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Neutrophil-to-lymphocyte ratio as a prognostic factor in patients during palliative treatment of pancreatic ductal adenocarcinoma with a FOLFIRINOX regimen

Małgorzata Domagała-Haduch, Jakub Wnuk, Łukasz Michalecki, Iwona Gisterek

Department of Oncology and Radiotherapy, Medical University of Silesia, Katowice, Poland

Introduction. Difficulties in advanced pancreatic ductal adenocarcinoma (PDAC) treatment require a constant search for novel prognostic factors. The aim of this study is to determine the role of various morphological parameters in predicting the prognosis of advanced PDAC during systemic therapy with a FOLFIRINOX regimen.

Material and methods. The data of 52 patients, treated with FOLFIRINOX chemotherapy due to metastatic PDAC were analyzed retrospectively in this study.

Results. The median time of overall survival (OS) in the group of patients with neutrophil-to-lymphocyte ratio (NLR) ≥3 was 5.8 months, compared to 14.5 months in patients with NLR < 3. Median progression-free survival (PFS) in patients with NLR ≥ 3 was 4.1 months, compared to 8.5 months in patients with NLR < 3. There were no statistically significant differences among patients concerning the lymphocyte-to-monocyte ratio (LMR) and platelets-to-lymphocyte ratio (PLR).

Conclusions. Higher NLR is a negative prognostic factor in metastatic PDAC.

Key words: pancreatic ductal carcinoma, chemotherapy, overall survival, time to progression, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelets-to-lymphocyte ratio

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the most aggressive cancers with increasing rates of incidence and mortality. It is estimated that PDAC will be the second cause of death among oncological patients in USA by 2030 [1]. Among Polish patients, PDAC was the cause of death in 5000 cases, and was diagnosed in 3837 patients in 2018 [2].

Despite the progress in diagnosis and treatment, PDAC remains a disease with poor survival. Even with radical treatment including surgical approach and adjuvant systemic therapy, the median overall survival does not exceed 5 years.

In metastatic PDAC, multi-drug regimens such as FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, levofolic/folinic acid), gemcitabine with nab-paclitaxel or gemcitabine in monotherapy are recommended in systemic therapy [3–5]. The FOLFIRINOX regimen was compared to gemcitabine in monotherapy in Connroy study, which included advanced PDAC without a previous history of treatment. The median time of overall survival in the group of patients treated with the FOLFIRINOX regimen was 11.1 months, compared to 6.8 months in the gemcitabine group. Adverse effects of used therapy were more common during treatment with

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FOLFIRINOX regimen, although it did not significantly affect patients quality of life [6].

In the study comparing gemcitabine in monotherapy to gemcitabine accompanied by nab-paclitaxel, OS was 6.7 months compared to 8.5 months in the two-drug regimen [7]. Limited effectiveness of the systemic approach in PDAC treatment might be caused by the microenvironment surrounding the growing tumor. The desmoplastic response of surrounding tissues and low angiogenesis are the cause of inadequate chemotherapy effects [8]. Besides relative drug resistance, PDAC might avoid the systemic immunological response. This phenomenon is related to the presence of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSC), and regulatory T-cells activated by TGF beta. Those cells are able to inactivate CD4+ and CD8+ lymphocytes, dendritic cells, NK cells, and macrophages [9]. This might be the reason for the poor effects of immunotherapy trials in PDAC. With increasing knowledge about the role of immunological response and inflammation in tumor tissue, more studies concerning prognostic factors based on immunological cells are being published. Those prognostic factors include the neutrophil-to--lymphocyte ratio (NLR), platelets-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR). Increased NLR is considered a poor prognosis factor in renal cell carcinoma, malignant melanoma, metastatic colorectal cancer or non--small cell lung cancer [10, 11].

The aim of this study was to determine the role of NLR, PLR, LMR as prognostic factors in patients treated with FOLFIRINOX chemotherapy in metastatic PDAC.

Material and methods

There were 52 patients who were enrolled for this study. We have included the patients who were undergoing systemic treatment with the FOLFIRINOX regimen due to metastatic PDAC between 2017 and 2021. Inclusion criteria contained a PDAC diagnosis in clinical stage IV, systemic treatment with the FOLFIRINOX regimen. We have collected demographic data such as the patients' sex, age, height, weight, results of CBC tests, progression-free survival time in months, overall survival in months, and localization of metastases. Parameters such as NLR, PLR and LMR were based on CBC results.

The CBC was assessed at the day of the treatment initiation, before the start of systemic therapy.

The overall survival- and progression-free figures were calculated by subtracting the date of the metastatic disease diagnosis from the date of death and disease progression, respectively for complete observations or from the date of the last follow-up for censored observations. The cut-off values for NLR, PLR, and LMR were pre-set, based on current literature. The log rank test was used for comparing the survival between two groups. The relationships between quantitative variables were analyzed using the Spearman's rank correlation coefficient. The analysis was performed using STATISTICA 13.3 software (TIBCO software). The $p < 0.05$ values were considered significant. Inclusion criterium was an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. The observed cohort of patients comprised 25 male (48%) and 27 female (52%). The median age of patients was 62 years (range from 31 to 72 years).

The most common metastases localizations were liver (39 patients – 75%) and peritoneum (5 patients – 9.6%). Lungs were the localization of single metastases in 1 patient (2%) and multi-organ metastatic disease was observed in 5 patients (9.6%). The reason for termination of treatment was disease progression (41 patients – 79%) and adverse effects of treatment (4 patients – 8%). There are 4 patients still being observed during observation and 3 patients have been lost to follow-up.

Results

The median time of overall survival was 10.33 months (range 5.3–16.6 months) and the median of progression-free survival was 6.8 months (3.03–14 months). The median values with minimum and maximum ranges for NLR, PLR, and LMR were 2.56 (0.92–15.63), 140.35 (75.47–661), and 3.2 (0.7–9.6), respectively. There was a statistically significant correlation between NLR and OS ($r = –0.320$, $p < 0.05$) NLR and PFS ($r= –0.452$, $p < 0.05$) and LMR and OS ($r = 0.312$, $p < 0.05$). The results are presented in table I. In the case of NLR, we have performed the log rank test for an NLR cut-off value of 3. The results are presented in table II. The likelihood of survival in patient groups based on the NLR result is presented in figure 1. There was no statistically significant correlation in BMI and PFS ($r = 0.197$, $p = 0.222$), or BMI and OS ($r = 0.185$, $p = 0.267$). In terms of PLR (cut off value 150) and LMR (cut off value 3), we have not determined statistically significant differences in PFS or OS (tab. III, IV).

Discussion

The growth of solid tumors is related to inflammation of surrounding tissues, affecting every stage of oncogenesis. On the other hand, the growth of a tumor increases the local inflammation, causing the self-escalating process of tumor progression [12]. An increasing inflammation state leads to

Table I. Spearman's rank correlation coefficient

Tested quantitative data	R coefficient
NLR and PFS	–0.320 ($p < 0.05$)
NRL and OS	–0.452 ($p < 0.05$)
PLR and PFS	–0.177 ($p = 0.245$)
PLR and OS	–0.296 ($p = 0.054$)
LMR and PFS	0.219 ($p = 0.148$)
LMR and OS	0.312 ($p = 0.052$)

NLR – neutrophil-lymphocyte ratio; PFS – progression-free survival; OS – overall survival

Table II. Log-rank test results for groups based on NLR result

	Median in NLR < 3 group (months)	Median in NLR ≥ 3 group (months)	Log-rank test results
PFS	8.46 (3.67–14.5)	4.11 (2.4–9.97)	p = 0.0587
OS	14.5 (8.7–17.87)	5.78 (4.53–11.33)	p < 0.05

PFS – progression-free survival; OS – overall survival

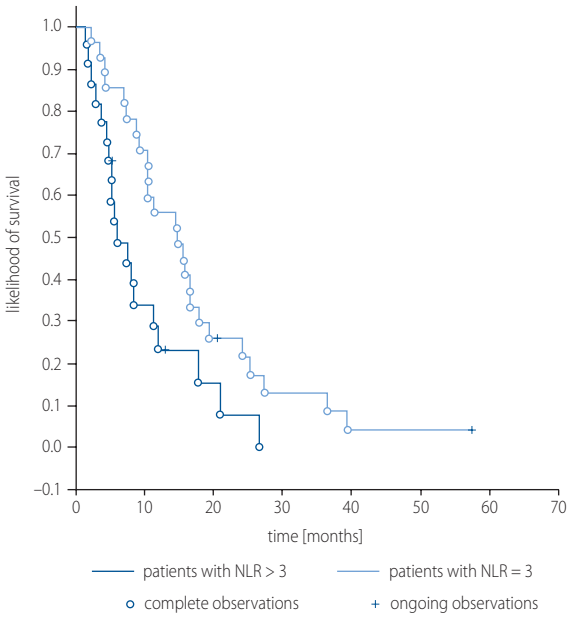

Figure 1. The Kaplan–Meier estimator of survival in patient groups based on NLR result

chemotaxis of immunologic cells such as neutrophils, macrophages, dendritic cells, lymphocytes, and mastocytes, which through expression of various cytokines determine the local immunologic response and affect tumor growth. The dominance of pro-inflammatory cytokines lead to the collapse of a systemic immunological response [13]. Granulocytes, as a part of immunological response affect oncogenesis on many levels. The release of reactive oxygen and nitrogen forms by neutrophils cause local damage of epithelium, what stimulates prostaglandin E2 synthesis directly affecting oncogenesis [14, 15]. What is more, those cells produce neutrophilic elastase, which increases tumor cell proliferation [16]. Granulocytes can also decrease the immunological response of CD8 lymphocytes through nitrate oxygen synthase and TGF beta production [17]. Morphological evidence of local activity of immunological cells is the neutrophil-to-lymphocyte ratio.

In recent years, a few studies have determined the role of NLR as a prognostic factor in patients with PDAC in different clinical stages of disease [18–20]. In this study, NLR levels were evaluated in patients beginning systemic treatment with the FOLFIRINOX regimen due to metastatic PDAC. Values of NLR above 3 were associated with shorter median of overall survival. For NLR above 3, PFS and OS medians were 4.1 and 5.8 months, respectively. In the group of patients with an NLR lower than 3, the medians were 8.5 month and 14.5 months. These results are in accordance with previous studies. In the M. Piciucchi study in patients with metastatic PDCA, the values of NLR above 5 were associated with shorter OS, compared to patients with NLR below 5 (3 months *vs.* 7 months, p < 0.003) [21].

In the M. Shusterman study, NLT turned out to an independent prognostic factor in advanced PDAC. The median time of OS was 7.4 months for patients with NLR above 5, compared to patients with NLR below 5 (range of OS from 5 to 20 months) [22]. A study by S. Cetin presents greater differences between groups with NLR above 3.54 and below 3.54. For those cut-off values, median OS times were 9 months and 17 months respectively [23]. The presented results are also compatible with meta-analyses, proving that increased NLR was associated with poor prognosis in metastatic PDAC [24, 25].

In the case of LMR and PLR, we did not observe such results. This is contradictory to observations of meta-analyses proving

Table III. Log-rank test results for groups based on PLR result

	Median in PLR < 150 group (months)	Median in PLR ≥ 150 group (months)	Log-rank test results
PFS	8.15 (3.03–14.0)	4.76 (3.0–14.03)	p = 0.8565
OS	11.36 (6.03–17.87)	7.68 (4.53–11.93)	p = 0.6746

PFS – progression-free survival; OS – overall survival

Table IV. Log-rank test results for groups based on LMR result

	Median in LMR < 3 group (months)	Median in LMR ≥ 3 group (months)	Log-rank test results
PFS	5.50 (3.7–10.33)	8.25 (2.8–14.03)	p = 0.2461
OS	8.3 (4.76–16.5)	10.85 (6.28–17.23)	p = 0.4469

PFS – progression-free survival; OS – overall survival

that LMR and PLR might be independent prognostic factors [26–30]. The most probable reason for such discrepancy is the relatively small number of patients in the present study, together with the relative weak impact of LMR and PLR on the prognosis shown in the meta-analyses. LMR and PLR are parameters that require further analysis in patients with metastatic PDAC during systemic therapy.

Our study is one of the few studies that have proved the utility of NLR for a selected group of patients with metastatic PDAC during first line systemic therapy with FOLFIRINOX regimen.

Conclusions

This study proves the prognostic value of NLR in patients with PDAC in IV clinical stage treated with FOLFIRINOX chemotherapy.

Conflict of interest: non declared

Małgorzata Domagała-Haduch
Medical University of Silesia
Department of Oncology and Radiotherapy
ul. Ceglana 35
40-514 Katowice, Poland
e-mail: malgorzatadom@interia.pl

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Results of the treatment of adrenocortical cancer patients at the Maria Sklodowska-Curie National Research Institute of Oncology – Krakow Branch

Elżbieta Pluta, Magdalena Michta, Anna Patla, Anna Mucha-Małecka, Krzysztof Wójcicki, Piotr B. Madej

Department of Radiotherapy, Maria Sklodowska-Curie National Research Institute of Oncology, Krakow Branch, Krakow, Poland

Introduction. Adrenocortical carcinoma (ACC) has an incidence of 1–2 cases per million and the 5-year overall survival (OS) is 16–47%. Surgery is the treatment of choice. Post-operative radiotherapy has been shown to prolong overall survival and the purpose of this work was to show our own, first time in Poland, results of adjuvant radiotherapy in treating this disease.

Material and methods. Between 2012 and 2021, 12 patients with ACC were treated. The analyzed group included 9 women and 3 men at a mean age of 44 years (range: 33 to 76 years). A significant increase of tumor size was found in 30% of the subjects. In the analyzed group, 12 patients were qualified to adjuvant radiotherapy, but it was feasible only in 7 patients. The other 5 patients did not undergo radiotherapy. Two patients were disqualified due to metastatic disease and in 3 patients radiotherapy could not be performed due to excessive tumor size and too high a risk of complications within the critical organs.

Results. 3 out of 7 patients who received adjuvant radiotherapy are still alive and 4 of them died. Mean overall survival time was 32 months. The 12-month overall survival rate was 80%. In the group of 5 patients who have not received radiotherapy, 2 patients are still alive. The mean overall survival time is 13.5 months and the 12-month overall survival rate is 60%.

Conclusions. Due to rapid disease progression and poor prognosis associated with ACC, patients with tumors located in the adrenal gland require urgent surgical treatment at a reference center. Adjuvant radiotherapy improves treatment results significantly, but is not feasible in some patients due to cancer progression or the tumor location. In patients with ACC, it is important to diagnose the disease and to start adequate treatment as early as possible.

Key words: adrenocortical cancer, surgery, radiotherapy, mitotane

Introduction

Adrenocortical carcinoma (ACC) is a very rare and aggressive malignancy, with an incidence of 1–2 cases per million [1–11, 14–16]. In 2018, 56 cases of ACC were noted among men and 70 cases – among women in Poland. In the Małopolska region there were 2 and 3 cases, respectively. In Poland, in 2018,

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this cancer was the cause of death in 33 men and 36 women. In the Małopolska region there were 2 and 6 deaths, respectively [2]. ACC occurs most often between 40 and 50 years of age. It may induce mixed Cushing's syndrome and hyperandrogenism/virilization or may show no hormonal activity. Any focal lesion in the adrenal area found in the ultrasound examination requires confirmation by a CT or MRI scan. Wide access to imaging studies results in more and more frequent detection of adrenal lesions, in about 4% of the middle-aged population and in 10% of the elderly [5]. Surgery, performed after appropriate hospital-based preparation, is the treatment of choice for ACC. Videoscopy/laparoscopy adrenalectomy is the primary reference method of surgery. This procedure is only possible in reference centers experienced in the treatment of this difficult problem [4–6]. Only definitive surgery gives the patient a chance of cure. The risk of recurrence after such definitive surgery is 30% whereas in the case of a non-definitive operation this risk is as high as 65% [9]. Liver metastases are found in 42% of patients [9–11]. The risk of metastatic disease increases with advancing local tumor stage and two years after surgery it is 27%, 46%, and 63% for stages I, II, and III, respectively [11]. Adjuvant treatment with mitotane and radiotherapy prolongs the time to disease progression. It has been demonstrated that post-operative radiotherapy in patients with ACC has an effect on the time to local recurrence and overall survival and reduces the risk of death of patients with positive surgical margins by 40% [17]. Post-operative radiotherapy reduces the risk of recurrence by 50% [18].

Material and methods

In reaction to the reports published in 2012, suggesting that adjuvant post-operative radiotherapy in patients with ACC prolongs the time to progression and is likely to prolong the overall survival, at the National Research Institute of Oncology in Krakow, in cooperation with the Clinic of Endocrinology of the Medical College of the Jagiellonian University in Krakow, we started treatment with radiotherapy in this group of patients.

Until recently, adjuvant treatment of ACC has been conducted only by endocrine medicine specialists. In association with study results that showed prolongation of the time to local recurrence and overall survival in the ACC patients with postoperative radiotherapy, the purpose of this work was to show our own, first time in Poland, results of adjuvant radiotherapy of this rare and very aggressive cancer.

Between 2012 and 2021, 12 patients with this disease were treated. The analyzed group included 9 women and 3 men at a mean age of 44 years (range: 33 to 76 years). Patients reported the following symptoms prior to the diagnosis of ACC:

- high-amplitude blood pressure fluctuations (90%),
- hormonal disorders (40%),
- body weight increase (40%),
- depressive disorders (20%),
- weakness (80%),
- diabetes (20%).

Based on imaging studies, such as ultrasound, CT, and MRI, a rapid increase in tumor size was observed, up to 8 cm per year, in 40% of the patients. In the analyzed group, a significant increase of tumor size was found in 30% of the subjects. The size of the operated tumor ranged from 4 to 23.5 cm – the mean diameter was 9 cm (tab. I).

All patients underwent non-definitive (R1) surgery in the first instance, which was the main indication for adjuvant radiotherapy. All patients received adjuvant treatment with mitotane. 12 patients were qualified to adjuvant radiotherapy, but it was feasible only in 7 patients due to technical limitations. Radiotherapy was performed with a photon beam of energy adjusted to the depth of the tumor bed, using the conformal IMRT or VMAT technique in a period of 6 to 12 weeks after surgery. The patients received a total dose of 45 Gy to 50.4 Gy and the fraction dose was 1.8 Gy with mean overall radiotherapy time of 37 days [12]. The irradiated volume included the tumor bed and the regional lymph nodes (fig. 1). All patients completed the treatment in accordance with the treatment plan. Radiotherapy was well tolerated, and the most common complaints reported during the treatment included fatigue and intermittent diarrhea of minor severity.

5 patients were not treated with radiotherapy. In two cases, metastatic disease was the cause of disqualification from radiotherapy – one patient had liver and lung metastases

Table I. Characteristics of the analyzed group of ACC patients

Patients	Treatment with use of radiotherapy	Treatment without radiotherapy
gender:		
female	5	4
male	2	1
mean age: 44 years	range: 33–76	range: 33–60
disease stage:		
I	1 (14%)	0
II	4 (57%)	2 (40%)
III	2 (29%)	2 (40%)
IV	0	1 (20%)
mean tumor size: 9 cm	range: 4–8.5 cm	range: 8–23 cm
Ki-67 index:		
<20%	2	1
≥20%	2	1
not examined	3	3
location:		
right-sided	5	4
left-sided	2	1
non-definitive surgery	7 (100%)	5 (100%)
mitotane	7 (100%)	5 (100%)
cortisol production:		
yes	3	3
no	4	2

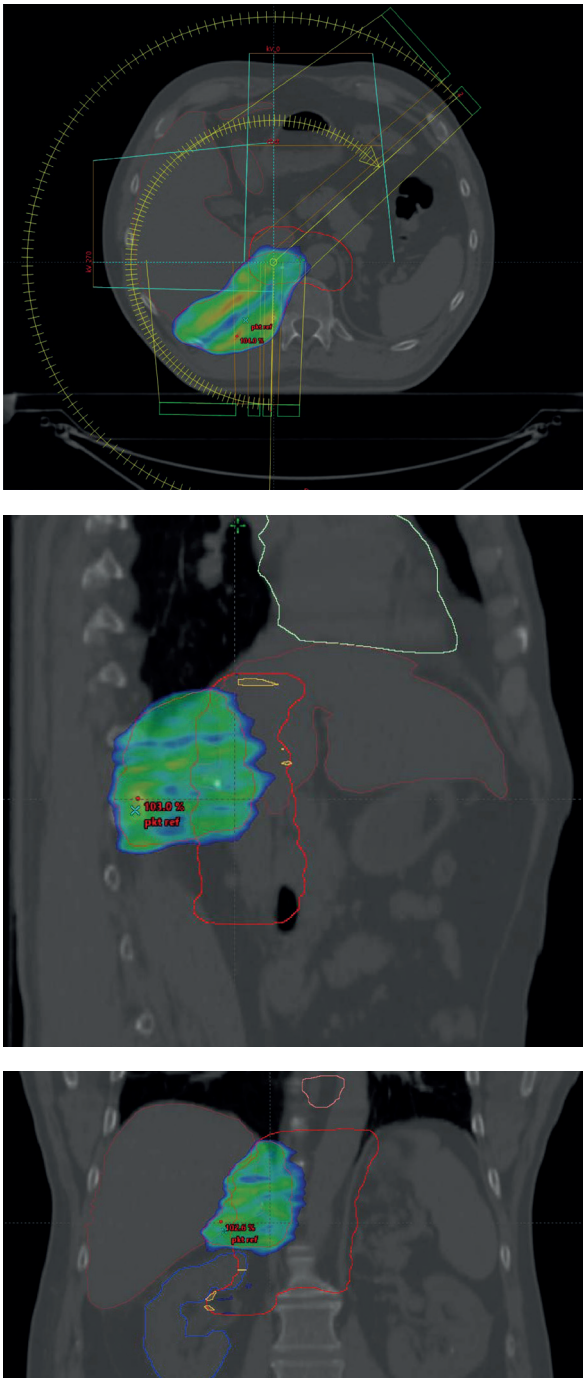

Figure 1. A 56-year-old man with adrenocortical carcinoma status post adrenalectomy and post tumor recurrence surgical resection. Postoperative radiation therapy during mitotane chemotherapy to decrease the risk of total recurrence. The planned target volume (PTV) of the elective lymph node group is in red. The PTV of the tumor bed with dose distribution is colored

and in the other one the disease had spread to the inguinal nodes and scrotum. In 3 patients, radiotherapy planning had started but due to the tumor size and/or right-sided tumor location, radiotherapy could not be performed due to an excessive risk of treatment-induced complications within the critical organs when balanced against any possible benefit [13].

Results

Out of 7 patients who received adjuvant radiotherapy 3 are still alive (43%) and 4 of them (57%) have died. The mean overall survival was 32 months. The 12-month overall survival rate was 80%. In one patient tumor-bed recurrence and generalized metastatic disease was found after 3 years of follow-up. In the group of 5 patients who did not receive radiotherapy, 3 (60%) have died and 2 (40%) are alive. The mean overall survival is 13.5 months. The 12-month overall survival rate is 60%. In 3 (60%) patients, liver and lung metastases were found.

Discussion

The results of treatment of patients with ACC are unsatisfactory, with 5-year overall survival varying from 16 to 47% [14], and for the advanced disease (stage 4) overall survival is less than one year. Local recurrence was found in 85% of patients who underwent definitive surgery (data for the year 2009). ACC used to be considered a radiation-insensitive tumor. Patient age less than 54 years, no endocrine activity, and localized disease are associated with a better prognosis of patients with ACC.

In 2009, Polat et al. [14] observed that 57% of patients treated for ACC responded to radiotherapy. Non-definitive surgery (the R1 feature) was the indication for adjuvant radiotherapy. Post-operative radiotherapy has been found to reduce the risk of local recurrence. The authors report that in some patients, the location of the tumor prevents radiotherapy because tolerance doses would be exceeded in such critical organs as the kidney and liver. These studies have contributed to the initiation of adjuvant radiotherapy in patients with ACC. Radiotherapy was well tolerated and in some patients only nausea and loss of appetite were noted.

In 2014, Sabolch et al. [15] have shown in a group of 360 patients with ACC that post-operative radiotherapy significantly reduced the risk of local recurrence. An improvement of treatment results was noted for all ACC stages, regardless of surgery radicality and mitotane treatment. However, no effect on the overall survival was noted.

Viani et al. [16] have shown in 2019 that adjuvant radiotherapy in patients with ACC significantly reduces the risk of local recurrence and the treatment is well tolerated. Gharzai et al. [17] reported in 2019 that post-operative radiotherapy in patients with ACC significantly improved the 3-year overall survival rate from 48.8% to 77.7%, and the 3-year local recurrence-free survival rate from 34.2% to 59.5%. The size of the tumor in the irradiated group ranged from 0.6 to 22.5 cm (mean: 10.4 cm) and in the non-irradiated group – from 4.1 to 23 cm (mean: 11.7 cm). In this study group, 46.2% of patients showed no disturbances of hormone levels and 56.4% – no cortisol production. Radiotherapy was well tolerated and only nausea and loss of appetite were noted.

In 2020, Zhu et al. [18] found that the use of adjuvant radiotherapy in patients with ACC has a statistically significant effect on prolongation of the overall survival and of the time

to progression and reduces the chances of local recurrence. These studies also have confirmed the role of adjuvant radiotherapy in the treatment of ACC. According to Cerquetti et al. [19], mitotane used in combination with radiotherapy acts as a radiosensitizer.

The mean age of patients in our group was 44 years, which is consistent with the literature data [8]. Similarly to other investigators, we have observed that patients undergoing radiotherapy live longer [17, 18]. In the analyzed group, 80% of patients treated with post-operative radiotherapy survived 12 months, compared to 60% of patients who did not receive this treatment. The mean overall survival in the irradiated group was 32 months, as compared to 13.5 months in the non-irradiated group.

We found a treatment failure in one patient in the treated group. The size of the tumor in the irradiated group was smaller, which enabled the use of this adjuvant modality. In 40% of patients, a rapid increase in the tumor mass was noted based on imaging studies (ultrasound, CT, MRI), up to 8 cm per year. In the study group, the high dynamics of tumor growth in some patients resulted in an inability to perform post-operative radiotherapy (too large an area requiring irradiation) and an inability to deliver a curative dose due to the high risk of complications in the critical organs. In 3 non-irradiated patients, a rapid metastatic spread of the disease was found. Symptoms reported by the patients, such as blood pressure jumps, large blood pressure amplitude fluctuations, hormonal disturbances, weight gain, depressive disorders, weakness, or diabetes should prompt physicians to perform urgent diagnostics, including imaging studies such as: ultrasound and abdominal CT and MRI scans. Only an early diagnosis of ACC gives the patient a chance for curative treatment. Abnormal adrenal function and disorders of the somatrotopic pituitary axis are related to mental disorders observed in patients. 20% of patients treated for ACC reported mood disturbances and these observations are in line with the Baranowska-Bik report [20].

Limitations

Adrenocortical carcinoma is a rare neoplasm, therefore the study group is small. The main purpose of this work is to present our experience in the treatment of this disease. For this reason, binding and firm conclusions regarding adjuvant radiotherapy should be drawn on the basis of larger groups that can be obtained by meta-analysis.

Conclusions

Due to the rapid disease progression and poor prognosis associated with ACC, patients with tumors located in the adrenal gland require urgent surgical treatment at a reference center. Adjuvant radiotherapy improves treatment results significantly, but it is not feasible in some patients due to cancer progression or tumor location. In patients with ACC, it is important to diagnose the disease and to start adequate treatment as early as possible.

Conflict of interest: none declared

Piotr B. Madej
Maria Sklodowska-Curie National Research Institute of Oncology
Krakow Branch
Department of Radiotherapy
ul. Garncarska 11
31-115 Kraków, Poland
e-mail: piotr.madej@onkologia.krakow.pl

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Evaluation of the incidence of splenic hilar lymph node metastasis in patients operated on for esophagogastric junction cancer

Tomasz Olesiński[1], Marek Szpakowski[1], Wojciech Kaźmierczak[1], Urszula Sulkowska[2], Andrzej Rutkowski[1]

[1] *Division I of the Department of Surgery for Tumors of the Gastrointestinal System and Neuroendocrine Tumors, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2] *Mazovian Cancer Registry, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Introduction. The purpose of this study is to evaluate the effect of esophagogastric junction cancer (EGJC) staging on the risk of splenic hilar lymph node involvement.

Material and methods. 312 patients with EGJC after R0 surgery were analyzed; 118 (38%) women and 194 (62%) men, median age 58 (29–80) years. In 81 (25.27%) cases, metastases were found in splenic lymph nodes (gr. 10).

Results. in stage I and II A (IA and IB), no metastases were found in splenic hilar lymph nodes (0/42 and 0/18, respectively), in stage IIB 9.61% (5/52), in IIIA 21.74% (15/69), in IIIB 36.36% (16/44), in IIIC 46.83% (37/79), and in stage IV 100% (8/8).

Conclusions. The highest risk of metastasis of esophagogastric junction cancer to splenic hilar lymph nodes exists in caners stage III and IV. Spleen-sparing elective splenectomy or group 10 lymphadenectomy may be of importance in the treatment of patients with stage III and IV gastroesophageal junction cancer, however, the assessment of its usefulness requires further prospective clinical trials.

Key words: gastric cancer, esophagogastric junction cancer, lymphadenectomy, splenectomy

Introduction

The extent of surgery in the radical surgical treatment of esophagogastric junction cancer has been debated for many years [1–13]. For tumours located in the greater curvature, esophagogastric junction and gastric fundus, the extent of elective lymph node removal (station 10 and 11) is the determinant of the extent of surgery. In recent years, the discussion has been revived because more and more centres are performing lymphadenectomies with spleen sparing, rather than extending the operation to include elective removal of additional organs (the spleen, the tail of the pancreas) as before. Elective removal of the tail of the pancreas and/or spleen during radical treatment of esophagogastric junction cancer has been currently abandoned due to the increased risk of postoperative complications, increased postoperative mortality [2, 3, 5, 10–12, 14–16] and the lack of conclusive reports of a positive effect on distant outcomes [1, 3, 6, 9, 11, 12]. In deciding the extent of resection, it is important to assess the risk of splenic hilar lymph node

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metastasis [17–19]. In this paper, we present an assessment of the incidence of lymph node metastasis of station 10 in patients operated on for adenocarcinoma of the esophagogastric junction based on our own material from the Department.

Purpose of the work

To evaluate the effect of the stage of esophagogastric junction carcinoma on the risk of splenic node involvement (station 10).

Material and methods

The accepted standard of care for radical surgical treatment of esophagogastric junction cancer (Ziewert 1 and 2) in the Surgical Department of the Oncology Gastroenterology Department is complete removal of the stomach, distal oesophagus with a D2 lymphadenectomy, with access via laparotomy or left thoraco-laparotomy. When performing a D2 lymphadenectomy, the lymph nodes of the initial splenic artery (station 11) and the lymph nodes of the splenic hilum (station 10) were removed electively, in addition to other lymph node stations. In most cases, the preparation was removed *en bloc*, and in all cases, after the operation was completed, the removed tissues were divided into individual lymph node groups in the operating room by the surgeon. In this way, the prepared lymph node groups were sent separately for histopathological examination (fig. 1).

Between 1996 and 2009, a total of 312 patients with adenocarcinoma of the esophagogastric junction (types I, II and III according to Siewert) were operated on in the Department. In the mentioned group, there were 118 women and 194 men, the median age was 58 (29–80) years. The characteristics of the study group are presented in table I. These patients were not treated with neoadjuvant chemotherapy. All patients underwent surgery with the intention to cure, with no macroscopic tumor tissue being left in the surgical field. In the analyzed group of patients, the total number of lymph nodes removed in the specimen per patient ranged from 16 to 80 (on average, 34 lymph nodes were found in the surgical specimen). The number of lymph nodes found in the splenic hilum ranged from 1 to 18, with an average of 4.2. In all cases, resectability was assessed as R0. For retrospective analysis, the pathological staging of tumors according to TNM-AJCC edition 8 was adopted (tab. II).

Regional lymph nodes for the stomach are: perigastric nodes located along the lesser and greater curvature (stations 1–6; according to Japanese Gastric Cancer Association (JGCA) nodes located along the left gastric artery [7], common hepatic artery [8], splenic artery [11], coeliac trunk [9] and hepatoduodenal nodes [12]. Metastases in extra-regional lymph nodes, such as behind the pancreatic head [13], mesenteric [14, 15] and periaortic [16] lymph nodes, are classified as distant metastases (M1).

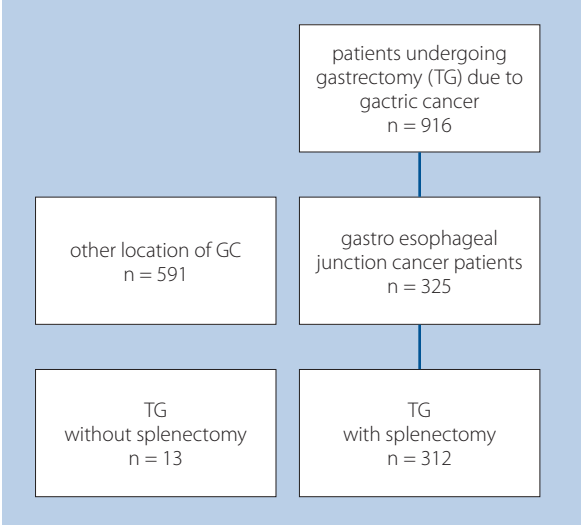

Figure 1. Study flow chart; TG – gastrectomy; GC – gastric cancer

Results

In the analyzed group of patients, pathological stage IA was found in 5.12% of patients (16/312 patients), stage IB was found

Table I. The characteristics of the study group

Characteristic	n
gender female (%) male (%)	 118 (38) 194 (62)
age – median (range)	58 (29–80)
BMI – median (range)	25.1 (22.2–28.3)
lymph node resection – median (range)	34 (16–80)
tumor (%) T1 T2 T3 T4	 48 (15.4) 85 (27.2) 108 (34.6) 71 (22.8)

Table II. Pathological staging of gastric cancer according to TNM-AJCC 8th edition

Clinical stage	TNM
IA	T1N0M0
IB	T1N1M0, T2N0M0
IIA	T1N2M0, T2N1M0, T3N0M0
IIB	T1N3aM0, T2N2M0, T3N1M0 T4aN0M0
IIIA	T2N3aM0, T3N2M0, T4aN1–2M0, T4bN0M0
IIIB	T1–2N3bM0, T3–4aN2bM0, T4bN1–2M0
IIIC	T3–4aN3bM0, T4bN3a–3bM0
IV	T1–4N1–3M1
N N1: 1–2; N2: 3–6; N3a: 7–15; N3b: >16	

in 8.33% of patients (26/312 patients), stage IIA in 5.76% of patients (18/312 patients), stage IIB in 16.66% of patients (52/312 patients), stage IIIA in 22.11% of patients (69/312), stage IIIB in 14.10% of patients (44/312), stage IIIC in 25.32% of patients (79/312), stage IV in 2.5% of patients (8/312).

The overall incidence of metastasis of adenocarcinoma of the esophagogastric junction to the splenic hilar lymph nodes was estimated at 25.27% (in 81 out of 312 patients), and the probability of their involvement increased with the clinical stage of the tumor. After subdividing according to the pathological stage, the following results were obtained: in stage I and II A (IA and IB), no metastases were found in the splenic hilar lymph nodes (0/42 and 0/18 pts, respectively), in stage IIB 9.61% (5/52 pts), in IIIA 21.74% (15/69 pts), in IIIB 36.36% (16/44 pts), in IIIC 46.83% (37/79 pts) and in stage IV 100% (8/8 pts) (tab. III).

Comparing the correlation between the frequency of splenic hilar lymph node involvement and concomitant metastasis to other perigastric lymph node stations, it was assessed that the most common correlation was between the lymph nodes of the greater curvature (short gastric vessels) and right perigastric lymph nodes (tab. IV).

Table III. Lymph node involvement according to clinical stage

Clinical stage	% of involved lymph nodes in the spleen hilum
IA and IB	0% (0/42)
IIA	0% (0/18)
IIB	9.61% (5/52)
IIIA	21.74% (15/69)
IIIB	36.36% (16/44)
IIIC	46.83% (37/79)
IV	100% (8/8)

Table IV. Correlation of splenic hilar lymph node involvement and other perigastric lymph node stations

Lymph node station	% of simultaneously involved nodes
along the greater curvature – station 4	52%
right cardia – station 1	42%
along the splenic artery – station 11	40%
left cardia – station 2	28%
along the left gastric artery – station 7	26%
around the coeliac trunk – station 9	26%
along the common hepatic artery – station 8	24%
infrapyloric – station 6	16%
along the lesser curvature – station 3	16%
suprapyloric – station 5	4%

Discussion

A splenectomy, according to a lot of the literature data, is considered an independent prognostic factor that significantly increases the number of septic complications and postoperative mortality [5, 10, 11, 14–16]. Chicara et al., analysing the need for an extended lymphadenectomy in the treatment of gastric cancer [6], noted the incidence of metastasis in removed periaortic lymph nodes with concomitant involvement of the splenic hilar lymph nodes. He found that at the time of splenic hilar node metastasis, 46% of patients had concurrent periaortic lymph node metastasis. Csendes et al. analysed a group of nearly 250 cases [9], and attempted to identify predictive factors that can help the surgeon decide whether splenic removal was warranted. No metastasis to the splenic hilum was found in the absence of serosal infiltration (0%), a low rate of metastasis was observed for tumor sizes less than 40 mm in the largest dimension (metastasis in only 1.7%) and for signet ring cell carcinoma histologic stroma (metastasis in 5.3% of cases). The incidence of gr. 10 node metastasis for proximal gastric cancer based on retrospective studies is about 15% [17, 19–21].

Son et al. [19] retrospectively reviewed 602 cases of proximal gastric cancer who had gr. 10 lymph nodes removed with (258) or without a splenectomy (344). In the study group, 14.5% had metastases in the splenic hilar nodes (25% in our group of patients, but we only evaluated EGJC cancer in our group). The authors compared the prognosis of these patients with patients who had metastasis to non-splenic nodes (gr. 9, 11, 12a) and found that the risk of recurrence in both cases was similar (5-year survival of 24.1%), but these patients still had a better prognosis than in the presence of distant metastases ($p < 0.05$). A meta-analysis of 15 papers evaluating the risk of splenic hilar metastasis confirmed that grades 3 and 4 were independent prognostic factors ($p < 0.01$). Other factors included tumor size >5 cm, location on the greater curvature, diffuse type according to Lauren, low tumor differentiation, T3–4 tumor, N2–3, M1 nodes and vascular infiltration [22].

A retrospective evaluation of a group of 995 originally laparoscopically operated patients with proximal gastric cancer, 564 of whom underwent resection of gr 10 nodes with spleen sparing and 431 of whom did not, showed that OS for patients with extended an lymphadenectomy was higher (63.3% *vs.* 52.2%, $p = 0.003$). An analysis of a small group of 39 patients after neoadjuvant therapy in the same study did not confirm such favourable results (50.6% *vs.* 31.3%, $p = 0.150$) [21].

Due to the results of the JCOG 0110 study [11], the latest JGCA 2018 guidelines [12] removed group 10 from the scope of the D2 lymphadenectomy. A randomized evaluation of 505 patients confirmed that a splenectomy in proximal gastric cancer does not affect survival, but rather increases the risk of complications; HR 0.88 (90.7%, confidence interval 0.67–1.16). Many authors debate these guidelines due to the focus of this study on splenectomy rather than lymphadenectomy with spleen sparing [20–25]. Currently, as experience is gained, more and more centres are removing a group of 10 lymph nodes without performing a splenectomy. Based on a retrospective study, Japanese authors [25] suggest that a resection of group 10 with spleen sparing may be beneficial for tumors infiltrating the greater curvature and for patients with cancer in the gastric stump (prior resection of the left gastric t. lymphatic drainage). A phase II study is currently underway to evaluate laparoscopic and robotic methods for resection of a group of 10 lymph nodes with splenic sparing (JCOG1809).

In summary, our own experience, as well as the literature data regarding expanding surgical procedures to include elective splenectomy to remove splenic hilar lymph nodes is still a debatable issue, despite existing surgical treatment recommendations that do not recommend performing elective splenectomy. Particularly problematic is the performance of an elective splenectomy in patients in whom, on staging studies and in the surgeon's intraoperative assessment, we can expect the tumor to be significantly advanced (stage III). The removal of lymph nodes in the D2 range along with a splenectomy or splenopancreatectomy results in increased complications and mortality, and does not improve distant treatment outcomes [11, 26]. Excision of the lymphatic system in the D2 range with spleen sparing only slightly increases expected survival and has little effect on the number of postoperative complications [20, 23, 27]. Extending the lymphadenectomy to include periaortic nodes does not improve outcomes [28]. However, the removal of the spleen when enlarged splenic hilar lymph nodes or splenic infiltration through continuity (elective splenectomy) is found is questionable. Selection of patients for an extended lymphadenectomy in the preoperative period is difficult and inconclusive (only in a few Japanese and Korean studies does a D2+ lymphadenectomy improve patient outcomes). Maruyama's program [29–30] for assessing the risk of nodal lesions (age, sex, Bormann classification, depth of infiltration, lesion diameter, location, WHO classification) may be helpful in decision-making. With all the above-mentioned caveats, "overtreatment rather than undertreatment" is still suggested.

Conclusions

1. The highest risk of metastasis of esophagogastric junction cancer to splenic hilar lymph nodes exists in stage III and IV.
2. An elective splenectomy or group 10 lymphadenectomy with splenic sparing may be of value in the treatment of patients with stage III and IV esophagogastric junction cancer, but evaluation of its usefulness requires further prospective clinical studies.

Conflict of interest: none declared

Tomasz Olesiński
Maria Sklodowska-Curie National Research Institute of Oncology
Division I of the Department of Surgery for Tumors of the Gastrointestinal System and Neuroendocrine Tumors
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: Tomasz.Olesinski@pib-nio.pl

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Histophysiology study of interleukin-4 in thyroid cancer patients

Ali Reda Hussein[1], Dhamia Kasim Suker[2], Sanaa Jameel Thamer[2], Majid Hameed Alabbood[3]

[1]*Ph.D. student, Physiology, Biology Department, College of Sciences, Basrah University, Basrah, Iraq*
[2]*Biology Department, College of Sciences, Basrah University, Basrah, Iraq*
[3]*Alzahraa College of Medicine, Basrah University, Basrah, Iraq*

Introduction. Interleukins have promising prospects in the clinical treatment of cancer. Interleukin-4 (IL-4) is an anti-inflammatory cytokine with an immunosuppressive effect on antitumor activity by immune cells, but the mechanical action of IL-4 in thyroid cancer is unknown. Aim: to investigate the effect of IL-4 expression in thyroid cancer patients. Furthermore, to clarify the association between obesity and thyroid cancer.

Material and methods. The present study was conducted on 115 subjects with thyroid nodules (36 with thyroid cancer and 79 with benign lesions) in Basrah, Iraq, from November 2019 to April 2022. To conduct a histophysiology study of IL-4.

Results. There was a significant difference in serum IL-4 between the thyroid cancer and control subjects. A higher level of serum IL-4 was observed in the Hashimoto thyroiditis group. There was no significant difference in body mass index (BMI) between thyroid cancer and control subjects. The expression of tissue IL-4 in thyroid cancer patients was strong in 8 (22.22%) slides, moderate in 7 slides (19.44%), weak in 8 slides (22.22%), and negative in 13 slides (36.11%), while in the control group, it was strong in 7 (30.44%) slides, moderate in 8 slides (34.79%), weak in 5 slides (21.74%) and negative in 3 slides (13.03%).

Conclusions. These findings indicate that serum levels of IL-4 may help diagnose thyroid cancer and identify patients with active disease who deserve closer medical attention. Furthermore, the secretion of IL-4 was systematic and not localized in thyroid cancer tissues. Obesity was not associated with a prevalence of thyroid cancer.

Key words: thyroid cancer, IL-4, obesity, thyroid gland, histophysiology

Introduction

Cancer is a significant public health problem worldwide [1]. Cancer is a class of disease characterized by the uncontrolled division of cells and the ability of these cells to invade other tissues, either by direct invasion into adjacent tissue or by implantation into distant sites (metastasis) [2, 3]. Thyroid cancer is the most dominant cancer type of the endocrine system [4]; its prevalence has increased dramatically worldwide in recent decades [4–7] as a result of environmental factors, radiation exposure, and the rapid development of available imaging and tools used for the detection of thyroid nodules [7–9]. Thyroid cancer accounts for approximately 2.3% of all new cancer cases in the U.S. [4]. Furthermore, it accounts for ≤1% of all human malignancies, a relatively rare disease responsible for

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six deaths per million annually [10]. Thyroid nodules represent the majority of lesions found in 19–68% of randomly selected people, and most benign nodules are without complications [10]. Seven percent of them may have a suspicious nodule for thyroid cancer depending on age, sex, radiation exposure, family history, and other factors [5, 11].

In the Iraqi population, thyroid nodules are common. However, thyroid cancer accounts for 1.7% of these nodules [12], while Mansour et al. [13] found that the prevalence of thyroid cancer was 0.4% (No. = 77) from 17878 patients who presented with thyroid lesions in Basrah province.

Many studies have documented that the overall incidence of thyroid carcinoma has increased more rapidly than that of any other malignancy in recent years, especially in women [14], and many serum interleukins have been medically used as diagnostic and prognostic markers or treatments for various types of diseases especially malignant disease [15, 16]. IL-4 has an essential role in inhibiting growth in many kinds of human cancers, including renal and gastric carcinoma [17]. Although many studies demonstrated that IL-4 and IL-10 are anti-inflammatory cytokines that have the immunosuppressive effect of antitumor activity, allowing tumor cells to escape recognition and attack by the immune system which can lead to cancer cell proliferation and metastasis. The mechanism of action of IL-4 in thyroid cancer is unknown [18–20], so understanding the mechanisms of interleukins in thyroid cancer will provide new targets for immunotherapy of thyroid cancer or finding alternative tools to discriminate thyroid cancer from benign lesions. The overall goal of this work was to investigate the effect of IL-4 expression in the blood serum and tissues of thyroid cancer patients. Furthermore, it aims to clarify the association between obesity and thyroid cancer.

Materials and methods

The study population consisted of 36 patients with thyroid cancer (11 men, 25 women) and 79 with benign thyroid lesions (7 men, 72 women); the mean age of thyroid cancer samples was 36.166 ± 16.84 years, and the mean age of control samples was 40.016 ± 10.519 years. All subjects were undergoing health checkups in Iraq/Basrah province hospitals and medical centers from November 2019 to April 2022. For the immunohistochemistry (IHC) study of IL-4 expression in thyroid cancer patients, all blood samples were collected by collecting 5 ml of peripheral venous blood without anticoagulant and allowed to clot in gel tubes at room temperature to study IL-4 expression in thyroid cancer patients. The IL-4 ELISA kit (catalog No.: E-EL-H0101) by Elabsceince/China (USA brand) was used to determine human IL-4 in blood serum. BMI was determined according to [21].

Fifty-seven paraffin wax-embedded tissues were collected from patients after surgery for both thyroid cancer (n = 36) and benign (control) subjects (n = 23) and were divided into three categories, Graves' disease (n = 4), Hashimoto's disease (n = 4), and multinodular goiter (n = 15). Then, the samples were stored at 5–8ºC until use in the study.

For investigating IL-4 expression in tissues, the IL-4 primary antibody (catalog No.: E-AB-62102) from Elabsceince/China was used, and IHC staining was accomplished according to [22]. A semiquantitative method (Allred) was used to interpret IL-4 immunohistochemical staining [23].

The effect sample size of this was calculated depending on the Kish formula [24]:

$$n = \frac{Z^2\, p(p-1)}{d^2} = \frac{(1.96)^2\, \xi\, 0.02(0.02-1)}{(0.05)^2} = 30.11 \qquad [24]$$

Statistical analysis: SPSS software version 26 was used for data analysis, and the ANOVA table and *post hoc* general liner model (GLM) were used to test the significance between different means. The Pearson correlation and Chi-square were used to examine the association between category variables [25].

Results

The result showed that there was no significant difference ($p \leq 0.05$) in BMI between cancer patients and control subjects since the values were 25.383 ± 5.39 kg/m^2 and 26.819 ± 3.92 kg/m^2, respectively (fig. 1). At the same time, there was a significant difference ($p \leq 0.05$) in serum IL-4 (pg/ml) between thyroid cancer patients and control subjects, with the value of 360.693 ± 241.493 pg/ml and 278.609 ± 82.729 pg/ml, respectively (fig. 2).

During the comparison of the IL-4 (pg/ml) level among diagnosis categories, the results showed a significance difference ($p \leq 0.05$) between thyroid cancer and multinodular goiter (MNG), since the value was 342.788 ± 234 pg/ml and 269.126 ± 76.05 pg/ml respectively. A higher serum IL-4 pg/ml level was observed in the Hashimoto thyroiditis group (383.67 ± 119.01 pg/ml) (tab. I).

There was a significant positive correlation ($r = 0.75$, $p = 0.013$) between serum level IL-4 (pg/ml) in thyroid cancer patients and BMI (kg/m^2). In contrast, the results of the Pearson correlation analysis in benign samples showed a negative correlation between serum level IL-4 and BMI (kg/m^2) ($r = –0.035$, $p = 0.756$) (fig. 3, 4).

For the histological study, all thyroid tissues were divided into two major groups of thyroid cancer and benign thyroid lesions, the benign thyroid tissues were divided into three categories, Graves' disease (n = 4), Hashimoto's (n = 4), and multinodular goiter (n = 15).

Thyroid cancer

The examination of thyroid cancer slides shows that all 36 samples (11 men and 25 women) belonged to papillary thyroid carcinoma, characterized by typical distinctive features. The tumor area and the normal thyroid parenchyma consists of different size follicles surrounded by normal

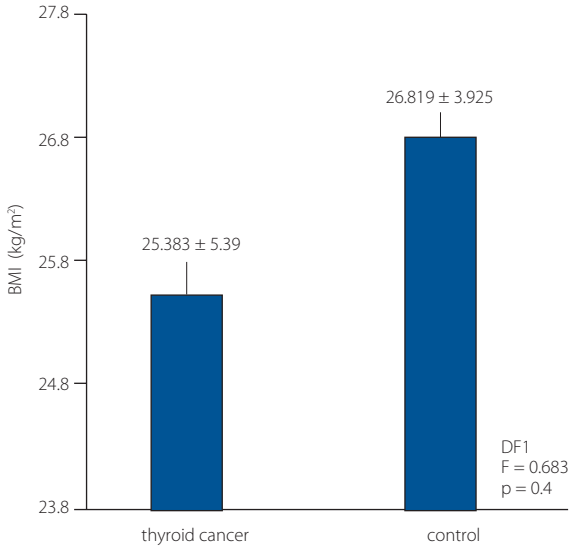

Figure 1. Distribution of BMI (kg/m^2) in thyroid cancer and control subjects

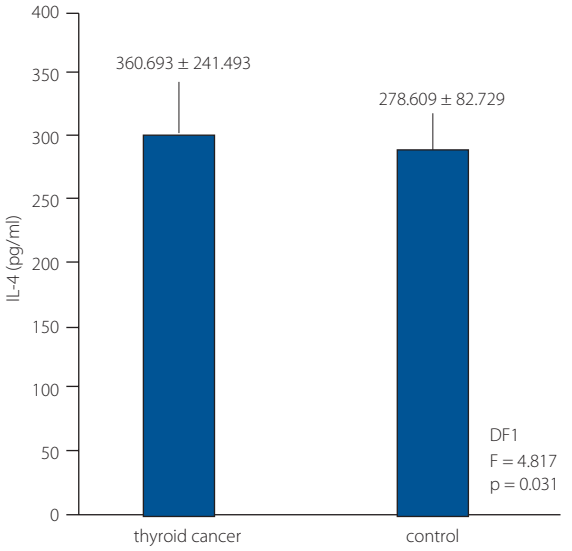

Figure 2. Level of serum IL-4 (pg/mL in thyroid cancer and control subjects

Table I. Level of IL-4 (pg/ml) in all subjects

Diagnosis		No.	Percent (%)	IL-4 (pg/ml) mean ± SD
cancer		25	24.03	342.788 ± 234[a]
control group	hyperthyroidism	9	8.66	310.195 ± 65.035[ab]
	hypothyroidism	2	1.93	324.082 ± 155.77[ab]
	Graves	10	9.61	262.839 ± 133.376[ab]
	MNG	54	51.92	269.126 ± 76.05[b]
	Hashimoto	4	3.84	383.67 ± 119.01[ab]

LSD – cancer × MNG = 73.66, p = 0.046*, cancer × hyperthyroidism, p = 0.523N.S., cancer × hypothyroidism, p = 0.822N.S., cancer × Graves, p = 0.338N.S., cancer × Hashimoto, p = 0.52N.S.. The mean difference is significant at p ≤ 0.05. N.S – non-significant at level p ≤ 0.05

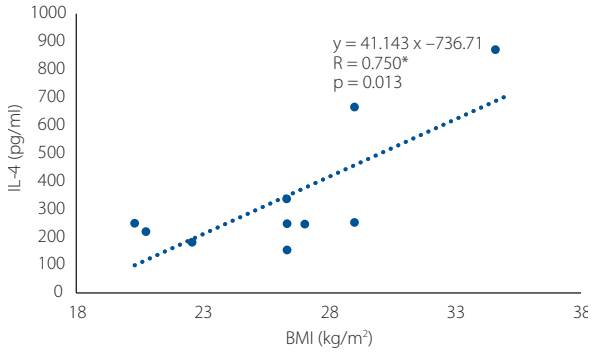

Figure 3. Correlation between IL-4 (pg/ml) level and BMI (kg/m^2) in thyroid cancer samples

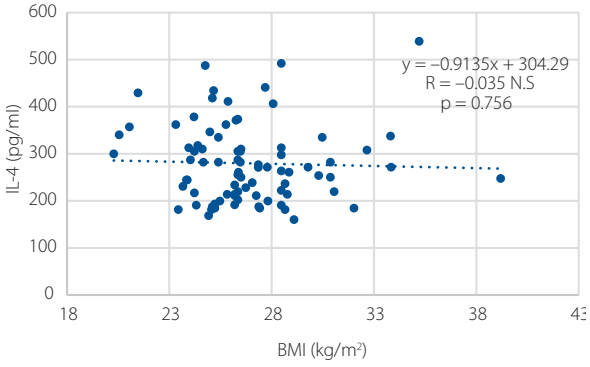

Figure 4. Correlation between IL-4 (pg/ml) level and BMI (kg/m^2) in control samples

thyroid cells filled with colloids separated by thin and thick capsules of collagen bundles, while the papillary tumor area is characterized by many papillary nuclear features, nuclear enlargement, nuclear clearing, and nuclear grooves, with multiple blood vessels (fig. 5).

In addition, another section of the papillary thyroid carcinoma shows papillary and follicular patterns, solid growth, and micro follicles separated by collagen fibers. During high power magnification, there were many sites of capsular and vesicular invasion, with papillary nuclear features such as nuclear clearing, nuclear grooves, and inclusion bodies, in addition to many sites of vascular and capsular invasion by malignant cells inside the vascular space of the tumor capsule (fig. 6).

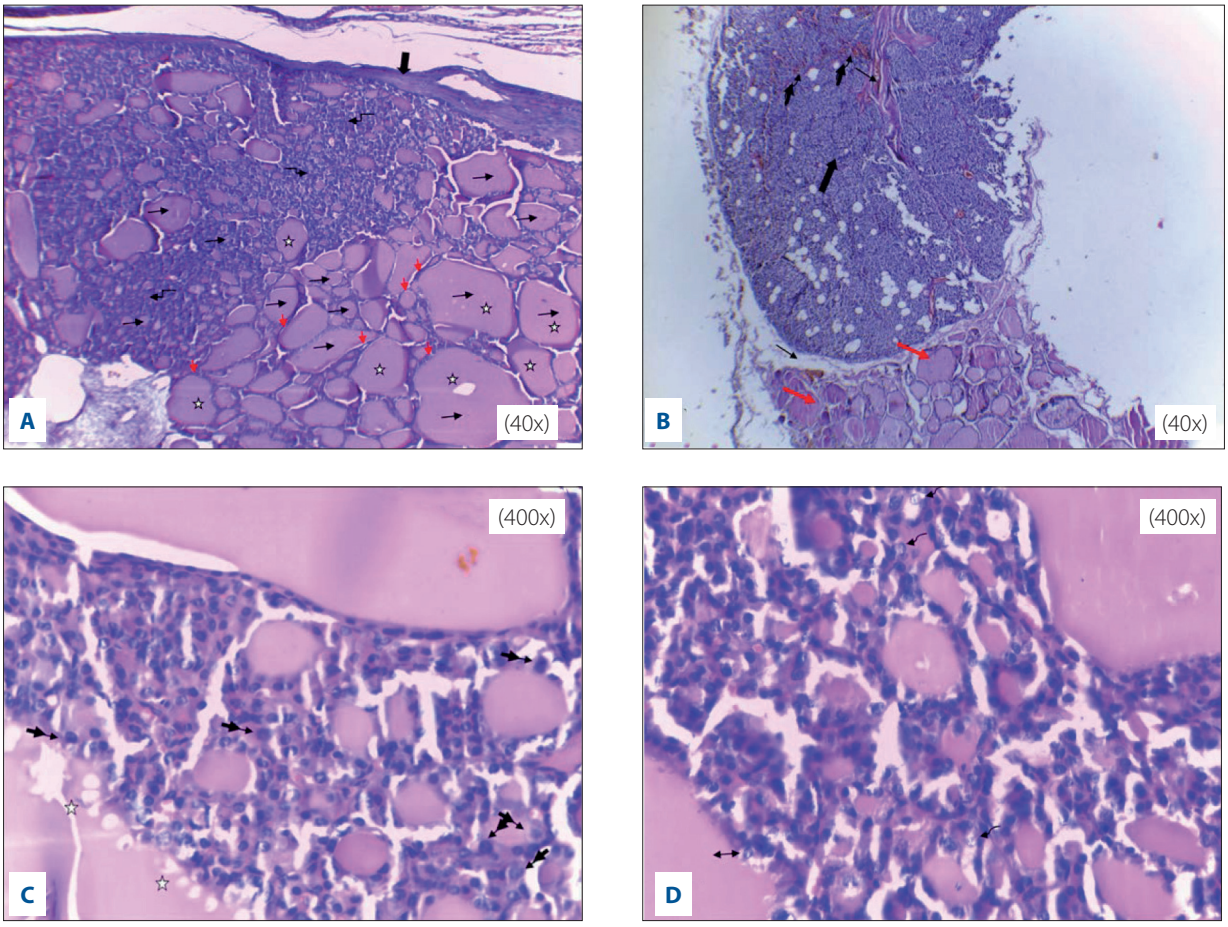

Figure 5. A section of the papillary thyroid carcinoma; (**A**) representative view showing a mixture of different size follicles black arrow (→) diffusely present papillary nuclear features cells (↳), follicles filled by colloid (pink color) (☆) and lined by normal-appearing cells (→), thick capsule (➡); (**B**) shows papillary nuclear feature cells (➡), follicle growth pattern (→), capsule of collagen fibers (→) blood vessels also presented (↳), (H&E); stain (40x). (**C**) and (**D**) section show enlarged and irregular nuclei (➡), nuclear groove (↔), and nuclear clearing (↳) with follicles growth pattern filled with colloid (pink color ☆) (H&E); stain 400x

Semiquantitative detection of IL-4 in thyroid gland tissues by immunohistochemistry assay

The expression of IL-4 in the thyroid tissues of cancer patients was strong in 8 (22.22%) slides (total 36 slides), moderate in 7 (19.44%), weak in 8 (22.22%), and negative in 13 (36.11%), with no significant difference $p \leq 0.05$ between the two groups (cancer and control) (Chi-square 5.345, $p = 0.148$) (tab. II and fig. 7).

The expression of IL-4 in the control group was strong in 7 slides (30.44%), moderate in 8 slides (34.79%), weak in 5 slides (21.74%), and negative in 3 slides (13.03%) (tab. II and fig. 8).

Discussion

Interleukins are immunoregulatory proteins secreted in response to several stimuli and play a vital role in cancer diseases as initiation, progression, and elimination [16]. IL-4 is an anti-inflammatory cytokine that regulates the immune response in normal health conditions and under cancers [26]. The present study demonstrates a significant difference in level of IL-4 in thyroid cancer patients than both control subjects and MNG groups, and these findings agree with Zivancevic-Simonovic et al. [27], who found that IL-4 level was higher in thyroid cancer patients than in control subjects. IL-4 is a potent immunosuppressive cytokine that has an important role in maintaining and proliferating cancer cells and helping them to escape from the immune system [20]. Safi et al. [28] found that a high level of IL-4 was associated with the reoccurrence of lung cancer, and Todaro et al. [29] found that IL-4 is required for the survival and growth of thyroid cancer cells. Although thyroid cancer cells do not constitutively produce IL-4, our results support a thyroid cancer induce infiltrating cells to produce IL-4.

Z. Li et al. [30] suggested that endogenous IL-4, the product of host immune response, can be used by tumor cells to facilitate their growth. IL-4 might act as a pro tumoral agent [31]. On the other hand, IL-4 may have an antitumor role since it acts synergistically with interferon-c to prime maturing antigen-presenting dendritic cells to produce high levels of a Th1 cytokine IL-12 that induces the differentiation of tumor-specific Th1-cells and cytotoxic T lymphocytes [32]. In contrast, previous studies indicate that although genetic variants in IL-4 do not affect the risk or outcome of differentiated thyroid cancer (DTC) patients, their influence on

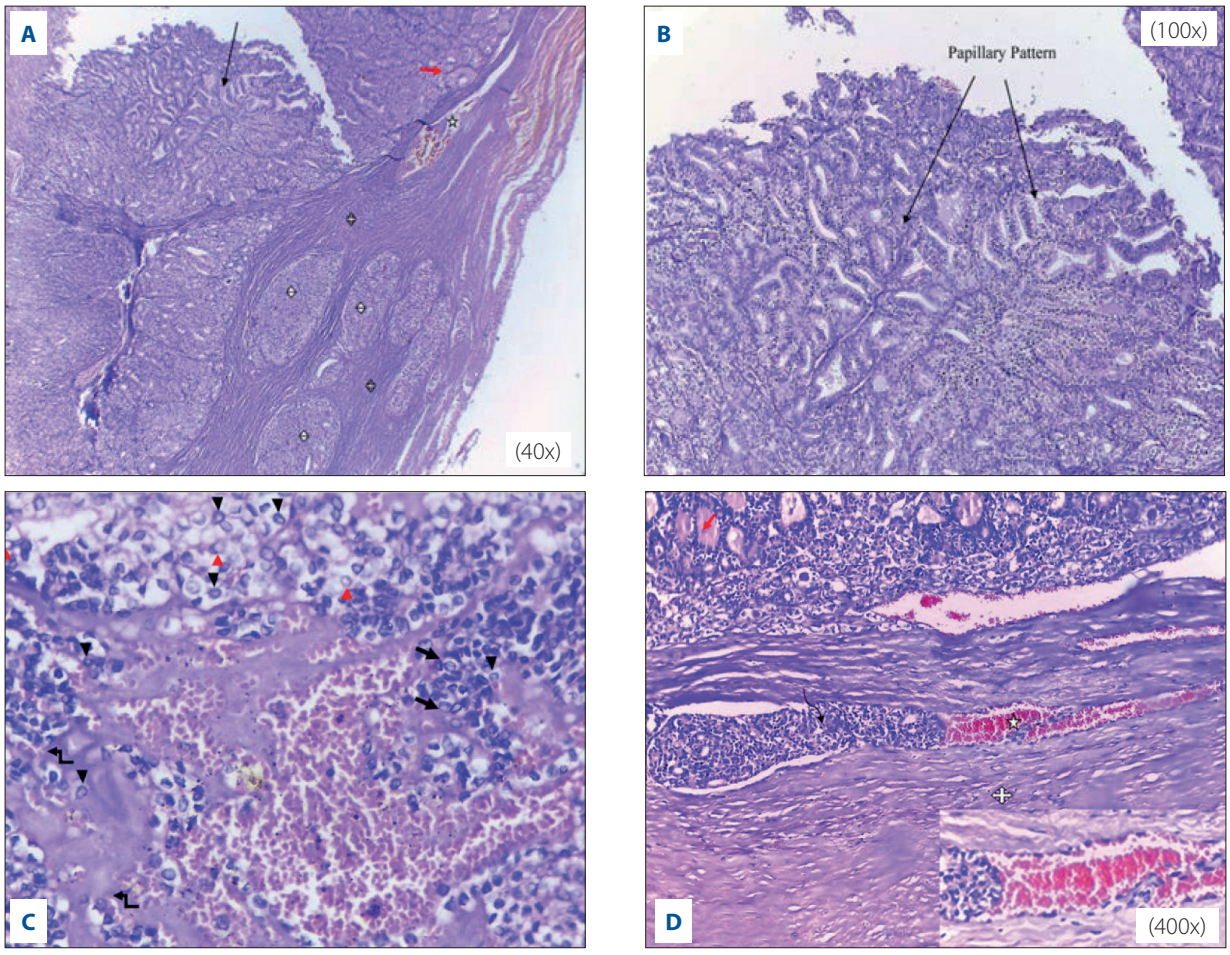

Figure 6. Papillary thyroid carcinoma; (**A**) showing a papillary pattern (⟶) with solid growth pattern (◈) and micro follicle pattern (⟶) separated by prominent collagen fibrosis tissue (✥) H&E; stain 40x. (**B**) in high magnification view from the same section, H&E; stain 100x. (**C**) shows many sites of capsular invasion (↰), nuclear clearing (▲), nuclear grooves (↘), and inclusion body (▼) (H&E); stain 400x. (**D**) shows vascular invasion (⤳) inside the vascular space (☆) of the tumor capsule, H&E stain; (100x) and a high-power picture in the left corner; stain 400x

Table II. The immunohistochemistry score of IL-4 in thyroid cancer and control tissues

Diagnosis		Immunohistology score						
		negative	week	moderate	strong	total	person Chi-square	p value
malignant	count	13	8	7	8	36	5.345	0.148$^{N.S.}$
	%	36.11%	22.22%	19.44%	22.22%	100%		
benign	count	3	5	8	7	23		
	%	13.03%	21.74%	34.79%	30.44%	100%		

N.S. – non-significant at level $p \leq 0.05$

the behavior of thyroid tumors deserves further investigation [31]. Many studies reported a direct inhibitory effect of IL-4 on the growth of human gastric cancer, melanomas, spontaneous adenocarcinoma, fibrosarcoma, and renal cell carcinoma [17, 33–35].

The higher production of serum IL-4 in the present study was observed in the Hashimoto thyroiditis group. Moreover, Hashimoto's is an autoimmune disease characterized by infiltrating lymphocytes inside thyroid tissue [36]. Many studies have demonstrated that significant amounts of IL-4 are secreted by T cells, helper T lymphocyte type 2 (Th2), mast cells, eosinophils, and basophils [20, 37]. The high level of IL-4 in the Hashimoto thyroiditis group in our study was in response to the increasing number of lymph cells which have an essential role in the secretion of IL-4. Our results are in agreement with Zivancevic-Simonovic et al. [27] and Schuetz et al. [38] since they have also found increased IL-4 production in patients with Hashimoto thyroiditis.

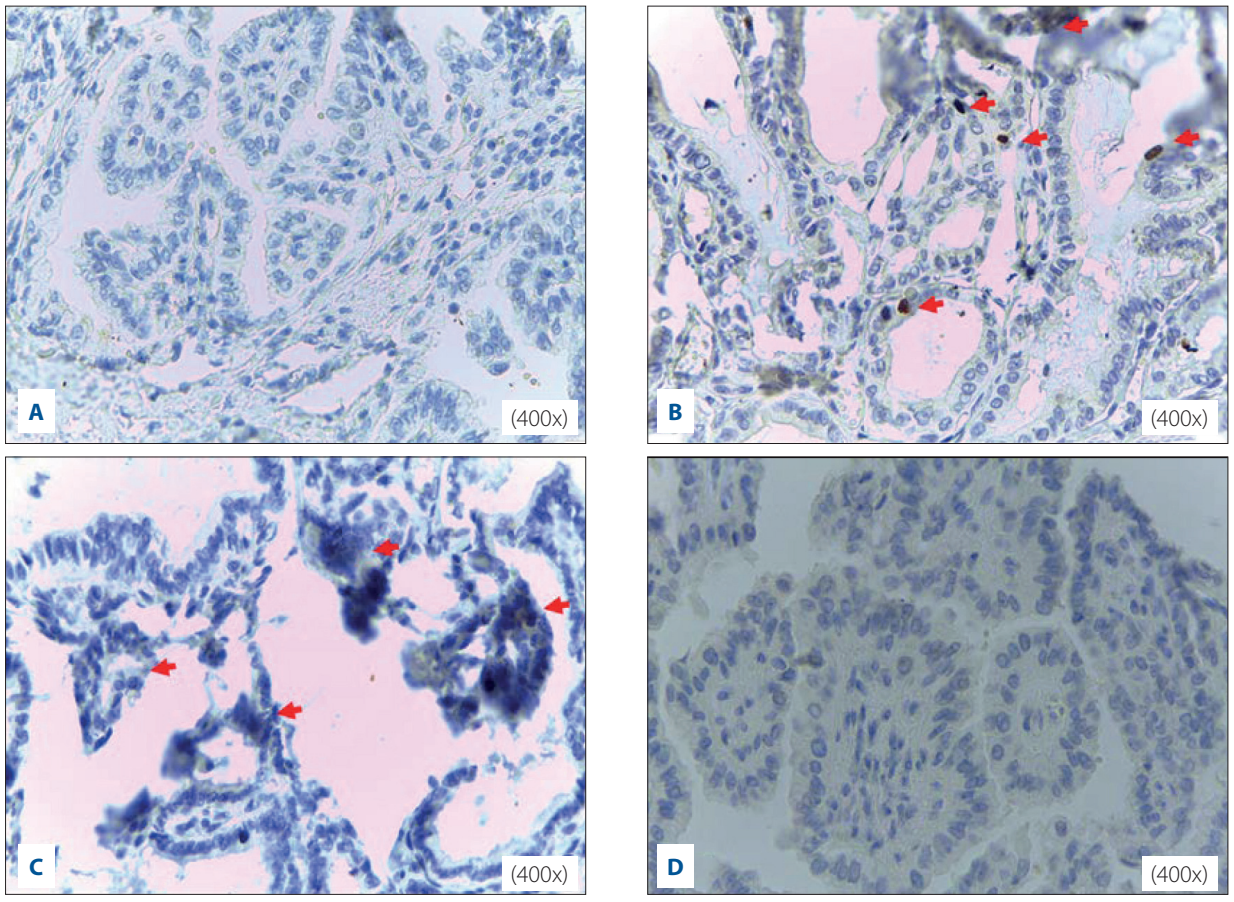

Figure 7. Immunohistochemical expression of IL-4 in thyroid cancer tissues; (**A**) section showing a negative expression; (**B**) weak positive staining, a red arrow (⟶); (**C**) strong positive staining, (red arrow); (**D**) negative control of thyroid cancer tissue; stain 400x

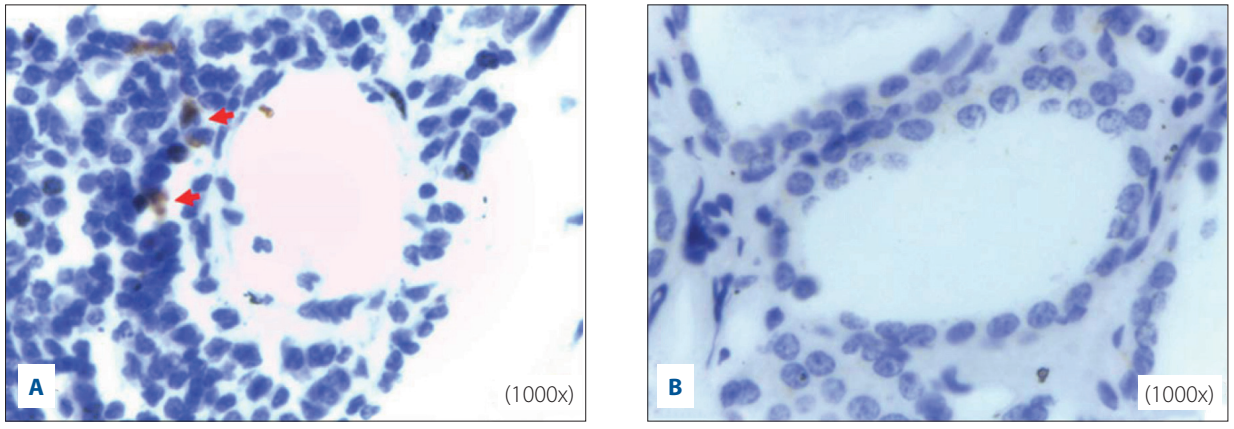

Figure 8. Immunohistochemical expression of IL-4 in benign thyroid tissues; (**A**) positive staining, red arrow (⟶); (**B**) negative control of benign thyroid tissue; stain 1000x

Because thyroid cancer is a rare disease and accounts for less than 1% of all cancer types in the human body [10], and the majority of thyroid cancer is papillary carcinoma [39], our study supports this finding (that the majority of thyroid cancer is papillary carcinoma) due to all the cancer samples belonging to papillary thyroid carcinoma, is the most prevalent type of thyroid cancer [40, 41], but we did not record any other thyroid cancer type due to its rare prevalence.

The present study confirms that obesity was not associated with a prevalence of thyroid cancer, there was no significant difference in BMI between cancer patients and control subjects.

Obesity has become a widely prevalent global health problem [42]. It has been posited that obesity causes thyroid cancer [43–45]. Furthermore, a correlation between being overweight and thyroid cancer is not widely accepted. A retrospective study of 4849 patients with thyroid nodules

(3809 females and 1040 males) did not confirm the positive correlation between thyroid cancer and obesity [46]. A similar conclusion has been reported by Ramdass et al. [47], which concluded that there was no correlation between BMI and development of thyroid cancer clinicopathological features [48].

In a histological study of IL-4, the current study revealed that the tissue expression of interleukin did not correlate with serum interleukin levels. A similar conclusion was reached by [49]. The results of IL-4 expression in the current study revealed no significant difference between thyroid cancer and the control groups. The expression of IL-4 was similar in both the control and thyroid cancer tissues. These findings are in agreement with de Oliveira et al. [50] which found that IL-4 regulates the immune system response, the expression of IL-4 in tissues is not engaged in the clinicopathology characteristics of cancer. However, many studies have investigated that IL-4 expression increases independently of the duration and severity of the disease, the expression of IL-4 has been detected in many tissues, in brain tissue and cerebral nuclei (in the lateral ventricle) in mice affected by Angiostrongylus (a parasitic infection) [51]. IL-4 expression was detected in the wounds on days 1 to 4 after wounding and then decreased progressively and disappeared on day 21 [52]. Abbas (2017) [54] showed that in cancer cachectic patients, IL-6 produces in large quantities which may be this trigger the different cells to release more cytokines.

Others have shown that expressing IL-4 in tissue improves the immune response against human ovarian melanoma, breast carcinoma [55], and thyroid cancer [20].

Conclusions

These findings indicate that serum levels of IL-4 may help diagnose thyroid cancer and identify patients with the active disease who deserve closer medical attention. Although thyroid cancer does not produce IL-4, it can induce other cells to produce IL-4. The tissue expression of interleukin did not correlate with serum interleukin levels. Furthermore, secretion of IL-4 was systematic and not localized in thyroid cancer tissues. Obesity was not associated with a prevalence of thyroid cancer.

Conflict of interest: none declared

Ali Reda Hussein
Basrah University
College of Sciences
Physiology, Biology Department
Ph.D. student
Basrah, Iraq
e-mail: ali_reada1984@yahoo.com

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External hemipelvectomy. A last resort operation

Leszek Kołodziejski[1, 2], Józef Duber[1], Piotr Pomykacz[1], Andrzej L. Komorowski[3, 4]

[1]*Saint Luke's Hospital, Tarnow, Poland*
[2]*University of Applied Sciences, Tarnow, Poland*
[3]*University of Rzeszow, Rzeszow, Poland*
[4]*Department of General Surgery, Edmund Biernacki Specialist Hospital, Mielec, Poland*

An external hemipelvectomy (hindquarter amputation) is a major mutilating amputation that includes the lower extremity and half of the pelvic rim. It is rarely performed due to its mutilating character and the technical difficulties involved. The main indications for the operation include sarcomas and extensive trauma. In this paper, the authors discuss the historical aspects and current status of this rare operation, as well as its role in the oncological approach to sarcomas.

Key words: sarcoma, hemipelvectomy, hindquarter amputation

Introduction

An external hemipelvectomy is considered to be one of the most mutilating operations in surgery. The indications for an operation where the lower extremity and half of the pelvis is amputated include bone sarcoma, soft tissue sarcoma, and trauma [1–4]. The highly mutilating character of the operation together with crucial technical difficulties as well as the resulting high morbidity and mortality all account for the infamy of this surgical approach [4–6]. All too common is a situation where the decision to perform an external hemipelvectomy is postponed virtually until the last moment, when all other treatment methods prove futile and the pain of the cancer has become unbearable [7, 8]. This treatment philosophy unfortunately leads to many patients being disqualified from surgery as the metastatic foci become apparent [9]. In this article, the authors present the indications for external hemipelvectomy and the surgical technique involved.

The history of the surgical approach

The first attempt at amputation of the lower extremity with half of the pelvic rim was performed by Theodore Billroth in 1891 in Vienna. Unfortunately, the patient died a few hours after surgery was completed. In addition, the second operation, performed by Mathieu Jaboulay in Lyon in 1893, also ended with the death of the patient [8]. Since Jaboulay – contrary to Billroth – published the description of his case, some surgeons suggest that an external hemipelvectomy should be referred to as a "Jaboulay operation" [10]. From the available literature we know that of the first 6 operations of this type, all resulted in the death of the patient in matter of hours or days [10]. The first patient to survive an external hemipelvectomy was operated on in 1895 in Geneve by Charles Girard [11]. The technical approach to the external hemipelvectomy was established in 1916 by James Hogarth Pringle from Glasgow. Pringle's description constitutes the technical basis for the later modifications of the technique. The various modifications differ from Pringle's approach mainly in the manner in which the large defect is dealt with, while the resection part remains almost unchanged [11].

Indications

The indication for an external hemipelvectomy have remained mostly intact for the last 120 years. It should be considered

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in cases of large bone or soft tissue sarcomas located within the pelvic rim [4]. It is also considered for crash trauma patients in which the destruction of the pelvis makes it impossible to spare elements of the pelvic rim. [12, 13]. Historically, the large tuberculotic involvement of the pelvis was also considered to be an indication for an external hemipelvectomy. Of the first 21 cases described in the literature from 1889 to 1909, 18 were performed for sarcomas and three for tuberculosis [10].

The most common cancers that may require performing an external hemipelvectomy are: chondrosarcoma, Ewing sarcoma, plasmocytoma, and osteosarcoma [8]. All the above cited cancers are rare [14]. Moreover, only a fraction of these cancers develop within the pelvic rim, e.g. 7% of all osteosarcomas [8]. Finally, a big proportion of these patients can be qualified for smaller, limb preserving resections. In a series by Pieńkowski et al., it was possible in 53 consecutive pelvic chondrosarcoma patients [15]. If we add to this data the fact that some of those patients are disqualified from surgery due to the stage of the disease and general performance, it becomes clear why an external hemipelvectomy is one of the rarest surgical operations performed nowadays.

Technique

Currently there are two approaches to a hemipelvectomy, namely an external and internal hemipelvectomy. The introduction of advanced prosthetic materials and techniques in the last decades of the 20th century created the possibility of performing a resection on part of the pelvic rim without the need to undertake a lower extremity amputation. This approach is called an internal hemipelvectomy [8]. While being obviously less mutilating than the classic external hemipelvectomy, its use is limited to patients without involvement of the thigh.

In an external hemipelvectomy, the dissection starts in the anterior wall of the abdomen, and dissection aims at conserving the peritoneum intact while respecting the "no touch: and *en bloc* rules for cancer surgery. The urinary bladder, peritoneum, fascia, kidney, and urethra are exposed (fig. 1).

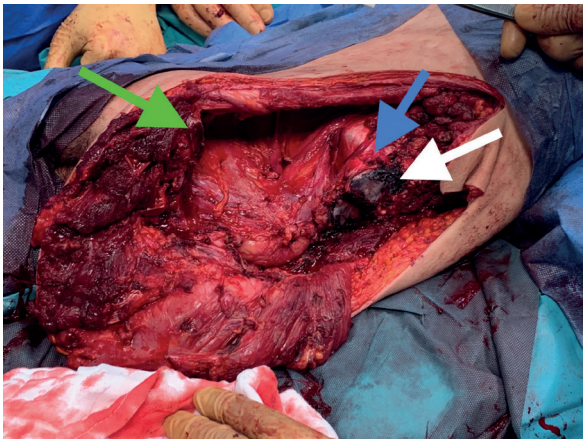

Figure 1. Full exposition of the operative field after resection: the green arrow points to the cut left pubic bone; the blue arrow points to the promontorium, with the left urethra seen on its surface; the white arrow points to the cut surface of the sacral bone

The pubic bone is resected within or very close to the symphysis pubis. The dissection of the sacro-iliac connections is made with the posterior approach. This element is required for the operation to be classified as an external hemipelvectomy [16]. If required, lateral vertebral processes of the lumbar spine are resected. Common iliac vessels are closed and sutured with transfixing sutures (fig. 2). Depending on how much surrounding tissue was spared during the operation (which in turn is a function of direct involvement of the cancer tissue), the defect is closed in a manner chosen by the operating surgeon. If not infiltrated, the following muscles can be used to form musculo-cutaneous flaps to cover the defect: abdominal muscles (rectus, obliques), thigh flexors, quadriceps, gluteus.

The final surgical specimen includes half of the pelvis and lower extremity. The defect is covered depending on the formerly prepared flaps (fig. 3). Although the extent of mutilation is important, patients are able to proceed with their personal and professional life after the operation and dedicated physiotherapy.

Discussion

It is quite difficult to standardize such a rare operation as the external hemipelvectomy. In a recent meta-analysis, only 5 studies of 183 patients were found to compare the results

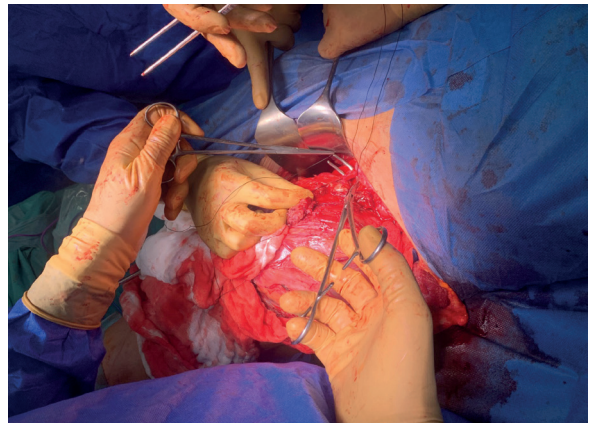

Figure 2. Transfixing sutures of the left common artery. The specimen can be seen to the left of the picture

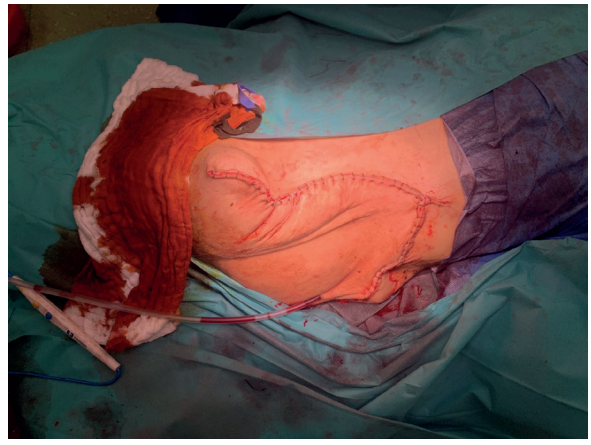

Figure 3. The final view of the operative field after flap closure

of internal and external hemipelvectomies over a span of 35 years [17]. The majority of even high volume cancer hospitals do not have significant numbers of these operations. The reasons for this phenomena are three-fold: the rarity of the tumors, the existence of other, less mutilating techniques, and usually a late diagnosis. The patient, whose operation can be seen on the photographs included in this article, was diagnosed with gigantocellular bone tumor only 2 years after the first pain symptoms in his groin area. Indeed, the pain is present in almost all patients with pelvic sarcoma – it was the main symptom of all 40 patients in a Dutch series from 1978–1995 [1]. After resection of the tumor with hip replacement, he started the physiotherapy only to be diagnosed with G3 fibroblastic osteosarcoma of the previously operated area. He was qualified for AP3 cisplatin and doxorubicin systemic therapy, apparently with palliative intent [1]. During chem therapy, the patient suffered further progression of the tumor which reached dimensions of 141 x 109 x 163 mm without the evidence of distant metastasis. Judged marginally operable, the patient had to desperately look for a center willing to perform the surgery and due to uncontrollable pain, was willing to undergo any mutilation needed, including the placement of fecal and urinary diversion if required. The operation was performed after neoadjuvant volumetric modulated arc therapy (VMAT) radiotherapy 25 Gy in 5 fractions [18]. The postoperative course was uneventful, the histopathology report confirmed the R0 resection, and 3 months after the operation the patient started to work as a professional driver using an automatic gear box.

Radical operation, i.e., R0 resection, is fundamental for the long-term survival of patients undergoing a resection for pelvic sarcoma [1, 3, 5, 19]. In the case presented on the illustration, the main technical difficulty was to obtain free margins from the spinal side. In order to maximize the possibility of R0 resection, preoperative radiotherapy was undertaken [20] with the use of the VMAT technique [18]. During surgery, a resection of the spinal L3 and L4 processes as well as part of the sacral bone was required. This part of the operation resulted in the highest intraoperative blood loss that was evaluated at 2l during an 8 hour surgery.

According to authors from the Mayo Clinic, neoadjuvant chemo and radiotherapy allows better than expected local and distant control of the bone sarcoma of the extremities [20].

The importance of the technical aspects of the hemipelvectomy was analyzed in possibly the biggest series of hemipelvectomies from the same center. Over a 20-year period (1985–2005), 160 hemipelvectomies were performed in the Mayo Clinic. Almost half of the patients (45%) received radiotherapy and similarly 46% underwent chemotherapy. The mean operation time was 6.4 hours and the mean number of blood units transfused was 13.4. Intraoperative mortality was 5%. Complications with the flap was present in 26% of patients and wound infection in 39%. The main factors influencing local complications were operation durations exceeding 7.3 hours and the need to close the common iliac vessels [6, 9, 21].

In a personal series by Miller, who performer 100 hemipelvectomies between 1946–1972, all patients had their common iliac vessels cut and closed. It did not, however, influence the healing process of the large posteriori flap, similarly to our case [22].

Interestingly, in the patient seen on the images, the malnutrition (BMI 14.2) did not result in perioperative complications. The patient was able to be sent home with primary healed wounds two weeks after surgery, compared to the 26 and 27 days reported by Senchenkov and Bohm [6, 23].

Since the patient suffered significant pain before the operation, once the surgery was completed he was eager to restart physical activity. Also, even with a partial resection of the lumbar plexus, he did not suffer any bowel or urinary control problems. The emotional element must be stressed. A willingness to undergo a very mutilating surgery was definitely an important factor in influencing his quick recovery [3, 24, 25].

It is difficult to evaluate the prospect for long term survival of a patient with advanced bone sarcoma requiring an external hemipelvectomy, even after R0 resection, since long follow-up is relatively low [23, 26]. The vast majority of patients die as a result of massive metastasis to the lungs [1–3].

Conclusions

The external hemipelvectomy is a rarely performed mutilating operation. In selected cases it is the last resort, and, as such, should be taken into consideration for patients who have been disqualified from other forms of radical treatment.

Conflict of interest: none declared

Andrzej L. Komorowski
University of Rzeszow
ul. Kopisto 2a
35-959 Rzeszów, Poland
e-mail: z5komoro@cyf-kr.edu.pl

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Osteoporosis – a partially recognized challenge for oncology

Krzysztof Jeziorski[1, 2]

[1]*Department of Gerontology, Public Health and Didactics, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland*
[2]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Osteoporosis is a huge challenge for medicine, especially public health and geriatrics, but also oncology, because it is a chronic disease requiring long-term, sometimes lifelong care. With the ageing of the population, falls are the third most common cause of disability in the elderly and one of the main reasons for admissions to nursing homes. Although there are approximate data on the incidence of osteoporosis worldwide, there are unfortunately no data on the incidence of osteoporosis in cancerous diseases. The incidence of cancer-related osteoporosis is expected to increase as the incidence of cancer in general increases. There are specific problems that concern osteoporosis in cancer patients, including: the mechanisms of development of osteoporosis in cancer diseases, the distinction between cancerous and osteoporotic lesions, undertreatment of patients, the lack of an integrated care system for osteoporosis in cancer patients.

Key words: osteoporosis, bone fracture, densitometry, malignant diseases

Osteoporosis is a huge challenge for medicine, especially public health and geriatrics, but also oncology because it is a chronic disease requiring long-term, sometimes lifelong care. Elderly patients often show signs of frailty (reduced mobility, malnutrition, comorbidity, cognitive impairment, polypharmacy, neurosensory deficits, reduced muscular functionality) which are associated with a high risk of falls leading to fracture [1]. Osteoporosis and the fractures caused by it lead to increased mortality. In the case of hip fractures, the increased risk of mortality is particularly pronounced 3–6 months after the fracture. With the ageing of the population, falls are the third most common cause of disability in the elderly, and one of the main reasons for admissions to a nursing home [2, 3].

According to the World Health Organization (WHO), osteoporosis is defined as bone densitometry (DXA) T-scores less than 2.5 at the lumbar spine or femoral neck and microarchitectural deterioration of bone tissue [4, 5]. Osteoporosis is also defined as a systemic skeletal disease characterised by low bone mass, with a consequent increase in bone fragility and susceptibility to fracture [6, 7]. Despite significant progress in the treatment of cancer, the problem of osteoporosis that accompanies these diseases is often neglected.

While osteoporosis is not a precursor for cancer, many people with oncological diseases develop osteoporosis as a result of the malignant effects of the disease or its treatment. Interestingly, despite the growing problem, osteoporosis issues are generally omitted in oncology textbooks. And yet osteoporosis may be one of the actual side effects of oncological treatment [8].

Do we have data on the epidemiology of osteoporosis in cancerous diseases?

Unfortunately, there are no detailed data on the epidemiology of osteoporosis in the world. Also, estimates of the incidence

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of osteoporosis vary significantly. Osteoporosis is estimated to affect approximately 200 million people worldwide while osteoporosis fractures are estimated to affect 2.7 million men and women in Europe [6, 9, 10]. At least 40% of postmenopausal women develop osteoporosis and 15–30% of men. According to the National Health Fund data, the estimated number of people suffering from osteoporosis in Poland in 2018 was 2.1 million, of which 1.7 million were women [11]. The incidence of osteoporosis increases with age and particularly affects people who are in their 70s. Population ageing is a global public health challenge. According to WHO figures, the percentage of the population over the age of 60 years will increase from 12% in 2015 to 22% in 2050 [12]. It is estimated that by 2050 this age group will increase to 2 billion. According to the National Health Fund data, the degree of underestimation of osteoporotic patients in Poland in 2018 was 74%. This corresponds to 1.56 million undiagnosed people, of whom almost 500,000 were over 80 years of age [11]. When the inhabitants of the European Union aged 50–80 are stratified into five-year age groups, the highest percentage of women diagnosed with osteoporosis (approximately 3.9 million women) is observed in the 75–79 age group, and among men in the 60–64 age group (about 0.8 million men) [13].

Although there are approximate data on the incidence of osteoporosis worldwide in the general population, there are unfortunately no data on the incidence of osteoporosis in cancerous diseases. The incidence of cancer-related osteoporosis is expected to increase as the incidence of cancer in general increases, including two hormone-dependent cancers in particular: breast cancer in women and prostate cancer in men.

In Poland in 2020, the most common cancer in men was prostate cancer (19.6% of all malignant tumours in men) whilst for women that was breast cancer (23.8% of all malignant tumours in women). In the same year, the second leading cause of cancer deaths was prostate cancer in men (10.6% of all malignant tumours in men) and breast cancer in women (15.3% of all malignant tumours in women) [14]. Among men in the oldest age group (the over 65 age group), the most common cancer was prostate (23% of incidences, 13% of deaths) and among women in the same age group, the most prevalent was breast cancer (19% of incidences, 14% of deaths) [14]. Bone changes that lead to osteoporosis in cancer can be caused by cancer itself (cancer-induced bone disease – CIBD) or bone loss caused by oncological treatment (cancer treatment-induced bone loss – CTIBL). Osteoporosis observed in cancer may be the result of the disease itself or the adverse effects of therapy that reduces bone mineral density. The bone microenvironment is a good substrate for the growth of cancer cells.

Risk factors for the development of osteoporosis in neoplastic diseases

Among the factors influencing the development of osteoporosis, are modifiable and non-modifiable factors. The first group of factors includes:

- low calcium intake,
- reduced exposure to sunlight,
- prolonged immobility,
- excessive alcohol intake,
- smoking,
- eating disorders,
- long time immobility,
- low body mass index (BMI),
- low physical activity,
- several medications (glucocorticoids, anticonvulsants, chemotherapy and hormonotherapy of breast and prostatic cancer).

The second group of factors includes:

- older age,
- female sex,
- white race,
- personal and parental history of osteoporosis and fractures,
- low body frame size [15].

Virtually all oncological patients are exposed to an increased risk of osteoporosis and associated fractures as a result of an unfavourable combination of factors: cancer, often advanced age, treatment regimens, which all directly or indirectly affect bone cells [16]. Although osteoporosis in oncological patients is usually associated with hormone-dependent cancers (breast cancer, prostate cancer), it can occur during the course of all cancers. As a co-existing disease with cancer, it can significantly worsen the prognosis of cancer patients, because osteoporosis and the fractures caused by it lead to increased mortality. For hip fractures, the increased risk of mortality is particularly exacerbated in the 3–6 months after the fracture. The peak of bone mass formation occurs in most people between the ages of 16 and 25, followed by a slow but steady loss of bone mass of 0.3% per year in men and 0.5% per year in women. But in postmenopausal women, bone loss within 5 years of osteoporosis can be 5–6% per year [17].

Specific problems of osteoporosis in cancer patients

There are specific problems that concern osteoporosis in cancer patients, including:

- the mechanisms of development of osteoporosis in cancer diseases,
- the distinction between cancerous and osteoporotic lesions,
- undertreatment of osteoporosis in cancer patients,
- the lack of an integrated care system for osteoporosis in cancer patients.

Osteoporosis is the end result of various mechanisms leading to its development. The causes of osteoporosis during cancer treatment include:

- therapy-induced hypogonadism,
- use of glucocorticoids in chemotherapy regimens,
- toxic effects of chemotherapy and radiotherapy,

- immobilization,
- eating disorders [18].

In hormone-dependent cancers (breast cancer, prostate cancer), hypogonadism is an intended part of the treatment strategy and substitution treatment cannot be used. The opposite is true in hormone-independent cancers, where hypogonadism is not the intended goal of treatment.

Chemotherapy and hormone therapy cause thinning of the trabecular and cortical bones. The development of osteoporosis is influenced by the type of chemotherapeutic, its dose and duration of use. Drugs used in systemic cancer therapy contribute to the development of osteoporosis, especially: cyclophosphamide, cisplatin, taxanes, aromatase inhibitors, which all reduce calcium levels and lead to bone loss. Steroids that are used in cancer chemotherapy as part of chemotherapy regimens or as an antiemetic cause impaired calcium absorption and bone loss [18].

Similarly, drugs used in bone marrow transplants increase the risk of bone loss. The use of high doses of drugs in bone marrow transplantation is associated with the risk of developing osteoporosis in the first years after transplantation. This is related to the direct and indirect effects of chemotherapy: hypogonadism, increased bone resorption and renal dysfunction, secondary hyperparathyroidism and the use of glucocorticosteroids. The reduction in bone formation is due to malabsorption due to graft-versus-host disease (GVHR), mucositis with reduced absorption of calcium and vitamin D and the direct effect of chemotherapy on osteoblasts [19].

Radiation therapy has direct and indirect effects on bones. Direct action induces local bone and bone marrow atrophy, leading to bone loss, growth factor deficiency and retardation of bone growth. In turn, the indirect effect of radiotherapy causes vascular changes leading to fractures, especially of the pelvis and ribs [20].

The following factors have an indirect influence on the development of osteoporosis in cancer diseases:

- myelosuppression,
- damage to the gastrointestinal mucosa,
- malabsorption,
- intensification of catabolic processes,
- weakness or fatigue during the course of the cancer,
- weight loss,
- frequent generalised and chronic infections accompanying the underlying disease.

In the development of osteoporosis during the course of breast cancer, a key role is played by the induction of inflammatory stress in osteoblasts, which leads to the synthesis of cytokines acting on osteoclasts, resulting in an increase in bone resorption and a reduction in bone formation. Tamoxifen, used in hormone therapy for breast cancer, has an anti-resorptive effect, but does not affect bone growth. On the other hand, aromatase inhibitors (anastrazole, letrozole and exemestane) inhibit the production of oestrogens, which leads to a decrease in bone density [18]. In patients with breast cancer:

- bone pain occurs in 40–80%,
- osteoporosis in 40–50%,
- pathological fractures in 10–30%,
- hypercalcaemia 10–30%,
- bone marrow weakness in about 20%,
- spinal cord damage in about 10%.

The risk of developing osteoporosis is 68% higher in women with a history of breast cancer than in healthy women [21]. The risk of developing osteoporosis in women with a history of breast cancer diagnosed ≤50 years of age is 1.98 times higher than in healthy women.

The risk of developing osteoporosis in breast cancer survivors treated with chemotherapy and hormone therapy is 2.7 times higher than in healthy women. Thus, there is an increased risk of osteoporosis in women with a history of breast cancer who were: younger, had tumours that expressed oestrogen receptors and were treated with hormones or in a combination way (hormone therapy and chemotherapy) [21].

The mechanisms of osteoporosis development in antiandrogenic therapy include: testosterone deficit, decreased aromatization of testosterone to oestrogen. GnRH agonists cause increased activation of osteoclasts dependent on parathyroid hormone. The strongest osteoporotic effect occurs during the first year but persists throughout the therapy. Osteoporosis in hormone-independent tumours mainly affects patients with:

- multiple myeloma,
- lung cancer (glandular),
- kidney cancer (clear cell),
- neuroblastoma,
- Ewing's sarcoma,
- large cell bone tumour,
- tumours of the central nervous system.

Multiple myeloma accounts for 1% of all cancers and 10% of hematologic cancers. The morbidity is estimated at 3/100,000, and the peak of incidence falls in the years 55–75 years. The disease consists in the monoclonal production of plasma cells and their precursors – B lymphocytes.

There are 4 main mechanisms for the development of osteoporosis in multiple myeloma:

1. increased expression of the RANK ligand on multiple myeloma cells, which leads to the stimulation of osteoclasts,
2. other pro-osteoclastic factors: IL-6.IL-11, TGF-ß, which cause osteoclast activation and bone resorption,
3. protection of multiple myeloma cells from osteoprotegerin by phagocytosis and intracellular lysis,
4. DKK-1 (Dickkopf-related protein 1) synthesis by myeloma cells, which inhibits the differentiation of cells into osteoblasts and thus inhibits the formation of new bone structures.

In patients with multiple myeloma, histological growth type correlates with bone remodelling: paratrabecular/node type leads to a high degree of osteoclastic bone resorption, which is associated with an unfavourable prognosis and is an indication of bisphosphonate therapy. There is no apparent increased osteoclastic resorption in interstitial type and this type of multiple myeloma carries a more favourable prognosis [22].

Tumours of the central nervous system have a complex mechanism at the onset of osteoporosis, which consists of: the use of glucocorticoids, antiepileptic and anticoagulant drugs, chemotherapy and radiotherapy, eating disorders, immobilization and paralysis [8]. In oncology, it is extremely important to distinguish metastatic lesions during the course of cancer from osteoporotic lesions. The clinical picture, as well as radiological and biochemical parameters help to distinguish these changes. In the case of bone metastases, pain is often present clinically, usually in multiple places, while in osteoporosis, the lesions are usually painless unless there are bone fractures [23]. In bone metastases, the radiological picture is rarely normal, while in osteoporosis, unless there are fractures, the radiological picture is usually normal [23]. In biochemical tests, alkaline phosphatase and markers of bone resorption in the urine are usually elevated in bone metastases and hypercalcaemia is common. On the other hand, in osteoporosis, biochemical parameters are usually normal, bone resorption parameters are slightly elevated in the urine and there is no hypercalcemia [23].

In the treatment of osteoporosis, three key elements should be taken into account:

- pain,
- immobility, and
- as a result of the first two, a complete deterioration of the patients' quality of life.

The main goal of therapy should not only be to control osteoporosis in its active phase (fractures), but also to prevent further fractures. Non-pharmacological measures include a diet, exercise, smoking cessation and reduction of alcohol consumption.

Pharmacological treatment includes the use of bisphosphonates, RANK ligand inhibitor (denosumab), sclerostin inhibitor (romosozumab), recombinant parathyroid hormone (teriparatide) [20]. In the latest recommendations, the American College of Physicians (ACP) recommends that clinicians use bisphosphonates for initial pharmacologic treatment to reduce the risk of fractures in postmenopausal females (strong recommendation; high-certainty evidence) and in males diagnosed with primary osteoporosis (conditional recommendation; low-certainty evidence). Also, ACP suggests that clinicians use the RANK ligand inhibitor (denosumab) as a second-line pharmacologic treatment to reduce the risk of fractures in postmenopausal females (conditional recommendation; low-certainty evidence) and in males (conditional recommendation; low-certainty evidence) diagnosed with primary osteoporosis who have contraindications to or experience adverse effects of bisphosphonates. Other recommendations apply only to women and ACP suggests that clinicians use the sclerostin inhibitor (romosozumab, moderate-certainty evidence) or recombinant parathyroid hormone (teriparatide, low-certainty evidence), followed by a bisphosphonate, to reduce the risk of fractures only in females with primary osteoporosis with very high risk of fracture (conditional recommendation). Also, ACP suggests that clinicians take an individualised approach regarding whether to start pharmacologic treatment with a bisphosphonate in females over the age of 65 with low bone mass (osteopenia) to reduce the risk of fractures (conditional recommendation; low-certainty evidence) [24].

Bisphosponates such as risedronate, alendronate, ibandronate, zoledronic acid and pamidronate are a group of drugs that work by slowing bone loss. They are used to treat and prevent osteoporosis. The osteoclast cells absorb the bisphosphonates and their activity is slowed down. Denosumab is a bone anti-resorptive drug used to treat osteoporosis. Denosumab is a total human IgG2 monoclonal antibody that binds to the receptor activator of NF kappa B ligand (RANKL) and competitively inhibits its binding to the receptor activator of NF kappa B (RANK). Denosumab binds to RANKL with high affinity and blocks it from binding to and oligomerizing its receptor RANK, thus inhibiting osteoclast maturation and bone resorption [25]. Abaloparatide is a human parathyroid hormone-related protein (PTHrP) that has been modified in order to potentiate the osteoanabolic effect [26–27]. Teriparatide is a recombinant fragment of the human parathyroid hormone consisting of its first amino(N)-terminal 34 amino acids and a potent osteoanabolic agent. The anabolic effects are mediated by upregulated transcriptional expression of pro-osteoblastogenic growth factors, modulation of the wnt/beta-catenin osteoanabolic signalling pathway by down-regulating the synthesis of the wnt-antagonist sclerostin, and increased expression and activity of Runx2 – a transcription factor essential for differentiation of osteoblasts [28–29]. Romosozumab is the first anabolic medication that both increases bone formation and decreases bone resorption. Data suggest that romosozumab is more effective than oral bisphosphonates in preventing osteoporotic fractures [30].

Raloxifene belongs to a class of drugs called selective oestrogen receptor modulators (SERMs). Raloxifene is a selective oestrogen receptor modulator that produces both oestrogen-agonistic effects on bone and lipid metabolism and oestrogen-antagonistic effects on uterine endometrium and breast tissue. It acts as an antiresorptive, with preservation of both bone mineral density and bone strength [31]. Posology and adverse reactions for osteoporosis according to Qaseem et al. are presented in table I [24].

Undertreatment of osteoporosis

The probable causes of insufficient treatment of osteoporosis are: fear of adverse effects of treatment, low awareness

Table I. The posology and most common adverse reactions for osteoporosis therapy

Drug	Dose	Side effects
alendronate (bisphosphonate)	10 mg orally, once a day or 70 mg once a week	upper gastrointestinal disturbances, osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
risedronate (bisphosphonate)	35 mg orally, once a week	upper gastrointestinal disturbances, osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
zoledronate (bisphosphonate)	usually 5 mg/100 ml by intravenous injection once a year	osteonecrosis of the jaw, atypical femur fractures, severe bone, joint and muscle pain
denosumab (RANK ligand inhibitor)	60 mg by subcutaneous injection every 6 months	joint and muscle pain, constipation, dermatologic reactions and serious infections, including skin infections, osteonecrosis of the jaw, atypical fractures, delayed fracture healing
abaloparatide (parathyroid hormone-related protein)	80 µg per day by subcutaneous injection	hypercalcaemia and hypercalciuria, dizziness, headache, back, joint and muscle pain, nausea, hypertension, palpitations, hypersensitivity reactions
teriparatide (recombinant human parathyroid hormone)	20 µg per day by subcutaneous injection	confusion, constipation, depression, dry mouth, headache, incoherent speech, increased urination, loss of appetite, metallic taste, muscle weakness, nausea, stomach pain, thirst, tiredness, vomiting, weight loss, arm, back or jaw pain, chest pain. fast or irregular heartbeat, fever or chills, sweating
romosozumab (sclerostin inhibitor)	210 mg once a month for 12 months (two consecutive 105 mg injections at different injection sites) supplemented with calcium and vitamin D	arthralgia, headache, hypersensitivity, increased risk of infection, muscle spasms, neck pain, skin reactions, cataract, hypocalcaemia, myocardial infarction, stroke, angioedema
raloxifene (selective oestrogen receptor modulator)	60 mg orally, once a day	hot flashes, action, abdominal pain, indigestion, flu-like symptoms, blood pressure. headache (including migraine), bulging, leg muscle spasms, breast pain, enlargement and tenderness, peripheral circumference, thrombocytopenia, stroke, thromboembolic event in the venous system, including deep vein thrombosis, pulmonary embolism, thrombosis of the yellow vein, superficial thrombophlebitis, circulatory thromboembolism

of the problem of osteoporosis among both medical staff and patients, problems with reimbursement of treatment and poor coordination of health care – especially in patients suffering from co-existing diseases such as cancer [32]. In addition, treatment of osteoporosis is hampered by poor patient compliance, which is particularly evident with the use of bisphosphonates [33–35]. This is made worse by the fact that the prescription of bone-protective drugs is declining worldwide [34].

Between 2001 and 2011, the number of prescriptions for bone-protective drugs in the United States fell from 40% to 21% [35]. A similar decline was observed in other countries [36–39]. Treatment of osteoporosis in cancer patients can be initiated in patients at risk of bone fractures, even in old age, and continued as long as evidence indicates the effectiveness of this treatment.

The need for an integrated care system

An opportunity to improve the fate of oncology patients diagnosed with osteoporosis is the creation of an integrated care system such as Fracture Liason Services (FLS). Such a system would not only ensure effective and safe care, but also improve the correct intake of the drug [40, 41]. As opposed to England and Wales, where only 51% of NHS trusts have an FLS, there is a 100% coverage of FLS in Scotland and Northern Ireland.

Conclusions

1. Osteoporosis can occur in virtually all cancerous diseases.
2. In order to assess the scale of the osteoporosis and its therapeutic procedures, there is a need to create a registry of osteoporosis, especially in malignant diseases.
3. In order to provide optimal care for oncological patients diagnosed with osteoporosis, integrated care centres should be established.

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Krzysztof Jeziorski
National Institute of Geriatrics, Rheumatology and Rehabilitation
Department of Gerontology, Public Health and Didactics
ul. Spartańska 1
02-637 Warszawa, Poland
e-mail: krzysztof.jeziorski@spartanska.pl

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Radiotherapy in the combined treatment

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Radiotherapy and targeted therapy – a review of the literature

Maksymilian Kruczała[1, 2], Beata Sas-Korczyńska[1]

[1]*Department of Oncology, Radiotherapy and Translational Medicine, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland*
[2]*Mrukmed Medical Center, Rzeszow, Poland*

Radiotherapy (RT) is an important treatment modality for cancer treatment patients. Approximately 50% of all cancer patients receive RT during the course of their illness. A great potential to improve treatment results involves combination RT with other methods. The combination of RT and cytotoxic chemotherapy is a clinically well-established and documented method to improve survival. Integration of targeted therapy with RT may provide therapeutic benefit by exploiting biologic and genetic differences between cancer and normal tissues while minimizing additional toxicity. The aim of this paper is to present a literature review of the effectiveness of combination radiotherapy and molecular targeted therapy.

Key words: radiotherapy, targeted therapy, monoclonal antibodies, small-particle drugs

Introduction

Radiotherapy (RT) is an important treatment modality for cancer treatment patients. Approximately 50% of all cancer patients receive RT during their course of illness [1]. The mechanism of RT is based on the interaction of ionising radiation with matter (biological material – tissue of body). The consequence of this interaction is the deposition energy of ionizing radiation in the cells of tissues it passes through. An important biological result of RT is DNA damage which may arise directly through the ionization atoms that make up DNA molecules, or indirectly, through generating free radicals. These processes cause double-stranded or single-stranded breaks of DNA, which lead to cell death and failure of mitosis. Therefore, ionizing radiation induces DNA damage and disrupts cell cycle progression, resulting in impeding cell division and blocking proliferation [2–6].

The main goal of RT is depriving cancer cells of proliferation and the killing off of these cells. There are a variety of mechanisms for killing cancer cells by RT:

- mitotic death (or mitotic catastrophe) – which occurs during or after aberrant mitosis and cell death due to chromosome missegregation during mitosis [7–9],
- apoptosis – programmed cell death, the major mechanism of cell death which is involved in cancer therapy, RT particular [10–12],
- necrosis – the process when a cell visibly swells with the breakdown of cell membrane, this mechanism is seen less frequently after RT [13],
- senescence – permanent loss of cell proliferative capacity, this mechanism occurs in cancer cells following extensive stress (RT-induced also) and later cells die by a process of apoptosis [14, 15],
- autophagy is a form of cancer cell death in response to radiotherapy, it is a genetically regulated form of programmed cell deaths [5, 16].

Because radiation damages both cancer and normal cells, the goal of RT is to maximize of dose to the tumour while

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minimizing exposure to normal cells which are adjacent to the cancer or in the path of the radiation) [17]. Through the advanced technologies used in the delivery of RT, it is possible to administer maximum RT dose to the tumor whilst sparing normal tissues. Moreover, precision delivery of RT enables dose escalation [2].

The biological effectiveness of RT (cell killing) depends on factors such as linear energy transfer, fractionation rate and the radio-sensitivity of targeted cells, and is a result of processes occurring within the cells [2, 18, 19]:

- repair of sublethal damage,
- reassortment of cells in the cycle,
- repopulation of cells during the course of RT,
- reoxygenation of hypoxic cells.

Consideration of the above factors is the rationale for the application of modified dose fractionation regimens [2, 5]. Another possibility to improve treatment results refers to combination RT with other methods. The combination of RT and cytotoxic chemotherapy is a clinically well-established and documented method to improve survival [20]. Integration of targeted therapy with RT may provide therapeutic benefit by exploiting biologic and genetic differences between cancer and normal tissues while minimizing additional toxicity [4].

Rapid development of molecular targeted therapy enabled the improvement of the results of cancer therapy by combining targeted therapies with RT [21]. Targeted therapy is connected with the concept of individually tailored treatment because it is effective in patients whose cancers have a specific molecular target [5, 22]. Targeted therapy involves drugs that block proliferation of cancer cells, or induce apoptosis.

Targeted therapy uses monoclonal antibodies or small-particle drugs. Monoclonal antibodies block a specific target in cancer cells, and they are used with chemo- and/or radiotherapy. Whereas small molecules inhibitors interrupt the cellular process by interfering with intracellular signalling of tyrosine kinases (which initiate molecular cascade to cell growth, proliferation, migration, angiogenesis) [2].

The pathways targeted in cancer therapy can be inhibited at multiple levels by binding ligands to the specific site of a receptor, by occupying receptor-binding sites preventing ligand binding, by blocking receptor signalling or by interfering with downstream intracellular molecules [2, 22].

The aim of this paper is to present a literature review of the effectiveness of combining radiotherapy and molecular targeted therapy.

EGFR inhibitors

At present, cetuximab (EGFR inhibitor) is the only molecularly targeted drug registered in Europe and the US in combination with RT in head and neck cancer patients. In the Bonner et al. trial [23], patients were randomly assigned to receive either radiotherapy alone or radiotherapy with cetuximab. Radiotherapy plus cetuximab proved to be more effective in terms of overall survival (OS): 49 *vs.* 29.3 months, 5-year OS: 45.6% *vs.* 36.4%. Combination therapy also contributed to a significant prolongation of progression-free survival (PFS) without significant effect on the toxicity of treatment (except for infusion reactions and a cetuximab-specific rash). The Bonner et al. trial proved the efficacy of cetuximab combined with radiotherapy, however, it should be noted that there was no arm with cisplatin in this study. Two large trials (De-Escalate [24] and RTOG 1016 [25]) proved the superiority of cisplatin–RT over cetuximab–RT. The De-Escalate study showed similar toxicity in both arms with significantly higher efficacy of cisplatin–RT (2-year OS: 89.4% *vs.* 97.5% respectively). In the RTOG 1016 trial, cetuximab also failed to meet the assumed non-inferiority criterion with similar early- and long-term toxicity of treatment. Moreover, despite encouraging results in head and neck cancer patients, cetuximab has not demonstrated an effective radiosensitizing effect in other cancers where the EGFR pathway is an important therapeutic target.

Erlotinib, an oral inhibitor of EGFR tyrosine kinase, was studied in combination with radiotherapy and temozolomide in patients with EGFR-overexpressed glioblastoma multiforme. Despite the theoretical assumptions for the effectiveness of such a combination, the phase II studies demonstrated contrasting results, however, with the overall tendency to increase the toxicity of treatment without the obvious survival benefit. Among patients with pancreatic cancer, erlotinib has also not demonstrated sufficient efficacy in combination with radiotherapy (both as an adjuvant treatment or for locally advanced, non-restrictive disease [26–30]).

Everolimus, an mTOR inhibitor (another molecule downstream of the EGFR/PI3K pathway) also did not demonstrate sufficient efficacy in combination with radiotherapy. In phase II studies in glioblastoma multiforme patients, NCCTG N057K [31] and RTOG 0913 [32] showed no improvement in survival and increased toxicity.

Radiosensitizing molecules targeting hypoxic tumor cells

Nimorazole (molecule targeting hypoxic tumor cells) proved to be relatively effective as a radiosensitizer. In the phase III trial, a 16% improvement in the locoregional control of cancer of the supraglottic larynx and pharynx was achieved, compared to radiotherapy alone [33]. At present, except for Denmark, this drug is not adopted as a standard of care.

In two large phase II clinical trials, promising results of the ARCON molecule (in combination with radiotherapy in head and neck and bladder cancer patients) were achieved. As a result, phase III studies were conducted – BCON [34] and Janssens et al. [35], in which the effectiveness of ARCON in patients with bladder cancer and laryngeal cancer, respectively, was studied. In the case of bladder cancer patients, the combination of ARCON and radiotherapy proved to be

more effective in terms of OS and local control than radiotherapy alone. In patients with laryngeal cancer, the effectiveness of the drug was proven only in patients with hypoxemic tumors. Finally, given the inconclusive results of the phase III studies, the difficulty in delivering the drug and the identification of patients with highly hypoxemic tumors, the drug did not gain widespread acceptance.

Clinical trials of tirapazamine – another hypoxia-oriented radiosensitizing molecule [36] – also failed. There were no improved outcomes both in cervical and head and neck cancer patients when tirapazamine was combined with chemoradiation compared to conventional chemoradiation alone.

Drugs targeting DNA damage response mechanisms

The phase I study evaluated the efficacy of veliparb (PARP inhibitor) with concurrent radiotherapy in patients with inflammatory or recurrent breast cancer [37]. Despite acceptable overall treatment toxicity (only five – 16.7% – patients experienced a dose limiting toxicity), nearly half of surviving patients experienced G3 adverse events at 3 years. Half of the patients experienced disease control failure and 43% died after 3 years of follow-up. Considering these results, a long-term follow-up seems to be essential in trials of radiosensitizing drugs. In another phase I study, veliparb was studied in combination with radiochemotherapy in locally advanced homology recombination repair deficient pancreatic cancer patients [38]. The median OS was 15 months. Currently, a phase II study comparing radiotherapy with or without olaparib (another PARP inhibitor) is ongoing in patients with inflammatory breast cancer. Olaparib has also been studied in combination with cetuximab and radiotherapy in squamous cell head and neck cancer patients with a long-term tobacco history [39]. This combination turned out to be safe, with a 2-year OS of 72%, which is better than in historical studies without olaparib (60%).

Adavosertib, a WEE1 inhibitor, has recently been studied in a phase I study with radiotherapy and gemcitabine in 34 patients with locally advanced pancreatic cancer [40]. The median OS was 21.7 months, which is much more than in previous studies evaluating radiotherapy with gemcitabine. Another promising molecule is peposertib (DNA-PKC inhibitor), phase I studies with this drug are currently ongoing.

Nanotechnology

NBTXR3 is the first in its class radiosensitizer (hafnium oxide nanoparticle). In the phase II/III trial, a significantly higher percentage of total pathological responses was obtained in patients whose soft tissue sarcomas were injected with NBTXR3 prior to radiotherapy. No significant increase in treatment toxicity was observed between the groups [41]. The main problem in this type of treatment is the delivery of the drug to the tumor.

Conclusions

The dynamic development of targeted drugs in oncology inevitably involves attempts to use these drugs in combination with radiation therapy. Despite the theoretical preconditions for the effectiveness of such a procedure, cetuximab is currently the only widely registered targeted drug used with radiotherapy. Despite its lower efficacy than classical radiochemotherapy, the use of cetuximab is associated with lower toxicity than standard chemotherapy, which is particularly important for patients with contraindications to cisplatin. In the case of other molecules, phase III studies often did not show their superiority over the current standard of care. Another problem is how the drug is delivered to cancer cells, in the case of a route of administration other than intravenous or oral, even with the promising efficacy of a given molecule, it is unlikely that it will be widely used in everyday practice.

At the moment the greatest hope of success, in combining targeted therapies with radiotherapy, seems to be drugs targeted at mechanisms of DNA repair. A major challenge in the case of modern, extremely expensive drugs will be finding the right predictive factors so that as many patients as possible benefit from the treatment.

Conflict of interest: none declared

Maksymilian Kruczała
Medical College of Rzeszow University
Institute of Medical Sciences
Department of Oncology, Radiotherapy and Translational Medicine
al. Mjr. W. Kopisto 2a
35-959 Rzeszów, Poland
email: m_kruczala@onet.pl

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Cancerogenic food contaminants in European countries

Elwira Gliwska[1, 2], Paweł Koczkodaj[1], Marta Mańczuk[1]

[1] *Cancer Epidemiology and Primary Prevention Department, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2] *Department of Food Market and Consumer Research, Institute of Human Nutrition Sciences, Warsaw University of Life Sciences-SGGW, Warsaw, Poland*

Contamination of food is inevitable in the production process from manufacturing to preparation for consumption. Some of the contaminants in food are serious health hazards and may increase the risk of cancer. Carcinogenic food contaminants include mycotoxins, dioxins, benzopyrene, acrylamide, cadmium and arsenic. European Union countries are required to meet standards for individual contaminants that may be present in food and to monitor these contaminants in products on the market. However, based on the European warning system for carcinogenic contaminants, it can be seen that they are still present in various countries of the EU. In view of the increasing number of cancer cases and the overall burden of non-communicable diseases on society, it is recommended to consider not only the nutritional value of food, but also the contamination of food with carcinogenic substances.

Key words: food contamination, risk assessment, human exposure, cancer risk, cancer prevention

Introduction

Cancer is a chronic disease characterized by specific risk factors, disease progression, and symptoms. It is the leading cause of death in Europe and has become one of the most urgent public health issues [1, 2]. The increasing number of cancer cases may be due to both individual and environmental factors, many of which are preventable. It is estimated that 30–50% of cancer cases are preventable [3]. In particular, lifestyle, including diet, is responsible for more than half of cancer cases in Europe [4, 5]. Food can promote carcinogenesis through naturally occurring substances, contaminants, or additives. The intake of carcinogenic food contaminants cannot be fully controlled by individuals, so making regulation and monitoring of its' levels is an important task for policymakers. Carcinogenic food contaminants can be of plant, fungal, and anthropogenic origin and can be present in the product both before and after processing. They also arise from contact with food packaging [6]. As far as diet and dietary habits have a significant impact on individual cancer risk, carcinogenic food contaminants should also be considered. Food contaminants can be a risk factor for many cancers, so irresponsible behavior by manufacturers and consumers can lead to increased cancer incidence. In addition, the lack of appropriate regulations on testing, monitoring, and standards may pose an additional cancer risk to consumers. The effects of ingesting food contaminants can be observed immediately or over time. Some compounds may even be recovered in other generations [7]. Therefore, some food contaminants appear to contribute to the cancer burden due to chronic exposure in Europe in addition to other external risk factors. Noteworthy, food contaminants originate from the environment (water, soil, air), residues from agricultural activities, breeding activities, residues from technological processes, or packaging. In addition, carcinogenic compounds can occur during transportation, storage, and preparation for consumption. Since many of these processes where contamination can occur

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are beyond the control of the individual, the importance of monitoring contamination levels is repeatedly emphasized.

The objective of this review is to identify and characterize the contaminants in foods classified as carcinogenic in European countries that may pose a risk to humans and to present recommended methods for reducing exposure.

Food contamination monitoring in Europe

According to the International Agency for Research on Cancer of the World Health Organization (IARC) definition, a carcinogen is a compound or mixture of chemical compounds that induce the formation of a malignant tumor or increase the incidence of its recurrence [8]. The primary food ingredients, as well as chemical compounds added to foods (e.g., preservatives) or accidental food contamination, may be responsible for the carcinogenic effects of some foodstuffs.

The legal basis for regulating food contamination in Europe is Council Regulation 315/93/EEC [9]. This document sets maximum levels for certain contaminants to protect public health. The regulation states that contamination levels must be kept as low as reasonably achievable while following recommended good working practices. It also states that food contaminated to an extent unacceptable to public health, particularly in toxicological terms, shall not be placed on the market. The maximum levels for certain food contaminants are set in Commission Regulation (EC) No. 1881/2006 [10]. The maximum levels set in the documents are reviewed and modified as new scientific evidence becomes available. However, compliance with the European recommendations must be verified by the competent control bodies.

To provide appropriate verification procedures, the EU has established the Rapid Alert System for Food and Feed (RASFF), which serves to exchange information between official control authorities in Europe. Information on food, feed and food contact materials that are potentially hazardous to human, animal or environmental health is entered into the system when such products are identified. When a risk related to food, feed or food contact materials is identified, the national contact point of a given member of the network must send a notification to the iRASFF electronic system. In accordance with Art. 52 sec. 1 of Regulation 178/2002 and Art. 24 sec. 3, the European Commission makes information on alert, information and border rejection notifications publicly available through the RASFF [11].

Of the numerous contaminants that have been identified in food in the European Union, some have proven carcinogenic or potentially carcinogenic properties; some of them are described in this overview.

Food contaminants which pose a carcinogenic threat to humans

Mycotoxins

Mycotoxins are secondary metabolites of molds such as *Aspergillus*, *Fusarium* and *Penicillium* that are toxic and carcinogenic to humans. These fungi are widely distributed on agricultural crops and contaminate subsequently produced food and feed. The most common mycotoxins are aflatoxin, ochratoxin A, patulin, fumonisins, deoxynivalenol, and zearalenone. In addition, molds are capable of producing more than one toxin under certain climatic conditions. This results in co-exposure to many mycotoxins from one product and the risk of associated adverse effects, including carcinogenicity [12]. Mycotoxins have been shown to have mutagenic, teratogenic, carcinogenic, and estrogenic properties. They are usually produced by improper food storage, and the most commonly contaminated products include corn and peanuts. They are also found in many other agricultural foods, such as cereals and cereal derivatives, spices, coffee, cocoa, tea, dried fruit, beer, wine, and powdered milk [13]. Mycotoxins can cause acute poisoning with damage to internal organs (liver, kidneys), however cases of acute poisoning are not so frequent [14]. On the other hand, chronic exposure may affect these organs and increase the risk of developing kidney or liver cancer, which will manifest as a long-term complication of exposure.

Aflatoxin is classified as carcinogenic to humans, and ochratoxin A is defined as possibly carcinogenic to humans according to the IARC classification and it primarily causes an increased risk of liver cancer [13]. Maximum allowable levels for aflatoxin b1 range from 0.1 µg/kg for wheat infant products to 8 µg/kg for peanuts. For ochratoxin, the permitted levels range from 0.5 µg/kg in infant products to 10 µg/kg for coffee or dried fruit. Between 2021 and 2022, the RASFF system issued 467 notifications of aflatoxin contamination on EU territory, of which 62 concerned aflatoxin B1 (tab. I). For example, one notification requested a rejection at the border due to aflatoxin in nutmegs on Danish territory. Notifications of aflatoxin also involved date syrup made with organic dates in Belgium, and nootmuskaat and basmati rice in the Netherlands. Ochratoxin A appeared 62 times in the RASFF system and was detected in organic whole rye pasta from Poland, among other products.

The recommended methods to reduce exposure to mycotoxins in daily life are to buy food as fresh as possible and consume it immediately. In addition, consumers should avoid hoarding purchases. It is recommended to store foodstuffs under proper conditions and in a cool place. Bread boxes and similar items should be cleaned once a week and rinsed with vinegar and water to prevent mold growth. It is also recommended to remove bread crumbs from bread boxes as they promote mold growth. Food that is already moldy should be removed immediately. Cereals and flour should be stored in a cool, dry place and shaken occasionally. Moldy jams and jellies should always be discarded, and those with lower sugar content should also be stored in the refrigerator [15].

Dioxins

The term "dioxin" generally refers to a group of structurally and chemically related aromatic hydrocarbons, including

Table I. Some of the RASFF notifications for aflatoxin in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
nuts, nut products and seeds	food	aflatoxins in pistachios kernels from the United States	04.10.2022 14:13:32	Italy	border rejection notification	serious
nuts, nut products and seeds	food	aflatoxins in groundnut kernels from the United States	03.10.2022 11:18:23	Netherlands	border rejection notification	serious
fruits and vegetables	food	exceeding the MRL for aflatoxin and the sum of aflatoxins in dried figs from Turkey	30.09.2022 16:00:28	Poland	information notification for attention	serious
nuts, nut products and seeds	food	aflatoxin in Argentine groundnuts	30.09.2022 08:10:33	Netherlands	border rejection notification	serious
fruits and vegetables	food	aflatoxins B1 in organic dried figs from Turkey	29.09.2022 15:05:59	Germany	border rejection notification	serious
nuts, nut products and seeds	food	aflatoxins in pistachios	18.09.2022 14:46:08	Bulgaria	border rejection notification	serious
nuts, nut products and seeds	food	almonds from US with aflatoxins level higher than allowed levels	16.09.2022 13:28:59	Spain	border rejection notification	serious
herbs and spices	food	aflatoxin in Pakistan Chapli Kabab	14.09.2022 14:39:17	Netherlands	border rejection notification	serious
nuts, nut products and seeds	food	aflatoxin in USA groundnuts	13.09.2022 16:09:23	Netherlands	border rejection notification	serious
nuts, nut products and seeds	food	aflatoxin in Argentine groundnuts	13.09.2022 16:07:41	Netherlands	border rejection notification	serious
nuts, nut products and seeds	food	aflatoxins in groundnuts from Nigeria	13.09.2022 16:00:27	Belgium	border rejection notification	serious

75 polychlorinated hydrocarbons, dibenzo-p-dioxins (PCDDs) – chlorinated dibenzo-1.4-dioxin derivatives, and 135 polychlorinated dibenzofurans (PCDFs). Sometimes the term "dioxins" refers generally to the group of halogen derivatives of aromatic hydrocarbons that have a similar structure and similar properties, or it is used to refer to the most biologically active member of this group of contaminants, i.e., 2,3,7,8-tetrachlorodibenzo--p-dioxins [16]. Dioxins are formed as by-products of various uncontrolled combustion processes, as well as in industrial processes (in ferrous and nonferrous metal smelters, cement plants), and also in fires and volcanic eruptions. These substances are persistent in all elements of the environment (the half--life in humans is 7–8 years on average). Dioxins are subject to bioaccumulation and are transported for long distances through air, water, and migratory species. As a result, they are deposited far from the sites of their emission, where they then accumulate in terrestrial and aquatic ecosystems and pose a threat to the environment and human health [17–19].

Accumulation of dioxins in the food chain is particularly hazardous and should be of interest to public health professionals. Food is responsible for the majority of dioxin intake in humans, and the most common dietary sources of dioxins are:

- meat and meat products – 27.5%,
- fish and fish products – 27.0%,
- milk and canned foods – 26.9%,
- oils – 3.8% [20].

Dioxins are fat-soluble compounds, therefore dietary fat increases their absorption. In addition, dioxins can accumulate in the body, which increases the health burden of dioxins with age [21]. The carcinogenicity of dioxins has been investigated in several epidemiological studies, which found an increased risk of cancer, but no cancer type was the main focus. Therefore, in the case of dioxins, an overall increase in cancer risk was found rather than an increase in the likelihood of developing cancer at a specific site [22].

Dioxins, particularly 2,3,7,8-tetrachlorodibenzo-para-dioxin, are classified as carcinogenic to humans according to the IARC classification. Maximum allowable levels for dioxins in food range from 0.3 pg/g fat in vegetable oils to 12 pg/g fat in animal meat. The RASFF notification for dioxins in the EU territory between 2021and 2022 concerned, for example, dioxins and dioxin-like PCBs in goose breast fillets and legs from Hungary or fish oil from China in the territory of the Netherlands (tab. II).

Suggested methods to limit dioxin exposure include, for example, restricting the consumption of animal fats, since dioxins are compounds that are fat-soluble. In addition, it is recommended to choose products with a lower fat content, for e.g. as low fat dairy products. It is also recommended to remove the skin from meat products. Additionally washing of vegetables and fruits before consumption may also have a positive impact on the potential risk of dioxin contamination from other sources [23].

Table II. The RASFF notifications for dioxins in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
feed materials	feed	dioxins (sum of dioxins and furans: 0.75 ng/kg) in copper sulphate pentahydrate from Thailand	02.08.2022 17:31:15	Netherlands	information notification for attention	not serious
feed materials	feed	dioxins in refined fish oil from China	14.06.2022 15:02:42	Netherlands	information notification for attention	serious
fats and oils	feed	exceedance of the action threshold for dioxin in palm fatty acids (animal feed) from Germany	03.05.2022 17:55:33	Germany	information notification for follow-up	undecided
fats and oils	food	dioxins and dioxin-like PCBs in goose breast fillets and thighs from Hungary	21.12.2021 17:00:17	Hungary	alert notification	serious

Benzopyrene

Benzopyrene is one of the PAHs (polycyclic aromatic hydrocarbons), a group of chemical compounds formed naturally or by humans during pyrolysis or incomplete combustion of organic materials, including wood, coal, petroleum and its products, as well as petrochemical processes, food processing, smoking, etc. These compounds are widely distributed in the environment and can be found in the air, soil or water. Depending on the conditions, they can be absorbed through the respiratory tract as solid aerosols, through the skin, or through the gastrointestinal tract after ingestion with drinking water, food, soil (especially in children), and breast milk [24–26]. PAHs are a ubiquitous and highly diverse group of contaminants found in both the natural environment and in food. The extent of contamination with PAH compounds from natural sources is low. The main source of contamination is industrial processes resulting from human activities.

The group of PAHs includes several compounds with a complex structure that may contain two to several dozen interconnected benzene rings, indicating different physicochemical and toxic properties. PAHs are mainly formed during pyrolysis, especially during incomplete combustion of organic raw materials, and thus also during smoking (smoked foods). They are usually formed during the combustion process, which takes place at temperatures between 500°C and 1000°C or higher. Most PAHs are formed during combustion at a temperature of 500°C to 700°C with limited air access to the combustion zone, e.g. during wood combustion. Up to 10,000 chemical compounds with the structure of polycyclic aromatic hydrocarbons and their derivatives can be formed during combustion processes. Therefore, PAHs in food are mainly caused by environmental pollution and some technological food preservation processes, such as smoking, frying, or grilling [27].

Benzopyrene is considered one of the most convincing carcinogens because of its structure that allows easy alkylation of DNA. Damage to DNA structure combined with increased production of reactive oxygen species (ROS) makes benzopyrene a potent carcinogen, and these mechanisms are well described in the literature [28, 29]. Despite the lack of epidemiological studies, benzopyrene has been classified as a human carcinogen based on sufficient number of mechanistic evidence and animal model studies [30].

The major sources of benzopyrene in foods are fried, grilled, and smoked meats as well as fried, baked, and deep-fried products [high-temperature processing]. Benzopyrene can be also found in cereals and other grains or vegetables grown on contaminated soils. The maximum allowable level of benzopyrene in food ranges from 1 µg/kg in infant formula products to 10 µg/kg for clams. From 2021 to 2022, there were 13 notifications in the RASFF system of benzopyrene, for example in sunflower oil from Ukraine on the territory of Lithuania or in kabanos sausage in Slovakia (tab. III).

To reduce exposure to benzo[a]pyrene, it is recommended to reduce the consumption of smoked and fried foods or highly processed food [31].

Akrylamide

Acrylamide is an organic chemical compound of the amide group that does not occur naturally in the environment. Acrylamide is obtained by hydrolysis of acrylonitrile and is an odorless, crystalline substance. The main use of acrylamide is in the manufacture and synthesis of polyacrylamides, which are used in the production of plastics, paints, adhesives, varnishes and mortars. Acrylamide is found in many foods such as bread, French fries, cakes, and fried meats. Acrylamide is a chemical compound usually formed in starchy products by frying or baking at high temperatures (120–150°C). The main chemical reaction is the so-called Millard reaction, in which naturally occurring sugars and amino acids in starch products combine to form substances that yield new flavors and aromas. It also leads to a brown coloration of the skin of heated foods and the formation of acrylamide.

According to the EFSA opinion, epidemiological studies available to date have shown that acrylamide intake was not associated with an increased risk of most common cancers, including gastrointestinal or respiratory tract cancers, breast, prostate and bladder cancers. Several studies suggest an in-

Table III. The RASFF notifications for benzopyren in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
herbs and spices	food	benzopyrene and polycyclic aromatic hydrocarbons (PAHs) in dried bay leaves from Bangladesh, *via* Spain	19.09.2022 15:31:34	Germany	alert notification	serious
cocoa and cocoa preparations, coffee and tea	food	benzopyrene and polycyclic aromatic hydrocarbons (PAHs) in matcha tea powder from China, *via* the Netherlands	05.08.2022 10:59:23	Germany	information notification for follow-up	not serious
fats and oils	food	exceeding the MRL for benzopyrene in sunflower oil from Ukraine	29.06.2022 17:25:29	Lithuania	information notification for attention	serious
herbs and spices	food	benzopyrene and polycyclic aromatic hydrocarbons (PAH) organic paprika powder from Spain	04.05.2022 14:18:25	Germany	alert notification	serious
herbs and spices	food	benzopyrene and polycyclic aromatic hydrocarbons in organic paprika powder from Spain	21.12.2021 17:41:06	Germany	alert notification	serious
fish and products thereof	food	benzopyrene e PAH4 in smoked *sardinella aurita*	19.10.2021 12:49:04	Italy	information notification for attention	serious

Table IV. The RASFF notifications for acrylamide in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
cereals and bakery products	food	acrylamide content	04.10.2022 14:37:54	Slovenia	border rejection notification	no risk
cereals and bakery products	food	acrylamide in crunchy haverkoek	05.07.2022 16:57:40	Netherlands	information notification for attention	undecided
cereals and bakery products	food	content of acrylamide above the achieving level in crackers	29.06.2022 11:18:18	Slovenia	border rejection notification	not serious
cereals and bakery products	food	high content of acrylamide in biscuits from Bosnia and Herzegovina	02.05.2022 08:35:40	Croatia	border rejection notification	serious
cereals and bakery products	food	acrylamide in organic spelt biscuits	29.12.2021 15:59:02	Netherlands	information notification for follow-up	not serious

creased risk of renal, endometrial [especially in nonsmoking women], and ovarian cancers, but the evidence is insufficient [32]. From the IARC monograph, it can be concluded that acrylamide and its metabolite glycidamide form covalent adducts with DNA in mice and rats. In addition, acrylamide causes genetic mutations and chromosomal aberrations in rodent somatic cells *in vivo*, cultured cells *in vitro*, and mouse germ cells. The final assessment states that acrylamide is possibly carcinogenic to humans (Group 2A) [13].

The European Commission's maximum limits for acrylamide in food range from 50 µg/kg or wheat-based bread to 850 µg/kg for instant coffee. Acrylamide was reported in the RASFF system five times between 2021 and 2022, and all notifications involved cereals and bakery products on the territory of Slovenia, the Netherlands, and Croatia (tab. IV).

To reduce exposure to acrylamide, it is recommended to reduce cooking time to avoid severe crispiness or browning, blanch potatoes before frying, and avoid storing potatoes in the refrigerator. In addition, post-drying (drying in a hot air oven after frying) has been shown to reduce acrylamide levels in some foods [33].

Cadmium

Cadmium is one of the heavy metals present in the environment through both natural occurrence and industrial and agricultural sources. Exposure to cadmium in the nonsmoking population occurs primarily through food. The accumulation of dangerously high concentrations of cadmium in the environment is mainly due to anthropogenic activities such as phosphate fertilizers, sewage, sewage sludge, and manure [34].

Due to various factors, cadmium enters water and soil, from where it is absorbed into plants. Thus, cadmium enters the food chain and poses a risk to human health [35] osteoporosis, diabetes, cardiovascular disease and cancer. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) cadmium is usually found in vegetables [leafy greens, potatoes], cereals, or kidneys and livers of animals.

Symptoms such as stomach irritation, abdominal cramps, nausea, vomiting, and diarrhea may be observed in acute cadmium poisoning, but usually only small amounts of this element are absorbed from food. Nevertheless, small doses of dietary cadmium can accumulate in the body and cause long-term side effects such as cancer. Chronic cadmium exposure has also been associated with chronic kidney disease, diabetes, and osteoporosis [36–38]. Cadmium has been found to disrupt hormone balance, interact with antioxidant enzymes, deregulate cell proliferation, or inhibit cell apoptosis, which likely accounts for its pro-carcinogenic properties [39]. Scientific evidence has confirmed the association between cadmium and increased risk of lung cancer, but it has also been found to be associated with breast, kidney, and prostate cancer [40].

According to Commission Regulation (EU) 2021/1323 of August 10, 2021, amending Regulation (EC) No. 1881/2006 as regards the maximum levels of cadmium in certain foodstuffs, the cadmium content limits were reduced, for example, to 1.20 mg/kg wet weight in poppy seeds or to 0.02 mg/kg wet weight for fruits. Between 2021 and 2022, information on excessive cadmium levels in foods was identified 58 times in the RASFF system (tab. V). The high cadmium content was detected in flaxseed, seafood, and avocado, among others. In addition, some of the notifications were related to warnings about high migration of cadmium from glass.

To reduce cadmium exposure, it is recommended to avoid smoking and second-hand smoke. Washing fruits and vegetables as well as peeling roots and tubers can also reduce cadmium contamination to some extent [41].

Arsenic

Arsenic is counted among the semimetals because of its specific properties. It is a highly toxic element widely distributed in nature, which is absorbed into the body through the digestive and respiratory tract. Under certain conditions, arsenic found in soils and minerals can be released into water.

Table V. Some of the RASFF notifications for cadmium in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
fish and products thereof	food	cadmium in giant squid arms from Lithuania	26.09.2022 16:14:29	Germany	alert notification	serious
meat and meat products (other than poultry)	food	cadmium in horse meat from Romania	20.09.2022 12:39:56	Belgium	alert notification	serious
fruits and vegetables	food	cadmium in spinach	19.09.2022 12:12:54	Belgium	alert notification	serious
bivalve molluscs and products thereof	food	cadmium in cooked mussel meat from Chile	14.09.2022 17:24:43	Netherlands	alert notification	serious
fruits and vegetables	food	cadmium in green asparagus from Peru	12.09.2022 16:26:03	Netherlands	information notification for attention	serious
fruits and vegetables	food	frozen carrot finding that the MRL for cadmium has been exceeded	06.09.2022 15:55:15	Poland	information notification for follow-up	not serious
fruits and vegetables	food	cadmium in spinach from Poland, raw material from Germany	02.09.2022 15:24:53	Poland	information notification for attention	serious
food contact materials	food contact material	migration of cadmium and lead from glasses	22.08.2022 15:27:34	Poland	alert notification	serious
cephalopods and products thereof	food	Patagonias squid, presence of cadmium higher than the legal limits in calamar Patagonico – Patagonias squid	22.08.2022 12:24:51	Italy	alert notification	serious
fruits and vegetables	food	cadmium in carambola	05.08.2022 15:27:00	Netherlands	information notification for attention	serious
fruits and vegetables	food	cadmium in organic avocado from Peru	02.08.2022 17:27:24	Netherlands	information notification for attention	serious

Table VI. The RASFF notifications for arsenic in foodstuffs between 2021–2022

Category	Type	Subject	Date	Notifying country	Classification	Risk decision
feed materials	feed	arsenic in monocalciumphosphate for feed from Turkey	20.04.2022 17:19:41	Denmark	information notification for follow-up	undecided
feed materials	feed	increased arsenic content in the supplementary feed for horses from Germany	29.03.2022 17:16:10	Germany	information notification for follow-up	undecided
fish and products thereof	food	arsenic (11.2 mg/kg – ppm in frozen cod [Gadus Morhua]) from Russia	08.11.2021 11:35:35	Poland	information notification for attention	undecided

The largest amounts of arsenic enter the environment through anthropogenic activities such as smelting, mining, and pesticide use. In many countries [e.g., India, Vietnam, or Taiwan], arsenic levels in groundwater are alarmingly high. In Europe, the most severe water contamination by arsenic was found in Hungary, Serbia, and Romania, where 600,000 people were at risk of drinking water that may have had elevated arsenic levels [42, 43].

Drinking water is the most common route of arsenic exposure in humans. Food studies have shown that arsenic is also present in foods, with arsenic levels depending on the type of food. Although the studies conducted to date have not detected significant levels in foods, it is important to monitor its levels because of the highly toxic properties of arsenic [44]. Inorganic arsenic compounds are known to cause lung, urinary bladder, and skin cancer. In addition, a positive association has been also found for arsenic exposure and kidney, liver and prostate cancer [45].

The maximum levels for inorganic arsenic in food are 0.1 µg/kg in rice intended for the manufacture of food for infants and young children and 0.3 µg/kg in rice cakes, rice wafers, rice crackers, and rice cakes. Three notifications of high levels of inorganic arsenic in food have appeared in the RASFF system, of which two warnings related to feed and one to food for human (tab. VI).

The recommended methods to reduce exposure to inorganic arsenic are polishing the grains, washing the paddy rice, boiling [in excess water], rinsing the rice grains (3 cycles), and then boiling in excess water. In addition, rice-based beverages should not be used in infants and children to protect sensitive populations [46].

Conclusions

Food can pose a carcinogenic threat to humans through the content of harmful substances naturally occurring in food, but also through carcinogenic pollutants. The food studies conducted so far have shown that the global problem of environmental pollution is also reflected in foods that may be contaminated with carcinogenic compounds. In the European Union, food contamination monitoring is carried out by dedicated food safety authorities, and exceedances of the recommended standards are recorded in the RASFF alert system. Despite setting precise standards for carcinogenic food contaminants in the RASFF system, there are reports of harmful levels of some contaminants.

Carcinogenic food contaminants include, but are not limited to, mycotoxins, dioxins, benzopyrene, acrylamide, cadmium and arsenic. These substances are classified as carcinogenic to humans and for each of them it was confirmed that the acceptable level was exceeded at least several times in the last year. Due to the fact that food can be an important element influencing the individual and population cancer risk, not only the nutritional value of the diet should be considered but also the quality of products and the levels of contaminants present in them.

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Elwira Gliwska
Maria Sklodowska-Curie National Research Insitute of Oncology
Cancer Epidemiology and Primary Prevention Department
ul. Wawelska 15B
02-034 Warszawa, Poland
e-mail: elwira.gliwska@pib-nio.pl

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Non-smoking lung cancer and environmental exposure

Mark Parascandola

Research and Training Branch, Center for Global Health, National Cancer Institute, Rockville, United States

While lung cancer mortality has been decreasing in many countries due to tobacco control efforts, at least one quarter of global lung cancer cases occur among non-smokers. There is growing attention being paid to the role of environmental exposures, such as radon and air pollution, in lung cancer. Additionally, recent research efforts have sought to elucidate the distinct characteristics of and mechanisms involved in lung cancer among never smokers. Continued research on non-smoking lung cancer is critical to identifying new opportunities for intervention and addressing the global burden of lung cancer.

Key words: lung cancer, air pollution, prevention

Introduction

The story of lung cancer in the twentieth century has been dominated by the growth of the mass-produced cigarette. A familiar dynamic played out across many countries where a rise in cigarette smoking was followed, decades later, by a rise in lung cancer mortality. Eventually, as countries implement tobacco control measures, lung cancer mortality began to decrease [1]. In Poland, lung cancer mortality tripled among men between 1960 and the 1980s, but then began to fall as smoking dropped in response to the economic crisis of the 1980s and the tobacco control efforts of the 1990s [2]. By 2015, lung cancer mortality had nearly returned to the level it had been in 1960 (though this drop has not been seen among women to date) [3]. Worldwide, lung cancer incidence is twice as high on average among men compared with women, though this ratio varies across countries, and three to four times higher in transitioned versus transitioning economies. Thus, for example, the 2020 age standardized incidence rate per 100,000 for lung cancer among men varies from 49 in Eastern Europe to 2.8 in Western Africa [4]. These differences largely reflect trends in cigarette smoking; in the future these patterns may change as the number of cigarette smokers is projected to rise in Africa while it decreases in Europe.

However, it is estimated that at least one quarter of global lung cancer cases occur among non-smokers, though this proportion varies across populations with estimates ranging from less than 20% in the United States [5] to 40% or higher in Asia and Africa [6]. Recent headlines have called attention to an apparent rise in lung cancer among younger nonsmokers [7]. While it is not clear whether incidence of non-smoking lung cancer is in fact increasing, the reduction in cases attributable to smoking means that a greater proportion of new lung cancer cases are being diagnosed among non-smokers. This has, in turn, brought attention to other causes of lung cancer, from environmental exposures such as radon and air pollution [8].

Lung cancer is the leading cause of cancer mortality worldwide and is second only to female breast cancer in incidence. Among men, lung cancer remains the most frequently diagnosed form of cancer. In 2020 there were over 2.2 million new cases and around 1.8 million deaths, accounting for 11.4% of overall cancer incidence and 18% of deaths [9]. An estimated

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10–20% of lung cancers occur in non-smokers, yet this proportion varies widely across countries and populations. For example, in Asia the proportion of lung cancer attributable to smoking is estimated to be much lower, particularly among women where the majority of lung cancers occur in non-smokers [6]. Additionally, patterns of lung cancer attributable to smoking are changing over time; while lung cancer mortality attributable to smoking has been decreasing in the U.S. and Europe, it is increasing in other parts of the world, particularly in many low- and middle-income countries [10]. Thus, this paper seeks to summarize current knowledge and important questions around environmental causes of lung cancer.

History

Before the twentieth century, lung cancer was a very rare disease. It first attracted attention as an occupational disease of miners. Cobalt and nickel miners in Schneeberg, Saxony, had long been known to suffer from lung disease, referred to as "Schneeberg mountain sickness." In 1879, German physicians F.H. Harting and W. Hesse, conducted autopsies on 20 miners and described a pulmonary malignancy found in three quarters of them. It was not until the 1950s that radon exposure was understood to be the cause, but the Harting and Hesse work was significant in linking lung cancer to an external environmental exposure [11].

As lung cancer rates rose rapidly during the first half of the twentieth century, a number of potential culprits were suggested, including automobile exhaust, road tar, and industrial pollution, in addition to cigarette smoking. For example, lung cancer was more common among those who lived in urban, rather than rural areas, which suggested that the density of automobiles or industrial pollution could be important factors. Early epidemiologic studies of lung cancer used the case control method: investigators compared the smoking habits of a group of lung cancer patients with another group without lung cancer. The case control method was particularly useful where very little was known about disease etiology, as was the case for cancer, because it allowed investigators to make comparisons on countless suspected agents. But the strength of the relationship between cigarette smoking and lung cancer was so strong that it soon overshadowed other factors [12].

At the same time, however, air pollution was gaining attention as a growing public health threat. In the U.S., during a smog episode at Donora, Pennsylvania, in 1948, at least 20 people died, and thousands suffered adverse respiratory effects triggered by a combination of weather conditions and pollution generated by a nearby steel plant. Additionally, Los Angeles, New York, and other cities were also facing growing challenges with air pollution. The 1955 Air Pollution Control Act, the first national legislation on air pollution, established a nationwide air sampling network to provide valuable data. Epidemiologist and occupational health expert Thomas Mancuso of the Ohio State Department of Health argued that air pollution was a likely contributor to urban lung cancer, emphasizing that urban areas were associated with higher lung cancer incidence even after accounting for cigarette smoking. In 1958, headlines in the national news warned – "US links cancer to air in cities", "Dirty air linked to cancer – aid seeks health drive", "smog is termed a cancer cause".

In June 1962, the U.S. Surgeon General released a 450-page report on motor vehicles, air pollution, and health. The report described statistical studies comparing lung cancer mortality across different cities and urban versus rural conditions, noting that the patterns recorded could not be entirely explained by differences in smoking prevalence. "It would appear, therefore, that there is evidence that air pollutants, related to vehicular emissions, play a role, at least as a co-factor, in the production of lung cancers under these conditions," the report concluded [13]. It is noteworthy that this report appeared two years before the landmark 1964 report of the Surgeon General on Smoking and Health in 1964, which concluded that smoking is a cause of lung cancer [14]. Both reports did eventually lead to policies controlling tobacco smoking and air pollution, though the 1964 report on smoking generated much more attention at the time.

Environmental causes

The International Agency for Research on Cancer (IARC) has identified several environmental exposures associated with lung cancer as known human carcinogens. Outdoor air pollution (including particulate matter in air pollution), diesel exhaust, radon, household coal combustion, secondhand smoke, and asbestos are all classified as class 1 carcinogens for which sufficient evidence is available of their carcinogenicity in humans [15]. Additionally, a range of air pollutants, such as polycyclic aromatic hydrocarbons, have been individually reviewed for carcinogenicity by IARC since the 1980s.

When IARC first classified outdoor air pollution and particulate matter as class 1 carcinogens in 2013, they cited the findings from large case control and cohort studies dating back to the 1970s [16]. The American Cancer Prevention Study, for example, followed over 500,000 people for over 20 years. The European Study of Cohorts for Air Pollution Effects (ESCAPE) study was also cited. These large cohort studies were important for having detailed information on cigarette smoking to rule it out as a potential confounder. Additionally, the IARC report cited other forms of evidence supporting the effects of air pollution on cancer. In particular, ambient air pollution contains specific chemical agents known to cause cancer (including arsenic, cadmium, benzene, beryllium, and polycyclic aromatic hydrocarbons, such as benzo[a]pyrene), and human exposure to outdoor air pollution is associated with forms of genetic damage that are predictive of cancer in humans.

However, characterizing the burden of lung cancer attributable to air pollution, distinct from cigarette smoking, remains

challenging. According to estimates from the Global Burden of Disease, the proportion of lung cancer deaths worldwide attributable to outdoor ambient PM2.5 (known as "fine particulate matter") air pollution was 14% in 2017, ranging from 4.7% in the United States to 20.5% in China [17]. A recent meta-analysis of the relative risk of lung cancer associated with PM2.5 exposure showed a higher risk for former smokers and never smokers compared with current smokers; the authors suggested that this may be due to the effect of PM2.5 being obscured by cigarette smoking in current smokers [18]. In another meta-analysis, Huang and colleagues, using data from 17 studies from different countries, found a relative risk of 1.11 for each 10 $\mu g/m^3$ increase in exposure to PM2.5; in other words, each 10 $\mu g/m^3$ unit increase in PM2.5 exposure was associated with an 11% increase in lung cancer [19]. However, as this was a pooled estimate based on multiple studies, the actual relative risk may vary across countries with different exposure patterns and competing risks. For example, relative risks tended to be higher in studies from Asia compared with Europe.

While radon is also a known cause of lung cancer, there remains controversy over the extent of the burden. Radon exposure has been clearly linked to lung cancer among uranium miners who experience high levels of occupational exposure. However, the level of radon exposure in homes is much lower and the extent of its role in the development of lung cancer remains unclear. In a meta-analysis of 13 case control studies, the authors estimated the excess risk associated with home-based exposure to radon across different exposure levels. They found excess risk associated with home exposure and also concluded that the risk from radon was 25 times higher among smokers compared with non-smokers. Based on this information, the authors estimated that radon exposure might be responsible for up to two percent of lung cancer deaths in Europe [20].

Causes of lung cancer may also act together through synergistic interactions to increase risk. Under a multicausal model, environmental exposures may interact with cigarette smoking to multiply the risk of lung cancer. For example, as early as the 1960s it was noted that while occupational exposure to asbestos and cigarette smoking were associated with lung cancer, those who smoked and also worked with asbestos had many times the lung cancer risk of those only exposed to one of the two carcinogens [21]. Thus, while it is correct to say that smoking causes most cases of lung cancer, environmental exposures can also contribute substantially and should not be underestimated. Recent attention to the potential long term health impacts of climate change also highlights the importance of continuing to monitor air pollution and other environmental factors for lung cancer [22].

Non-smoking lung cancer

There has been increased attention to understanding lung cancer in never smokers (typically defined as those who have smoked less than 100 cigarettes in their lifetime), though research remains limited. Because lung cancer has been so strongly linked to cigarette smoking, non-smoking patients are particularly confused to learn about their diagnosis and seek answers. One important analysis, derived from 35 databases around the world (13 cohorts and 22 cancer registries on lung cancer), indicates that death rates among never-smokers with lung cancer are greater in men, African Americans, and Asians living in Asia, compared with those of European ancestry [23].

Courad and colleagues [24] reported the results of one of the largest prospective European trials conducted in lung cancer in never-smokers (defined as less than 100 cigarettes in a lifetime). The study recruited 384 French patients in 75 participating centers, each individually contacted to perform an interview on risk exposure. The authors showed that 13% of patients had been exposed to at least one occupational carcinogen (men 35%, women 8%), whereas domestic exposure (passive smoking and cooking oil) was higher in women (41% *versus* 18% for exposure to cooking oil fumes). Domestic exposure to passive smoking, 62% of which began during childhood, was significantly more frequent among women than men (64% *versus* 38%). Overall, it appears men are more exposed to occupational carcinogens and women more exposed to domestic carcinogens.

More than one third of all newly diagnosed lung cancers and nearly 40% of deaths globally occurred in China, and the number is expected to increase in the future [25]. While smoking prevalence is high among men in China, it is very low among women, who also suffer a high burden of lung cancer. High lung cancer mortality among non-smoking women in China has been attributed to household air pollution from cooking and the use of coal for heating [26]. Lung cancer among women in China has historically been higher in the northeast of the country, where indoor heating exposure would be expected to be higher [27, 28]. Geographic studies have also linked ambient air pollution levels to lung cancer mortality in China [29]. A recent analysis also estimated that (based on 2,005 figures) 13.7% of lung cancer deaths (10% for men and 18% for women) could be attributed to PM2.5 exposure [30].

There are two primary forms of lung cancer:

- small cell lung cancer, which is found almost exclusively in cigarette smokers, and
- non-small cell lung cancer, which is the most common form of lung cancer, and appears in smokers and non-smokers.

Adenocarcinoma, the most frequent type of non-small cell lung cancer, starts in the cells of mucus making glands in the lining of the airways. Recent reports in popular media have highlighted "a surge in 'non- smoking' lung cancer" in China [31], noting a rise in adenocarcinoma relative to other lung cancer subtypes since 2000. While the increase in adenocarcinoma has been attributed by some to high levels of ambient air pollution

in China, this shift is likely partly explained by changes in cigarette smoking behavior. A similar shift in lung cancer histology was seen in previous decades in the U.S. and European countries and attributed to changes in cigarette design [32]. During the 1960s and 1970s, tobacco companies increasingly marketed "light" and low-tar cigarette brands with lower machine-measured levels of tar and nicotine, and these brands came to dominate the market in large part due to the perception that they were less harmful than other cigarettes. As smokers switched to low-tar cigarettes, they tended to inhale more deeply, transporting carcinogens more distally into the lungs where adenocarcinomas arise. At the same time, greater use of reconstituted tobacco, with higher concentrations of nitrosamines, may have also contributed to a shift towards adenocarcinomas. China has experienced a similar shift towards "low tar" cigarettes, though more recently. Thus, it is likely that the increase in adenocarcinomas relative to other lung cancer subtypes is attributable, at least in part, to changes in cigarette design and smoking behavior. At the same time, long term air pollution exposure may also account for some portion of adenocarcinomas [33]. A similar pattern has been seen in other LMICs, such as India, and also linked to tobacco use patterns [34].

There is increasing documentation that lung cancer in never smokers is different from lung cancer seen in smokers. For example, in Taiwan, where never smoking patients are predominant (53%), especially among females (93%), lung cancer tends to have an earlier onset at younger ages with a predominance of *EGFR* mutations [35]. Recent studies have revealed that lung cancer in never smokers exhibits a distinct pattern of oncogenic mutations and a distinct natural history compared with lung cancer caused by smoking [36]. Last year, an international team of researchers, led by investigators at the National Cancer Institute, completed whole genome sequencing of tumor and normal tissue from 232 never smokers diagnosed with non-small cell lung cancer (primarily adenocarcinomas). By looking at patterns of mutations, they identified three distinct subtypes of lung cancer in never smokers:

- the "piano" subtype, which has the fewest mutations and grows very slowly,
- the "mezzo-forte" subtype, which exhibits chromosomal changes and mutations in the growth factor receptor gene *EGFR*, and
- the "forte" subtype, which exhibits a phenomenon known as whole genome doubling, typically seen in lung cancer in smokers [37].

These findings provide clues to the origins of these distinct tumor subtypes and might help to develop treatments that target specific pathways through which these cancers develop. Another genomic study, comparing adenocarcinoma cells from smoking and never-smoking lung cancer patients, found that the tumors from never-smokers were more likely to contain driver mutations, alterations in certain genes that drive oncogenesis. A number of clinical therapies have been developed recently that target driver mutations and show promise for treating lung cancer [38].

A new study from investigators at the Francis Crick Institute recently provided some novel findings on the mechanisms by which air pollution may cause lung cancer. The researchers observed that cancer-driving mutations in *EGFR* genes found in lung cancer are also frequently present in normal tissue in patients without cancer, suggesting that some additional step was involved. They hypothesized that inhaled PM2.5 particles produced an inflammatory response in the lungs which activates the mutated cells. They tested this idea in mice with *EGFR* mutant cells and found that the mice exposed to air pollution were more likely to develop lung cancer than those not exposed [39]. The findings depart from the conventional model that cancer develops from an accumulation of mutations due to repeated air pollution exposure. While the mutations are a necessary step in the process, air pollution may in fact cause lung cancer through a different route, by triggering an inflammatory response. These findings are also noteworthy because they suggest another possible route for intervention to prevent cancer through controlling the immune response.

Discussion

The growth in lung cancer caused by environmental exposures seen in non-smokers is likely to continue under current trends. Both indoor and outdoor air pollution are important contributors to the global burden of lung cancer, and multiple exposures may interact together in a synergistic manner. However, reducing exposure to air pollution should reduce the future lung cancer burden. That said, while strategies exist to reduce exposure, implementing these measures involves additional challenges which should be addressed through further research. For example, the use of cleaner cooking stoves could reduce indoor air pollution exposure, but large-scale replacement of home stoves with new stoves and fuel requires education and support for adoption [40]. Future research in implementation science can help address this gap between discovery and public health impact.

Greater efforts are needed to reduce the global burden of lung cancer. According to the Surveillance, Epidemiology, and End Results (SEER) database, maintained by the U.S. National Cancer Institute, the 5-year survival rate for patients with lung cancer is 26% (though it rises to 64% when identified at a localized stage). This figure reflects the experience in the United States, but may be different in other countries, particularly where capacity for diagnosis is limited. Regular screening for lung cancer with low-dose computed tomography has so far only been shown to be beneficial in high-risk patients with a history of cigarette smoking [41]. Moreover, while there have been some efforts to amplify the voices of lung cancer patients, lung cancer has not received the focused advocacy and attention other cancers have. Lung cancer patients are

more likely to experience stigma; while experience may differ between smoking and non-smoking patient, patients report discomfort sharing a lung cancer diagnosis regardless of their smoking history [42].

Conclusions

The good news is that ongoing research continues to elucidate the mechanisms of lung cancer and suggest new opportunities for intervention. As recent work on the role of air pollution in *EGFR*-mutant cancers shows, there is still more to learn about how environmental exposures cause lung cancer. Increased understanding of these cancers, and the distinct characteristics of non-smoking lung cancer, may reveal new approaches to address the global burden of lung cancer.

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Mark Parascandola
National Cancer Institute
Center for Global Health
Research and Training Branch,
9609 Medical Center Drive
Bethesda, MD 20892-9761
USA
e-mail: paramark@mail.nih.gov

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Solitary cutaneous focal mucinosis during immunotherapy for melanoma

Przemysław Baran[1], Wojciech M. Wysocki[1, 2, 3]

[1]*Department of General and Oncological Surgery, 5th Military Clinical Hospital, Krakow, Poland*
[2]*Chair of Surgery, Faculty of Medicine and Health Sciences, Andrzej Frycz Modrzewski Krakow University, Krakow, Poland*
[3]*Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

A **B**

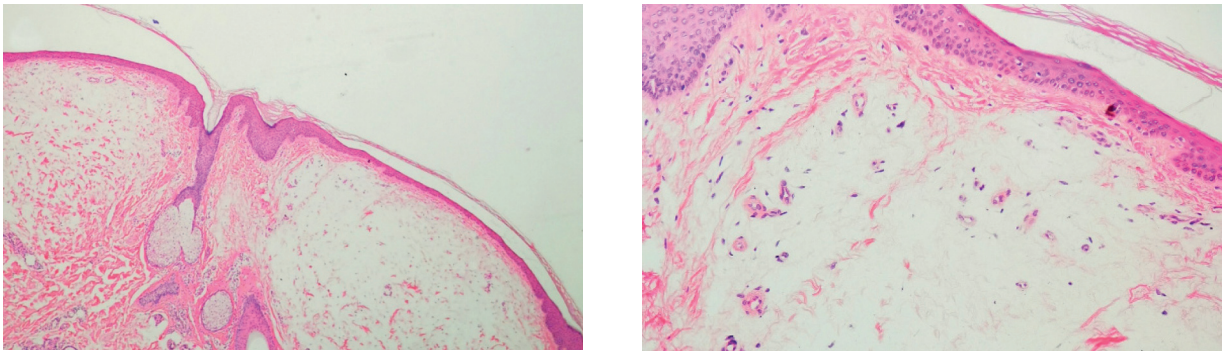

Figure 1. Microscopic presentation of hematoxylin and eosin-stained sections of a solitary cutaneous focal mucinosis on the right lower leg of a 40-year-old woman. Pallor of the dermis is a consequence of increased amounts of interstitial mucin. (**A**) x40, (**B**) x200

A 40-year-old woman was diagnosed with pT3b melanoma of the right thigh (fig. 1). The patient underwent wide local excision and sentinel node biopsy with clinically occult metastases; subsequently an inguinal lymphadenectomy was performed and adjuvant pembrolizumab introduced. Ten months since the start of immunotherapy, an asymptomatic, plateau-shaped, white-colored lesion of the right lower leg was noted. An excisional biopsy was taken and a diagnosis of "cutaneous focal mucinosis" was established. "Solitary cutaneous focal mucinosis" is a rare skin lesion characterized by the increased presence of mucin in the dermis and is mostly an idiopathic condition. The lesion typically presents as an asymptomatic dome-shaped papule or nodule on the extremities. The color varies from flesh-colored to white to red. It occurs in adults with a male predominance. The lesion has been reported in less than 200 individuals. It is rarely clinically diagnosed due to variable morphologic presentation and the necessity of a surgical biopsy to establish the diagnosis [1]. Association of this infrequent skin lesion with immunotherapy has been previously observed in a very few cases [2]. Typically, a surgical biopsy provides adequate treatment of the solitary cutaneous focal mucinosis; additionally the lesion does not tend to reoccur. There are additional studies necessary.

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Autophagy in cancer cytopathology: a case of intraoperative touch imprint of lung metastasis from TFE3-rearranged renal cell carcinoma

Gabriele Gaggero[1], Marta Ingaliso[2], Davide Taietti[3]

[1]*UO Anatomia patologica ospedaliera, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Policlinico San Martino, Genova, Italy*
[2]*Division of Anatomic Pathology, Department of Integrated Surgical and Diagnostic Sciences, Scuola di Scienze Mediche e Farmaceutiche, Università di Genova, Genova, Italy*
[3]*Pathology Unit, Azienda Socio-Sanitaria Territoriale del Garda, Desenzano del Garda, Brescia, Italy*

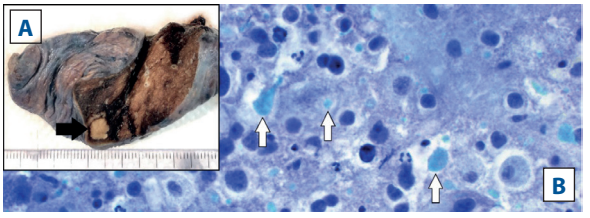

Figure 1. Macroscopy, showing a beige lung nodule (black arrow) (**A**). Intraoperative touch imprint cytology (toluidine blue, 60x), showing epithelioid neoplastic cells and scattered densely stained globular intracytoplasmic inclusions (white arrows) (**B**)

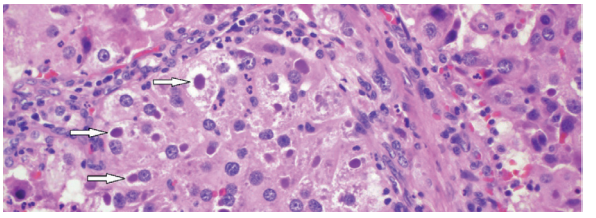

Figure 2. Histology (hematoxylin and eosin, 40x) confirmed the presence of intracytoplasmic autophagic eosinophilic inclusions (white arrows)

A 67-year-old man presented with a lung nodule, suspected metastatic as he underwent nephrectomy 4 years earlier for an unclassified renal cell carcinoma (RCC). Such nodule was sent for an intraoperative microscopic evaluation (fig. 1A) and cytology was consistent with a metastasis. The intriguing feature was the intracytoplasmic hyaline globules (IHG) (fig. 1B), confirmed on histology (fig. 2), suspected to be phagolysosomes from aberrant autophagy. Immunohistochemistry allowed both the diagnosis of metastasis from TFE3-rearranged RCC (RCC+, CD10+, Vimentin+, PAX8+, TFE3+; TTF1–, Napsin–) and the IHG autophagic nature (LC3B+, p62+, ATG5+, PD-L1+). Microphthalmia transcription factor (MiT) family translocation RCC (tRCC) is a very rare RCC, and is characterized by translocations involving TFE3 or TFEB, the former being the more aggressive. Recent studies identify autophagy as a molecular player in tRCC [1]. Autophagy is the physiological mechanism of human cells to incorporate and fragment autologous structures to obtain elements essential for cellular life itself; autophagy is also crucial in cells process of antigen presentation. However, autophagy impairment plays a role in cancer progression, particularly in: immune evasion; conversion of metastatic cells to stem cells resulting chemo-resistant; motility of metastatic cells [1, 2]. To date, the molecular relationship between autophagy and PD-L1 expression in cancer is not clear.

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