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Review Article

Diagnostic Challenges in Pancreatic Tumors

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Abstract

Background: Pancreatic tumors have a large diversity, with an increasing incidence and mortality. Although the diagnosis methods have improved in recent years, establishing a diagnosis and a histopathological type of pancreatic tumor can still pose a challenge.

Aim: We propose to present a concise list of difficulties regarding the clinical, biological, and imagistic diagnosis of pancreatic tumors.

Key information: The clinical manifestations of pancreatic tumors depend on their location and size, on the presence of metastatic lesions, but the difficulty of orientation towards this diagnosis is determined by the fact that most lesions are asymptomatic or present in the early stages of non-specific symptoms. The usual biological parameters are non-specific in pancreatic tumors in the early stages, but studies are underway regarding a series of biomarkers, genetic micro-sequences, or inorganic nanomaterials that could be used in the early diagnosis of pancreatic cancers. An essential stage in the diagnosis of pancreatic tumors is represented by imaging investigations, which are associated with endoscopic and tumor biopsy procedures and can outline a picture regarding the presence of the tumor at the level of the pancreas, the relationship with the neighboring organs, the nature of the tumor and the histopathological type. There are a series of indications and limitations regarding each of these investigations, trying to develop various algorithms for the diagnosis of pancreatic tumors.

Conclusion: The medical research conducted to develop new diagnostic procedures has the objective of ensuring an early diagnosis of pancreatic tumors, in a stage that offers the best chances of recovery for the patient.

Introduction

Pancreatic tumors can present a wide spectrum. Various classifications divide them into primitive or secondary tumors, benign or malignant tumors, solid, cystic, or mixed tumors, exocrine (epithelial), and endocrine or mixed-origin tumors.

Several clinical studies have highlighted an increase in both the incidence and mortality of pancreatic tumors [1-5]. Also, the advances made in recent years in medical imaging have led to more frequent discovery of these types of tumors [6,7]. However, establishing the diagnosis of a pancreatic tumor and its histopathological type can often prove difficult.

Diagnostic challenges in pancreatic tumors

Screening: Regarding the screening of pancreatic tumors, a higher risk for the development of pancreatic neoplasia has been demonstrated among patients with a family history of pancreatitis or pancreatic cancer [8-10], Peutz-Jeghers syndrome [11], hereditary nonpolyposis colorectal cancer (HNPCC) [12], familial syndrome of atypical nevi [13] or mutations of BRCA-2 gene [11,14-16]. However, patients from these risk groups represent only a small proportion of all pancreatic neoplasms, up to 5% - 10%, so screening using this algorithm is not feasible, and the efficiency/cost ratio is low [17,18]. Some studies have also been conducted on various screening methods regarding the correlation between pancreatic cancer and newly discovered diabetes [18-22], respectively glucose intolerance as an early manifestation of pancreatic cancer in a resectable stage [18,21,23-25].

Clinical diagnosis: The clinical manifestations of pancreatic tumors depend on their location and size, on the presence of metastatic lesions, but the difficulty of orientation towards this diagnosis is determined by the fact that most lesions are asymptomatic or present in the early stages non-specific symptoms such as abdominal

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pain, nausea, vomiting, fatigue, the differential diagnosis being imposed with a series of diseases from the biliary, gastroduodenal or cardiovascular areas [26-28]. Thus, the diagnosis of pancreatic tumors is made most of the time in advanced stages. In the case of malignant tumors, more than half of the patients present metastases and only approximately 8% of the tumors are localized [29].

Biological diagnosis: The usual biological parameters are non-specific in pancreatic tumors in the early stages, suggesting this diagnosis with the onset of the icteric syndrome in tumors located in the head of the pancreas, respectively with the appearance of protein depletion in the advanced stages. In pancreatic neoplasms, the most used marker is cancer antigen 19-9 (CA 19-9), with a sensitivity and specificity that can reach up to 90% in the case of symptomatic patients, values over 100 U/mL suggesting an unresectable tumor or the presence of metastatic disease [30,31]. Another use of this marker is the prognostic role in monitoring tumor recurrence after pancreatic resections. However, CA 19-9 is not used as a screening method, having a positive predictive value between 0.5% - 0.9% [32]. This marker can also be present in other inflammatory or obstructive hepatobiliary diseases, in other pancreatic diseases, as well as in various other cancers. In addition, in patients with a negative Lewis blood phenotype, CA 19-9 will have low values, even in advanced pancreatic neoplasms [17].

In case of suspicion of a pancreatic neuroendocrine tumor, a series of biological markers can be determined, such as chromogranin A, neuron-specific enolase, pancreatic polypeptide, human chorionic gonadotropin, alpha-fetoprotein, gastrin, insulin, glucagon, somatostatin or intestinal vasoactive peptide. They are not routinely analyzed, but they can guide the diagnosis of this type of tumors [33-36]. Currently, studies are underway regarding a series of biomarkers, genetic micro-sequences, or inorganic nanomaterials that could be used in the early diagnosis of pancreatic cancers [37-40]. One such example is the serum value of macrophage inhibitory cytokine 1 (MIC-1), which proved a high sensitivity for the diagnosis of pancreatic adenocarcinoma, especially in association with CA 19-9 values [17,41].

Imagistic diagnosis: An essential stage in the diagnosis of pancreatic tumors is represented by imaging investigations, which are associated with endoscopic and tumor biopsy procedures and can outline a picture regarding the presence of the tumor at the level of the pancreas, the relationship with the neighboring organs, the nature of the tumor and the histopathological type. There are a series of indications and limitations regarding each of these investigations, trying to develop various algorithms for the diagnosis of pancreatic tumors, such an example is highlighted in Figure 1.

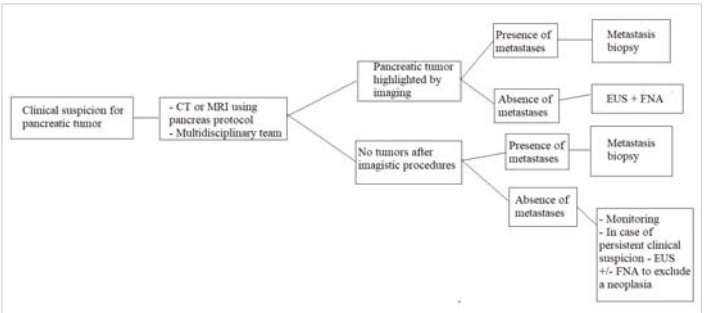

Figure 1: Algorithm for the diagnosis of pancreatic tumors; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EUS: Endoscopic Ultrasonography; FNA: Fine Needle Aspiration; reproduced after [17].

Numerous protocols and studies have suggested Computed Tomography as the first imaging investigation for the detection of pancreatic tumors, especially the multi-detector variant (MDCT) [17,42]. Pancreatic neoplastic lesions are described on the CT scan as poorly defined tumoral masses, which are enhanced less with contrast substance compared to the adjacent parenchyma. Other changes highly specific to pancreatic neoplasms include dilatation of the main bile duct, pancreatic contour abnormalities, distal pancreatic atrophy, disruptions/dilatations of the Wirsung duct, or pancreatic hypoattenuation [17,43]. Computer tomography is also useful for the staging of pancreatic neoplasms, especially regarding the involvement of the mesenteric artery and vein, as well as the celiac trunk, with implications on tumor resectability [44-47]. In addition, the CT scan can highlight the presence of peritoneal carcinomatosis, ascites, carcinomatous epiploitis, or pulmonary metastases [17,46].

Limitations of the CT scan include patients with renal impairment or risk of nephrotoxicity, as well as exposure to a significant radiation dose [17]. Also, the enhancement with contrast substance of the pancreatic parenchyma can be influenced by the concentration of the solution used, the injection rate, the age, the degree of obesity of the patient, or the presence of congestive heart failure [48].

Pancreatic lipomatosis, found especially in elderly patients with obesity or diabetes, can be seen as a focal hypodense mass on the CT scan, being difficult to differentiate from a malignant lesion, in which case the suggested exam is the abdominal MRI [49]. Also, chronic focal pancreatitis is often difficult to differentiate from pancreatic cancer on CT or MRI examinations and can be described as a mass that obstructs the bile or pancreatic duct. The investigations that can differentiate the two conditions are represented by EUS elastography and contrast-enhanced EUS, as well as EUS with FNA [44]. Another disease whose differential diagnosis with pancreatic cancer on the CT scan can be difficult to achieve is autoimmune pancreatitis, which usually has a diffuse pancreatic predisposition, but can also present as a localized pancreatic mass [44,50]. For differentiation, positron emission tomography (PET/CT)

using 18-fluorodeoxyglucose (18FDG) as a contrast agent, EUS with FNA [51,52], or serum levels of immunoglobulin 4 (Ig4) are used. Ig4 has a high specificity for autoimmune pancreatitis, with values usually at least twice the normal value, in contrast to pancreatic cancer, where Ig4 has slightly increased values in approximately 7% of cases [50,53]. In addition, unlike pancreatic cancer, autoimmune pancreatitis usually responds to steroid treatment [54].

The MRI examination can be used instead of computed tomography for the diagnosis of pancreatic tumors in patients with renal failure, with a history of allergy to iodinated contrast material, or as a second-line imaging investigation when there is a high clinical suspicion for a pancreatic lesion that is not detectable on CT scan. It also can provide additional information on hepatic tumors identified on the CT scan [17]. The MRI examination can detect early the presence of a pancreatic tumor, providing information on alterations of the pancreas or the Wirsung duct or information regarding local invasion, the specificity and sensitivity for pancreatic cancer being located at approximately 89% [55]. However, numerous studies have failed to show a clear benefit compared to CT examination, which is added to the high costs and more difficult accessibility compared to computed tomography [17]. In the context of the development of digital imaging techniques, a recent study suggested that the GRE (Gradient Echo Sequences) MRI exam, using 3D technology, combined with MR cholangiopancreatography (MRCP) would provide superior results to MDCT regarding pancreatic tumor detection and similar results regarding evaluation ot the resectability of a neoplastic lesion [56,57].

PET/CT with 18FDG has been shown to have no benefit in the usual diagnosis of pancreatic tumors compared to CT or MRI examinations [17]. Although it was hoped that it could differentiate chronic pancreatitis from neoplastic lesions, this was not the case due to similar uptake of the radiotracer in the two conditions [58]. The usefulness of PET/CT in pancreatic tumors is described in the detection of metastases, especially bone metastases [59], as well as in the tumor response to chemotherapy and radiotherapy, by measuring changes in radiotracer uptake before and after performing these procedures [60,61].

Although frequently used in the past, the role of endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of pancreatic tumors decreased with the development of imaging methods [62,63], having these investigations the supplementary risk of developing complications such as digestive perforations or acute pancreatitis [64]. There are currently several promising studies analyzing the obtaining of cytological samples during ERCP using an endoscopic naso-pancreatic tube, which is placed in the Wirsung canal, aspirating pancreatic juice repeatedly, a technique called SPACE ("serial pancreatic juice aspiration cytologic examination") [65-67].

Endoscopic ultrasound is another procedure used in the diagnosis of pancreatic tumors, thanks to the high-resolution images, being especially useful in small tumors [65]. Usual EUS has a sensitivity of 98% in the diagnosis of small pancreatic neoplasms, better compared to a sensitivity of 86% in computed tomography (p = 0.012) [68]. In particular, in the case of pancreatic tumors with a maximum diameter of 30 mm, EUS has a sensitivity of 93%, compared to the sensitivity of 67% of MRI or 53% of computed tomography [69]. Also, EUS has a better sensitivity than CT examination (67% *vs.* 41%, $p < 0.001$) in terms of local tumor staging [68], with the mention of a limitation regarding tumor invasion at the level of the superior mesenteric artery and vein due to their distance from the probe [70,71]. In the case of pancreatic neuroendocrine tumors, which are characterized by hypervascularization, EUS with a Doppler signal can be useful in establishing the diagnosis, unlike pancreatic adenocarcinoma, which usually presents local hypovascularization [63].

Elastography can be used to diagnose pancreatic tumors, [72,73], but is non-specific in the initial tumor stages due to the distribution of tissue elasticity [63,72]. Regarding the diagnosis of pancreatic cancer, various meta-analytic studies have highlighted a sensitivity of 95% - 97%, but with a specificity of only 67% - 76% [74,75].

EUS with intravenously administered contrast is a promising modality for the diagnosis of pancreatic tumors, with meta-analytic studies suggesting a sensitivity of 94% and a specificity of 89% for the diagnosis of pancreatic cancer [76]. This procedure may also be useful when there is a high risk of bleeding using fine needle aspiration [63].

EUS associated with pancreatic FNA is currently a common modality for the diagnosis of pancreatic tumors detected by other imaging methods such as CT or MRI. Recent studies suggest a sensitivity of 86% - 91% and a specificity of 94% - 99% for the diagnosis of a pancreatic mass [77-79]. In addition, the superiority of FNA using EUS compared to FNA using abdominal ultrasound was found in terms of the quality of the samples obtained, the rate of complications being similar [80]. There are also several limitations of this procedure, regarding the type of needle used, the experience of the endoscopist, or the presence of a pathologist to perform an extemporaneous histopathological examination [63].

Conclusion

Pancreatic tumors present a diagnostic challenge, both in tumoral detection and in establishing a histopathological type.

Clinical manifestations and usual biological parameters are non-specific in early tumoral stages, but several markers are currently studied regarding the early diagnosis

of pancreatic cancer. Imagistic diagnostic procedures encompass computer tomography, magnetic resonance imaging, and endoscopic ultrasound with fine needle aspiration, but each of them has certain limitations and diagnostic algorithms have been proposed.

The medical research conducted to develop new diagnostic procedures has the objective of ensuring an early diagnosis of pancreatic tumors, in a stage that offers the best chances of recovery for the patient.

References

1. Wu W, He X, Yang L, Wang Q, Bian X, Ye J, Li Y, Li L. Rising trends in pancreatic cancer incidence and mortality in 2000-2014. Clin Epidemiol. 2018 Jul 9;10:789-797. doi: 10.2147/CLEP.S160018. PMID: 30022856; PMCID: PMC6042490.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017 Jan;67(1):7-30. doi: 10.3322/caac.21387. Epub 2017 Jan 5. PMID: 28055103.
3. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016 Nov 28;22(44):9694-9705. doi: 10.3748/wjg.v22.i44.9694. PMID: 27956793; PMCID: PMC5124974.
4. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019 Feb;10(1):10-27. doi: 10.14740/wjon1166. Epub 2019 Feb 26. PMID: 30834048; PMCID: PMC6396775.
5. Klein A. Pancreatic cancer: a growing burden. The Lancet - Gastroenterology and Hepatoloy 2019; 4(12):895-6.
6. Dumitrascu T. Tumorile pancreatice. In: Beuran M, Patrascu T, editors. Curs de chirurgie pentru studentii din anul IV si V. 2 ed. Bucuresti: Editura Universitara Carol Davila. 2020; 315-40.
7. Buchler M. Neoplasms of the pancreas. In: Buchler M, Uhl W, Malfertheiner P, Sarr M, editors. Diseases of the pancreas. Karger. 2004; 125-67.
8. Copur MS, Talmon GA, Wedel W, Hart JD, Merani S, Vargasi LM. Hereditary vs Familial Pancreatic Cancer: Associated Genetic Syndromes and Clinical Perspective. Oncology (Williston Park). 2020 Jun 10;34(6):196-201. PMID: 32609864.
9. Ma DM, Dong XW, Han X, Ling Z, Lu GT, Sun YY, Yin XD. Pancreatitis and Pancreatic Cancer Risk. Technol Cancer Res Treat. 2023 Jan-Dec;22:15330338231164875. doi: 10.1177/15330338231164875. PMID: 36972517; PMCID: PMC10052482.
10. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA. 2001 Jul 11;286(2):169-70. doi: 10.1001/jama.286.2.169. PMID: 11448279.
11. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, Gerdes B, Kress R, Ziegler A, Raeburn JA, Campra D, Grützmann R, Rehder H, Rothmund M, Schmiegel W, Neoptolemos JP, Bartsch DK. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003 Feb 5;95(3):214-21. doi: 10.1093/jnci/95.3.214. PMID: 12569143.
12. Koornstra JJ, Mourits MJ, Sijmons RH, Leliveld AM, Hollema H, Kleibeuker JH. Management of extracolonic tumours in patients with Lynch syndrome. Lancet Oncol. 2009 Apr;10(4):400-8. doi: 10.1016/S1470-2045(09)70041-5. PMID: 19341971.
13. Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, Fontaine LS, Organic SM, Dracopoli NC, Clark WH Jr, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med. 1995 Oct 12;333(15):970-4. doi: 10.1056/NEJM199510123331504. PMID: 7666916.
14. Goggins M, Schutte M, Lu J, Moskaluk CA, Weinstein CL, Petersen GM, Yeo CJ, Jackson CE, Lynch HT, Hruban RH, Kern SE. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996 Dec 1;56(23):5360-4. PMID: 8968085.
15. Ozçelik H, Schmocker B, Di Nicola N, Shi XH, Langer B, Moore M, Taylor BR, Narod SA, Darlington G, Andrulis IL, Gallinger S, Redston M. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. Nat Genet. 1997 May;16(1):17-8. doi: 10.1038/ng0597-17. PMID: 9140390.
16. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, Hruban RH, Kern SE. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res. 2002 Jul 1;62(13):3789-93. PMID: 12097290.
17. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. World J Gastroenterol. 2018 May 21;24(19):2047-2060. doi: 10.3748/wjg.v24.i19.2047. PMID: 29785074; PMCID: PMC5960811.
18. Chari ST. Detecting early pancreatic cancer: problems and prospects. Semin Oncol. 2007 Aug;34(4):284-94. doi: 10.1053/j.seminoncol.2007.05.005. PMID: 17674956; PMCID: PMC2680914.
19. Noy A, Bilezikian JP. Clinical review 63: Diabetes and pancreatic cancer: clues to the early diagnosis of pancreatic malignancy. J Clin Endocrinol Metab. 1994 Nov;79(5):1223-31. doi: 10.1210/jcem.79.5.7962312. PMID: 7962312.
20. Gullo L, Pezzilli R, Morselli-Labate AM; Italian Pancreatic Cancer Study Group. Diabetes and the risk of pancreatic cancer. N Engl J Med. 1994 Jul 14;331(2):81-4. doi: 10.1056/NEJM199407143310203. PMID: 8208269.
21. Permert J, Ihse I, Jorfeldt L, von Schenck H, Arnqvist HJ, Larsson J. Pancreatic cancer is associated with impaired glucose metabolism. Eur J Surg. 1993 Feb;159(2):101-7. PMID: 8098623.
22. Jain M, Howe GR, St Louis P, Miller AB. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. Int J Cancer. 1991 Feb 1;47(3):384-9. doi: 10.1002/ijc.2910470313. PMID: 1993545.
23. Tsuchiya R, Noda T, Harada N, Miyamoto T, Tomioka T, Yamamoto K, Yamaguchi T, Izawa K, Tsunoda T, Yoshino R, et al. Collective review of small carcinomas of the pancreas. Ann Surg. 1986 Jan;203(1):77-81. doi: 10.1097/00000658-198601000-00013. PMID: 3942423; PMCID: PMC1251042.
24. Cersosimo E, Pisters PW, Pesola G, McDermott K, Bajorunas D, Brennan MF. Insulin secretion and action in patients with pancreatic cancer. Cancer. 1991 Jan 15;67(2):486-93. doi: 10.1002/1097-0142(19910115)67:2<486::aid-cncr2820670228>3.0.co;2-1. PMID: 1985741.
25. Chari ST, Klee GG, Miller LJ, Raimondo M, DiMagno EP. Islet amyloid polypeptide is not a satisfactory marker for detecting pancreatic cancer. Gastroenterology. 2001 Sep;121(3):640-5. doi: 10.1053/gast.2001.27210. PMID: 11522748.
26. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. Am Fam Physician. 2006 Feb 1;73(3):485-92. PMID: 16477897.
27. DiMagno E. Cancer of the pancreas and biliary tract. In: Winawer S, editor. Management of gastrointestinal diseases.New York: Gower Medical Publishing; 1992; 1-37.
28. Tomasello G, Ghidini M, Costanzo A, Ghidini A, Russo A, Barni S, Passalacqua R, Petrelli F. Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies. J Gastrointest Oncol. 2019 Apr;10(2):259-269. doi: 10.21037/jgo.2018.12.08. PMID: 31032093; PMCID: PMC6465486.
29. Jemal A, Tiwari RC, Murray T, Ghafoor A, Samuels A, Ward E, Feuer EJ, Thun MJ; American Cancer Society. Cancer statistics, 2004. CA Cancer J Clin. 2004 Jan-Feb;54(1):8-29. doi: 10.3322/canjclin.54.1.8. PMID: 14974761.

30. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol. 2012 Jun;3(2):105-19. doi: 10.3978/j.issn.2078-6891.2011.021. PMID: 22811878; PMCID: PMC3397644.

31. Huang Z, Liu F. Diagnostic value of serum carbohydrate antigen 19-9 in pancreatic cancer: a meta-analysis. Tumour Biol. 2014 Aug;35(8):7459-65. doi: 10.1007/s13277-014-1995-9. Epub 2014 May 1. PMID: 24789274.

32. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, Pinto E, Roviello F. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg. 2009 Sep;198(3):333-9. doi: 10.1016/j.amjsurg.2008.12.031. Epub 2009 Apr 17. PMID: 19375064.

33. Bocchini M, Nicolini F, Severi S, Bongiovanni A, Ibrahim T, Simonetti G, Grassi I, Mazza M. Biomarkers for Pancreatic Neuroendocrine Neoplasms (PanNENs) Management-An Updated Review. Front Oncol. 2020 May 27;10:831. doi: 10.3389/fonc.2020.00831. PMID: 32537434; PMCID: PMC7267066.

34. Sansone A, Lauretta R, Vottari S, Chiefari A, Barnabei A, Romanelli F, Appetecchia M. Specific and Non-Specific Biomarkers in Neuroendocrine Gastroenteropancreatic Tumors. Cancers (Basel). 2019 Aug 4;11(8):1113. doi: 10.3390/cancers11081113. PMID: 31382663; PMCID: PMC6721814.

35. Walter T, Chardon L, Chopin-laly X, Raverot V, Caffin AG, Chayvialle JA, Scoazec JY, Lombard-Bohas C. Is the combination of chromogranin A and pancreatic polypeptide serum determinations of interest in the diagnosis and follow-up of gastro-entero-pancreatic neuroendocrine tumours? Eur J Cancer. 2012 Aug;48(12):1766-73. doi: 10.1016/j.ejca.2011.11.005. Epub 2011 Nov 29. PMID: 22133573.

36. Perry RR, Vinik AI. Clinical review 72: diagnosis and management of functioning islet cell tumors. J Clin Endocrinol Metab. 1995 Aug;80(8):2273-8. doi: 10.1210/jcem.80.8.7629220. PMID: 7629220.

37. Ni XG, Bai XF, Mao YL, Shao YF, Wu JX, Shan Y, Wang CF, Wang J, Tian YT, Liu Q, Xu DK, Zhao P. The clinical value of serum CEA, CA19-9, and CA242 in the diagnosis and prognosis of pancreatic cancer. Eur J Surg Oncol. 2005 Mar;31(2):164-9. doi: 10.1016/j.ejso.2004.09.007. PMID: 15698733.

38. O'Brien DP, Sandanayake NS, Jenkinson C, Gentry-Maharaj A, Apostolidou S, Fourkala EO, Camuzeaux S, Blyuss O, Gunu R, Dawnay A, Zaikin A, Smith RC, Jacobs IJ, Menon U, Costello E, Pereira SP, Timms JF. Serum CA19-9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. Clin Cancer Res. 2015 Feb 1;21(3):622-31. doi: 10.1158/1078-0432.CCR-14-0365. Epub 2014 Jun 17. PMID: 24938522; PMCID: PMC4181906.

39. Madhavan B, Yue S, Galli U, Rana S, Gross W, Müller M, Giese NA, Kalthoff H, Becker T, Büchler MW, Zöller M. Combined evaluation of a panel of protein and miRNA serum-exosome biomarkers for pancreatic cancer diagnosis increases sensitivity and specificity. Int J Cancer. 2015 Jun 1;136(11):2616-27. doi: 10.1002/ijc.29324. Epub 2014 Nov 25. PMID: 25388097.

40. Yang F, Jin C, Subedi S, Lee CL, Wang Q, Jiang Y, Li J, Di Y, Fu D. Emerging inorganic nanomaterials for pancreatic cancer diagnosis and treatment. Cancer Treat Rev. 2012 Oct;38(6):566-79. doi: 10.1016/j.ctrv.2012.02.003. PMID: 22655679.

41. Koopmann J, Buckhaults P, Brown DA, Zahurak ML, Sato N, Fukushima N, Sokoll LJ, Chan DW, Yeo CJ, Hruban RH, Breit SN, Kinzler KW, Vogelstein B, Goggins M. Serum macrophage inhibitory cytokine 1 as a marker of pancreatic and other periampullary cancers. Clin Cancer Res. 2004 Apr 1;10(7):2386-92. doi: 10.1158/1078-0432.ccr-03-0165. PMID: 15073115.

42. Al-Hawary M, Francis I, Chari S, Fishman E, Hough D, Lu D. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014; 270:248-60.

43. Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. Eur Radiol. 2009 Oct;19(10):2448-55. doi: 10.1007/s00330-009-1422-6. Epub 2009 May 5. PMID: 19415290.

44. Raman SP, Horton KM, Fishman EK. Multimodality imaging of pancreatic cancer-computed tomography, magnetic resonance imaging, and positron emission tomography. Cancer J. 2012 Nov-Dec;18(6):511-22. doi: 10.1097/PPO.0b013e318274a461. PMID: 23187837.

45. Yang R, Lu M, Qian X, Chen J, Li L, Wang J, Zhang Y. Diagnostic accuracy of EUS and CT of vascular invasion in pancreatic cancer: a systematic review. J Cancer Res Clin Oncol. 2014 Dec;140(12):2077-86. doi: 10.1007/s00432-014-1728-x. Epub 2014 Jun 11. PMID: 24916170.

46. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol. 2008 Dec;6(12):1301-8. doi: 10.1016/j.cgh.2008.09.014. Epub 2008 Sep 27. PMID: 18948228.

47. Bockhorn M, Uzunoglu FG, Adham M, Imrie C, Milicevic M, Sandberg AA, Asbun HJ, Bassi C, Büchler M, Charnley RM, Conlon K, Cruz LF, Dervenis C, Fingerhutt A, Friess H, Gouma DJ, Hartwig W, Lillemoe KD, Montorsi M, Neoptolemos JP, Shrikhande SV, Takaori K, Traverso W, Vashist YK, Vollmer C, Yeo CJ, Izbicki JR; International Study Group of Pancreatic Surgery. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014 Jun;155(6):977-88. doi: 10.1016/j.surg.2014.02.001. Epub 2014 Feb 7. PMID: 24856119.

48. Brennan DD, Zamboni GA, Raptopoulos VD, Kruskal JB. Comprehensive preoperative assessment of pancreatic adenocarcinoma with 64-section volumetric CT. Radiographics. 2007 Nov-Dec;27(6):1653-66. doi: 10.1148/rg.276075034. PMID: 18025509.

49. Kim HJ, Byun JH, Park SH, Shin YM, Kim PN, Ha HK, Lee MG. Focal fatty replacement of the pancreas: usefulness of chemical shift MRI. AJR Am J Roentgenol. 2007 Feb;188(2):429-32. doi: 10.2214/AJR.05.1095. PMID: 17242252.

50. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. Lancet. 2016 Jul 2;388(10039):73-85. doi: 10.1016/S0140-6736(16)00141-0. Epub 2016 Jan 30. PMID: 26830752.

51. Lee TY, Kim MH, Park DH, Seo DW, Lee SK, Kim JS, Lee KT. Utility of 18F-FDG PET/CT for differentiation of autoimmune pancreatitis with atypical pancreatic imaging findings from pancreatic cancer. AJR Am J Roentgenol. 2009 Aug;193(2):343-8. doi: 10.2214/AJR.08.2297. PMID: 19620430.

52. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009 Oct;7(10):1097-103. doi: 10.1016/j.cgh.2009.04.020. Epub 2009 May 4. PMID: 19410017.

53. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS, Farnell MB. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol. 2007 Aug;102(8):1646-53. doi: 10.1111/j.1572-0241.2007.01264.x. Epub 2007 Jun 6. PMID: 17555461.

54. Kamisawa T, Imai M, Yui Chen P, Tu Y, Egawa N, Tsuruta K, Okamoto A, Suzuki M, Kamata N. Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. Pancreas. 2008 Oct;37(3):e62-7. doi: 10.1097/MPA.0b013e318175e3a0. PMID: 18815540.

55. Treadwell JR, Zafar HM, Mitchell MD, Tipton K, Teitelbaum U, Jue J. Imaging Tests for the Diagnosis and Staging of Pancreatic Adenocarcinoma: A Meta-Analysis. Pancreas. 2016 Jul;45(6):789-95. doi: 10.1097/MPA.0000000000000524. PMID: 26745859.

56. Jeong M, Jeong H. Imaging diagnosis of pancreatic cancer: CT and MRI. In: Kim S, Yamaue H, editors. Pancreatic cancer - With special focus on topical issues and surgical techniques. Springer. 2017; 95-114.

57. Park HS, Lee JM, Choi HK, Hong SH, Han JK, Choi BI. Preoperative evaluation of pancreatic cancer: comparison of gadolinium-enhanced dynamic MRI with MR cholangiopancreatography versus MDCT. J Magn Reson Imaging. 2009 Sep;30(3):586-95. doi: 10.1002/jmri.21889. PMID: 19711405.

58. Kato K, Nihashi T, Ikeda M, Abe S, Iwano S, Itoh S, Shimamoto K, Naganawa S. Limited efficacy of (18)F-FDG PET/CT for differentiation between metastasis-free pancreatic cancer and mass-forming pancreatitis. Clin Nucl Med. 2013 Jun;38(6):417-21. doi: 10.1097/RLU.0b013e3182817d9d. PMID: 23486318.

59. Okano K, Kakinoki K, Akamoto S, Hagiike M, Usuki H, Yamamoto Y, Nishiyama Y, Suzuki Y. 18F-fluorodeoxyglucose positron emission tomography in the diagnosis of small pancreatic cancer. World J Gastroenterol. 2011 Jan 14;17(2):231-5. doi: 10.3748/wjg.v17.i2.231. PMID: 21245997; PMCID: PMC3020378.

60. Kittaka H, Takahashi H, Ohigashi H, Gotoh K, Yamada T, Tomita Y, Hasegawa Y, Yano M, Ishikawa O. Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in predicting the pathologic response to preoperative chemoradiation therapy in patients with resectable T3 pancreatic cancer. World J Surg. 2013 Jan;37(1):169-78. doi: 10.1007/s00268-012-1775-x. PMID: 22955953.

61. Choi M, Heilbrun LK, Venkatramanamoorthy R, Lawhorn-Crews JM, Zalupski MM, Shields AF. Using 18F-fluorodeoxyglucose positron emission tomography to monitor clinical outcomes in patients treated with neoadjuvant chemo-radiotherapy for locally advanced pancreatic cancer. Am J Clin Oncol. 2010 Jun;33(3):257-61. doi: 10.1097/COC.0b013e3181a76a0b. PMID: 19806035; PMCID: PMC3848057.

62. Ogawa T, Kawamoto H, Harada R, Kurihara N, Kato H, Hirao K, et al. EUS-FNA is more advantageous than ERCP in tissue sampling for pathological diagnosis of pancreatic cancer. Gastrointest Endosc 2009; 69:S258.

63. Itoi T, Sofuni A. Endoscopic diagnosis. In: Kim S, Yamaue H, editors. Pancreatic cancer - With special focus on topical issues and surgical techniques. Springer; 2017. 115-22.

64. Adamek HE, Albert J, Breer H, Weitz M, Schilling D, Riemann JF. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. Lancet. 2000 Jul 15;356(9225):190-3. doi: 10.1016/S0140-6736(00)02479-X. PMID: 10963196.

65. Satoh T, Kikuyama M, Kawaguchi S, Kanemoto H, Muro H, Hanada K. Acute pancreatitis-onset carcinoma in situ of the pancreas with focal fat replacement diagnosed using serial pancreatic-juice aspiration cytologic examination (SPACE). Clin J Gastroenterol. 2017 Dec;10(6):541-545. doi: 10.1007/s12328-017-0776-6. Epub 2017 Oct 6. PMID: 28986726.

66. Hanada K, Okazaki A, Hirano N, Izumi Y, Teraoka Y, Ikemoto J, Kanemitsu K, Hino F, Fukuda T, Yonehara S. Diagnostic strategies for early pancreatic cancer. J Gastroenterol. 2015 Feb;50(2):147-54. doi: 10.1007/s00535-014-1026-z. Epub 2014 Dec 14. PMID: 25501287.

67. Mikata R, Ishihara T, Tada M, Tawada K, Saito M, Kurosawa J, Sugiyama H, Sakai Y, Tsuyuguchi T, Miyazaki M, Yokosuka O. Clinical usefulness of repeated pancreatic juice cytology via endoscopic naso-pancreatic drainage tube in patients with pancreatic cancer. J Gastroenterol. 2013 Jul;48(7):866-73. doi: 10.1007/s00535-012-0684-y. Epub 2012 Oct 10. PMID: 23053424.

68. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, Ciaccia D, Lane KA, Maglinte D, Kopecky K, LeBlanc J, McHenry L, Madura J, Aisen A, Cramer H, Cummings O, Sherman S. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004 Nov 16;141(10):753-63. doi: 10.7326/0003-4819-141-10-200411160-00006. PMID: 15545675.

69. Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. 1994 Mar;190(3):745-51. doi: 10.1148/radiology.190.3.8115622. PMID: 8115622.

70. Faigel DO, Kochman ML. The role of endoscopic ultrasound in the preoperative staging of pancreatic malignancies. Gastrointest Endosc. 1996 Jun;43(6):626-8. doi: 10.1016/s0016-5107(96)70206-7. PMID: 8781948.

71. Aslanian H, Salem R, Lee J, Andersen D, Robert M, Topazian M. EUS diagnosis of vascular invasion in pancreatic cancer: surgical and histologic correlates. Am J Gastroenterol. 2005 Jun;100(6):1381-5. doi: 10.1111/j.1572-0241.2005.41675.x. PMID: 15929774.

72. Itokawa F, Itoi T, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Umeda J, Tanaka R, Yokoyama N, Moriyasu F, Kasuya K, Nagao T, Kamisawa T, Tsuchida A. EUS elastography combined with the strain ratio of tissue elasticity for diagnosis of solid pancreatic masses. J Gastroenterol. 2011 Jun;46(6):843-53. doi: 10.1007/s00535-011-0399-5. Epub 2011 Apr 20. PMID: 21505859.

73. Săftoiu A, Vilmann P, Gorunescu F, Janssen J, Hocke M, Larsen M, Iglesias-Garcia J, Arcidiacono P, Will U, Giovannini M, Dietrich CF, Havre R, Gheorghe C, McKay C, Gheonea DI, Ciurea T; European EUS Elastography Multicentric Study Group. Efficacy of an artificial neural network-based approach to endoscopic ultrasound elastography in diagnosis of focal pancreatic masses. Clin Gastroenterol Hepatol. 2012 Jan;10(1):84-90.e1. doi: 10.1016/j.cgh.2011.09.014. Epub 2011 Oct 1. PMID: 21963957.

74. Ying L, Lin X, Xie ZL, Hu YP, Tang KF, Shi KQ. Clinical utility of endoscopic ultrasound elastography for identification of malignant pancreatic masses: a meta-analysis. J Gastroenterol Hepatol. 2013 Sep;28(9):1434-43. doi: 10.1111/jgh.12292. PMID: 23731128.

75. Mei M, Ni J, Liu D, Jin P, Sun L. EUS elastography for diagnosis of solid pancreatic masses: a meta-analysis. Gastrointest Endosc. 2013 Apr;77(4):578-89. doi: 10.1016/j.gie.2012.09.035. Epub 2012 Nov 27. PMID: 23199646.

76. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. Gastrointest Endosc. 2012 Aug;76(2):301-9. doi: 10.1016/j.gie.2012.02.051. Epub 2012 Jun 15. PMID: 22703697.

77. Puli SR, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: A meta-analysis and systematic review. Pancreas. 2013 Jan;42(1):20-6. doi: 10.1097/MPA.0b013e3182546e79. PMID: 23254913.

78. Chen G, Liu S, Zhao Y, Dai M, Zhang T. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer: a meta-analysis. Pancreatology. 2013 May-Jun;13(3):298-304. doi: 10.1016/j.pan.2013.01.013. Epub 2013 Feb 10. PMID: 23719604.

79. Hébert-Magee S, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, Eltoum IA. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. Cytopathology. 2013 Jun;24(3):159-71. doi: 10.1111/cyt.12071. PMID: 23711182; PMCID: PMC4159090.

80. Matsuyama M, Ishii H, Kuraoka K, Yukisawa S, Kasuga A, Ozaka M, Suzuki S, Takano K, Sugiyama Y, Itoi T. Ultrasound-guided vs endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer diagnosis. World J Gastroenterol. 2013 Apr 21;19(15):2368-73. doi: 10.3748/wjg.v19.i15.2368. PMID: 23613631; PMCID: PMC3631989.

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