

Endoscopic Methods in the Diagnosis and Treatment of Pancreatic Cancer

Zoltán Berger^{*}, Maria Ester Bufadel Godoy, Alex Navarro Reveco

University of Chile Clinical Hospital, Department of Medicine, Gastroenterology Section, Santiago, Chile.
Email: ^{*}berger.zoltan@gmail.com

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ABSTRACT

Endoscopic methods are widely used in the diagnosis and palliative treatment of pancreatic cancer. The most sensitive method in early diagnosis is endosonography (EUS) which can also provide histological diagnosis. Diagnostic ERCP became a rather rare procedure as a consequence of wide availability of Magnetic Resonance Cholangiopancreatography (MRCP) but ERCP assisted intraductal methods have gained importance (brush-cytology, intraductal ultrasound, optical coherence tomography) and finally, peroral pancreatoscopy has become technically feasible but available only in some specialized centers. Minimally invasive endoscopic methods play an important role in the palliative treatment of unresectable pancreatic cancer which represents the majority of cases. EUS-guided histological confirmation of adenocarcinoma is crucial in the election of chemotherapy. Celiac plexus blockade and endoscopic biliary and pancreatic stent placement contribute to pain reduction, drainage of obstructed bile duct and assure a better quality of life.

Keywords: Endoscopist; Early Diagnosis; Palliative Treatment

1. Introduction

Pancreatic cancer continues to be one of the most lethal malignancies: surgical resection is possible in only about 20% of detected cases and even in this group, the 5 year survival is low [1]. The diagnosis of cancer is established with conventional imaging procedures in the majority of these cases: CT-scan demonstrates the presence of the pathological mass and, at the same time, estimates the eventual vascular invasion, hepatic or peritoneal metastases, *i.e.* evident criteria of unresectability. If the tumor is considered resectable, surgery is the next step, without previous histological diagnosis except in those patients with clinical or radiological suspicion of another benign disease mimicking pancreatic cancer. Thus endoscopists face principally two extreme stages of pancreatic cancer: efforts in early diagnosis of small lesions and, on the other hand, palliative treatment of patients with advanced cancer.

2. Endoscopy in the Early Diagnosis

Thanks to systematic studies of surgical specimens, cancer precursor PanIN lesions have been identified. Unfor-

tunately, direct endoscopic access to visualize and resect these lesions—as in the case of adenomatous colon polyps—is not possible in everyday practice. A different emerging entity, pancreatic cystic lesions permit curative pancreatic surgery in initial phases of malignant transformation or even before, which consequently prevents cancer. However, early diagnosis of the most typical and most frequent adenocarcinoma of the pancreas continues to be unresolved. Five-year survival is far better in the subgroup of patients operated on with small malignant lesions, without metastasis. Early diagnosis is particularly important in genetically high-risk individuals. However, detection of small tumors—although not impossible—is extremely difficult.

There are some benign diseases of the pancreas which can produce tumor-like lesions or masses [2]. The differentiation of these diseases from pancreatic cancer is seldom easy. Our knowledge about the autoimmune pancreatitis has increased and differential diagnosis has become possible in the vast majority of these cases even without pancreatic biopsy [3,4]. Endoscopic methods, biopsy from the Vater papilla or even from gastric mucosa can be useful: IgG₄ positive lymphoplasmocytic infiltration was found in every biopsy of Vater's papilla

^{*}Corresponding author.

[5-7] and 12 of 13 cases of autoimmune pancreatitis in gastric mucosa [7]. These findings can be considered as histological proof of the IgG₄ related benign disease with systemic involvement. Underdiagnosis of autoimmune pancreatitis can lead to unnecessary operations. On the other hand, “treatment” of pancreatic cancer with steroids could be the result of an opposite diagnostic error. Other benign disease, groove-pancreatitis [8] has no specific medical treatment and surgery is sometimes necessary.

2.1. ERCP

Pancreatography used to be the most sensitive method in detecting ductal changes [9] such as stenosis and consecutive dilatation of the pancreatic duct. Nevertheless, ERCP is an invasive method with potential complications, pancreatitis being the most frequent among them [10], which could make impossible to continue with the diagnostic work-up and delay the eventual surgery. MR cholangiography also provides excellent images of the pancreatic duct and its sensitivity seems comparable to that of ERCP [11]. However, cannulation of the pancreatic duct offers some advantages: we can obtain pancreatic juice or samples from the stenotic segments for brush cytology [12]. Pancreatic sphincterotomy and guide-wire placement also allow the introduction of special endoscopes (“babyscope”) or accessories (spy-glass or intraductal ultrasound) in order to further investigate the lesions [11,13,14].

ERCP does not add more information to a pancreatic focal lesion that was clearly demonstrated and characterized by other non-invasive images. In contrast, it can be useful to differentiate pancreatic cancer from benign inflammatory diseases which can produce ductal changes. Focal stenosis can be a part of inflammatory pancreatic diseases. However, in cancer patients upstream dilatation is almost always present with atrophy of surrounding parenchyma, but these changes are almost always lacking in autoimmune [3,4] or groove-pancreatitis [8]. Brush cytology can help to confirm the presence of cancer. Although specificity was high, the sensitivity of brush cytology has never been over 70% (only about 40% - 50% in most publications) and its negative predictive value was about 30%—reaching almost 50% in combination with intraductal biopsy [15]. In a recent publication, sensitivity of cytology was 65.8%, specificity 100% and overall diagnostic accuracy 76.4% [12], with only 2 mild pancreatitis in 58 ERCPs. These values are quite similar to those obtained 10 years ago [16], in spite of progress in technology. Some additional advanced techniques can improve the results of cytology [17], but the negative predictive value remains low. Both brush cytology and intraductal forceps biopsy under fluoroscopic control are

technically demanding and invasive methods, having a relatively high probability of sampling error. However, both are reasonably safe and represent a real possibility of early detection of some small malignant lesions. As expected, pancreatoscopy-guided tissue sampling has dramatically improved diagnostic accuracy and sensitivity [13] but this method is only exceptionally available.

2.2. Endosonography (EUS)

EUS provides an excellent high resolution image of the pancreas. Pancreatic cancer is seen as a hypoechoic inhomogeneous solid mass with irregular borders. The sensitivity of EUS in detection of pancreatic masses is somewhat superior to CT scan and MRI, particularly in the case of small lesions [18,19]. EUS alone is highly sensitive to demonstrate focal lesions and eventual vascular involvement. Using contrast-enhancement [20] with the Doppler method or digital image procession [21] can further improve its sensitivity. Diagnostic accuracy of EUS is over 80%. It seems to be the method of choice to establish diagnosis and define unresectability, being cost-effective avoiding unnecessary and hopeless surgery. However, EUS is a more expensive, minimally invasive method with some complications; it is not widely available and is operator-dependent. In addition, its 60% - 65% negative predictive value is relatively low, particularly in the presence of chronic pancreatitis and/or a previously implanted biliary stent [22]. As a consequence, CT scan continues to be the first method in the diagnostic work-up for pancreatic cancer, followed by EUS only in case of doubts in diagnosis or when biopsy is required. Linear EUS allows us to obtain biopsy specimens from virtually any pancreatic region, whatever its origin: not only from lesions related to the ductal system as is the case of brush cytology. On the other hand, although tumor seeding does exist [23] it is rather exceptional in spite of several passes as compared to US or CT-guided percutaneous biopsies. However, an acute inflammatory reaction provoked by EUS-FNA, can transform a small tumor into a nonresectable lesion [24]. EUS was also used to tattoo a small, otherwise undetectable lesion preoperatively and the small tumor was surgically resolved [25]. Marking the small tumor with silver pins provided the same result in another case reported [26].

Diagnostic sensitivity of FNA cytology improves with increasing tumor size, *i.e.* it is less useful in early diagnosis. The negative predictive value is also lower in the case of small lesions. This means that a negative cytology result does not exclude malignant nature of a small lesion and surgery is the next step even despite of negative cytology if the clinical suspicion is strong enough.

Like any other endoscopic technique, direct visualization of the pancreatic ductal system could be of great

value. Thanks to pancreatoscopy, visualization is already a real possibility, although its availability is limited to rather few specialized centers. Apart from its cost and restricted availability, the small caliber of normal pancreatic duct represents a technical difficulty and limitation. Furthermore, tortuosity and strictures may prevent the scope from reaching the lesion in question. Intraductal US sondes [27] and intraductal optical coherence tomography [28] also offer greater precision to investigate ductal lesions and distinguish benign from malignant strictures, as compared to pancreatography. Utility of these methods is also limited to lesions originating in the main duct.

3. Advanced Cancer

Unfortunately, pancreatic cancer is advanced in the vast majority of cases at the time of diagnosis. Even relatively small <2 cm lesions are not really early cancers; although resectable, lymph node metastasis, portal vein invasion and survival did not differ significantly as compared to major lesions [29]. The diagnosis is sometimes established during an ERCP performed for an obstructive jaundice of unknown cause. In such cases, if the obstructed bile duct is contrasted and probably contaminated, plastic stent placement is recommended. Self-expanding metal stents could probably interfere with posterior surgery [30]. In contrast, if the diagnosis of a resectable pancreatic cancer is established via other non-invasive methods, preoperative stent placement has no clinical utility, although it decreases the bilirubin-level [31].

Nowadays, the principal role of endoscopic methods is the palliative treatment of unresectable tumors.

1) Obstructive jaundice: This is one of the first clinical manifestations of tumors located in the head of the pancreas. Resolution of the obstruction and consecutive decrease in the jaundice reduces or completely controls pruritus. Technical success rate of endoscopic palliation is high. The placement of self-expanding metal endoprosthesis is the method of choice: they remain patent significantly longer than plastic stents. Obstruction and cholangitis are more frequent with plastic stents, needing emergency hospitalizations and repeated endoscopic interventions, thus deteriorating the quality of life. However, no difference was found in the survival in comparing polyethylene and metal stents [32]

2) Pain: The mechanism of pain in pancreatic cancer is complex and only partially understood. However, one of the components is probably the obstruction of the pancreatic duct. If pancreatography reveals a stricture with upstream dilatation it seems reasonable to place a plastic stent through the stricture and drain the obstructed pancreatic segment. Insufficient literature data prevent mak-

ing definitive conclusions, but several results support the usefulness of pancreatic stents in the treatment of the pain [33]. There are also some initial results with radioactive stents placed either in the common bile duct or in the pancreatic duct which could stabilize the disease and delay progression [34]. Metal stents covered by a paclitaxel-incorporated polyurethane membrane gave similar results in 9 patients with bile duct strictures caused by unresectable pancreatic cancer [35].

3) Gastric outlet obstruction, duodenal stenosis: Simultaneous or consecutive obstruction of the bile duct and duodenum has been the cause of relatively complex surgical interventions in advanced pancreatic cancer (gastro-jejunal anastomosis and hepatico-jejunostomy). In addition, these are frequently a high surgical risk patients or even unfit for operations. Self-expanding metal stent placement by endoscopy [36] reestablishes almost normal caliber duodenal lumen, avoids vomiting and allows although somewhat limited but oral feeding. It also makes posterior endoscopic access to the papilla possible for the treatment of obstructive jaundice.

3.1. Endosonography (EUS)

1) EUS is the most sensitive method in the diagnosis of focal pancreatic lesions. However, in the case of advanced cancer the pancreatic mass has already been detected and declared unresectable by other methods. There are two questions to answer: a) Is the mass a ductal adenocarcinoma or of different histological nature? b) Is the patient fit for chemotherapy or another minimally invasive palliative treatment? If the patient's general condition does not allow even minimally invasive interventions and chemotherapy is considered unsuitable, the only possibility is conservative symptomatic treatment. Histological diagnosis is useless in these cases. On the other hand, except in the terminal stage, histological confirmation of the lesion is recommended to exclude benign diseases mimicking pancreatic cancer or malignant lesions different from adenocarcinoma, which may require different treatment and have better prognosis. The best way to obtain histological samples at present is the EUS-guided fine-needle biopsy [37-39], with high diagnostic accuracy and low risk of complications, including tumor seeding. The only argument against EUS is the cost and lack of wide availability in several countries.

2) EUS guided interventions:

a) Celiac plexus blockade (CPB) and neurolysis (CNL) are safely performed when guided by EUS. Results in pain control are similar to the radiologically-guided percutaneous or surgical interventions: CPB and/or CNL permit a reduction in the dose of analgesic drugs and result in better pain control. Published complications have been mild and transient [40].

b) EUS-guided drainage can facilitate pancreatic or biliary stent placement via “rendez-vous” techniques. Bilio-digestive drainage, choledocho-duodenostomy with stent placement can also be performed in cases of duodenal stenosis.

c) There are also some rather experimental interventions guided by EUS. Jin *et al.* [41] implanted iodine-125 seeds inside of unresectable pancreatic tumors of 22 patients. Combined with traditional chemotherapy, partial remission was achieved in 3 and stabilized the disease in another 10 patients, while pain diminished in 18 of the 22 patients with a statistically significant decrease in pain intensity as measured by visual analogue scale. Half of the patients presented fever which was treated with antibiotics, but no other serious complication was observed. EUS was used to guide intratumoral injection of a virus: ONYX-015, which selectively replicates in and destroys tumor cells, that are deficient in p53 function but not in cells with functional p53 [42,43]. This treatment was also associated with gemcitabine and the cancer did not progress in 8 of 21 patients who participated in the study.

4. Conclusion

Algorithm of diagnosis and treatment of pancreatic cancer is depicted in **Figure 1**. Early diagnosis has somewhat improved but has not been resolved. The best, most sensitive and more and more widely available method for early detection is the EUS, with or without FNA, but it is not good enough. Its negative predictive value has improved in recent years, but surgery must be performed in spite of negative EUS and cytology results if the clinical suspicion is strong. More direct methods to visualize ductal lesions are in progress. On the other hand, endoscopic methods play an increasingly important role in

the palliative treatment of pancreatic cancer patients. Self-expanding metal duodenal and biliary stents represent a good alternative treatment to replace relatively complex surgery in patients with less than 1 year life expectancy.

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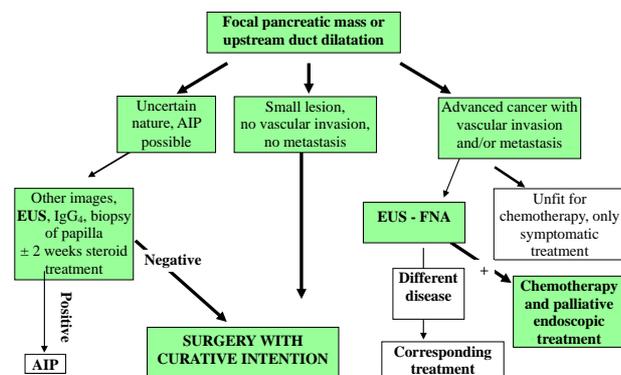


Figure 1. Endoscopic methods in the algorithm of diagnosis and treatment of pancreatic cancer. Pancreatic lesion initially detected with generally non-invasive imaging (CT, RM), rarely with ERCP. EUS is the best method in the differential diagnosis, with or without FNA. Other endoscopic methods have their dominant role in the palliative treatment of advanced lesions.

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Abbreviations

EUS: Endosonography;

FNA: Fine Needle Aspiration;

AIP: Autoimmune pancreatitis.