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Pancreatic cancer concomitant with other malignancies – a single centre experience

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

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

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

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

Key words: pancreatic cancer, oncology, survival

Introduction

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

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

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

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

Materials and methods

Patients and data collection

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

Histopathology

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

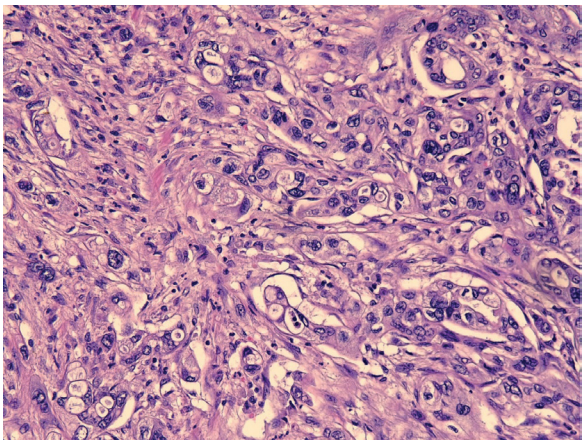

Figure 1. Histopathological image of pancreatic ductal adenocarcinoma (H&E, original magnification, 200×)

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

Statistical analysis

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

Ethics approval and consent to participate

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

Results

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

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

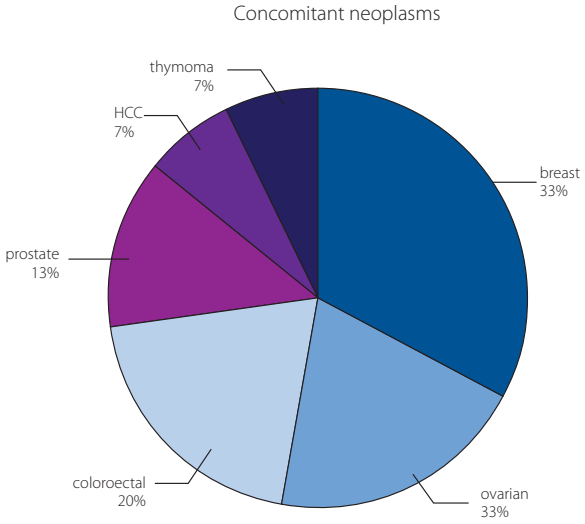

Figure 2. Distribution of neoplasms concomitant with pancreatic cancer

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

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

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

Table I. The summary of clinicodemographic variables

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

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

Table II. The summary of the clinicopathological variables

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

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

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

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

→

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

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

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

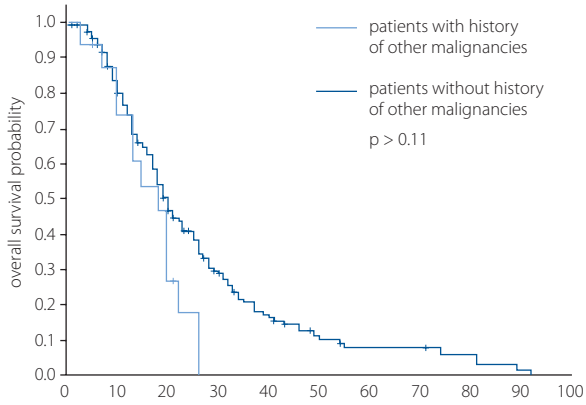

Figure 3. The Kaplan–Meier curve for overall survival in the two studied groups

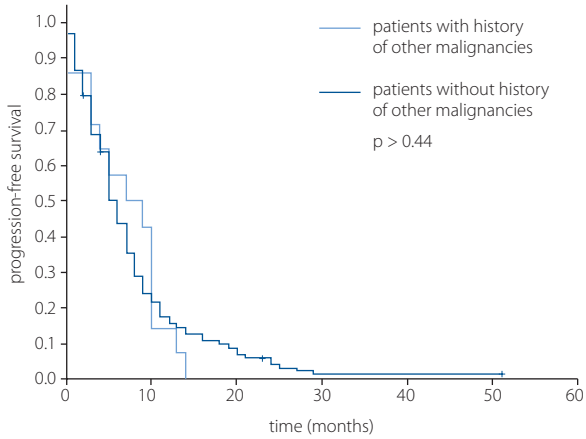

Figure 4. The Kaplan–Meier curve for progression-free survival in the two studied groups

Discussion

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

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

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

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

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

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

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

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

Conclusions

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

Article information and declarations

Data availability statement

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

Ethics statement

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

Authors contribution

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

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Conflict of interest

None declared

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