EUS: A one-stop shop approach for pancreatic head masses: Dream or reality?

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The approach to the head of the pancreas (HOP) masses causing distal biliary obstruction has rapidly changed over the last decade. In patients with unresectable disease, tissue confirmation and biliary drainage are required to allow for chemotherapy administration. EUS-guided fine-needle tissue acquisition (EUS-TA), when available, is now considered the best method to reach a definitive diagnosis.[1] The choice of the biliary stent to be placed by endoscopic retrograde cholangiography (ERC) is based on the predictable survival of the patient, being 4 months the cutoff to decide between a plastic stent (<4-month survival) and a self-expandable metal stent (SEMS) (>4-month survival).[2]

Differently, in patients with resectable disease, two major issues are still a matter of debate: (i) is tissue confirmation needed in all cases? (ii) is preoperative endoscopic biliary drainage required? Based on a recent consensus statement, a HOP mass highly suspicious for malignancy disease, deemed resectable by new-generation computed tomography or magnetic resonance imaging, does not require any tissue confirmation before surgery.[3] Exceptions to this rule are a specific request by the patient who expresses willingness to undergo such a major surgery only in the presence of a definitive diagnosis of malignancy or when a different diagnosis, *i.e.*, autoimmune pancreatitis or pancreatic lymphoma, is highly suspected.[3] The major points against the performance of TA in these patients are as follows: (i) the risk of seeding for the percutaneous route, which is less of a concern with EUS transduodenal sampling, since the needle tract is resected in cases that proceed to pancreaticoduodenectomy;[4] (ii) the low negative predictive value, based on which a negative result cannot exclude malignancy;[5,6] and (iii) the observance that preoperative EUS-TA has no influence on overall and cancer-specific survival in these patients.[7]

Regarding the need for endoscopic biliary drainage before surgery, a Dutch multicenter randomized

Access this article online	
Quick Response Code:	Website: www.eusjournal.com
	DOI: 10.4103/eus.eus_61_18

How to cite this article: Larghi A, Rimbaş M, Crino SF, Rizzatti G, Gasbarrini A, Costamagna G. EUS: A one-stop shop approach for pancreatic head masses: Dream or reality? Endosc Ultrasound 2019;8:217-9.

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Received: 2018-09-18; **Accepted:** 2018-11-16; **Published online:** 2019-02-20

controlled trial published in 2010 performed in patients with resectable HOP cancer and a bilirubin concentration between 2.3 and 14.6 mg/dl demonstrated that preoperative drainage with plastic stents was associated with increased complication rates compared to surgery alone.[8] A subsequent prospective multicenter cohort study found that preoperative fully covered SEMS yielded a better outcome compared with plastic stents.[9] An ongoing multicenter randomized trial comparing immediate surgery *versus* preoperative drainage with SEMSs will soon provide a definitive word to this important issue (ClinicalTrials.gov NCT01774019).

Some major innovations that have occurred in the last couple of years may bring a real breakthrough in the approach to HOP masses, independently on their resectability. First of all, recent data favor neoadjuvant therapy also for resectable cases.[10,11] If this will become standard of care, tissue confirmation and endoscopic biliary drainage will turn out to be indispensable to administer chemotherapy in these patients. Second, whole-genome sequence of pancreatic ductal adenocarcinoma has revealed four subtypes (aberrantly differentiated endocrine exocrine, progenitor, squamous, and immunogenic) with potentially diverse prognosis and response to therapy.[12] Molecular characterization, which may be predictive and/or provide therapeutic stratification, requires substantial neoplastic tissue. Up to now, only surgical specimens satisfy this need. However, newly developed EUS-guided biopsy needles have now become available, which are able to provide enough tissue to perform molecular studies, and to usher pancreatic cancer therapy into the era of personalized medicine.[13,14] Third, three randomized controlled trials comparing ERC *versus* EUS for primary drainage of distal malignant biliary obstruction have become available.[15-17] The first two studies, in which EUS-guided biliary drainage (EUS-BD) was performed using standard ERC biliary SEMSs, concluded that EUS-BD and ERC were comparable regarding both primary outcomes (adverse event rate and stent patency) and secondary outcomes (technical and clinical success).[15,16] Both studies, however, were underpowered to support their conclusions.[18] In a third noninferiority randomized controlled trial in 125 patients, EUS-BD was performed using specifically designed stents mounted on a dedicated small 7-Fr introducer, which functioned without the need for predilation or use of electrocautery.[17] Technical and clinical success rates were similar in the two groups. Importantly, EUS-BD showed significantly lower rate of early (6.3% *vs.* 19.7%, $P = 0.03$) and late adverse events (4.7% *vs.* 19.4%, $P = 0.01$), shorter median length of hospital stay ($P = 0.03$), higher 6-month stent patency rates (85.1% *vs.* 48.9%, $P = 0.001$), longer mean patency time (208 days *vs.* 165 days), and lower reintervention rates (15.6% *vs.* 42.6%, $P = 0.001$), as compared to ERC.[17] If these results will be replicated in the future by other studies, coupled with the broad development of accessories specifically designed for EUS-BD, this procedure can become the method of choice to drain malignant distal biliary obstruction, even in patients with resectable disease in whom the stent does not preclude subsequent surgery.[15]

Based on all the above novelties, how can we envisage the future approach to a patient with a HOP mass fit for chemotherapy? EUS-TA using a therapeutic echoendoscope will be performed with one of the available biopsy needles. The histological specimen acquired will be utilized for the touch imprint cytology technique to perform rapid on-site evaluation (ROSE) to reach an instantaneous definitive diagnosis,[19] while the remaining part will be placed in formalin or in a methanol-based preservative solution for molecular studies. In this context, ROSE will become cost-effective by allowing the performance of diagnosis and drainage with the appropriate stent during the same procedure, with the same instrument. Indeed, after exchanging the biopsy needle for a specifically designed accessory to enter the biliary system, EUS-guided choledocoduodenostomy or hepaticogastrostomy will be carried out by placing specifically designed SEMSs to drain the biliary tree. Finally, in unresectable patients with pain, a 19-G or the 20-G CPN needle (Cook Medical) will be used to perform early celiac plexus neurolysis, which has been found to be more effective than medical treatment and to moderate morphine consumption in this patient population.[20]

Are all the above speculations a pleasant dream or will they become real? Only time and efforts by companies to develop dedicated accessories for interventional EUS will answer this question.

Conflict of Interest

There are no conflicts of interest.

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