# The resectable pancreatic ductal adenocarcinoma: To FNA or not to FNA? A diagnostic dilemma, FNA pros

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Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has become the preferred method for acquiring tissue from pancreatic lesions, playing an essential role in the diagnostic and staging algorithms in patients with pancreatic cancer. Recent metanalyses indicate a highly accurate sensitivity and specificity of EUS-FNA for the diagnosis of pancreatic solid lesions;[1,2] however, some authors have suggested that EUS-FNA should not be performed on patients with potentially resectable pancreatic cancer.

The question is: If we found a resectable solid pancreatic lesion, what should we do? To fine-needle aspirate (FNA) or not to FNA the lesion? The answer is yes, we should perform the biopsy.

In 2014, a group of experts in pancreatic surgery published a consensus statement on the need for an objective histologic diagnosis of malignancy before proceeding with a pancreatoduodenectomy for a patient with a highly suspected pancreatic cancer.[3] Considering this statement, confirmation of malignancy is mandatory for patients with advanced or borderline resectable disease to be treated with neoadjuvant therapy, but biopsy is not required if the lesion is resectable.[3] However, the incidence of benign disease found on pathologic review after pancreatoduodenectomy is reported as high as 5%–13%, many of which are autoimmune pancreatitis.[4]

The point is that not all resectable pancreatic lesions are equal, and this is very well shown in a recent multicenter retrospective study whose aim was to determine the etiology of small solid pancreatic lesion of 15 mm (or less) of diameter.[5] Among the about 400 lesions with a definite diagnosis included in the analysis, <40% were finally diagnosed as pancreatic ductal adenocarcinoma (PDAC). That means that about 60% of small solid pancreatic lesions were finally diagnosed as lesions other than PDAC. In fact, 40% of the lesions were a pancreatic neuroendocrine tumor and 7% were pancreatic metastases. Without a preoperative diagnosis, an unacceptably large proportion of patients would be exposed to radical

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surgery with significant morbidity and mortality. So why not biopsy the resectable pancreatic lesion? Are we scared by potential complications related to the procedure? EUS-FNA is a safe procedure, with a low complication rate (0.2%–2%) more frequently related to the biopsy of cystic pancreatic lesions.[6] EUS-FNA, moreover, is not associated with increased risk of gastric or peritoneal recurrence, as demonstrated by different studies. A recent retrospective study assessed the impact of preoperative EUS-FNA on overall and cancer-specific survival in patients with locoregional pancreatic cancer who underwent surgery with curative intent. The patients were divided into two groups: About 500 patients underwent preoperative EUS-FNA and 1500 patients did not receive EUS-FNA. Patients were followed up over a mean time of 21 months with 57% of deaths occurring in the EUS-FNA group and 76% in the non-EUS-FNA group, with EUS-FNA having a borderline significant association with improved overall survival (Hazard Ratio: 0.84, 95% confidence interval: 0.72–0.99, $P = 0.03$).[7] The authors of the study concluded that preoperative EUS-FNA did not adversely affect overall or cancer-specific survival and is, therefore, safe to be performed as part of the work-up of suspicious pancreatic lesions.

On the other hand, concerning adverse events, pancreatic surgery keeps having a high rate of peri- and post-operative morbidity and mortality. In fact, although these rates have decreased during the latest years, morbidity rate is still around 27% and mortality around 1%–3% in high-volume centers, and even higher in low-volume centers.[8]

Finally, we have to think about the fact that management of resectable pancreatic cancer is evolving rapidly. The current recommendation for the management of early stage resectable PDAC promotes upfront surgical resection followed by systemic chemotherapy with or without radiation.[9] In fact, decades of surgical experience have demonstrated that surgical resection alone provides a limited median survival benefit. Despite the optimization of surgical technique and perioperative management over the past three decades, little progress has been made to improve the limited survival of patients with localized pancreatic cancer who receive surgery. Within 6 months of successful surgery, up to 60% of patients who underwent curative-intent surgery had already experienced disease relapse, as reported in the CONKO-001 trial.[10] In fact, the occult micrometastatic disease may be present in the majority of patients with pancreatic cancer at the time of diagnosis.[11] There is an evolving recognition that pancreatic cancer is an already systemic disease at the time of diagnosis, even among patients with the apparent localized disease, and a chance to resect is not necessarily a chance to cure.[12]

For this reason, some authors compared overall survival between patients who received neoadjuvant therapy followed by resection with those who received upfront resection, as well as a subgroup of upfront resection patients who also received adjuvant therapy, for early stage PDAC.[13] Patients who underwent neoadjuvant therapy followed by curative-intent resection (2005 patients) were matched by propensity score with patients whose tumors were resected upfront (6015 patients). In patients with resected pancreatic head adenocarcinoma, a significant survival benefit (26 months *vs.* 21 months) was observed for patients who underwent neoadjuvant therapy followed by resection, compared with upfront resection, and this survival advantage held for patients who received upfront resection plus adjuvant therapy.

The enthusiasm for adopting neoadjuvant therapy for resectable pancreatic cancer is emerging, but there is, of course, some additional work to do. However, this emerging data lend further support to the need to biopsy all suspected pancreatic lesions even if resectable because confirmation of malignancy is mandatory for neoadjuvant therapy.

In conclusion, EUS-FNA has to be considered the method of choice to diagnose small solid pancreatic lesions, is a safe procedure with a very low complication rate in terms of bleeding, pancreatitis and tumor cell seeding. Interestingly, the rational for a novel management strategy for patients with resectable pancreatic cancer is emerging, supporting the decision to perform FNA in all resectable pancreatic solid lesions.

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