Medical Sciences 2021 Vol. 9 (2), p. 129-139

e-ISSN: 2345-0592
Online issue
Indexed in *Index Copernicus*

Medical Sciences

Official website:
www.medicsciences.com

Pancreatic cancer: diagnostics and surgical treatment. Is there anything new?

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Abstract

Pancreatic cancer (PC) is an intractable malignancy which more often occurs in more developed countries. PC has high mortality and morbidity rate, is fourth leading cause of cancer death worldwide. Symptoms depend on the localisation of the tumor, but there are no specific symptoms and that leads to late diagnosis. Carbohydrate 19-9 antigen (Ca 19-9) is the only marker used in clinical practice, but there are other biomarkers for earlier diagnosis at the research levels. The standard for PC diagnosis and staging is multi-detector computed tomography (MDCT). Surgical resection is the only potentially curative treatment for PC. Two main surgical methods are pacreaticoduodenectomy for tumors of the head of the pancreas and distal pancreatectomy for tumors localised in the tail or body of the pancreas. Minimally invasive surgery use is increasing, however, so far it does not have many advantages over open surgery.

Keywords: pancreatic cancer, biomarkers, cancerseek, pancreaticoduodenectomy.

1. Introduction

Pancreatic cancer (PC) is an intractable malignancy which more often occurs in higher-income countries. Pancreatic tumors are divided into two main groups: adenocarcinoma (90% of cases) and pancreatic endocrine tumors which are less common (less than 5%) [1, 2]. PC ranks 11th place among men's most common malignancies and, respectively, 12th place among women [3]. It is the fourth leading cause of cancer deaths worldwide. Approximately 57,600 new cases of PC and around 47,050 deaths were expected in 2020 in the USA [4]. The risk of developing of PC correlates with age: the majority of patients are older than 40 - 45 years and at diagnosis mean age is 70 years [5, 6]. Other risk factors include smoking, type 2 diabetes, high body mass index, family history, long-term alcohol use and chronic pancreatitis [1, 5, 7, 8]. The larger amounts of cases are diagnosed at advanced stages of PC when lymph nodes and other organs are already affected. The prognosis of 5-year survival rate is approximately 6% [8]. That shows how important it is to increase diagnostic and treatment abilities to reach greater survival rate. The purpose of this literature review is to summarize the main diagnostic and surgical treatment methods and to review the latest diagnostic findings.

2. Diagnostics

2.1. Symptoms

This section will review the symptoms caused by pancreatic adenocarcinoma (PAC), as it is, as mentioned earlier, the most common pancreatic tumor. In addition, the onset of initial symptoms depends on the location of the tumor. About two-thirds of PACs are localized in the head of the pancreas, about 20% in the body or tail and the rest involves whole organ [9-11]. However, the symptoms are nonspecific. The most frequent symptoms associate with constitutional syndrome: weight loss, anorexia, asthenia and cachexia [12]. The second most common symptom is abdominal pain. Tumors located in the head cause symptoms of the biliary tree obstruction as jaundice, pruritus, dark urine and pale stools [9, 10]. PACs in the body or tail of the pancreas rarely cause symptoms of obstruction. Patients commonly have such symptoms as pain in the epigastrium or back, early satiety, dyspepsia and weight loss [13]. The sudden onset of type 2 diabetes, which is hardly treated with medications in patients older than 50 years, may be a sign of PC [14]. The distribution of frequency of symptoms described in literature is shown in Table 1.

Table 1. Frequency of symptoms.

Symptom	Frequency
Weight loss	85 – 92%
Asthenia	86%
Anorexia	64 – 83%
Jaundice	56 – 82%
Abdominal pain	72 – 79%
Epigastric pain	71%
Dark urine	59 – 63%
Pale stool	62%
Nausea	43 – 51%
Back pain	49%
Diarrhea	44%
Weakness	35 – 42%
Vomiting	33 – 37%

2.2. Physical examination

Findings of physical examination also vary and depend on localisation of the tumor. The examination in early stages of the PAC is usually normal, without any changes. Biliary tract obstruction with jaundice, abdominal pain and cachexia occur in advanced stages of PAC located in the head of the pancreas [9, 15]. Enlarged, nontender gallbladder may be felt during palpation of the abdomen. Courvoisier's sign (painless jaundice and enlarged gallbladder) is quite specific (83 – 90%), but rare and only 26 – 55% sensitive, because most commonly pain also occurs [9, 15, 16]. Other findings include hepatomegaly, palpable mass at pancreas projection, enlarged supraclavicular (Virchow's node) or other lymph nodes and superficial migrantory thrombophlebitis (Trousseau's sign) [15 – 17]. Pancreatic panniculitis, known as nodular fat necrosis, manifestation in lower extremities is rare (up to 3%), but possible finding with acinar cell variant of PC [18].

2.3. Laboratory findings

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase and bilirubin tests have to be performed for patients who have developed jaundice, epigastric pain to assess for cholestasis [11, 19]. Also, for patients with epigastric pain, a test of serum lipase is important for differentiation with acute pancreatitis.

The aforementioned laboratory analytes may show changes induced by pancreatic cancer but are not specific. More specific is serum tumor marker carbohydrate 19-9 antigen (Ca 19-9). Ca 19-9 can be an additional factor in confirming the diagnosis in symptomatic patients or in helping to predict (1) tumor resectability (serum level < 200 U/ml – resectable tumor, >1000 U/ml – probably metastatic PC), (2) treatment efficacy

[20, 21]. However, literature sources provide that sensitivity and specificity of this cancer marker are only 50 – 81% and 82 – 90%, respectively, in symptomatic patients making it unreliable for the diagnosis or screening [13, 20, 21]. Also, there is a possibility for (1) false negative results in patients with a Lewis negative genotype, when Ca19-9 cannot be expressed (about 10% of the population) or (2) false positive results in cases of diabetes mellitus, chronic pancreatitis, cirrhosis, cholestasis and etc. [20, 22].

2.4. Imaging

First imaging test for patients with symptoms of PC is typically a transabdominal ultrasound (TUS), because of its low cost and high accessibility. TUS has high sensitivity and specificity of 88% and 94%, respectively for tumors larger than 3cm [11, 13, 23]. However, there are less sensitivity and specificity in smaller tumors. The standard for PC diagnosis and staging is multi-detector computed tomography (MDCT) which involves arterial, late and venous phases cross-sectional imaging [9]. MDCT is sufficient to detect pancreatic mass and metastases, is quite fast and more accessible than magnetic resonance imaging (MRI). Otherwise, MRI is as sensitive and specific as MDCT and is an alternative for people with allergy to contrast media. Also, it can detect isoattenuating pancreatic lesions, which are not or poorly visible at MDCT [9, 20, 23]. Endoscopic ultrasonography (EUS) should be performed if no lesions of the pancreas are visualized using imaging methods mentioned above and high suspicion of PC remains. This method excels by higher sensitivity of 80% detectioning small cancers (<1 cm) compared with MDCT and MRI [24, 25]. Fine needle aspiration (FNA) biopsy could be done during EUS. It is indicated for patients with unresectable tumor for decision on further treatment. As Robert Freelove and Anne D. Walling say, biopsy for resectable cancer is not necessary and patients can undergo surgery without preoperative histological conformation [13]. Another method is endoscopic retrograde cholangiopancreatography (ERCP), which is used to relieve cholestasis due to tumor obstruction by placing biliary stent. Also, forceps biopsy or brush cytology can be performed during the ERCP for histological diagnosis, but its sensitivity is lower than FNA biopsy's. However, bile duct stenting before CT scanning is not recommended, because it can cause inflammatory changes or artifacts and mask the tumor [11, 13, 20]. Magnetic resonance cholangiopancreatography (MRCP) can replace ERCP for patients with gastric outlet or duodenal stenosis [11, 26]. 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) can also be used for early detection and staging, but in the literature this method is still very controversial and not included in the systematic staging of PCA [20, 27]. The distribution of sensitivity and specificity of imaging modalities found in the literature is shown in Table 2.

Table 2. Sensitivity and specificity of imaging modalities for the diagnosis of PCA.

Imaging method	Sensitivity	Specificity
TUS	83 – 90%	87 – 99%
MDCT	89 – 97%	79 – 93%
MRI	88 – 96%	82 – 94%
EUS	87 – 94%	81 – 91%
ERCP	70 – 92%	94 – 96%
MRCP	84 – 91%	94 – 97%
FDG-PET	85 – 96%	54 – 84%

TUS – transabdominal ultrasound, MDCT – multi-detector computed tomography, MRI – magnetic resonance imaging, EUS – endoscopic ultrasonography, ERCP – endoscopic retrograde cholangiopancreatography, MRCP – magnetic resonance cholangiopancreatography, FDG-PET – 18-Fluorodeoxyglucose positron emission tomography.

2.5. New ways of biomarkers using

As mentioned above, Ca 19-9 is the only clinically used protein biomarker for PAC diagnosis. Though there are several studies who tested other biomarkers. One of them is carcinoembryonic antigen (CEA), which is found in serum of 30 – 60% of patients with PC [22, 28]. Sensitivity and specificity of CEA alone are of 45% and 75%, respectively. Ca 19-9 and CEA when used together increase specificity to 84% but decrease sensitivity to 37% [29]. Darragh P. O'Brien and co-authors in their study established that cancer antigen 125 (Ca 125) and Ca 19-9 combined together gave sensitivity and specificity of 56,7% and 90,6%, respectively, but there was no significant difference by using Ca 19-9 alone [30]. Also, CEA and Ca 125 biomarkers are one of the solutions for Lewis negative patients with PCA [31]. Another promising marker is macrophage inhibitory cytokine 1 which, as mentioned in literature, shows better differentiation between healthy patients and patients with resectable PAC comparing to Ca 19-9. Other prognostic biomarkers are osteopontin (OPN) and matrix metalloprotease which spread to the bloodstream because of PAC fibrotic stroma remodulation. Literature sources mention that the sensitivity and specificity of these markers are similar to Ca 19-9 and high levels associates with poor survival [22].

New blood test, called CancerSEEK, for early cancer detection was presented in 2018. It can detect eight most common human cancers types including cancer of pancreas [32, 33]. Tests consist of a combination of genetic marker - circulating tumor DNA (ctDNA) and eight protein markers (Ca 125, CEA, Ca 19-9, prolactin, hepatocyte growth factor, OPN, myeloperoxidase). A test could detect about 81% of PC, its sensitivity for PC is about 72%, specificity – 99% [34]. However, there is still a possibility for false positive results for individuals with comorbidities which can increase protein markers levels [33]. Also, as Alain R Thierry says, there is a possibility of overdiagnosis and overtreatment, because this test cannot predict the tumor's growing rate and foresee possible tumor's changes [32]. This test

looks very promising, but needs further investigation in larger, more various population.

3. Treatment

Surgical resection is the only potentially curative treatment for PAC. However, only 15-20% of patients can undergo this treatment because of late diagnosis of the disease [13, 35]. According to NCCN guidelines, tumors are resectable if there is no arterial tumor contact including celiax axis (CA), superior mesenteric aretry (SMA), common hepatic artery (CHA). Also, resectable tumors are with no contact with the superior mesenteric vein (SMV), portal vein (PV) or if there is <180° contact without vein contour irregularity. Borderline resectability is possible for solid tumor contact with CHA without extension to CA or hepatic artery bifurcation; solid tumor contact with the SMA of <180°; solid tumor contact with variant arterial anatomy; solid tumor contact with the CA <180° or >180° without involvement of the aorta. Furthermore, borderline resection can be applied for solid tumor contact with the inferior vena cava or solid tumor contact with SMV/PV of >180°, contact of <180° with contour irregularity of the vein or thrombosis of the vein but with suitable complete resection and vein reconstruction [36]. Resectable tumors of the head of the pancreas account for 20%, of the body and tail accounts for 5%. To achieve R0 resection is the main goal of the surgery [37, 38].

For PAC localized in the head of the pancreas the standard operation is pancreaticoduodenectomy (PD), also known as Whipple procedure [9]. It involves resection of pancreatic head, gallbladder, common bile duct, duodenum, part of jejunum and partial gastrectomy [9, 35]. There are some modified methods: pylorus-preserving PD to avoid postoperative dumping or subtotal stomach-preserving PD to preserve more stomach. One study found that patients who underwent stomach-preserving PD lived longer than patients who undergo PD or pylorus-preserving PD [39]. Also, there are two ways to reconstruct the integrity of the digestive tract after PD by anastomosing left part of pancreas to jejunum or stomach. However, there is no difference between these procedures [40]. Vascular resection has not been extensively studied, but in literature there are promising outcomes described for venous resection (VR) comparing to arterial resection. PD with VR comparing to PD alone has similar mortality rates, however PD with VR is associated with increased operative time and blood loss [41, 42].

Distal pancreatectomy with splenectomy is a typical surgery for tumors in the tail or body of the pancreas. However, as mentioned above, tumors in this localization are diagnosed only in advanced stages because they do not cause obstruction of the common bile duct, there are no early symptoms, so total resection of tumor is rare [35].

With the development of medicine, the use of minimally invasive surgeries for the treatment of pancreatic tumors has also increased. Laparoscopic or robotic-assisted pancreatectomy can also be performed. Patients who underwent laparoscopic PD comparing to those who underwent open PD have had shorter hospital stays, less blood loss and better survival rate of 3-5 years, postoperative complications rate was the same [43, 44]. Robotic PD results in longer operation duration, less blood loss and more lymph nodes harvested than open PD [45]. In the literature sources there was no significant

difference between robotic and laparoscopic methods [46]. All in all, further research is required to evaluate advantages of minimally invasive treatment.

4. Conclusion

Pancreatic cancer is a global problem due to its late diagnosis and poor 5-year survival rate. MDCT remains the main diagnostic method. However, there are promising findings in biomarkers, but further studies must be conducted. Surgical treatment is the only potentially curative treatment, but available just to a small portion of patients. Resectability is determined by special criteria. Pancreaticoduodenectomy is a standard operation for resectable tumors in the head of pancreas, distal pancreatectomy for – tumors in the body or tail of pancreas. The use of minimally invasive surgeries is increasing, because these operations result in less blood loss, shorter hospital stays, but there are no significant differences in complications, mortality and survivance rates comparing to open surgeries. Further studies must be conducted for treatment.

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