Raczkiewicz Przemysław, Kalicka Maria, Korzec Tomasz, Kania Konrad, Cyboran Katarzyna. Diagnosis of the pancreatic cancer. Journal of Education, Health and Sport. 2021;11(9):67-73. eISSN 2391-8306. DOI http://dx.doi.org/10.12775/JEHS.2021.11.09.009
https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2021.11.09.009
https://zenodo.org/record/5457575

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 21.08.2021. Revised: 26.08.2021. Accepted: 05.09.2021.

Diagnosis of the pancreatic cancer

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Abstract

Introduction: The pancreatic cancer arises from non-invasive precursor lesions and develops through the accumulation of characteristic gene mutations. The recent scientific reports based on genetic tests state that the approximate time between cancerous initiation and the development of cancer with metastasisis15 years. We candistinguish three main precancerous lesions leading to the pancreatic cancer: pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN). The imaging tests used for the diagnostics and observation of precancerous pancreas lesions are MR, MRC, CT and EUS.

Method: review of the recent literature based on PubMEd, Google scholar research based onthe following key words: pancreatic cancer, precancer of the pancreas, pancreatic cyst, tuber of the pancreas, medical imaging of the pancreas

Purpose of the work: systematizing information about precancers of the pancreatic cancer based on the latest research and findings

Key words: precancer of the pancreas, pancreatic cyst, pancreatic cancer, pancreatic ductal adenocarcinoma

Introduction:

More than 200 000people in the world die annually because of the pancreatic cancer. The prognosis is not optimistic, since it is estimated that until 2030, the pancreatic cancer will become the second most common type of cancer causing deaths in the United States. The situation in Europe is similar. The following risk factors of the pancreatic cancer can be found in literature: positive family history, cigarette smoking, diabetes, obesity, chronic pancreatitis, genetic syndromes, such as: familial breast and ovarian cancer, familial atypical multiple mole melanoma syndrome, Peutz-Jeghers syndrome, hereditary pancreatitis, hereditary non-polyposis colorectal cancer–Lynch syndrome, familial pancreatic cancer, ataxia-telangiectasia[1].

State of knowledge:

The increasing rate of morbidity due to malignant tumours of the digestive tract, especially the pancreatic cancer, rises motivation for systematizing the knowledge about precancers which precede the development of the cancer[2]. The purpose of this review is to present the data about the nosogenesis, differential diagnosis and the newest recommendations for the diagnostics and monitoring of pancreas precancers.

The recent scientific reports based on genetic tests state that the approximate time between cancerous initiation and the development of cancer with metastasisis 15 years. It appears to be quite a lot of time for preventing the development of the cancer[3]. The pancreatic cancer arises from non-invasive precursor lesions and develops through the accumulation of characteristic gene mutations. The cancer can be located originally as the in situ lesion, most commonly in the pancreas head (60%), body (15%) or tail (5%). The remaining 20% of cases concern the disseminated variant o fpancreatic lesions. In the further part of this paper the notion of the pancreatic cancer is understood as the adenocarcinoma of the pancreas. Admittedly, there are other histologic types of the pancreatic cancer (adenomatous squamous cell carcinoma and undifferentiated cancer with giganticcells). However, they are unusually rare. The adenocarcinoma most commonly manifests itself late and that is why patients very often see the general practitioner when they experience advanced symptoms of the illness.

The following precancerous lesions ofthe pancreatic cancer are considered:

- Pancreatic intraepithelial neoplasia (PanIN)

- Mucinous cystic neoplasms (MCN),

- Intraductal papillary mucinous neoplasms (IPMN) [4].

PanIN– pancreatic intraepithelial neoplasm–is the most significant, well-known and the most frequent precursor of the pancreatic duodenal carcinoma. It is simply the intraepithelial

neoplasia of the pancreatic duct. The lesion is non-invasive and does not produce mucus. As the name itself suggests, **PanIN** develops in pancreatic ducts. Epithelium cells show radical shortening of telomeres in PanIN, which leads to the accumulation of additional chromosomal irregularities. Telomeres shorten as the cells age and the number of divisions of the cell increases. [4.5] Shortened telomeres lead to an abnormal merger of chromosomes causing the instability of the chromosomes, which fosters cancerous progression in the cells. We can distinguish 3 degrees of the atypia: PanIN-1, PanIN-2, and PanIN-3. PanIN-1A (flat) and PanIN-1B (papillary) are considered low-grade atypia, PanIN-2 is intermediate-grade atypia, PanIN-3 is high-grade atypia (Figure 1). It is often possible to find PanIN-3 as"carcinoma in situ". All the above-mentioned variants often come with the invasive cancer and the following mutations common for the pancreatic cancer are detected in them:

• activation of protooncogenes: KRAS

•inactivation of suppressor genes: BRCA1/BRCA2 (familial breast and ovarian cancer), CDKN2A/p16 (familial atypical multiple moles melanoma syndrome) – the p16 inactivation leads to irregularities in phase G1 of the cell cycle, DPC4 gene (located on chromosome 18q), encoding the SMAD4 protein which plays an important role in signalling through the transforming β growth factor (TGFβ).The SMAD4 path takes part in monitoring the growth through the regulation of the expressions of certain genes. Therefore SMAD4 loss causes the reduced growth inhibition, and hence it fosters the growth of cancer cells. TP53 gene –the suppressor gene – encodes the p53 protein which participates in the regulation of the cell cycle, impeding the G2/M phase of the cell cycle and the induction of the apoptosis. P53 loss causes the deregulation of the cell' s death and cell division processes.

• inactivation of the DNA repair genes: MLH1, MSH2 [5.6]

Changes of the PanINs type are not visible on CT (computed tomography) scans, or MRI (magnetic resonance imaging).Only using EUS (endoscopic ultrasound, endoscopic ultrasonography) it is possible to detect lobular atrophy of the pancreas as well as the PanINs or IPMN lesions, which is discussed in the further part of the paper[7].

Intraductalmucinous cystic neoplasm(IPMN) is the most frequent cystic cancer of the pancreas (PCN). Intraductal mucinous cystic neoplasm is a cancerous lesion which develops intraductally through the proliferation of verrucous cells that produce the mucin, and demonstrates different degrees of cancerous dysplasia. This constitutes a non-invasive precursor lesion and it develops through the accumulation of characteristic gene mutations. As mentioned above, KRAS, p16/CDKN2A, SMAD4 and TP53, as well as GNAS are common and specific to IPMN, and it appears that they play the key role in the activation of the signalling system of the G protein. [6]

The main threat associated with precancers of the pancreas is the risk of progression and transformation into the adenocarcinoma of the pancreas[4]. The IPMN was divided in two main subtypes :*main duct*– MD-IPMN, in which cancerous cysts interface with the main pancreatic duct, and *branch duct*– BD-IPMN, in which cancerous cysts interface with the branch of the main pancreatic duct[8]. It should be noted that there is a significant difference between the potential of the malicious progression between IPMN in the main duct(MD-

IPMN) and IPMN in the branch duct (BD-IPMN). Undoubtedly, the risk of progression in MD-IPMN is higher than in BD-IPMN [9]. The lesions are most commonly located in the head of the pancreas. They are usually diagnosed about the age of 65. The most frequent lesions are BD-IPMNs, and 21–41 % of such cases are multifocal. The progression to the focal point of invasive cancer is observed in 11–17% of BD-IPMNs, 44–48% of MD-IPMNs and 45% of the mixed-IPMNs. It is reflected in the results of surgical treatment: 91% of patients with BD-IPMNs, 65% patients with MD-IPMNs,and 77% patients with mixed IPMNsachieve five-year survival.

Mucinous cystic cancers are the rarest precursor lesions of pancreatic cancer. They constitute 25% of pancreatic cysts in patients undergoing the resection. MCNs are diagnosed significantly more often in the population of women. In a retrospective examination of 163 patients who underwent the resection of the pancreas because of MCN, a malignant tumour was confirmed in 17,5% of cases[10]. The lesions of this type are located in the body or tail of the pancreas. They grow slowly, and the inside of the cyst is filled with thick, sticky mucus. The cysts are lined with cylindrical, mucigenous epithelium. It is possible to divide the non-invasive MCNs into lesions with a low-grade dysplasia, intermediate dysplasia and high-grade dysplasia (Figure 1). The prognosis for patients with non-invasive MCN is very favourable (almost100 % of patients achieve five-year survival). In patients who undergo resection for the invasive MCN, the five-year survival rate is almost 60%. It is estimated that around⅓ of these cysts can develop into the adenocarcinoma. The pathogenesis of the MCNs has not been fully recognised yet. The KRAS mutation is more frequently found in the lesions with a low-grade dysplasia, and MCNs are slightly morefrequentin high-dysplastic lesions. The TP53, p16 and SMAD4/DPC4 mutationsare observed in high–grade dysplasiaas well as the lesions with an invasive cancer component. The examined MCNs did not contain the GNAS mutation, which gives some potential diagnostic opportunities for diversifying MCN and IPMN[6].

INVASIVE PANCREATIC CARCINOMA		
PanIN	IPMN	MCN
Pan IN- 1A/ PanIN- 1B	IPMN low- grade dyspasia	MCN low-grade dysplasia
PanIN-2	IPMN intermediate dyspasia	MCN intermediate dyspasia
PanIN-3	IPMN high-grade dyspasia	MCN high-grade Dysplasia
INVASIVE PANCREATIC CARCINOMA		

Figure 1. Differentiation of three pathways leading to invasive pancreatic canser, based on item No. 6 - bibliograpgy

We can distinguish a few methods of medical imaging applied in the diagnostics and observation of the pancreas precancers: MR (magnetic resonance), MRCP (magnetic resonance cholangiopancreatography), CT (computed tomography) and EUS (endoscopic ultrasonography). The majority of literature shows that MR and EUS are the most sensitive methods used for the detection of small cystic lesions. However, in terms of diversifying benign and malicious IPMN and MCN lesions, better diagnostic results are achieved using MRCPthan EUS. Moreover, MR/MRCP present greater sensitivity in displaying connections between cysts and the pancreatic duct as well as wall tumours. It can also determine whether there is one isolated lesion or many cancerous cysts[11].

CT imaging should be taken into consideration in the case of suspecting the post-operative recurrence of cancer, vascular lesions, metastasis to the peritoneum, diversifying cystic cancers of the pancreas from pseudocysts, and detection of parenchyma atrophy of the pancreas[12]. In terms of the supervision of patients with cystic precancers, CT is said to be of the similar diagnostic value as compared with MR. It is difficult, however, to reach the clear-cut agreement. Undoubtedly, the advantage of the MR method is the protection of patients fromionizingradiation, which cannot be avoided in the case of computed tomography. Using MR decreases the risk of developing the malignant tumour, especially inpatients who need to be examined with CT scanner repeatedly, as their precancers are observed for several years. However, the fact of diagnosing a precancer which can lead to a malignant tumour is much more advantageous than the risk of CT imaging itself. Therefore, the matter of the harmfulness of CT examination in this group of patients is left for further discussion.

Discussion:

In the differential diagnosis of cystic tumours of the pancreas, the significance of the endoscopic ultrasound scan (EUS) has been increasing. The advantage of this method is not the imaging itself, since CT or MR are more precise, but the possibility to do a fine-needle biopsyduring the examination. The fluid collected this way constitutes a material for further histopathological diagnostic testing. Thanks to the examination we can confirm, whether we encounter benign or invasive neoplastic lesion[13]. In serous cancerous tumours ,the levels of amylase and tumour markers, such as carcinoembryonic antigen (CEA) or 19-9 antigen, are not increased. There is also no mucin in the collected fluid. The level of 19-9 antigen in malignant cysts is higher as compared to benign lesions and it reaches222 ± 31.5 U/ml and 18.5 ± 1.9 U/ml[14] respectively. More precise measurement of lesions requires other examinations, such as computed tomography or magnetic resonance. The latter examination allows for more thorough recognition of the lesion’s cystic character.

Conclusions:

In conclusion, the above-presented literature review shows that the diagnostics of precancers of the pancreas is quite complicated and an unambiguous result of the diagnosis is very difficult to be achieved. The majority of lesions are diagnosed accidentally, during

medical imaging of the abdominal cavity. The diagnosis is often provided too late, when the lesions point to an advanced neoplastic disease. In these cases, such symptoms as pain complaints or weight loss are the reasons for the diagnostic testing. Unfortunately, there is no screening program for pancreatic cancer in Poland. It is probably caused by the fact that pancreatic cancer is relatively rare as compared to other types of cancer, e.g. breast cancer or colorectal cancer, which already have screening programs because of their high frequency. In spite of the rareness of the pancreatic cancer, it paradoxically is characterised by high mortality rates. Therefore, we hope that a screening program for pancreatic cancer will soon be carried out in Poland.

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