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REVIEW

The endoscopist's role in the diagnosis and management of pancreatic cancer

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ABSTRACT

Pancreatic cancer remains one of the most lethal malignancies with little improvement in survival over the past several decades in spite of advances in imaging, risk factor identification, surgical technique and chemotherapy. This disappointing outcome is mainly due to failures to make an early diagnosis. In fact, the majority of the patients present with inoperable advanced stages of the disease. Though some of the new tumor markers are promising, we are still in search of the one that has a high sensitivity and accuracy, yet is inexpensive and easy to obtain. The paradigm of management has shifted from up-front surgery followed by adjuvant chemotherapy to neoadjuvant chemoradiation followed by surgery, especially for borderline resectable cancers and even for some resectable cancers. In this article, we will critically assess the limitations of tumor markers and review the advancements in endoscopic techniques in the management of pancreatic cancer.

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1. Introduction

Pancreatic cancer is the third leading cause of cancer death in the United States. If detected early with only localized disease, the survival rates are better but still dreadful at approximately 25%. Regrettably, most patients with pancreatic cancer are present in the late stages of the disease, and only 10–15% of the patients are amenable for surgical resection [1]. The most recent Surveillance, Epidemiology, and End Results (SEER) data show the overall 5-year survival rate of pancreatic cancer at 6–7% [2]. Given these sobering statistics, the goal in managing pancreatic cancer is to detect the cancer in the early stages, as early detection is the key to better survival. Once cancer is suspected, it is crucial to promptly establish the diagnosis and proceed to therapy in an efficient and timely manner, specifically to optimize the patients for surgical resection, as this is the only hope for cure. This review discusses the risk factors for pancreatic cancer, potential tumor markers and their limitations, the rationale for screening high-risk patients, the tools to establish a diagnosis, various approaches to relieve biliary obstruction, local endoscopic therapy currently available for the cancer and their limitations, and future directions.

2. The risk factors for pancreatic cancer

The risk factors for development of pancreatic cancer include cigarette smoking (1.6–2.5-fold), long-standing diabetes (2.0 for type 1 diabetes and 1.8 for type 2 diabetes), family history of pancreatic cancer, history of pancreatitis, obesity (1.72-fold), and alcoholism (chronic pancreatitis [CP], 18.5–26.3-fold) [3].

3. Screening for pancreatic cancer

Even though we have seen a survival benefit from endoscopic colon cancer screening [4] and thus, screening colonoscopy has become a standard of care for all who are 50 years of age or older, this strategy could not be applied to pancreatic cancer screening due to the innate differences of the two cancers and financial limitations. A key issue is lifetime risk. According to SEER data, the lifetime risk of pancreatic cancer in United States is 1.5% versus 4.5% for colorectal cancer. Another is therapeutic options for unresectable disease [2].

Colonoscopy is a procedure that is relatively easy to perform with a low complication rate and low cost. On the other hand, pancreatic cancer screening is costly requiring imaging studies, such as CT scan or MRI, and/or endoscopic ultrasound (EUS) examination that have undefined efficacy in this setting [5]. Moreover, EUS is an operator-dependent procedure and the accuracy of EUS is highly dependent upon the endosonographer's training and expertise, not to mention that EUS is not currently available in all community centers.

Needless to say, pancreatic cancer screening has been a challenging task with little advancement and no proven benefit in survival. This is mainly due to the fact that pancreatic cancer is a unique cancer where early detection markers or easily identified pancreatic cancer precursors (comparable to adenomas) have not been identified and validated. An ideal biomarker of pancreatic cancer should have a high sensitivity and specificity.

To overcome these obstacles, many researchers and clinicians have been looking for a tumor marker that is sensitive and specific with a high accuracy, easily obtainable, and

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inexpensive. Many biomarkers have been studied including the serum protein carbohydrate antigen 19-9 (CA 19-9), vascular endothelial growth factor, and nuclear factor kappa B, however, still no blood test or other fluid analysis reliably predicts patients with disease.

Among the potential markers that have shown promising results are mesothelin, glypican-1 (GPC1), circulating microRNAs (miRNAs) in pancreatic juice, and serum thrombospondin-1 (TSP-1).

3.1 Mesothelin

Mesothelin is consistently elevated in mesothelioma, ovarian cancer, and pancreatic cancer but not in normal pancreatic tissue. Zheng et al. reported overexpression of mesothelin in human pancreatic cancer cell lines [6]. Furthermore, silencing of mesothelin expression significantly decreased cell proliferation and promoted apoptosis in pancreatic cancer cells *in vitro* and inhibited tumor growth *in vivo*. The authors concluded that mesothelin was an important factor in pancreatic cancer growth and a potential target for monoclonal antibody therapy in pancreatic cancer treatment. Hence, assays could be potentially devised to detect mesothelin in the blood, in duodenal and pancreatic fluids, or in stool samples, thereby providing a new marker of pancreatic malignancy.

3.2 Glypican-1

Exosomes, being secreted by all cells and circulate in the blood, are lipid-bilayer-enclosed extracellular vesicles that contain proteins and nucleic acids. Using mass spectrometry, Melo et al. identified a cell surface proteoglycan, GPC1, specifically enriched on cancer-cell-derived exosomes. The authors were able to monitor and isolate GPC1 circulating exosomes (crExos) from the serum of patients and mice with cancer using flow cytometry. The results showed that GPC1 crExos were detected in the serum of patients with pancreatic cancer with absolute specificity and sensitivity, distinguishing healthy subjects. GPC1 could also distinguish patients with a benign pancreatic disease from patients with early- and late-stage pancreatic cancer. Furthermore, the levels of GPC1 crExos, correlated with tumor burden and the survival of pre- and postsurgical patients, reliably detect pancreatic intraepithelial lesions in mice, despite negative signals by magnetic resonance imaging (MRI). The authors felt that GPC1 crExos may serve as a potential noninvasive diagnostic and screening tool to detect early stages of pancreatic cancer to facilitate possible curative surgical therapy [7].

This study still needs validation in clinical trials before making an impact in pancreatic cancer screening.

3.3 Circulating miRNAs in pancreatic juice

In an effort to find a tumor marker for pancreatic cancer, Wang et al. performed profiling of miRNAs of pancreatic juice from six pancreatic ductal adenocarcinoma (PDAC) patients and two pooled samples from six non-pancreatic, non-healthy (NPNH) as controls. Circulating miRNAs were subsequently validated in 88 pancreatic juice samples from 50 PDAC, 19 CP patients, and 19 NPNH controls. The authors found that there was a marked difference in the profiles of four circulating miRNAs (miR-205, miR-210, miR-492, and miR-1427) in pancreatic juice collected from patients with PDAC and those without pancreatic disease. Elevated levels of the four miRNAs together predicted PDAC with a specificity of 88% and sensitivity of 87%. When combined with serum CA19-9, miRNAs had an increased sensitivity of 91% and the specificity of 100%. Furthermore, elevated levels were associated with decreased overall survival [8].

3.4 Serum TSP-1

Jenkinson et al. reported that there was a significant reduction in levels of TSP-1 up to 24 months prior to diagnosis of PDAC [9].

The authors found that TSP-1 was also decreased in PDAC patients compared to healthy controls ($P < 0.05$) and patients with benign biliary obstruction ($P < 0.01$). Furthermore, low levels of TSP-1 correlated with poorer survival, preclinically ($P < 0.05$) and at clinical diagnosis ($P < 0.02$). Finally, in PDAC patients, reduced TSP-1 levels were more frequently observed in those with confirmed diabetes mellitus ($P < 0.01$). A combination of TSP-1 and CA19-9 gave an AUC of 0.86, significantly outperforming both markers alone (0.69 and 0.77, respectively; $P < 0.01$). Significantly, lower levels were also observed in PDAC patients with diabetes compared to individuals with type-2 diabetes mellitus ($P = 0.01$).

3.5 Carbohydrate antigen 19-9 (CA 19-9)

CA 19-9 is an epitope of sialylated Lewis blood group antigen. CA 19-9 lacks sufficient sensitivity and specificity for detecting early pancreatic cancer. It is elevated in only 50% of pancreatic adenocarcinomas less than 3 cm in size [10]. Lacking specificity, CA 19-9 is elevated in gastric cancer, colorectal cancer, cholangiocarcinoma, as well as any biliary obstruction, and acute and CP [11–15].

Despite the poor sensitivity and specificity, for the lack of alternatives, CA 19-9 is widely used as a serum biomarker for PDAC, especially monitoring treatment response and post-treatment surveillance; however, it has not been recommended for cancer screening. The American Society of Clinical Oncology 2006 guidelines for the use of tumor markers do not recommend CA 19-9 as a screening test for pancreatic cancer [16,17].

Currently, no clinically useful tumor marker to screen for patients with PDAC has been established. Nonetheless, research is ongoing, focusing not only on biomarker discovery that could discriminate between pathological pancreas conditions (disease-related biomarkers), but also to evaluate the aggressiveness of PDAC and to determine therapy response (drug-related biomarkers).

Realistically, even though an abnormal tumor marker level may suggest cancer, this alone is usually not enough to establish a diagnosis. Therefore, measurements of tumor markers are usually combined with biopsy results to diagnose cancer.

4. Screening for pancreatic cancer in high-risk population

While population-based mass screening is not possible or practical in pancreatic cancer with an incidence of 8–12 per 100,000 [17], screening and early detection in asymptomatic high-risk groups should be considered. The high-risk groups include hereditary pancreatitis (mutations in PRSS1, SPINK1, 52-fold increased risk of developing pancreatic cancer), familial pancreatic cancer (at least 2 first-degree relatives with pancreatic cancer, 6.4-fold increase; 3 or more, 32-fold), Peutz–Jegher syndrome (STK11/LKB1, 132-fold), Lynch syndrome (MLH1 and MSH2, relative risk [RR] <6), familial atypical multiple mole melanoma (FAMMM, CDKN2A, 13.1-fold), melanoma-pancreatic cancer syndrome (CDKN2A), hereditary breast and ovarian cancer (BRCA1:RR 3.1; BRCA2: RR 6.6) [3].

In a multicenter, prospective trial involving 225 asymptomatic high-risk patients, 5 US institutions compared multidetector computed tomography per pancreas protocol (CT), MRI, and EUS as screening tools and showed that EUS was the best modality to detect a pancreatic abnormality (11%, 33.3%, and 42.6%, respectively) [18].

5. Diagnosis

5.1 Imaging studies

Cross-sectional imaging such as CT, MRI, and F-18 FDG positron emission tomography (PET) are the currently used modalities in the diagnosis and staging of pancreatic adenocarcinoma [19]. The NCCN guidelines recommend CT or MRI for imaging pancreatic cancer [20].

Multidetector CT (MDCT) is widely available and is considered the primary modality in assessing resectability of pancreatic cancer [19]. MDCT protocol for pancreatic cancer typically involves a biphasic technique of contrast enhancement. The first phase helps in identification of the tumor and the adjacent arteries whereas the second phase helps in identification of liver metastases and the adjacent venous structures to determine resectability. All the images are acquired at <3 mm slice thickness and reconstructed in the sagittal and the coronal plane.

Pancreatic carcinoma typically is lower in attenuation compared to the pancreatic parenchyma, but can be isoattenuating to the pancreatic parenchyma, making visualization difficult in approximately 10% of cases [21]. In situations where the tumor is not optimally visible, one can rely on the additional clues such as abrupt termination of the pancreatic (and/or bile) duct with proximal ductal dilatation, double duct sign (dilatation of both pancreatic and common bile duct), pancreatic contour abnormalities, mass effect, and obstructive pancreatic atrophy (higher ductal–parenchymal ratio).

MRI is usually performed if the patient is allergic to iodinated contrast material. MRI may be optimally performed with 1.5 or 3-T gradient systems. Several sequences can be obtained to optimally visualize the pancreatic cancer; however, it is time consuming and unfortunately is susceptible to motion artifacts. The typical imaging protocol includes T1-weighted and T2-weighted sequences followed by gadolinium enhanced dynamic sequences acquired at 20, 60, 120, and 180 s [22]. Axial fast imaging employing steady-state acquisition (FIESTA; GE Medical Systems, Milwaukee, WI) sequence with fat suppression can be helpful in assessing vessels and the tumor. Pancreatic cancers have a low signal on the pre-contrast as well as the contrast-enhanced images. On T2-weighted and diffusion images, the tumor has a high signal. A meta-analysis showed CT to have a better sensitivity than MRI for detection of pancreatic cancer (84% vs. 91%). However, subtle lesions may be better visualized on MRI due to high soft tissue contrast resolution [23]. Unfortunately, CP is difficult to differentiate from a pancreatic carcinoma on both CT and MRI as both entities share similar imaging characteristics [24,25].

The currently used agent to evaluate pancreatic cancer with PET is the F-18 FDG. Usually, PET/CT is performed without iodinated contrast and thus has a limited role in staging of pancreatic cancer. Additionally, inflammatory lesions can be FDG-avid, similar to pancreatic cancers. Contrast-enhanced PET/CT has a better accuracy compared to non-contrast-enhanced PET/CT (88% vs. 76%) for staging of pancreatic cancer [26].

5.2 Utility of imaging in staging of pancreatic cancer

The key question for imaging to answer is tumor resectability. A tumor is considered unresectable if it has metastasized to the liver or the peritoneum, encases the peripancreatic arteries (common hepatic/proper hepatic artery, superior mesenteric artery [SMA], celiac axis), or invades into the adjacent solid organs (kidney, stomach, spine, adrenal gland, and the spleen) [27]. Vascular involvement is defined using two radiological terms: abutment and encasement. When the tumor circumferentially involves greater than 180° of the vessel, it is considered encasement. In contrast, abutment means the tumor circumferentially involves less than 180° of the adjacent vessel and was originally describe by Lu and colleagues [28]. Depending on the degree of circumferential vascular involvement, presence of indeterminate lesions, and performance status, patients are classified as borderline resectable as follows: Group A: tumor abutment of the visceral arteries or short-segment occlusion of the superior mesenteric vein (SMV), abutment of the SMA, abutment or encasement of the common hepatic artery over a short segment, or occlusion of the SMV–portal vein (PV) confluence, with sufficient vein above and below such that venous reconstruction is possible. Group B: indeterminate lesions on imaging suggestive but not diagnostic of metastasis. Group C patients are of marginal performance status [29]. Some of the borderline resectable pancreatic cancers may become resectable in the hands of skilled surgeons who are able to perform primary venous reconstruction and interposition grafting (using great saphenous, internal jugular, or left renal venous grafts) and with the introduction of novel neoadjuvant regimens [27,30,31] (Figure 1a–d). Although it is difficult to compare between MRI and CT, several studies have shown comparable results for local staging, but MRI has better soft tissue contrast whereas CT offers higher spatial resolution [32,33]. The sensitivity for resectability of the pancreatic cancer for MRI and CT

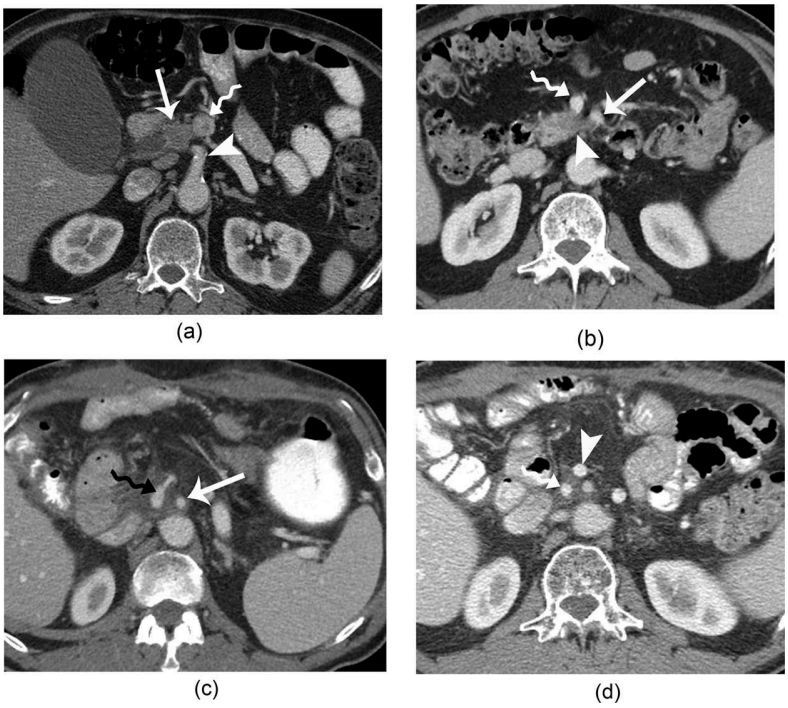

Figure 1. Axial CT scan of the 65 year old female shows (a) a mass in the pancreatic head (arow) abuts the SMV (squiggly arrow) and is seperate from the SMA (arrowhead) as a fat plane is present between the tumor and the SMA (b) Following radiation, however, note that the tumor (arrowhead) has decreased in size, yet now does abut the SMA; in this setting it is difficult to differentiate between fibrotic tissue and involvement of the SMA. The tumor does not encase the SMA and this makes it still resectable. (c) Fluid is present inbetween the SMV (squiggly arrow) and the SMA (arrow), an expected finding after surgery. (d) Six months later the fluid has decreased in amount.

is similar ranging from 82–90% to 81–90%, respectively [32,34,35]. In one study for assessment of vascular involvement, the specificity of CT was 96% on a vessel-by-vessel basis, compared to that of MRI of 98%, respectively [32].

On imaging, it is difficult to differentiate viable versus nonviable tumor after preoperative chemoradiation. Radiation therapy may cause soft tissue stranding around surrounding vessels. Thus, it is imperative to compare the baseline pretherapy exam to identify the true extent of disease in order to prevent upstaging of the patients and preclude them for undergoing surgical resection [36]. Unenhanced PET/CT does not have a role in local vascular staging of pancreatic cancer.

5.3 Nodal disease

The criteria used to diagnose nodal metastasis on cross-sectional imaging such as CT and MRI is the short axis size of the lymph node >1 cm; however, this is nonspecific. The lymph node involvement is based on the location of the primary tumor. For example, if the tumor is located in the anterior pancreatic head, involved lymph nodes will be along the gastrocolic trunk; if the tumor is located in the uncinate process, it will drain into the jejunal nodes. Similarly, carcinoma in the pancreatic tail may involve nodes in the splenic hilum and the retroperitoneal lymph nodes [37]. In assessing lymph node metastases, FDG-PET performs poorly. Reported sensitivities and specificities for FDG-PET are 46% and 63%, respectively [38]. The low sensitivity to detect locoregional adenopathy is likely due to the close proximity of the peripancreatic lymph nodes to the primary tumor, which can lead to a partial volume averaging effect and thereby obscure tumor in the nodes [39,40]. To overcome this limitation, the use of contrast-enhanced PET/CT may be useful [41]. In addition, FDG uptake in the peripancreatic lymph nodes is nonspecific since reactive adenopathy can demonstrate FDG uptake. Reactive adenopathy can occur after biopsy of the pancreatic cancer or after biliary manipulation such as placement of a stent. Thus, confirmation of metastatic adenopathy on histology is needed.

Pancreatic adenocarcinoma can spread along the nerves and is suggestive of a poor prognosis [42,43]. This perineural spread is often overlooked on imaging, is underreported, and is a common cause of a positive margins following surgical resection [43]. The perineural invasion appears as soft tissue thickening on CT along the adjacent vessels. Tumors located in the ventral and dorsal pancreatic head will spread along the plexus pancreaticus capitalis 1 (PPC1), located posterior to the PV, or the gastroduodenal artery (GDA) plexus, located along the GDA, and can extend along the hepatic artery, respectively. Tumors located in the uncinate process will infiltrate along the plexus PPC2 and on imaging, soft tissue thickening can be seen along the posteroinferior pancreaticoduodenal artery and along the SMA [42,43].

5.4 Metastases

Pancreatic cancer commonly spreads to the liver, peritoneum, lungs, and the bones. Presence of metastatic disease to distant

organs renders pancreatic cancer unresectable. However, cross-sectional imaging cannot reliably detect peritoneal disease.

MRI has a better sensitivity for depicting hepatic metastases versus CT (92–94% vs. 74–76%) [44]. MRI can be used as a problem solving tool if the liver lesions cannot be appropriately characterized on CT. PET/CT may be beneficial in the setting of locally advanced cancer to assess for occult metastases and has a sensitivity ranging from 61% to 88% [45–48]. The sensitivity and specificity of FDG-PET for detecting hepatic metastases >1 cm is 68% and 95%, respectively [38,49]; however, the sensitivity decreases as the size of the metastases decreases. The utility of PET still remains controversial; PET may be, however, complementary to conventional imaging in detecting distant metastases [47,50].

5.5 Recurrent disease

Despite resection, many patients develop early recurrence in 6–12 months after surgery (Figure 2a–d). Patients are usually followed by serial CA 19-9 levels and at our institution with CT scans. An elevated tumor marker is suggestive of recurrent disease but does not provide the exact site of disease, which is crucial for subsequent treatment planning and management. PET/CT is useful in the setting of elevated tumor markers without evidence of disease on conventional imaging modalities. A recent study demonstrated that contrast-enhanced PET/CT had a sensitivity, specificity, and accuracy of 91.7%, 95.2%, and 93.3% versus that of CT of 66.7%, 85.7%, and 75.6%, respectively [51]. Following Whipple's procedure, postoperative changes are commonly present posterior to the SMA, SMV, and the hepatic artery; however, these areas are also the most common sites of recurrent disease. Therefore, these areas should be carefully monitored and most importantly compared to the baseline postoperative exam. Any enlarging soft tissue in this region should raise the concern for recurrent disease.

Lymph nodes may enlarge after surgical resection and may be difficult to assess for lymph node metastases, unless there is progressive enlargement in size. Some authors have demonstrated utility of PET/CT in assessing recurrent disease in the lymph nodes in the setting of inconclusive CT [52,53].

In summary, CT is the preferred modality to stage a primary pancreatic cancer. MRI may be used if the patient is unable to get intravenous iodinated contrast or as a problem solving tool to assess indeterminate liver lesions. Contrasted PET/CT performs well in locally advanced pancreatic cancer and helps in detecting unsuspected metastases but is not routinely used. It can also be used to assess recurrent disease when CT is inconclusive.

5.6 Endoscopic procedures in establishing diagnosis

Over the past four decades, endoscopic retrograde cholangiopancreatography (ERCP) has been utilized, initially as a diagnostic tool and later as a therapeutic tool for the evaluation. While ERCP allows the imaging of the bile duct under fluoroscopy, ERCP with brushing and biopsy has a poor diagnostic yield in the range of 35–70% [54–60]. On the other hand, EUS-guided fine needle aspiration (EUS-FNA) has been shown to be highly accurate for the diagnosis of pancreatic masses (Figure 3). Even when MDCT was

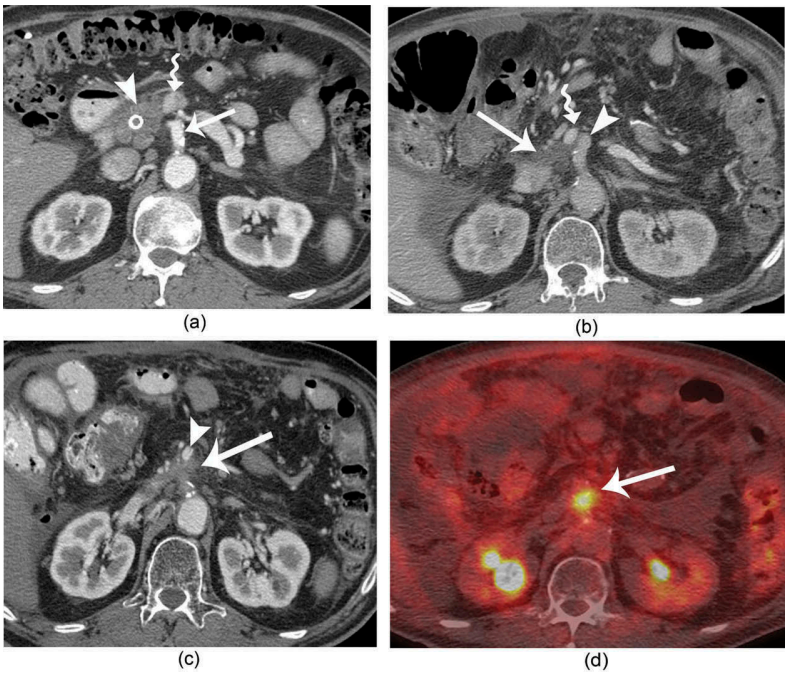

Figure 2. Axial CT and a PET/CT scan in a 70 year old male show (a) a mass in the pancreatic head (arow) abutting the SMV (squiggly arrow) and is sperate from the SMA (arrowhead) as a fat plane is present between the tumor and the SMA. A stent is present in the common bile duct. (b) Fluid is present posterior to the vessels (arrow), an expected finding after surgery. (c) Soft tissue thickening is present posterior to the SMA (arrow). Note the SMV is not seen and obliterated. The soft tissue thickening represents recurrent disease. (d) Axial PET/CT shows FDG uptake (arrow) in the region of the soft tissue thickening suggesting recurrent disease.

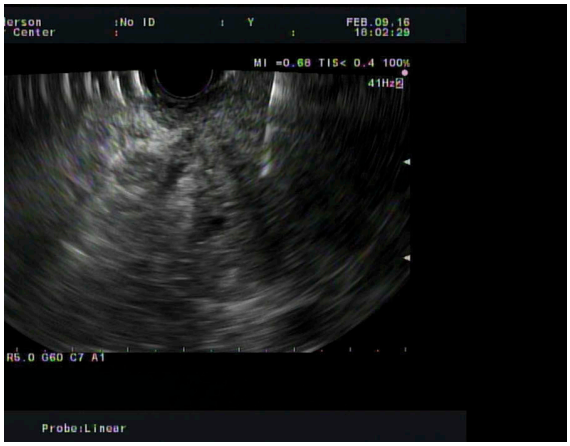

Figure 3. EUS-FNA of pancreatic adenocarcinoma located in the head of the pancreas.

indeterminate, EUS was found to be highly sensitive and accurate in patients whose clinical presentation was suspicious for pancreatic cancer as shown by Wang et al., who reported EUS-FNA had a sensitivity, specificity, positive predictive value (PPV), and accuracy of 87.3%, 98.3%, 98.5%, and 92.1%, respectively, in this setting [61]. To further differentiate malignant lesions from benign processes, contrast-enhanced power Doppler EUS (CED-EUS) and elastography (E-EUS) were introduced. In CED-EUS, a contrast media is injected and then the micro-vascularized pattern of the lesion is studied using EUS and power Doppler. In pancreatic adenocarcinoma, there is reduced contrast enhancement, compared with that of the surrounding tissue. On the other hand, E-EUS examines tissue elasticity and the differences of tissue elastic properties are shown in a colorized scale. Tumors and inflammatory conditions would lead to tissue changes resulting in hardening. E-EUS reports the level of hardness as qualitative scores and/or quantitative methods, strain ratio (SR); SR is considered to be more objective assessment of the two E-EUS reporting methods. A prospective, single-blinded study reported that the sensitivity, specificity, PPV, negative predictive value (NPV), and accuracy rate of E-EUS were 86.2%, 66.7%, 89.3%, 60%, and 81.6%, respectively, thus, concluding the sensitivity of E-EUS was not superior to EUS-FNA [62]. Another study that evaluated the yield of contrast-enhanced EUS (CED-EUS) and of SR EUS-elastography (SR-E-EUS) for differentiating pancreatic solid lesions showed that there were no statistically significant differences concerning sensitivity (79%, 90%, 93%) and specificity rates (85%, 75%, 67%) of EUS-FNA, SR-E-EUS, and CED-EUS. The authors concluded that the clinical utility of CED-EUS remains questionable, although patients with inconclusive EUS-FNA could benefit from CED-EUS; the accuracies of CED-EUS and SR-E-EUS are similar to EUS-FNA [63].

Cholangioscopy allows direct visualization of the biliary tract enabling target-specific tissue acquisition. However, the fiberoptic cholangioscope (mother–daughter system) was plagued by its fragility, technical difficulty in use requiring two operators, and poor image quality. To overcome these limitations, SpyGlass (Boston Scientific, Natick, MA, USA) was introduced; SpyGlass is a single-operator cholangioscopy system with 4-way steering and separate working and irrigation channels. It also allows direct tissue acquisition by small biopsy forceps through the working channel. The diagnostic accuracies of SpyGlass in indeterminate biliary strictures were reported to be 72–85% with a sensitivity of 49–82%, a specificity of 82–100%, a PPV of 100%, and a NPV of 69–100% [64,65].

In a retrospective, single-center study involving 88 patients, Tieu et al. reported technical success in 87.5% and clinical success in 77.3%; for indeterminate biliary strictures, it had 100% PPV [66].

Another device that can assist in discerning indeterminate stricture is probe-based confocal laser endomicroscopy (pCLE, Mauna Kea Technologies, Paris, France). In this technique, a confocal probe is advanced into the bile duct through the working channel of a duodenoscope. Following an intravenous injection of fluorescein, a low-power laser directs light onto a single point on the biliary mucosa providing 'real-time histology.'

A recent study of 61 patients showed that the sensitivity, specificity, PPV, NPV, and accuracy with combination of pCLE with endobiliary and EUS-FNA were 100%, 71%, 91%, 100%, and 93%, respectively [67].

6. Endoscopic therapy

6.1 Should we drain the biliary obstruction or not?

Approximately, 80% of pancreatic cancers occur at the head of the pancreas and may cause biliary obstruction [68]. Previously, it was thought that preoperative drainage was beneficial as theoretically, drainage would decrease complications related to cholestasis including cholangitis, impaired clotting and immunological response, and fat malabsorption. While biliary drainage in patients with malignant obstruction also provides relief of jaundice and improves symptoms of nausea, loss of appetite, and pruritis, routine preoperative biliary decompression remains a controversial issue as it poses risks of contamination of the sterile biliary system, bleeding, and procedurally induced pancreatitis. To provide some helpful guidance in this controversial issue, a prospective, multicenter, randomized trial was carried out involving 202 patients, 96 in early surgery group and 106 in preoperative biliary drainage group. The authors reported the rates of serious complications of 39% in the early-surgery group and 74% in the biliary-drainage group ($P < 0.001$). The mortality and length of hospital stay did not differ between the two groups [69]. This study, however, had a low ERCP technical success rate of 75% on the first attempt, a high stent occlusion rate of 15% due to using a plastic stent, and 2% bleeding rate post-ERCP where sphincterotomy was not absolutely necessary.

Though it is difficult to conclude between the preoperative biliary drainage and no drainage, there are clear cases as to drain or not to drain (Figure 4).

- If a patient were to undergo early surgical resection for resectable pancreatic cancer, no attempts should be made to drain the biliary system before surgery.

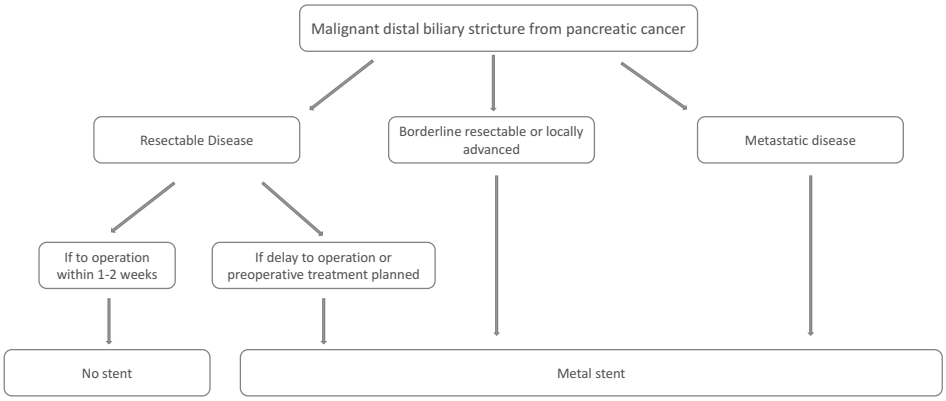

Figure 4. Endoscopic management of malignant biliary stricture in pancreatic cancer.

- If surgery will be delayed for any reason and the patient is symptomatic from biliary obstruction, then biliary drainage should be established.
- If the patient is to undergo preoperative chemoradiation, biliary drainage should be established.
- If the patient, who has metastatic disease, will receive chemotherapy, biliary drainage should be established.

6.2 How should we drain the biliary obstruction

Before the 1980s, the biliary drainage was predominantly a surgical procedure. Since then, first percutaneous and later endoscopic drainage has become the main modality for palliation of biliary obstruction. Percutaneous transhepatic biliary drainage (PTBD), while effective in draining the biliary obstruction, comes with the inconvenience of having an external drainage bag at least for 6 weeks, not to mention loss of bile which is an essential component in emulsifying ingested fat for efficient absorption. Multiple randomized controlled, prospective, and retrospective studies have compared surgical drainage to endoscopic drainage for malignant biliary obstruction. The trials have shown endoscopic drainage to be equally efficacious to surgical drainage, with reduced mortality and morbidity [70,71].

6.3 Techniques in ERCP

6.3.1 Biliary cannulation

Although ERCP for biliary access and drainage is successful in 90–95% of cases, biliary cannulation can be quite challenging in patients with pancreatic cancer due to changes in anatomy, obscured and/or friable ampulla from tumor infiltration, and duodenal obstruction from the bulky tumor.

6.3.2 Conventional cannulation

In a systematic review comparing the effectiveness and safety of the guidewire-assisted cannulation technique (GWAC) compared to the conventional contrast-assisted cannulation (CAC) technique for the prevention of post-ERCP pancreatitis (PEP), 12 randomized controlled trials comprising 3450 patients, the GWAC technique significantly reduced PEP compared to the CAC technique (RR 0.51, 95% CI 0.32–0.82). Furthermore, the GWAC technique was associated with greater primary cannulation success (RR 1.07, 95% CI 1.00–1.15), less precut sphincterotomy (RR 0.75, 95% CI 0.60–0.95), and no increase in other ERCP-related complications [72].

Therefore, GWAC should be the first-line cannulation technique.

When GWAC is not successful, the first salvage technique used most often is the 2-wire technique with the first wire placed in the pancreatic duct. Since the first wire is occupying the pancreatic duct orifice, the second wire is likely to be deflected off the first wire and guided into the bile duct. This is also the most utilized technique after GWAC failure in Japan [73].

6.3.3 Precut needle-knife sphincterotomy

There are two different practices in performing precut needle-knife sphincterotomy. The needle-knife sphincterotomy can be performed with cutting upward from the ampullary os with or without pancreatic duct stent in place. The other technique is cutting through the intraduodenal segment of the ampulla above the ampullary os without involving the ampullary os. This technique has a lower risk of causing pancreatitis as the ampullary os is not touched. However, it also requires training and experience before becoming proficient.

6.3.4 EUS-guided ERCP

EUS-guided ERCP can be performed in two ways. In the rendezvous technique (EUS-RV), the extrahepatic bile duct (preferably the common bile duct, rather than the common hepatic duct) or left hepatic duct is accessed using a 19-gauge EUS needle. Then, a 0.035 guidewire is introduced into the bile duct and advanced down to the duodenum through the ampulla. Subsequently, with change of the scope to duodenoscope, the guidewire is retrieved by a snare. Over the retrieved guidewire, a sphincterotome can be advanced. The published data on EUS-RV show an overall success rate of 81% with a complication rate of 10% [74].

This technique was compared with precut papillotomy in 206 patients; 58 patients in EUS-RV group and 144 patients in precut papillotomy group. The technical success rate was significantly higher for EUS-RV than for precut papillotomy; 98.3%

versus 90.3%; $P = 0.03$ with no significant difference in the complication rate [75].

However, when there is duodenal obstruction due to the tumor mass, the ampulla cannot be reached or accessed despite rendezvous technique. In this setting, the second technique (choledochoduodenostomy) can bring biliary drainage without having to reach the second portion of the duodenum. In a choledochoduodenostomy, the dilated bile duct is directly accessed using EUS-guided 19-gauge needle from the bulb. Next, a 0.035 guidewire is advanced into the bile duct toward the liver. Over the guidewire, a metal stent can be advanced thus establishing biliary drainage.

The preponderance of evidence from published studies shows a good technical and functional success with EUS-guided ERCP in cases of failed conventional ERCP when performed by endoscopists in centers with experience and proficiency performing both procedures. However, the complication rates associated with EUS-guided ERCP are still significant, and it does not appear to fare better than the alternatives. Until these techniques have demonstrated lower overall complication rates when compared to the alternatives such as PTBD, EUS-guided ERCP for biliary drainage should be carefully considered as an alternative for failed conventional ERCP.

6.3.5 Which stent should we use in biliary drainage by ERCP?

Over the past two decades, there have been multiple reports comparing different biliary stents for optimal drainage, polyethylene–plastic stents versus self-expanding metal stent (SEMS), uncovered SEMS (USEMS) versus covered SEMS (CSEMS), mostly in retrospective studies and some prospective studies of small sample size.

Plastic stents are often occluded at 3–4 months due to their small luminal diameters, the formation of adherent bacterial biofilm, and accumulation of biliary sludge. Therefore, SEMS are increasingly used for their longer patency and more efficient drainage due to the larger diameter. In addition, SEMS are also often cost effective. The initial higher cost associated with metal stent placement was equaled or surpassed by the need for repeat procedures in the plastic stent group requiring stent exchanges [76].

Traditionally, SEMS have been used for palliation of jaundice in unresectable tumors. However, more recently these stents are increasingly being used in resectable cancers when neoadjuvant therapy is planned. Throughout the past two decades in managing pancreatic cancer, the approach of an operation first followed by adjuvant therapy failed to show any significant improvements in patient survival. Over the past decade, there has been a paradigm shift to move toward preoperative neoadjuvant chemotherapy and radiation in the setting of borderline resectable cancer and even resectable pancreatic cancer [76]. Neoadjuvant therapy efficiently delivers early treatment of micrometastic disease. Although the longer preoperative interval was not associated with local tumor progression during the preoperative therapy, it required durable biliary decompression. Consequently, effective preoperative biliary drainage has become a paramount concern to avoid the potential hepatotoxicity of chemotherapeutic agents used during the preoperative treatment.

In this setting, SEMS insertion resulted in fewer ERCPs, shorter hospital stay, and fewer complications than plastic stents during the preoperative treatment period (Figure 5) [76–79].

Recently, Strom et al. reported a 12-year experience on the effect of preoperative biliary drainage on recurrence and survival among patients with resectable pancreatic cancer. The authors found that the median and 5-year survival for PTBD, ERCP, and no biliary drainage were 17.5 months and 3%, 22.4 months and 24%, and 28.9 months and 32%, respectively. The reasons why PTBD patients had a higher hepatic recurrence and worse survival could be that PTBD patients had more advanced disease with lymph node involvement, but perhaps the PTBD track allowed tumor cell seeding to the liver [80].

6.3.6 Should we use CSEMS or USEMS?

Multiple studies compared types of SEMS – USEMS versus fully CSEMS. The majority of these studies have shown no significant differences in the patency rate or overall survival between USEMS and CSEMS for malignant biliary strictures. USEMS are susceptible to occlusion by tissue in growth through their mesh design (Figure 5). While CSEMS are protected from tissue ingrowth, they have a higher tendency to migrate, especially in the setting of effective chemoradiation.

In addition to the higher rate of stent migration, multiple studies have suggested that CSEMS pose an increased risk of cholecystitis and/or pancreatitis by blocking the cystic duct orifice and/or pancreatic duct when compared to USEMS. However, the study with the largest number of patients up to date showed CSEMS had only a higher rate of pancreatitis without an increased rate of cholecystitis [81]. Therefore, if the patient is scheduled to undergo surgical resection within 5 months (which is usually the case in preoperative chemoradiaton followed by surgery), and would like to reduce the risk of stent migration, USEMS is a reasonable choice.

Figure 5. Metal stent draining dark bile.

6.3.7 How did eluting stents perform?

More than a decade ago, Kalinowski et al. showed that paclitaxel has a dose dependent inhibition of cell proliferation of human epithelial gallbladder cells, human fibroblasts, and pancreatic carcinoma cells [82]. This served as the basis in developing drug-coated or drug-eluting stents for malignant biliary trictures. Paclitaxel inhibits proliferation of cell lines responsible for metal stent obstruction: possible topical application in malignant bile duct obstructions [80]. A decade later, an animal study confirmed that metal stents coated with paclitaxel and various concentration of Pluronic F-127 in phosphate-buffered saline solution was safe and provided enhanced local drug delivery [83]. In a prospective comparative study, the efficacy and complication rates of paclitaxel-eluting covered metal stents (PECMS) were compared with those of CSEMS in patients with malignant biliary obstruction [84]. The final analysis included 49 of 52 patients, 24 with PECMS and 25 with CSEMS, and showed no significant difference between the two groups in stent patency ($P = 0.307$) or survival time ($P = 0.596$). The complications occurred in four PECMS patients (three cholangitis and one pancreatitis) and in one CSEMS patient (pancreatitis) [84]. While there exists theoretical advantage in PECMS over CSEMS, a larger study needs to be done to discern whether PECMS delivers a clear benefit in managing malignant biliary obstruction.

7. Is local therapy for pancreatic cancer effective or just an exercise with no clear benefit?

7.1 Ablation

With the success in treating hepatocellular carcinoma over the past decade, radiofrequency ablation (RFA) has been introduced into the management of malignant biliary stricture. ERCP-directed RFA provides coagulative necrosis via thermal energy using a bipolar catheter. The most widely used RFA catheter is an 8-Fr device with two electrodes spaced 8 mm apart at the end of the catheter that can be passed over a guidewire (Habib EndoHPB; EMcision, London, United Kingdom). Several studies with a small number of patients reported some benefits of RFA in managing biliary strictures, mainly in cholangiocarcinoma and some in pancreatic cancer [85–88]. On the other hand, a study involving 12 patients reported significant biliary bleeding 4–6 weeks after RFA of the bile duct in 3 patients where 2 patients died from bleeding. In one patient, spontaneous hemobilia occurred, and in the other, during the stent extraction. In the third patient, insertion of an USEM stopped the bleeding [89]. Thus, although some studies of small populations suggest the procedure is safe and feasible, RFA of the bile duct should be carried out with caution under research protocol at this time. Clearly, the benefits of RFA in the bile duct appears to be limited and confined within the realms of stent patency, not in survival in patients with pancreatic cancer.

7.2 Injection therapy

EUS-guided antitumor injection has been studied in advanced unresectable pancreatic cancer where the prognosis is dismal. Not only does EUS allow visualization of the tumor in real time, but also provides a way to inject an agent into the tumor directly. With the idea of delivering a high level of an agent into the tumor without a systemic side effect, multiple agents have been introduced in clinical trials: an allogenic mixed lymphocyte culture [90], TNFerade [91,92], Onyx 015 (E1B-55kD gene deleted replication selective adenovirus) [93,94], tumor-antigen loaded dendritic cells [95], and gemcitabine [96–98]. The benefits derived from the local injection therapy could not be clearly discerned as most of the patients received a concomitant systemic therapy. Clearly, local therapy alone provides no significant clinical benefit as pancreatic cancer is a systemic disease. Further better designed studies are needed to tease out the benefits of local injection therapy.

8. EUS-guided therapy for gastric outlet obstruction (GOO)

Due to the direct invasion and/or inflammatory process from the pancreatic cancer, gastric outlet obstruction (GOO) can occur at the duodenal bulb, second portion, or third portion of the duodenum. Patients with malignant GOO suffer from inability to eat, nausea, vomiting, and discomfort. When these patients are unable to undergo surgical bypass, endoscopic SEMS placement across the stricture in the duodenum has been the alternative. In a large retrospective cohort study of 334 patients, 241 patients underwent enteral SEMS placement and 93 patients underwent gastrojejunostomy (GJY). The study showed that the mean time to tolerate a liquid and soft diet was significantly shorter in the SEMS group (2.2 vs. 4.8 days) than in the GJY group, with a lower complication rate (4.6% vs. 10.8%). However, the reintervention rate was significantly higher for the SEMS group (14.9 % vs. 3.2%, $P = 0.002$) [99]. To overcome the limitations of frequent reintervention in enteral SEMS placement, endoscopic GJY has been attempted.

To date, two clinical studies ($N = 15$ and 18) were reported using magnetic compression anastomosis and flared type fully covered metal stents; the technical success rates were 89% and 67%; in the first study, four minor complications were seen during the follow-up [100]. On the other hand, the second study was terminated prematurely due to a serious adverse events (stent perforation) leading to mortality with 25% stent migration rate [101]. To overcome the tendency of migration, a new lumen-apposing covered CSEMS with perpendicular flanges has been recently introduced. In 2013, Itoi et al. reported EUS-guided GJY by using an enteric balloon and lumen-apposing covered metal stent in an animal study involving five pigs. Four out of five stents were successfully deployed without any adverse events with a mean time to stent placement of 44.2 min (range 28–64 min). At 1 month follow-up, no complications were seen [102]. In another animal study of nine pigs, again the technical success rate was high at 100% with one (11%) pneumoperitoneum [103]. Now, a cautery-enabled access and delivery catheter with the preloaded therapeutic lumen-opposing stent is also available. This system eliminates exchange maneuvers required in aforementioned procedures.

While EUS-guided anastomosis is feasible utilizing real-time visualization and Doppler to avoid vascular structures thus

potentially minimizing complications, it requires expertise and experience to avoid fatal outcomes.

9. Multidisciplinary approach

Early detection, accurate staging, proper plan of treatment, and skilled management can lead to better outcomes in pancreatic cancer. This effort clearly requires a multidisciplinary team approach, including gastroenterologists, radiologists, surgical oncologists, radiation oncologists, and medical oncologists. With ongoing collaborative research and clinical trials, we hope to see an improvement in the 5-year survival rate.

10. Expert commentary

Management of pancreatic cancer is one of the most challenging tasks we face today. In spite of the unceasing efforts we have made over the past several decades, the 5-year survival has not improved much and rests at 6–7%. There are several practical reasons why no significant advancement has been achieved yet in this field. First, the patients with pancreatic cancer remain asymptomatic until the disease is too far advanced to the point where surgical resection is impossible. To overcome the delay in making the diagnosis, many researchers and clinicians have collaborated in discovering a tumor marker that has a high sensitivity, specificity, and accuracy. Among the promising tumor markers are mesothelin, GPC1, circulating miRNA, and serum TSP-1. Though all four showed promising results in research settings, none of them has been validated in clinical setting to be used as the tool to screen asymptomatic pancreatic cancer patients. Consequently, we are still relying on CA 19-9 that provides limited information about the disease, due to its poor sensitivity and specificity. Second, establishing the diagnosis has been challenging, especially in the early stage where the tumor is not visible on imaging studies despite the clinical presentation that is suspicious for harboring malignancy. With advancement in diagnostic and therapeutic endoscopic techniques, we have become much more proficient in visualizing and accessing the biliopancreatic system.

Lastly, the nature of the disease itself poses a difficulty in management; pancreatic cancer is a systemic disease. Even with excellent local control of the cancer with margin negative resection, the patients often encounter recurrence in a few months due to microscopic satellite lesions remaining in the surrounding tissues. To prevent recurrence and improve survival rate, preoperative chemoradiation has been introduced. With this approach, the rate of margin negative resection has increased thus bringing an improved 5-year survival rate for those who underwent surgery after chemoradiation. While the task of managing pancreatic cancer is daunting, we may continue to make small steps forward with collaborative efforts among all who devote themselves to this arduous mission.

11. Five-year view

With continued effort in development of new potential tumor markers, we may find a biomarker that will enable us to make an early diagnosis of pancreatic cancer, well before patients become symptomatic. The marker may be easy to obtain and inexpensive, so that we can use not only in high-risk population, but also in general population as in colon cancer screening. In parallel to advancements in finding tumor markers, the endoscopic armamentarium and techniques will continue to evolve facilitating tissue acquisition for diagnosis as well as guiding therapy in a personalized manner. In addition, EUS may develop into the screening modality of choice and be a means to deliver endoscopic therapy in pancreatic cancer.

12. Key issues

- The risk factors for development of pancreatic cancer include cigarette smoking (1.6-2.5 fold), long-standing diabetes (2.0 for type 1 diabetes and 1.8 for type 2 diabetes), family history of pancreatic cancer, history of pancreatitis, obesity (1.72 fold), and alcoholism (chronic pancreatitis, 18.5-26.3 fold).
- Among the potential markers that have shown promising results are mesothelin, glypican-1, circulating microRNAs in pancreatic juice, and serum thrombospondin-1.
- CA 19-9 lacks sufficient sensitivity and specificity for detecting early pancreatic cancer. It is elevated in only 50% of pancreatic adenocarcinomas less than 3 cm in size. Lacking specificity, CA 19-9 is elevated in gastric cancer, colorectal cancer, cholangiocarcinoma, and any biliary obstruction, and acute and chronic pancreatitis.
- In a multicenter, prospective trial involving 225 asymptomatic high-risk patients, five US institutions compared multidetector computed tomography per pancreas protocol (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) as screening tools and showed that EUS was the best modality to detect a pancreatic abnormality (11%, 33.3%, and 42.6% respectively).
- If a patient were to undergo early surgical resection for resectable pancreatic cancer, no attempts should be made to drain the biliary system before surgery.
- If surgery will be delayed for any reason and the patient is symptomatic from biliary obstruction, then biliary drainage should be established.
- If the patient is to undergo preoperative chemoradiation, biliary drainage should be established.
- If the patient, who has metastatic disease, will receive chemotherapy, biliary drainage should be established.

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