinazy z rodziny Src. Sunitynib, który poza blokowaniem *KIT*, hamuje również receptor czynnika wzrostu śródbłonka naczyniowego (VEGFR), także został zarejestrowany do leczenia czerniaka [11]. Ponadto terapia ukierunkowana na *KIT* i szlaki leżące poniżej prawdopodobnie może pomagać w kontrolowaniu progresji nowotworu. Wykazano również, że hamowanie *KIT* przyczyniło się do wzmocnienia odpowiedzi immunologicznej. A to zwiększyło efekt przeciwnowotworowy – dzięki aktywacji limfocytów T i klonalnej ekspansji komórek cytotoksycznych, tzw. „naturalnych zabójców" (*natural killers* – NK). Wyniki badań nad terapiami z zastosowaniem inhibitorów KIT wskazują na poprawę stanu ogólnego chorych oraz wydłużenie czasu wolnego od progresji. W pojedynczych przypadkach odnotowano całkowitą remisję choroby. Jednak poprawa dotyczy jedynie części osób poddanych leczeniu. Dlatego konieczne są dalsze badania u pacjentów z mutacjami w genie *KIT* [11].

Immunoterapia

Jedną z cech charakterystycznych dla nowotworów jest ich zdolność ucieczki przed działaniem układu immunologicznego. W piśmiennictwie można znaleźć jednak opisy kilku pacjentów chorych na czerniaka, u których doszło do samoistnej aktywacji układu immunologicznego i autoregresji nowotworu [12]. Zwróciło to uwagę naukowców na potencjalne możliwości dotyczące modulacji układu immunologicznego do walki z nowotworami.

U pacjentów z nieresekcyjnym lub przerzutowym czerniakiem immunoterapia skierowana jest na inhibicję szlaku złożonego z immunologicznych punktów kontrolnych, które w warunkach fizjologicznych odpowiadają za utrzymanie homeostazy i zapobiegają reakcjom autoimmunologicznym [12] .

Pierwszym zatwierdzonym lekiem, który blokuje punkty kontrolne układu immunologicznego, był ipilimumab – przeciwciało monoklonalane przeciw cytotoksycznemu antygenowi (anty-CTLA-4 [*cytotoxic T cell antigen 4*]). CTLA-4 to antygen obecny na powierzchni aktywowanych limfocytów T, który konkuruje z CD28 o wiązanie ligandów CD80 (B 7.1) i CD 86 (B 7.2) obecnych na komórkach prezentujących antygen [13]. CD28 jest stale obecny na powierzchni limfocytów T i jako pierwszy wiąże się z CD80 i CD86. To z kolei wywołuje aktywację wewnątrzkomórkową, która prowadzi do przemieszczenia CTLA-4 na powierzchnię limfocytu. CTLA-4 wykazuje większe niż CD28 powinowactwo do ligandów CD80 i CD86. Prowadzi to do wyciszenia/wyhamowania reakcji immuno-

logicznej (ujemne sprzężenie zwrotne) [14]. Zablokowanie CTLA-4 przez ipilimumab nie doprowadza do zahamowania reakcji immunologicznej, a limfocyty T zachowują aktywność do zwalczania komórek nowotworowych. Jednak odpowiedź na leczenie ipilimumabem obserwuje się dopiero po kilku miesiącach, dlatego lek powinien być stosowany u chorych w stanie ogólnym dobrym. Ponadto odpowiedź obserwowana jest tylko u niewielkiego odsetka chorych (około 10%), a reakcje niepożądane pochodzenia immunologicznego (*immune-related adverse effects* – irAEs) są poważne. To m.in.:

- stany zapalne różnych tkanek, najczęściej skóry,
- reakcje przewodu pokarmowego (zapalenie jelit),
- zapalenie wątroby,
- endokrynopatie [15].

Znacznie mniej skutków ubocznych obserwowanych jest w immunoterapii skierowanej na punkt kontrolny programowanej śmierci, który stanowi receptor PD-1 (*programmed cell death protein 1*) obecny na limfocytach T. W warunkach fizjologicznych receptor PD-1 łączy się z ligandami PD-L1 (*programmed death-ligand 1*) i PD-L2 (*programmed death-ligand 2*) obecnymi na różnych komórkach ciała. Dzięki temu nie dochodzi do reakcji autoimmunologicznych [16, 17]. Często na powierzchni komórek nowotworowych stwierdza się nadmierną ekspresję PD-L1, co wiąże się z „ukryciem nowotworu" przed układem immunologicznym. Zablokowanie receptora PD-1 wpływa na zwiększenie aktywności limfocytów T [13].

Aktualnie w immunoterapii zaawansowanego czerniaka stosowane są dwa przeciwciała monoklonalne anty-PD-1: niwolumab oraz pembrolizumab. Zarówno dla niwolumabu jak i pembrolizumabu odnotowano statystycznie istotne wydłużenie czasu całkowitego przeżycia oraz czasu wolnego od progresji choroby u pacjentów z przerzutowym czerniakiem w porównaniu z pacjentami leczonymi ipilimumabem [16, 17]. Co ciekawe, badania retrospektywne wskazują, że pacjenci z mutacją *NRAS* uzyskują większe korzyści z immunoterapii niż pacjenci z innymi zmianami genetycznymi [18, 19]. Prawdopodobnie jest to związane ze zwiększoną ekspresją PD-L1 na powierzchni komórek nowotworowych u pacjentów z mutacją *NRAS*.

Kolejne badania kliniczne wykazały, że podwójna blokada punktów kontrolnych układu immunologicznego, czyli jednoczesne podanie ipilimumabu i niwolumabu, wydłużyła czas wolny od progresji i całkowity czas przeżycia pacjentów w porównaniu z rozłącznie stosowanymi immunoterapiami (badania Checkmate 067 i 069). Dodatkowo w leczeniu ze zredukowaną dawką ipilimumabu + pembrolizumab stwierdzono silne działanie przeciwnowotworowe, trwałą odpowiedź, korzystne długoterminowe przeżycie oraz możliwą do opanowania toksyczność (badanie KEYNOTE-029) [20–22].

W Polsce od 1 września 2020 roku refundowany jest nowy schemat terapeutyczny (tzw. *combo*) dla wybranej grupy pacjentów. Umożliwia on jednoczasowe podawanie leków niwolumab (Opdivo) + ipilimumab (Yervoy) w leczeniu skojarzonym w pierwszej linii terapii przerzutowego lub nieresekcyjnego czerniaka. Natomiast od stycznia 2021 roku w programie lekowym, w ramach leczenia adjuwantowego u pacjentów z czerniakiem w stopniu III resekcyjnym, dostępna jest immunoterapia (pembrolizumab lub niwolumab) oraz skojarzona terapia celowana z użyciem BRAFi + MEKi (dabrafenib + trametynib). Dzięki temu polscy pacjenci zyskali dostęp do najnowocześniejszej formy leczenia, która obniża ryzyko nawrotu choroby o około 20%.

Podsumowanie

Analiza genetyczna zmian somatycznych w czerniakach umożliwiła wprowadzenie personalizowanej terapii przeciw onkogenom i/lub ścieżkom przekazywania sygnałów, które są aktywowane jako wyraz utraty funkcji genów leżących nadrzędnie w danym szlaku. Najbardziej znanym celem terapii jest inhibicja *BRAF* u pacjentów z przerzutami i z mutacją aktywującą *BRAF*. Wykazano, że terapia celowana z użyciem inhibitorów BRAF ma ogromny wpływ na naturalny przebieg zaawansowanego czerniaka, co z kolei pociągnęło za sobą rozwój badań nad nowymi terapeutykami ukierunkowanymi, m.in. aktywacją naturalnych mechanizmów obronnych. Aktualnie poszukuje się leków, które zahamują równocześnie pierwotne i wtórne ścieżki aktywacji onkogenów, prowadzące do nabywania oporności w trakcie leczenia.

Konflikt interesów: nie zgłoszono

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List do Redakcji / Letter to the Editor

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Paper mill-derived cancer research: the improbability of prostate cancer in women, and ovarian and breast cancer in men

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Paper mill-derived research has penetrated biomedical literature, and it is affecting the integrity and reliability of research [1]. The use of paper mills (i.e., pay-to-create services) is an act of misconduct if the use of such services is not declared since it gives the false impression of the authors' effort, input, and originality, when in fact none was involved; moreover authorship is false since the data is created or fabricated by others, and not generated honestly in a laboratory by the authors themselves. Paper mill-derived research has itself become an academic cancer in urgent need of a cure and solutions.

Several sleuths, anonymous and named, continue to examine cancer literature, and their efforts may or may not be related to the cancer reproducibility project by the Center for Open Science. Independent of the source of these discoveries, the discoveries themselves are cause for concern and alarm. In the most recent paper mill exposé, which may or may not be related to other paper mills, three papers are highlighted in this letter: Hu et al. (2018), Pan et al. (2019), and Liu et al. (2020) [2–4]. What is curious about these papers was the discovery of breast cancer in males (Hu et al. [2]), ovarian cancer in males (Liu et al. [4]), and prostate cancer in females (Pan et al. [3]). In all three studies, genders were described as binary, i.e., exclusively biological male and female, and none of the study subjects were indicated as being transgender, which might be associated with altered hormone levels [5] and thus the possibility of confusing genders.

While it is not unusual to discover breast cancer in males, it is a very rare (about 1% of all cases of breast cancer) phenomenon [6]. Despite this, Hu et al. [2] reported a >59% incidence of breast cancer in males (38/64 subjects), apparently detected using a quantitative real-time polymerase chain reaction (qRT-PCR) with a long non-coding RNA (lncRNA), LINC01116. Not only the extremely high value, but also the fact that cases in males were higher than in females (a potentially first extraordinary finding in the cancer literature) suggest that these findings are too good to be true, or, in other words, false.

In Liu et al. [4], ovarian cancer was found in 28 males among 49 subjects, i.e., >57% incidence, as apparently detected by LINC00675, while in Pan et al. [3], prostate cancer was found in 27 females among 52 subjects, i.e., an almost 52% incidence, as apparently detected by microRNA-605-3p, both using qRT-PCR. In these cases, the incidence of ovarian cancer in males and prostate cancer in females should theoretically be 0%, since, evidently, biological males do not have an ovary while biological females do not have a prostate. Would it thus be safe to assume that these findings are either extraordinary, or that they are false? The clue may lie in the fact that Pan et al. (2019) has already been retracted for very opaque reasons. Its retracted status is (unfortunately) not – but should be – indicated on its PubMed entry.

This case also draws concern about the journal in which three papers were published – the European Review for Medical and Pharmacological Sciences – which has a 2019 Clarivate Analytics Journal Impact Factor (JIF) of 3.024 and is indexed in the Web of Science and PubMed. The fact that it is an open access journal fortifies the risk of potentially fictitious paper

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mill-derived cancer research because it is so easy to access, and thus cite. In fact, a Google Scholar search for Hu et al. (2018), Pan et al. (2019), and Liu et al. (2020) [2–4] reveals that they have been cited 44, 4, and 0 times, respectively. In the case of Pan et al. (2019), those citations could be considered to be *unfair* contributors to the journal's JIF, and the JIF itself would need to be adjusted downwards to account for the retracted paper's citations [7].

This letter provides a bird's-eye view of three papers among dozens or hundreds of papers on cancer with potentially fabricated data and findings, most likely derived from one (and the same) or more paper mills that might have served multiple clients with recycled or fabricated data, including figures, tables, and text, often confusing cancer cell lines within and among papers. Ultimately, readers are left confused, doubt regarding the validity of the findings increases, and mistrust in some of the most basic elements of *trust* in biomedical and academic publishing, such as the blind claim of the peer review, and the *quality* aspect of PubMed [8], Clarivate Analytics and the JIF, are now on the increase.

This letter has obvious limitations: it only provides a brief three-paper snapshot of a potentially far-reaching problem regarding the integrity of peer-reviewed and indexed cancer literature. This letter also focuses on one issue almost exclusively, namely the improbability of prostate cancer in women, and ovarian and breast cancer in men, or at least at the levels reported by Hu et al. (2018), Pan et al. (2019), and Liu et al. (2020) [2–4]. There are many other issues in these related papers that need to be explored and discussed.

The criminality of individuals working for and supporting paper mills, and the networks of researchers, editors, journals, and publishers that may be involved, deserves heightened awareness and further investigation.

Conflict of interest: none declared

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Leszek Miszczyk

Zdjęcie: Bogdan Łoziński

Leszek Miszczyk zginął tragicznie w wypadku drogowym 11 maja 2021 roku w drodze na konsultacje chorych w Szpitalu Chirurgii Urazowej w Piekarach Śląskich, w którym przed 25 laty utworzył Międzydyscyplinarny Zespół Guzów Kości, i którym od lat kierował.

Nagle i niespodziewanie odszedł jeden z uznanych w kraju i społeczności międzynarodowej onkologów – specjalistów radioterapii. Od ukończenia studiów nieprzerwanie pracował w gliwickim oddziale Narodowego Instytutu Onkologii im. M. Skłodowskiej-Curie. Wiedzę, doświadczenie i umiejętności w dziedzinie radioterapii doskonalił w znaczących ośrodkach europejskich i amerykańskich. Był m.in. uczniem prof. Emmanuela van der Schuerena w Leuven, twórcy nowoczesnej radioterapii. Przeszedł wszystkie kolejne etapy awansu zawodowego i naukowego. W 2008 roku uzyskał tytuł dr hab. n. med. Od ponad 20 lat kierował Zakładem Radioterapii gliwickiego oddziału Instytutu Onkologii. W połowie lat 90. został powołany przez Międzynarodową Agencję Energii Atomowej w Wiedniu na eksperta i organizatora szkoleń z zakresu radioterapii dla lekarzy z krajów Afryki, Ameryki Południowej i Azji.

Leszek Miszczyk był autorem ponad 170 prac naukowych opublikowanych w recenzowanych krajowych i anglojęzycznych periodykach naukowych, w około połowie będących na Liście Filadelfijskiej. Wygłosił ponad 200 wykładów podczas licznych konferencji i zjazdów międzynarodowych.

Najważniejszym elementem całej jego działalności naukowej był fakt, że wszystkie jego badania dotyczyły klinicznej radioterapii i poszukiwania coraz bardziej skutecznych metod leczenia. Chory na nowotwór był jego głównym obiektem zainteresowania. Wdrożył do praktyki wiele nowoczesnych metod radioterapii. Zainicjował i wdrożył dozymetrię *in vivo* w realizację radioterapii, nowoczesne techniki radioterapii 3D, radioterapię stereotaktyczną, nóż cyfrowy. Wykorzystywał radioterapię w leczeniu wielu nowotworów. Był pionierem w zastosowaniu radioterapii w leczeniu choroby Parkinsona. Zresztą w zakresie radioterapii nienowotworowej był jednym z kilku światowych liderów.

Te wszystkie fakty nie oddają jednak w pełni osobowości Leszka Miszczyka (nie przywiązywał wagi do tytułów poprzedzających jego nazwisko). Był on przede wszystkim człowiekiem niezmiennie i niezłomnie prawym. Wprawdzie nie należał do zbyt rozmownych, ale wyróżniała go empatia wobec każdego, nie tylko współpracowników. Nigdy nikomu, kto się do niego zwrócił, nie odmówił rady lub pomocy. Był nie tylko szanowany, ale ważniejsze – ogromnie lubiany. Dla nas to niepowetowana strata, że tak wspaniałego człowieka nie ma już wśród nas.

Bogusław Maciejewski i przyjaciele

Z kalendarium Zarządu PTO

maj – czerwiec 2021

V Kongres Onkologii Polskiej

Trwa rejestracja na V Kongres Onkologii Polskiej. Komitet naukowy wprowadza ostatnie poprawki w programie. Zaplanowano wykłady wybitnych ekspertów z zagranicy oraz z Polski. Zachęcamy do udziału.

Szczegóły na stronie www.kongres.pto.med.pl.

Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy rozpoczął współpracę z Instytutem Curie w Paryżu

27 maja 2021 roku została zawarta umowa o współpracy naukowo-badawczej łącząca dwa Instytuty Curie: Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie – Państwowy Instytut Badawczy w Warszawie oraz Instytut Curie w Paryżu. Głównym celem współpracy jest wymiana doświadczeń oraz promowanie wysokiej jakości badań naukowych, które są podstawą rozwoju onkologii.

Szczegóły na stronie www.pib-nio.pl.

Pilotaż Krajowej Sieci Onkologicznej realizowany przez Dolnośląskie Centrum Onkologii zajął II miejsce w międzynarodowym konkursie *Value Based Health Care Grants & Endorsement 2021* w kategorii *Endorsment*.

Do konkursu zgłoszono kilkanaście projektów z całej Europy. Z Polski – dwa: pilotaż Krajowej Sieci Onkologicznej oraz pomorski model zintegrowanej opieki dla chorych na zaawansowaną POChP. Pierwsze miejsce zajęło rozwiązanie holenderskie dotyczące opieki okulistycznej. Wśród projektów poświęconych onkologii pilotaż Krajowej Sieci Onkologicznej oceniono najwyżej z całej Europy.

Szczegóły na stronie www.pto.med.pl.

Wywiady i artykuły

Warszawski Instytut Radowy – promienny pomysł Marii Skłodowskiej-Curie

29 maja 1932 w Warszawie przy ulicy Wawelskiej otwarto Instytut Radowy, który powstał z inicjatywy polskiej noblistki. Ambitną koncepcję Skłodowskiej-Curie udało się zrealizować dzięki hojności Polaków. Pierwszym dyrektorem placówki został dr med. Franciszek Łukaszczyk – funkcję tę pełnił aż do swojej śmierci w 1956 roku. W momencie otwarcia instytut dysponował pięcioma aparatami rentgenowskimi. Do końca 1933 roku do szpitala przyjęto na leczenie około siedmiuset osób.

Źródło: Polskie Radio

Prof. Krzakowski: Bez współpracy z radiologami nie ma mowy o skutecznym leczeniu raka płuca

Rośnie rola radiologów w leczeniu onkologicznym. Prof. Maciej Krzakowski podkreśla, że dobra współpraca specjalistów w tych dziedzinach – i to na każdym etapie: diagnostyki, leczenia i monitorowania efektów – jest podstawą skutecznej terapii.

– Bez współpracy z radiologami, my, onkolodzy, nie będziemy w stanie sobie poradzić i skutecznie leczyć raka płuca – przyznaje prof. dr hab. n. med. Maciej Krzakowski, konsultant krajowy w dziedzinie onkologii klinicznej.

Źródło: Termedia

Gliwicki Instytut Onkologii w europejskim badaniu leczenia arytmii radioterapią

Oddział Narodowego Instytutu Onkologii w Gliwicach jest jednym z inicjatorów powstania międzynarodowego konsorcjum *STOPSTORM*, które zweryfikuje skuteczność leczenia arytmii serca za pomocą radioterapii. Gliwicki ośrodek ma już sukcesy w leczeniu chorych na serce za pomocą promieniowania.

Źródło: Radio Opole

O pieniądzach, koordynacji i karcie DiLO, a to wszystko w dobie pandemii, mówi dr hab. n. med. Adam Maciejczyk, prezes Polskiego Towarzystwa Onkologicznego, dyrektor Dolnośląskiego Centrum Onkologii

– Obecnie na pierwszy plan zaczyna wysuwać się problem niedofinansowania onkologii. Przez wiele lat była ona słabo wyceniana, a pandemia ten problem jeszcze pogłębiła. Wzrosły koszty utrzymania placówek. Obostrzenia sanitarne spowodowały wzrost kosztów ochrony osobistej, a podwyżki minimalnego wynagrodzenia i wydłużenie realizacji procedur z powodu reżimu sanitarnego podniosły koszty realizowanych świadczeń. Niestety, nowe wyceny części procedur nie zrekompensowały strat. Niektóre procedury nadal są niedoszacowane nawet o kilkadziesiąt procent, np. biopsja prostaty z wykorzystaniem fuzji z MRI, cystoskopia czy badanie MRI piersi. Część procedur na ścieżce pacjenta nie jest w ogóle refundowana, np.

biopsja piersi pod kontrolą MRI. Największy problem dotyczy finansowania zabiegów chirurgicznych, szczególnie w urologii. Taka sytuacja sprzyja brakowi zainteresowania procedurami nisko wycenianymi. Centra onkologii wykonują kompleksowo zabiegi we wszystkich zakresach, nawet tych, które przynoszą straty, dlatego najdotkliwiej odczuwają niedofinansowanie.

Źródło: Termedia

Prof. Krzakowski: epidemia dodatkowo zaburzyła proces przedłużającej się diagnostyki raka

Problemem obecnej onkologii, także płucnej, jest „przewlekająca się diagnostyka", a pandemia COVID-19 dodatkowo pogłębiła ten stan. Krzakowski zauważył, że „procesy diagnostyczne w onkologii, a w przypadku raka płuca w szczególności, powinny być zreformowane" niezależnie od istnienia pandemii. Ponadto mamy w Polsce ośrodki, które „diagnozują, ale nie leczą", a „w ośrodkach, które leczą, często brakuje dostępności wszystkich metod leczenia".

Źródło: Rynek Zdrowia

Akademia Czerniaka obchodzi jubileusz 10-lecia działalności

Zmniejszenie poziomu zachorowalności i śmiertelności spowodowanych czerniakiem to główne cele Akademii Czerniaka – sekcji naukowej Polskiego Towarzystwa Chirurgii Onkologicznej – obowiązujące od początku jej istnienia. Prof. Piotr Rutkowski podkreśla, że Akademia Czerniaka przyczyniła się do tych wielkich zmian. Była inicjatorem wielu działań w zakresie promocji profilaktyki czerniaka.

– Nie spoczywamy na laurach, zamierzamy z niesłabnącym zaangażowaniem kontynuować dzieło akademii przy wsparciu wszystkich tych, którzy chcą się przyczynić do zmniejszenia liczby zachorowań i umieralności na czerniaki. W końcu życie mamy jedno, dlatego musimy o nie dbać – dodaje prof. Piotr Rutkowski.

Źródło: Termedia

Rak pęcherza. Prof. Fijuth: „To brzydkie kaczątko wśród nowotworów"

Problem z rakiem pęcherza moczowego nie tylko w Polsce, ale również na świecie jest taki, że ten nowotwór jest rozpoznawany w późnych stadiach zaawansowania. Pewnie dlatego, że na początku ma skąpoobjawowy a wręcz bezobjawowy przebieg, a choroba ujawnia się dopiero, gdy jest już zaawansowana.

Źródło: Radio Zet

Konferencje i wydarzenia z udziałem członków Zarządu Głównego PTO

- 11 maja 2021 r. odbyła się konferencja *Wizjonerzy zdrowia 2021, Przyszłość ochrony zdrowia w Polsce 2021–23*. W jej trakcie Dolnośląskie Centrum Onkologii kierowane przez dr. hab. Adama Maciejczyka, otrzymało nagrodę *Wizjonerskie Rozwiązania w Medycynie* za „przekierowanie" systemu ochrony zdrowia na pacjenta, odwagę we wdrażaniu kompleksowych rozwiązań organizacyjnych i nowych technologii, prowadzanie pilotażu Krajowej Sieci Onkologicznej. Dzięki pilotażowi pacjent onkologiczny nie jest zagubiony w systemie ochrony zdrowia, kontrolowana jest jakość wykonywanych badań histopatologicznych i radiologicznych, wprowadzane są ścieżki diagnostyki i leczenia. Doświadczenia z pilotażu będą wykorzystywane przy wprowadzaniu Krajowej Sieci Onkologicznej w całej Polsce.
- W dniach 17–18 maja 2021 r. miała miejsce konferencja *Priorities and challenges in Polish and European drug policy*. W panelu *Zdrowie kobiety – diagnostyka i dostęp do leczenia chorób nowotworowych* udział wziął dr hab. Adam Maciejczyk, prezes PTO.
- 18 maja 2021 r. zorganizowano V Ogólnopolską Konferencję *Ewidencja świadczeń zdrowotnych podstawą bezpieczeństwa prawno-finansowego placówki medycznej*, w której wzięli udział prof. dr hab. Stanisław Góźdź oraz dr hab. Adam Maciejczyk. Wystąpili w panelu *Krajowa Sieć Onkologiczna. Założenia i praktyczna realizacja opieki koordynowanej w Polsce*.
- 9 czerwca 2021 r. odbyła się konferencja *Szczyt ochrony zdrowia*. W panelu *Przełomowe terapie w onkologii* uczestniczył dr hab. Adam Maciejczyk. Pełny zapis ze spotkania znajduje się na stronie www.medexpress.pl.
- W dniach 14–16 czerwca 2021 r. zorganizowano *VI Kongres Wyzwań Zdrowotnych*, w ramach którego odbył się panel *Onkologia w Polsce – sesja systemowa*. Wziął w nim udział dr hab. Adam Maciejczyk. Podczas dyskusji na temat Krajowej Sieci Onkologicznej zaznaczył, że w raporcie końcowym z pilotażu KSO znajdą się rekomendacje dotyczące mierzenia jakości w onkologii. Chodzi o to, aby bazować np. na miernikach szkockich, które pozwolą na porównanie wyników naszych szpitali z wynikami innych tego typu placówek w Europie.
- 22 czerwca 2021 r. miało miejsce spotkanie ekspertów *Było. Jest. Będzie?* o błędach przeszłości, wyzwaniach teraźniejszości i perspektywach na przyszłość w systemie ochrony zdrowia w kontekście wynagrodzeń lekarzy oraz innych pracowników ochrony zdrowia. Spotkanie zorganizowała Okręgowa Rada Lekarska. Uczestniczył w nim dr hab. Adam Maciejczyk.
- – Bliskie jest mi podejście do wynagrodzenia złożonego z bazy i elementu motywacyjnego – powiedział. Skuteczność tego rozwiązania udowadniał przykładem z własnej placówki. – Gdy ustandaryzowaliśmy zadania patomorfologów, ich praca stała się łatwiejsza, ale też bardziej przejrzysty stał się ich system wynagradzania. Wiedzieliśmy, za co płacimy – wyjaśnił.

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Idecabtagene vicleucel in relapsed and refractory multiple myeloma

Munshi N., Anderson L., Jr., Shah N. i wsp.
N. Engl. J. Med., 2021; 384: 705–716

Idecabtagene vicleucel (*ide-cel*, nazywany również bb2121), zawierający limfocyty T z chimerycznym receptorem antygenowym (*chimeric antygen receptor* – CAR), ukierunkowanym na dojrzewanie komórek B, wykazał kliniczną aktywność u chorych na nawrotowego lub opornego szpiczaka plazmocytowego, bez niespodziewanych działań niepożądanych.

Metody. Do badania II fazy oceniającego skuteczność i bezpieczeństwo *ide-cel* włączono chorych na aktywnego nawrotowego lub opornego szpiczaka plazmocytowego, po przynajmniej 3 liniach leczenia, w tym inhibitorem proteasomu, lekami immunomodulującymi i przeciwciałem anty-CD38. Chorzy otrzymali docelową dawkę *ide-cel* 150×10^6 do 450×10^6 CAR-dodatnich komórek T. Pierwszorzędowym punktem końcowym był udział odpowiedzi na leczenie (co najmniej częściowa odpowiedź), a drugorzędowym – udział całkowitych odpowiedzi.

Wyniki. *Ide-cel* otrzymało 128 spośród 140 chorych włączonych do badania. Po 13,3-miesięcznej medianie obserwacji u 94 spośród 128 chorych (73%) stwierdzono odpowiedź na leczenie, u 42 spośród 128 (33%) była to odpowiedź całkowita lub lepsza. Minimalnej choroby resztkowej (*minimal* residual disease – MRD) czyli $<10^{-5}$ komórek jądrowych) nie stwierdzono u 33 chorych, co odpowiadało 26% spośród 128 wszystkich chorych poddanych leczeniu i 79% spośród 42 chorych z odpowiedzią całkowitą lub lepszą. Mediana czasu wolnego od progresji wynosiła 8,8 miesiąca (95% przedział ufności [*confidence interval* – CI] 5,6–11,6). Do częstych działań niepożądanych należały: neutropenia u 117 chorych (91%), niedokrwistość u 89 (70%) i małopłytkowość u 81 (63%). Zespół uwalniania cytokin zaobserwowano u 107 chorych (84%), w tym u 7 (5%) miał on nasilenie 3. lub wyższego stopnia. Toksyczność neurologiczną stwierdzono u 23 chorych (18%), w tym u 4 chorych (3%) była ona w stopniu 3., nie wystąpiła toksyczność neurologiczna wyższego stopnia. Analiza kinetyki komórkowej potwierdziła obecność komórek CART u 29 spośród 49 chorych (59%) w 6. miesiącu i u 4 spośród 11 chorych (36%) w 12. miesiącu od podania leku.

Wnioski. Zastosowanie *Ide-cel* wiązało się z odpowiedzią na leczenie u większości chorych na nawrotowego lub opornego szpiczaka plazmocytowego po kilku wcześniejszych liniach leczenia, w tym u 26% leczonych chorych nie stwierdzono MRD. U większości chorych wystąpiła toksyczność 3. i 4. stopnia, głównie hematologiczna, oraz zespół uwalniania cytokin.

Genome sequencing as an alternative to cytogenetic analysis in myeloid cancers

Duncavage E., Schroeder M., O'Laughlin M. i wsp.
N. Engl. J. Med., 2021; 384: 924–935

Analiza genomu ma istotne znaczenie podczas oceny ryzyka u chorych na ostrą białaczkę szpikową (*acute myeloid leukemia* – AML) i zespół mielodysplastyczny (*myelodysplastic syndrome* – MDS). Sekwencjonowanie całego genomu mogłoby potencjalnie zastąpić standardowe sekwencjonowanie i badanie cytogenetyczne, ale jego dokładność, wykonalność i użyteczność kliniczna nie była dotychczas badana.

Metody. Przeprowadzono sekwencjonowanie całego genomu u 263 chorych na nowotwory mieloidalne, w tym u 235 posiadających wynik badania cytogenetycznego. przygotowanie próbek, sekwencjonowanie i analizę mutacji dostosowano do istniejących wytycznych Europejskiej Sieci Białaczkowej (European Leukemia Network – ELN) w celu określenia ryzyka i zminimalizowano czas realizacji wymienionych procedur. Oceniono sekwencjonowanie całego genomu i porównano wyniki badania cytogenetycznego i celowanego sekwencjonowania.

Wyniki. Za pomocą sekwencjonowania całego genomu wykryto 40 translokacji i 91 zmienności liczby kopii, znalezionych wcześniej w badaniu cytogenetycznym. Dodatkowo u 40 spośród 235 chorych (17%) znaleziono nowe zaburzenia molekularne. Mediana czasu prospektywnego sekwencjonowania próbek uzyskanych od 117 chorych wynosiła 5 dni. Sekwencjonowanie dostarczyło nowych informacji genetycznych u 29 chorych (24,8%), a zmieniło grupę ryzyka u 19 (16,2%). Określona przez sekwencjonowanie genomu zamiast badania cytogenetycznego standardowa grupa ryzyka AML wiązała się z wynikami klinicznymi. Sekwencjonowania całego genomu użyto również do określenia ryzyka u chorych, u których wyniki badania cytogenetycznego nie były spójne z wynikami klinicznymi.

Wnioski. Sekwencjonowanie całego genomu zapewnia szybkie i dokładne profilowanie genomowe u chorych na AML i MDS. Takie sekwencjonowanie zapewnia również większe możliwości diagnostyczne niż badania cytogenetyczne i bardziej skuteczne zróżnicowanie na podstawie standardowych kategorii.

Vemurafenib plus rituximab in refractory or relapsed hairy-cell leukemia

Tiacci E., De Carolis L., Simonetti E., i wsp.
N. Engl. J. Med., 2021; 384: 1810–1823

Białaczka włochatokomórkowa (*hairy cell leukemia* – HCL) jest nowotworem z indolentnych C20-dodatnich komórek B, w którym znaczącą rolę odgrywa mutacja aktywująca kinazę *BRAF* V600E. W badaniach klinicznych zastosowanie doustnego inhibitora *BRAF*, celowanego na mutację *BRAF* V600E – wemurafenibu – prowadziło do odpowiedzi u 91% chorych na oporną lub nawrotową HCL, w tym u 35% do całkowitej odpowiedzi, ale po zakończeniu leczenia, mediana czasu wolnego od nawrotu wynosiła tylko 9 miesięcy.

Metody. W jednoośrodkowym badaniu II fazy oceniono bezpieczeństwo i skuteczność wemurafenibu (960 mg dwa razy dziennie przez 8 tygodni) z jednoczasowym lub sekwencyjnym stosowaniem rytuksymabu (375 mg/m^2; 8 dawek przez 18 tygodni) u chorych na oporną lub nawrotową HCL. Pierwszorzędowym punktem końcowym był udział całkowitych odpowiedzi po zakończeniu leczenia.

Wyniki. Mediana poprzednich linii leczenia wyniosła 3. Wśród 30 chorych na HCL włączonych do badania, całkowitą odpowiedź stwierdzono u 26 (87%) w grupie zgodnej z zamiarem leczenia. Wszyscy chorzy na HCL oporną na chemioterapię (10 chorych) lub na rytuksymab (5) oraz poprzednio leczeni inhibitorami *BRAF* (7) uzyskali całkowitą odpowiedź. Mediana czasu do ustąpienia małopłytkowości wyniosła 2 tygodnie, a neutropenii – 4 tygodnie. U 17 spośród 26 chorych (65%), u których stwierdzono całkowitą odpowiedź, nie wykazano minimalnej choroby resztkowej (MRD). Po medianie obserwacji wynoszącej 37 miesięcy udział przeżyć wolnych od progresji wśród 30 chorych stanowił 78%, a wśród 26 chorych z odpowiedzią po medianie obserwacji 34 miesięcy – 85%. W analizie *post-hoc*, brak MRD i brak wcześniejszego leczenia inhibitorami *BRAF* wiązały się z dłuższym przeżyciem wolnym od nawrotu białaczki. Działania niepożądane, głównie w stopniu 1. i 2., były podobne do wcześniej opisywanych dla zastosowanych leków.

Wnioski. W małym badaniu, krótkie, wolne od chemioterapii, niemielotoksyczne leczenie wemurafenibem z rytuksymabem wiązało się z uzyskaniem trwałych całkowitych odpowiedzi u większości chorych na oporną lub nawrotową HCL.

[^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial

Hofman M.S., Emmett L., Sandhu S. i wsp.
Lancet, 2021; 397: 797–804

Swoisty błonowy antygen sterczowy (*prostate specific membrane antigen* – PSMA) znakowany lutetem 177 ([^{177}Lu]Lu-PSMA-617) to mała radioaktywnie znakowana cząsteczka, dostarczająca promieniowanie β do komórek z ekspresją antygenu błonowego swoistego dla gruczołu krokowego. Jest to bezpieczny i aktywny lek stosowany u chorych na rozsianego raka gruczołu krokowego opornego na kastrację. Celem badania było porównanie [^{177}Lu]Lu-PSMA-617 z kabazytakselem w tej grupie chorych.

Metody. Do wieloośrodkowego otwartego badania II fazy prowadzonego w 11 ośrodkach w Australii włączono chorych na rozsianego raka gruczołu krokowego opornego na kastrację, z odpowiednią czynnością nerek, szpiku kostnego i wątroby, w stopniu sprawności 0–2 według Eastern Cooperative Oncology Group, u których planowano podanie w kolejnej linii standardowego leczenia kabazytakselu. Dozwolone było wcześniejsze leczenie blokujące receptor androgenowy. Wykonywano badanie PET-TK z użyciem PSMA znakowanego galem [^{68}Ga-PSMA-11] i fluorodeoksyglukozą (^{18}F-FDG). Kryterium włączenia do badania była potwierdzona w PET-PSMA obecność rozsianej choroby, a kryterium wyłączenia sprzeczne wyniki badań obrazowych (obecność zmian FDG-dodatnich i PSMA-ujemnych). Chorych przydzielano losowo (w stosunku 1:1) do leczenia [177Lu]Lu-PSMA-617 (6,0–8,5 GBq dożylnie co 6 tygodni do 6 cykli) lub do leczenia kabazytakselem (20 mg/m^2 dożylnie co 3 tygodnie do 10 cykli). Pierwszorzędowym punktem końcowym było zmniejszenie stężenia antygenu swoistego dla gruczołu krokowego (*prostate-specific antigen* – PSA) o co najmniej 50% w stosunku do wartości wyjściowej.

Wyniki. Od 6 lutego 2018 roku do 3 września 2019 roku spośród 291 chorych poddanych badaniom przesiewowym PET włączono do badania 200 mężczyzn. Leczeniu poddano 98 spośród 99 (99%) losowo przydzielonych do [^{177}Lu]PSMA-617 oraz 85 spośród 101 (84%) losowo przydzielonych do leczenia kabazytakselem. Obniżenie stężenia PSA częściej obserwowano wśród leczonych [^{177}Lu]Lu-PSMA-617 w porównaniu z leczonymi kabazytakselem (65% *vs.* 37%; 66% *vs.* 37% w grupie zgodnej z zamiarem leczenia, różnica 29% [95% CI 16–42; p < 0,0001]; 66% *vs.* 44% w grupie zgodnej z protokołem, różnica 23% [9–37; p = 0,0016]). Zdarzenia niepożądane 3.–4. stopnia wystąpiły u 32 spośród 98 chorych (33%) leczonych [^{177}Lu]Lu-PSMA-617 w porównaniu z 45 spośród 85 (53%) leczonych kabazytakselem. Nie stwierdzono zgonów związanych ze stosowaniem [^{177}Lu]Lu-PSMA-617.

Wnioski. Użycie [^{177}Lu]Lu-PSMA-617 wiązało się z lepszą odpowiedzią wyrażoną stężeniem PSA i mniejszą liczbą zdarzeń niepożądanych 3. lub 4. stopnia u chorych na rozsianego raka gruczołu krokowego opornego na kastrację w porównaniu ze stosowaniem kabazytakselu. [^{177}Lu]Lu-PSMA-617 to nowa skuteczna opcja leczenia i potencjalna alternatywa dla kabazytakselu.

A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial

Pal S. K., Tangen C., Thompson I. M., Balzer-Haa's N. i wsp.
Lancet, 2021; 397: 695–703

Sygnalizacja *MET* (znanego również jako receptor czynnika wzrostu hepatocytów) jest ważnym czynnikiem rozwoju brodawkowatego raka nerkowokomórkowego (*papillary renal cell carcinoma* – PRCC). Poszukując najlepszego sposobu leczenia chorych na PRCC, porównano istniejący standard – leczenie sunitynibem, z inhibitorami kinazy MET: kabozantynibem, kryzotynibem i sawolitynibem.

Metody. W otwartym badaniu II fazy prowadzonym w 65 ośrodkach w USA i Kanadzie chorych na rozsianego PRCC (w wieku co najmniej 18 lat) którzy przebyli co najmniej jedną linię leczenia (z wyłączeniem leków ukierunkowanych na czynnik wzrostu śródbłonka naczyniowego i *MET*) przydzielano losowo do jednej z 4 grup: otrzymujących sunitynib, kabozantynib, kryzotynib lub sawolitynib, ze stratyfikacją według wcześniejszego leczenia i podtypu PRCC. Wszystkie leki podawano doustnie: sunitynib 50 mg przez 4 tygodnie z 2-tygodniową przerwą (dozwolone zmniejszenie dawki do 37,5 mg i 25 mg), kabozantynib 60 mg dziennie (dozwolone zmniejszenia dawki do 40 mg i 20 mg), kryzotynib 250 mg dwa razy na dobę (dozwolone zmniejszenie do 200 mg dwa razy na dobę i 250 mg raz na dobę) oraz sawolitynib 600 mg na dobę (dozwolone zmniejszenia dawki do 400 mg i 200 mg). Pierwszorzędowym punktem końcowym był czas wolny od progresji (*progression-free survival* – PFS). Analizy przeprowadzono w grupie zgodnej z intencją do leczenia. Z analiz bezpieczeństwa wykluczono chorych, którzy nie otrzymali leczenia zgodnie z protokołem.

Wyniki. Od 5 kwietnia 2016 roku do 15 grudnia 2019 roku 152 chorych przydzielono losowo do leczenia; pięciu chorych nie spełniło kryteriów włączenia, toteż do analiz włączono 147 chorych. Przydział do grup z sawolitynibem (29 chorych) i kryzotynibem (28 chorych) został wstrzymany po wcześniej określonej analizie daremności, planowany nabór został zrealizowany zarówno dla grupy leczonej sunitynibem (46 chorych) i kabozantynibem (44 chorych). W grupie leczonej kabozantynibem PFS był dłuższy (mediana 9,0 miesiąca, 95% CI 6–12) niż w grupie sunitynibu (5,6 miesiąca, 3–7; współczynnik ryzyka progresji lub zgonu wynosił 0,60, [0,37–0,97]; jednostronne p = 0,019). Udział odpowiedzi wyniósł 23% dla leczonych kabozantynibem w porównaniu z 4% wśród leczonych sunitynibem (dwustronne p = 0,010). Sawolitynib i kryzotynib nie wydłużyły PFS w porównaniu z sunitynibem. Zdarzenia niepożądane 3. lub 4. stopnia wystąpiły u 31 spośród 45 (69%) otrzymujących sunitynib, u 32 spośród 45 (74%) otrzymujących kabozantynib, dziesięciu spośród 27 (37%) otrzymujących kryzotynib oraz 11 spośród 28 (39%) otrzymujących sawolitynib; w grupie leczonej kabozantynibem wystąpiło jedno zdarzenie zakrzepowo-zatorowe stopnia 5.

Wnioski. Leczenie kabozantynibem znamiennie wydłużyło PFS u chorych na rozsianego PRCC w porównaniu ze stosowaniem sunitynibu.

Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma

Bajorin D., Witjes J.A, Gschwend J.E. i wsp.
N. Engl. J. Med., 2021; 384: 2102–2114

Rola leczenia uzupełniającego u chorych na raka pęcherza moczowego naciekającego błonę mięśniową jest niejasna.

Metody. W wieloośrodkowym, podwójnie zaślepionym, badaniu III fazy z grupą kontrolną przeprowadzonym z udziałem chorych na raka pęcherza moczowego naciekającego błonę mięśniową po doszczętnym zabiegu operacyjnym, uczestników badania przydzielano losowo (w stosunku 1:1) do leczenia niwolumabem (240 mg dożylnie) lub placebo podawanych co 2 tygodnie do roku. Chorzy mogli być poddawani przedoperacyjnej chemioterapii opartej na cisplatynie. Pierwszorzędowym punktem końcowym było przeżycie wolne od choroby wśród wszystkich chorych (grupa zgodna z zamiarem leczenia) oraz wśród chorych z ekspresją co najmniej 1% liganda programowanej śmierci 1 (PDL-1). Drugorzędowym punktem końcowym był czas wolny od nawrotu poza układem moczowym.

Wyniki. Łącznie 353 chorych przydzielono do leczenia niwolumabem, a 356 do grupy otrzymującej placebo. Mediana przeżycia wolnego od choroby w grupie zgodnej z zamiarem leczenia wyniosła 20,8 miesięcy (95% CI 16,5–27,6) wśród leczonych niwolumabem i 10,8 miesięcy (95% CI 8,3–13,9) w grupie placebo. Udział 6-miesięcznych przeżyć wolnych od nawrotu wyniósł 74,9% wśród leczonych niwolumabem i 60,3% w grupie otrzymujących placebo (współczynnik ryzyka nawrotu lub zgonu 0,70; 98,22% CI 0,55–0,90; p < 0,001), a wśród chorych z ekspresją PDL-1 co najmniej 1% – odpowiednio 74,5% i 55,7% (współczynnik ryzyka 0,55; 98,72% CI 0,35–0,85; p < 0,001). Mediana przeżycia wolnego od nawrotu poza układem moczowym w grupie zgodnej z zamiarem leczenia wyniosła 22,9 miesięcy (95% CI 19,2–33,4) wśród leczonych niwolumabem i 13,7 miesięcy (95% CI 8,4–20,3) w grupie placebo. Udział 6-miesięcznych przeżyć bez nawrotu choroby poza układem moczowym wyniósł 77% dla leczonych niwolumabem i 62,7% w grupie otrzymującej placebo (współczynnik ryzyka nawrotu poza układem moczowym lub zgonu 0,72; 95% CI 0,59–0,89), a wśród chorych z ekspresją PDL-1 co najmniej 1% – odpowiednio 75,3% i 56,7% (współczynnik ryzyka 0,55; 95% CI 0,39–0,79). Działania niepożądane związane z leczeniem w stopniu 3. zaobserwowano u 17,9% chorych w grupie z niwolumabem i 7,2% w grupie placebo. Stwierdzono dwa zgony związane z zapaleniem płuc w przebiegu leczenia niwolumabem.

Wnioski. U chorych na raka pęcherza moczowego naciekającego błonę mięśniową po doszczętnym zabiegu operacyjnym przeżycie wolne od choroby było dłuższe wśród leczonych niwolumabem zarówno w grupie leczonej zgodnie z zamiarem leczenia, jak i u chorych z co najmniej 1% ekspresją PD-L1.

^{18}F-fluciclovine-PET/CT imaging versus conventional imaging alone to guide postprostatectomy salvage radiotherapy for prostate cancer (EMPIRE-1): a single centre, open-label, phase 2/3 randomised controlled trial

Jani A., Schreibmann E., Goyal S. i wsp.
Lancet, 2021; 397: 1895–1904

Obrazowanie molekularne jest coraz częściej wykorzystywane w podejmowaniu decyzji terapeutycznych i planowaniu leczenia raka gruczołu krokowego. Oceniono wpływ PET-TK z zastosowaniem flucyklowiny (^{18}F) na poprawię kontroli choroby nowotworowej po zastosowaniu ratującej pooperacyjnej radioterapii w porównaniu z zastosowaniem standardowego obrazowania (scyntygrafia kości i TK lub MRI).

Metody. W jednoośrodkowym otwartym badaniu II/III fazy EMPIRE-1 chorych na raka gruczołu krokowego z oznaczalnym stężeniem PSA po prostatektomii, bez nawrotu w standardowym obrazowaniu (bez przerzutów w obrębie kości lub poza miednicą), przydzielano losowo (w stosunku 1:1) do radioterapii po standardowym obrazowaniu lub do dodatkowego badania PET-TK z flucyklowiną (^{18}F). Randomizacja była stratyfikowana według wartości stężenia PSA, niekorzystnych cech histopatologicznych i intencji leczenia przeciwandrogenowego. W grupie z PET-TK z flucyklowiną (^{18}F) decyzja odnośnie do zastosowania radioterapii zależała od wyniku PET-TK, również w zakresie wyznaczania obszarów do napromieniania. Pierwszorzędowym punktem końcowym był udział 3-letnich przeżyć wolnych od zdarzeń (klinicznego lub biochemicznego nawrotu, progresji lub do rozpoczęcia leczenia systemowego).

Wyniki. Od 18 września 2012 roku do 4 marca 2019 roku przydzielono losowo do leczenia z medianą obserwacji 3,52 lat (95% CI 2,98–3,95) 165 chorych. Po otrzymaniu wyników PET-TK z flucyklowiną (^{18}F) odstąpiono od radioterapii u 4 chorych, których wyłączono z analizy przeżycia. Mediana czasu przeżycia nie została osiągnięta w żadnej z grup (w grupie poddawanej standardowemu obrazowaniu [95% CI 35,2–nie osiągnięto] zdarzenia wystąpiły u 33% spośród 81 chorych w porównaniu z 20% spośród 76 chorych w grupie, w której obrazowania dokonywano za pomocą z PET-TK z flucyklowiną [95% CI nie osiągnięto]). Udział 3-letnich przeżyć wolnych od zdarzeń wyniósł 63% (95% CI 49,2–74,0) w grupie standardowego obrazowania w porównaniu z 75,5% (95% CI 62,5–84,6) w grupie PET-TK z flucyklowiną (różnica 12,5; 95% CI 4,3–20,8; p = 0,0028). W skorygowanej analizie grupa badana (współczynnik ryzyka 2,04 [95% CI 1,06–3,93], p = 0,0327) charakteryzowała się znamiennie dłuższym czasem przeżycia wolnego od zdarzeń. Toksyczność była podobna w obu grupach, najczęstszym działaniem niepożądanym był częstomocz lub nagłe parcie na mocz (37 spośród 81 chorych [46%] w grupie w której stosowano standardowe obrazowanie i 31 spośród 76 chorych [41%] w grupie, w której wykorzystano PET-TK) oraz ostra biegunka (11 [14%] w grupie ze standardowym obrazowaniem i 16 [21%] w grupie z PET-TK).

Wyniki. Dołączenie badania PET-TK z flucyklowiną (^{18}F) u chorych po prostatektomii zakwalifikowanych do radioterapii znacząco poprawiło przeżycie wolne od biochemicznej progresji. Wykorzystanie nowych radioznaczników w badaniu PET-TK w podejmowania decyzji i planowaniu radioterapii wymaga dalszych badań.

Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial

Moreau P., Dimopoulos M.-A., Mikhael J. i wsp.
Lancet, 2021; 397: 2361–2371

Izatuksymab jest przeciwciałem monoklonalnym przeciw-CD38 zatwierdzonym w połączeniu z pomalidomidem i deksametazonem oraz z karfilzomibem i deksametazonem u chorych na nawrotowego lub opornego na leczenie szpiczaka mnogiego. W otwartym badaniu III fazy porównano skuteczność izatuksymabu w skojarzeniu z karfilzomibem i deksametazonem oraz stosowanego wyłącznie karfilzomibu z deksametazonem u chorych na nawrotowego szpiczaka mnogiego.

Metody. W prospektywnym otwartym badaniu III fazy w grupach równoległych, przeprowadzonym w 69 ośrodkach badawczych w 16 krajach w Ameryce Północnej, Ameryce Południowej, Europie i regionie Azji i Pacyfiku, chorych na nawrotowego lub opornego na leczenie szpiczaka mnogiego w wieku co najmniej 18 lat, po uprzednim leczeniu (od jednej do trzech linii leczenia), z mierzalnym białkiem M w surowicy lub w moczu, przydzielano losowo (w stosunku 3:2) dostosowania izatuksymabu z karfilzomibem i deksametazonem (grupa izatuksymabu) lub karfilzomibu z deksametazonem (grupa kontrolna). Chorzy w grupie badanej otrzymywali izatuksymab w dawce 10 mg/kg mc. dożylnie co tydzień przez pierwsze 4 tygodnie, a następnie co 2 tygodnie. Obie grupy otrzymały zatwierdzony schemat dożylnego podawania karfilzomibu i doustnego lub dożylnego deksametazonu. Leczenie kontynuowano do wystąpienia progresji lub niedopuszczalnej toksyczności. Pierwszorzędowym punktem końcowym był czas wolny od progresji oceniany w grupie zgodnej z zamiarem leczenia. Bezpieczeństwo oceniano u wszystkich chorych, którzy otrzymali co najmniej jedną dawkę leku.

Wyniki. Od 15 listopada 2017 roku do 21 marca 2019 roku włączono do badania 302 chorych z medianą dwóch poprzednich linii leczenia, w tym 179 przydzielono losowo do grupy izatuksymabu, a 123 – do grupy kontrolnej. Mediana czasu wolnego od progresji nie została osiągnięta w grupie izatuksymabu w porównaniu z 19,15 miesiąca (95% CI 15,77–nie osiągnięto) w grupie kontrolnej, ze współczynnikiem ryzyka 0,53 (99% CI 0,32–0,89; jednostronne p = 0,0007). Zdarzenia niepożądane związane z leczeniem stopnia 3. lub wyższego wystąpiły u 136 spośród 177 chorych (77%) w grupie izatuksymabu w porównaniu z 82 spośród 122 (67%) w grupie kontrolnej, poważne zdarzenia niepożądane związane z leczeniem – odpowiednio u 105 (59%) w porównaniu z 70 chorych (57%). Doprowadziły one do przerwania leczenia odpowiednio u 15 (8%) w porównaniu z 17 chorymi (14%). Zgony związane z leczeniem odnotowano odpowiednio w przypadku sześciu (3%) w porównaniu z czterema (3%) chorymi.

Wnioski. Dodanie izatuksymabu do karfilzomibu z deksametazonem znamiennie wydłuża czas wolny od progresji i głębokość odpowiedzi u chorych na nawrotowego szpiczaka mnogiego, co stanowi nowy standard opieki w tej grupie chorych.

Sotorasib for lung cancers with *KRAS* p.G12C mutation

Skoulidis F., Li B.T., Dy G.K. i wsp.
N. Engl. J. Med., 2021; 384: 2371–2381

W badaniu I fazy sotorazyb wykazał działanie przeciwnowotworowe u chorych na zaawansowane guzy lite z mutacją G12C *KRAS*, szczególnie w podgrupie chorych na niedrobnokomórkowego raka płuca.

Metody. W jednogrupowym badaniu II fazy oceniono aktywność sotorazybu podawanego doustnie w dawce 960 mg raz dziennie chorym na zaawansowanego niedrobnokomórkowego raka płuca z mutacją G12C *KRAS*, wcześniej leczonym standardowymi metodami. Pierwszorzędowym punktem końcowym była obiektywna odpowiedź (całkowita lub częściowa) według niezależnej centralnej oceny. Najważniejsze drugorzędowe punkty końcowe obejmowały czas trwania odpowiedzi, kontrolę choroby (odpowiedź całkowita, częściowa lub stabilizacja choroby), czas wolny od progresji, przeżycie całkowite i bezpieczeństwo leczenia. Oceniano również zależność pomiędzy biomarkerami a odpowiedzią na leczenie sotorazybem.

Wyniki. Spośród 126 chorych włączonych do badania, większość (81%) otrzymywała wcześniej zarówno pochodne platyny, jak i immunoterapię w postaci inhibitorów PD-1/PD-L1. W centralnej ocenie zmiany mierzalne w wyjściowym badaniu obrazowym, które mogły być wykorzystane do oceny odpowiedzi znaleziono u 124 chorych. Obiektywną odpowiedź stwierdzono u 46 chorych (37,1%), w tym u 4 (3,2%) całkowitą, a u 42 (33,9%) częściową. Mediana czasu trwania odpowiedzi wyniosła 11,1 miesiąca. Kontrolę choroby uzyskano u 100 chorych (80,6%). Mediana czasu wolnego od progresji wyniosła 6,8 miesiąca, a mediana czasu całkowitego przeżycia 12,5 miesiąca. Działania niepożądane związane z leczeniem wystąpiły u 88 spośród 126 chorych (69,8%), w tym w stopniu 3. u 25 chorych (19,8%), a w stopniu 4. u jednego chorego (0,8%). Odpowiedzi obserwowano w podgrupach określonych na podstawie ekspresji PD-L1, nagromadzenia mutacji w guzie i współwystępujących mutacji w genach *STK11*, *KEAP1* lub *TP53*.

Wnioski. W badaniu II fazy leczenie sotorazybem przyniosło trwałe korzyści kliniczne u chorych na niedrobnokomórkowego raka płuca z mutacją G12C w genie *KRAS*, bez nowych sygnałów związanych z bezpieczeństwem.

Acquired resistance to KRASG12C inhibition in cancer

Awad M. M., Liu S., Rybkin I. I. i wsp.
N. Engl. J. Med., 2021; 384:2 382–2393

W badaniach klinicznych wykazano obiecującą aktywność inhibitorów KRAS: – adagrazybu i sotorazybu – w nowotworach z mutacją G12C *KRAS* (zamiana glicyny na cysteinę w kodonie 12.). Mechanizmy nabytej oporności na to leczenie nie są znane.

Metody. Przeprowadzono analizy genomowe i histologiczne wśród chorych na nowotwory z mutacją *KRAS* G12C leczonych adagrazybem, w których porównano próbki sprzed leczenia z próbkami uzyskanymi po nabyciu oporności. Przeprowadzono badania na liniach komórkowych w celu zbadania mutacji wywołujących oporność na inhibitory *KRAS*.

Wyniki. Do badania włączono 38 chorych: 27 na niedrobnokomórkowego raka płuca, 10 na raka jelita grubego, 1 na raka wyrostka robaczkowego. Domniemane mechanizmy oporności na adagrazyb wykryto u 17 chorych (45%), w tym 7 (18%) posiadało wiele zbieżnych mechanizmów. Nabyte zmiany w genie *KRAS* obejmowały G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C i wysokiego stopnia amplifikację alleli KRASG12C. Wykryto także amplifikację genu *MET*; aktywujące mutacje genów *NRAS*, *BRAF*, *MAP2K1*, *RET*, fuzje onkogenne genów *ALK*, *RET*, *BRAF*, *RAF1*, *FGFR2*, mutacje skutkujące utratą funkcji genów *NF1* i *PTEN*. U 2 spośród 9 chorych na gruczolakoraka płuca zaobserwowano histologiczną transformację do raka płaskonabłonkowego, bez jakichkolwiek innych mechanizmów oporności. Dzięki dokładnej analizie mutacji *in vitro*, określono szereg mutacji odpowiadających za oporność na inhibitory KRAS.

Wyniki. Różnorodne mechanizmy genomiczne i histologiczne wywołują oporność na stosowane inhibitory KRASG12C. Potrzebne są nowe strategie, aby opóźnić i przezwyciężyć oporność na te leki u chorych na nowotwory.

Adjuvant olaparib for patients with *BRCA1*- or *BRCA2*-mutated breast cancer

Tutt A.N.J., Garber J.E., Kaufman B. i wsp.
N. Engl. J. Med., 2021; 384: 2394–2405

Inhibitory polimerazy poli(ADP-rybozy) są ukierunkowane na nowotwory, w których obserwuje się uszkodzenie jednego z mechanizmów naprawy DNA – homologicznej rekombinacji. Potrzebne są nowe sposoby leczenia, które zmniejszą udział nawrotów u chorych na wczesnego raka piersi związanego z mutacją germinalną w genie *BRCA1* lub *BRCA2*.

Metody. W podwójnie zaślepionym badaniu III fazy chore na wczesnego raka piersi bez nadekspresji HER2 (*human epidermal growth factor receptor* 2), z patogennymi wariantami germinalnymi *BRCA1* lub *BRCA2*, z kliniczno-patologicznymi czynnikami wysokiego ryzyka, wcześniej poddane leczeniu miejscowemu i indukcyjnej lub uzupełniającej chemioterapii, przydzielano losowo (1:1) do grupy otrzymującej doustny olaparyb lub placebo przez rok. Pierwszorzędowym punktem końcowym był czas wolny od choroby.

Wyniki. Do leczenia przydzielono losowo 1836 chorych. We wstępnie określonej analizie pośredniej opartej na liczbie zdarzeń po medianie okresu obserwacji 2,5 roku udział 3-letnich przeżyć wolnych od choroby wyniósł 85,9% wśród otrzymujących olaparyb i 77,1% w grupie placebo (różnica 8,8%, współczynnik ryzyka choroby inwazyjnej lub zgonu 0,58), a udział 3-letnich przeżyć bez odległych przerzutów odpowiednio 87,5% i 80,4% (różnica 7,1%, współczynnik ryzyka przerzutów odległych lub zgonu 0,57). Stosowanie olaparybu wiązało się z mniejszą liczbą zgonów (59 *vs.* 86), jednak różnica pomiędzy grupami nie była znamienna w analizie przeprowadzonej w trakcie trwania badania ($p < 0,01$). Dane dotyczące bezpieczeństwa były zgodne ze znanymi działaniami niepożądanymi olaparybu. Nie obserwowano poważnych zdarzeń niepożądanych czy zdarzeń o szczególnym znaczeniu.

Wnioski. Stosowanie olaparybu po zakończeniu leczenia miejscowego i indukcyjnej lub uzupełniającej chemioterapii u chorych na wczesnego, HER2-ujemnego raka piersi z mutacją germinalną *BRCA1*/*BRCA2*, wiązało się ze znamiennie dłuższym przeżyciem wolnym od choroby i przeżyciem bez przerzutów odległych. Olaparyb miał ograniczony wpływ na ogólną jakość życia ocenianą przez chore.

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IV Konferencja Akademii Dermatoskopii (18–19 czerwca 2021) Doniesienia konferencyjne

Porokeratoza jako problem kliniczny

Aleksandra Kapuśniak
Oddział Kliniczny Dermatologii, Szpital Wojewódzki w Opolu

Wprowadzenie. Porokeratozy stanowią rzadką grupę schorzeń, których istotą jest zaburzenie procesu rogowacenia skóry. Należą do chorób z grupy genodermatoz zakwalifikowanych do rogowaceń kanalikowych. Etiopatogeneza porokeratoz jest złożona i wieloczynnikowa. Etiologia schorzenia nie jest dokładnie poznana. W patogenezie rozważa się predyspozycje genetyczne z autosomalnie dominującym modelem dziedziczenia. Przypadki nabyte spowodowane są mutacjami somatycznymi. Choroba częściej występuje u chłopców oraz u młodych dorosłych mężczyzn.

Dyskusja. Do czynników ryzyka rozwoju choroby należą:

- immunosupresja,
- podatność genetyczna – niestabilność krótkiego ramienia chromosomu 3 (3p12–14),
- promieniowanie UV, w tym fotochemioterapia,
- zakażenia wirusem brodawczaka ludzkiego (*human papillomavirus* – HPV),
- urazy mechaniczne.

Obraz kliniczny. Wykwitem pierwotnym jest czerwonobrązowa grudka z czopem rogowym w centrum zmiany. Zmiana szerzy się odśrodkowo, tworząc obrączkowate, nieregularne ogniska z zanikiem w centrum i na obwodzie wyraźnie odgraniczonym białym rowkiem, wypełnionym łuską (ryc. 1). Każdą z odmian porokeratozy charakteryzują pewne odmienne cechy kliniczne, wszystkie jednak łączy podobny obraz histopatologiczny oraz dermatoskopowy.

Obraz histopatologiczny. Wąskie kolumny ciasno ułożonych parakeratotycznych komórek, tzw. blaszek rogowych (*cornoid lamellae*), wychodzących z ognisk ścieńczałej lub nieprawidłowej warstwy ziarnistej.

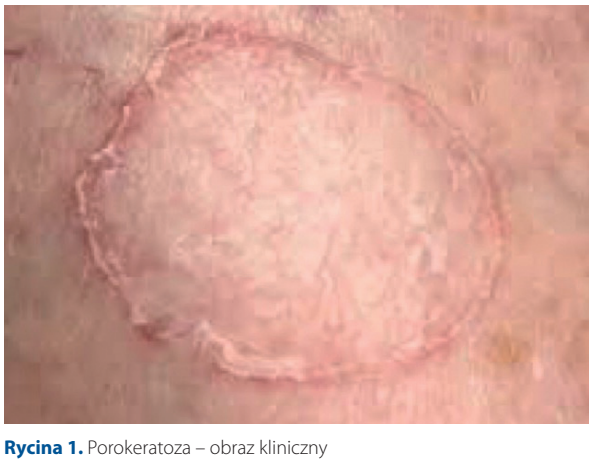
Obraz dermatoskopowy. Widoczne są:

- jasne homogenne zanikowe centrum,
- biała dyskretna łuska,
- białe lśniące struktury,
- brązowoczerwone grudki i globule wzdłuż brzegu zmiany,
- hiperpigmentacyjna lub biała obwódka z podwójnym brzegiem,
- polimorficzne naczynia w postaci kropek, kłębuszków, linii,
- drobne nadżerki i wynaczynienia na obwodzie zmiany (ryc. 2).

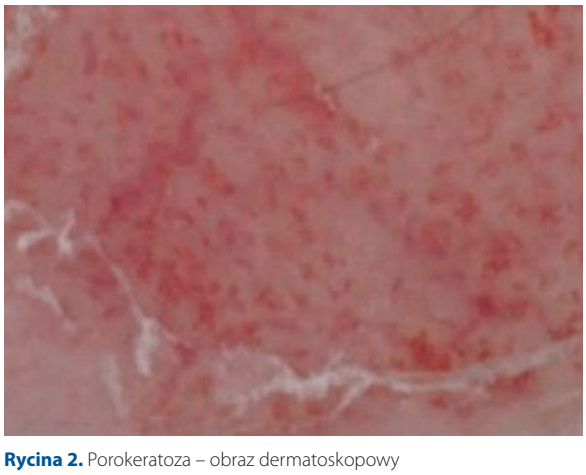
Około 7,5 % zmian związanych z występowaniem ognisk porokeratozy może ulec transformacji nowotworowej. Na podłożu ognisk porokeratozy mogą rozwinąć się: rak kolczystokomórkowy, rak podstawnokomórkowy oraz choroba Bowena.

Podsumowanie. Ze względu na możliwość rozwoju procesu nowotworowego w obrębie ogniska porokeratozy zasadne jest jego skuteczne leczenie i ścisła obserwacja z regularną oceną dermatoskopową.

Słowa kluczowe: porokeratozy, dermatoskopia



Rycina 1. Porokeratoza – obraz kliniczny



Rycina 2. Porokeratoza – obraz dermatoskopowy

Usunięcie rozległej brodawki łojotokowej skóry lewej piersi ultradźwiękami o wysokiej częstotliwości (HIFU) u 68-letniej pacjentki – opis przypadku

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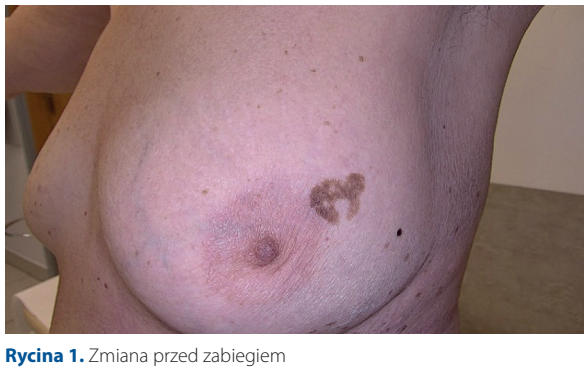
[1]*Old Town Clinic, Wrocław*
[2]*Dolnośląskie Centrum Onkologii we Wrocławiu*

Wstęp. Rogowacenie łojotokowe jest powszechnym łagodnym rozrostem komórek naskórka, który może wystąpić niemal w każdej lokalizacji na skórze, z wyjątkiem błon śluzowych oraz części podeszwowej stóp i dłoni. Problem ten dotyczy na ogół osób po 30. r.ż., a częstotliwość występowania wzrasta z wiekiem. Pomimo łagodnego charakteru, zmiany mogą stanowić problem natury funkcjonalnej i estetycznej. Z tego powodu pacjenci często decydują się na ich usunięcie.

Opis przypadku. Prezentujemy przypadek usunięcia brodawki łojotokowej przy zastosowaniu fali ultradźwiękowej o wysokiej częstotliwości (*high intensity focused ultrasound* – HIFU) za pomocą urządzenia System ONE-M (TOOsonix Horsholm, Dania). 68-letnia kobieta zgłosiła się do poradni onkologicznej zaniepokojona rosnącą od 3 lat i swędzącą zmianą na lewej piersi (ryc. 1). Dermatoskopowo zdiagnozowano brodawkę łojotokową. Cechowały ją: dobre odgraniczenie, obecność grubych, brązowych, zagiętych linii, brązowy obszar bezstrukturalny, naczynia typu pętli, brązowe grudki (ryc. 2). Ze wskazań funkcjonalnych zmianę poddano zabiegowi HIFU w ustawieniach: głowica 0,8 mm, czas ekspozycji 150 ms, energia 1,1 J. Następnie, po upływie 4 i 8 tygodni przeprowadzono badania kontrolne z archiwizacją wideodermatoskopową (ryc. 3, 4). Po 4 tygodniach stwierdzono znaczną regresję zmiany z obecnością licznych szaro-niebieskich grudek i kropek oraz licznych, linijnych, rozgałęzionych, odczynowych naczyń krwionośnych. Po 8 tygodniach liczba naczyń krwionośnych zmniejszyła się, mniejsza była też intensywność kolorów szaro-niebieskich grudek (ryc. 5).

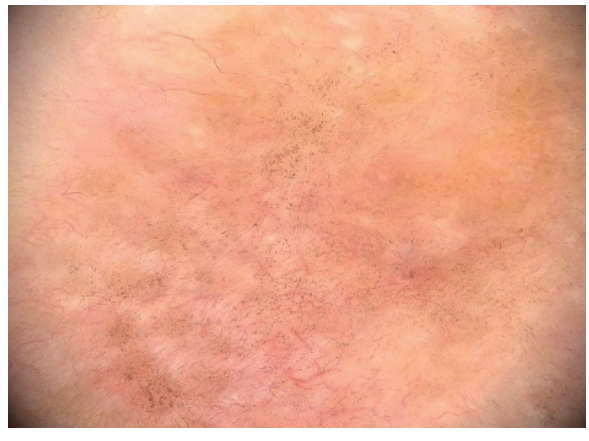
Podsumowanie. Zastosowanie HIFU pozwoliło na skuteczne, częściowe usunięcie brodawki łojotokowej z dobrą tolerancją zabiegu. W oparciu o monitoring cyfrowy wykazano, że procesy resorpcji zmiany zachodzą w skórze przez wiele tygodni przy jedocześnie bardzo szybkim i trwałym efekcie wizualnym.

Słowa kluczowe: brodawka łojotokowa, HIFU

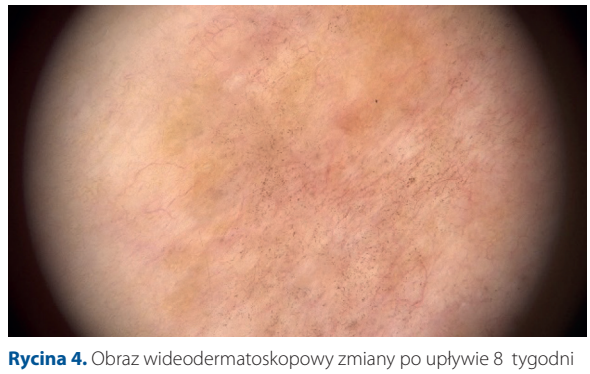


Rycina 1. Zmiana przed zabiegiem

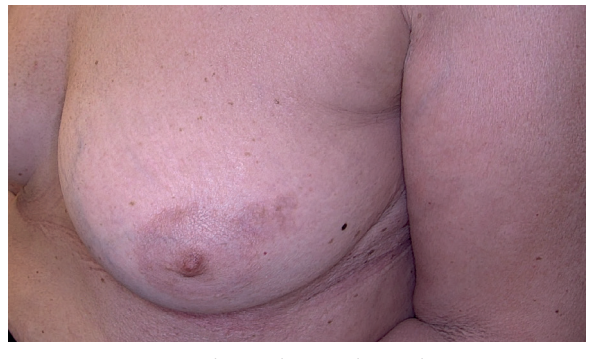
Rycina 2. Obraz wideodermatoskopowy zmiany przed zabiegiem (powiększenie 20x)



Rycina 3. Obraz wideodermatoskopowy zmiany po upływie 4 tygodni od zabiegu (powiększenie 20x)



Rycina 4. Obraz wideodermatoskopowy zmiany po upływie 8 tygodni od zabiegu (powiększenie 20x)

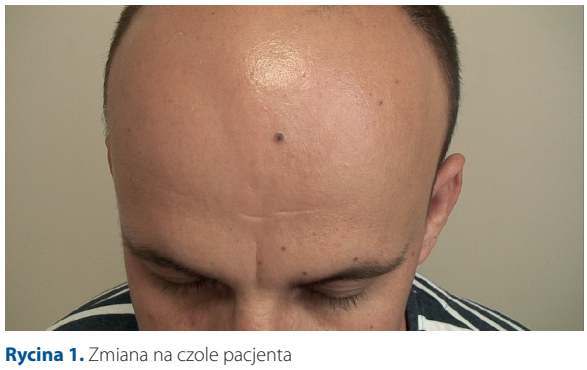


Rycina 5. Zmiana 8 tygodni po zabiegu – obraz makro

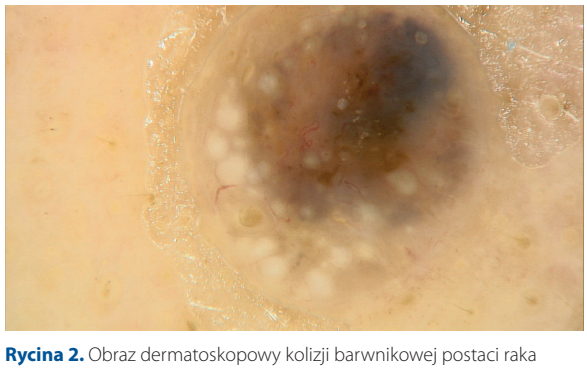
Guzy kolizyjne. Kolizja barwnikowej postaci raka podstawnokomórkowego z hiperplazją gruczołów łojowych – opis przypadku

Bartosz Woźniak[1, 3] Jacek Calik[1, 2]
[1]*Old Town Clinic, Wrocław*
[2]*Dolnośląskie Centrum Onkologii we Wrocławiu*
[3]*Wojewódzki Szpital Specjalistyczny we Wrocławiu*

Wstęp. Termin guzy kolizyjne (*collision tumors*) oznacza jednoczesne współistnienie dwóch lub więcej różnych nowotworów w obrębie jednego obszaru skóry. Możliwy jest każdy wariant koegzystencji guzów – zarówno zmiany łagodnej z łagodną, złośliwej ze złośliwą, jak i złośliwej z łagodną. Najczęstszym zestawieniem zmiany złośliwej z łagodną jest współistnienie raka podstawnokomórkowego z brodawką łojotokową.
Opis przypadku. Prezentujemy przypadek rzadkiego współwystępowania barwnikowej postaci raka podstawnokomórkowego z hiperplazją gruczołów łojowych. Zmiana pojawiła się na czole 36-letniego mężczyzny, który zawodowo dużo czasu spędza na wolnym powietrzu (ryc. 1). Obraz dermatoskopowy składał się z dwóch wzorów: białych grudek poprzeplatanych linijnymi naczyniami nieprzechodzącymi przez środkową część zmiany oraz z dużej niebieskiej grudki ze współistnieniem naczyń linijnych rozgałęzionych oraz linijnych w kształcie pętli (ryc. 2). W diagnostyce różnicowej, poza guzem kolizyjnym, należy brać pod uwagę nowotwór z przydatków skóry, np. nabłoniaka włosowego, czerniaka lub brodawkę łojotokową. Wynik badania histopatologicznego wykazał współistnienie zmiany łagodnej będącej przerostem gruczołów łojowych oraz raka podstawnokomórkowego.



Rycina 1. Zmiana na czole pacjenta



Rycina 2. Obraz dermatoskopowy kolizji barwnikowej postaci raka podstawnokomórkowego z hiperplazją gruczołów łojowych

Podsumowanie. Diagnostyka dwóch zmian współistniejących jest trudna i obaczona dużym ryzkiem błędnego rozpoznania. W efekcie może to prowadzić do nieprawidłowego leczenia. Dlatego w diagnostyce guzów kolizyjnych niezwykle ważna jest współpraca klinicysty z patomorfologiem.
Słowa kluczowe: guzy kolizyjne, rak podstawnokomórkowy, przerost gruczołów łojowych, dermatoskopia

Rak Arninga – opis przypadku

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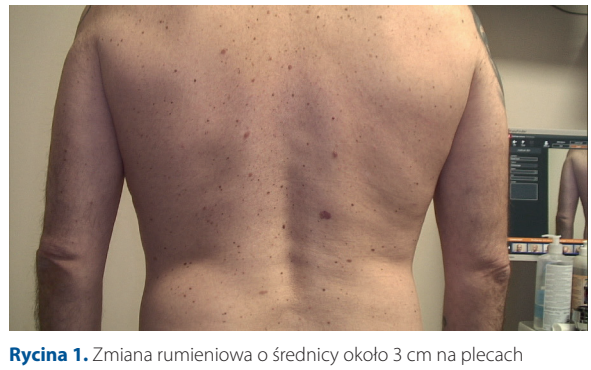
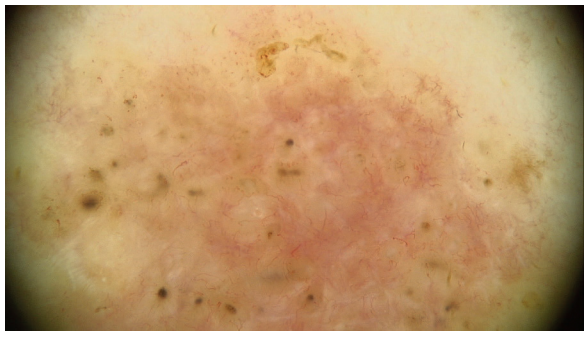
[3]*Wojewódzki Szpital Specjalistyczny we Wrocławiu*

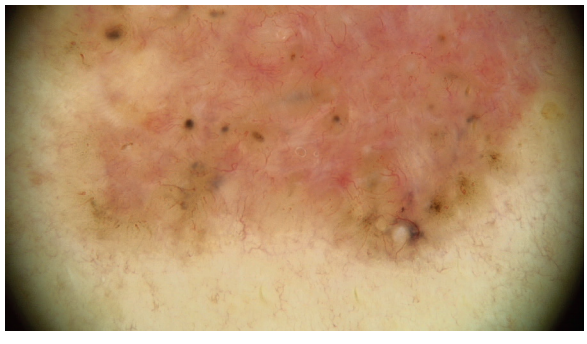
Wprowadzenie. Rak Arninga, czyli wieloogniskowy powierzchowny rak podstawnokomórkowy (*superficial multicentric basal cell carcinoma*) stanowi blisko 20% wszystkich raków podstawnokomórkowych. Czyni to go drugim najczęstszym podtypem tego nowotworu. Inaczej niż pozostałe podtypy raka podstawnokomórkowego, które najczęściej lokalizują się w okolicy głowy i szyi, rak Arninga zwykle diagnozowany jest na tułowiu lub kończynach. Jest to najmniej inwazyjny podtyp raka podstawnokomórkowego.
Opis przypadku. Pacjent 52-letni ze zmianą rumieniową o średnicy około 3 cm na plecach (ryc. 1). Dermatoskopowo na różowym tle znajdują się liczne szaroniebieskie różnej wielkości grudki rozmieszczone niesymetrycznie. Na całej powierzchni zmiany widać różnokształtne jasnopomarańczowe grudki odpowiadające owrzodzeniom. W dolnym biegunie zmiany znajduje się biała grudka – pseudotorbiel rogowa. Ponadto widoczne są białe linie ułożone prostopadle wobec siebie. W obrębie różowego tła znajdują się liczne naczynia linijne rozgałęzione oraz krótkie proste naczynia linijne. Na całej powierzchni zmiany widoczne są (przede wszystkim w świetle spolaryzowanym) małe białe homogenne obszary bezpostaciowe (ryc. 2, 3).
Wnioski. Opisywany przypadek wskazuje na duże znaczenie dermatoskopii w różnicowaniu wolno wzrastających rumieniowych zmian w obrębie tułowia i kończyn, które należy różnicować z łuszczycą, wypryskiem, a także chorobą Bowena.



Rycina 1. Zmiana rumieniowa o średnicy około 3 cm na plecach pacjenta



Rycina 2. Obraz dermatoskopowy zmiany



Rycina 3. Obraz dermatoskopowy – pseudotorbiel rogowa

Prawidłowe rozpoznanie struktur dermatoskopowych charakterystycznych dla raka Arninga pozwala na szybkie wdrożenie skutecznej terapii.

Słowa kluczowe: wieloogniskowy powierzchowny rak podstawnokomórkowy, zmiany rumieniowe, dermatoskopia.

Rozmieszczenie wzorców naczyniowych w rogowiakach jasnokomórkowych

Paweł Pietkiewicz[1,2,3]

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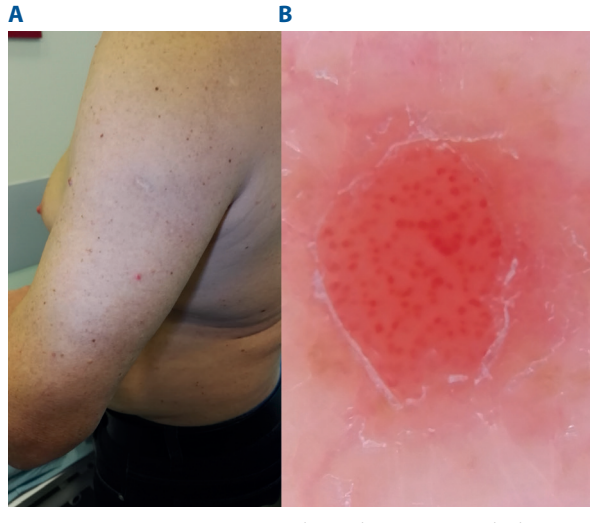
[2]Polska Grupa Dermatoskopowa

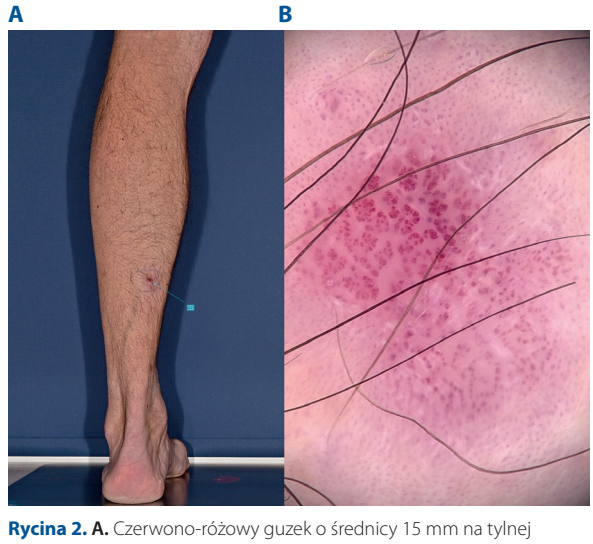
[3]Skin Cancer Institute, Singapur

Wstęp. Rogowiak jasnokomórkowy (*clear cell acanthoma* – CCA) jest rzadkim łagodnym guzem pochodzenia naskórkowego. Występuje przeważnie w populacji starszych pacjentów, jako pojedynczy, wyraźnie odgraniczony wolno rosnący różowo-czerwony guzek, który nie daje żadnych objawów subiektywnych. Jego obraz kliniczny może sugerować podrażnioną brodawkę wirusową, rogowacenie łojotokowe lub słoneczne, ziarniniaka naczyniowego, włókniaka twardego, gruczolaka potowego ekrynowego, guzkowo-torbielowatego gruczolaka potowego, raka podstawnokomórkowego, raka kolczystokomórkowego *in situ*, a nawet achromicznego czerniaka. Zaprezentowano 2 przypadki CCA z charakterystycznym rozmieszczeniem odmiennych wzorców naczyniowych (ryc. 1, 2).

Dyskusja. Uważa się, że CCA wykazuje wysoce swoisty wzorzec rozmieszczenia naczyń – wężowaty, określany metaforycznie jako „przypominający sznur pereł" (*string of pearls*). Budują go przeważnie naczynia typu kropek, ale opisywano również naczynia kłębuszkowate, kojarzone zwykle z rakiem kolczystokomórkowym *in situ* lub rogowaceniem łojotokowym. Pojawienie się naczyń kłębuszkowatych w CCA może wynikać z mechanicznego drażnienienia guza (w przypadku ognisk rogowacenia łojotokowego), lub z zastoju żylnego w kończynach dolnych (w przypadku naczyń kłębuszkowatych w łuszczycy). Rozmieszczenie wężowate opisano dotychczas również w innych łagodnych zmianach (rogowacenie łojotokowe, łagodne rogowacenie liszajowate). Ponadto, jak każdy



Rycina 1. A. Czerwono-różowy guzek o średnicy 3 mm na tylnobocznej powierzchni ramienia lewego u 68-letniego mężczyzny odnaleziony w skryningu oportunistycznym (Honor7); **B.** Guzek otoczony delikatnym keratynowym kołnierzykiem łuski. Typowy dla rogowiaka jasnokomórkowego monomorficzny wzorzec naczyniowy zbudowany jest z naczyń typu kropki o rozmieszczeniu wężowatym (Honor7, DL4)



Rycina 2. A. Czerwono-różowy guzek o średnicy 15 mm na tylnej powierzchni podudzia lewego u 59-letniego mężczyzny odnaleziony w rutynowym badaniu dermatoskopowym (ATBM Master, Fotofinder GmbH); **B.** Obraz dermatoskopowy – polimorficzny wzorzec naczyniowy (naczynia typu kropki i kłębuszkowate) o wężowatym rozmieszczeniu i obecność białych niekrzyżujących się linii zależnych od polaryzacji (Medicam 1000s, Fotofinder GmbH)

uszkadzany lub krwawiący różowy guzek, CCA może wykazywać obecność pomarańczowych, czerwonych, brązowych lub nawet czarnych grudek (strupy), czerwono-purpurowych obszarów bezstrukturalnych (wybroczyna), delikatnej łuski lub objawu kołnierzyka (obwodowej keratynowej lub surowiczo-keratynowej łuski). Dodatkowo pewna część CCA może prezentować białe linie zależne od polaryzacji oraz zagięte białe linie niezależne od polaryzacji.

Podsumowanie. W obrazie dermatoskopowym CCA bardzo często wykazuje wężowate rozmieszczenie naczyń. Znajomość tego wzorca naczyniowego umożliwia ustalenie rozpoznania bez konieczności uzyskiwania potwierdzenia histopatologicznego.

Słowa kluczowe: rogowiak jasnokomórkowy, dermatoskopia

Szybko rosnący różowy guzek na skórze policzka – opis przypadku

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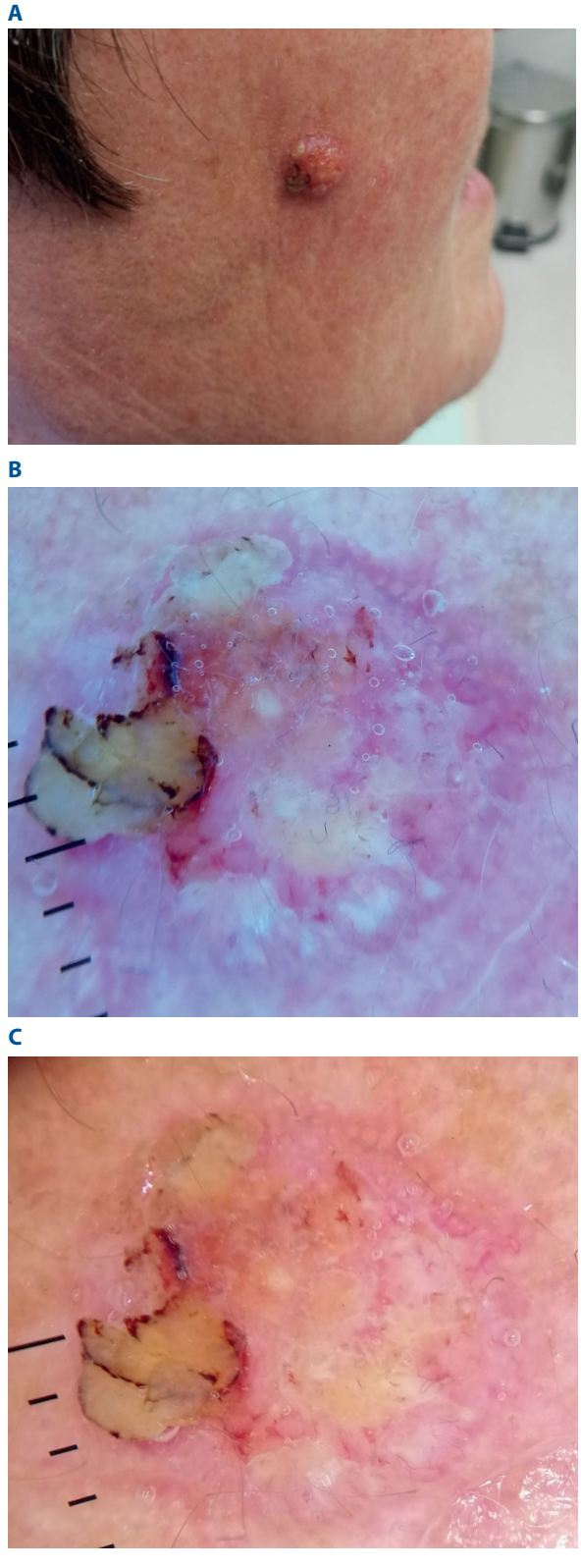
Wprowadzenie. Twarz jest najczęstszą lokalizacją nowotworów skóry, a najczęstszym z nich jest rak podstawnokomórkowy. Mimo że drugim najczęstszym nowotworem w tej lokalizacji jest rak kolczystokomórkowy, to formę różowego guzka mogą przybierać również rak z komórek Merkla, *atypical fibroxanthoma*, mięsak Kaposiego oraz liczne guzy przydatkowe.

Opis przypadku. 56-letnia kobieta została skierowana do poradni z powodu szybko rosnącego owrzodziałego guzka prawego policzka. Według relacji pacjentki, zmiana miała pierwotnie formę drobnej, okresowo krwawiącej grudki i była obecna od roku, ale miesiąc przed wizytą zaczęła gwałtownie rosnąć (ryc. 1). Fototyp skóry pacjentki (*Fitzpatrick III*), wywiad rodzinny i osobniczy nie stanowiły czynników ryzyka rozwoju nowotworów skóry. Kobieta pracowała wiele lat jako gospodyni, również w ogrodzie warzywnym, a skóra jej twarzy wykazywała cechy przewlekłego uszkodzenia UV. W różnicowaniu ujęto raka kolczystokomórkowego (G2) lub wysokozróżnicowanego (G1) oraz raka metatypowego (*basosquamous carcinoma*). Wynik histopatologiczny potwierdził rozpoznanie inwazyjnego raka kolczystokomórkowego G2.

Dyskusja. Bezbarwnikowe guzy skóry mogą stanowić problem diagnostyczny. Wzory złośliwości, obecne w zmianach pozbawionych barwnika, z mniejszą pewnością pozwalają określić rozpoznanie niż bardziej swoiste barwnikowe wzory złośliwości. Rak kolczystokomórkowy, stanowiący ok. 20% wszystkich nowotworów skóry w populacji kaukaskiej, może występować w 3 stopniach zróżnicowania (G1–3), które są



Rycina. 1. A. Owrzodziały różowy guzek na skórze twarzy u 56-letniej kobiety; dermatoskopia w świetle niespolaryzowanym (**B**) i spolaryzowaym (**C**). Zmiana prezentuje się jako biało-różowy guzek z obecnością białych wzorów złośliwości (obszary bezstrukturalne i białe koła, świadczące o hiperkeratozie). Ponadto obecne są białe grudki, lepiej widoczne w świetle niespolaryzowanym, które odpowiadają perłom rogowym. W centrum zmiany widać żółto-czarno-czerwone grudki (strupołuska). Naczynia są polimorficzne, rozmieszczone nieswoiście: linijne serpentynowate, otoczone białym halo, kłębuszkowate oraz linijne rozgałęzione.

odmienne klinicznie oraz dermatoskopowo (odpowiednio białe, różowe i czerwone guzy).

Podsumowanie. Obraz dermatoskopowy raka kolczystokomórkowego pozwala nie tylko na przyporządkowanie zmiany do grupy guzów keratynizujących, ale także – dzięki obecności wzorów keratynowych – pozwala na przybliżone określenie stopnia zróżnicowania tego nowotworu.

Słowa kluczowe: rak kolczystokomórkowy, dermatoskopia

Skuteczne leczenie acytretyną raka kolczystokomórkowego rozwijającego się w obrębie liszaja płaskiego przerostowego – opis przypadku

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Wprowadzenie. Liszaj płaski (*lichen planus* – LP) jest chorobą grudkowo-złuszczającą skóry, dotyczącą 1–2% populacji. Łagodne przypadki mogą nie wymagać leczenia, a zmiany samoograniczają się przeważnie po 1–2 latach, niezależnie od zastosowanego leczenia. Przerostowy LP (*hyperthrophic lichen planus* – HLP) jest szczególnym wariantem choroby. Zwykle obejmuje skórę kostek i okolicy przedpiszczelowej. Rozwój nowotworu w obrębie zmian skórnych LP jest zjawiskiem rzadkim. Szacuje się, że w ok. 0,4% przypadków z LP rozwija się rak kolczystokomórkowy (*squamous cell carcinoma* – SCC). Większość przypadków SCC dotyczy HLP.

Opis przypadku. Prezentujemy przypadek 66-letniej kobiety ze swędzącymi czerwono-purpurowymi tarczkami, grudkami i guzkami na skórze obu kończyn dolnych. Pobrano 2 biopsje sztancowe – jedną z purpurowej tarczki na podudziu prawym, drugą z hiperkeratotycznego uniesionego rumieniowego guzka na podudziu lewym. W dermatoskopii drugiej ze zmian wykazano czerwone bezstrukturalne tło z obecnością białych kół i grudek, naczyń typu kropek z białym halo, łuski keratynowej i wybroczyn. Pierwszy i drugi wycinek zostały opisane odpowiednio jako HLP oraz SCC związane z HLP. Natychmiast chirurgicznie usunięto pierwszą zmianę i włączono leczenie doustne acytretyną, które w ciągu 5-miesięcznej terapii doprowadziło do pełnego wygojenia zmian i redukcji świądu.

Podsumowanie. Terapia HLP jest trudna z powodu ograniczonej odpowiedzi na leczenie klasyczne oraz związane z nim ryzyko rozwoju SCC. Dlatego pacjenci z tym rozpoznaniem muszą być ściśle monitorowani pod kątem ewentualnej transformacji nowotworowej. Dermatoskopia umożliwia klinicyście wybranie optymalnego miejsca biopsji podczas wizyt kontrolnych. Sugeruje się, aby acytretyna była lekiem z wyboru szczególnie w HLP o dużej rozległości oraz gdy jest oporny na leczenie miejscowe.

Słowa kluczowe: acytretyna, dermatoskopia, liszaj płaski przerostowy, rak kolczystokomórkowy

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