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MARCIN CHOLEWA[1], JULIA WÓJCIK[1], MACIEJ KUCA[1], KAROLINA JAGLARZ[2], MAKSYMILIAN JANECZEK[1], KAROLINA KINGA KANTOR[1], JULIA PLEWNIOK[1], WIKTORIA MARIA SZYMAŃSKA[1], KACPER WOJCIECH PAMUŁA[1], MARIA PARTYKA[1]

Pancreatic cancer – challenge for modern medicine

Abstract

Introduction. Pancreatic cancer is one of the most dangerous carcinomas of the digestive tract, with a very poor prognosis for patients. Annually, more than three and a half thousand people in Poland are diagnosed with this tumor.

Aim. The aim of the work was to assess and compile existing knowledge about pancreatic adenocarcinoma.

Materials and methods. Data for the paper was gathered with the usage of Google Scholar. Moreover, articles from sources like PubMed or National Institutes of Health were used. Materials were published between 2015 and 2024.

Results. Tumor morbidity is still increasing, the biggest group of patients are people who are more than 55 years old. Many modifiable and nonmodifiable factors play a role in the pathogenesis of pancreatic cancer. Lifestyle, stimulants, BMI or physical activity can be included into the first group. Nonmodifiable factors are sex, age, race, genetic predisposition or blood group. Typical symptoms of this tumor are loss of the body weight, fatigue, nausea, jaundice and abdominal pain. Clinicians use the following diagnostic methods: CT, MRI, ERCP, MRCP or USG. Only the radical chirurgical treatment gives a hope for total recovery, additionally chemotherapy can be admitted. Chemotherapy schemes are FOLFIRINOX or monotherapy with gemcitabine.

Conclusions. Pancreatic cancer is still a challenge for clinicians, as its treatment is limited by poor effectiveness of possible ways of treatment. The majority of tumors are diagnosed at the advanced stage, when full patient recovery is not possible. New ways of treatment such as immunotherapy, monoclonal antibodies or gene therapy are a ray of hope.

Keywords: pancreatic cancer, treatment of pancreatic cancer, epidemiology, diagnostic methods.

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INTRODUCTION

The earliest references to pancreatic cancer in the annals of medical history can be traced back to 1761, when the Italian pathologist Giovanni Battista Morgagni first described changes in the pancreas that could correspond to adenocarcinoma of this organ [1]. Despite the passage of centuries and remarkable advancements in medicine in both diagnostic and therapeutic domains, pancreatic cancer remains a pressing issue for many clinicians.

Periodic publications from the National Cancer Registry clearly indicate that the incidence of cancer in Poland continues to rise. The most recent data from 2021 reveal over 170,000 new cancer cases and 93,000 cancer-related deaths [2]. Among this number, pancreatic cancer is diagnosed annually in over three and a half thousand individuals of both sexes [2].

Pancreatic cancer is considered to be one of the most formidable malignancies of the digestive tract. It is characterized by extremely unfavorable prognosis, with the global five-year survival rate ranging from 0.5% to 9% [3]. In Poland, this rate averages 9% for men and 13% for women [4]. Currently, there is a lack of advanced and innovative treatment methods for pancreatic cancer, with distant treatment outcomes having remained unchanged for nearly two decades [4]. According to studies published in the United States, from 1975 to 2000, during 25 years of vigorous development in nearly every field of medicine, the five-year survival rate for pancreatic cancer increased from 2.5% to only 6.4% [5].

Pancreatic cancer presents an exceptionally challenging clinical dilemma due to its difficult diagnosis, the fact that it is often detected at an advanced stage, and the limited number of effective treatment options that can offer patients hope for recovery.

AIM

The primary objective of this study is to compile and systematize current knowledge regarding the epidemiology, diagnosis, and treatment of pancreatic cancers, with a particular emphasis on pancreatic adenocarcinoma.

MATERIAL AND METHODS

The materials for this study were obtained through publicly accessible educational platforms such as Google Scholar. During the preparation of this publication, the authors also utilized databases provided by PubMed, the National Institutes of Health, and Web of Science.

[1] Faculty of Medical Sciences, Medical University of Silesia in Katowice, Poland
[2] College of Medical Sciences, University of Rzeszów, Poland

The majority of the articles used as source materials came from the years 2015-2024, reflecting the usage of up-to-date and reliable knowledge resources. Priority was given to materials from the most recent journals with the highest impact factors.

Keywords used in the search for source materials included: pancreatic cancer, epidemiology of pancreatic cancer, pancreatic cancer treatment, and management of pancreatic cancer.

Description of the state of knowledge

Pancreatic cancer is a malignancy with a poor prognosis, as only one in ten patients has their disease detected at an early stage. Furthermore, 75% of these patients experience the recurrence of disease despite treatment [3]. Over the past two decades, the incidence of pancreatic cancer has more than doubled globally [6]. Demographic changes and the characteristics of the cancer, which predominantly affects individuals over the age of 55, suggest that the incidence of this disease will continue to rise. Interestingly, according to an article published in the prestigious journal *Lancet*, the surge in the prevalence of new cases of pancreatic cancer is currently more pronounced among individuals under the age of 55 [7].

Risk factors

The uneven age distribution observed in pancreatic cancer epidemiology can be attributed to multiple factors. Primarily, as with most cancers, risk factors for pancreatic cancer include non-modifiable patient characteristics such as age, sex, genetic predisposition, race, and blood type.

Pancreatic cancer predominantly affects older individuals, with approximately 90% of diagnosed patients being over the age of 55 [8]. Men are also at higher risk, potentially due to hormonal factors or lifestyle choices. Swedish researchers have demonstrated that women using hormone replacement therapy have a statistically significant reduction in the risk of pancreatic cancer compared to a control group [9]. This study suggests a potentially inhibitory effect of estrogens and progesterone on carcinogenesis.

Additional risk factors for pancreatic cancer include smoking, alcohol consumption, obesity, and lack of physical activity. A multicenter study conducted in 2020 with over 2,000 patients found that smoking increases the risk of pancreatic cancer by 1.72 times [10]. Furthermore, research conducted in the United States showed that smokers diagnosed with pancreatic cancer have a 1.37 times higher risk of death compared to non-smokers. This indicates that, statistically, the endpoint (in this study, patient death) is 1.37 times more likely among smokers than non-smokers [11]. Notably, the risk was found to be higher, the longer a patient had smoked.

A study involving over 2,000 pancreatic cancer patients demonstrated that alcohol consumption increases the risk of this cancer. The relative risk for patients consuming more than 30 grams of alcohol per day was 1.22. Research clearly shows the impact of substance use on pancreatic cancer development, with smoking being statistically more harmful than alcohol [12]. Additionally, the World Cancer Research Fund has reported that with each 5-unit increase in BMI above the normal range, the risk of pancreatic cancer rises by 10 percentage points. These findings underscore the direct correlation between lifestyle and cancer risk. Moreover, lifestyle, as a modifiable risk factor, can potentially be mitigated through proper health education.

Studies conducted in the United States have also shown that race is a risk factor for pancreatic cancer. African Americans have a 50-90% increased risk of developing this cancer compared to Caucasians [12]. This disparity may be attributable to differences in lifestyle, higher alcohol consumption, increased BMI, or a greater risk of diabetes relative to the white population [13].

Researchers from the University of Bergen in Norway have demonstrated that blood group, as an additional non-modifiable factor, may represent a risk for developing pancreatic cancer. In a cohort study involving over 6,000 individuals, they found that blood groups other than O are associated with an increased risk. In other words, individuals with blood group O, which is the second most common subtype in the ABO system after group A, have a lower risk of developing malignant pancreatic tumors [14]. Interestingly, this is not the only example of a correlation between blood group and cancer risk. It has been shown that the risk of gastric cancer is increased for patients with blood group A, while individuals with blood group AB have a lower risk of this type of cancer [15]. These findings underscore the significant influence of blood groups on the risk of malignant cancers. Further research could provide a more precise understanding of these correlations and potentially open new avenues for screening and early detection methods for particularly at-risk patients.

Type 2 diabetes mellitus is an extremely significant risk factor for pancreatic cancer. Currently, over 500 million people worldwide suffer from this metabolic disorder, with projections suggesting that this number could reach up to 780 million by 2045 [16]. Over 90% of diabetes cases are type 2 diabetes. A study published in 2023 demonstrated that type 2 diabetes is a significant risk factor for developing pancreatic cancer. Notably, nearly 40% of patients with pancreatic cancer had diabetes prior to their cancer diagnosis, while 42% had a diagnosis of diabetes that coincided temporally with their cancer diagnosis [17]. Further relevant data on this correlation is available on the mp.pl website, which shows that oncological patients experienced a substantial increase in HbA1c levels in the 3-6 months preceding the diagnosis of cancer [18]. These findings lead to two main conclusions: first, that type 2 diabetes, as a civilization disease, is associated not only with complications such as macroangiopathy, retinopathy, nephropathy, microangiopathy, and neuropathy but also with an increased risk of malignant tumors. Second, clinicians should present heightened vigilance, especially during the diagnosis of newly detected diabetes in patients aged around 55-60 years. It is crucial to assess whether other symptoms might indicate the presence of a neoplastic disease. Additionally, the presence of diabetes complicates therapeutic options due to the increased susceptibility to infections or impaired wound healing, which restricts surgical treatment methods which are especially important in small, localized pancreatic tumors. Chemotherapy is also challenging, particularly due to diabetic nephropathy, which necessitates the avoidance of potentially nephrotoxic drugs.

Initiation, promotion, and progression are inherent stages of carcinogenesis that can be triggered by various factors. One of these is chronic inflammation, which is characterized by the presence of cytokines such as IL-1, IL-6, reactive oxygen species (ROS), and elevated cyclooxygenase activity [19]. Chronic pancreatitis is a multifactorial disease with causes including alcoholism, smoking, hypercalcemia, hyperlipidemia, autoimmune factors, mechanical obstructions, or genetic mutations

such as in the *SPINK1* or *CFTR* genes (the latter responsible for the pathogenesis of cystic fibrosis). Patients with genetically predisposed chronic pancreatitis have up to a 20% increased risk of developing pancreatic cancer compared to healthy individuals [20]. In the case of alcohol-induced chronic pancreatitis, the risk increases to a lesser extent, though it is important to remember that alcohol itself is a carcinogen.

Genetic factors play a crucial role in the pathogenesis of pancreatic cancer. Researchers have identified several genes that contribute to tumor development, with key examples including *K-RAS*, *TP53*, *BRCA1*, *BRCA2*, *PRSS1*, *MMR*, *STK11*, and *CDKN2A* [8]. The highest risk of developing pancreatic cancer is associated with mutations in the STK11 gene (which controls the cell cycle), responsible for Peutz-Jeghers syndrome [21]. In this specific case, the risk of pancreatic cancer increases by up to 130 times compared to the healthy population [12]. The most common mutation leading to pancreatic cancer development is a defect in the *KRAS* oncogene, which encodes the K-Ras protein, contributing to up to 90% of genetically driven pancreatic cancer cases [22]. Research indicates that over 80% of pancreatic cancer cases are caused by spontaneous, non-familial monogenic mutations [8]. Patients with first-degree relatives affected by pancreatic adenocarcinoma have a 4.5 times increased risk of developing the disease [8]. In the context of pancreatic cancer pathogenesis it is worth mentioning *BRCA1* and *BRCA2* genes, which physiologically encode proteins involved in DNA repair. They are primarily known for their association with breast and ovarian cancer [23], but can also induce pancreatic cancer [22]. This leads to various diagnostic challenges, including the necessity of monitoring men whose mothers, as carriers of *BRCA1/2* mutations, may have had breast cancer. While the risk of breast cancer in these men is low due to their gender, there remains an increased risk for pancreatic and other cancers.

Symptoms of pancreatic cancer

In the diagnostic process, in addition to knowledge about the risk factors described above, understanding the symptoms of pancreatic cancer is crucial. Correlating and identifying patients who exhibit both specific risk factors and typical clinical signs and symptoms enables earlier diagnosis and improves prognosis. The most typical symptoms of pancreatic cancer largely overlap with common cancer-related symptoms, such as fatigue, weight loss, bloating, nausea, abdominal discomfort, or fever. The frequency of specific symptoms is closely related to the tumor location. In approximately 70% of cases, the tumor is located in the head of the pancreas, 20% in the body, and the remaining 10% in the tail of the organ [24]. When the tumor is located in the head of the pancreas, characteristic symptoms include weight loss, steatorrhea, and painless jaundice [25]. The painless nature of the jaundice is particularly important as it helps differentiate pancreatic cancer from bile duct stones or acute cholangitis, where patients typically report severe pain in the right upper abdomen. The presence of jaundice may also be accompanied by pruritus, the pathogenesis of which is not fully understood but may be related to the activation of the endogenous opioid system [26]. Other typical signs of extrahepatic jaundice include pale-colored stools and dark urine. Research has shown that the presence of jaundice can have prognostic value in pancreatic cancer, with better outcomes observed in patients presenting with painless jaundice [25].

Jaundice can also be reflected in laboratory tests, typically presented with conjugated hyperbilirubinemia, elevated GGTP, and increased alkaline phosphatase levels [27]. Laboratory abnormalities in pancreatic cancer may also include anemia, thrombocytosis, hypoalbuminemia, elevated inflammatory markers, and increased levels of the tumor marker CA19-9. A CA19-9 level exceeding 180 U/mL is considered an unfavorable prognostic indicator. This marker can be used as a prognostic factor or for monitoring potential recurrence of the disease [28].

The presence of cancer itself is associated with a prothrombotic risk, as numerous studies have shown [29-31]. This is driven by several factors, including inflammation and the production of tissue factors by cancer cells, which activate coagulation factors, such as factor Xa. Additionally, chemotherapy further increases blood clotting, with prothrombotic agents including methotrexate, 5-fluorouracil, and cisplatin. Pancreatic cancer can be manifested with pulmonary embolism, deep vein thrombosis (DVT) of the lower limbs, or the lesser-known but interesting Trousseau's syndrome. This syndrome, also called migratory superficial thrombophlebitis, is characterized by redness, tenderness, and swelling in one vein or „migrating" lesions in different locations [32].

Another specific sign related to pancreatic cancer is Courvoisier's sign, which refers to a palpable, painless gallbladder. This is caused by mechanical compression of the bile ducts by the tumor. Pancreatic cancer may also cause duodenal compression, leading to mechanical gastrointestinal obstruction or bleeding. Furthermore, compression of the splenic vein can result in secondary congestion of the spleen, leading to splenomegaly.

An extremely rare sign in pancreatic cancer is the so-called Sister Mary Joseph nodule. Named after a nurse who first observed it in a patient shortly after World War II, it involves the enlargement of umbilical lymph nodes, which form a characteristic nodule-like structure [33]. These nodules can also appear in other gastrointestinal cancers, but their occurrence is nearly anecdotal.

The symptoms of pancreatic cancer mentioned above are largely non-specific. It is challenging to find a symptom in a physical or subjective examination that allows for a so-called "strassen diagnose" – a diagnosis made at first glance. For these reasons, imaging and laboratory tests play a crucial role in diagnosis.

Imaging techniques

The most accessible and commonly performed examination is abdominal ultrasonography (USG); however, it only allows the detection of large tumors or secondary signs of malignancy, such as venous thrombosis, enlarged peripheral/retroperitoneal lymph nodes, or infiltration of major vessels, such as the aorta. This is not a diagnostic method that enables definitive diagnosis; it is routinely performed due to its high availability. The situation is entirely different when using endoscopic ultrasonography (EUS), which is more effective and sensitive than computed tomography (CT) for detecting lesions smaller than 1 cm. Additionally, EUS allows for the collection of tissue samples for histopathological examination, which is essential for establishing a final diagnosis [25]. EUS also enables very precise determination of the T (Tumor) and N (Nodules) characteristics, which are useful in tumor staging, i.e., assessing its clinical advancement. The drawbacks of this method include

the fact that it is not always possible to introduce the endoscope due to the patient's severe condition, strictures within the upper gastrointestinal tract, or coagulation disorders.

Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) are additional imaging methods used in pancreatic cancer. CT performed with the so-called pancreatic protocol is considered the gold standard of diagnostics, as it allows not only the assessment of local tumor advancement but also the detection of both local and distant metastases [34]. Contrast-enhanced MRI can also be used in the diagnosis of pancreatic cancer, and unlike CT, it does not expose the patient to ionizing radiation. According to studies, MRI is the best method for detecting small pancreatic cancer metastases in the liver [34]. Additionally, MRI is recommended for diagnosing potentially precancerous conditions in the pancreas, such as IPMN (intraductal papillary mucinous neoplasms), MCN (mucinous cystic neoplasms), or SCN (serous cystic neoplasms) [35]. Certainly, the disadvantages of both examinations include the high cost of the required equipment, limited availability in smaller centers, and, in the case of contrast studies, the risk of complications such as anaphylactic reactions, contrast extravasation, or contrast-induced nephropathy.

ERCP, or endoscopic retrograde cholangiopancreatography, is an invasive diagnostic method. It is not routinely used in cases of suspected pancreatic cancer, despite its high sensitivity of 92% and even higher specificity of 96% [34]. Performing ERCP carries several risks, such as bleeding, gastrointestinal tract injury, acute pancreatitis post-ERCP, or acute cholangitis. Additionally, it may not be feasible for all patients due to strictures, adhesions, or anatomical obstructions. Among the undeniable advantages of ERCP is the ability to obtain tissue samples for histopathological examination, visualize small neoplastic changes located in the common bile duct, and place stents in the bile ducts, particularly in palliative treatment protocols [34]. When a non-invasive method for imaging the bile ducts is required, magnetic resonance cholangiopancreatography (MRCP) offers an alternative, also providing better visualization of cystic lesions [28].

Ways of treatment

The treatment of pancreatic cancer remains a challenge and is associated with uncertain therapeutic outcomes. Treatment methods include conventional chemotherapy, surgical intervention, or radiotherapy. The only chance for a permanent cure is radical surgery; unfortunately, this is feasible in only 20-30% of cases. Moreover, the 5-year survival rate in this group of patients still does not exceed 20% [28].

Surgical treatment of pancreatic cancer can be performed using the Whipple or Traverso procedures. The Whipple procedure, in other words pancreatoduodenectomy, involves the removal of part of the pancreas, the duodenum, part of the pyloric region of the stomach, and the gallbladder [34]. The Traverso modification allows for the preservation of the stomach. In both cases, lymphadenectomy is also performed. These surgeries can be carried out either via traditional „open" surgery or laparoscopic techniques, which are more advantageous for the patient. Laparoscopy allows for earlier hospital discharge, better pain control, and quicker recovery; however, it is more technically demanding for the operating surgeon and requires considerable experience [8]. Currently, the postoperative mortality rate in pancreatic cancer is approximately 3%, though in many cases, complete and radical tumor removal remains impossible [8]. The assessment of resectability can be classified into three categories. An R0 resection indicates the complete removal of the tumor, R1 indicates microscopic evidence of cancer cells in the postoperative specimen, and R2 indicates macroscopic tumor remnants visible to the surgeon. Researchers from Heidelberg University in Germany analyzed over 500 patients who underwent surgery for pancreatic cancer. In this group, 20% of operations achieved R0 resection, while 80% resulted in R1 [36]. This study highlights that, despite employing risky and burdensome surgical treatments, only 2 out of 10 patients may achieve a radical tumor resection, leaving cancer cells in the remaining cases incompletely removed.

Chemotherapy can be used as an induction treatment before a planned surgery to reduce tumor mass (neoadjuvant chemotherapy), as an adjuvant treatment following surgical resection, or in the form of palliative care.

The most effective chemotherapy regimen used in pancreatic cancer is FOLFIRINOX, which consists of fluorouracil, leucovorin, irinotecan, and oxaliplatin. This is an extremely intensive chemotherapy cycle, recommended for patients in good general condition [28]. It can cause neutropenia, gastrointestinal complications, and fatigue syndrome. According to studies, the FOLFIRINOX regimen extended patient survival to an average of 54 months, whereas treatment with gemcitabine, another chemotherapeutic agent used for pancreatic cancer, resulted in an average survival of 35 months [12]. Additionally, FOLFIRINOX has a threefold higher objective response rate compared to gemcitabine monotherapy [28]. The 1-year survival rate also favors FOLFIRINOX (48% vs. 21%). The gemcitabine regimen, when used after surgery, extended the time to disease recurrence compared to surgery alone, from an average of 6.7 months to 13.4 months [12]. Monotherapy with gemcitabine is recommended for patients in poor general condition or in cases of locally advanced pancreatic cancer, combined with radiotherapy [8].

Preoperative (neoadjuvant) chemotherapy aims to reduce tumor mass and eliminate micrometastases, which may be located, for example, in the liver [12]. A Dutch study demonstrated that patients undergoing surgery after receiving neoadjuvant chemotherapy had significantly longer survival times compared to those who underwent surgery alone – 26.1 months vs. 15 months [37]. Similar results were obtained in Denmark, where patients were divided into two groups: the first group received neoadjuvant chemotherapy followed by surgery, while the second group underwent surgery without chemotherapy. In the first group, the median survival time was 17.1 months, while in the second group, it was 13.7 months [12]. Both studies clearly show that preoperative chemotherapy is effective and prolongs overall survival. However, it is important not to overlook its side effects, such as nausea, vomiting, neutropenia, increased susceptibility to infections, potentially prothrombotic effects, or chronic fatigue syndrome.

In the palliative treatment of metastatic pancreatic cancer, the FOLFIRINOX regimen may be used, which, particularly in patients with a good overall condition, results in an average survival increase of 4 months compared to gemcitabine therapy [12]. Biliary stenting, gastric-intestinal or biliary-intestinal bypass procedures are other interventions used in the palliative treatment of pancreatic cancer. These procedures aim to provide the patient with the best possible quality of life and alleviate pain. The cornerstone of pain management is opioids, while in critical cases, celiac plexus neurolysis may be employed [28].

CONCLUSIONS

Malignant pancreatic tumors continue to pose a significant therapeutic challenge. Despite multicenter studies and the rapid advancement of both surgery and clinical oncology, the survival rates for pancreatic cancer have not been acceptably improved. A number of factors involved in the pathogenesis of pancreatic adenocarcinoma have been identified, which enables health promotion and appropriate screening for individuals with non-modifiable risk factors. Unfortunately, despite these advancements, the vast majority of patients are diagnosed at an advanced stage of cancer development. This negatively affects overall survival, which remains one of the poorest among all malignant tumors. New chemotherapy regimens are gradually extending patients' survival, yet it is still measured in months. Some hope arises from reports on novel therapies, such as immunotherapy, gene therapy, or treatments using monoclonal antibodies. Unfortunately, most of these studies are still in the clinical trial phase.

REFERENCES

1. Griffin JF, Poruk KE, Wolfgang CL. Pancreatic cancer surgery: past, present, and future. Chin J Cancer Res. 2015;27(4):332-48.
2. Nowotwory złośliwe w Polsce w 2021 roku [https://onkologia.org.pl/sites/default/files/publications/2024-01/0_krn-2023-book-2024-01-22.pdf] (access: 25.08.2024)
3. Raczyński I, Didkowska J, Radecka B. Zaawansowany rak trzustki – ewolucja w zakresie rozpoznawania i leczenia systemowego chorych w ostatnich dziesięcioleciach. Gastroenterolog Klin. 2022;14(3).
4. Lewandowski T, Stelmasiak P. Rak trzustki – wczesne rozpoznanie i prawidłowe leczenie. Po dyplomie. 2020;04:20.
5. Trends in seer incidence and U.S. mortality [https://seer.cancer.gov/archive/csr/1975_2004/results_merged/sect_22_pancreas.pdf] (access 31.08.2024)
6. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol. 2021;18(7):493-502.
7. Cause for concern: the rising incidence of early-onset pancreatic cancer. Lancet Gastroenterol Hepatol. 2023;8(4):287.
8. Zhao Z, Liu W. Pancreatic cancer: A review of risk factors, diagnosis, and treatment. Technol Cancer Res Treat. 2020;19:1533033820962117.
9. Sadr-Azodi O, Konings P, Brusselaers N. Menopausal hormone therapy and pancreatic cancer risk in women: a population-based matched cohort study. United European Gastroenterol J. 2017;5(8):1123-8.
10. Molina-Montes E, Van Hoogstraten L, Gomez-Rubio P, et al. PanGenEU study investigators. pancreatic cancer risk in relation to lifetime smoking patterns, tobacco type, and dose-response relationships. Cancer Epidemiol Biomarkers Prev. 2020;29(5):1009-18.
11. Yuan C, Morales-Oyarvide V, Babic A, et al. Cigarette smoking and pancreatic cancer survival. J Clin Oncol. 2017;35(16):1822-8.
12. McGuigan A, Kelly P, Turkington RC, et al. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846-61.
13. McLaurin N, Tabibi D, Wang T, et al. Coping with discrimination among African Americans with type 2 diabetes: Factor structure and associations with diabetes control, mental distress, and psychosocial resources. Prev Chronic Dis. 2024;21:230189.
14. El Jellas K, Hoem D, Hagen KG, et al. Associations between ABO blood groups and pancreatic ductal adenocarcinoma: influence on resection status and survival. Cancer Med. 2017;6(7):1531-40.
15. Yu H, Xu N, Li ZK, et al. Association of ABO blood groups and risk of gastric cancer. Scand J Surg. 2020;109(4):309-13.
16. Sun H, Saeedi P, Karuranga S, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
17. Amri F, Belkhayat C, Yeznasni A, et al. Association between pancreatic cancer and diabetes: insights from a retrospective cohort study. BMC Cancer. 2023;23(1):856.
18. Kwiatkowska M. Rak trzustki a cukrzyca. Med Prakt. 2017.
19. Singh N, Baby D, Rajguru JP, et al. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-6.
20. Le Cosquer G, Maulat C, Bournet B, et al. Pancreatic cancer in chronic pancreatitis: Pathogenesis and diagnostic approach. Cancers (Basel). 2023;15(3):761.
21. Wu M, Krishnamurthy K. Peutz-Jeghers Syndrome. StatPearls. 2023. https://www.ncbi.nlm.nih.gov/books/NBK535357/] (access: 26.08.2024)
22. Idachaba S, Dada O, Abimbola O, et al. A review of pancreatic cancer: Epidemiology, genetics, screening, and management. Open Access Maced J Med Sci. 2019;7(4):663-71.
23. Chen F, Roberts NJ, Klein AP. Inherited pancreatic cancer. Chin Clin Oncol. 2017;6(6):58.
24. Ansari D, Tingstedt B, Bodil Andersson, et al. Pancreatic cancer: Yesterday, today and tomorrow. Future Oncol. 2016;12(16):1929-46.
25. Gheorghe G, Bungau S, Ilie M, et al. Early diagnosis of pancreatic cancer: The key for survival. Diagnostics (Basel). 2020;10(11):869.
26. Charakterystyka i patogeneza świądu skóry w chorobach wątroby. [https://gastroenterologia-praktyczna.pl/a3549/Charakterystyka-i-patogeneza-swiadu-skory-w-chorobach-watroby.html] (access: 27.08.2024)
27. Żółtaczka [https://www.mp.pl/interna/chapter/B16.I.1.41] (access: 31.08.2024)
28. Potemski P, Polkowski W. Nowotwory układu pokarmowego zalecenia PTOK. [http://onkologia.zalecenia.med.pl/pdf/zalecenia_PTOK_tom1_04_Nowotwory_ukladu_pokarmowego_20151202.pdf] (access: 01.09.2024)
29. Zaanona M, Mantha S. Cancer-associated thrombosis. StatPearls; 2023.
30. Abdol Razak NB, Jones G, Bhandari M, et al. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. Cancers (Basel). 2018;10(10):380.
31. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers. 2022;8(1):11.
32. Liu H, Jiang M, Wu N, et al. A case of Trousseau syndrome: Screening, detection and complication. Open Life Sci. 2024;19(1):20220824.
33. Liu JW, Ma DL. An ominous sign from Sister Mary Joseph. Lancet. 2018;392(10149):776.
34. Tonini V, Zanni M. Pancreatic cancer in 2021: What you need to know to win. World J Gastroenterol. 2021;27(35):5851-89.
35. Torbiele trzustki [https://www.mp.pl/interna/chapter/B16.II.5.3] (access: 29.08.2024)
36. Strobel O, Hank T, Hinz U, et al. Pancreatic cancer surgery: The new r-status counts. Ann Surg. 2017;265(3):565-73.
37. Versteijne E, Vogel JA, Besselink MG, et al. Dutch pancreatic cancer group. Meta-analysis comparing upfront surgery with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic cancer. Br J Surg. 2018;105(8):946-58.

Corresponding author
Marcin Cholewa
Faculty of Medical Sciences, Medical University of Silesia in Katowice, Poland
e-mail: matremgm@gmail.com