Role Of Fine-needle Aspiration In The Surgical Management Of Pancreatic Neuroendocrine Tumors

Utility and Limitations in Light of the New WHO Classification

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Background

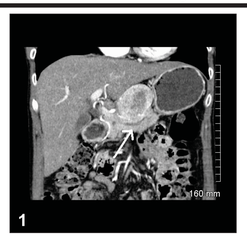
- Cross-sectional imaging, endoscopic ultrasound and fine-needle aspiration (FNA) are important in the pre-operative evaluation of pancreatic masses.
- While the majority of pancreatic tumors are ductal adenocarcinomas, other neoplasms also occur.
  - Neuroendocrine tumors, acinar cell carcinomas, solid pseudopapillary neoplasms, cystic neoplasms and metastases.
- Pancreatic neuroendocrine tumors (PancNETs) are a particularly interesting group of neoplasms since they can present clinically with neuroendocrine manifestations or remain silent until their presence is heralded by mass effect.
- They can be single and sporadic or can be a component of several syndromes.
- The biological behavior of PancNETs is unpredictable especially in the absence of locoregional spread or metastases. Thus the management is controversial.
- However, there is now a growing consensus that the new World Health Organization (WHO) classification has significantly contributed to the prognostic stratification of these patients.
- Concurrently, there have been advances in surgical techniques for benign or low-grade pancreatic tumors.
  - These procedures include minimally invasive and parenchyma-sparing operations such as laparoscopy and enucleation

Objective

- Herein, we report on the utility and limitations of FNA in the pre-operative evaluation and management of PancNETs in light of these mentioned developments.

Materials and Methods

- A retrospective analysis between 2002 and 2012 yielded 25 cases of PancNETs that were localized and staged by medical imaging and diagnosed by FNA, and 17 surgical pathology resections with prior FNA (Table 1)
- 12/25 were obtained using percutaneous ultrasound-guided FNA, 13/25 were obtained by endoscopic ultrasound FNA
- All 25 FNA cases and 17 resection cases were stained for neuroendocrine markers (synapthophysin, chromogranin A, and CD56)
- A cell block or representative tissue block was also stained for Ki67
  - Ki67 was determined by 2 of the authors by photographing hot spots at x20 magnification and counting at least 2000 cells



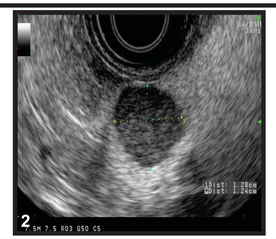


Figure 1. Case 10 in Table 1: axial and coronal enhanced computed tomography of the abdomen reveals an arterial enhancing lesion in the pancreatic head; there is no associated pancreatic duct dilatation (arrow) or distal atrophy (in contrast to ductal adenocarcinoma).
Figure 2. A 62-year-old woman (case 16) with pancreatic tail mass (1.3 3 1.2 cm) seen from the stomach using a 7.5-MHz GF-UCT140-AL5 echoendoscope (Olympus, Toronto, Canada).

Results

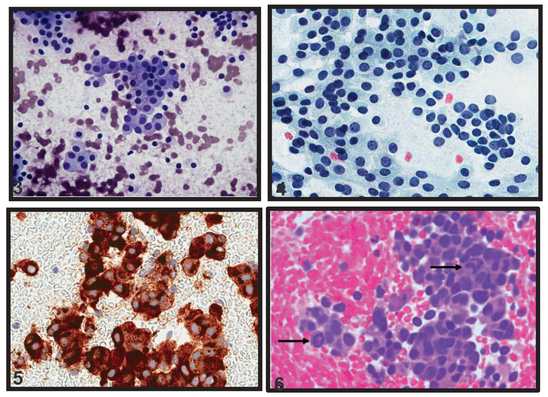


Figure 3. Diff-Quik stain showing single cells and small groups of tumor cells with mostly round nuclei and pale cytoplasm (original magnification x40).
Figure 4. Papanicolaou stain showing loosely cohesive overlapping aggregates of cells. The nuclei have a salt-and-pepper chromatin pattern and inconspicuous nucleoli (original magnification x40).
Figure 5. Cell block section depicting strong positivity (brown-staining cells) for chromogranin A. Most of the pale unstained cells in the background are red blood cells (immunocytochemistry, original magnification x40).
Figure 6. Cell block preparation showing the tumor that was grade 3 on the resection specimen. Mitoses (arrows) were more readily identified than in the other cases (hematoxylin-eosin, original magnification x63).

Table 1 & 2
•Of the 25 patients, 13 were men, 12 were women. Age range was 37-82 years, mean of 61 years
•Percutaneous FNA performed on 12 patients, EUS on the other 13
•Follow up period ranged from 4-96 months (mean = 37 months)
•Fourteen of 25 patients (56%) underwent laparotomy. Six of them had a distal pancreatectomy and
splenectomy, 4 required a pancreaticoduodenectomy, and in another 3 the tumors were enucleated. In 1 patient, the tumor was deemed to be unresectable at exploratory laparotomy and only core biopsies of the tumor were taken.
•4/25 patients (16%) underwent laparoscopy, and in all 4 a distal pancreatectomy and splenectomy was carried out; in 2 of the 4, it was a hand-assisted laparoscopic procedure.
•The follow-up period ranged from 4 to 96 months, with a mean follow-up of 37 months.
•More than half of the patients (14 of 25) were alive and well with no evidence of disease. A little more than a quarter of the patients (7 of25) were alive with disease, including all 4 patients who were observed, 1 patient who was inoperable, and 2 other patients who were originally staged as T2N0M0 andT3N1M0 respectively but subsequently developed liver metastasis.
•Three patients (3 of 25) died of disease; all 3 were inoperable based on medical imaging findings (n ¼ 2)
or at laparotomy (n ¼ 1).
•One patient (1 of 25) was lost to follow-up after 84 months. The overall survival of those patients who underwent resection and those who only had a biopsy are shown in Figure 7.

Table 1. Clinicopathologic Features of Patients With Pancreatic Neuroendocrine Tumors

Patient No.	Age, y/Sex	FNA Type	Surgical Operation	Pathologic and Radiologic Staging
1	55/F	EUS	Distal pancreatectomy and splenectomy	T3N1M0
2	44/F	EUS	Enucleation	T1N0M0
3	66/M	Percutaneous	Distal pancreatectomy and splenectomy	T3N1M0
4	48/M	Percutaneous	Pancreaticoduodenectomy	T3N0M0
5	54/M	Percutaneous	Inoperable because of comorbidity	T2N0M0
6	82/F	Percutaneous	Serial observations; no surgical intervention	T2N0M0
7	56/M	EUS	Inoperable on imaging	T4N0M0
8	81/F	EUS	Serial observations; no surgical intervention	T1N0M0
9	65/M	Percutaneous	Inoperable on imaging	T4N0M0
10	58/F	EUS	Enucleation	T3N0M0
11	47/F	EUS	Inoperable on imaging	T4N1M0
12	70/M	Percutaneous	Inoperable at laparotomy	T4N1M0
13	71/M	Percutaneous	Hand-assisted laparoscopic distal pancreatectomy and splenectomy	T2N0M0
14	76/M	EUS	Serial observations; no surgical intervention	T2N0M0
15	37/F	EUS	Distal pancreatectomy and splenectomy	T1N0M0
16	62/F	EUS	Laparoscopic distal pancreatectomy and splenectomy	T1N0M0
17	61/M	EUS	Enucleation	T1N0M0
18	61/F	Percutaneous	Hand-assisted laparoscopic distal pancreatectomy and splenectomy	T1N0M0
19	50/M	Percutaneous	Distal pancreatectomy and splenectomy	T2N0M0
20	70/M	Percutaneous	Hand-assisted laparoscopic distal pancreatectomy and splenectomy	T1N0M0
21	60/F	EUS	Pancreaticoduodenectomy	T3N0M0
22	71/F	Percutaneous	Distal pancreatectomy and splenectomy	T2N1M0
23	49/F	Percutaneous	Distal pancreatectomy and splenectomy	T3N1M0
24	53/M	EUS	Pancreaticoduodenectomy	T3N0M0
25	72/M	EUS	Pancreaticoduodenectomy	T3N1M0

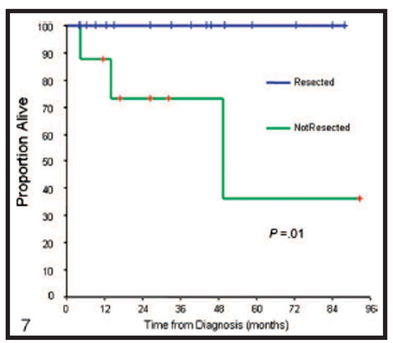
Abbreviations: AAW: alive and well; Abd, abdomen; AWD: alive with disease; DOD: died of disease; EUS: endoscopic ultrasound; FNA: fine-needle aspiration; LTFU: lost to follow-up; mets: metastases.

Table 1. Extended

Ki67 Index on Resection, %	Ki67 Index on Cell Block, % (Total No. of Cells Counted)	Follow-up
12	1 (400)	AAW at 31 mo
1	3 (500)	AAW at 8 mo
2	Cell block exhausted	AAW at 72 mo
10	8 (100)	Liver mets 45 months postsurgery; LTFU at 84 mo
	6 (100)	Liver mets at 51 mo; AWD at 92 mo
	5 (700)	AWD at 31 mo; tumor now 4.3 cm; no mets
	8 (1000)	DOD after 4 mo
	10 (1600)	AWD at 12 mo; no mets
	1 (100)	Liver mets 30 mo; DOD at 45 mo
4	2 (13 700)	AAW at 4 mo
	5 (1500)	Liver mets at 4 mo; AWD at 26 mo
	7 (800)	Abd mets; DOD at 16 mo
3	2 (1200)	AAW at 55 mo
	4 (1400)	AWD at 19 mo; no mets
2	5 (300)	AAW at 14 mo
2	2 (100)	AAW at 23 mo
5	6 (100)	AAW at 33 mo
1	9 (200)	AAW at 38 mo
10	2 (100)	Liver mets at 54 mo; AWD at 96 mo
2	4 (100)	AAW at 55 mo
16	7 (3100)	AAW at 8 mo
9	1 (300)	AAW at 7 mo, LTFU
30	35 (5300)	Abd and liver mets at 12 mo; AWD at 40 mo
8	4 (3600)	AAW at 44 mo
1	2 (2400)	AAW at 7 mo

Table 2. Management of Patients Who Had Pancreatic Neuroendocrine Tumors

	Mean Follow-up, mo	Recurrences, No.	Metastases, No.
Resected			
Pancreaticoduodenectomy (n = 4)	35.8	0	1
Distal pancreatectomy and splenectomy			
Open (n = 6)	36.3	0	2
Laparoscopic (n = 4)	42.8	0	0
Enucleation (n = 3)	15.0	0	0
Not resected			
Unresectable			
By imaging (n = 3)	25.0	. . .	3
At laparotomy (n = 1)	16.0	. . .	1
Observed (n = 4)	38.5	. . .	1



Discussion

•In this study, we showed that FNA can be used to accurately to diagnose PancNET in most cases.
•FNA compares favorably with core biopsies because the latter are technically more difficult, especially with smaller lesions, and also more limited in their capacity to sample the tumor.
•Only 3 cases during the time frame of this study were complicated by patient discomfort or hemorrhage, all of which during the era of the percutaneous approach
•The establishment of a correct diagnosis using FNA, combined with localization and staging through imaging provides important information in the preoperative evaluation and management.
  •For example, non-functional Panc-NETs confined to pancreas in the elderly are appropriately considered for observational management with periodic cross-sectional imaging instead of surgical intervention.
  •The 3 patients in our series that were managed this way had a mean age of 80 years. All of them are still alive with no evidence of metastases after a mean follow-up of 21 months,
•4 of our patients underwent laparoscopic surgery, all achieving negative surgical resection margins.
  •All these patients are alive and well with no evidence of disease after a mean follow-up of 42.8 months.
•In 3 patients, an enucleation of the tumor was carried out, a procedure generally considered when the morphology is known to be a PancNET rather than the more aggressive ductal adenocarcinoma.
•There is still a role for pancreaticoduodenectomy, however the proportion of cases is significantly less, thanks to improvements in imaging, FNA and minimally invasive surgery.
•One of the drawbacks of FNA, is that the tumor cells are mostly in the form of single cells or small dispersed groups of cells, which puts some limitations in assessing tumor grade.
•The WHO grading of PancNETs is based on number of mitotic counts per unit area, and accurate quantification of this is curtailed by the disruption of tissue architecture, making hot spots more difficult to define.
  •Distinguishing neuroendocrine cells from contaminant cells (which tend to stain with Ki67) may be difficult in the absence of tissue architecture, influencing tumour grade.
•Despite the fact that 2000 tumor cells are recommended for accurate tumor grading, the minimum threshold of 500 cells is sometimes not attained in cell block sections.
  •However, with the increasing utilization of EUS-FNA, the latter problem can ameliorated by requesting additional passes at the time of rapid on-site adequacy assessment.
•In conclusion, although immunocytochemistry has now become an indispensable tool in routine cytology for diagnosis, prognostication, and targeted therapies, there are also areas that warrant caution. This retrospective study describes the utility of FNA as a diagnostic adjunct to medical imaging in the preoperative evaluation and management of patients with PancNETs but at the same time shows the limitations of this technique with regard to grading PancNETs.