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Pancreatic Endoscopy and Rapid on Site Evaluation by Cytopathology

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No relationship exists that represents a possible conflict of interest with respect to the content of this presentation.
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OBJECTIVES

- Understand the potential diagnostic impact of rapid on site evaluation (ROSE) with regard to EUS-guided FNAs of the pancreas.
- Utilization of the aspirate specimen for proper ancillary studies.
- Effectively communicate intra-procedurally to the performing gastroenterologist.
- Gain insight into the perspective of the gastroenterologist.
Goals of ROSE in FNA Cytology

- Optimize aspirate smears.
- Inform the operator of specimen adequacy.
- Avoid the need for repeat procedures.
- Garner a preliminary diagnosis.
- Determine whether ancillary studies are required to render a diagnosis and appropriate the specimen accordingly.
Rapid On-Site Evaluation (ROSE)

- ROSE has significant potential to improve adequacy rates and diagnostic performance of FNAs.
- ROSE does incur significant costs and many sites do not have resources to implement.
- It is important to determine the circumstances where ROSE can have the most benefit.
Factors that affect success of EUS-FNA

- Endoscopist skill
- Endoscopist experience
- Pathologist skill
- Pathologist experience
- Interaction between cytologist & endoscopist
- Tumor related factors:
  - Tumor visibility
  - Tumor accessibility
  - Tumor vascularity
  - Presence or absence of tumor necrosis
Needle Selection

- Scientific:
  - Needle size
  - Needle tip construction
  - Stylet construction/operation
  - Needle visibility during EUS

- Not-so scientific:
  - Perceived comfort of handle/ease of operation
  - Institutional vendor contracts
Three sizes currently available:
  • 19g
  • 22g
  • 25g

Larger gauge needles may garner more tissue, but may also be more traumatic:
  • Bleeding
  • Pancreatitis
Effect of Needle Size on EUS FNA

- Affolter, Schmidt, Matynia, Adler, Factor DDAS 2012
- Meta-analysis of 11 studies on needle size
  - No difference in number of passes overall
  - No difference in needle visibility via EUS
  - No difference in overall penetrability
  - No difference in overall complications
No difference in adequacy between 19g & 22g

When 22g and 25g needles compared:
• 25g needles showed a trend toward greater adequacy but also showed significant heterogeneity overall

Core needles had lowest technical success rate
• Evaluated older, more cumbersome core needles
Effect of Needle Size on EUS FNA

- 25G needles had a slight advantage in adequacy rates
- No overall difference:
  - Accuracy
  - Complication rates
  - Number of needle passes
  - Needle visibility
- Conclusion:
  - Needle can be selected based on personal preference
ROSE: Rapid On-Site Evaluation

- Presumes the presence of a pathologist or a cytopathologist
- Sample obtained from patient is taken directly for evaluation
- If diagnostic, procedure complete
- If non-diagnostic, further needle passes obtained
If pathologist/cytopathologist not available, most endoscopists will default to what is known as a “Fixed Approach.”

“Fixed Approach” entails:
- Obtaining a fixed number of passes (3-5)
- Absence of any immediate interpretation
- Tissue either air dried or placed in Cytolyte
- Interpretation made at later time and place
Evaluating the Impact of ROSE

- EUS FNA is a complex and multistep procedure.
- Therefore, there are many factors that can affect the diagnostic yield of the process:
  - Number of needle passes
  - Needle type and size
  - Aspirator experience
  - Assessor experience
  - Lesion characteristics
  - ROSE
How to Determine the Effect of ROSE

- Optimal studies are those that compare the performance of 2 cohorts (with and without ROSE).
- Studies that are conducted at a single institution.
  - Minimizes operator and assessor variability
  - Minimizes variation in technique (needle size/type)
Systematic Review and Meta-Analysis on Impact of ROSE on Adequacy (Multiple Body Sites)

- All anatomic sites included
- 25 articles met our inclusion criteria (MEDLINE and EMBASE) from 9 anatomic sites
- Findings:
  - Overall ROSE improves per case adequacy rate by 12%
  - ROSE had a statistically significant impact on adequacy in 6/9 anatomic sites studied
  - Non-ROSE adequacy rate was the most significant confounder

Schmidt et al. Am J Clin Pathol (2013);139:300-308
ROSE: Impact on EUS-FNA of Pancreas

- Systematic review and meta-analysis of the literature (EMBASE, MEDLINE, SCOPUS) performed
- Only studies comparing either adequacy or diagnostic yield between 2 cohorts of EUS-FNA of the pancreas (with ROSE vs without ROSE) at a single site were included
- Only 5 / 36 potentially relevant studies met our inclusion criteria

## The Included Studies in our Series

### Table 1 Study characteristics

<table>
<thead>
<tr>
<th>Study group</th>
<th>Study</th>
<th>Study period</th>
<th>Report type</th>
<th>Study location</th>
<th>Guidance</th>
<th>Evaluator</th>
<th>Reported outcome</th>
<th>Solid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included studies</td>
<td>Alsohaibani 2009</td>
<td>2005–2007</td>
<td>Full</td>
<td>Canada</td>
<td>EUS-FNA</td>
<td>Cytotech</td>
<td>Diagnostic Yield</td>
<td>100 %</td>
</tr>
<tr>
<td></td>
<td>Cermak 2012</td>
<td>2004–2009</td>
<td>Full</td>
<td>USA</td>
<td>EUS-FNA</td>
<td>Residents Fellows</td>
<td>Diagnostic Yield</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cytotech</td>
<td></td>
<td>(85 %)</td>
</tr>
<tr>
<td></td>
<td>Cleveland 2010</td>
<td>1997–2007</td>
<td>Full</td>
<td>USA</td>
<td>EUS-FNA</td>
<td>Cytotech</td>
<td>Adequacy</td>
<td>100 %</td>
</tr>
<tr>
<td></td>
<td>Iglesias-Garcia 2011</td>
<td>NR</td>
<td>Full</td>
<td>Spain</td>
<td>EUS-FNA</td>
<td>Pathologist</td>
<td>Adequacy</td>
<td>100 %</td>
</tr>
<tr>
<td>Not included but potentially relevant</td>
<td>Nguyen 2009</td>
<td>NR</td>
<td>Abstract</td>
<td>USA</td>
<td>EUS-FNA</td>
<td>NR</td>
<td>Diagnostic Yield</td>
<td>100 %</td>
</tr>
</tbody>
</table>

NR not reported, EUS-FNA endoscopic ultrasound-guided fine-needle aspiration, Full complete research study (vs. a letter or abstract)

## ROSE Versus Non-ROSE (How It’s Impact Relates to Initial Adequacy)

<table>
<thead>
<tr>
<th>Study</th>
<th>Without ROSE Success Rate</th>
<th>With ROSE Success Rate</th>
<th>Difference with Implementation of ROSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alsohaibani</td>
<td>14/22 (63.6%)</td>
<td>14/22 (63.6%)</td>
<td>0%</td>
</tr>
<tr>
<td>Cleveland</td>
<td>24/24 (100%)</td>
<td>198/200 (99%)</td>
<td>-1.0%</td>
</tr>
<tr>
<td>Iglesias-Garcia</td>
<td>76/87 (87.3%)</td>
<td>94/95 (98.9%)</td>
<td>+11.6%</td>
</tr>
<tr>
<td>Klapman</td>
<td>35/48 (72.9%)</td>
<td>79/85 (92.9%)</td>
<td>+20%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>311/395 (78.7%)</td>
<td>509/569 (89.4%)</td>
<td><strong>+10.7%</strong></td>
</tr>
<tr>
<td>Nguyen (abstract)</td>
<td>22/56 (39.3%)</td>
<td>54/55 (98.2%)</td>
<td>+58.9%</td>
</tr>
<tr>
<td>Saleh (EUS-guidance not specified)</td>
<td>15/23 (65.2%)</td>
<td>8/12 (66.7%)</td>
<td>+1.5%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>348/474 (73.4%)</td>
<td>571/636 (89.8%)</td>
<td><strong>+16.5%</strong></td>
</tr>
</tbody>
</table>
Distribution of Adequacy Rates Without ROSE

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**Fig. 5** Distribution of adequacy rates for studies without ROSE. 
CI = confidence interval. The squares indicate the estimated change in success rate (adequacy or diagnostic yield) for an individual study. The associated bars show the confidence interval. The diamonds indicate overall averages and the width of the diamond corresponds to the confidence interval of the average. The overall average is weighted by the study size. ES = Effect size (adequacy rate).

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iglesias-Garcia (2007)</td>
<td>0.82 (0.73, 0.92)</td>
<td>3.51</td>
</tr>
<tr>
<td>Chang (1994)</td>
<td>0.83 (0.62, 1.04)</td>
<td>1.02</td>
</tr>
<tr>
<td>Guillermo (2005)</td>
<td>0.83 (0.62, 1.04)</td>
<td>1.02</td>
</tr>
<tr>
<td>Imazu (2009)</td>
<td>0.83 (0.68, 0.98)</td>
<td>1.84</td>
</tr>
<tr>
<td>Klapman (2003)</td>
<td>0.85 (0.76, 0.93)</td>
<td>3.87</td>
</tr>
<tr>
<td>Binmoeller (1998b)</td>
<td>0.85 (0.74, 0.96)</td>
<td>2.88</td>
</tr>
<tr>
<td>Song (2010)</td>
<td>0.86 (0.79, 0.92)</td>
<td>5.27</td>
</tr>
<tr>
<td>Binmoeller (1998a)</td>
<td>0.86 (0.77, 0.95)</td>
<td>3.82</td>
</tr>
<tr>
<td>Hwang (2009)</td>
<td>0.88 (0.82, 0.93)</td>
<td>6.04</td>
</tr>
<tr>
<td>Alsibai (2006)</td>
<td>0.88 (0.81, 0.96)</td>
<td>4.50</td>
</tr>
<tr>
<td>Wegener (1995)</td>
<td>0.91 (0.74, 1.08)</td>
<td>1.49</td>
</tr>
<tr>
<td>Mortensen (2001)</td>
<td>0.91 (0.79, 1.03)</td>
<td>2.56</td>
</tr>
<tr>
<td>Moller (2009)</td>
<td>0.93 (0.89, 0.96)</td>
<td>7.47</td>
</tr>
<tr>
<td>Touchefeu (2009)</td>
<td>0.93 (0.88, 0.99)</td>
<td>6.36</td>
</tr>
<tr>
<td>Fritscher-Ravens (2001b)</td>
<td>0.94 (0.88, 1.01)</td>
<td>5.54</td>
</tr>
<tr>
<td>Fritscher-Ravens (2002)</td>
<td>0.97 (0.94, 0.99)</td>
<td>8.39</td>
</tr>
<tr>
<td>Kopelman (2011)</td>
<td>0.97 (0.94, 1.00)</td>
<td>7.79</td>
</tr>
<tr>
<td>Yiagan (2002)</td>
<td>0.99 (0.96, 1.01)</td>
<td>8.41</td>
</tr>
<tr>
<td>Hunerbein (1998)</td>
<td>1.00 (0.99, 1.01)</td>
<td>9.03</td>
</tr>
<tr>
<td>Oppong (2010)</td>
<td>1.00 (0.99, 1.01)</td>
<td>9.16</td>
</tr>
<tr>
<td>Overall (I-squared = 82.8%, p = 0.000)</td>
<td>0.93 (0.91, 0.95)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Conclusions of ROSE Impact on EUS-Guided Pancreatic FNA

- ROSE frequently can have a statistically significant impact on adequacy rates when implemented at locations where the per-case adequacy rate without ROSE is low (<90%)
- About half of sites appear to have non-ROSE adequacy rates below 90%
- ROSE is associated with small but clinically insignificant changes in needle passes per case
  - ROSE: 2.7 needle passes per case
  - No ROSE: 2.9 needle passes per case
Case 1

- 60 year-old male with a pancreatic mass
- One pass made
- A single Diff-Quik® slide prepared on site
Renal Cell Carcinoma

- Mostly cohesive groups of large cells
- Abundant vacuolated cytoplasm
- Nuclei are enlarged with occasional nucleoli and some contour irregularity
- Associated endothelial cells are useful clue

Metastatic renal cell carcinoma is among the most frequent metastases to the pancreas.

Case #1: Take Home Points

- A history of renal cell carcinoma was communicated by the endoscopist during ROSE
- A diagnosis was able to be rendered morphologically on a single pass
- Communication obviated the need for more passes; reducing the time of procedure
Case 2

- 81 year-old female presented to ER with upper abdominal pain, nausea/vomiting
- CT abdomen/pelvis showed a pancreatic head mass with surrounding lymphadenopathy, as well as multiple bilateral liver lesions
Pass #1: From Pancreatic Head Mass
Pass #2: From Peripancreatic Lymph Node

Diff Quik® 40x: Lesional cells

Diff Quik® 60x: Benign ductal epithelial cells by comparison
Pass #2: Needle Rinse

Pap stain
40x
Pancreatic Ductal Adenocarcinoma

- Nuclear enlargement (3x size of RBC)
- Nuclear contour irregularity
- Anisonucleosis (3-4x nuclear size variation in same group)
- Nuclear molding (nuclei don’t respect each other)
- Chromatin clumping (Pap stain)

- The highlighted criteria had a sensitivity of 98% and a specificity of 100%

Cohen et al. Diagn Cytopathol. 1991
Case #2: Take Home Points

- Communicating lack of viability at initial sampling site prompted endoscopist to change targets
- Viable and diagnostic cells were obtained from the second site
Case 3

- 39 year-old female with large pancreatic tail mass identified incidentally on abdominal CT performed for trauma.
Pass #2: From Pancreatic Tail Mass

Diff Quik® 10x

Diff Quik® 40x
Pass #2: Alcohol-Fixed Slide

Pap stain 40x
Cell Block

Synaptophysin 40x

Chromogranin 60x
Pancreatic Neuroendocrine Tumor

- Cellular smear comprised of a fairly monotonous cell proliferation
- Loosely cohesive with areas of single cell dispersion
- Round, regular nuclei with even chromatin
- Salt and pepper chromatin on Pap stain
- Some cells with a plasmacytoid appearance
Differential Diagnosis for Pancreatic Neuroendocrine Tumors

- Acinar cell carcinoma
- Solid-Pseudopapillary Tumor
- Potentially: Melanoma or Plasmacytoma

→ A cell block for specimen triage is needed to navigate this differential diagnosis due to overlapping cytomorphology
Case #3: Take Home Points

- Based on ROSE interpretation (an entity with a differential diagnosis), further passes were requested and triaged into a cell block.
- Immunostains allowed for a definitive diagnostic interpretation.
Case 4

- 75 year-old male with a pancreatic head mass and peripancreatic lymphadenopathy
- EUS FNA was performed
Case #4: Take Home Point

- Specimen triage (only 1 pass needed for morphology)
- 2 additional passes requested and put directly into RPMI® solution for flow cytometry

Result: Consistent with a CD10+ B-cell Lymphoma
• Dispersed cells with scant cytoplasm
• Lymphoglandular bodies
• Monomorphic lymphoid population
• Obvious population of small cleaved lymphocytes (Follicular lymphoma, Mantle cell lymphoma) or small lymphocytes with clumped chromatin (CLL/SLL)
• Obvious population of medium-sized cells (Lymphoblastic lymphoma, Burkitt’s lymphoma, Ewing’s sarcoma/PNET)
• Population of large lymphoid cells with convoluted nuclei +/- prominent nucleoli (Hodgkin lymphoma, Diffuse Large B-cell lymphoma, Anaplastic T-cell lymphoma)

Caraway NP. Cancer (Cytopathology) 2005;105:432-442.