Chapter 1

The Role of ERCP and EUS in Pancreatic Adenocarcinoma

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Abstract

Pancreatic adenocarcinoma is considered as fourth leading cause of cancer death in men and women in most countries. It has a relatively high incidence as well, making it one of the top ten incidence cancer in Europe and USA, with an overall 5-year survival rate of less than 5%. Pancreatic cancer due to aggressive behavior of the tumor and relative frequency that appears to be increasing is a major health problem. The clinical presentation of pancreatic cancer can widely vary, due to tumor location and disease stage.

Due to the high cost of surgery as the only chance of a cure pancreatic cancer and the rapid progression of the cancers, early detection of the cancer through screening will be required to improve long-term outcomes. Several imaging modalities are currently available for the evaluation of pancreatic cancer. Modern imaging techniques such as transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), Endoscopic Ultrasound (EUS) and Endoscopic Retrograde Cholangiopancreatography (ERCP) are less invasive and less costly than surgery. The main aim of imaging tests is early detection as well as an accurate staging of lesion extension and possible vessel invasion. This is done in order to choose the best clinical and therapeutic management.

EUS is considered one of the most sensitive imaging modalities to detect pancreatic masses. EUS is able to gain accurate images, with high negative predictive value, ranging from 87 to 100%. Another important method in
the diagnosis of pancreatic cancer is ERCP. The role of ERCP in the diagnosis of pancreatic cancer is considerably reduced, if compared to the past. Due to the post-procedural risk of pancreatitis, ERCP is mainly a therapeutic modality with stent placement in patients with obstructive disease, whereas its diagnostic role has been replaced by EUS.

The Role of EUS and ERCP in the Diagnosis of Pancreatic Cancer

Pancreatic cancer ranks as one of the most lethal malignancies, being the fourth leading cause of cancer death in most countries. Although the incidence of pancreatic cancer is stable, there seems to have been a shift from localized to regional disease in recent years. Consequently, the prognosis is grim, with an overall 5-year survival rate of less than 5% [1-3].

The only chance for cure of the pancreatic cancer is currently surgical resection; however, only 10-15% of patients have an early diagnosis and a chance for potential curative resection [4,5]. Furthermore, due to a non-specific clinical presentation of the cancer, it is often diagnosed at an advanced stage and is rarely amenable for curative treatment. Therefore early diagnosis and appropriate staging of pancreatic cancer are still essential to define the best care and to improve patient survival [1,6].

There are three steps in the diagnosis of pancreatic carcinoma before deciding on the treatment method. The first step in the diagnosis of pancreatic carcinoma is to detect the tumor. One of the reasons for the low survival rates of patients with pancreatic cancer is the difficulty in making an early diagnosis. The higher the sensitivity for detecting pancreatic tumors, the greater the number of patients with early pancreatic cancer can be expected to be. The next step is to differentiate pancreatic adenocarcinoma from other pancreatic diseases such as chronic pancreatitis, benign or malignant islet cell tumor, and intraductal papillary mucinous neoplasm. Finally, imaging should be able to permit staging of the tumor. In the case of pancreatic cancer, any infiltration of vessels and lymph nodes as well as possible distant metastases takes on special importance due to the impact on the assessment of resectability of the tumor or the decision to initiate chemotherapy [7-9].

In recent years, diagnostic imaging techniques such as multi-detector-row computed tomography (MDCT), MRI, ERCP and EUS have been developed, elevating the ability to diagnose pancreatic carcinoma, although there are still inherent limitations. Each method has advantages and limitations, making the selection of the proper diagnostic technique, in terms of purpose and characteristics, especially important [8,10]. These methods have variable sensitivity for the diagnosis of specific pancreatic disor-
ders. All these imaging methods improve the specificity of the diagnosis substantially, usually providing complementary information that determines the best treatment option [4,11]

**Diagnostic Role of EUS**

Endoscopic ultrasound was first introduced by Dr. Eugene DiMagno in the 1980s by combining a high frequency ultrasound transducer to an endoscope [12]. EUS has been shown to be a cost-effective technique for evaluating pancreatobiliary disorders, particularly where others diagnostic methods have failed, and has a higher diagnostic yield than positron emission tomography (PET), CT and US for recognizing early pancreatic tumors [13,14]. EUS appeared as a promising imaging method for the study of pancreatobiliary diseases, because it allows the placement of a high-frequency ultrasound transducer near the targeted organ, thus providing detailed high-resolution images. Moreover, due to the small distance between the probe and the pancreas and the capability of tissue acquisition, EUS is considered the best imaging technique for the study of pancreas [12,15].

The technology of EUS progressed with the introduction of new electronic radial and linear EUS transducers with digital image processing, enhanced resolution, and color Doppler capability [4]. EUS is able to gain accurate images, with high negative predictive value, ranging from 87 to 100%. Furthermore, this diagnostic method allows us to perform targeted pancreatic biopsy of visualized changes and to obtain rapid histopathologic confirmation [2].

Pancreatic cancers can have different ultrasound appearance, depending both on tumor location and on the lesion intrinsic nature. The cancer is usually seen as ill-defined, hypoechoic mass. It can have inhomogeneous pattern and can cause dilation of the distal pancreatic duct [15]. EUS is considered a safe procedure with complication rates as low as 1.1-3% for diagnosis of pancreatic cancer. Sensitivity of EUS in pancreatic mass detection can reach 97%, with a better yield than transabdominal US and conventional CT scan, mainly with small size lesions (<3 cm). EUS can assess tumor invasion and presence of metastatic lymph nodes with high accuracy. For better diagnostic yield, EUS should be performed after contrast enhanced CT and before ERCP. Despite high sensitivity of EUS, specificity is quite limited, especially in the differential diagnosis with inflammatory processes, which can mimic the same sonographic morphology [1,16].

**EUS guided fine needle aspiration (EUS-FNA)**

The introduction of EUS guided fine needle aspiration (EUS-FNA) in the early 1990s represented a major breakthrough by offering the possibility to obtain a tissue diagnosis, especially for confirmation of malignancy
in pancreatic mass lesions [17]. EUS-FNA is a safe and highly accurate method for tissue diagnosis of patients with suspected pancreatic carcinoma. This technique is currently performed routinely at many endoscopic units and it is obvious that this procedure has a major impact on therapeutic management of the patients by obtaining a definite tissue diagnosis. EUS-FNA is very useful in establishing a clear tissue diagnosis of malignancy, but also in accurately staging the disease preoperatively, influencing the decision making process and thereby reducing the morbidity that accompanies inappropriate surgical interventions in advanced pancreatic cancer patients. Moreover, EUS-FNA has a lower risk of needle tract seeding when compared with a percutaneous approach due to a short needle track, which does not pass through peritoneal or pleural surfaces [1,18,19].

The ability to perform EUS-FNA may overcome some of the specificity problems encountered with EUS in distinguishing benign from malignant lesions, allowing an improvement of EUS accuracy, mainly as a result of enhanced specificity, without losing too much in sensitivity [7]. The technique of EUS-FNA has a success rate of 90–95%, with an overall sensitivity and specificity of 90% and 100%, respectively. Even minute lesions of 5 mm can be visualized and biopsied. Contrary to what might be expected, the size of the lesions, whether small (≤25 mm) or large (>25 mm) does not influence the overall diagnostic yield, sensitivity, specificity, or accuracy of the method. Overall, EUS-FNA can still yield better sensitivity and specificity than ERCP brushing and CT/US-guided FNA in the diagnosis of pancreatic cancer [1,4].

**EUS guided fine needle aspiration (EUS-FNA)**

EUS-guided core needle biopsy (EUS-CNB) is another tissue sampling method, developed to overcome the limitations of EUS-FNA, especially the low cellularity sample. It is a device with a 19 gauge needle and an 18 mm specimen tray, which can collect a tissue core for histologic assessment, useful also for gene and immuno-histochemical analysis. It may improve the diagnostic yield of EUS, especially in lymphomas, where a cytology specimen does not allow assessment on tissue architecture, as well as subepithelial tumors, autoimmune pancreatitis, tuberculous lymphadenopathy and microcystic pancreatic tumors [4,20].

EUS-CNB was designed to overcome the limitations of EUS-FNA by providing a histologic specimen that increases the accuracy of diagnosis. The overall diagnostic accuracy of EUS-CNB with fewer passes was initially reported to be higher than that of EUS-FNA (85% versus 62%), although the difference was not statistically significant [4].
Diagnostic Role of ERCP

Another important method in the diagnosis of pancreatic cancer is an endoscopic retrograde cholangiopancreatography (ERCP). During an ERCP, cannula is passed from the endoscope into the pancreatic or biliary ducts. Contrast dye is injected through the cannula into the ducts and the biliary and pancreatic ductal systems are visualized fluoroscopically. This technique is a combined endoscopic-radiographic examination method which is the gold standard in the diagnosis of pancreatic tumors, especially in patients with enlarged bile and pancreatic ducts. Most tumors are ductal adenocarcinomas, which affect and obstruct main pancreatic duct or its branches so ERCP provides best visualization [2,21].

ERCP allows for visualization of the hepatobiliary tree, sampling of pure pancreatic juice and assessment for genetic analysis of tissue from biopsies and brushings. Unlike other imaging modalities, tissue diagnosis of the involved ducts in ERCP may be achieved using needle aspiration, brush cytology, and forceps biopsy. ERCP directed brush cytology has a low sensitivity between 33% and 57% and a specificity between 97-100%. Even adding ERCP-directed biopsies the sensitivity does not exceed 70%. Triple sampling using brush cytology, FNA and forceps biopsy of biliary stricture during ERCP improves the sensitivity for diagnosing cancer to 77% [1,7].

The role of ERCP in the diagnosis of pancreatic cancer is considerably reduced, if compared to the past. Indirect findings such as combined dilation of the bile and the pancreatic duct or abrupt cutoff in the main pancreatic duct or a solitary long stricture of the pancreatic duct could raise suspicion of malignant disease but may also be observed in chronic pancreatitis. Moreover, due to the post-procedural risk of pancreatitis, it is mainly a therapeutic modality with stent placement in patients with obstructive disease, whereas its diagnostic role has been replaced by EUS and MR cholangiopancreatography (MRCP), where available [1,16].

Overall, diagnostic ERCP may not be indicated in patients with clinically evident pancreatic cancer, but it may be valuable if a tumor is suspected despite negative results on US and CT, or may be used as an additional aid to differentiate between chronic pancreatitis and cancer [22].

The Role of EUS and ERCP in the Staging of Pancreatic Cancer

Surgical resection is the only potentially curative treatment for pancreatic adenocarcinoma, although most of the patients are found with unresectable disease at the time of surgery. It should be limited to those patients without metastatic disease and in which the entire lesion can be resected with negative margins. In some patients the only obstacle for a radical resection is represented by
the involvement of the portal or superior mesenteric vein [23].

The staging of pancreatic cancer underwent major changes in the 6th revision (2002), with T3 tumors defined as extending beyond the pancreas, but not involving the superior mesenteric artery or the celiac axis, while T4 tumors are defined as involving the superior mesenteric artery or the celiac axis. The change of previous criteria of vascular invasion of the portal vein and superior mesenteric vein, which were notoriously difficult to assess, is likely to increase the overall staging accuracy. Accurate staging of patients with pancreatic cancer is critical to avoid the expense, morbidity, and mortality related to unnecessary surgery [11,16]. The most used staging system for pancreatic cancer is the TNM (Tumor-Node-Metastasis), proposed by AJCC (American Joint Committee on Cancer), showed in Table 1.

The major role of imaging techniques is to identify with high accuracy the patients that might benefit from a major surgical intervention with curative intention and not to refer patients with locally advanced or metastatic pancreatic cancer to surgery. While several tests are available for assessing such patients, consensus has not been achieved on the optimal approach [4,16]. Currently, the preferred modality for pancreatic cancer staging and assessing resectability is CT because its low cost and high availability and MRI for preoperative assessment of pancreatic cancer, with an accuracy of 86% vs 71% even with comparable sensitivity of MRI for detecting pancreatic cancer (88%-96%). However, Complementary and a combination of helical/multidetector CT with EUS seems to be the best approach for accurate staging and diagnosis of tumor resectability. ERCP has a limited role in staging of pancreatic and biliary cancers [16,21].

Table 1. TNM Classification for Pancreatic Cancer [24].

| Primary tumor (T) | | | |
|------------------|----------------|----------------|
| T0               | No evidence of primary tumor | | |
| T1               | Tumor limited to the pancreas, ≤ 2 cm in greatest dimension | | |
| T2               | Tumor limited to the pancreas, > 2 cm in greatest dimension | | |
| T3               | Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery | | |
| T4               | Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor) | | |

| Regional lymph node (N) | | | |
|-------------------------|----------------|----------------|
| N0                      | No regional lymph node metastasis | | |
| N1                      | Regional lymph node metastasis | | |

| Distant metastasis (M) | | | |
|------------------------|----------------|----------------|
| M0                     | No distant metastasis | | |
| M1                     | Distant metastasis | | |

The primary impact of endosonography on the management of pancreatic cancer is in detection and cytologic diagnosis. Early in its introduction there was considerable excitement for EUS as an accurate staging tool in these patients. EUS has been found to be superior to the recent multidetector CT (MDCT) for T staging, with less risk of overstaying in comparison to both CT and MRI so that
patients are not being ruled out of a potentially beneficial resection [25,26]. The reported accuracy of EUS method for T staging ranges from 63% to 94%, whereas N staging varies between 41 and 86%, superior to both transabdominal US and CT. EUS has shown a good ability to detect vascular invasion, showing low sensitivity in the superior mesenteric artery (17%) and celiac artery (50%), although the portal venous system was correctly assessed by EUS in 95% of cases, compared with angiography (85%) and CT (75%) [1,4].

Staging accuracy of EUS can be influenced by several factors including the experience level of the endosonographer, imaging artifacts, and the endosonographer’s knowledge of the results of previous imaging tests. In general, T stage accuracy for EUS is highest in patients with smaller tumors, whereas helical CT is more accurate in staging larger tumors. The accuracy of EUS for detecting invasion into the superior mesenteric artery and vein is lower than that for detecting portal or splenic vein invasion [11].

EUS in combination with FNA is a highly accurate method of preoperative staging of pancreatic cancer, especially those too small to be characterized by CT or MRI, and it has the ability to obtain cytological confirmation of pancreatic cancer. With the availability of EUS and EUS-guided FNA procedures in major medical centers around the world, earlier diagnosis and more accurate staging have improved the management of pancreatic cancer [11].

The Role of EUS and ERCP in the Treatment of Pancreatic Cancer

Therapeutic Role of EUS

The prognosis of pancreatic cancer is dismal, with a 1 and 5 year survival rate at all stages at diagnosis of 24% and 5%, respectively, according to the latest from the American Cancer Society. Without treatment, the average survival of patients with pancreatic cancer is four months. EUS can be used for direct antitumor therapy by injection, ablation, fiducial implantation to guide radiotherapy, pain treatment, and treatment of jaundice [16,24].

Antitumor therapy

EUS-guided injection of antitumor agents is an attractive treatment option in pancreatic cancer. Intratumoral injection for pancreatic cancer has been performed in several trials. Vaccination with dendritic cells as immunotherapy is considered a potential anti-cancer tool, and OK-432 represents a maturation stimulus for dendritic cells [27].

Other antitumor agents for treatment of pancreatic cancer including allogeneic mixed lymphocyte culture (cytioimplants), ONYX-015, and TNFerade. Cytoimplants lead to activation of immune effector cells and release cytokines, causing tumor regression. Furthermore, ONYX-015 is an E1B 55-kDa gene-deleted replication-
selective adenovirus that preferentially replicates in malignant cells, leading to cell death. TNFerade is a second-generation replication-deficient adenovector, expressing the complementary DNA for human tumor necrosis factor (TNF). The gene is upregulated by a radiation-inducible promoter Egr-1 (early growth response) that ensures maximal gene expression and subsequent TNF secretion to be constrained in space and time by radiation therapy. This approach helps to localize the antitumor effects, thereby reducing systemic toxicity [27,28].

**EUS fiducial implantation**

The development of imaging-guided radiation therapy has been a major advancement in the palliation of pancreatic cancer. It involves the placement of fiducial markers, which are radiopaque spheres, coils, or seeds directly implanted into the tumor. EUS guidance can be used for the placement of radio-opaque fiducial markers in or near the tumor. They are deployed into the mass by using the 19G or the less stiff 22G needle, by means of a stylet, or by injecting sterile water into the needle. A mean number of 2-4 fiducial markers per patient have to be placed [27,29,30].

The advantages of imaging-guided radiation therapy include accurate localization of the tumor with precise delineation of its local extent, the use of escalating doses of radiation with minimal toxicity to surrounding normal tissues, and the fact that it does not require target tissue immobilization as it allows quantification of respiratory-associated tumor motion, unlike external beam radiotherapy [27].

**EUS-guided tumor ablation**

EUS-guided tumor ablation, a minimally invasive technique allowing selective ablation of tumor masses, might improve the efficacy of neoadjuvant treatments in patients not suitable for any other kind of treatment. Local ablative therapies such as radiofrequency ablation, photodynamic therapy, and brachytherapy have been applied in animal models or humans [31,32].

Radiofrequency ablation (RFA) relies on the generation of high-frequency alternating electromagnetic energy resulting in thermal injury to the target tissue. The role of RFA in the pancreas has been limited by its restricted accessibility by a percutaneous approach. Thus, EUS may be a suitable alternate vehicle for RFA therapy. EUS-guided RFA in the pancreas was initially explored in a porcine model by Goldberg and colleagues in 1999 [33].

Photodynamic therapy (PDT) is based on the ability of photosensitizers to generate cytotoxic oxygen species in the target tissue upon exposure to light of an appropriate wavelength. This results in generation of a singlet oxygen that causes extensive tumor necrosis with minimal damage to the surrounding normal tissues. EUS-guided PDT requires insertion of a quartz optical fiber through
the EUS needle to illuminate the target tissue with laser light. The mechanisms of the antitumor effects include direct cytotoxicity, vascular damage, and induction of an inflammatory response with development of systemic immunity [27,33].

Brachytherapy consists of placing radioactive seeds directly into the tumor, and has been widely used in various malignancies, including pancreatic cancer. The radioactive seeds used in brachytherapy include iodine-125, iridium-192, and palladium-103. Iodine-125 has the longest half-life, and hence is useful in rapidly growing pancreatic cancers by delivering high-dose radiation therapy from within the gland with minimal toxicity to the adjacent organs. The technique of placement of these seeds is similar to EUS-guided fiducial placement using 19-gauge needles. However, tumor volume is assessed by EUS to calculate the number and locations of radioactive seeds required [34,35].

Pain palliation by EUS-guided celiac plexus neurolysis

Pain is one of the most prevalent symptoms in pancreatic cancer at presentation (75%) and its incidence increases as the disease advances to more than 90% of patients. Pain control is the main therapeutic goal for clinicians in palliative care of pancreatic cancer patients and the conventional management with high doses of narcotics and the inherent adverse effects may further impair quality of life. The NCCN guidelines for pancreatic adenocarcinoma recommend EUS-guided celiac plexus neurolysis (EUS-CPN) for the treatment of severe tumor-associated pain. The ability to identify the celiac axis bifurcation at the time of EUS is crucial to deliver palliative pain management in patients with locally advanced and unresectable pancreatic cancer. EUS-CPN performed for the palliation of pancreatic cancer pain appears to be as safe and effective as CPN performed by other routes such as CT guided and surgical approaches. An added advantage of the EUS approach is that it can be performed during staging and biopsy of the tumor [16,35].

EUS-guided drainage for biliary obstruction

EUS-guided drainage for biliary obstruction should be offered as an effective alternative for percutaneous transhepatic biliary drainage when ERCP fails and surgery is not indicated. It is composed of two techniques, a rendezvous technique and a direct access technique with success rates of 75-100 and 65-100% respectively. EUS rendezvous involves puncturing of the bile duct through the gastric or duodenal wall followed by placement of a guidewire through the papilla to allow subsequent ERCP. EUS-guided direct access techniques involve a direct transgastric (hepaticogastrostomy) or transduodenal approach (choledocho-duodenostomy) and placement of stents to create bilioenteric anastomosis in situations where ERCP is not
possible [27,36,37].

**Therapeutic Role of ERCP**

Endoscopic retrograde cholangiopancreatography (ERCP) and bile duct stenting is the procedure of choice in obstructive jaundice resulting from advanced pancreatic cancer. ERCP was first used to place stents for the palliation of malignant obstructive jaundice in 1979. Palliation of biliary obstruction in patients with pancreatic and biliary cancer may be performed with biliary stent placement with ERCP or a surgical bypass. The available evidence does not indicate a major advantage to either alternative, so the choice may be made depending on clinical availability and patient or practitioner preference. ERCP is a widely available imaging modality and this modality may be preferable to surgery in some cases due to lower overall resource utilization and shorter hospitalization. The role of ERCP in biliary drainage prior to surgery for potentially resectable pancreatic cancers is currently debated and should be individualized based on specific clinical situation [21,38].

Currently, ERCP method has become the dominant technique for placement of biliary stents in patients with malignant obstructive jaundice. Successful endoscopic cholangiography with relief of obstruction should be technically achievable in more than 90% of patients. Cholangioscopy at ERCP is used infrequently but may be helpful in the management of bile-duct stones and in assessing suspected malignancies [38,39].

**Conclusion**

Pancreatic cancer remains a challenging disease to diagnose at an early stage. EUS is useful for the detection of pancreatic cancers less than 3 cm in diameter and for the staging of cases in which CT is inconclusive. This diagnostic method is the best single modality for tissue acquisition and it is complementary to the other imaging modalities as a staging tool, EUS-FNA establishes the tumor type with high accuracy and a very low rate of complications, and it is useful for differential diagnosis. EUS can be used for direct antitumor therapy by injection, ablation, fiducial implantation to guide radiotherapy, pain treatment, and treatment of jaundice. The role of ERCP in the diagnosis of pancreatic cancer is considerably reduced, if compared to the past. Indirect findings such as combined dilation of the bile and the pancreatic duct or abrupt cutoff in the main pancreatic duct or a solitary long structure of the pancreatic duct could raise suspicion of malignant disease but may also be observed in chronic pancreatitis.
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