Invited Special Paper

INTERNATIONAL JOURNAL OF SURGERY

OPEN

Endoscopic workup in pancreatic cancer

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Abstract

Pancreatic cancer is a highly lethal disease with a rising incidence. It is projected to become the second-leading cause of cancer-related mortality by 2030. The staging of pancreatic cancer can be broadly categorized into three groups: resectable cancers, locally advanced or borderline resectable cancers, and metastatic cancers. Endoscopy plays a crucial role in the management of pancreatic cancer for the establishment of the diagnosis, for the palliation of symptoms due to biliary and/or gastric outlet obstructions, and more recently, for the palliative ablation of cancer. The objective of this review is to provide an overview of the endoscopic evaluation and management of patients with pancreatic cancer. It will specifically cover the diagnostic approach utilizing endoscopic ultrasound, palliative interventions such as endoscopic retrograde cholangiopancreatography, and the emerging field of tumor debulking through radiofrequency ablation.

Keywords: endoscopy, ERCP, EUS, pancreas cancer, PDAC, workup

Background

Pancreatic cancer represents a significant challenge to the scientific community. Just in the USA every year more than 60 000 new cases are diagnosed[1]. Despite the increasing incidence, the prognosis for pancreatic cancer has remained largely unchanged over the past several decades and 5 years after the diagnosis the overall survival is only 2–9%[2].

Pancreas cancer is expected to become the second cause of cancer-related death within 2030[3]. Most pancreatic cancer cases (around 70%) present with obstructive jaundice since the majority of tumors are located in the head of the pancreas. From a staging perspective, pancreatic cancer can be categorized into three groups: upfront resectable tumors, borderline resectable/locally advanced tumors, and metastatic tumors. Approximately 20% of cases are considered primary resectable, meaning that the tumor can be surgically removed upfront. Around 30% of cases are classified as borderline/locally advanced. In such cases, the tumor has grown extensively and may involve the vena porta, superior mesenteric vein and artery or liver artery. Most cases (50%) are already metastatic at the time of diagnosis, with cancer spread to distant sites in the body[1].

HIGHLIGHTS

- Endoscopy plays a crucial role in the management of pancreatic cancer.
- Endoscopy in pancreatic cancer patients is fundamental for the establishment of the diagnosis.
- Palliation of symptoms due to biliary and/or gastric outlet obstructions are other important fields of activities for endoscopy in pancreatic cancer patients.
- More recently, endoscopy could also represent a valid tool for palliative ablation of pancreatic cancer.

The different stages of pancreatic cancer necessitate tailored usage of endoscopy, which plays a major role in both the diagnosis and in the palliation of the disease. The focus of this review is to provide a comprehensive overview of the role of endoscopy in the management of pancreas cancer, including different diagnostic and therapeutic possibilities.

Primary resectable PDAC: preoperative biliary drainage

In the context of upfront resectable tumors in pancreatic cancer, the role of endoscopy, including fine-needle aspiration (FNA) by endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) with stenting, has been a subject of debate. While upfront surgery is generally the primary treatment approach for resectable pancreatic tumors, there are certain situations where endoscopy may still have a role. For example, in cases of diagnostic uncertainty, such as when there is a strong suspicion of autoimmune pancreatitis, performing EUS-FNA or other diagnostic procedures can help confirm the diagnosis and guide treatment decisions. Similarly, in the presence of medical conditions that could worsen the postoperative outcome, such as acute cholangitis, ERCP with stenting may be necessary to provide relief and improve the patient's condition before

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery (2024) 110:6064–6069

Received 13 July 2023; Accepted 10 September 2023

Published online 22 September 2023

http://dx.doi.org/10.1097/JS9.0000000000000777

proceeding with surgery. However, the decision to perform endoscopic procedures in these cases should be carefully evaluated on an individual basis, weighing the potential benefits against the risks and take into account the overall treatment strategy for the patient[4]. The goal is to proceed with surgical resection without delay, as it is considered the primary treatment for resectable pancreatic tumors. This approach aims to achieve optimal outcomes by removing the tumor and minimizing the risk of disease progression.

Thus, the preoperative diagnostic approach of solid pancreatic lesions that may require surgical intervention remains a bit controversial, as the advantages of diagnosing benign diseases that do not require surgery must be weighed against the risk of false negatives. EUS-FNA has a sensitivity that ranges between 54 and 74%[5], indicating that it is not highly accurate in definitively ruling out the presence of a neoplasm. Additionally, there is a small risk of neoplastic seeding associated with EUS-FNA, although the incidence is relatively low at ~2.2%[6]. The International Study Group of Pancreatic Surgery, in their consensus statement, advises against performing EUS-FNA for solid pancreatic tumors, unless there is a strong suspicion of autoimmune pancreatitis. In cases where autoimmune pancreatitis is suspected, a biopsy and/or a short trial of steroid therapy can be considered before proceeding with surgery. This approach is recommended to minimize the risk of complications associated with EUS-FNA and to ensure appropriate surgical management of the condition[7].

In the context of a primary resectable pancreas cancer also the value of preoperative drainage has been questioned. Jinkins *et al.* conducted a retrospective study using the SEER registry, which included 2573 patients who underwent pancreaticoduodenectomy. The study aimed to evaluate the use of preoperative drainage in clinical practice. The results of their study showed that although preoperative drainage is associated with a higher complication rate, more than half of the patients (52.6%) still underwent preoperative drainage. Among those who received preoperative drainage, the majority (75.3%) were stented endoscopically, while a smaller proportion (18.9%) were drained percutaneously. Interestingly, the study also observed a significant increase in the number of preoperative drainages between 1992 and 2007, nearly doubling over that period[8]. Van Der Gaag *et al.* conducted a randomized controlled trial in which patients were assigned to either receive preoperative biliary drainage or undergo upfront surgery despite cholestasis. The study, which included 202 patients, demonstrated higher risks of serious complications in the preoperative drainage group compared to the group that underwent upfront surgery (74 vs. 39%, RR 0.54, 95% CI: 0.41–0.71). Additionally, the study found that also surgically related complications were more common in the preoperative drainage group compared to the upfront surgery group (46 vs. 37%, RR 0.79, 95% CI: 0.57–1.1). Based on these findings, the authors concluded that preoperative drainage was associated with an increased risk of complications in patients eligible for pancreatoduodenectomy[9]. Scheufele *et al.* performed a systematic review and meta-analysis on 25 studies, including 1816 patients to assess the impact of preoperative biliary drainage on postoperative morbidity and mortality of patients with pancreatic cancer undergoing surgery. Complications were statistically more prevalent in patients who have undergone preoperative drainage (OR 1.40, 95% CI: 1.14–1.72). Similarly, infections rate was also higher in the group who have had preoperative drainage (1.94, 95% CI: 1.48–2.53)[10]. For patients with mild jaundice and no acute cholangitis, the risks associated with preoperative drainage outweigh the potential benefits. In these cases, the patient can proceed directly to surgical treatment without the need for preoperative drainage. On the other hand, in patients with severe obstructive jaundice and bilirubin levels greater than or equal to 250 μmol/l, the risks associated with the surgical procedure may be increased, and preoperative drainage may be considered beneficial. Although guidelines recommend the placement of a biliary stent prior to surgery in patients with severe jaundice, a recent retrospective series from the Netherlands has demonstrated no significant difference in postoperative complications and mortality between patients with or without severe jaundice. This raises questions about the potential benefits of preoperative drainage even in this category of patients[11]. Preoperative drainage can be achieved by endoscopic or percutaneous procedures. ERCP and, more recently, EUS-guided drainages of the bile duct[12] are the preferred methods since they have been shown to be superior to percutaneous transhepatic drainage in terms of both complications and efficacy. ERCP allows for the placement of plastic or metal stents to relieve the obstruction and improve the hyperbilirubinemia before surgery. The ESGE guidelines recommend the use of self-expanding metal stents (SEMS) in each patient with biliary obstruction, since they have a longer patency, a less degree of stent dysfunction and an overall better cost-effectiveness[13].

In a prospective multicenter study by Jamg *et al.* 53 patients underwent biliary drainage with SEMS, while 102 patients underwent preoperative drainage with plastic stents. The study reported a higher complication rate in patients undergone plastic stenting compared to those with covered metal stents (46 vs. 24%). Stent-related complications were also more frequent in the plastic stent group (31 vs. 6%). However, there was no statistically significant difference in terms of surgical complications between the two stent types (40 vs. 47%). Overall, the study showed that surgery had lower complication rates (39%) compared both to covered metal stents and to plastic stents in the comparison of preoperative drainage methods (51 and 74%, respectively)[14]. Jun *et al.* performed a multicenter, prospective randomized trial comparing fully covered SEMS versus plastic stents in 86 patients with obstructive jaundice because of hepato-pancreatic-biliary malignancy planned for surgery. The authors reported similar outcomes between the two groups (SEMS vs. plastic stents), and no statistically significant difference in terms of procedure-related complications (16.3 vs. 16.3%, $P = \text{NS}$), need for restenting (16.3 vs. 14%, $P = \text{NS}$), time to surgery (14.2 days vs. 12.3 days, $P = \text{NS}$). Postsurgical complications rates were also similar (43 vs. 40%, $P = \text{NS}$)[15].

Primary bile duct cannulation with ERCP is unsuccessful in up to 5–10% of cases and can be particularly challenging in certain situations. Factors that can cause difficult cannulation include; papillary inaccessibility, altered anatomy (especially due to previous surgical modifications), strictures at the level of the papilla, or gastric outlet obstruction due to cancer. In such settings EUS-guided bile duct drainage might overcome the problem and allow bile to drain through a choledoco-duodenostomy or through an hepatic gastrostomy[12].

Martins *et al.* have performed a meta-analysis to compare EUS-guided gastrostomy with surgical bypass and endoscopic stenting, as a treatment for malignant gastric outlet obstruction. Authors aimed at investigating technical success, complications

rate, needs for reintervention rate, length of hospital stay, and time to oral intake. Out of 5878 studies, the authors included 10 studies in the final analysis. When compared to endoscopic stenting, gastroenterostomy had a higher rate of clinical success (91.1 vs. 78.7%, $P = 0.003$) and similar technical success (93.6 vs. 96.6%, $P = 0.29$). The hospital stay was shorter for the group undergoing endoscopic drainage (– 2.82 days, $P = 0.01$), and there was a lower need for reintervention (4.2 vs. 32.7%, $P < 0.01$). In terms of time to tolerate oral intake again, one study favored endoscopic stenting over endoscopic drainage (1.38 vs. 2.48 days, $P = 0.005$). The rate of serious complications was higher in endoscopic stenting (34.8 vs. 12%, $P < 0.001$). Endoscopic drainage was also superior to surgical drainage, although without statistical significance (90.7 vs. 88.6%, $P = 0.37$). Technical success was higher for surgical drainage compared to EUS drainage (99 vs. 91.5%, $P = 0.008$). Endoscopic drainage had an average of 5.95 fewer days of hospital stay than surgical drainage ($P < 0.001$), while time to oral diet was lower for EUS by 2.89 days ($P < 0.001$). The reoperation rate did not show a statistically significant difference between endoscopic and surgical drainage, and there was no difference in terms of serious complications between the two methods (15.7 vs. 14.2%, $P = 0.37$)[16].

Borderline PDAC: sampling and biliary drainage

The presence of locally advanced disease poses two important needs. The first is to achieve adequate drainage of the biliary tract to allow for neoadjuvant chemotherapy. The goal is to maintain a wide patency of the stent to avoid recurrent episodes of cholangitis, which can be particularly risky during chemotherapy.

Cooper *et al.* conducted an analysis using data from the NSQIP Pancreatectomy Demonstration Project, which included 1562 patients from 43 hospitals. The study aimed to compare the rates of postoperative complications and mortality in patients undergoing pancreatic resection for pancreatic cancer, based on whether they received upfront surgery or neoadjuvant therapy followed by surgery. From this large database and its analysis, we can extract some data that allow us to understand the role of biliary drainage. The results showed that preoperative drainage was more common in the group of patients who underwent neoadjuvant therapy followed by surgery (57.9 vs. 44.7%, $P = 0.0005$). This percentage is likely to increase if we focus solely on patients with adenocarcinoma of the pancreatic head. Although biliary drainage is a necessary maneuver to enable the implementation of neoadjuvant therapies, it is not without consequences. In fact, the same study reports that the biliary stent is a predictor of postoperative complications with an odds ratio of 1.6 (95% CI: 1.1–2.0)[17]. This information is of particular interest when considering that neoadjuvant therapies are no longer performed exclusively in patients with borderline or locally advanced tumors, but also in patients with upfront resectable tumors[17].

The second need is to obtain a cytological or histological diagnosis to initiate neoadjuvant therapy. This is particularly true, considering the continuous expansion of surgical indications, even for patients who were once deemed nonresectable. An emerging concept in pancreatic surgery is the necessity to personalize treatments based on tumor biology rather than solely relying on staging. In such a context, endoscopy plays a pivotal role in staging, acquiring histological specimens, and optimizing the patient's condition for receiving oncological treatment[4,18,19].

There are various methods to acquire tissue for establishing a diagnosis. During the drainage procedure, brush cytology of the biliary tract can be applied. Brush cytology during ERCP often contains sufficient cellular material infiltrated by cancer to establish a diagnosis. In particular, this is true if the cytology is combined with immunofluorescence FISH (Fluorescence in Situ Hybridization) analysis. Navaneethan *et al.* performed a systematic review and meta-analysis on nine studies, including 730 patients (63% of which with malignant strictures)[20]. The authors compared the diagnostic yield of biliary cytology and intraductal biopsies for the detection of cancer in biliary strictures of diverse origins showing as the combination of intraductal biopsies and brushings displayed a the pooled 59.4% (95% CI: 53.7–64.8%) sensitivity and 100% (95% CI: 98.8–100.0%) specificity for the detection of cancer in biliary strictures[20].

Alternatively, or in addition to the cytologic cells obtained via ERCP, diagnostic cells/tissue can be acquired through EUS-FNA or EUS-FNB (Fine-Needle Biopsy). These methods provide additional options for obtaining diagnostic tissue in cases where biliary tract cytology alone may not be sufficient. In addition, EUS allows for even a thorough evaluation of vessel involvement, which is essential for the staging and planning of subsequent surgical interventions. In this situation, EUS is the preferred modality for obtaining a biopsy core and establishing a diagnosis because compared with percutaneous punctures, EUS carries a lower risk of neoplastic seeding, and allows for evaluation of the presence of pathological lymph nodes[21].

EUS involves the use of an endoscope with an ultrasound transducer mounted on the tip. There are three types of endoscopes: radial (sector array), linear, and forward. The radial-type endoscope has historically been used and allows for a 360° evaluation in a plane perpendicular to the instrument. However, the disadvantage of this type of endoscope ultrasound is the impossibility of performing a biopsy sampling, which is instead possible through the linear probe (convex array).

There are different types of needles available for performing needle biopsy during EUS, including 19-gage, 22-gage, and 25-gage needles. Rapid On-site Evaluation (ROSE) of cytopathology is commonly performed to examine the collected tissue samples. However, a recent multicenter randomized trial has demonstrated that utilizing multiple passes of the biopsy needle through the tumor (more than seven passes) yields similar diagnostic results compared to the traditional 'ROSE' technique, but at a lower cost. The reported sensitivity and specificity of the EUS-FNA is 85–89% and 98–99%, respectively[22].

Crino' *et al.* recently conducted a multicenter, randomized, crossover trial comparing the use of wet-suction with the slow-pull technique during EUS-guided FNB. The study found that the wet-suction technique resulted in a higher concentration of tissue but with similar diagnostic accuracy compared to the slow-pull technique[23].

The same group also investigated the role of ROSE in the diagnosis of pancreatic solid lesions through a randomized controlled noninferiority trial involving 800 patients. Among the 771 patients analyzed, the authors confirmed the noninferiority of non-ROSE EUS-FNB compared to EUS-FNB with ROSE, with an overall diagnostic accuracy of 97.4 vs. 96.4% ($P = 0.3$), respectively[24].

Facciorusso *et al*. recently conducted a network meta-analysis to investigate the diagnostic accuracy of different needle sizes for acquiring cytology or histology tissue samples. Specifically, the authors compared the diagnostic yield of FNA using 22–25-gage needles to FNB using a 19-gage needle. By conducting a systematic literature review, they included studies published up to November 2018, comprising a total of 27 randomized controlled trials with 2711 patients. The network meta-analysis did not reveal the superiority of one needle type over the other in terms of diagnostic accuracy, specimen retrieval rate, and adequacy of cyto-histological specimens[25].

Metastatic and locally advanced PDAC: palliation of obstructive symptoms and new ablatives possibilities

The palliative setting is where endoscopy finds its greatest applications. In cases of advanced pancreatic cancer with metastasis, endoscopy can be utilized for palliative purposes such as relieving jaundice (ERCP and EUS drainages) , obtaining biopsies or cytology (through EUS-FNA and FNB or ERCP with brush cytology), and alleviating duodenal obstruction (through the deployment of a duodenal metal stent or the performance of an EUS-guided gastro-enterostomy)[26,27].

Palliation of jaundice

In the case of asymptomatic obstructive jaundice, which is a common feature of pancreatic cancer, ERCP is the primary method for biliary drainage. Various types of stents can be used to treat the biliary strictures caused by pancreatic cancer, including plastic stents, fully covered self-expandable metallic stents, partially covered self-expandable metallic stents, and uncovered self-expandable metallic stents. Plastic stents are cost-effective but have shorter patency, requiring replacement, in up to every 3–4 months[28]. Metallic stents are more expensive but provide longer-term patency[29]. Fully-covered metallic stents inhibit cancer growth within the stent but carry a higher risk of migration. Partially covered or uncovered metallic stents have a lower risk of migration but can many times not be removed if dysfunction occurs, making them suitable for patients with a shorter life expectancy.

Current European guidelines recommend the use of covered metal stents in all palliative cases due to the favorable cost-effectiveness compared to the need for multiple ERCP procedures with plastic stents. A Dutch study comparing different stenting strategies (plastic vs. covered metal) found no significant difference in total costs at one year ($7770 vs. $7356)[30].

Stent dysfunction is a frequent occurrence and can have significant impacts on morbidity and mortality in patients with previously stented pancreaticobiliary cancer. In a study conducted by Lamarca *et al*., the outcomes of patients with advanced pancreaticobiliary cancer who had undergone stenting prior to starting chemotherapy were evaluated. The study included 93 patients, and the authors reported that 43% of these patients experienced stent dysfunction. Furthermore, among those who developed stent dysfunction, 32% ultimately died as a result of this complication. These findings highlight the importance of monitoring and managing stent function in patients with advanced pancreaticobiliary cancer to optimize outcomes and reduce the associated risks[31].

Recently, Yuen *et al*. conducted a multicenter randomized controlled trial comparing EUS-guided choledocho-duodenostomy and lumen-apposing stent deployment with ERCP and deployment of fully covered metal stents for the treatment of bile duct strictures in patients with unresectable hepato-pancreatic-biliary cancer. The study demonstrated similar 1-year stent patency and clinical success rates, comparable rates of adverse events and mortality within 30 days, and a shorter procedural time for EUS-guided drainage compared to ERCP-guided drainage [10 min (5.75–18) vs. 25 min (14–40), $P < 0.001$]. The authors concluded that both procedures provide options for the drainage of the bile duct in cases of unresectable malignant obstructions. They suggested that the EUS approach may be considered upfront in cases where cannulation through ERCP is expected to be challenging[32].

Palliation of the gastric outlet obstruction

Recently, Vanella *et al*. published a prospective study involving 104 patients who underwent EUS-guided gastroenterostomy for malignant gastric outlet obstruction. Among the patients, 75.7% had pancreatic cancer, and 60.0% of those displayed a metastatic phenotype. The procedure was successful in 97% of cases, with a median follow-up of 105 days, and 7.5% of patients experienced recurrence. The complication rate was 12.9%. When compared to endoscopic stenting, EUS-guided gastroenterostomy showed a faster resolution of symptoms (100 vs. 75%, $P = 0.006$) and lower recurrence rates (3.7 vs. 33.3%, $P = 0.007$)[27].

Ge *et al*. conducted a retrospective study using a database of prospectively collected patients, comparing 100 consecutive individuals. Out of these, 78 patients underwent enteral stenting, and 22 patients underwent EUS-guided gastroenterostomy. The group that underwent EUS-guided gastroenterostomy had a lower rate of postoperative complications (20.8 vs. 40.2%, $P = 0.098$) and higher overall success rates (95.8 vs. 76.3%, $P = 0.042$). The authors concluded that in high-volume centers, EUS-guided gastroenterostomy could be a viable alternative to enteral stenting[33].

Radiofrequency ablation

In recent years, intraductal radiofrequency ablation has emerged as a palliative treatment for external malignancies of the biliary tract, including pancreatic cancer.

Radiofrequency treatment induces irreversible cellular damage and promotes apoptosis by generating coagulative necrosis by reaching a temperature between 60°C and 100°C. The treated area typically consists of a central zone of coagulative necrosis surrounded by a zone of partial damage, and further peripherally, a zone that remains unaffected. Radiofrequency ablation also leads to increased oxidative stress and the exposure of new antigens with major histocompatibility complexes. These effects have the potential to stimulate an autoimmune response against the tumor[34]. Radiofrequency ablation has shown successful outcomes in various tumor types, including hepatocellular carcinoma, esophageal mucosal dysplasia, and as a complementary treatment for residual adenoma of the papilla of Vater[35–37]. Recent advancements in endoscopic devices have enabled the application of radiofrequency ablation inside the bile duct.

Sharaia *et al*. conducted a study involving 66 patients and demonstrated a survival difference showing RFA to be an independent predictor of survival, with a hazard ratio of 0.29

(CI: 0.11–0.76, $P = 0.012$)[38]. Kallis *et al.*, in a retrospective study focusing on malignant biliary strictures, including those from pancreatic cancer, reported a survival difference of 7.5 months versus 4.1 months ($P = 0.010$)[39]. This suggests that patients who undergo RFA as part of their treatment have a significantly improved survival outcome compared to those who do not receive RFA but further evidence is needed, hopefully in the setting of a randomized controlled trial.

Study limitations

Despite our study aiming to provide a broad overview with the highest degree of scientific accuracy, it inherently carries some limitations typical of nonsystematic literature reviews. Firstly, the presented study offers a comprehensive overview of the role of endoscopy in diagnosing and staging pancreatic adenocarcinoma, without being grounded in a hypothesis focused on addressing a singular aspect of this research topic. Secondly, the research has been strongly guided by the authors' insights and expertise in the field. Thirdly, the literature search was conducted solely using PubMed. Fourthly, the results of various articles have been described without any additional analysis. Lastly, this type of study could be somewhat influenced by the authors' perspectives and intentions, even though the risk of this bias is minimized given that the authors of this work are all surgeons and endoscopists trained and working in different countries. In our opinion, this aspect represents a strength of this work.

Conclusion

In recent years, endoscopy has become increasingly important in the diagnosis and treatment of pancreatic tumors. While its role may be limited in cases where the tumor is upfront resectable and surgical intervention is the primary treatment, endoscopy plays a crucial role in diagnosing patients eligible for chemotherapy treatment and requiring histological confirmation. It is instrumental in obtaining tissue samples for accurate diagnosis and guiding appropriate treatment decisions.

In the palliative care setting, endoscopy is invaluable for managing metastatic pancreatic cancer. Endoscopy offers effective palliation of biliary and enteric strictures through minimally invasive approaches, improving patients' quality of life by relieving symptoms such as jaundice and obstruction. Finally, the application of ablative treatments directly into the tumor mass represents the cutting edge of minimally invasive procedures. Techniques like intraductal radiofrequency ablation enable endoscopic debulking of tumors by delivering targeted energy through the bile duct wall. These advancements provide additional options for managing pancreatic tumors and slowing their progression.

Ethical approval

Not applicable.

Patient consent

Not applicable.

Sources of funding

The study was supported by the following grants: the Swedish Cancer Society (Cancerfonden), 19 0513 Fk 01 H (UA), Bengt Ihre fellowship research grant (RV); Cancer och allergi fonden 10384 (UA); Cancerforskningsfonden i Norrland/Lions' cancer research foundation, Umeå University; AMP 21-1058 (RV), and LP22-2301 (UA); IngaBritt och Arne Lundbergs Forskningsstiftelse (RV); Svenska Läkaresällskapet SLS-961923 (RV), SLS-961919 (RV), City Council of Västerbotten: RV-970141 (RV), RV-982725 (RV), RV-980274 (RV).

Author contribution

R.V. and U.A.: conceptualization, design, data collection, writing and reviewing, supervising; A.C. and C.M.S.: conceptualization, design, data collection, writing and reviewing, editing.

Conflicts of interest disclosure

Dr Arnelo is co-PI of a Boston Scientific-sponsored study of the use of intraoperative pancreatoscopy in IPMN patients. Dr Arnelo is a consultant to Boston Scientific and Ambu. Dr Valente is a consultant for Boston Scientific.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
2. Unique identifying number or registration ID: not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): not applicable.

Guarantor

Alessandro Coppola.

Data availability statement

Available upon reasonable request.

Provenance and peer review

The paper was invited in the Special Issue 'Updates on Pancreatic Cancer Treatment'.

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