Team approach is essential incorporating: radiology, gastroenterology, surgery and pathology.

Successful performance is operator dependent.

In pancreaticobiliary cytology there are often 3 or more operators involved in ERCP brushings, percutaneous FNA or EUS guided FNA.

Trust and proof of utility of method is built through experience.
Committee V - Post brushing and FNA management options

Follow up recommendations are made in the framework of the proposed terminology for:

- Non-diagnostic samples
- Benign samples
- Atypical
- Neoplastic
- Suspicious
- Malignant

I. Non-diagnostic

As discussed and developed by the Terminology Committee, “A non-diagnostic sample is inadequate for interpretation due to inadequate cellularity or obscuring artifacts.”

Management in the face of sample inadequacy is clearly more involved than in superficial FNA or more accessible exfoliative procedures.

It would be optimum to consider procedure repetition in team context with review of clinical and radiologic evidence. Rapid on-site evaluation by the cytopathology team will decrease the frequency of non-diagnostic procedures and significantly improve performance characteristics.

Technique failure will likely necessitate more invasive studies up to and including laparoscopy or formal laparotomy.
II. Negative

- Findings are negative for malignancy based on the cytomorphology.
- However; the cytologist should attempt to make the interpretation as specific as possible and generated in the framework of a “Triple Test” where the clinical, radiologic and pathologic findings correlate.
- A negative diagnosis has a significant chance of being wrong in a patient population highly selected for neoplasia.

II. Negative

Specific Diagnoses include:
- Acute, chronic, or autoimmune pancreatitis
- Pseudocyst
- Splenule
- Lymphoepithelial cyst
II. Negative Management

- Acute pancreatitis is usually handled by institutional protocol that broadly consists of putting the pancreas at rest with minimal oral intake and intravenous hydration.
- Pain and nausea are handled via medication as they arise
- Progress is monitored by clinical assessment and serum enzyme analysis (lipase and amylase)
- Chronic pancreatitis is treated by removing or modifying the etiology, principally ethanolism or gall stones, treating pain and whatever exocrine and endocrine impairment might arise.
- Autoimmune pancreatitis usually responds to steroids
- Pseudocysts are drained
- Lymphoepithelial cysts may be left alone or resected.

III. Atypical

- Findings that are atypical for normal pancreatic cytology with abnormal cytologic, nuclear or architectural features, but that are not sufficient for a diagnosis of malignancy.
- Similar to the situation of the inadequate pancreatic sample, simply repeating the procedure is a much greater undertaking than sampling a more superficial site.
- Determination of management options may be assisted in some cases by biochemical markers. Positivity for Dpc4 has been correlated with benign situations. Alternatively, loss of p16 and activation of K-ras are seen in over 90% of malignancies.
Bile Duct Brushing Outcomes

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Number</th>
<th>Percent Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>105</td>
<td>25</td>
</tr>
<tr>
<td>Atypical Reactive</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Atypical NOS</td>
<td>45</td>
<td>62</td>
</tr>
<tr>
<td>Suspicious</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>Malignant</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

Unpublished data 216 Cases
Lester Layfield University of Missouri 2013

IV. Neoplastic - Benign

Clinical, radiologic and cytologic findings all are consistent and lead to the interpretation of benign disorders such as:
- Serous Cystadenoma
- Teratoma
- Schwannoma

All of these are managed by simple excision
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IV. Neoplastic - Other

- PANet (Pancreatic Neuroendocrine Tumor)
- Mucinous Cyst (IPMN or MCN*) NOS
- Mucinous Cyst (IPMN or MCN) with low grade atypia/dysplasia
- Mucinous Cyst (IPMN or MCN) NOS with low grade atypia/dysplasia
- Solid Pseudopapillary Neoplasm (SPN)
- Gastrointestinal Stromal Tumor (GIST)

* IPMN = Intraductal Papillary Mucinous Neoplasm. MCN = Mucinous cystic neoplasm
PANet present two clinical problems - tumor growth and hormonal activity

50-60% show local invasion or metastatic behavior

“Functional” PANets have clinically observed hormonal activity and are usually discovered earlier. Medical therapy for secretions include proton pump inhibitors or histamine H2-receptor antagonists for Zollinger-Ellison syndrome. Other hormones may respond to somatostatin analogues (Octreotide)

Optimum outcome is achieved with surgical resection

With unresectable or recurrent metastatic disease a number of molecular based therapies are available including the tyrosine kinase inhibitor sunitinib and mTOR inhibitor rapamycin. There is also peptide receptor radionuclide therapy.

Biochemical workup for PANets include serum chromogranin A and possible pancreatic polypeptide (PP) in non-functioning PANets.

Functioning PANets may also have elevated PP as well as insulin, C-Peptide, pro-insulin, gastrin, VIP, glucagon, calcitonin or somatostatin.

Levels of the latter hormones should be drawn and monitored in accord with the clinical picture.

Germline testing should be performed if family or personal history is suggestive of MEN1 or Von Hippel Lindau Disease. Somatic testing of the tumor is not indicated.

Cell block testing for chromogranin, synaptophysin, Ki-67 and mitotic index should be done. Specific hormone testing is directed by symptomology.
IV. Neoplastic - Other

PANet (Pancreatic Neuroendocrine tumors) with extrapancreatic extension or liver metastasis

- Local and or hepatic resection is done for functioning and non-functioning tumors with the aim of curative resection or debulking/palliation dependent on size and location.
- Embolization or radiofrequency ablation may be considered.
- Transplantation
  - With resection specific anesthetic procedures may be indicated to avoid hormonal crises.

Mucinous Cysts IPMN or MCN

- Resection is the usual therapy.
- Careful histologic sampling of the neoplastic wall must be performed to confirm the presence or absence of invasive disease
- MCN’s
  - Most occur in the body and tail
  - MCN’s less than 3cm are usually cured by resection
- IPMN’s
  - Usually occur in the pancreatic head and surgery may be complicated by variable anatomy and variable dysplasia. Nearly 40% may have an invasive component. (Fisher)
IV. Neoplastic - Other

- **Solid Pseudopapillary Neoplasm (SPN)**
  - Most cases are localized and cured by resection (95% or better survival at 5 years)

- **Gastrointestinal Stromal Tumor (GIST)**
  - Rare in the pancreas.
  - At other sites 20-50% of GIST’s may be aggressive and evolve metastatic disease. Tyrosine kinase inhibitor therapy Imatinib (Gleevec®) is the well known therapy for advanced/recurrent disease.

V. Suspicious

- When the cytologic sample exhibits severe cellular atypia, but due to small sample size or lack of some malignant criteria the cytologists cannot make the call.
- In most cases the lesion is malignant
- Ancillary studies may provide additional diagnostic clues if there is material.
There is definitive diagnosis of malignancy. In most hands there should be high specificity with few, if any, false positive diagnoses. It must be recognized that high grade non-invasive lesions cannot easily be differentiated from invasive disease; however, the clinical/radiologic findings should provide correlation. Management and prognosis relates to the specific type of malignancy. At times cytology alone may not be above define the subset of malignancy. To date the ability of CT scanning and EUS cytology to determine resectability is approximately 80%. One in five attempts at laparotomy will end in closure in the face of unresectable disease.

LFT’s and Coagulation profiles help determine the patient’s functional status. Patient’s with long standing biliary obstruction may have considerable liver damage. CA19-9 is elevated in 70-80% of cases of ductal carcinoma and can serve as a monitoring tool if present. 10% of cases present with localized disease without metastasis (R0). With adjuvant chemotherapy median survival for ductal carcinoma 20-23 months and some sources claim at best 20% five year survival for localized disease. Others are more pessimistic. 8% 5 year for disease spread to regional nodes. 1.7% 5 year for distant metastasis. Overall 5 year is on the order of 5% (SEER data 1996-2003).
### Pancreatic Ductal Carcinoma

**Outcome**

<table>
<thead>
<tr>
<th>Victorian Cooperative Oncology Group in collaboration with Victorian Cancer Registry</th>
<th>830 patient responses from 927 eligible patients</th>
<th>87 eligible for resection</th>
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<td>30 day mortality 5.3%</td>
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<td>Of 10 remaining patients 3 had recurrent disease within 6 years.</td>
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**830 patient responses from 927 eligible patients**

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### Ampullary Adenocarcinoma

- Tumors of the head of the pancreas and ampullary region tend to cause obstructive symptoms and may be discovered earlier.
- For unresectable disease the problems are pain, jaundice and small bowel obstruction.
- Narcotics, nerve blocks and nerve lysis have been used to deal with pain.
- Stents and bypass are used for biliary and bowel obstruction.
VI. Positive-Malignant

- The usual procedure for tumors of the head of the pancreas is a pylorus preserving pancreaticoduodenectomy (modified Whipple procedure).

- Tumors of the body and tail usually have a distal pancreatectomy and splenectomy.

Pancreatic Ductal Adenocarcinoma

Staging

T1 ≤ 2cm and limited to pancreas
T2 > 2cm and limited to pancreas
T3 extend beyond the pancreas and do not involve the celiac axis or superior mesenteric artery (SMA)
T4 tumors do involve the celiac axis or SMA. T4 tumors are generally considered unresectable.

T1, N0 : Stage I
T2, N0 : Stage II
T3: Stage IIA
T3, N1 or greater: Stage IIB
T4: Stage III
Distant Metastasis (Liver, Lung, Malignant Ascites): Stage IV
Pancreatic Adenocarcinoma

- 60% present with metastatic disease.
- For these patients even with gemcitabine therapy the 1 year survival is only 20%.
- Adding the tyrosine kinase inhibitor erlotinib has shown a few percent improvement.

Other tumor types

- Acinar Carcinoma
  - K-ras does not show mutation in this tumor, nor does it show changes in p53, p16/CDKN2a or SMAD4 genes.
  - There is loss of 11p and APC/Beta
- High Grade Neuroendocrine tumors
- Pancreatoblastoma
- Lymphoma
- Metastatic disease
For the Future
Pancreatic Cancer Pathways

As in the other major tumors, the hope is for Targeted chemotherapy


Ductal Adenocarcinoma
Pancreatic/Biliary Guidelines

To continue the discussion

Your comments and experience are welcome as this effort attempts to bring consensus to pancreatic/biliary cytology. Please consider adding to this program by using our website forum or by personal communication.

Pancreatic/Biliary Forum at www.papsociety.org/pscoforum
Committee V

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