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Review Article

Early pancreatic cancer — The role of endoscopic ultrasound with or without tissue acquisition in diagnosis and staging

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ABSTRACT

Pancreatic cancer (PC) is one of the deadliest cancers with a 5-year overall survival of less than 6%. Due to its insidious clinical course and unspecific symptoms, the diagnosis is usually late, with only 15–20% patients presenting with potentially curable disease. It is, therefore, extremely important to identify patients with PC at early stages of the disease when tumors may be amenable to surgical resection. For unresectable and borderline resectable PC it is consensual to perform a biopsy to have a cyto/histological confirmation of malignancy before treatment. However, for patients presenting with promptly resectable disease, the role of biopsy is more debatable. There are, in the literature, arguments both for and against the usefulness of a preoperative biopsy. Endoscopic ultrasound (EUS) is an important technique assisting in the diagnosis and staging of PC. EUS-guided tissue acquisition is a well-established tool to demonstrate the malignant nature of a pancreatic lesion. This review focuses on the role of EUS in the diagnosis and staging of PC, and highlights the controversy related to the role of EUS-guided tissue acquisition in the preoperative assessment of patients presenting with promptly resectable tumors (early PC).

1. Introduction

Pancreatic cancer (PC) is a fatal disease with a 5-year overall survival of less than 6% [1,2]. A recent European study showed that PC is the fourth leading cause of cancer-related death in men and women [3,4]. Over the last 20 years, prognosis of PC has not improved, with 49,000 new diagnoses and 41,000 deaths in the United States in 2015 and a rising number of deaths in Europe, from 75,439 in 2009 to 82,300 in 2014 [2,4]. It is estimated that PC will become the second leading cause of cancer-related death in the United States during the next decade [5].

The dismal prognosis of PC mostly stems from the late stage at which PC is usually diagnosed. Indeed, only 15–20% of patients present with potentially resectable tumors [4,6]. Cancer-related symptoms, such as weight loss, abdominal pain, nausea and vomiting, changes in bowel habits and jaundice, occur only at an advanced stage. New-onset diabetes is common in patients with PC, usually manifesting during preclinical or early stages of PC. Although still controversial, it is possible that it may serve as clue for the early detection of PC [1,4].

There is no single definition of early PC. It may be defined based on resectability, size or curability. A restricted definition is related to the concept of maximum curability of the disease, defining it as minute (<=10 mm) well differentiated stage I lesions. A broader definition that is generally accepted considers a small (<20 mm) localized lesion, promptly eligible for surgical resection [7]. Resectable PC is defined when there is no distant metastasis and no evidence of superior mesenteric vein or portal vein distortion or absence of clear fat planes around celiac axis, hepatic artery and superior mesenteric artery. On the other hand, borderline resectable and locally advance PC is defined by the presence of variable degree of invasion of surrounding structures, such as superior mesenteric vein, portal vein, confluence, duodenal wall, gastric wall and/or biliary system. Patients presenting with this group of lesions are nowadays candidates to neoadjuvant chemotherapy with or without radiotherapy with the aim of downstaging for future resectability [8,9]. Lastly, non-resectable and/or metastatic disease are by far the most common presentations. In these last scenarios a definitive cyto/histological diagnosis is mandatory before oncological treatment is started. However, there is controversy in case of patients with promptly resectable PC. The question is whether a pre-surgical biopsy is always necessary.

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Over the last years, EUS has emerged as an important diagnostic tool for the evaluation of various digestive malignancies, including PC [4,10]. Importantly, it also allows the acquisition of tissue for pathological purposes, what has increased its role in the management of PC. EUS and EUS-guided tissue acquisition have shown to increase the diagnostic yield and staging accuracy of PC [4,10,11]. The role of EUS is also largely discussed in the PC screening scenario, taking into account its ability for detecting very small pancreatic lesions and its importance in the diagnosis and management of pre-malignant lesions, such as intraductal papillary mucinous neoplasms (IPMN) and mucinous cystic neoplasms (MCN) [12].

Here, we review the literature to discuss the most recent developments in the preoperative management of patients with an early resectable PC. In particular, we discuss the contribution of EUS for an accurate pre-treatment diagnosis and staging.

2. Early diagnosis of pancreatic cancer: a field for EUS?

As mentioned above, the silent nature of PC contributes to its poor outcome. Yachida et al. estimated that the majority of patients with PC are only diagnosed in the last 2 of the 10-years tumorigenic process [13]. The earlier the PC is diagnosed, the better the prognosis will be [14]. Unfortunately, early detection of PC is generally difficult, since there are certain limitations for optimal diagnosis. A big effort in searching for screening strategies of PC is on-going over the last years. This approach has been considered an option to detect early stages and pre-cancerous conditions. This strategy has been recommended to individuals with more than 5% of lifetime risk for the disease [15]. However, it is well known that the incidence of PC is rather low (lifetime risk 1.3%), so general screening cannot be considered to be feasible [15]. Experts recommend to screen individuals with more than 10-fold increased risk, as the case of familial PC and several genetic syndromes associated with an increased risk (Peutz-Jeghers syndrome, familial atypical multiple mole melanoma, familial adenomatous polyposis, hereditary pancreatitis, Li-Fraumeni syndrome and Lynch syndrome) [16–19]. Recent meta-analysis has shown the potential role of magnetic resonance imaging (MRI) and EUS in the surveillance of high-risk patients for PC, for detecting pancreatic lesions, with similar accuracy for both methods [20,21].

Radiological studies are essential in diagnosis and staging of PC. However, they have important limitations, including the variability of the descriptive terminology to define disease extent and incomplete documentation of disease sites, which can affect the clinical decision-making process [22]. Multidetector computed tomography (MDCT), performed with a pancreatic protocol is usually considered as the method of choice for initial evaluation in patients with the suspicion of PC [22,23]. MRI has similar sensitivity and specificity; however, due to lack of wide availability, needed expertise, higher cost, and limited spatial resolution as compared to CT, it is not widely used as the primary imaging modality [4,22,24]. The main role of MRI is to evaluate isoattenuated pancreatic lesions and to better characterize indeterminate liver lesions identified at prior CT. Furthermore, it allows an exceptional view of the biliary and pancreatic duct, demonstrating the “double duct sign”, highly specific for PC [4,22,24,25].

The main imaging modality for the evaluation of pancreatic diseases, including solid pancreatic lesions, is EUS, with reported sensitivities between 87 and 100% [26–28]. EUS has shown a significantly better accuracy for the diagnosis of PC when compared to CT (sensitivity of 100% for EUS vs 86% for MDCT) [11,27,29–32]. EUS is particularly useful for identification of tumors <30 mm. In this setting, it presents a sensitivity of 93% compared to 53% for MDCT and 67% for MRI [27,30,33]. Despite this high accuracy, EUS has some limitations in the differential diagnosis between PC and some non-neoplastic lesions, such as mass-forming chronic pancreatitis or autoimmune pancreatitis [26]. There are some strategies to improve this accuracy and overcome its limitations. Advanced imaging related to EUS has shown to improve the characterization of solid pancreatic lesions, among them contrast-enhanced EUS (C-EUS) and EUS-guided elastography. C-EUS is based on the administration of a specific contrast agent, which highlights the microvasculature of pancreatic masses during real-time evaluation. PC usually presents a hypovascular pattern, neuroendocrine tumors a hypervascular pattern and mass-forming chronic pancreatitis an isovascular one [34]. Yamashita et al. reported that hypoenhancement behaviour diagnosed pancreatic carcinoma with a sensitivity of 95% and specificity of 89%, findings supported by other authors [26,35,36]. EUS-guided elastography, a method that evaluates tissues’ stiffness by measuring the degree of strain generated by external pressure, has demonstrated to be an excellent tool for management of pancreatic lesions [37]. Both a qualitative evaluation (based on the color map and pattern) and a quantitative evaluation (based on strain ratio or strain histogram) are available nowadays. Overall, hard lesions, shown by a blue pattern, high strain ratio (>10) or low strain histogram (<50), are mostly related to malignancy [38]. Although sensitivity of EUS-guided elastography for determine malignancy is very high it still lacks specificity [39,40].

Besides capable of improving lesion characterization, both C-EUS and elastography, also aid in the selection of the best area to perform EUS-guided tissue acquisition if indicated. Another strategy to improve diagnostic accuracy is the use of rapid on-site evaluation (ROSE) of the specimen by an experienced pathologist during the EUS exam. In fact, ROSE was found to result in fewer repeated procedures and higher percentage of definitive diagnosis as it determines whether the aspirate obtained is sufficient or not to permit a definitive diagnosis [41].

3. EUS in pancreatic cancer staging

The decision regarding resectability status should be made by consensus at multidisciplinary discussions, in high volume centers [4,8]. Although, PC staging was in the past based on the TNM classification, it is now defined with a more specific classification. PC should now be described as resectable, borderline resectable, locally advanced, unresectable or metastatic. All these features will guide treatment selection and constitute major prognostic factors for survival [4,22,42].

Both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines consider MDCT angiography as a major modality [4,8]. Positron emission tomography does not add much information for staging PC and is not currently recommended. ESMO work-up suggests performing EUS for further assessment if initial MDCT does not reveal distant metastasis, whereas NCCN guidelines suggest that EUS is complimentary to CT in selected cases [4,8,43]. In fact, it is generally accepted that EUS has an important role in preoperative staging. Besides its capacity to delineate tumor location and size, it presents a good accuracy for detecting lymph node metastasis, vascular invasion and predicting resectability. In a recent meta-analysis of 29 studies (including 1330 patients), EUS showed a pooled sensitivity of 69% and specificity of 81% for metastatic lymph node detection, and a pooled sensitivity of 85% and specificity of 91% for vascular invasion [10]. This analysis compared EUS and CT to detect arterial and venous invasion and concluded that both perform similarly for venous invasion but CT may be superior in assessing arterial invasion, namely the celiac axis and superior mesenteric artery [10]. There were no differences between EUS and CT in predicting resectability, with the former showing a pooled sensitivity

Table 1
EUS-guided tissue acquisition in diagnosis and staging of early pancreatic cancer.

Arguments against a preoperative biopsy
• Available imaging techniques have high diagnostic sensitivity.
• A negative result may not exclude malignancy.
• Potential seeding can hamper curative surgery.
• Can delay patient's treatment.
Arguments favoring a preoperative biopsy
• Has very good accuracy.
• Is a safe procedure.
• Increases surgeon's confidence.
• Increases patient's convincement.
• Avoids unnecessary surgery (in "mimickers").
• Allows the creation of a biobank for research purposes.

of 90% and specificity of 86%. Moreover, the possibility of performing tissue acquisition during EUS was also highlighted in this meta-analysis, especially its role in the characterization of atypical portocaval lymph nodes, ascitic fluid, peritoneal nodules and/or suspected liver metastasis. Thus, EUS may now be considered standard of care along with MDCT in preoperative staging of pancreatic carcinoma [10].

4. EUS-guided tissue acquisition in the diagnosis and staging of early PC: dismissible or recommended?

EUS is not only important to characterize morphologically the lesions, but also has the ability to obtain tissue samples [4,44,45]. EUS-guided tissue acquisition was first described in 1992 and is the preferred method for sampling pancreatic lesions [27,46]. EUS-guided tissue acquisition has a reported sensitivity of 79–98%, specificity of 71–100%, positive predictive value (PPV) of 96–100%, negative predictive value (NPV) of 33–85% and overall accuracy of 82–98%, with false negative and false positive rates of 12–14% and 0–5% respectively [45,47–52].

There is complete consensus regarding the need for tissue acquisition for a definite cancer diagnosis if administration of oncological therapy is indicated, as in the case of borderline resectable, locally advanced or metastatic disease [4,8]. However, controversy exists in the scenario of promptly resectable lesions: is a presurgical biopsy necessary or can these patients be proposed for immediate surgery without a prior PC definitive diagnosis? (Table 1).

According to the NCCN and the ESMO guidelines on PC patient's management, a biopsy proof of malignancy is not required for early resectable PC [4,8].

In this "early PC", the main objectives of EUS-guided tissue acquisition would be to accurately identify malignant lesions suitable for surgical resection and which type of resection would be needed (not all solid pancreatic lesion deserves the same surgical approach), but also to evaluate the need of neoadjuvant therapy, with recent data suggesting the role of this approach even in resectable pancreatic lesions. Moreover, patients with benign mimicking conditions can be spared from unnecessary surgery. The arguments more frequently pointed out for rejecting a preoperative biopsy are the high diagnostic sensitivity of the various imaging techniques, the fact that a negative result may not exclude malignancy and the possibility of hampering curative surgery because of potential seeding risk.

4.1. Arguments against a preoperative biopsy

As previously stated, imaging studies have a high diagnostic sensitivity for the diagnosis of pancreatic masses. MDCT has shown a sensitivity that can reach 90% and specificity as high as 99% [14,53,54]. Nonetheless, MDCT scan and EUS alone do not always allow a precise diagnosis, especially for tumors <2 cm or in the setting of chronic pancreatitis [55,56]. In these circumstances, a EUS-tissue acquisition should always be considered.

When analyzing the results of EUS-guided tissue acquisition, and despite its excellent accuracy, the NPV still remains limited (approximately 60%). Moreover, chronic pancreatitis decreases diagnostic accuracy of tissue acquisition techniques, with difficult cytological interpretation. EUS-guided tissue acquisition can also have false positive results, usually in cases of chronic pancreatitis [27,57,58]. In patients with atypical/suspicious cytology but without a definitive diagnosis, it is recommended to repeat the puncture or treat as if the result was positive because surgery should never be delayed [59]. This is also related with another drawback of EUS-guided tissue acquisition is its ability in obtaining adequate cellular material, with reported unsatisfactory aspirates in 1.5–13% of cases [59,60].

Another issue against preoperative biopsy is its potential risk of tumor seeding [61]. There are anecdotal cases of tumor seeding after EUS-guided tissue acquisition along the needle tract, but with much lower frequency than with the percutaneous approach [62–64]. These cases were reported in tumors located on pancreatic body or tail, as in these locations tissue is obtained via transgastric approach that it will not be included in the surgical resection. On the other hand, lesions located on the head of the pancreas, which are sampled through the duodenum, should not harbor this risk, as the needle track will be included in the surgical specimen [65]. In 2013, Ngamruengphong et al. discussed this issue in a paper where 256 patients with similar baseline characteristics were analyzed: 48 patients in the non-EUS-guided tissue acquisition group and 208 in the EUS-guided tissue acquisition group. Recurrence data was available for 207 patients with a median length of follow-up of 23 months. Three patients had recurrence in the gastric wall: one (2.6%) in the non-EUS-guided tissue acquisition group *vs.* two (1.2%) in EUS-guided tissue acquisition group ($p = 0.46$). A total of 16 patients had peritoneal recurrence: 5 (12.8%) in the non-EUS-guided tissue acquisition group and 11 (6.5%) in the EUS-guided tissue acquisition one ($p = 0.19$) [66]. In multivariate analysis, undergoing EUS-guided tissue acquisition was not associated with an increased cancer recurrence or decreased overall survival, suggesting that it is not associated with an increased risk of needle track seeding. More recently, the same author, using the linked Surveillance, Epidemiology, and End Results-Medicare data, identified a total of 2034 patients with locoregional PC who underwent curative intent surgery from 1998 to 2009 [67]. Patients who received EUS-guided tissue acquisition within the peridiagnostic period were included in the EUS-guided tissue acquisition group ($n = 498$) whereas patients who did not receive EUS evaluation or who underwent EUS without tissue acquisition were included in the non-EUS-guided tissue acquisition group. Overall survival and PC-specific survival were compared after controlling for relevant covariates. In multivariate analysis, EUS-guided tissue acquisition was marginally associated with improved overall survival (HR 0.84, 95% CI 0.72–0.99), but did not affect cancer-specific survival (HR 0.87, 95% CI 0.74–1.03). The authors concluded that preoperative EUS-guided tissue acquisition was not associated with an increased risk of mortality and suggested that it can be safely performed for the work-up of suspicious pancreatic lesions.

The argument that a preoperative biopsy can delay the treatment of these ideal surgical candidates should not be considered as most of these individuals should be evaluated and treated in tertiary well-experimented centers, where waiting lists for EUS-guided tissue acquisition procedures should not exist.

4.2. Arguments favoring a preoperative biopsy

EUS has demonstrated to be highly accurate in the diagnosis of solid pancreatic masses, being accepted as a minimally inva-

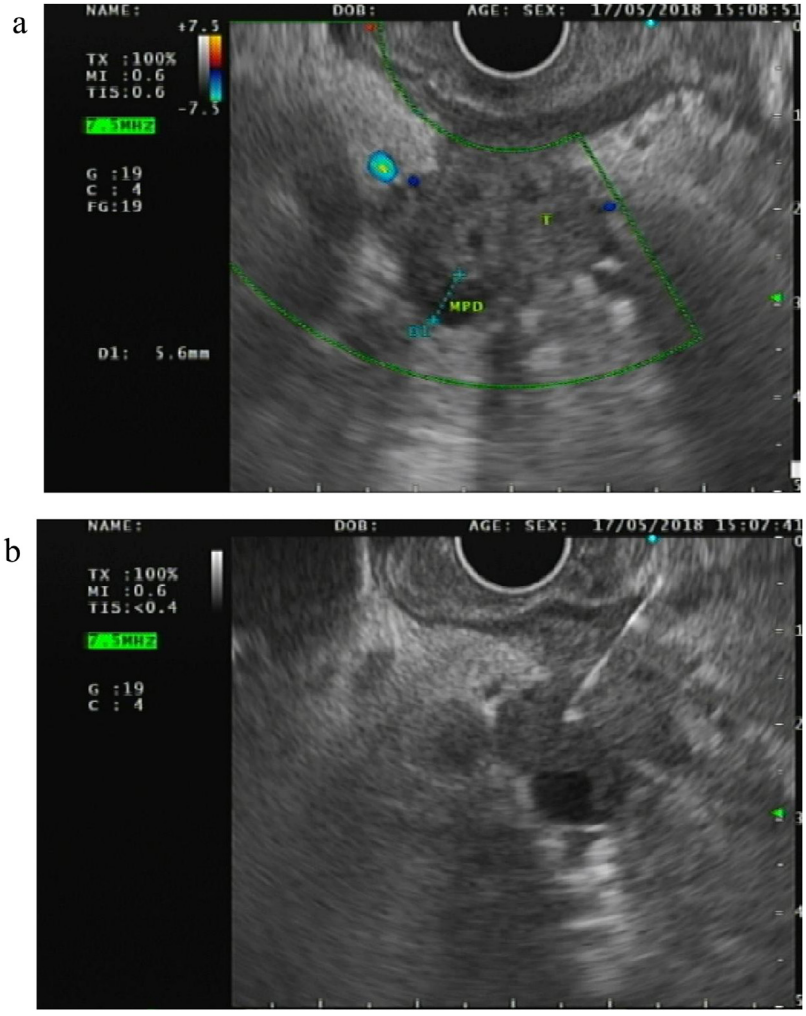

Fig. 1. (a) Hypoechogenic solid 2 cm lesion, in the head of the pancreas, causing dilation of main pancreatic duct (5.6 mm). (b) EUS-FNA of the pancreatic lesion, using a 25 gauge needle.

sive, well-tolerated, operator-dependent procedure. The addition of fine-needle techniques provides samples for cytopathological analysis, which represents a major advantage over other imaging techniques (Fig. 1a and b).

Hewitt et al. recently published a meta-analysis assessing the diagnostic capability of EUS-guided tissue acquisition in PC patients [57]. Thirty-three studies published between 1997 and 2009 were included, with a total of 4984 patients, using a reference standard of definitive surgical histology or clinical follow-up of at least 6 months. Cytology results were classified as inadequate, benign, atypical, suspicious or malignant. The pooled sensitivity for malignant cytology was 85% and pooled specificity was 98%. If atypical and suspicious cytology results were included to determine true neoplasms, the sensitivity increased to 91% and the specificity was reduced to 94%. The diagnostic accuracy of EUS-guided tissue acquisition was enhanced in prospective, multicenter studies. Taking these results into account, the authors concluded that EUS-guided tissue acquisition should be considered when algorithms for investigating solid pancreatic lesions are planned.

Diagnostic accuracy based solely in imaging studies remains unsatisfactory, with nearly 10% of resected specimens considered preoperatively as PC being other lesions in the pathological exam of the surgical specimens. These are the so-called PC "mimickers" and include benign lesions, such as focal chronic pancreatitis, autoimmune pancreatitis, pancreatic tuberculosis and malignant ones, like pancreatic lymphoma and metastasis from other organs' neoplasia [68–71]. This becomes especially important as overall mortality after pancreatic surgery ranges from 0 to 10% and morbidity from 10 to 60% [72,73]. Therefore, an EUS-guided tissue acquisition with a diagnosis of a PC "mimicker" can spare patients from unnecessary surgery.

EUS-guided tissue acquisition is considered a safe procedure. The most common complication is mild-to-moderate pancreatitis which occurs in 0–3.4% of cases [45,51,74,75]. Rare but serious complications have been reported such as rupture of pseudo-aneurysm, severe bleeding and perforation, formation of pancreatic pseudocyst and abscess [51,76–78]. Bacteremia was an issue of concern due to the disruption of mucosal integrity occurs. Nonetheless, some studies showed that bacteremia rates in patients undergoing EUS-guided tissue acquisition were comparable to that of diagnostic endoscopies [79–81]. Taking into account that the frequency and severity of complications may vary from center to center and may be related to operator experience, Wang et al. conducted a systematic review to assess the morbidity and mortality associated with EUS-guided tissue acquisition [75]. Fifty-one articles with a total of 10,941 patients were included. The overall rate of EUS-guided tissue acquisition specific morbidity and mortality were 0.98% and 0.02%, respectively. In the small group of patients with complications of any kind, mild-to-moderate pancreatitis and post procedure pain were the more frequent events.

Another important advantage of a preoperative definitive diagnosis of malignancy is its role in the patient-doctor relationship. In fact, and even considering the nowadays "acceptable" rates of surgical morbidity and mortality, in high volume centers, from the patient's and surgeon's point of view, a biopsy proof of malignancy increases surgeon's confidence and patients convincement of the urgent need of a demanding and often complex surgery.

Finally, the disseminated use of EUS-guided tissue acquisition in suspected pancreatic tumors can contribute for upcoming research, allowing the creation of a biobank. In this way, for example, in the near future, novel biomarkers could be discovered with the ability to detect PC in early phases or be used in testing new therapeutic agents [27,82].

5. Summary

EUS is undoubtedly an important tool to diagnose and stage PC and is often used complementary to MDCT. EUS-guided tissue acquisition is a safe procedure and the method of choice to sample pancreatic lesions with high diagnostic accuracy. The fear of tumor spread has limited its use in the past, but recent studies have demonstrated that EUS-guided tissue acquisition is a safe procedure, with rare and mild complications, and have contributed to the spreading of this technique in PC management algorithm [4,55,67]. EUS-guided tissue acquisition is especially useful in atypical and doubtful situations and in patients with high surgical risk, as it can avoid surgery and its associated morbimortality in lesions that can mimic PC, such as autoimmune pancreatitis or lymphoma. A biopsy proving malignancy increases the certainty of the indication of a surgical treatment, facilitating the surgeon-patient dialogue. Having EUS-guided tissue acquisition made its proof of concept when performed preoperatively to determine the definitive diagnosis, improving staging and supporting the correct indication for surgical resection of a pancreatic tumor, why should it not be considered in suspected early PC?

Conflicts of interest

None declared.

References

[1] Kosmidis C, Sapalidis K, Kotidis E, Mixalopoulos N, Zarogoulidis P, Tsavlis D, et al. Pancreatic cancer from bench to bedside: molecular pathways and treatment options. Ann Transl Med 2016;4(May (9)):165.

[2] Khorana AA, Mangu PB, Katz MHG. Potentially curable pancreatic cancer: American society of clinical oncology clinical practice guideline update summary. J Oncol Pract 2017;13(June (6)):388–91.

[3] Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2014. Ann Oncol 2014;25(August (8)):1650–6.

[4] Ducreux M, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, et al. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;(September (26 Suppl. 5)):v56–68.

[5] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74(June (11)):2913–21.

[6] Cucchetti A, Ercolani G, Cescon M, Brandi G, Taffurelli G, Maroni L, et al. Estimation of the survival benefit obtainable from screening for the early detection of pancreatic cancer. Pancreas 2016;45(June (5)):714–9.

[7] Chari ST. Detecting early pancreatic cancer: problems and prospects. Semin Oncol 2007;34(August (4)):284–94.

[8] Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2017;15(August (8)):1028–61.

[9] Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol 2014;20(August (31)):10740–51.

[10] Nawaz H, Fan CY, Kloke J, Khalid A, McGrath K, Landsittel D, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. JOP 2013;14(September (5)):484–97.

[11] Bhutani MS, Koduru P, Joshi V, Saxena P, Suzuki R, Irisawa A, et al. The role of endoscopic ultrasound in pancreatic cancer screening. Endosc Ultrasound 2016;5(February (1)):8–16.

[12] Lariño-Noia J, Iglesias-Garcia J, de la Iglesia-Garcia D, Dominguez-Muñoz JE. EUS-FNA in cystic pancreatic lesions: where are we now and where are we headed in the future? Endosc Ultrasound 2018;7(April (2)):102–9.

[13] Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467(October (7319)):1114–7.

[14] Kim VM, Ahuja N. Early detection of pancreatic cancer. Chin J Cancer Res 2015;27(August (4)):321–31.

[15] Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley J-W, Kamel I, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62(March (3)):339–47.

[16] Greer JB, Brand RE. Screening for pancreatic cancer: current evidence and future directions. Gastroenterol Hepatol (N Y) 2007;3(December (12)):929–38.

[17] Moutinho-Ribeiro P, Coelho R, Giovannini M, Macedo G. Pancreatic cancer screening: still a delusion? Pancreatology 2017;17(October (5)):754–65.

[18] Poruk KE, Firpo MA, Adler DG, Mulvihill SJ. Screening for pancreatic cancer: why, how, and who? Ann Surg 2013;257(January (1)):17–26.

[19] Poruk KE, Firpo MA, Mulvihill SJ. Screening for pancreatic cancer. Adv Surg 2014;48:115–36.

[20] Corral JE, Mareth KF, Riegert-Johnson DL, Das A, Wallace MB. Diagnostic yield from screening asymptomatic individuals at high risk for pancreatic cancer: a meta-analysis of cohort studies. Clin Gastroenterol Hepatol 2018;(May).

[21] Signoretti M, Bruno MJ, Zerboni G, Poley J-W, Delle Fave G, Capurso G. Results of surveillance in individuals at high-risk of pancreatic cancer: a systematic review and meta-analysis. United Eur Gastroenterol J 2018;6(May (4)):489–99.

[22] Al-Hawary MM, Francis IR, Chari ST, Fishman EK, Hough DM, Lu DS, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014;270(January (1)):248–60.

[23] Zamboni GA, Kruskal JB, Vollmer CM, Baptista J, Callery MP, Raptopoulos VD. Pancreatic adenocarcinoma: value of multidetector CT angiography in preoperative evaluation. Radiology 2007;245(December (3)):770–8.

[24] Ansari NA, Ramalho M, Semelka RC, Buonocore V, Gigli S, Maccioni F. Role of magnetic resonance imaging in the detection and characterization of solid pancreatic nodules: an update. World J Radiol 2015;7(November (11)):361–74.

[25] Al-Hawary M. Role of imaging in diagnosing and staging pancreatic cancer. J Natl Compr Canc Netw 2016;14(May (5 Suppl.)):678–80.

[26] Yamashita Y, Kato J, Ueda K, Nakamura Y, Kawaji Y, Abe H, et al. Contrast-enhanced endoscopic ultrasonography for pancreatic tumors. Biomed Res Int 2015;2015:491782.

[27] Luz LP, Al-Haddad MA, Sey MSL, DeWitt JM. Applications of endoscopic ultrasound in pancreatic cancer. World J Gastroenterol 2014;20(June (24)):7808–18.

[28] Dewitt J, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. Clin Gastroenterol Hepatol 2006;4(June (6)):717–25, quiz 664.

[29] Puli SR, Kalva N, Bechtold ML, Pamulaparthy SR, Cashman MD, Estes NC, et al. Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: a systematic review and meta analysis. World J Gastroenterol 2013;19(June (23)):3678–84.

[30] Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology 1994;190(March (3)):745–51.

[31] DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med 2004;141(November (10)):753–63.

[32] Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol 2004;99(May (5)):844–50.

[33] Wang W, Shpaner A, Krishna SG, Ross WA, Bhutani MS, Tamm EP, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. Gastrointest Endosc 2013;78(July (1)):73–80.

[34] Kitano M, Yamashita Y. New imaging techniques for endoscopic ultrasonography: contrast-enhanced endoscopic ultrasonography. Gastrointest Endosc Clin N Am 2017;27(October (4)):569–83.

[35] Dietrich CF, Sahai AV, D'Onofrio M, Will U, Arcidiacono PG, Petrone MC, et al. Differential diagnosis of small solid pancreatic lesions. Gastrointest Endosc 2016;84(December (6)):933–40.

[36] Fusaroli P, Napoleon B, Gincul R, Lefort C, Palazzo L, Palazzo M, et al. The clinical impact of ultrasound contrast agents in EUS: a systematic review according to the levels of evidence. Gastrointest Endosc 2016;84(October (4)), 587–596.e10.

[37] Iglesias-García J, Lariño-Noia J, Domínguez-Muñoz JE. New imaging techniques: endoscopic ultrasound-guided elastography. Gastrointest Endosc Clin N Am 2017;27(October (4)):551–67.

[38] Iglesias-Garcia J, Lindkvist B, Lariño-Noia J, Abdulkader-Nallib I, Dominguez-Muñoz JE. Differential diagnosis of solid pancreatic masses: contrast-enhanced harmonic (CEH-EUS), quantitative-elastography (QE-EUS), or both? United Eur Gastroenterol J 2017;5(March (2)):236–46.

[39] Ignee A, Jenssen C, Arcidiacono PG, Hocke M, Möller K, Saftoiu A, et al. Endoscopic ultrasound elastography of small solid pancreatic lesions: a multicenter

study. Endoscopy 2018;(April), http://dx.doi.org/10.1055/a-0588-4941 [Epub ahead of print].
[40] Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology 2010;139(October (4)):1172–80.
[41] Collins BT, Murad FM, Wang JF, Bernadt CT. Rapid on-site evaluation for endoscopic ultrasound-guided fine-needle biopsy of the pancreas decreases the incidence of repeat biopsy procedures. Cancer Cytopathol 2013;121(9):518–24.
[42] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17(June (6)):1471–4.
[43] Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16(July (7)):1727–33.
[44] Dwyer J, Pantanowitz L, Ohori NP, Pai RK, Vrbin C, Brand RE, et al. Endoscopic ultrasound-guided FNA and ProCore biopsy in sampling pancreatic and intra-abdominal masses. Cancer Cytopathol 2016;124(February (2)):110–21.
[45] Matsubayashi H, Matsui T, Yabuuchi Y, Imai K, Tanaka M, Kakushima N, et al. Endoscopic ultrasonography guided-fine needle aspiration for the diagnosis of solid pancreaticobiliary lesions: clinical aspects to improve the diagnosis. World J Gastroenterol 2016;22(January (2)):628–40.
[46] Vilmann P, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. Gastrointest Endosc 1992;38(April (2)):172–3.
[47] Ryozawa S, Kitoh H, Gondo T, Urayama N, Yamashita H, Ozawa H, et al. Usefulness of endoscopic ultrasound-guided fine-needle aspiration biopsy for the diagnosis of pancreatic cancer. J Gastroenterol 2005;40(September (9)):907–11.
[48] Hikichi T, Irisawa A, Bhutani MS, Takagi T, Shibukawa G, Yamamoto G, et al. Endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic masses with rapid on-site cytological evaluation by endosonographers without attendance of cytopathologists. J Gastroenterol 2009;44(4):322–8.
[49] Itoi T, Tsuchiya T, Itokawa F, Sofuni A, Kurihara T, Tsuji S, et al. Histological diagnosis by EUS-guided fine-needle aspiration biopsy in pancreatic solid masses without on-site cytopathologist: a single-center experience. Dig Endosc 2011;1(May (23 Suppl. 1)):34–8.
[50] Fisher L, Segarajasingam DS, Stewart C, Deboer WB, Yusoff IF. Endoscopic ultrasound guided fine needle aspiration of solid pancreatic lesions: performance and outcomes. J Gastroenterol Hepatol 2009;24(January (1)):90–6.
[51] Matsuyama M, Ishii H, Kuraoka K, Yukisawa S, Kasuga A, Ozaka M, et al. Ultrasound-guided vs endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer diagnosis. World J Gastroenterol 2013;19(April (15)):2368–73.
[52] Lee JK, Choi JH, Lee KH, Kim KM, Shin JU, Lee JK, et al. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. Gastrointest Endosc 2013;77(May (5)):745–51.
[53] Long EE, Van Dam J, Weinstein S, Jeffrey B, Desser T, Norton JA. Computed tomography, endoscopic, laparoscopic, and intra-operative sonography for assessing resectability of pancreatic cancer. Surg Oncol 2005;14(August (2)):105–13.
[54] Beinfeld MT, Wittenberg E, Gazelle GS. Cost-effectiveness of whole-body CT screening. Radiology 2005;234(February (2)):415–22.
[55] Tyng CJ, Almeida MFA, Barbosa PNV, Bitencourt AGV, Berg JAAG, Maciel MS, et al. Computed tomography-guided percutaneous core needle biopsy in pancreatic tumor diagnosis. World J Gastroenterol 2015;21(March (12)):3579–86.
[56] Chen J, Yang R, Lu Y, Xia Y, Zhou H. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. J Cancer Res Clin Oncol 2012;138(September (9)):1433–41.
[57] Hewitt MJ, McPhail MJW, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc 2012;75(February (2)):319–31.
[58] Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc 2005;62(November (5)):728–36, quiz 751, 753.
[59] Hou X, Jin Z, Xu C, Zhang M, Zhu J, Jiang F, et al. Contrast-enhanced harmonic endoscopic ultrasound-guided fine-needle aspiration in the diagnosis of solid pancreatic lesions: a retrospective study. PLoS One 2015;10(3):e0121236.
[60] Matynia AP, Schmidt RL, Barraza G, Layfield LJ, Siddiqui AA, Adler DG. Impact of rapid on-site evaluation on the adequacy of endoscopic-ultrasound guided fine-needle aspiration of solid pancreatic lesions: a systematic review and meta-analysis. J Gastroenterol Hepatol 2014;29(April (4)):697–705.
[61] Minaga K, Takenaka M, Katanuma A, Kitano M, Yamashita Y, Kamata K, et al. Needle tract seeding: an overlooked rare complication of endoscopic ultrasound-guided fine-needle aspiration. Oncology 2017;93(Suppl. 1):107–12.
[62] Chong A, Venugopal K, Segarajasingam D, Lisewski D. Tumor seeding after EUS-guided FNA of pancreatic tail neoplasia. Gastrointest Endosc 2011;74(October (4)):933–5.
[63] Sakurada A, Hayashi T, Ono M, Ishiwatari H, Ogino J, Kimura Y, et al. A case of curatively resected gastric wall implantation of pancreatic cancer caused by endoscopic ultrasound-guided fine-needle aspiration. Endoscopy 2015;(47 Suppl. 1). UCTN:E198-199.
[64] Paquin SC, Gariépy G, Lepanto L, Bourdages R, Raymond G, Sahai AV. A first report of tumor seeding because of EUS-guided FNA of a pancreatic adenocarcinoma. Gastrointest Endosc 2005;61(April (4)):610–1.
[65] Albanese C, Rodriguez OC, VanMeter J, Fricke ST, Rood BR, Lee Y, et al. Preclinical magnetic resonance imaging and systems biology in cancer research: current applications and challenges. Am J Pathol 2013;182(February (2)):312–8.
[66] Ngamruengphong S, Xu C, Woodward TA, Raimondo M, Stauffer JA, Asbun HJ, et al. Risk of gastric or peritoneal recurrence, and long-term outcomes, following pancreatic cancer resection with preoperative endosonographically guided fine needle aspiration. Endoscopy 2013;45(August (8)):619–26.
[67] Ngamruengphong S, Swanson KM, Shah ND, Wallace MB. Preoperative endoscopic ultrasound-guided fine needle aspiration does not impair survival of patients with resected pancreatic cancer. Gut 2015;64(July (7)):1105–10.
[68] Kudo T, Kawakami H, Kuwatani M, Eto K, Kawahata S, Abe Y, et al. Influence of the safety and diagnostic accuracy of preoperative endoscopic ultrasound-guided fine-needle aspiration for resectable pancreatic cancer on clinical performance. World J Gastroenterol 2014;20(April (13)):3620–7.
[69] Wolfson D, Barkin JS, Chari ST, Clain JE, Bell RH, Alexakis N, et al. Management of pancreatic masses. Pancreas 2005;31(October (3)):203–17.
[70] Smith CD, Behrns KE, van Heerden JA, Sarr MG. Radical pancreatoduodenectomy for misdiagnosed pancreatic mass. Br J Surg 1994;81(April (4)):585–9.
[71] Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all chronic pancreatitis? Am J Surg Pathol 2003;27(January (1)):110–20.
[72] Gooiker GA, van Gijn W, Wouters MWJM, Post PN, van de Velde CJH, Tollenaar RA, et al. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg 2011;98(April (4)):485–94.
[73] Diener MK, Seiler CM, Antes G. [Systematic reviews and meta-analyses in surgery]. Chirurg 2007;78(October (10)):938–44.
[74] Al-Haddad M, Wallace MB, Woodward TA, Gross SA, Hodgens CM, Toton RD, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. Endoscopy 2008;40(March (3)):204–8.
[75] Wang K-X, Ben Q-W, Jin Z-D, Du Y-Q, Zou D-W, Liao Z, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointest Endosc 2011;73(February (2)):283–90.
[76] Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Matsuda S, et al. Severe bleeding and perforation are rare complications of endoscopic ultrasound-guided fine needle aspiration for pancreatic masses: an analysis of 3,090 patients from 212 hospitals. Gut Liver 2014;8(March (2)):215–8.
[77] Chung KH, Ryu JK, Oh HS, Seo JY, Jin E, Lee DH, et al. Pancreatic pseudocyst after endoscopic ultrasound-guided fine needle aspiration of pancreatic mass. Clin Endosc 2012;45(November (4)):431–4.
[78] Matsumoto K, Hara K, Sawaki A, Mizuno N, Hijioka S, Imamura H, et al. Ruptured pseudoaneurysm of the splenic artery complicating endoscopic ultrasound-guided fine-needle aspiration biopsy for pancreatic cancer. Endoscopy 2010;42(Suppl. 2):E27–8.
[79] Barawi M, Gottlieb K, Cunha B, Portis M, Gress F. A prospective evaluation of the incidence of bacteremia associated with EUS-guided fine-needle aspiration. Gastrointest Endosc 2001;53(February (2)):189–92.
[80] Levy MJ, Norton ID, Wiersema MJ, Schwartz DA, Clain JE, Vazquez-Sequeiros E, et al. Prospective risk assessment of bacteremia and other infectious complications in patients undergoing EUS-guided FNA. Gastrointest Endosc 2003;57(May (6)):672–8.
[81] Janssen J, König K, Knop-Hammad V, Johanns W, Greiner L. Frequency of bacteremia after linear EUS of the upper GI tract with and without FNA. Gastrointest Endosc 2004;59(March (3)):339–44.
[82] Ogura T, Yamao K, Sawaki A, Mizuno N, Hara K, Hijioka S, et al. Clinical impact of K-ras mutation analysis in EUS-guided FNA specimens from pancreatic masses. Gastrointest Endosc 2012;75(April (4)):769–74.