OFFICIAL JOURNAL OF THE POLISH SOCIETY OF CLINICAL ONCOLOGY

Oncology IN CLINICAL PRACTICE

2021, Vol. 17, Number 3

ISSN 2450–1654
e-ISSN 2450-6478

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ONCOLOGY
IN CLINICAL PRACTICE

Official Journal of the Polish Society of Clinical Oncology

https://journals.viamedica.pl/oncology_in_clinical_practice

Oncology in Clinical Practice (ISSN 2450–1654, e-ISSN 2450-6478) is published six times a year by

VM Media sp. z o.o. VM Group sp.k.
ul. Świętokrzyska 73, 80–180 Gdańsk, Poland
Phone: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
e-mail: redakcja@viamedica.pl,
http://www.viamedica.pl, wap.viamedica.pl

20-0826.012.001

Editorial Address

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Phone: (+48 22) 546 21 69
e-mail: sekretariat4@pib-nio.pl

Indexed in Index Copernicus (ICV 2019 = 89.65), Ulrich's Periodicals Directory and CAS.

According to the statement of the Polish Ministry of Science and Higher Education publication in the journal has been awarded with 20 points.

Editorial policies and author guidelines are published on journal website: http://journals.viamedica.pl/oncology_in_clinical_practice

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Professor Krzysztof Krzemieniecki Award for the best case report accepted for publication

Case Report Contest Policies

This policy defines the scope, requirements and regulations regarding **The Krzysztof Krzemieniecki Award** for the best case report published in "Oncology in Clinical Practice" (OCP) Sixth Edition.

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5. The first author of the winning paper will be eligible for a prize of gross 1000,00 Euro gross (one thousand euro).
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7. Winner will be notified via email.
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10. The award amount shall be paid based on the copyright transfer agreement to the paper.
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ORIGINAL ARTICLE

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High prevalence of somatic complaints and psychological problems despite high self-declared quality of life in long-term cancer survivors

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 89–97
DOI: 10.5603/OCP.2021.0005

ISSN 2450–1654
e-ISSN 2450-6478

ABSTRACT

Introduction. To assess the quality of life (QoL) of long term cancer survivors and its determinants.

Material and methods. The research covered a group of 272 disease-free cancer survivors (mean OS = 8 years). Methods: 1) Evaluation of somatic and psychological complaints (with the NCCN Clinical Practice Guidelines in Oncology — Survivorship Assessment, NCCN Guidelines®, V.1.2015); 2) Evaluation with numeric rating scales (NRS, 0–10 points): health status life satisfaction; social support and acceptance; 3) Assessment of the quality of life as dependent variable (NRS).

Results. Analysis revealed high prevalence of numerous somatic complaints, assessment of emotional disturbances, cognitive dysfunctions and surprisingly high global QoL (66%), high overall (77%) and present (74%) life satisfaction, good health (55%), strong impact of illness on life (42%), high social acceptance (80%) and satisfying support (62%). QoL correlated significantly ($p < 0.05$) with most of NRS measured subjective variables especially health status (–0.74), life satisfaction (0.66) and joy of life (0.63).

Conclusions. High Qol despite somatic ailments might reflect high levels of received support, as well as attitudes towards life and illness. Positive correlations between the QoL and other subjective variables imply that those parameters might be equally important determinants of QoL as somatic indices. Specialized care should provide cognitive evaluation and therapy for cancer survivors to a larger extent than before.

Key words: cancer survivors, quality of life, somatic complaints, satisfaction with life

Oncol Clin Pract 2021; 17, 3: 89–97

Introduction

Both duration of survival and survival rates of cancer patients improve dramatically as a result of progress in oncological diagnosis and treatment. However, this co-exists with an increase in cancer incidence rates due to progressive population aging. These phenomena are observed both in Poland and worldwide. Epidemiological studies conducted by the National Cancer Institute demonstrated that the number of cancer survivors in the United States has increased from 3 million in 1971 to 16.9 million in 2019, probably in 2030 22,2 million and

the proportion of survivors among all cancer patients approximates 66% [1, 2]. Although the survival rate of Polish cancer patients is somewhat lower (ca. 40%), this proportion still corresponds to a large absolute number of survivors. Despite the increase in their number, the quality of life in cancer survivors has been studied relatively rarely, especially in Poland. Previous studies conducted in the United States and some Western European countries demonstrated that although most cancer survivors present with good health and are actively involved in professional and social life, a considerable proportion of them experience somatic and/or psychological problems and cannot fully enjoy normal activities of daily living.

With no doubt, the difficulties experienced by people who had recently completed an anticancer treatment differ considerably from the problems encountered by long-term cancer survivors. This refers to most areas of the quality of life (QoL), especially to the somatic (greater severity of ailments), psychological (higher incidence of depression and anxiety) and cognitive domain.

The aim of this study was to comprehensively analyze various domains of QoL in cancer survivors. This knowledge may be crucial for offering this group with optimal forms of assistance, tailored to their needs.

Published data about the problems experienced by long-term cancer survivors

According to literature, the term 'long-term survivors' typically refers to people diagnosed with cancer at least 6 years (64%) [3]. The vast majority of patients with such long survival suffered from breast, prostate or colorectal cancer. They frequently (50%) report numerous ailments associated with either early or late anticancer therapy. Some of them may be diagnosed with secondary malignancies [4]. The most common among multiple ailments found in this group are sexual disorders, sleep problems, especially trouble falling asleep (30–50%), fatigue (40–50%) and pain (35%). Other frequently reported problems include oedema (breast cancer) and gastrointestinal dysfunction [5–9].

The list of mental problems reported by cancer survivors includes emotional disorders, such as depression (17–20%) and anxiety (9–23%). Particularly alarming is a high incidence of cognitive disorders, such as memory loss, learning difficulties and problems with fast thinking [5–7]. However, it should be stressed that the above-mentioned statistics are based primarily on subjective self-assessment, and according to some authors, the incidence of cognitive disorders is higher among persons who were previously informed that they may be more prone to such ailments [10].

Psychological response of patients to a disease experienced years earlier and/or to the treatment thereof usually differs from the reaction of people who still undergo or have just finished oncological therapy. Psychological ailments observed in the latter group, e.g. anxiety or depression, may be directly related to the disease and its harmful treatment (e.g. chemotherapy). Such emotional response may persist for some time after the treatment or be evoked by late physical consequences of the disease and anticancer therapy, such as fatigue, pain, sexual dysfunction, disorders of sleep, and/or cognitive impairment [11, 12].

Moreover, it should be remembered that anxiety and depression are also relatively common in the general population and do not necessarily need to be associated with the disease or its treatment.

A well-established consequence of psychological and social distress experienced by cancer survivors is higher (up to 22-fold) frequency of suicidal thoughts/attempts in this group, as well as their lesser involvement in rehabilitation programs and health-oriented behaviors [13].

Available data on the quality of life in long-term cancer survivors are inconclusive [14–16].

Quite frequently, psychological problems experienced by long-term survivors may manifest similarly to post-traumatic stress disorder.

However, aside from the negative consequences of cancer, also some its beneficial effects are increasingly recognized, among them higher self-esteem, a greater appreciation of life, spirituality and internal peace. Harmonized development of these traits is sometimes referred to as post-traumatic growth [17–20].

Studies in this area, although vitally important, turned out to be particularly challenging, due to the lack of appropriate research instruments.

On the other hand, these positive consequences of the disease may indirectly explain why most cancer survivors examined in previous studies evaluated their QoL as good or even very good [21–23]. However, this hypothesis has never been proved directly, since most previous studies involving cancer survivors centered around physical and psychosocial aspects of QoL, and ailments from these domains usually are disproportional to generally good overall QoL estimates.

While a number of previous studies analyzed QoL in cancer patients during the disease and its treatment, only a few authors examined this problem in cancer survivors, especially those with relatively long survival time.

To fill this gap, we have conducted a study in the latter group; aside from routinely determined measures of QoL in physical, psychological and health behavior domain, we also focused on positive aspects of the disease.

Table 1. Demographic and medical characteristics of the study group

General characteristics of study participants		
	Initially enrolled	Qualified for analysis
n	**320**	**285**
Sex	Male: 111 (40.8%), female: 161 (59.2%)	
Age, mean [years]	men: 64.9 ± 12.6, women: 63.6 ± 11.1 (ns)	
Place of residence	Countryside, 20.7%; towns up to 100 000, 32.7%; towns above 100 000, 38.9%	
Marital status	**n**	**%**
Married/common law	190	69.8
Single	13	4.8
Divorced	25	9.2
Widowed	36	13.3
Missing information	8	2.9
Total	272	100
Disease-free survival after treatment, mean [years]	men: 8.1 ± 4.9, women: 8.8 ± 5.6 (ns)	
Cancer location	**n**	**%**
Head/neck	65	23.90
Melanoma	47	17.28
Prostate	15	5.51
Breast	74	27.21
Gastrointestinal tract	36	13.24
Genital system	8	2.94
Other	12	4.41
Unknown	4	1.47
Missing information	11	4.04
Total	272	100

Objectives

The aim of the study was to analyze QoL and its complex determinants in long-term cancer survivors.

Specifically, the study centered around:

1. Subjective assessment of participant:
   a) global quality of life;
   b) physical condition and psychological status;
   c) the attitudes to life;
   d) the attitudes to support offered by the others.
2. Complex analysis included a relationship between global QoL and the following factors:
   a) sociodemographic characteristics (sex, age, family status);
   b) physical and psychological status;
   c) attitudes to life and its values;
   d) attitudes to support offered by the others.

Material and methods

The study was conducted between January and December 2015 after receiving approval of bioethics committee. Informed consent was obtained from all individual participants included in the study. Out of 320 disease-free cancer survivors initially enrolled in the study, 285 were qualified for the analysis. General characteristics of the study subjects are listed in Table 1.

The participants were examined with following tools:

1. Evaluation of physical and psychological health status according to Survivorship Assessment NCCN Clinical Practice Guidelines in Oncology patient version (NCCN Guidelines®) for cancer survivors, V.1.2015 © 2015 National Comprehensive Cancer Network Inc * The abovementioned guidelines/survey were used with NCCN permission [22].
2. Assessment of independent variables (by NRS):
   a) physical condition;
   b) psychological status;
   c) the attitude to life and health;
   d) impact of disease on participant's life;
   e) the attitude to support offered by others.
   f) overall and present satisfaction with life (NRS, 0–10 p.).
3. Assessment of global Quality of life (by NRS) — dependent variable.
4. Statistical analysis.

Table 2. Items 1-9 Survivorship Assessment, NCCN Guidelines (patient version)

Survivorship Assessment, NCCN Guidelines, items 1–9								
Symptoms		**Yes**		**No**		**Missing**		**Total**
		n	**%**	**n**	**%**	**n**	**%**	
Cardiac toxicity	1. Toxic effect on cardiovascular system, did patient receive previous anthracycline therapy	34	12.50	134	49.26	104	38.23	272
	2. Post-exercise dyspnea or pain	70	25.73	132	48.52	70	25.73	272
	3. Resting dyspnea	51	18.75	154	56.6	67	24.61	272
Anxiety and Depression	4. Loss of interest	55	20.22	150	55.14	67	24.63	272
	5. Depressiveness	60	22.05	148	54.41	64	23.52	272
	6. Worrying	69	25.36	137	50.36	66	24.26	272
Cognitive function	7. Ability to concentrate	74	27.20	142	52.20	56	20.58	272
	8. Remembering many things	113	41.54	107	39.33	50	19.11	272
	9. Slower thinking	121	44.48	102	37.50	49	18.01	272

Table 3. Reported fatigue and its severity (0–10 scale), item 10, 11 and 12 of Survivorship Assessment NCCN Guidelines

Survivorship Assessment, NCCN Guidelines, items 10, 11 and 12												
Symptoms						**Yes**		**No**		**Missing**		**Total**
						n	**%**	**n**	**%**	**n**	**%**	
Fatigue	10. Constant fatigue					86	31.61	135	49.63	51	18.75	272
	11. Fatigue interfering with normal activity					92	33.82	125	45.95	55	20.20	272
12. Fatigue level scale 0–10	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
n	22	5	12	14	13	59	18	14	16	5	14	272
%	8.08	1.83	4.41	5.14	4.77	21.69	6.61	5.14	5.88	1.83	5.14	100
	Mean fatigue score 4.88 ± 2.76											

The goal of this study was to analyze the effect exerted by the above-mentioned variables on the global quality of life of the study subjects (Pearson's coefficients of linear correlation).

The statistical analysis was carried out with STATISTICA v.12. Statistical significance of intergroup differences was verified with parametric Student t-test for continuous variables or chi-squared test for categorical variables. Power and direction of relationships between pairs of variables were estimated on the basis of Spearman's coefficients of rank correlation and Pearson's coefficients of linear correlation (r). Multivariate analyses were carried out using the Classification and Regression Trees (CART) [23].

Results

Survivorship Assessment NCCN showed that a high percentage of the patients had reported somatic complaints. Anxiety and depression symptoms were present in approximately 20% of cases. At least every third patient noticed decreased cognitive functions — the ability to concentrate (27%), remembering many things (41.5%), slower thinking (44.5%), (Table 2) constant fatigue (32%) and fatigue interfering with normal activity (33.82%, mean fatigue level was within medium range (4.9 points, 0–10 scale, Table 3).

Almost 40% of patients reported the presence of pain, with weak/medium intensity — mean =3.7 points in NRS Scale (Table 4).

About 30% of patients suffered from decreased satisfaction with sex, difficulty falling asleep (42.6%) (Table 5).

Scores for NCCN items in the study group — results transformed onto a 0–100 scale are displayed in Figure 1. High severity of self-reported cognitive decline is the most prominent result out of this assessment.

Patients reported high quality of life, overall and present life satisfaction and mostly no willingness to change it (all items scored about 7 or more points in 0–10 NRS scale. Health assessment scored relatively high — 6.9/10 points.

Table 4. The pain and its severity, item 13 and 14 of Survivorship Assessment, NCCN Guidelines

Survivorship Assessment, NCCN Guidelines, items 13 and 14												
13. Pain						**Yes**		**No**		**Missing**		**Total**
						n	**%**	**n**	**%**	**n**	**%**	
						108	39.70	103	37.86	61	22.42	100
14. Pain level scale 0–10	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
n	57	5	4	16	11	23	17	11	11	4	10	272
%	20.95	1.83	1.47	5.88	4.04	8.45	6.25	4.04	4.04	1.47	3.67	100
	Mean pain score 3.69 ± 3.27											

Table 5. Items 15–25 Survivorship Assessment, NCCN Guidelines (patient version)

Survivorship Assessment, NCCN Guidelines, items 15–25							
Symptom		**Yes**		**No**		**Missing**		**Total**
		n	**%**	**n**	**%**	**n**	**%**	
Sexual Function	15. Satisfaction with sexual life	102	37.5	81	29.77	89	32.72	272
	16. Sexual life concerns	58	21.32	126	46.32	88	32.35	272
	17. Sexual life concerns as a source of worries	39	14.33	139	51.10	94	34.55	272
Sleep Disorders	18. Difficulty falling asleep	116	42.64	103	37.86	53	19.48	272
	19. Excessive sleepiness	61	22.42	149	54.77	62	22.79	272
	20. Snoring	85	31.25	128	47.05	59	21.69	272
Healthy Lifestyle	21. Regular physical activity	104	38.23	118	43.38	50	18.38	272
	22. Fruit and vegetable intake	120	44.11	98	36.02	54	19.85	272
	23. Slimming diet	45	16.54	167	61.39	60	22.05	272
Immunizations and Infections	24. Influenza vaccination	43	15.80	180	66.17	49	18.01	272
	25. Any vaccination	44	16.17	181	66.54	47	17.27	272

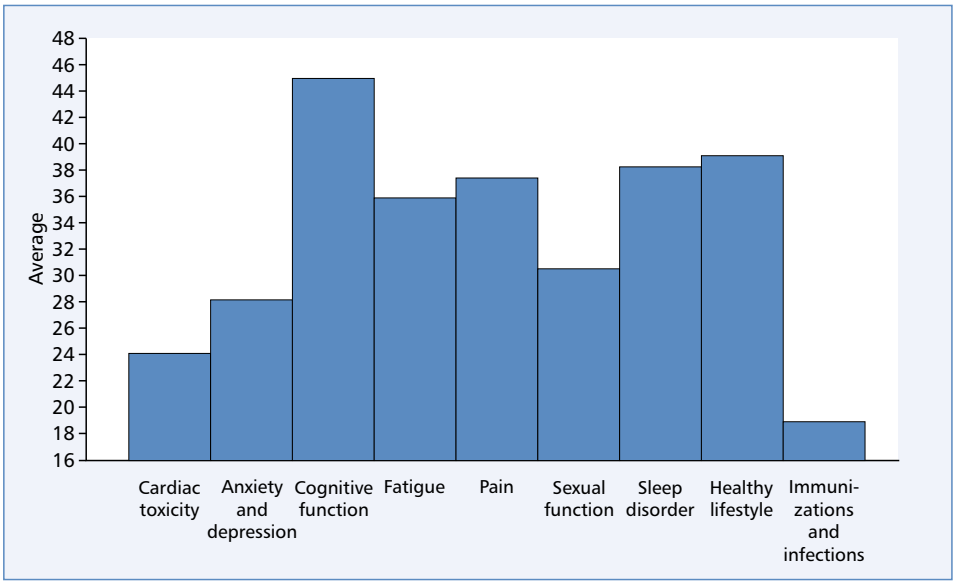

Figure 1. Scores for NCCN items in the study group (the result transformed onto 0–100 scale)

Table 6. Study subjects' attitudes to life and health, and life impact of their illness

Variable	Overall life satisfaction		Present life satisfaction		Life impact of illness		I would not change anything in my life		Health assessment		Quality of Life (QoL)	
Mean	M = 7.79		M = 7.73		M = 5.32		M = 6.9		M = 6.64		M = 7.23	
Score range	n	%	n	%	n	%	n	%	n	%	n	%
0–3	11	4.04	19	6.98	90	33.08	42	15.44	18	6.61	13	4.77
4–6	49	18.01	46	16.91	54	19.85	58	21.32	95	34.92	70	25.73
7–10	209	76.83	202	74.26	122	44.85	164	60.29	152	55.88	182	66.91
Missing	3	1.10	5	1.83	6	2.20	8	2.94	7	2.57	7	2.57
Total	272	100	272	100	272	100	272	100	272	100	272	100

Table 7. Study subjects' attitudes to external support and acceptance by others

Variable	Need for support		Received support		Acceptance by others	
Mean	M = 5.95		M = 7.09		M = 8.18	
Score range	n	%	n	%	n	%
0–3	80	29.41	46	16.91	35	12.86
4–6	44	16.17	48	17.64	19	6.98
7–10	140	51.47	171	62.86	209	76.83
Missing	8	2.94	7	2.57	9	3.30
Total	272	100	272	100	272	100

Approximately 67% of all respondents declared they need support from others (mean = 5.95/10, a great need for support — 51%), and that they receive it (M = 7.09 — highly satisfying support 62%). Mostly they and feel definitely accepted by other people (M = 8.18, 76%).

Chi-squared test showed a significant relationship between the items of NCCN Survivorship survey and quality of life in cancer survivors. Higher scores in anxiety and depression fatigue, pain, sleeplessness, depression, problems with concentration and disorders of memory affected negatively overall quality of life.

Spearman correlation of coefficients showed that quality of life correlated most strongly with health assessment (r = –0.74), life satisfaction (0.67), joy of life (0.63), and with "I would not change anything in my life" attitude (0.53) see Table 9.

Multivariate analysis showed predictor importance ranking of data affecting quality of life, overall and present life satisfaction, and no willingness to change anything in life, attitude and self-health assessment scored highest on 0–100 scale.

Discussion

Based on the assessment of psychophysical status in line with the NCCN guidelines, approximately 20% of the study subjects experienced emotional disorders (depressiveness, lack of joy, periodical worries), and 30–40% reported impaired cognitive functions.

These findings seem to be consistent with the results of studies conducted in other countries, especially for emotional factors, and partially also for cognitive ones (reported prevalence of cognitive disorders in European cancer survivors varies considerably, between 19% and 35%) [11, 12]. However, it needs to be emphasized that previous studies were conducted in different settings, and this fact should be considered while comparing their results with our findings.

Our patients reported physical ailments, such as fatigue and pain, more often than cancer survivors from other European countries (fatigue more than 30% *vs.* 17–26%, pain approximately 40% *vs.* 31%). The prevalence of sleep disorders among our patients and cancer survivors from other European countries was at a similar, relatively high level, approximately 30 *vs.* 50% [6]. This is not surprising owing that sleeplessness is also a common ailment in general population, especially among the elderly, and our study group was comprised primarily of older patients.

To summarize, 30–40% of long-term cancer survivors included in our study reported somatic ailments and cognitive impairment. The frequent occurrence of the latter is particularly alarming and deserves further extensive research.

Table 8. Health status determined in line with the NCCN guidelines. Relationship between the results and quality of life in cancer survivors, *p-values determined with chi-squared test

NCCN item		Y/N	Quality of Life			P*
			Low (0–3) %	Moderate (4–6) %	High (7–10) %	
Cardiac toxicity	1. Toxic effect on cardiovascular system, did patient receive previous anthracycline therapy	Yes	5.88	20.59	73.53	ns
		No	2.27	27.27	70.45	
	2. Post-exercise dyspnea or pain	Yes	8.70	31.88	59.42	< 0.05
		No	1.54	25.38	73.08	
	3. Resting dyspnea	Yes	4	28	68	ns
		No	3.95	25.66	70.39	
Anxiety and Depression	4. Lack of interest	Yes	7.41	33.33	59.26	0.05
		No	2.01	24.16	73.83	
	5. Depressiveness	Yes	11.67	36.67	51.67	< 0.001
		No	0.69	22.76	76.55	
	6. Worrying	Yes	10.14	33.33	56.52	< 0.001
		No	0.74	22.96	76.30	
Cognitive function	7. Ability to concentrate	Yes	5.48	42.47	52.05	< 0.001
		No	2.86	19.29	77.86	
	8. Remembering many things	Yes	6.25	32.14	61.61	< 0.05
		No	0.95	21.90	77.14	
	7. Slower thinking	Yes	5.79	33.88	60.33	< 0.01
		No	1.01	20.20	78.79	
Fatigue	8. Constant fatigue	Yes	9.52	34.52	55.95	< 0.001
		No	0.75	23.13	76.12	
	9. Fatigue interfering with normal activity	Yes	8.89	30	61.11	< 0.01
		No	0.81	24.19	75	
Pain	13. Pain	Yes	6.67	31.43	61.90	< 0.1
		No	1.94	23.30	74.76	
Sexual Function	14. Satisfaction with sexual life	Yes	0.00	24.75	75.25	< 0.05
		No	7.50	28.75	63.75	
	15. Sexual life concerns	Yes	8.77	24.56	66.67	ns
		No	1.60	28.80	69.60	
	16. Sexual life concerns as a source of worries	Yes	10.26	23.08	66.67	ns
		No	2.17	26.81	71.01	
Sleep Disorder	Difficulty falling asleep	Yes	5.22	39.13	55.65	< 0.001
		No	1.98	12.87	85.15	
	Excessive sleepiness	Yes	6.78	32.20	61.02	ns
		No	3.40	24.49	72.11	
	Snoring	Yes	4.76	29.76	65.48	ns
		No	3.97	24.60	71.43	
Healthy Lifestyle	Regular physical activity	Yes	3.92	25.49	70.59	ns
		No	3.45	29.31	67.24	
	Fruit and vegetable intake	Yes	2.52	25.21	72.27	ns
		No	6.25	30.21	63.54	
	Slimming diet	Yes	9.09	25.00	65.91	ns
		No	3.03	27.27	69.70	
Immunizations and Infections	Influenza vaccination	Yes	0.00	30.95	69.05	ns
		No	5.08	25.99	68.93	
	Any vaccination	Yes	2.38	28.57	69.05	ns
		No	4.47	26.82	68.72	

Approximately 40% of our participants declared undertaking regular physical activity and following a healthy dietary plan including fruits and vegetables. However, only 16% of the study subjects claimed that they have undergone a prophylactic vaccination.

Considering such somatic and psychological status of our participants, the results documenting their life and health attitudes and the impact of illness on their life seems to be quite surprising. Up to 70% of the respondents declared that they were satisfied with their current life, and approximately 60% assessed their subjective health as good or very good but emphasized that cancer had a very large or at least large impact on their life. Moreover, 90% of the respondents assessed their subjective quality of life as at least good or, even more often, very good.

These findings are partially inconsistent with the previously mentioned data about the somatic and psychological condition of the study subjects and imply that QoL of them might have been also influenced by other factors than the simple health indices.

Therefore, we investigated the role of support from friends and relatives, as the determinants of QoL in our study subjects. Approximately 80% of the study participants declared receiving support and being accepted by their relatives and friends, and according to more than 70% of the respondents, this type of support was highly desirable.

In light of the relationships mentioned above, we verified what was the impact of participants' health status, determined in line with the NCCN guidelines, on their QoL. Our analysis demonstrated that QoL in long-term cancer survivors was influenced both by their somatic and psychological status. This relationship was observed for some somatic ailments and psychological problems, namely fatigue, pain, sleeplessness, depression, problems with concentration and disorders of memory. These findings do not seem surprising in view of general concept of health-related quality of life.

As mentioned previously, we found an inconsistency between a relatively high prevalence of physical and psychological ailments and surprisingly high global QoL scores. We assumed that this discrepancy might result from the influence of other than physical and somatic determinants of health; according to literature, these

Table 9. Relationships between quality of life and the attitude to life, health, support and acceptance by other, p-values for Spearman's correlation coefficients

Variables	Quality of Life
Life satisfaction	0.6661 ($p < 0.001$)
I would not change anything in my life	0.5304 ($p < 0.0001$)
Joy of life	0.6340 ($p < 0.001$)
Health assessment	–0.7433 ($p < 0.001$)
Life impact of illness	–0.2262 ($p < 0.002$)
Need for support	–0.1241 ($p < 0.092$), ns
Received support	0.2230 ($p < 0.002$)
Acceptance by others	0.2703 ($p < 0.001$)
Age	0.0120 ($p < 0.871$), ns
Sociodemographic characteristics	–0.0396 ($p < 0.592$), ns

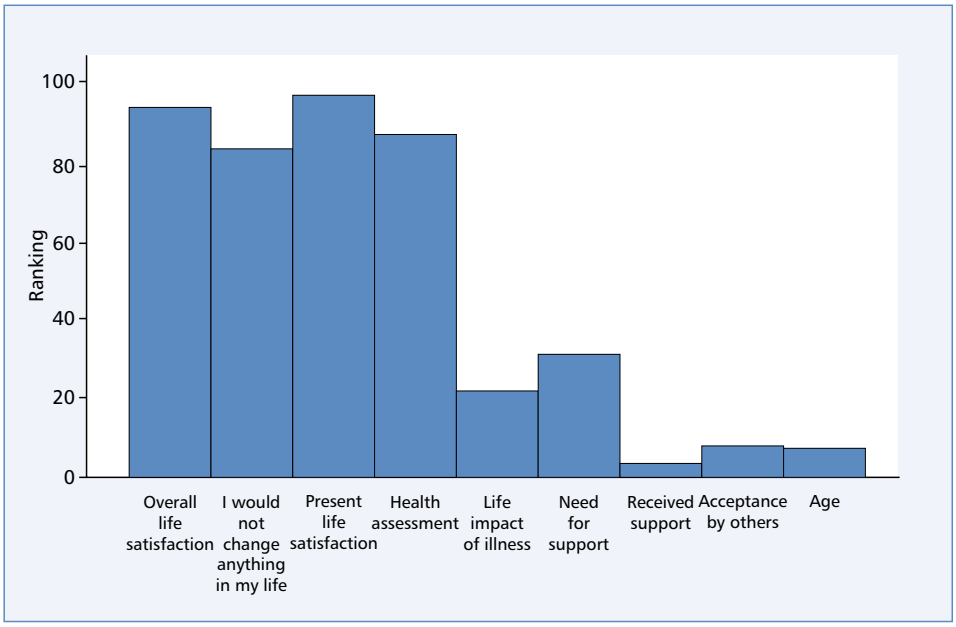

Figure 2. Ranking of predictors importance. Dependent variable: QL. Ranking from 0 (low validity) to 100 (high importance)

alternative determinants may include a disease-driven change in patients' attitude to life and support from others [19–22]. These changes are sometimes considered as a manifestation of post-traumatic growth. Therefore, we verified if the attitude to life, health and support influenced QoL in long-term cancer survivors. Nearly all these explanatory variables turned out to be significant correlates of QoL in our series. While most of them correlated positively with QoL, the inverse associations were found for the life impact of the illness: the higher was the score for this variable the lower was the QoL of the study subject. Positive correlations between the quality of life and other explanatory variables imply that those parameters might be equally important determinants of QoL as somatic indices. This fact should be considered during planning of comprehensive support for cancer survivors.

Conclusions

To summarize, this study demonstrates that:

— Characteristics of physical and psychological status in Polish cancer survivors were rather similar to those in cancer survivors from other countries.
— Relatively high prevalence of physical ailments and emotional disorders suggests that cancer survivors may require more specialist care than previously supposed.
— Alarmingly high prevalence of cognitive disorders in cancer survivors justifies research on their etiology and possible interventions.
— Considering their general characteristics, cancer survivors presented with surprisingly high global quality of life, life satisfaction and joy of life scores. This might reflect high levels of received support, acceptance, as well as attitudes towards life and illness. However, the latter hypothesis needs to be verified during the course of further research.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research ethics committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest

All authors declare that they have no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Lung cancer in women: is gynecological and obstetrical history important?

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Oncology in Clinical Practice
2021, Vol. 17, 98–102
DOI: 10.5603/OCP.2021.0004

ISSN 2450–1654
e-ISSN 2450-6478

ABSTRACT

Introduction. Lung cancer remains the most frequent cause of death related to cancers, reaching 1.8 mln worldwide. We observe globally that the incidence of lung cancer in the never smokers affects women disproportionately more often than men.

Material and methods. The aim of the study was to analyse the data about women suffering from lung cancer, with particular emphasis on their gynecological and obstetrical history. Women with confirmed primary lung cancer were evaluated (n = 29). Information about smoking, gynecological and obstetrical history was obtained from a self-administered questionnaire. Demographic data were also collected.

Results. The most frequent lung cancer was adenocarcinoma (51.7%), followed by squamous-cell carcinoma (31.0%) and small-cell lung cancer (17.2%). Epidermal growth factor receptor (EGFR) mutations were present in 3 cases. The vast majority of women were smokers (89.7%) with median 30 pack years (IQR 20–48). Evaluating the TNM classification, the highest number of patients was classified to stage III (44.8%).

The median age of menarche was 14 years, menopause — 50 years, the number of days with bleeding in the menstrual cycle — 4 and the length of the menstrual cycle — 28 days. An overwhelming majority of women have given birth to a child. Women reported extended menstrual cycles as the most frequent menstrual disorder (6 cases, 20.7%). Hormone replacement therapy and intrauterine contraceptive device use were declared in 10.3%.

Conclusions. The results based on the small group of patients did not reveal any significant gynecological dysfunctions in our sample group with lung cancer.

Key words: lung cancer, women, gynecological history, estrogen, smoking

Oncol Clin Pract 2021; 17, 3: 98–102

Introduction

The increasing number of cancers worldwide should prompt a search for relationship between cancers and various risks factors. The WHO data show that the number of new cases of lung cancer is around 2 million globally, which represents approximately 11.6% of all cancers and puts it in the first place. Lung cancer remains the most frequent reason of death related to cancers, reaching 1.8 million worldwide. The figures for women are as follows: 725 thousand cases and 576 thousand deaths due to that reason in 2018. In Europe, the age-standardized incident rate in females oscillates between 11.9–26.9 per 100 thousand [1]. Analyzing the data in Poland, the number of new diagnoses of lung cancer among women in last years is calculated to be 7,000 per year which represents approximately 10% of all cancer cases. Unfortunately, in Poland the number of deaths due to lung cancer in females is higher than the number of new cases (7,500 deaths per year which corresponds to 17% of all deaths caused by cancers) and the five-year survival rate for lung cancer is about 13.5% [2].

These calculations are worrying and encourage the world of science to find new interrelations of medical history with risk factors and endogenous causes.

Undoubtedly smoking still remains the main reason for lung cancers in the western populations, being responsible for more than 80% of cases [3]. Currently estimated global prevalence of tobacco smoking ac-

cording to WHO is 18.7% for both sexes and is much higher for men than women (31.9% for males and 5.4% for females). Data from the Global Adult Tobacco Survey disclosed that the male/female prevalence ratio for smoking was the highest in Egypt and the Asian countries and was the lowest among others in Poland [4].

Moreover, we observe the incidence of lung cancer in the never smokers which affects women disproportionately more often than men. The incidence of females with non-smoking lung cancer is estimated to be 14.4–20.8/100,000 and in contrast in males the rate is — 4.8–13.7/100,000 [5, 6]. This difference between men and women indicates that, besides smoking, there are other factors influencing the development of non-small cell lung cancer (NSCLC) in women. The most often non-smoking patients suffer from adenocarcinoma [7].

In a few articles the attention was drawn to some differences in lung cancer depending on sex. These are the following: the median age of diagnosis of lung cancer is lower among females than among males; females have better outcomes at all diagnosis stages; *EGFR* gene mutation is more common in females [8–10]. The association between carcinogenesis of lung cancer and female hormones, aromatase expression, pituitary sex hormone receptors are investigated [11].

Searching for the reasons of these differences, scientists investigated the role of female hormones. The results show that estrogens seem to play a role in development of lungs in both sexes — two types of estrogen receptors (ERα and ERβ) were found in lungs [12]. Rodriguez-Lara et al. [13] revealed that estrogen receptors (ERβ) are overexpressed in adenocarcinomas compared to normal lungs. Additionally, they noticed that premenopausal women with adenocarcinoma exhibited higher signals for ERβ compared to postmenopausal women and to men, who showed lower signals for these proteins.

In many reports the ER status was taken into consideration as a factor of non-small cell lung cancer patient survival. Some studies show that in particular nuclear ERβ positivity, which was observed in the majority of lung cancer cases, is assumed to be a favorable prognostic indicator [14]. In another study, significant survival benefit was showed among patients suffering from adenocarcinoma who had positive expression of hormonal receptors (among others Erα) [15].

Considering the influence of female hormones on lung cancer, we obviously should check the contribution of hormone replacement therapy (HRT).

When investigating the subject of female hormones, we cannot ignore the role of aromatase (the enzyme that catalyzes androgen aromatization into estrogen). Aromatase staining by immunohistochemistry is detected in up to 86% of NSCLC [16]. Niikawa et al. [17] found a significantly higher concentration of estradiol in the intratumoral NSCLC than in the non-neoplastic lung tissues and it was positively correlated with the intratumoral aromatase expression [17, 18].

The aim of the study was the analysis of information on women suffering from lung cancer, with particular emphasis on their gynecological and obstetrical history.

Material and methods

Women admitted to the Department with principal diagnosis of lung tumor were evaluated in this study. All patients were anticancer treatment-naive. Demographic data were collected and information about smoking history, gynecological and obstetrical history was obtained from a self-administered questionnaire. Patients were also evaluated according to the 8th edition of the TNM classification for lung cancer. All women gave their informed consent to participate in the study. The study was approved by the local bioethics committee.

Results

Finally, 29 women with pathologically confirmed primary lung cancer were enrolled. The median age of women with lung cancer was 67 (IQR 62–72). The most frequent lung cancer was adenocarcinoma (51.7%), followed by squamous-cell carcinoma (31.0%) and small-cell lung cancer which was diagnosed in 5 cases (17.2%). Activating mutations in the *EGFR* gene were found in 3 patients. The vast majority of women were smokers (89.7%) with median 30 pack years (IQR 20–48). Evaluating the TNM classification, the highest number of patients was classified as stage III (44.8%) (Table 1).

The median age of menarche was 14 years, menopause — 50 years, the number of days with bleeding in menstrual cycle — 28 and the length of the menstrual cycle — 4 days. An overwhelming majority of women have given birth to a child (natural labor — 86.2%, caesarean section — 10.3%). Miscarriage and gynecological operations were present in 31.0% of cases. Women reported extended menstrual cycles (defined as more than 35 days) as the most frequent menstrual disorder (6 cases, 20.7%). Hormone replacement therapy and intrauterine contraceptive device use were declared in 3 cases. The precise results are presented in Tables 2 and 3.

Discussion

The aim of the study was to analyse possible association of gynecological and obstetrical history with

Table 1. Characteristics of the study group

Number of women	29
Adenocarcinoma	15 (51.7%)
Squamous cell carcinoma	9 (31.0%)
Small cell lung cancer	5 (17.2%)
EGFR mutations	3 (10.3%)
TNM (I/II/III/IV) (% all cases)	3 (10.3 %)/5 (17.2 %)/ /13(44.8 %)/8 (27.6 %)
Smokers/non-smokers (% all cases)	26 (89.7%)/3 (10.3%)
Median pack years of smoking	30 (IQR 20–48)
Median age for a diagnosis of lung cancer	67 (IQR 62–72)

Data presented as number of cases (% all cases) or median; IQR — interquartile range

Table 2. Characteristics of menstrual cycle of women with lung cancer

Menarche (years old)	14 (IQR 13–15)
Menopause (years old)	50 (IQR 46–52)
The length of the menstrual cycle (days)	28 (IQR 28–30)
Number of days with bleeding in the menstrual cycle	4 (IQR 4–6)

Data presented as number of cases (% all cases) or median; IQR — interquartile range

Table 3. Gynecological and obstetrical history of women with lung cancer

Natural labor n (%)	25 (86.2%)
Miscarriage n (%)	9 (31.0%)
Week of miscarriage (week)	8 (IQR 7–12)
Gynecological operations n (%)	9 (31.0%)
Extended menstrual cycles n (%)	6 (20.7 %)
Intrauterine contraceptive device n (%)	3 (10.3%)
Caesarean section n (%)	3 (10.3%)
Hormone replacement therapy n (%)	3 (10.3%)
Shortened menstrual cycles n (%)	1 (3.4 %)
Intermenstrual bleeding n (%)	1 (3.4 %)

Data presented as number of cases (% all cases) or median; IQR — interquartile range

the risk of lung cancer among women. The rationale for this work comes from the knowledge on a possible role of steroid hormones in lung carcinogenesis [19, 20]. The clinical investigation of a relationship between hormonal status and lung cancer is worth undertaking in different populations. However, our results show that the simple gynecological and obstetrical history of lung cancer women was not specific and did not differ from Polish women.

Many studies have tried to evaluate the association of lung cancer with some menstrual and reproductive factors, but the results have been generally inconsistent. The pooled analysis of these factors was conducted in the international lung cancer consortium where data were collected from 8 different studies (from North America and Europe) involving more than 4,000 women. The majority of studied population was Caucasian (> 80%). The results showed that the mean age of women diagnosed with lung cancer was 63.3 years, adenocarcinoma was the most frequently found histological type (47%), followed by squamous-cell carcinoma (14%), while small-cell lung cancers were represented in 7% of all the cases [21]. The vast majority of women were current (46.3%) or former smokers (38.4%). Comparing to our results, adenocarcinoma was present in 51% cases, squamous-cell carcinoma in 31% and small-cell cancer in 17.2% of patients. In our study cigarette smoking is still an important single factor for lung cancer — these data coincide with national registers. High prevalence of smoking women and high median pack years show that there is still plenty to do in encouraging women to quit smoking in Poland. *EGFR* mutation was present in 10.3% of cases which is also on line with the estimated number for that mutation in Caucasian race [22].

The small number of patients represent main limitation of our study — there were limited possibilities for a deeper statistical analysis of the data. The results based on such a small group of patients did not reveal any significant gynecological dysfunction. The median age of menarche seems to be higher than current global average which is 12 years, but we need to notice that this age is declining in recent years [23].

Late age of menarche was assessed as a risk for lung cancer in many studies. One meta-analysis resulted in slightly, non-significantly decreased risk of lung cancer among women with late age of menarche [24], but it was not confirmed in many currently published studies [21, 25, 26].

The median length of the menstrual cycle (days) and the number of days with bleeding in menstrual cycle was within normal limits, but women reported extended menstrual cycles (> 35 days) as the most frequent disturbance. It is reported that longer length of menstrual cycle can be associated with a decreased lung cancer risk [24].

The median age of menopause in our study was 50 years, comparing to the global data with the mean age of menopause of 51 years (range of variation between 40 and 60 years old) [27]. There was some evidence that postmenopausal status is related to increased lung cancer risk particularly in Europe, what was presented in one meta-analysis concerning menopausal status and risk of lung cancer in women [28]. Also, data from the pooled analysis quoted above showed that menopausal

status was associated with a statistically significant 50% increased risk of lung cancer with minor differences according to the smoking behaviour [21]. That makes us wonder whether postmenopausal females should be taken under special care and appropriate observation in the screening programs.

Hormone replacement therapy (HRT) was not frequently used in our study group. The role of HRT in lung cancer seems to be unclear. Some study results suggest that the association of HRT with lung cancer was dependent on duration, with the highest risk for users of estrogen plus progestin for ≥ 10 years [29]. On the other hand, the meta-analysis of cohort studies has shown that HRT history had no effect on the risk of lung cancer in females [30]. The meta-analysis from 2019 suggests that ever use of HRT is associated with a decreased risk of lung cancer in women [31]. Contraceptive use was not often reported in our study as well. The meta-analysis based on twenty-five articles, representing 24 independent studies from 2012, showed that contraceptive use was not a factor associated with a significant risk for lung cancer [24].

An interesting study related to the topic from 2020 was performed in Korea. The reproductive factors and the risk of lung cancer in postmenopausal Korean women were taken into consideration. The study revealed that the risk for lung cancer was not significantly affected by early menarche age or late age at menopause. Other factors — number of children, duration of breastfeeding and use of hormone replacement therapy — were not associated with the risk for lung cancer [32]. These results are consistent with our observation.

In spite of the limitation in our study and nonconclusive results, we assume that the association between lung cancer and gynecological and obstetrical factors seems to be an interesting issue which needs further well-designed studies.

Conflict of interest

None of the authors have a conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

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Radiotherapy in Ewing's Sarcoma Family Tumor — experience from North-East India

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 103–111
DOI: 10.5603/OCP.2021.0008

ISSN 2450–1654
e-ISSN 2450-6478

ABSTRACT

Introduction. The multimodality management of Ewing's Sarcoma Family Tumors (ESFT) consists of neoadjuvant chemotherapy followed by local treatment: surgery, radiotherapy (RT) or a combination of both. The objectives of this study were to analyze disease control and overall survival in patients receiving radiotherapy as local treatment, as part of multimodality management of ESFT at our institute over a period of seven years.

Material and methods. This is a retrospective single institutional study. Hospital records were searched for patients with ESFT who received radiotherapy from January, 2012 to December, 2018. Forty-nine patients were found eligible and evaluated with respect to prognostic factors, treatment-related factors and outcomes. Time to event was measured from the date of diagnosis and survival curves were estimated by Kaplan-Meier method and log-rank test for comparison.

Results. Median follow up for patients was 18 months (range 3–81 months). Local failure/relapse was associated with worse survival. Five-year local control was 79.1% and overall survival 51.2% in the analyzed cohort. Local control did not differ significantly based on prognostic variables or treatment characteristics. Combined surgery and radiotherapy as local treatment along with good response to neoadjuvant chemotherapy were associated with significant improvement in overall survival (p-value < 0.05).

Conclusions. Combined modality local treatment with surgery and radiotherapy along with a favorable response to neoadjuvant chemotherapy are associated with improved survival in ESFT. For unresectable tumors, radiotherapy alone remains the optimum local treatment, albeit with inferior survival outcomes.

Key words: Ewing's Sarcoma, PNET, ESFT, radiotherapy, surgery, chemotherapy

Oncol Clin Pract 2021; 17, 3: 103–111

Introduction

The Ewing's Sarcoma Family of Tumors (ESFT) comprises of a group of primary bone and soft-tissue tumors that include classic Ewing's sarcoma (osseous and extra-osseous), peripheral primitive neuroectodermal tumor (PNET) and Askin tumor of the chest wall. Histologically they are malignant small-round-blue-cell tumors, first described by James Ewing in 1921 [1]. Around 90% of patients have a genetic translocation [t(11;22) or t(21;22)] involving the *EWS* and *FLI1* genes and frequent expression of *c-Myc proto-oncogene* [2].

The incidence of Ewing-family tumors peaks in adolescence, is slightly more common in males, and commonly arises in the extremities [3]. It has a high incidence in the Western population while being rarer in Asia and Africa [4].

Ewing's Sarcoma has a good prognosis nowadays with the advent of newer regimens of systemic therapy in combination with adequate local treatment [5–10]. Definitive local control of the primary tumor is a pre-requisite of cure, and local failures are associated with extremely poor prognosis. Local treatment modalities in Ewing's sarcoma consist of surgery and/or radiotherapy (RT). Because of the radiosensitive nature

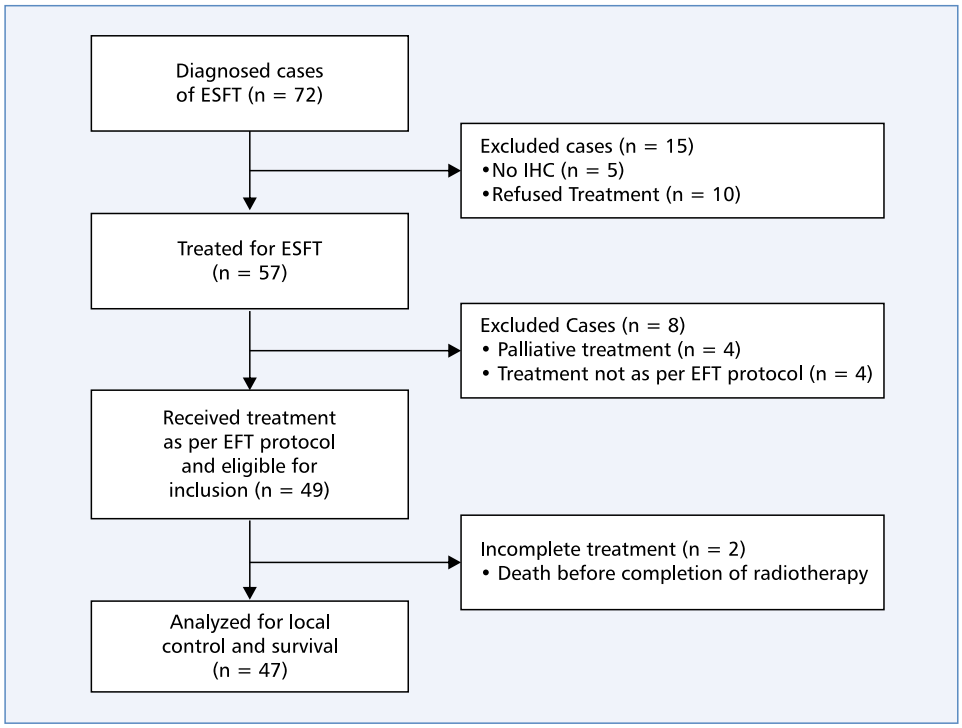

Figure 1. Schematic chart showing patient evaluation and analysis for the study

of this tumor, radiotherapy had been the local treatment of choice for many years. However, with better systemic control of disease, advances in orthopedic surgery and chances of second malignancy post irradiation, the use of radiotherapy in ESFT is gradually declining [11]. However, for lesions located in the axial skeleton or where surgery is not feasible, RT remains the sole option for local therapy.

In this single-institution retrospective study from North East India, we investigate the role of radiotherapy as local treatment in the multimodality management of ESFT patients. The objectives were to analyze disease control and overall survival in patients of this group of tumors receiving radiotherapy at our institute over the study period.

Material and methods

From the period of January, 2012 to December, 2018, patients registered with diagnosis of Ewing's Family Tumor in the hospital were assessed. All data were obtained from patients' case files and Hospital-Based Cancer Registry records and all the analyzed data for this study are included in this published article. The study was approved by the Institutional Ethics Committee and because this was a retrospective study, the requirement of patients' consent was waived.

Patients

Patients diagnosed as osseous or extra-osseous Ewing's Sarcoma, peripheral Primitive Neuro-Ectodermal Tumor (PNET) and Askin's tumor of the chest wall with Immunohistochemistry confirmation (CD 99, FLI-1 positive) were considered for evaluation in this study. Those without IHC confirmation of tumors and who declined or defaulted treatment were excluded. Also, patients who did not receive radiotherapy as part of their local treatment were omitted from assessment in this study. A summary of cases evaluated and analyzed is shown in Figure 1.

Taking into consideration the above criteria, 49 patients were found eligible for retrospective review during the study period. Patient demographics, tumor characteristics and treatment details for them were noted.

Treatment and follow-up

The intent of treatment received was as per the decision of the Multidisciplinary Joint Tumor Board of the institute and all patients received treatment as per Ewing's Family Tumor (EFT) protocol. Neoadjuvant Chemotherapy included two courses of Vincristine, Ifosfamide and Etoposide (VIE) 3 weekly followed by two courses of Vincristine, Adriamycin and Cyclophosphamide (VAC) 2 weekly. Local therapy in the form of surgery or radiotherapy or both, depending on the

location and resectability of the primary tumor, had to be offered between weeks 9 and 12 of treatment. Resectable tumors underwent surgery as the primary local treatment followed by adjuvant radiotherapy based on histopathology and margin status. Borderline resectable cases after induction chemotherapy underwent pre-operative radiotherapy followed by surgery, whereas tumors which were found inoperable received radical radiotherapy alone as local treatment. Radiotherapy doses were 45 Gy pre-operatively, 50–54 Gy post-operatively and 50–60 Gy in radical setting (at 180–200 cGy per fraction). Maintenance therapy after local treatment consisted of 3 weekly chemotherapy with 4 cycles of VAC, 2 cycles of VIE and 6 cycles of VCD – Actinomycin D replacing Doxorubicin after a cumulative dose of 360 mg/m^2. Vincristine was given weekly throughout the chemotherapy schedule and also along with radiotherapy [12].

Treatment records of patients were evaluated for details of chemotherapy, surgery and radiotherapy received by them. Follow up details of local examination and imaging of primary site as well as metastasis was also noted. Response to induction chemotherapy was assessed from the surgical specimen in resected cases and by imaging in unresected cases.

Outcome analysis

Response to treatment was classified as per the revised Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 [13]. A good response to induction chemotherapy was classified as > 90% necrosis in resected specimen in patients who underwent surgery and a complete or partial response in the tumor site for unresectable cases.

Tumors with complete or partial response or stable disease at the primary site without appearance of new metastatic lesions were considered locally controlled. Disease progression was defined as clinical or radiographic increase in the size of primary or metastatic tumor or appearance of new metastatic lesion. Overall survival (OS) was defined as the time interval from diagnosis till death.

Statistical analysis

SPSS version 19 (IBM Company Copyright 1989, 2010 SPSS, Inc.) was used for statistical analysis. Chi-square test was used to evaluate treatment and prognostic factors for local control. Survival and local control rates were calculated using Kaplan-Meier estimation and log-rank test was used for group comparisons. A Cox proportional hazards model was used to clarify independent predictive factor in multivariate analysis. Statistical significance was defined as a p-value of < 0.05.

Results

The median follow up of entire cohort was 18 months (Range 3–81 months). The various patient- and tumor-related variables of the study are shown in Table 1.

Patient characteristics

The mean age of patients was 15.29 years (SD: 10.13), with 53.1% patients aged 10–19 years and Male:Female ratio of 1.7:1. The median duration of symptoms among the patients was 5 months (Range: 1–12 months).

Tumor characteristics

The mean tumor size was 9.09 cm (SD = 3.44). The majority of cases showed presence of a soft tissue mass (85.7%) with radiological evidence of tumor necrosis in 34.6%. Most common sites of tumor location were the femur and pelvis (n = 7, 14.3% each). Most of tumors had skeletal origin (73.5%) and were centrally located (61.2%). Four patients (8.2%) had metastatic disease at diagnosis with bone metastasis being most common (3 cases).

Treatment characteristics

All 49 patients included in the study were planned with intent to cure or salvage (Fig. 1). Neoadjuvant chemotherapy was received by all except one patient. Surgery as local treatment was used in 14 cases, with 11 patients undergoing complete resection with clear margins (R0) while 3 had marginal/intralesional resection of their tumors. All patients that underwent surgery also received radiotherapy — 5 preoperative and 9 postoperatively.

Radiotherapy was the definitive local therapy planned in 71.4% (35/49) of our patients. Among them, a dose of 54 Gy or above was used in 28 patients, 5 patients received less than 54 Gy and 2 patients died before radiotherapy completion (one each from sepsis and disease progression). Radiotherapy was delivered using conventional planning techniques in majority (63.2%) of the patients (Tab. 1).

Local control and survival analysis

The 2 patients of ESFT who could not complete planned radiotherapy treatment were omitted from survival and disease specific analysis and hence the total number of cases for final evaluation was 47. The 5-year local control and overall survival for the study group was found to be 79.1% and 51.2%, respectively (Fig. 2). An important prognostic indicator of better survival was achievement of local disease control. Cases where

Table 1. Patient and tumor related characteristics

Variables	n (%)
Age	
< 18 years	38 (77.6%)
18 years and above	11 (22.4%)
Sex	
Male	31 (63.3%)
Female	18 (36.7%)
Duration of Symptoms	
< 6 months	26 (53.1%)
6 months and above	23 (46.9%)
Imaging for Staging	
CT Scan	27 (55.1%)
MRI	17 (34.7%)
PET-CT Scan	5 (10.2%)
Tumor Size	
Less than 8 cm	20 (40.8%)
8 cm and above	29 (59.2%)
Tumor Site	
Skeletal	36 (73.5%)
Extra-Skeletal	13 (26.5%)
Tumor Location	
Central	30 (61.2%)
Peripheral	19 (38.8%)
Metastasis at Diagnosis	
Yes	4 (8.2%)
No	45 (91.8%)
NACT	
Yes	48 (98%)
No	1 (2%)
Radiotherapy Technique	
Conventional	31 (63.2%)
3DCRT	14 (28.6%)
IMRT	4 (8.2%)

CT — computed tomography; MRI — magnetic resonance imaging; PET-CT — positron emission tomography-computed tomography; NACT — neo-adjuvant chemotherapy; 3DCRT — 3-Dimensional conformal radiotherapy; IMRT — intensity modulated radiation therapy

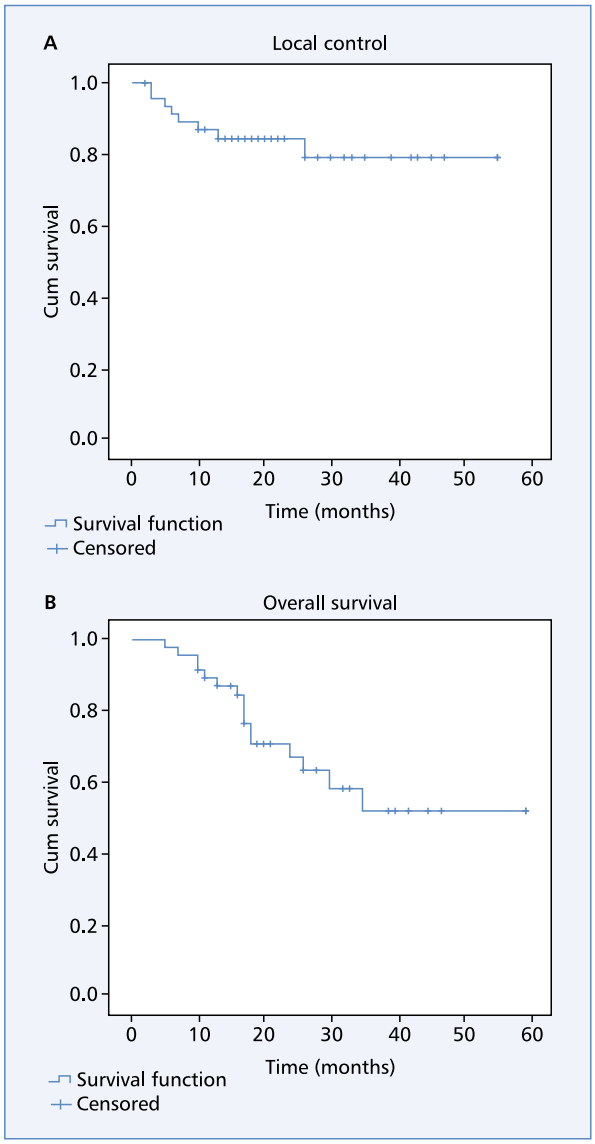

Figure 2. Kaplan-Meier curves showing local control (A) and overall survival (B) of study group (n = 47)

primary tumor was locally controlled following multimodality therapy had significantly better 5-year overall survival (53.3% *v.* 33.3%, p = 0.038, Fig. 3).

Univariate analysis of the patient-, tumour- and treatment-related characteristics with local control was carried out and is depicted in Table 2. Univariate and multivariate analysis of various prognostic factors with survival for these patients are shown in Table 3.

Local control rates did not differ significantly among the different enlisted prognostic variables (all p-values > 0.05). A subset analysis was performed to look into the impact of local treatment modality with respect to tumor size (< 8 cm *v.* 8 cm and above) and location (central vs peripheral), which is shown in Figure 4. Local control with combined surgery and radiotherapy was better compared to definite radiotherapy irrespective of these variables, but the difference was statistically insignificant.

A favorable response to neoadjuvant chemotherapy (p-value = 0.044) and combined surgery and radiotherapy as local treatment therapy (p-value = 0.022) were also associated with better survival in patients with non-metastatic ESFT. On multivariate analysis, response to neoadjuvant chemotherapy was found to be the only independent prognostic factor for OS (HR: 0.301, 95% CI: 0.093–0.970, p-value: 0.044).

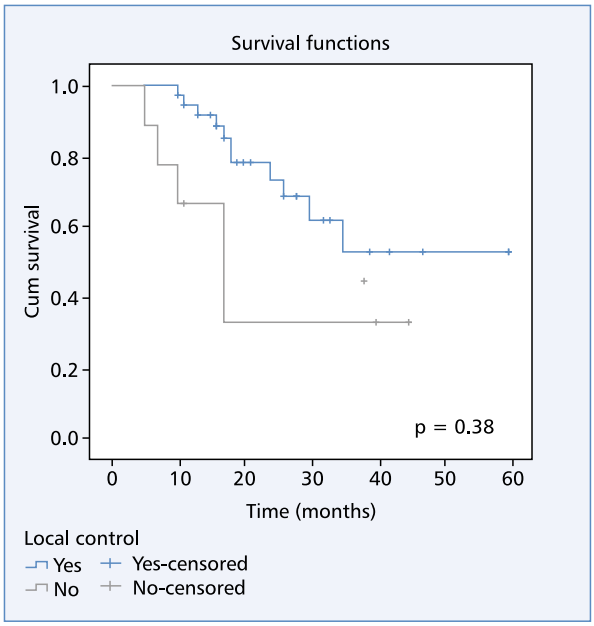

Figure 3. Kaplan-Meier curves showing overall survival based on local disease control status for study group (n = 49)

Discussion

ESFTs are comparatively rare in Asian population [4, 14]. Chakraborty et al. [15] reported that ESFT comprises 15% of all bone malignancies in India. They found 68% of the cases in 0–19 years age group with male preponderance (1.6:1) and a higher risk of tumor in the bones of limbs (1.6 times) compared to other bones. Our findings (Tab. 1) correlate with their observation except that most of our cases had tumors located in the axial skeleton and pelvis (61.2%) rather than in the limb bones. The median duration from symptoms to definitive diagnosis in our patients was 5 months, which correlates with the findings by Sneppen et al. [16] who reported a median duration of 3 to 9 months. The majority of patients in our study (59.2%) had large tumor size (≥ 8 cm) which is an established poor prognostic factor [9, 17, 18]. Another observation to be noted was the high percentage of patients with good response to neoadjuvant chemotherapy (76.5%) — a prognostic indicator of better survival [19–21]. Around one fourth of Ewing's sarcoma patients have metastatic disease upfront and often show a dismal prognosis. [3] In our study, however, the proportion of metastatic cases were low (n = 4, 8.2%). This was because the majority of metastatic ESFT cases often presented with poor general condition and hence received palliative therapy, which made them ineligible for inclusion in this study.

The role of chemotherapy in successful treatment of ESFT has evolved considerably over last few decades and is still evolving. [12] The Intergroup Ewing's Sarcoma Studies (IESS) I and II [5, 6] and the study by Grier et al. [7] established the role of multidrug chemotherapy in the management of ESFT. The Childrens Oncology Group AEWS-0031 study [8] subsequently demonstrated the

Table 2. Univariate analysis of local control of the localized Ewing's Sarcoma Family Tumor cases

Variables	n (%)	Univariate Analysis	
		5-year Local Control (%)	p-value
Age			
< 18 years	36 (76.5)	90.9	0.52
18 years & above	11 (23.5)	76.9	
Tumor Size			
< 8 cm	19 (40.4)	87.5	0.103
8 cm & above	28 (59.6)	75.3	
Tumor Location			
Central	28 (59.5)	80.9	0.756
Peripheral	19 (40.5)	78.3	
Response to NACT			
Yes	36 (76.5)	82.2	0.592
No	10 (21.2)	78.8	
Type of Local Treatment			
Surgery + RT	14 (29.8)	92.3	0.214
RT alone	33 (70.2)	71.0	
RT Dose (Definitive RT only)			
< 54 Gray	5 (15.2)	69.4	0.996
54 Gray and above	28 (84.8)	80.0	

NACT — neoadjuvant chemotherapy; RT — radiotherapy

Table 3. Univariate and Multivariate Analysis of Overall Survival of the Localized ESFT cases

Prognostic Factors	n (%)	Univariate Analysis		Multivariate Analysis	
		5-year OS (%)	p-value	HR (95% CI)	p-value
Age					
< 18 years	36 (76.5)	51.2	0.96	1.020 (0.273–3.809)	0.977
18 years & above	11 (23.5)	39.0			
Tumor Size					
< 8 cm	19 (40.4)	62.8	0.264	2.205 (0.627–7.753)	0.218
8 cm & above	28 (59.6)	41.5			
Tumor Location					
Central	28 (59.5)	32.9	0.055	0.283 (0.076–1.055)	0.060
Peripheral	19 (40.5)	78.9			
Duration of Symptoms					
< 6 months	25 (53.2)	60.5	0.463	1.302 (0.453–3.743)	0.624
6 months and above	22 (46.8)	43.4			
Response to NACT					
No	10 (21.2)	19.0	0.044	0.301 (0.093–0.970)	0.044
Yes	36 (76.5)	61.4			
Type of Local Treatment					
Surgery + RT	14 (29.8)	83.3	0.022	0.387 (0.079–1.887)	0.240
RT alone	33 (70.2)	31.1			

NACT — neoadjuvant chemotherapy; RT — radiotherapy; OS — overall survival; HR — hazard ratio; CI — confidence interval

benefit of dose intensification and interval compression of chemotherapy regimen without increased toxicity. So, the current standard of care is initial cytoreductive chemotherapy to eliminate micrometastasis followed by local therapy of primary disease and then consolidation chemotherapy to reduce tumor recurrence. In our study, all but one patient received treatment as per the Ewing Family of Tumors 2001 protocol. One patient did not receive neoadjuvant chemotherapy but underwent upfront surgery followed by adjuvant radiotherapy and chemotherapy. The reason for declining neoadjuvant chemotherapy for this patient could not be ascertained owing to the retrospective nature of this study.

Effective local treatment of the primary tumor plays a crucial role in the outcome of ESFT patients. In our study, local control showed significant correlation with survival: 5 year overall survival 53.3% in locally controlled patients as opposed to 33.3% in local failures or relapsed cases (p-value = 0.038). Till date, there are no randomized controlled trials comparing surgery versus radiotherapy in ESFT and all data available are retrospective in nature [9, 17, 18].

Schuck et al. [9] reviewed 1058 patients of localized ESFT for the impact of local therapy on local control and event free survival. Definitive radiotherapy showed higher incidence of local failure and poorer EFS after 5 years as compared to surgery with or without radiotherapy groups (p value < 0.05). They also demonstrated that intralesional or debulking surgeries followed by adjuvant radiotherapy offered no advantage over definitive radiotherapy and hence should be avoided.

Choi et al. [17] from South Korea reviewed 91 localized ESFT patients and reported higher local control rates with combined surgery and radiotherapy versus definitive radiotherapy (90.2% *v.* 64.8%, p value = 0.052). The superiority was found to be significant for tumors 8 cm or more in size (p value= 0.033) but not for smaller tumors (p value = 0.374).

Biswas et al. [18] in a single institution retrospective review have published the largest reported data on localized ESFT (224 cases) from India. They observed 5-year overall survival of 52.4% (± 4.3%) and local control rate of 63% (± 4.3%). On subgroup analysis, combined surgery and radiotherapy showed a hazard ratio of 2.5 (95% CI 1.2–5.19, p-valu e= 0.01) compared to radiotherapy alone for local control and also significantly improved 5-year event-free survival (50.4% *v.* 32.1%) and overall survival (69.1% *v.* 46.9%).

In our study, ESFT cases (n = 47) showed a 5-year local control rate of 79.1% and overall survival of 52.1%. Local control rates did not differ significantly among the various prognostic groups like age, tumor size, tumor location or response to neoadjuvant chemotherapy (all p-values > 0.05) as shown in Table 2. Fourteen patients (29.8%) underwent resection of their tumors in our study — 5 patients received radiation preoperatively and 9 patients postoperatively. Radiotherapy was delivered preoperatively in large tumors of resectable locations

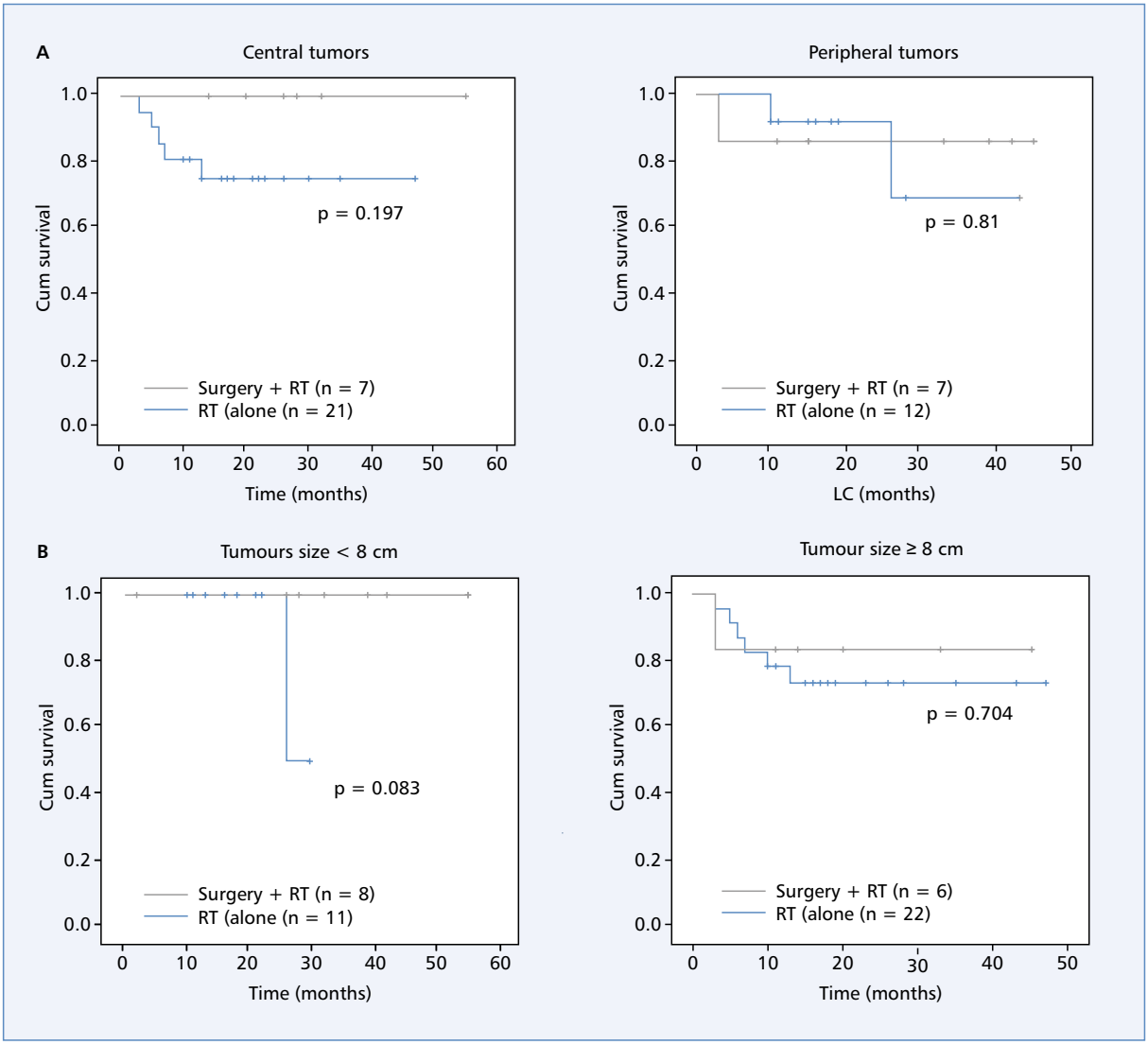

Figure 4. Subset analysis of local control according to treatment methods: Surgery and adjuvant radiotherapy versus radiotherapy alone; **A.** Comparison based on tumor location: central versus peripheral; **B.** Comparison based on tumor size: less than 8 cm versus 8 cm and above; LC — local control; RT — radiotherapy

(e.g. distal extremity) while the indications of postoperative radiotherapy were positive/close margins and poor histologic response (< 90% necrosis in resected tumor) after chemotherapy [9, 10, 22]. Surgery and RT showed superior local control rates than RT alone (92.3% versus 71%, p-value = 0.214), although the difference was not statistically significant unlike the results of Schuck et al. [9] and Biswas et al. [18].

A multitude of factors determine the choice of local therapy in ESFT. Smaller tumors in favorable locations (e.g. distal extremities) with significant response following neoadjuvant chemotherapy are treated more often with surgery. Tumors of large size or in central location (paravertebral, pelvic primaries) end up being treated with definitive radiotherapy. So we performed a subset analysis of local control according to local treatment modality with respect to tumor size (< 8 cm *v.* 8 cm and larger) and location (central versus peripheral). Among central tumors 25% (7/28) underwent resection, while for peripheral tumors the resection rate was 36.8% (7/19). With regards to tumor size, 21.4% (6/28) with dimension 8 cm or more underwent surgery while for tumors less than 8 cm size the rate of surgery was 42.1% (8/19). It was observed that local treatment with surgery and radiotherapy combined resulted in better 5-year local control rates than definitive radiotherapy alone for ESFT irrespective of tumor size and location (Fig. 4), even though statistical significance (all p-values > 0.05) was lacking. However, it must be understood that surgery as local treatment modality in ESFT requires special

expertise, especially in young children with growing bones. For tumors in critical locations like in the axial skeleton or advanced tumors in limbs, an organ preservation approach is often not feasible with surgery. Definitive radiotherapy remains the only local treatment option for such cases [23]. It can be expected that with the use of better imaging and treatment planning, newer techniques of precise radiation delivery and daily image guidance for treatment, radiotherapy to high doses can be safely and effectively delivered for optimum outcome in ESFT patients.

Patients receiving combined modality local therapy also had improved survival compared to radiotherapy alone (83.3% *v.* 31.1%, p = 0.022) as seen in results of our study (Tab. 3). Good response to neoadjuvant chemotherapy was another prognostic factor that translated into improved OS on both univariate and multivariate analysis (hazard ratio 0.301, 95% CI: 0.093–0.970, p = 0.044). Thus our study also shows that ESFT cases which respond favorably to cytoreductive chemotherapy and subjected to combined modality local treatment have significantly improved survival, even though the difference was not forthcoming in terms of local control.

Ours is a single institution retrospective review from a resource constrained region of the world, yet the results are not far from the studies in western population [4, 5, 11] and also correlate well with reports from Asia [17] and India [18]. However, our study is not without its limitations. There is a high rate of non-compliance to treatment among our patients, an issue that has previously been analyzed in pediatric population of our region by Hazarika et al. [24] who found that residence in rural areas, lack of maternal education, low socioeconomic status, age > 5 years and female sex were associated with higher risk of treatment abandonment. As evident from Figure 1, the non-compliance to diagnosis and treatment was 21% (15/72) in this study. Also, many patients could not receive treatment with curative intent and hence the final analysis of disease control and survival could be carried out for a cohort of 47 patients in our study. As a consequence of limited sample size, specific subset analysis based on tumor site, stage and patterns of failure could not be carried out in this study.

The retrospective nature of this study invariably allows for bias in choosing surgery versus radiotherapy as local treatment modality which might have affected the final outcome. There is a need for a randomized controlled trial to address this issue. However, in light of the available data demonstrating superiority of surgery over radiotherapy and also with the rapid advances in surgical techniques, whether any leading group in the world comes forward with such a comparative randomized trial remains to be seen.

Conclusions

Effective primary control significantly improves survival in ESFT. Favorable tumor response to neoadjuvant chemotherapy is also an independent prognostic factor that translates into better outcomes in ESFT as observed in our study. Our study results demonstrate that combined surgery and radiotherapy as local treatment provides better overall survival in these patients. However, for unresectable tumors definitive radiotherapy remains the only option which also can achieve effective local control, albeit with inferior survival rates. Thus a multidisciplinary treatment approach based on the prognostic factors and functional outcome should be made for optimum results. Radiotherapy, with or without surgery, remains an important component to achieving better local control in patients with ESFT.

Conflict of interest

All authors declare that they have no conflict of interest.

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VIA MEDICA

REVIEW ARTICLE

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Risk factors and primary prevention of lung cancer. Cessation of cigarette addiction

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 112–124
DOI: 10.5603/OCP.2021.0011

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Despite the huge knowledge about the risk factors associated with lung cancer, this disease remains the leading cause of cancer deaths in highly developed countries. The reason for this phenomenon is the increasing pollution of the natural environment and, above all, the difficulties in eliminating the addiction to smoking. In large Polish urban agglomerations, the exposure to particulate matter containing hydrocarbons on its surface, to free hydrocarbons, nitrogen and sulphur oxides is constantly increasing. Moreover, almost 25% of the Polish population smoke cigarettes and the elimination of smoking addiction through psychotherapy, nicotine replacement therapy and pharmacotherapy are sometimes ineffective. This article presents that the use of tobacco-burning products other than cigarettes (e.g., cigars or pipes) and products containing marijuana are as dangerous to health as classical cigarettes. Other nicotine-containing products have also appeared: e-cigarettes and tobacco heating systems. These products are highly addictive to nicotine, but the aerosols, that are produced by them, contain fewer toxic substances than cigarette smoke. Therefore, there are reasons to use these products instead of traditional cigarettes in people who are highly addicted to nicotine (after exhaustion of other treatment options) to reduce health risks, including lung cancer risk. However, it must be evoked that only a complete smoking cessation and the use of nicotine-containing products could be effective in reducing the risk of lung cancer.

Key words: lung cancer, environment, smoking, smoking cessation, e-cigarettes, heat not burn products

Oncol Clin Pract 2021; 17, 3: 112–124

Introduction

Lung cancer is the second most common cancer among men and women. According to the National Cancer Register (NCR), in 2018 lung cancer accounted for 16.1% of diagnosed cancer cases in men (after prostate cancer, which accounted for 19.6% of cancer cases in men) and 9.3% of diagnosed cancer cases in women (after cancer breast, which accounted for 22.5% of cancers in women). The NCR estimated that in 2020 there were 22,539 cases of lung cancer in Poland (13,553 in men and 8,986 in women). On the other hand, Globocan, operating under the patronage of the International Agency for Research on Cancer (IARC) and WHO (World Health Organization), estimated the number of new lung cancer cases in Poland in 2020 at 29,509 (18,277 men and 11,232 women). Lung cancer remains the leading cause of death from malignant cancers in highly developed countries. 28.2% of men and 17.5% of women with cancer die from lung cancer. According to Globocan, the number of deaths from lung cancer in Poland in 2020 was 27,444 patients.

For comparison, the second most common cause of death in cancer patients was colorectal cancer — 9,382 Poles died of colorectal cancer. The reasons for such a high number of deaths from lung cancer are the high incidence of this cancer due to the high exposure of a quarter of our population to tobacco smoke carcinogens and the still very poor prognosis (less than 20% of patients survive 5 years after diagnosis) [1, 2].

As can be concluded from the above data, it is necessary to conduct intensive lung cancer prevention programs. One of them should be primary prevention aimed at eliminating the addiction to smoking and exposure to other carcinogens. As part of secondary prevention, the use of low dose computed tomography should be developed to detect early asymptomatic cases of lung cancer in a group at high risk of developing this disease (tobacco smokers). The development of new, personalized therapy methods (immunotherapy, molecularly targeted therapies) is also important, as they increase the chance to cure patients after radical treatment (surgery, chemoradiotherapy) and significantly extend the life of patients with advanced cancer (even by over 5 years).

Environmental and occupational factors

The International Agency for Research on Cancer (IARC) recognizes outdoor air pollution as a risk factor for lung cancer. Air pollution data show that lung cancer incidence increases by 30–50% in areas with high levels of ambient air pollution compared to areas with lower levels of ambient air pollution [3, 4].

Particulate matter (PM) can damage various organs and cause many diseases. PM is classified according to particle size. PM10 (particles ≤ 10 μm in diameter), PM2.5 (particles ≤ 2.5 μm in diameter) also called fine particles and PM0.1 (particles ≤ 0.1 μm in diameter) also called ultrafine particles. Exposure to these particles has various health effects, which are partly due to how these particles travel in the lower respiratory tract and how they affect the lung defence mechanisms [5]. The health risks of PM0.1 are very high, but their exact role in many diseases is still unclear. Their high production and rapid redistribution make accidental exposure common in the general population. Many studies have shown that the smaller the size of the particles, the greater their mutagenic potential. The most important carcinogen was considered to be the total surface area of the retained particles, although the dose, particle type and exposure time were also important. The size of the particles depends largely on the size of the internal carbon core on which hydrocarbons and sulphate compounds responsible for the carcinogenesis process are absorbed [6, 7].

A positive correlation has also been observed between various indicators of indoor air pollution and the risk of lung cancer. Indoor air pollution is believed to be a risk factor for lung cancer, especially among female non-smokers and in less developed countries. Indoor air pollution is associated with coal combustion in poorly ventilated homes, combustion of wood and other solid fuels (biomass combustion), and the production of fumes from high-temperature cooking with unrefined vegetable oils. In addition, in airtight rooms in houses built mainly in volcanic areas, radon may accumulate from soil and water. Radon is a radioactive noble gas responsible for the greatest exposure of humans to natural ionizing radiation. It is believed that in some areas, inhalation of radon may be the second cause of lung cancer after smoking [8].

Exposure to several occupational factors carries with it consequences in the form of the development of lung diseases, including lung cancer. The most important occupational carcinogens include asbestos, silica, heavy metals, and polycyclic aromatic hydrocarbons [9, 10]. All forms of asbestos (chrysotile and amphibole, including crocidolite, amosite and tremolite) are carcinogenic, although chrysotile is less potent than other types, possibly because it is more efficiently cleared from the lungs. In many underdeveloped countries, occupational exposure to asbestos remains widespread [11, 12]. Chromium [VI] compounds increase the risk of lung cancer in people employed in the production of chromates, chromate pigments, chrome plating and ferrochrome plating. There was no such risk among workers exposed exclusively to chromium compounds [III]. Workers exposed to nickel salts and workers involved in the production of cadmium batteries using copper and cadmium alloys also have an increased risk of lung cancer. High exposure to inorganic arsenic occurs mainly among workers employed in the steel industry. An increased risk of lung cancer has also been reported among people exposed to high levels of arsenic in drinking water [13]. Other groups with an increased risk of exposure to arsenic are fur handlers (tanners), producers, people employed in the production of sheep fur and pesticide cleaning (bath) mixtures, and vineyard workers [14]. An increased risk of lung cancer has also been reported among patients with silicosis. Many studies have looked at workers exposed to crystalline silica in foundries, pottery, ceramics, diatomaceous earth mining, brickworks and stone cutting [15].

Polycyclic aromatic hydrocarbons are a complex and important group of chemicals formed during the combustion of organic material. An increased risk of lung cancer has been reported in several industries and occupations related to exposure to PAHs, such as aluminium production, coal gasification, coke production, iron and steel foundry, tar distillation, roofing, and chimney cleaning. An increased risk of lung cancer has

also been suggested for those employed in several other industries, including shale oil extraction, wood impregnation, roofing, and carbon electrode production [16].

Vehicle exhaust and other internal combustion engines constitute an important group of PAH mixtures as they contribute significantly to air pollution. Occupational exposure to exhaust fumes from diesel engines is common and the issue of its carcinogenicity has been the subject of many epidemiological studies in recent years. While the results are contradictory, many assessments seem to confirm that high occupational exposure to diesel exhaust over an extended period may be associated with an increased risk of lung cancer.

The SYNERGY project collected information on occupation and smoking in 13,304 lung cancer patients and 16,282 healthy people from 11 studies conducted in Europe and Canada. Exposure to diesel was associated with an increased risk of lung cancer with an Odds Ratio (OD) of 1.31 ($p < 0.01$) and depended on the exposure time and exhaust dose [17, 18]. Dai et al. [19] studied the relationship between exposure to exhaust fumes from diesel engines and the inflammatory response of the body. There was a significant decrease in blood levels of MIP-1β and IL-8 in people exposed to exhaust gases compared to the control group. Lower levels of these markers were also observed with increasing exposure to PM2.5. IL-8, MIP-1β are chemokines that play an important role in the recruitment of immunocompetent cells for immune defence and removal of cancer cells [19].

Air pollution is a silent epidemic. However, it is a threat that can be minimized with appropriate actions. Eliminating or at least reducing air pollution will result in an improvement in the health of the entire population. Prevention of lung cancer in this respect should include the control of occupational exposure, as well as indoor and outdoor air pollution [20, 21].

Smoking tobacco and other substances

Smoking is the cause of 90% of lung cancer in men and 80% in women. Smokers are thirty times more likely to die from lung cancer than non-smokers. Cigarette smoke contains over 7,000 chemical compounds, including over 70 compounds recognized as carcinogenic [22]. These compounds are formed during the combustion of tobacco at the end of a cigarette, which takes place at a temperature of over 750°C, and during pyrolysis, which takes place slightly deeper at the temperature of 300–700°C. In addition, the process of tobacco combustion at the end of a cigarette heats the air which is sucked by the smoker through the rest of the cigarette. Due to its high temperature, the air passing through the cigarette evaporates nicotine and other volatile substances contained in the cigarette. This mixture goes as far as to the alveoli and is then absorbed into the smoker's bloodstream. It contains 93 toxic compounds [Harmful or Potentially Harmful Constituents (HPHCs)] described by the Food and Drug Administration (FDA) in 2012, causing the five most serious health consequences of smoking (cancer, cardiovascular diseases, respiratory diseases, reproductive function disorders, addiction). Tobacco-dependent cancers, apart from lung cancer, include cancer of the larynx, throat, oesophagus, stomach, mouth, kidneys, bladder, and pancreas. Chronic obstructive pulmonary disease is one of the leading causes of premature death in cigarette smokers. Cardiovascular diseases caused by cigarette smoking include ischemic heart disease, lower limb vessel disease, cerebrovascular disease, and arterial hypertension. The number of years of life lost and disability among smokers compared to non-smokers is 10. Giving up smoking reduces the risk of serious diseases, but the risk of lung cancer is halved only 10 years after giving up smoking [23, 24].

The most dangerous substances found in very high concentrations in tobacco smoke include benzo(a)pyrene, nitrosamine, naphthalene, pyrene, naphthylamine, methanol, acetone, hydrogen cyanide, toluidine, ammonia, urethane, arsenic, cadmium, polonium, phenol, butane, vinyl chloride, dibenzo acridine, toluene, carbon monoxide. A highly addictive substance is nicotine, which has not been proven to be carcinogenic, although its metabolites have been established to be highly carcinogenic (this will be described in the chapter on e-cigarettes). The main carcinogenic factors of tobacco smoke are polycyclic aromatic hydrocarbons and volatile N-nitrosamines, which are converted in the body into metabolites of equally high toxicity [25, 26].

Epidemiological evidence of the harmfulness of cigarette smoking began to appear in the 1950s and concerned the association of cigarette smoking with the occurrence of lung cancer and cardiovascular diseases [27]. In 1964, the results of retrospective and prospective studies were announced in the United States which proved a 5- to 20-fold increase in the risk of lung cancer in smokers [28]. Since cigarette smoking has been linked to lung cancer and other diseases, the tobacco industry has started to reduce the content of harmful substances in their products. Filters were gradually added, they were modified with perforations (small spaces to dilute the smoke), tobacco was reconstructed, and the quality of paper and additives was improved. These effects reduced the content of nicotine and tar in cigarette smoke, which, however, remained one of the main causes of civilization diseases.

Comparing the effects of smoking cigarettes with smoking cigars and pipes is quite difficult. The design of the products and the different methods of their use, resulting in a different exposure to smoke, play a significant role here. Size aside, the main difference in the structure of cigars and cigarettes is the lack of

a filter. In cigarettes, the wrapping material for tobacco is paper and for cigars it is a tobacco leaf, increasing the final amount of nicotine and toxic substances released. For comparison, smoking one cigar provides from 100 to 200 mg of nicotine, and one cigarette provides an average of 8 mg. This means that the smoke from one cigar contains at least the same amount of nicotine as there is in one packet of unfiltered cigarettes. However, because cigars are consumed differently, the smoke usually remains in the mouth, rather than being inhaled into the lungs, as is the case with cigarettes. Similar dependencies as in the case of smoking cigars also occur in the users of pipes and water pipes. It should be noted that volatile substances are much better absorbed from the lungs than through mouth tissues, which explains the higher concentration of harmful substances in the blood of cigarette smokers compared to cigar and pipe smokers. At the same time, oropharyngeal cancer is much more common in cigar smokers than in traditional cigarette smokers [29–32].

All highly developed countries have legislation to eliminate smoking in society. In Poland, the Act of November 9, 1995, on health protection against the consequences of using tobacco and tobacco products is in force (Journal of Laws of 2015, items 298 and 1916, and of 2016, item 960). This act was updated on July 22, 2016. Many countries have adopted an endgame strategy to either eliminate tobacco from society completely or to reduce the proportion of smokers to 5% of the population. The first group included Sweden, Ireland and New Zealand (until 2025), Denmark and Finland (until 2030), and Canada and Scotland (until 2035). The second group includes Great Britain and France. Poland is set to become a tobacco-free country by 2030.

The carcinogenic effects of the substances generated during the combustion of cannabis have been studied very poorly. Depending on the species, cannabis contains over 420 chemicals, 61 of which are cannabinoids. More than 2,000 compounds are formed by pyrolysis when smoking cannabis and are represented by different classes of chemicals including nitrogen compounds, amino acids, hydrocarbons, terpenes, and simple fatty acids. Cannabis smoke also contains carcinogenic polycyclic aromatic hydrocarbons as well as other toxic products of combustion. They are similar to tobacco smoke, but the way cannabis is smoked results in higher exposure to smoke. However, the relationship between chronic obstructive pulmonary disease and cannabis smoking has not been fully proven, although chronic bronchitis (coughing, dyspnoea, and sputum production) is often observed in cannabis smokers. The impact of cannabis smoking on lung cancer risk was investigated in a group of 49,321 men aged 18–20 years during conscription in Sweden in 1969–1970. Participants in this study were followed up until 2009 in national medical registries for lung cancer. Analyses showed that heavy cannabis smoking was significantly associated with more than a twofold increase in the risk of lung cancer [OR = 2.12, 95% confidence interval (CI): 1.08–4.14] over the 40-year follow-up period [33–35].

Electronic cigarettes

E-cigarettes constitute a diverse group of rechargeable electronic nicotine inhalers with several thousand models. The device causes the inhalation liquid in the evaporator to change under the influence of high temperature (150–250°C) into an aerosol inhaled by the user (instead of the smoke inhaled when smoking cigarettes). The inhalation liquid usually consists of propylene glycol, glycerine, flavours, and nicotine in various concentrations (from 0 to 36 mg/mL). In the past, evaporators were disposable. Now, there are also models with liquid in the evaporator that can be refilled when the content of the refill container finishes. Due to the generally low nicotine content of e-cigarettes, e-cigarette users tend to use e-cigarettes frequently. Moreover, the use of e-cigarettes has become fashionable among adolescents, which may lead to nicotine addiction and then to the use of traditional cigarettes later in life. It is estimated that up to 5% of primary school students and over 20% of high school students have regular contact with e-cigarettes. In addition, using e-liquids after purchasing an expensive device is cheaper than buying cigarettes. That is why legal regulations have been created to limit access to e-cigarettes. The pulmonary toxicity of e-cigarettes and their influence on cancer incidence that is discussed with increasing frequency is also important [36].

In art. 20 of the Directive of the European Parliament and of the Council of the European Union (EU) of April 3, 2014, on tobacco products (2014/40/EU), there are provisions for electronic cigarettes sold in the EU. The directive specifies the maximum concentration of nicotine in vaporizers and removable containers and requires the composition of the liquid used in e-cigarettes to be specified, including the exact concentration of nicotine. According to the directive, e-cigarettes should be childproof and easy to handle and have a refilling mechanism that allows leak-free refilling. The ingredients of e-cigarettes must be of high purity, and e-cigarettes should provide a standardized amount of nicotine. Health warnings for e-cigarettes informing consumers that they contain nicotine and should not be used by non-smokers are mandatory in EU countries. The e-cigarette leaflet should contain information about side effects that must be reported and about addictive properties. In EU countries there is a ban on e-cigarette advertising [37]. "Public Health England" found that the use of standardized and certified

electronic cigarettes is 95% less harmful than smoking traditional cigarettes [38, 39].

In August 2016, the WHO recommended a ban on the use of e-cigarettes indoors or where smoking is prohibited [40]. This is because non-users of these products may be exposed to chemicals and e-cigarette aerosols.

In many EU countries, specific regulations are regulating the e-cigarette market. Unfortunately, in Poland, the approval of e-cigarettes for sale is insufficiently controlled by the Bureau for Chemical Substances established in the regulation of the Minister of Health of November 9, 2015 (Journal of Laws of 2015, item 1953). E-cigarettes are admitted to trading in Poland based on a notification, i.e., a notification by the manufacturer. Therefore, the composition of e-liquids is not controlled in any way. This creates a potential risk of interference with the composition of the liquid (so-called premixes). According to Polish legislation, an e-cigarette is not a tobacco product. The nicotine-containing liquid contained in the refill container must not exceed 10 mL or, in the case of single-use containers, 2 mL. The nicotine content in the liquid must not exceed 20 mg/mL. The liquid must not contain vitamins or other additives that give the impression that a tobacco product is beneficial to health, caffeine or taurine, or other additives and stimulants associated with energy and vitality (e.g. legal highs) and additives that in an unburned form have carcinogenic, mutagenic or reprotoxic properties. Despite these limitations, there are several hundred types of e-liquids and e-cigarettes available in Poland without proper authorization of the e-liquid composition [41].

Unlike Polish legislation, since August 8, 2016, the FDA ordered e-cigarettes to be subject to tobacco product regulations. As in the EU, in the USA there is a ban on selling e-cigarettes to minors. The FDA has classified e-cigarettes as stimulant delivery devices and they are therefore regulated under the Federal Food, Drug and Cosmetic Act (FDCA). After the detection of serious respiratory diseases related to the inhalation of untested substances from e-cigarettes, which resulted in the death of six people in the USA, in September 2019 the US government began working on introducing a complete ban on e-cigarettes [42].

In April 2019, there were reports of severe respiratory failure due to lung damage in e-cigarette users in the United States. There were more patients with this syndrome in Great Britain and Japan [43, 44]. By January 21, 2020, a total of 2,711 hospitalized patients and 60 deaths due to respiratory failure after the use of e-cigarettes were reported to the Centres of Disease Control and Prevention (CDC) [15]. Most of the cases concerned young people. 80% of patients reported the use of tetrahydrocannabinol (THC) in e-liquids, approximately 55% of patients reported THC added to nicotine-containing products, and 13% of patients reported exclusive use of nicotine-containing products. Symptoms of respiratory failure developed within days to weeks of exposure. THC is an organic chemical compound of the cannabinoid group and is the main psychoactive substance found in the cannabis plant. The CDC and the FDA, as part of the investigation carried out in 2019 and 2020, confirmed the presence of THC in vaporization products. Most vaporization liquids also contained significant amounts of Vitamin E Acetate (tocopherol), which was used in street sales to dilute flavours and THC [45]. Previously, vitamin E was used in low concentrations in e-liquids (up to 20% of the volume of the cartridge or was prohibited). Due to the limited availability of illegal marijuana, as well as the high demand for this type of e-cigarette, illegal vendors used about 50% or more of diluents in e-liquids [45]. For these reasons, the use of e-cigarettes, especially from an uncertain source, should be considered risky.

Concerns about the carcinogenicity of e-cigarettes result from both inhalation of nicotine [46] and other chemicals that may be contained in the aerosols [42]. The interaction of nicotine with nicotinic acetylcholine receptors (nAChR) activates signalling pathways that trigger several responses such as increased cell proliferation and survival. There is evidence from *in vitro* studies (breast, colorectal and lung cancer cell cultures) and in animal models (lung cancer) that nicotine may be carcinogenic and may accelerate tumour growth and promote metastasis [46]. *In vitro* studies have shown that nicotine increases cell proliferation, induces cell resistance to apoptosis, causes Epithelial-Mesenchymal Transition (EMT), which increases the migration and invasiveness of cancer cells and induces neoangiogenesis [47]. The pro-angiogenic effect of nicotine, resulting from the activation of endothelial cell proliferation and increasing the production of nitric oxide, which is a strong angiogenic factor, seems to be of the greatest importance for tumour progression. In high concentrations, nicotine damages DNA and can induce necrosis of normal cells, but also the formation of new somatic mutations and promotion of the carcinogenesis process with a decrease in the expression of suppressor genes such as CHEK2 (Checkpoint Kinase 2) [48]. Moreover, in *in vitro* cultures (lung cancer cell lines: H460 and A549), nicotine has been shown to reduce the antiproliferative and pro-apoptotic effects exerted by cytostatics and radiotherapy, which may result in a worse response to cancer treatment in patients who smoke or use other nicotine-containing products. This effect can be eliminated by the use of inhibitors of the alpha nAChR subunit, e.g., α-bungarotoxin. The products of nicotine metabolism proved to be very carcinogenic in *in vitro* cultures and in animal models. These are N-nitrosonornicotine (NNN), responsible for the occurrence of stomach and oesophageal cancers, and nitrosamine ketone (NNK),

which is one of the most carcinogenic substances, as well as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is a metabolite of the carcinogenic NNK in the lungs. All these substances have been found in the urine of people who smoke traditional cigarettes and use e-cigarettes. Nicotine may inhibit the anti-cancer immune response by influencing the antigen presentation and activity of dendritic cells, increasing the production of pro-inflammatory cytokines, and intensifying oxidative stress [48].

In addition, there is evidence that some substances found in e-cigarette fumes, such as formaldehyde and acrolein, certain flavour additives, vitamin E acetate, and even propylene glycol, can cause DNA damage and carcinogenesis, or be irritating to the respiratory tract, which may increase the risk of lung, mouth, and throat cancer. It is because e-liquids containing nicotine isolated from tobacco can contain contaminants such as nicotine oxides, cotinine, anabasine, anatabine, myosmine, acrolein and beta-nicotyrine, and even in small amounts toluene, and heavy metals such as cadmium, tin, nickel, and lead. Propylene glycol used in e-cigarettes can be contaminated with diethylene glycol and transform into propylene oxide. Some of these substances can form adducts with DNA, which leads to activating mutations in oncogenes (most often in the *KRAS* gene) and deactivating mutations in suppressor genes (most often in the *p53* and *RB1* genes). However, it should be noted that compared to traditional cigarette smoke, the levels of toxic substances identified in e-cigarette aerosols were 10 to 450 times lower [48–55].

Despite the risk of carcinogenesis and respiratory damage associated with the use of e-cigarettes, a 2014 report by the Surgeon General of the United States concluded that there was insufficient evidence of carcinogenic effects of nicotine alone *in vivo* in humans. However, further studies were recommended to check whether exposure to the nicotine contained in, for example, e-cigarettes does not increase the risk of oropharyngeal, oesophageal, lung and pancreatic cancer [56]. Moreover, the health consequences of inhaling aerosol from e-cigarettes are unknown because no reliable safety study has been carried out on e-cigarette use due to the variety and a large number of manufacturers. The content of hazardous substances in e-liquids has not been thoroughly tested, nor has their permissible level been determined [57]. Therefore, as early as in 2009, the FDA issued a warning that the use of e-cigarettes may pose a health risk [51]. In turn, the United Kingdom has introduced a procedure under which medically tested e-cigarettes can be registered as medicinal products indicated for the reduction of abstinence syndrome in the treatment of nicotinism [58].

Heat-not-Burn systems

Heat-not-Burn (HnB) devices heat tobacco to 200–350°C, releasing aerosols. The devices consist of a ceramic blade with electric wires connected to a battery with the possibility of charging from an external power source. The blade is located inside an acetate tube with a cellulose acetate mouthpiece. The polymer filter is designed to cool the resulting aerosol. The compressed tobacco rod is made of a suspension of dried tobacco, 70% of which is tobacco, and humectants (water, glycerine, propylene glycol) to generate an aerosol. In comparison to e-cigarettes, tobacco heating systems are subject to more rigorous procedures of standardizing the content of various substances in the inhaled aerosol [59, 60].

Tobacco heating systems are not subject to the Directive of the European Parliament and the EU Council of April 3, 2014, on tobacco products, like e-cigarettes, because the first HnB products were created in 2014. Therefore, there is no official position of EU agencies regarding HnB products. In November 2020, a document aimed at assessing and introducing regulations on tobacco heating systems, as well as new regulations governing the approval of e-cigarettes for sale was subjected to social discussion [60].

Some EU countries have internal regulations for HnB products. The German Federal Institute for Risk Assessment and the Dutch National Institute for Public Health and the Environment have carried out appropriate tests, finding a reduction in the content of toxic substances in aerosols from HnB devices ranging from 80% to 99% compared to cigarette smoke. However, it has been found that the use of heat-not-burn products is harmful to health, but most likely carries a significantly lower risk of disease than smoking [61, 62]. Public Health England found that, compared to cigarettes, heat-not-burn products may present less exposure of users and bystanders to particulate matter and harmful and potentially harmful chemicals. In turn, the British Committee on Toxicity (COT) stated that although heat-not-burn products are still harmful to health, they are probably less dangerous than smoking traditional cigarettes [38, 39, 63].

In Poland, HnB products, like e-cigarettes, are subject to registration by the Chemical Substances Office. However, unlike electronic cigarettes, the market for heat-not-burn devices is better controlled. The procedure for submitting heat-not-burn devices to the Office requires authorization (i.e., not only determining the aerosol composition, but also presenting test results for each new device), and not an only notification, as is the case with e-cigarette registration. Therefore, in December 2020, the Office stated that, like e-cigarettes, heat-not-burn products are often seen as an opportunity to give up smoking regular cigarettes. Declarations of

respondents affected by this situation may indicate that the effectiveness of heat-not-burn products in this respect is much higher than that of e-cigarettes, although due to the small size of the studied groups, this data requires confirmation in further studies [41].

In October 2019, the FDA issued the first-ever decision to award a Modified Risk Order to eight tobacco products that do not burn or produce smoke. These products were based on the snus technology (cellulose bags containing powdered, moist tobacco, usually placed behind the upper lip). In turn, in July 2020, as part of the MRTP (Modified-Risk Tobacco Product) procedure, after nearly 4 years of research analysis, the FDA decided to authorize the first tobacco heating system as a tobacco product that ensures lower exposure to harmful and potentially harmful substances compared to classic cigarettes. The registration process considered the state of scientific knowledge about these products, as well as the data of the manufacturer and independent researchers and the comments raised in the public debate [64, 65].

The content of harmful substances, including carcinogens, in tobacco heating systems, is usually comparable to the content of these compounds in certified and standardized e-cigarettes (however, as described in the previous chapter, not all e-liquids can be subject to such control). The nicotine content in HnB products is 0.5–1.3 mg per cartridge. The aerosol also contains glycerol, propylene glycol and water. Since the aerosol is made of real tobacco, when it is heated to a temperature of over 300°C, it may contain small amounts of toxic substances, such as compounds resulting from the chemical transformation of nicotine (similarly to e-cigarettes), nitrosamines, benzene, benzo(a)pyrene, 4-aminobiphenyl, acrolein, acetone, 2-butanone, methyl glycol, pyridine, hydroxyacetone, diacetyl, isopentane and numerous aldehydes (e.g. formaldehyde, acetaldehyde, propionic aldehyde, crotonic aldehyde, pentanal, benzaldehyde, heptanal, furfural). However, the content of toxic substances in the aerosol from HnB products is at the level of 8% to 3% of their content in the smoke of traditional cigarettes. The content of group 1 carcinogens from the IARC list in HnB aerosols is reduced compared to cigarette smoke by 97%, and of carcinogens identified by the FDA by 93%. The reduction of factors damaging the respiratory and cardiovascular systems and disrupting reproduction ranges from 92 to 94%. The levels of carbon monoxide, pyrene, acrylonitrile and aminophthalenes in aerosols from HnB products are reduced to almost zero, which is associated, among others, with a significant reduction in the content of carboxyhaemoglobin in the blood of people using HnB products compared to smokers of traditional cigarettes [66].

Due to the short presence of HnB products on the market, no retrospective observations are determining the level of reduction in the incidence of tobacco-related cancers compared to smoking. Therefore, attempts were made to estimate the carcinogenicity of the aerosol of the HnB product based on detailed toxicological data. In a study published in Tobacco Control BMJ, the carcinogenic potency was defined as at least one order of magnitude lower than that of cigarette smoke [67]. Public institutions in some countries also performed their own detailed oncological risk assessment of the use of tobacco heating systems. In studies conducted by the Ministry of Health of Japan and the National Institute of Public Health in the Netherlands, the risk of cancer resulting from the use of HnB was estimated to be about 10 times lower compared to smoking, and the reduction of cumulative exposure to the main carcinogens of tobacco smoke was 10 to 25 times lower [68, 69]. The risk of cancer induction in the case of passive exposure to HnB aerosols was estimated to be approximately 3,000 times lower than that of cigarette smoke.

There are many *in vitro*, animal, and human studies that have compared the effects of substances in an aerosol produced when tobacco is heated and that of tobacco smoke. A team of researchers from the Institute of Experimental Biology of the Polish Academy of Sciences showed a much greater effect of inhibiting oxygen consumption by the mitochondria of bronchial epithelial cells exposed to cigarette smoke in culture compared to an aerosol from the HnB device. Moreover, cigarette smoke had a much stronger effect on oxidative phosphorylation and expression of genes involved in the response to oxidative stress compared to an aerosol from the HnB device [70]. In a 6-month clinical trial Ludicke et al. [71] showed greater disorders of lipid metabolism (decrease in HDL cholesterol and increase in LDL cholesterol and triglycerides), increased inflammation (increase in the number of white blood cells, C-reactive protein and pro-inflammatory cytokines), impaired vascular endothelial function, blood clotting, oxidative stress (increase in the concentration of 8-epiprostaglandin F2, 8-epi-PGF2), the level of carboxyhaemoglobin in smokers compared to people using HnB products. In people who switched from traditional cigarettes to HnB products, after 6 months of observation, the above-mentioned biochemical parameters and respiratory function improved, expressed by increasing spirometric parameters, such as FEV1 (Forced Expiratory Volume in 1 second) [71].

Tobacco dependence therapy

Smoking tobacco causes a strong pharmacological addiction to nicotine and is at the same time the most important carcinogenic factor of lung cancer. When nicotine levels drop in blood, clinical withdrawal symptoms develop, forcing the smoker to continue smoking

and thus maintain adequate levels of nicotine in the blood. After a certain period of smoking, nicotine tolerance develops, which makes it necessary to take increasingly higher doses of nicotine to obtain the desired effect. Tolerance arises by increasing the activity of nicotine metabolising enzymes and by increasing the number of nicotine receptors in the central nervous system. In addition to pharmacological addiction, smoking causes a behavioural addiction that consists of complex psychological, environmental, cultural, and social factors [72].

Non-pharmacological treatments for tobacco dependence consist of three components. The first is education on the harmful effects of tobacco smoking, conducted through specialist telephone consultations, educational brochures, radio, and television programs and on the Internet. The next stage is anti-smoking counselling conducted in a doctor's office, among others, at a general practitioner and a specialist pulmonologist. The key to properly conduct anti-smoking counselling is a thorough interview, which can be used to assess the degree of nicotine addiction (including Schneider and Fagerström tests). The Fagerström questionnaire consists of 6 questions concerning the period from waking up to smoking the first cigarette, difficulties in refraining from smoking in forbidden places, the number of cigarettes smoked daily, the degree of difficulty in giving up the first cigarette, the time of the day when more cigarettes are smoked, smoking during a disease. The maximum number of points obtained in the Fagerström test is 10. The sum of points above 6 indicates a strong degree of nicotine addiction and is an indication for replacement treatment when giving up smoking [72]. On this basis, the type of the most appropriate medical advice and the frequency of subsequent appointments can be planned. The third stage of addiction treatment is behavioural therapy, consisting of comprehensive medical and psychological counselling and short personal consultations, including learning to eliminate pro-tobacco stimuli as well as relaxation and motivational techniques [72].

The pharmacological treatment of nicotine addiction includes nicotine replacement therapy (NRT), psychotropic drugs (bupropion) and nicotinic cholinergic antagonists (varenicline and cytisine). The use of tobacco heating systems as a method of treating tobacco addiction is still debatable [72].

Nicotine replacement therapy (NRT), introduced in the late 1970s, supplies the addicted smoker with nicotine, which eliminates acute withdrawal symptoms and reduces the number of nicotinic receptors, making it easier to abstain from smoking. Before starting replacement treatment, one should be ascertained whether they are dealing with pharmacological dependence based on the results of the Fagerström questionnaire [72].

Various forms of NRT are available: transdermal systems (patches), chewing gums, lozenges, sublingual tablets, aerosols, and oral inhalers. These products are available in Poland without a prescription.

Patches provide stable levels of nicotine in the blood, making it easier to stop smoking, but when using them, in the event of nicotine craving, it is necessary to use emergency oral products. The nicotine contained in a patch gradually penetrates the skin and subcutaneous tissue into the blood and the brain. Patches come in different doses (7, 14 and 21 mg of nicotine in 24-hour patches and 5, 10 and 15 mg in 16-hour patches). Patches are applied to dry and hairless skin, on the upper body (chest, back, arms). To reduce the risk of a local skin reaction, patients should change the application site. Nicotine patches are generally well tolerated, especially in those most addicted to nicotine. Full treatment usually lasts about 10 weeks, during which the nicotine dose is gradually reduced [72].

Oral nicotine replacement therapy delivers nicotine on demand. Nicotine is absorbed through the oral mucosa, satisfying short-term nicotine cravings. Chewing gum with nicotine and nicotine lozenges are available in doses of 2 mg and 4 mg. They are usually used as an addition to patches. The acidic environment of the oral cavity reduces the absorption of nicotine, therefore gums and lozenges should be used at least 15 minutes after eating or drinking [72].

The nicotine inhaler delivers nicotine in an aerosol to the oral mucosa where it is absorbed. The inhaler is not an e-cigarette (the liquid is not heated and no aerosol imitating smoke is produced). The device consists of a plastic tube in which a replaceable cartridge containing nicotine, often enriched with menthol as a fragrance, is placed. Nicotine is released as air flows through the inhaler. The inhaler is used as a cigarette and is especially useful for smokers with a behavioural addiction. Inhaler cartridges usually contain 10 mg of nicotine and are sufficient for four 20-minute inhalations [72].

Oral aerosols allow for the fast delivery of nicotine to the central nervous system. A dose contains 1 mg of nicotine. Usually, 1 or 2 doses are used every 30 minutes to 1 hour. The maximum allowable dose is 2 administrations at the same time or 4 administrations per hour. The maximum daily dose is 64 administrations over 16 hours. A gradual reduction in the number of doses is recommended. The recommended duration of use of this form of NRT is 3 to 6 months. Side effects of inhaler use include hiccups, headache, nausea, and throat irritation [72].

The results of a Cochrane systematic review of a meta-analysis of 133 randomized trials of 64,640 smokers smoking at least 15 cigarettes a day indicate a significantly greater likelihood of smoking cessation in the NRT groups compared to the placebo groups (OR = 1.55;

95% CI: 1.49–1.61) [23]. The effects were significant for all types of NRT: for users of nicotine gums, the odds ratio was 1.64, for users of nicotine patches — 1.52 and for users of nicotine inhalers — 1.90 [73].

Antidepressants can help in the fight against the addiction to smoking for several reasons. Withdrawal from nicotine can cause depressive symptoms, and antidepressants can relieve them. In addition, some antidepressants may have specific effects on the receptors and messenger pathways underlying nicotine addiction. Bupropion is an antidepressant that inhibits the postsynaptic uptake of dopamine and norepinephrine, reducing the feeling of pleasure from nicotine. Bupropion also blocks nAChR, alleviates withdrawal symptoms, including the urge to smoke, and reduces weight gain after giving up nicotine use [72].

Smokers should start using the drug one week before the planned smoking cessation date with an initial dose of 150 mg a day for 3 days, and then 150 mg twice a day for 6 to 12 weeks. A smoker can suddenly stop taking the drug without having to gradually reduce the dose. The most reported side effects of bupropion include insomnia, dry mouth, nausea, and skin allergic reactions [72].

Based on a meta-analysis of 45 randomized trials (17,866 participants) from a Cochrane systematic review that assessed the frequency of giving up smoking in a long-term follow-up with bupropion versus placebo, the drug effectiveness was demonstrated (OR = 1.64, 95% CI: 1.52–1.77) [25]. In comparison to the placebo group, smokers treated with bupropion more often resigned from participation in the study due to adverse events (OR = 1.37, 95% CI: 1.21–1.56; 25 studies, 12,340 participants). Those in the bupropion group were also more likely to report psychiatric adverse effects compared to those in the placebo group (OR = 1.25, 95% CI: 1.15–1.37; 6 studies, 4,439 participants). The meta-analysis did not provide sufficient evidence for the greater effectiveness of the combination therapy with bupropion and NRT compared to NRT alone (OR = 1.19, 95% CI: 0.94–1.51; 12 studies, 3,487 participants) or the advantage of combining bupropion and varenicline compared to varenicline alone (OR = 1.21, 95% CI: 0.95–1.55; 3 studies, 1,057 participants). A meta-analysis of 6 studies provided evidence that bupropion was less effective than varenicline (OR = 0.71, 95% CI: 0.64–0.79; 6 studies, 6,286 participants). In contrast, the likelihood of giving up smoking when using bupropion was similar to that with NRT (OR = 0.99, 95% CI: 0.91–1.09; 10 studies, 8,230 participants) [74].

Varenicline is a partial $\alpha 4\beta 2$ nAChR antagonist. It shows a strong antagonistic effect against nicotine. It is a partial competition agonist of nAChR, which reduces their availability for nicotine, decreasing the satisfaction with smoking and the feeling of reward after smoking a cigarette. Varenicline, although it is less agonist than nicotine on nAChR, leads to a reduction in the feeling of craving and withdrawal symptoms in people who give up smoking [72].

The 12-week treatment should be started 2 weeks before the planned smoking cessation date. In the initial phase, 1 tablet of 0.5 mg should be taken once a day for 3 days, for the next 4 days 2 × 1 tablet of 0.5 mg, and for the next week 2 × 1 tablet of 1 mg. In the treatment continuation phase after giving up smoking, it is recommended to take 1 tablet twice a day. If the attempt to give up smoking is unsuccessful, treatment continues, and the patient tries to stop smoking on the next day until successful. The most common side effects of varenicline include nausea, usually of moderate intensity, and intense dreaming with restlessness, insomnia, headache, arrhythmias, and mood changes. Cautious use of varenicline is recommended in patients with depressed mood, although a meta-analysis of 10 randomized, placebo-controlled studies on the effectiveness and safety of varenicline when giving up smoking showed similar rates of new symptoms and mental illness in the placebo (9.7%) and varenicline groups (10.7%) (OR = 1.02, 95% CI: 0.86–1.22) [74].

Based on a meta-analysis of 27 randomized trials (12,625 participants) included in the Cochrane systematic review, it was indicated that treatment with standard-dose varenicline more than doubled the chance of long-term smoking cessation compared to placebo (OR = 2.24, 95% CI: 2.06–2.43). A meta-analysis of 5 studies (5,877 participants) comparing the effectiveness of varenicline and bupropion, and a meta-analysis of 8 studies (6,264 participants) comparing the effectiveness of varenicline and NRT showed the superiority of varenicline in long-term smoking cessation (OR = 1.39, 95% CI: 1.25–1.54 and OR = 1.25, 95% CI: 1.14–1.37) [75].

Cytisine is a quinolizidine alkaloid extracted from the seeds of the golden chain (*Laburnum anagyroides*). It is a competitive, partial agonist of $\alpha 4\beta 2$ nAChR, and its mechanism of action is similar to varenicline. For several decades, cytisine has been available in Poland as an oral drug in the treatment of nicotine addiction [72]. Cytisine treatment should be started up to 5 days before the planned smoking cessation date. For the first 3 days, 1 tablet of 1.5 mg is used 6 times a day, for the next 9 days 1 tablet 5 times a day, from the 13th to the 16th day 1 tablet 4 times a day, from the 17th to the 20th day 1 tablet 3 times a day and from the 20th to the 25th day 1 tablet once or twice a day. The most common side effects during treatment include nausea, vomiting, diarrhoea, tachycardia, and an increase in blood pressure [76, 77].

A systematic review published in the Cochrane Library includes 3 studies on the effectiveness of cytisine in the treatment of smoking addiction. In two studies (937 participants) it was found that patients treated

with cytisine were four times more likely not to smoke after 6 months of follow-up in comparison to placebo (OR = 3.98, 95% CI: 2.01–7.87). One study compared the effectiveness of cytisine with NRT (1,310 subjects) and showed the advantage of cytisine six months after the start of treatment (OR = 1.43, 95% CI: 1.13–1.80) [75].

The use of e-cigarettes or heat-not-burn devices in the fight against smoking addiction is still debatable. All scientific societies dealing with this issue and agencies assessing medical technologies, such as the National Institute for Health and Care Excellence (NICE) or the FDA, emphasize that there are no completely safe products containing tobacco, and the most effective method of reducing health risk in tobacco smokers is to give up smoking completely. Both agencies state, however, that in people who are highly addicted to nicotine and who smoke cigarettes, reduction of health risk is possible thanks to the temporary or long-term use of licensed nicotine-containing products instead of traditional cigarettes [63–65].

Based on a toxicological analysis by the Committee on Toxicity [38], the NICE concluded that licensed nicotine products, approved by the MHRA, contain significantly less harmful substances compared to traditional cigarettes and under certain conditions can be used as an aid in reducing addiction to tobacco smoking if smokers decide to switch completely to smokeless products containing nicotine. However, the NICE made a reservation that strict control over the use of these products, the composition of an aerosol and the prohibition of access to them for children and adolescents, as well as further clinical and scientific research on their safety are required (e.g., NCT03569748 study aimed at comparing the safety and effectiveness of using e-cigarettes and HnB products in reducing tobacco addiction is in the process) [63, 78].

The use of e-cigarettes to reduce tobacco addiction is most controversial. As mentioned above, the e-cigarette market is not sufficiently controlled, resulting in the appearance of contaminated products, including THC-containing products, on the market-leading to serious and life-threatening pulmonary toxicity. Moreover, e-cigarettes are a fashionable and attractive product eagerly bought by children and adolescents, which leads to nicotine addiction and more frequent use of traditional cigarettes by people in this age group [46]. The results of a study conducted in 2020 by the National Institute of Public Health - National Institute of Hygiene showed that the products initiating nicotine consumption were traditional cigarettes for 52% of teenagers, electronic cigarettes for 32%, and HnB products for 0.2% [79]. Similar results were obtained in a study commissioned by the European Commission (Eurobarometer 2021), according to which in 87% of cases, traditional cigarettes and roll-your-own tobacco are responsible for the initiation of nicotine use. The remaining products played a much smaller role in the initiation of addiction (water pipes with tobacco — 4%, e-cigarettes — 2%, snus and HnB products < 1%) [80].

The FDA has issued an opinion on the use of tobacco heat-not-burn devices (but not e-cigarettes) as a way to reduce health risks in smokers, granting HnB products an MRTP status. The FDA opinion was based on 30 analyses and reports, the results of 10 clinical studies, 8 non-clinical studies, 141 independent scientific studies and 340 peer-reviewed articles. They have shown that a complete transition from traditional cigarettes to a tobacco heat-not-burn system significantly reduces exposure to harmful or potentially harmful substances, which can help addicted adult smokers give up smoking and reduce their exposure to harmful factors. In addition, the FDA has made a reservation that it will closely monitor how tobacco heating systems are used by consumers and whether they do not adversely affect their health and that the use of these products by adolescents is not increasing, which would lead this age group to nicotine addiction. It was emphasized that HnB products are not completely safe and people, especially young people who do not currently use tobacco products, cannot start using them [64, 65]. Similar recommendations were also issued by the Dutch National Institute of Public Health and the Environment (RIVM), the Belgian High Council for Health, the German Federal Institute for Risk Assessment (German Bundesinstitut für Risikobewertung, BfR) and the Japanese National Institute of Public Health [61–63, 79, 81].

In Poland, there are no such recommendations issued by state organizations. There are, however, expert opinions. One of them is the opinion of Szymański et al. [82], in which the authors state that HnB products may potentially be helpful in the treatment of tobacco addiction and in reducing the adverse health effects associated with this addiction. They also state that HnB products may be a safer alternative to cigarettes in people in whom all, including pharmacological, treatments for tobacco dependence have failed [82]. Polish guidelines for the management of lower limb artery disease by Jawień et al. [83] also emphasize that replacing traditional cigarettes with heat-not-burn products may be an alternative in the treatment of smoking addiction.

Summary

Lung cancer risk factors are largely known and well characterized. Therefore, primary prevention of this disease seems to be easy to implement by eliminating environmental threats and smoking. Nevertheless, lung cancer remains the leading cause of deaths among malignant cancers in all developed countries.

The reasons for this phenomenon should be sought for in the growing problem of environmental pollution, but above all in the difficulties in eliminating the addiction to smoking in the Polish population. Due to the lack of adequate education, young people still turn to nicotine-containing products, first e-cigarettes and then traditional cigarettes. On the other hand, nicotine addiction is extremely strong in many people and its elimination using traditional methods (psychotherapy, nicotine replacement therapy, pharmacotherapy) turns out to be impossible. In these people, reducing the health risks associated with smoking can be achieved by replacing cigarettes with smokeless nicotine-containing products. Many scientific studies have shown that aerosols from e-cigarettes and heat-not-burn devices contain over 90% fewer carcinogens than cigarette smoke. However, it should be remembered that while the composition of aerosols in heat-not-burn devices is known, in the case of e-liquids it may be modified by e-cigarette owners or companies producing them (this was the cause of many cases of acute lung damage in people using e-liquids containing THC and vitamin E acetate). Therefore, many countries (the USA, the Netherlands, Belgium, Germany) have identified HnB devices as products with a reduced health risk compared to traditional cigarettes, and experts from many countries issue cautious recommendations on the possibility of reducing the health risk in people smoking cigarettes by replacing them with heat-not-burn products.

Conflict of interest

The authors report no conflicts of interest.

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VIA MEDICA

REVIEW ARTICLE

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Endometriosis and risk of ovarian cancer

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 125–127
DOI: 10.5603/OCP.2021.0012

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Endometriosis is common in premenopausal women and affects about 10% of women of reproductive age. It is a benign condition but demonstrates malignant behaviour with recurrences and metastases. Its tendency to increase the risk of specific subtypes of ovarian cancer is being discussed, because they exhibit specific clinical features that distinguish them from classical ovarian cancer. Malignant transformation of endometriosis goes through its transition to atypical endometriosis. Although endometriosis-associated ovarian carcinomas have a good prognosis, adequate follow-up and monitoring after treatment of endometriosis are recommended.

Key words: endometriosis, ovarian cancer, endometriosis-associated ovarian carcinoma, rate, prognosis

Oncol Clin Pract 2021; 17, 3: 125–127

Endometriosis (E) is one of the most common diseases in premenopausal women, affecting about 10% of women of reproductive age [1]. It is a chronic disease characterized by endometrium-like tissue, glands, and stroma outside the uterine cavity. It is oestrogen-dependent and most commonly affects the ovaries, fallopian tubes, and the pelvic peritoneum. The disease often has a substantial impact on the quality of life of those affected. Usually, it manifests itself with the following symptoms: dysmenorrhea, dyspareunia, chronic pelvic pain, infertility, urinary or digestive symptoms [2]. The diagnosis can be suspected by ultrasound and MRI tests, but the final diagnosis is based on histopathological examination [3]. Various theories explain the occurrence of endometriosis, the most common being retrograde menstruation, genetic predisposition, lymphatic spread, immune dysfunction, metaplasia, or environmental causes [4, 5]. Although E is considered a benign disease, it increases the risk of ovarian cancer [6–9]. Two main mechanisms are suggested to explain this correlation: (1) both diseases coexist and are the result of shared risk factors and their effects; (2) endometriotic cells gradually transform into cancer cells [1].

Atypical E is considered an intermediate state between E and OC [10]. This leads to the conclusion that E is a precancerous condition. More than 2/3 of endometriosis-related ovarian tumours develop in the presence of atypical E [11]. Some of the risk factors for the development of atypical E are: early age of onset, long duration of disease, obesity, dysmenorrhea, perimenopause and menopause, irregular vaginal bleeding, a gynaecological examination of tumour fixation, tumour diameter over 80 mm, a rapid increase in tumour size, the number of abortions, uterine myoma, thyroid disease, and multiple foci of endometriosis [12].

Endometriosis and OC share some quite similar features such as local invasion, neoangiogenesis, increased expression of vascular endothelial growth factor (VEGF), lymphangiogenesis, resistance to the mechanisms of apoptosis, COX-2 overexpression, and genomic instability.

To determine whether endometriosis is associated with an increased risk of ovarian cancer, 13 extensive epidemiological studies were conducted in North America, Australia, and Europe on 23,000 women (13,326 controls; 7,911 with invasive ovarian carcinoma (OC), and 1,907 with borderline malignancies). The studies established the following results [13]. Women with a history of endometriosis have a significantly higher risk (> 2.5 times) of developing three specific

histotypes of ovarian carcinoma: clear cell carcinoma (atypical endometriosis is the immediate precursor of clear cell carcinoma) [14]; endometrioid carcinoma; low-grade serous carcinoma (LGSCO). Several studies published between 2008 and 2014 validate the term endometriosis-associated ovarian carcinomas (EAOC) [15–19]. EAOC is presented as an ovarian carcinoma with both cancer cells and endometriotic cells observed in the same ovary, cancer presence in one ovary, and endometriosis in the other ovary; or presence of ovarian cancer and pelvic endometriosis [20].

The most important conclusions reached by the authors of these studies are the following:

1. Ovarian endometriosis is a risk factor that can lead to the development of endometrioid and clear cell ovarian carcinomas within 5 years [15].
2. The risk of malignant transformation varies between 2 and 17% according to a meta-analysis [16].
3. Risk factors for EAOC are: ovarian endometrioma ≥ 9 cm, and peri- and post-menopausal patients [17].
4. EAOC patients are 10 years younger (mean age 50 years) than other ovarian cancer patients [18].
5. Hyperoestrogenemia is a risk factor for the development of EAOC [19].

EAOC is presented with some specific clinical features that distinguish it from OC: it affects younger patients, shows lower CA-125 levels, it has a better prognosis and a higher number of clear cells than in ovarian cancer [21].

The relative risk (RR) of developing specific histological subtypes of OC for patients with endometriosis is calculated as follows [16]:

1. clear cell ovarian carcinoma — 3.05;
2. endometrioid ovarian carcinoma — 2.04;
3. low-grade serous ovarian carcinoma — 2.11;
4. high-grade serous ovarian carcinoma — 1.13;
5. mucinous ovarian carcinoma — 1.02.

The most extensive and significant survey reported on this topic is a meta-analysis by Kim et al. (2014) [22], which included 1,625 studies and a contingent of 444,255 patients. The authors compare the EAOC with the non-EAOC and reach the following conclusions:

1. endometriosis increases the risk of OC (RR 1.265).
2. EAOC patients have better prognosis and survival.
3. EAOCs are more common in nulliparous women and are usually in FIGO stage I, II.
4. endometrioid (RR = 1.759) and clear cell (RR = 2.606) histological subtypes are more common in EAOC, while serous carcinomas are less frequent (RR = 0.733).

Specific histological, cellular, and molecular markers have been identified as responsible for the malignant transformation of E and underlie the pathogenesis of EAOC [22]. These are:

1. *KRAS* and *PTEN* genes mutations;
2. *ARID1A* gene mutation — it occurs in 46% of the cases of clear cell ovarian carcinoma (CCOC), and in only 30% of endometrioid ovarian carcinoma (EOC) cases; it is not found in high-grade serous ovarian carcinoma (HGSOC).

These mutations inhibit the expression of the BAF250a protein (a tumour-suppressor gene). They are regarded as markers of malignant transformation underlying the pathogenesis of the EAOC.

There are several stages of malignant transformation: normal endometrium, endometriosis, atypical endometriosis, EAOC. External and internal factors, inflammation, and oxidative stress contribute to the progression from one stage to the next. However, genetic factors and mutations in the genes mentioned above exert the most significant influence. It is assumed that the immune system (macrophages) and endometrioid cells' proliferative activity have an additional role as co-factors [23].

Apart from the indisputable evidence of endometriosis association with ovarian carcinoma, other factors are reducing the risk of ovarian cancer in women with endometriosis. Since 2004, oral contraceptives have been shown to reduce the risk of OC by 50–60% in women with endometriosis [24]. Studies published in 2013 established that unilateral oophorectomy significantly reduces the risk of OC compared to endometriosis patients who underwent conservative nonsurgical treatment. Additionally, the studies reported on the protective effect of childbirth and hysterectomy [25, 26].

The available data considered so far indisputably prove that endometriosis is associated with the development of some OC histological types. An intriguing question is whether there is a link between the location of E and the risk of cancer. The results of Finnish study (data retrieved from the Finnish Hospital Discharge Registry and the Finnish Cancer Registry) were published in 2018 [26]. The study covered the period of 1987 to 2012, and included 49,933 women with surgically verified endometriosis. Depending on the organ localization of endometriosis, the distribution is as follows: ovaries — 23,210 cases; peritoneum — 20,187 cases; deep infiltrating endometriosis (DIE) — 2,372 cases.

The Finnish study shows that patients with endometriosis have a 2.3 times higher risk of developing OC — EAOC are endometrioid and clear cell histological subtypes. In addition to these confirmatory results, the authors make an original contribution by proving that endometriosis patients have a significant risk of developing borderline ovarian tumours (BOT) [27]. Depending on the localization of endometriosis, ovarian cancer risk is highest among women with ovarian endometriosis; peritoneal and DIE do not increase the risk.

After a 10-year follow-up, the authors found that the excess risk of ovarian cancer among women with ovarian endometriosis translates into two excess cases per 1,000 patients.

In conclusion, the following clinical groups are at an increased risk of developing EAOC: patients aged > 45 years; nulliparous patients; diagnosis of endometriosis in postmenopausal women; endometriomas ≥ 9 cm; hyperoestrogenism.

The frequency of EAOC varies between 2 and 17%, and endometrioid and clear cell ovarian carcinomas are the most common. Only ovarian endometriosis (not peritoneal and deep infiltrating endometriosis) is related to the progression of EAOC. Malignant transformation progresses to atypical endometriosis and is most often due to mutations in several genes. Although EAOC has a good prognosis, adequate follow-up and monitoring after treatment of endometriosis are recommended.

Conflict of interest

The authors report no conflicts of interest.

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VIA MEDICA

CASE REPORT

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Pancreatectomy as a form of treatment for leiomyosarcoma metastasis to pancreas — case report and literature review

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 128–131
DOI: 10.5603/OCP.2021.0016

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Background: Pancreatic cancers represent about 2% of all malignant tumors. The prognosis for patients is rather poor and the five-year survival is only 9%. Metastases constitute 2–5% of this organ's tumors, and the management of such cases is determined individually depending on the type of cancer, the patient's condition and the medical center's experience. We present a rare case of pancreatic metastasis from a subcutaneous leiomyosarcoma.

Case: A 71-year-old woman with history of leiomyosarcoma — six years ago, two cancer outbreaks, located in the subcutaneous tissue of the thigh and shoulder treated by surgery and adjuvant radiotherapy. After 5 years, a lung metastasis was diagnosed and successfully resected. The following year, CT scan revealed a mass in the pancreas. The patient also complained of epigastric pain and bloating. The biopsy of the lesion confirmed leiomyosarcoma metastasis. The patient underwent 6 cycles of ADIC chemotherapy, after which the tumor size decreased and the laparotomy was performed. The metastasis was well-demarcated and did not infiltrate surrounding tissues, so distal pancreatectomy provided a complete tumor resection There were no complications throughout surgery During 12 months follow up no recurrence was observed.

Conclusions: Due to the relatively rare occurrence, standards for the treatment of pancreatic metastases have not been developed yet. This case shows that treatment by resection of the tumor while maintaining a surgical margin can be considered as a form of treatment in pancreatic secondary cancers.

Key words: leiomyosarcoma, pancreatectomy, pancreatic metastasis

Oncol Clin Pract 2021; 17, 3: 128–131

Introduction

Soft tissue sarcomas account for only 1% of solid malignancies [1]. One of the most commonly detected lesions is leiomyosarcoma. For primary leiomyosarcoma, the treatment of choice is tumor resection, which can be combined with adjuvant chemotherapy or radiotherapy. About 40% of these cases metastasise, which is associated with poor prognosis [2]. Secondary lesions, usually disseminated, are treated with systemic chemotherapy. In case of isolated metastasis, surgical treatment consisting of complete excision of the metastasis gives a chance for recovery.

Malignant neoplasms of the pancreas constitute 2% of all diagnosed cancers [3]. These tumors are usually detected at an advanced stage and are characterized by one of the highest mortality rates, where the five-year survival rate is around 9% [4]. The vast majority of lesions are primary malignancies, and secondary lesions account for 2 to 5% [5]. The most common cancers which metastasise to the pancreas are renal cell carcinoma,

colorectal cancer, melanoma and sarcomas. Due to the rare occurrence of pancreatic secondary tumors, no clear guidelines for therapeutic management have been developed. Metastasectomy is a therapeutic option for patients with single metastasis whose health condition allows pancreatectomy.

Case report

We present the case of a 71-year-old woman, ECOG score 0 — hitherto without severe medical conditions (post-appendectomy, cholecystectomy and resection of the uterus with appendages due to myomas over 20 years ago). The patient was supervised by a gastroenterology clinic and underwent regular prophylactic tests because of a history of abdominal pain, constipation and diarrhoea for several years, and cases of colorectal cancers in the family.

In April she 2014 presented with two subcutaneous well-delimited lesions — the left thigh (diameter 4 cm) and the left arm (diameter 3 cm) without local lymph nodes enlargement. Due to the benign picture of the lesion, a fine needle biopsy was ordered. The biopsy revealed cells specific to malignant mesenchymal tumor. After a coarse needle biopsy, the patient was qualified for tumor resection. Histopathological examination of both lesions showed Leiomyosarcoma, G1, caldesmon (+). Adjuvant radiotherapy at a total dose of 60 Gy was performed in both areas. In the meantime, abdominal and thoracic imaging did not show any abnormalities.

After five years, lesion in the middle lobe of the right lung was found — leiomyosarcoma metastasis was confirmed histopathologically and completely resected.

A year later, CT scan of the abdominal cavity revealed a 24 × 20 mm lesion in the pancreas tail (Fig. 1). The EUS identified the lesion as well delimited and poorly vascularized with dimensions of 27 × 21 mm, the remaining pancreatic parenchyma did not show signs of inflammation, the bile ducts were not dilated. Histopathological examination of the biopsy material confirmed leiomyosarcoma metastasis caldesmon (+), desmin (+), Brg1 (–), CD117 (–). The patient's condition was evaluated as ECOG 1 and qualified for the preoperative course of ADIC chemotherapy and splenopancreatectomy. During the operation, no macroscopic metastatic changes in the abdominal cavity were found, and the tumor itself was considered resectable, spleen preserving distal pancreatectomy was performed. The patient was discharged home without complications on the 5th day after surgery. The histopathological evaluation confirmed the diagnosis and no cancerous infiltration was found in surgical margin (Fig. 2–5). The patient was given postoperative chemotherapy. After over 12 months period of follow-up the state of pancreas is stable.

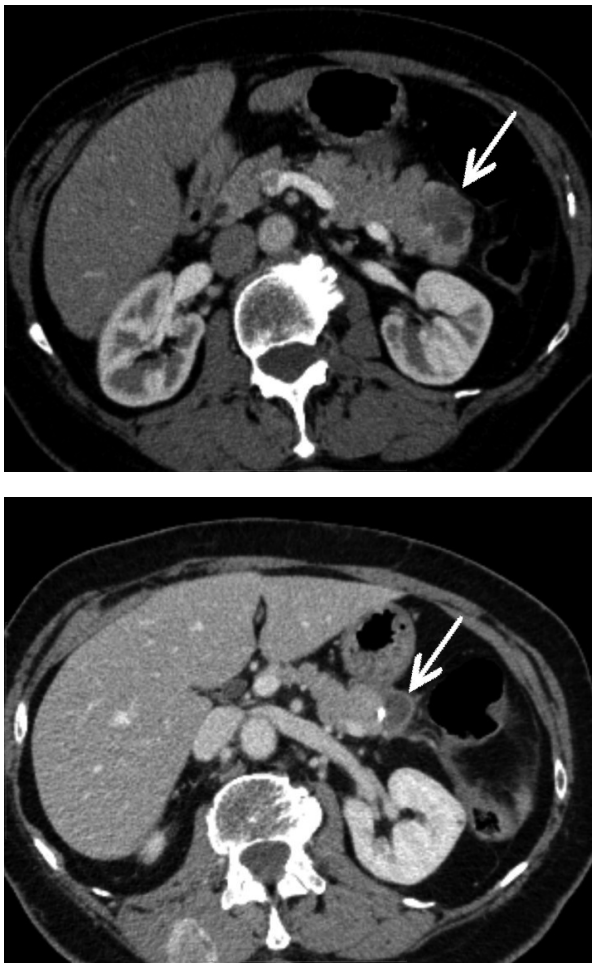

Figure 1. CT imaging before and after surgery, arrow points tumor in pancreatic tail

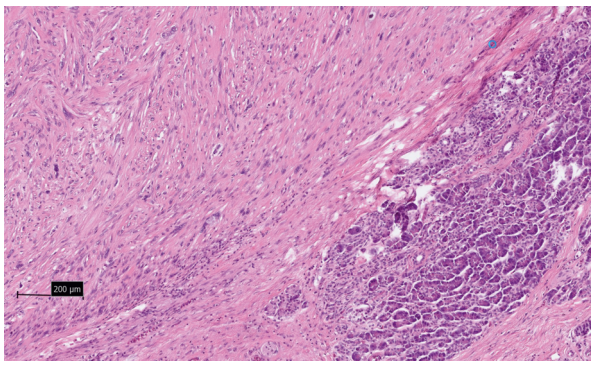

Figure 2. Leiomyosrcoma 10×, on the right pancreatic lobular tissue

Discussion

Soft tissue sarcomas (STS) are rare malignancies which arise from mesoderm. There are more than 50 types of different sarcomas belonging to this group. Leiomyosarcoma is one of the most common

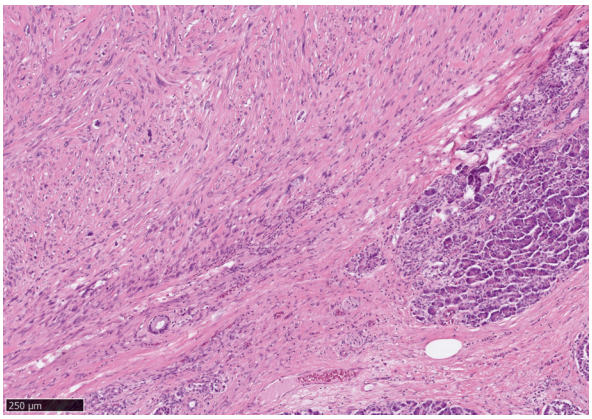

Figure 3. Leiomyosrcoma 10×, on the right pancreatic lobular tissue

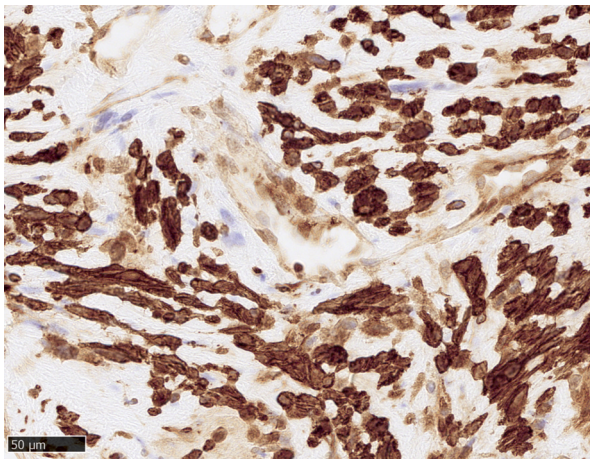

Figure 4. Desmin+, 40×

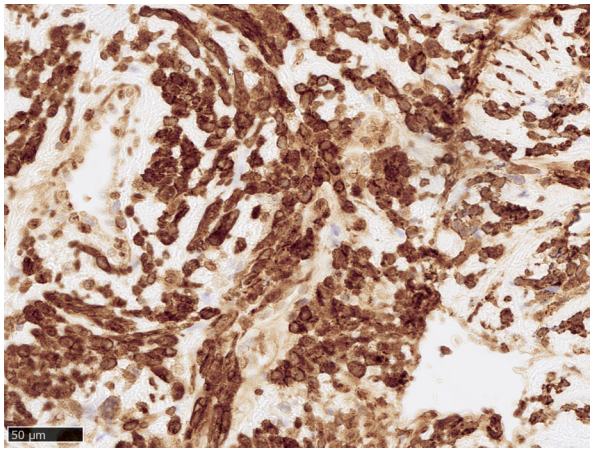

Figure 5. Caldesomon+, 40×

sarcomas which incidence is 10–20% of diagnosed STS [6]. They are usually located in the abdominal cavity, pelvis, less often on the limbs. Resection is the treatment of choice for primary lesions. In the case of metastases, some patients may benefit from surgery if there is a small number of metastases that appeared late after primary resection. Most secondary lesions are unresectable and they are treated with chemotherapy. Treatment for disseminated metastases is palliative.

Most pancreatic neoplasms are primary where ductal adenocarcinoma accounts for 85% of malignancies [4]. Metastatic tumors are estimated to be 2% [3]. The vast majority of metastases are from renal cell carcinoma (RCC). Other cancers that metastasise to this organ relatively often are colorectal cancer, melanoma, sarcomas [7]. The prognosis for patients with pancreatic leiomyosarcoma metastasis is unknown, although metastatic sarcoma usually indicates poor prognosis, where the average survival time is between 10–30 months [2]. Metastases can occur as a single neoplastic changes or disseminated lesions. However, there are usually multiple lesions when the metastases are detected. RCC often gives solitary metastases [5], which affects the possibility of surgery and gives chances for recovery.

Pancreatic tumors are usually diagnosed accidentally during abdominal imaging. Endosonography seems to be an especially useful tool, because it allows both biopsy and tumor evaluation. Other useful imaging methods are ultrasound, computerised tomography and magnetic resonance imaging. There are no specific symptoms that suggest pancreatic metastases. When a lesion in the pancreas is detected, rapid differential diagnosis is important because of the biology of the most common cancers of the organ.

Resection is the primary treatment for primary pancreatic tumors, but there are no established therapeutic standards for secondary tumors. Several hundred cases of dissemination of various tumors to the pancreas have been reported. It is difficult to assess the effectiveness of surgical treatment due to the lack of studies comparing this method of therapy with chemotherapy. Some publications suggest that resection can be a good therapeutic option for patients without metastases outside the pancreas and should always be considered. Other listed features that are worth considering while qualifying patients for such surgery are primary site control, the patient's condition allowing pancreatectomy and a prognosis for a primary type of cancer [3]. Some cases suggest that pancreatic metastasectomy is associated with improved survival rate, even with complete recovery. If a patient is qualified for secondary pancreatic tumor resection, it is reasonable to refer the patient to a high volume center because of greater experience of the clinics, which translates into better treatment results.

Conclusions

Resection of metastatic pancreatic cancer or sarcoma may be an effective form of treatment in certain cases.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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VIA MEDICA

CASE REPORT

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Early-stage gastric cancer presenting with tripe palm and acanthosis nigricans

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Oncology in Clinical Practice
2021, Vol. 17, No. 3, 132–134
DOI: 10.5603/OCP.2021.0014

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Tripe palm is a rare cutaneous paraneoplastic syndrome that can be overlooked and frequently appears with acanthosis nigricans. If tripe palm and acanthosis nigricans occur in a patient together, gastric cancer should come to mind. A 50-year-old female patient had signs of abdominal pain and velvety thickening in the palms and soles. Tripe palm and acanthosis nigricans were considered as paraneoplastic syndrome after other benign causes were excluded. It was determined that the underlying malignancy was gastric cancer. After neoadjuvant FLOT chemotherapy regimen, gastrectomy was performed, and the patient received adjuvant chemotherapy. With the recognition of tripe palm, a rare cutaneous paraneoplastic syndrome, patients can be diagnosed and treated early.
Key words: tripe palm, acanthosis nigricans, gastric cancer, paraneoplastic syndrome

Oncol Clin Pract 2021; 17, 3: 132–134

Introduction

Although the incidence of gastric cancer is decreasing worldwide, it is the 5th most common neoplasm and the 3rd most common cause of cancer death [1]. Gastric cancer is histologically divided into two groups as intestinal and diffuse type. The first one (intestinal) is well-differentiated type and it is the more common. Its prognosis is better [2]. The diffuse type has a worse prognosis and is diagnosed more frequently in women [2]. Neoadjuvant FLOT regimen (docetaxel, oxaliplatin, leucovorin and fluorouracil) is the standard therapy in the treatment of early stage (from Stage 1b) gastric cancer [3]. Detecting gastric cancer at an early stage is very important for overall survival. Several malignant diseases may be detected at an early stage with the diagnosis of paraneoplastic syndromes. Various skin findings herald the presence of an underlying malignancy. These skin evidence may be paraneoplastic signs such as Leser-Trelat, tripe palm and acanthosis nigricans [4]. Tripe palm is velvety hyperkeratosis of the palmar hands resembling the bovine stomach. Tripe palm is reported to be associated with malignancy and may occur especially together with acanthosis nigricans. Tripe palm occurs before or concurrently with the cancer diagnosis of patients [5]. When tripe palm occurs with acanthosis nigricans, gastric carcinoma is the most common malignancy. If tripe palm occurs alone, it is most often suggestive of pulmonary carcinoma [5, 6].

We aimed to present a case of early-stage gastric cancer presenting with rare tripe palm and acanthosis nigricans.

Case report

A 50-year-old woman presented with a 2-month history of abdominal pain and a 3-week history of hyperpigmentation in the armpits, knees, joints of the fingers and toes. She used a proton pump inhibitor because of abdominal pain. The other medical history was unremarkable. Family history was unremarkable. Vital signs were stable. Physical examination of the palms of her hands and soles revealed velvety appearance, thickened, moss-like, corrugated surface resembling tripe (Fig. 1). Hyperpigmentation in the nape, armpit, knee, joints of the fingers and toes was considered as acanthosis nigricans (Fig. 2). There was

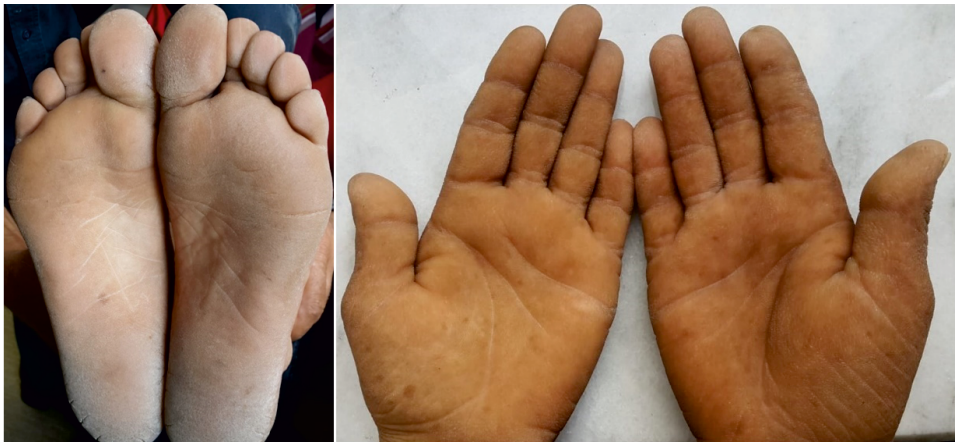

Figure 1. A rugose appearance with a ridged surface, mimicking the tripe of a ruminant, on the palms and soles

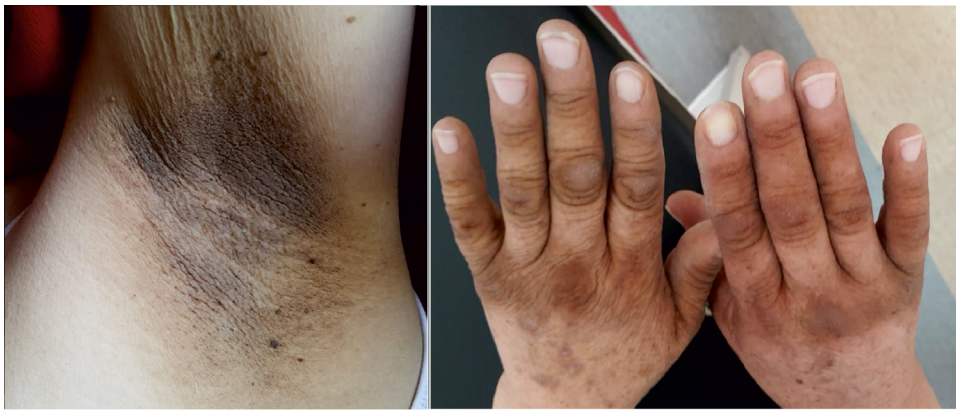

Figure 2. Hyperpigmentation of skinfolds (acanthosis nigricans) on the armpit and fingers

no abnormal value in the laboratory analysis. Abdominal ultrasonography was performed and there was no additional abnormality except grade 2 hepatosteatosis. The presence of tripe palm and acanthosis nigricans in our patient suggested malignancy. Gastroduodenoscopy was performed. Malignant ulcer was detected in the stomach (antrum) (Fig. 3) and biopsy was taken. The result showed gastric adenocarcinoma. Thoracic and abdominal computed tomography was performed for cancer staging. Stomach wall thickness increased and there were no distant metastases. Neoadjuvant chemotherapy in form of FLOT regimen was initiated because of the diagnosis of early-stage gastric cancer. Paraneoplastic tripe palm and acanthosis nigricans regressed. There was a slight decrease in gastric wall thickness after 4 cycles (detected in computed tomography of the abdomen). Total gastrectomy and D2 lymph node dissection were performed. Postoperative pathology report revealed adenocarcinoma. The same chemotherapy regimen was started again in the postoperative 8th week and 4 cycles were given. Paraneoplastic tripe palm and acanthosis nigricans completely disappeared. The patient was observed with no evidence of progressive disease.

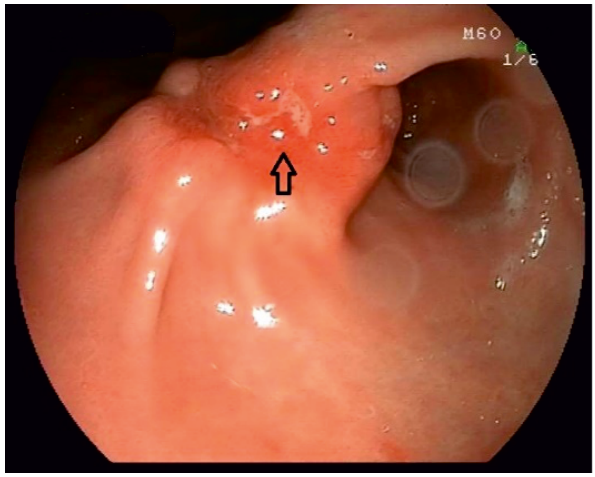

Figure 3. Malignant ulcer in the stomach antrum incisura angularis in gastroduodenoscopy

Discussion

Paraneoplastic syndromes are a group of pathological conditions caused by neoplasia that do not occur with

metastatic spread or local infiltration. Cutaneous paraneoplastic syndromes are non-adjacent skin and mucous membrane changes. The cause for the occurrence of cutaneous manifestations of gastric cancer may be the production of growth factors, hormones, peptides, or exhausting of various substances [7]. Successful treatment of gastric cancer, as in our case, often leads to disappearance of paraneoplastic dermatoses. Among many cutaneous paraneoplastic syndromes described tripe palm is defined by velvety thickening of the palms and soles and resembles the rugose stomach mucosa (tripe) of ruminants. In our case, it was present in both the palm and the soles. TGF-alpha, receptor tyrosine kinases, and oncogenes SRC may implicate in tripe palm pathogenesis [7]. Tripe palm presents before cancer diagnosis in approximately 40% of patients [8]. Tripe palm is particularly associated with 90% solid tumors such as stomach or lung cancer and 30% of tripe palm responds to cancer treatment [7, 8]. Tripe palm disappeared with treatment in our case. Tripe palm can occur with acanthosis nigricans (72%), florid cutaneous papillomatosis (30%), and the sign of Leser-Trelat (10%) [5]. If acanthosis nigricans occurs with tripe palms, gastric carcinoma is the most common malignancy, but if acanthosis nigricans is absent, pulmonary carcinoma is most frequent [5, 6]. In our case, tripe palm was seen together with acanthosis nigricans and the underlying malignancy was gastric adenocarcinoma. Acanthosis nigricans is a cutaneous marker of cancers; it typically displays hyperpigmented, roughened plaques of velvety and usually occurs in the intertriginous zones (neck, axilla, and groin). Acanthosis nigricans may also occur in familial or drug-induced and autoimmune diseases, diabetes mellitus, obesity, insulin resistance, and polycystic ovarian disease. Acanthosis nigricans occurs frequently in gastric cancer, but it may appeared in liver, lung, ovarian, kidney, and breast cancers [7, 9]. In our case, acanthosis nigricans was seen in the axilla, neck and groin and regressed with treatment.

The importance of paraneoplastic syndromes was emphasized with this case. With the diagnosis of paraneoplastic syndrome, cancer with high mortality was diagnosed at an early stage and cured. Tripe palm and acanthosis nigricans are rare paraneoplastic syndrome. Physician with awareness of these skin signs, will diagnose and treatment patients earlier with probably lifesaving outcomes.

Conflict of interest

The authors report no conflicts of interest.

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