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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

Role of Needle Size

- 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

Effect of Needle Size on EUS FNA

- 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

ROSE Alternative: Fixed Approach

- 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

Schmidt et al. *Dig Dis Sci*. (2013)58;3:872-882

The Included Studies in our Series

Table 1 Study characteristics

Study group	Study	Study period	Report type	Study location	Guidance	Evaluator	Reported outcome	Solid (%)
Included studies	Alsohaibani 2009	2005–2007	Full	Canada	EUS-FNA	Cytotech	Diagnostic Yield	100 %
	Cermak 2012	2004–2009	Full	USA	EUS-FNA	Residents Fellows Cytotech	Diagnostic Yield	NR (85 %)
	Cleveland 2010	1997–2007	Full	USA	EUS-FNA	Cytotech	Adequacy	100 %
	Iglesias-Garcia 2011	NR	Full	Spain	EUS-FNA	Pathologist	Adequacy	100 %
	Klapman 2003	1998–2002	Full	USA	EUS-FNA	Pathologist	Adequacy	NR
Not included but potentially relevant	Nguyen 2009	NR	Abstract	USA	EUS-FNA	NR	Diagnostic Yield	100 %
	Saleh 1996	1992–1994	Full	USA	NR	Pathologist	Adequacy	NR

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

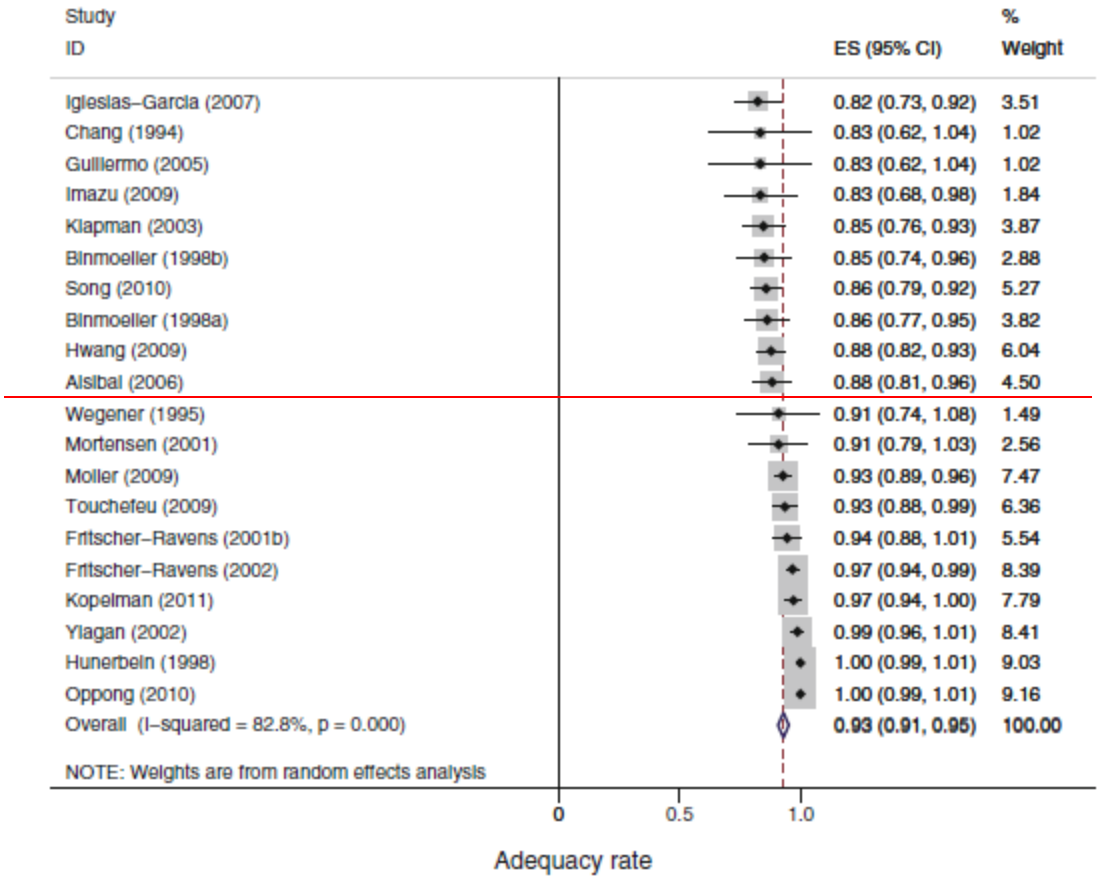
Schmidt et al. *Dig Dis Sci*. (2013)58;3:872-882.

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

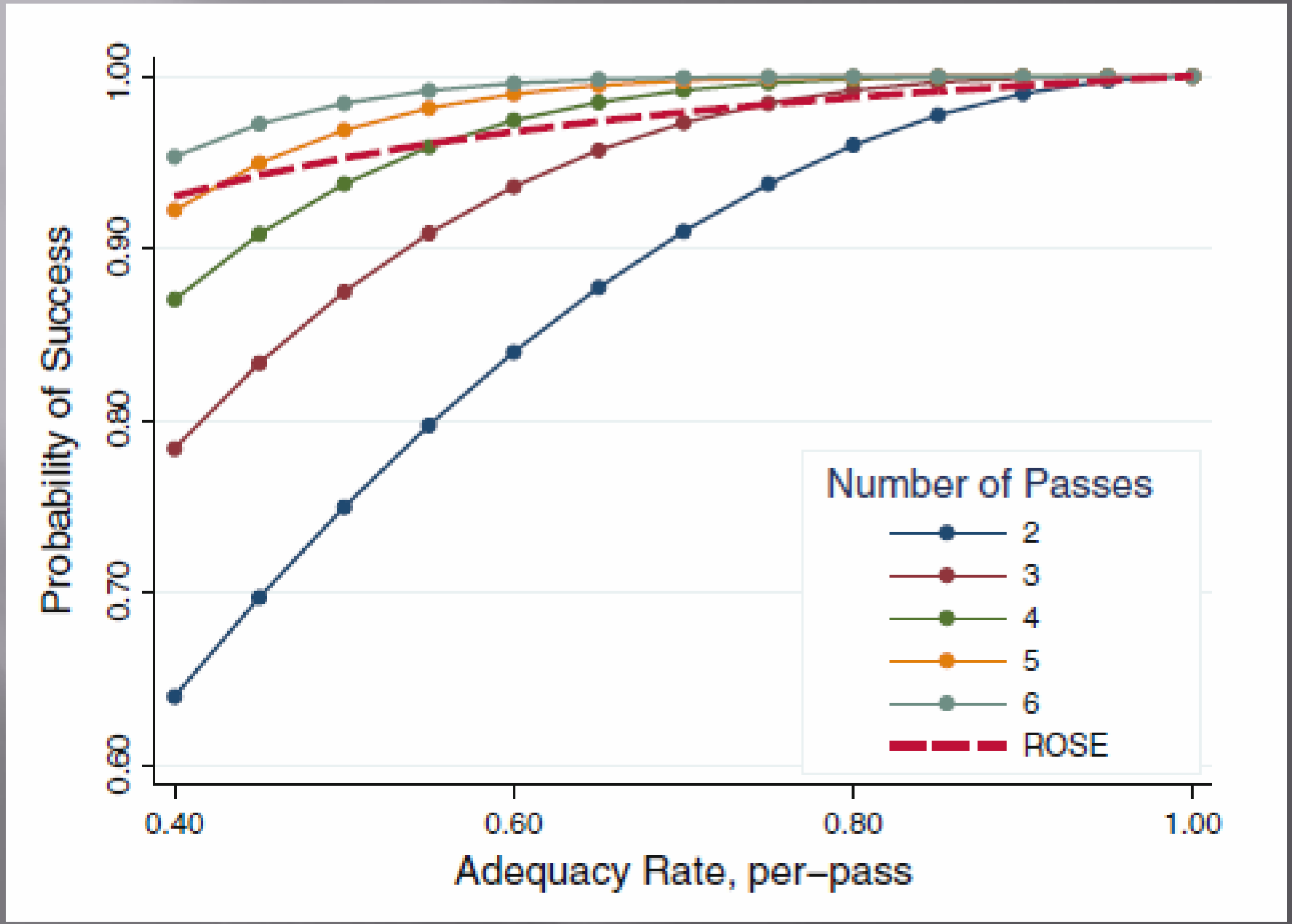
Study	Without ROSE Success Rate	With ROSE Success Rate	Difference with Implementation of ROSE
Alsohaibani	14/22 (63.6%)	14/22 (63.6%)	0%
Cleveland	24/24 (100%)	198/200 (99%)	-1.0%
Iglesias-Garcia	76/87 (87.3%)	94/95 (98.9%)	+11.6%
Klapman	35/48 (72.9%)	79/85 (92.9%)	+20%
Total	311/395 (78.7%)	509/569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

Distribution of Adequacy Rates Without ROSE

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)



Schmidt et al. *Dig Dis Sci*. (2013)58;3:872-882.


Probability of Success
0.60
0.70
0.80
0.90
1.00
0.40
0.60
0.80
1.00
Adequacy Rate, per–pass
Number of Passes
2
3
4
5
6
ROSE

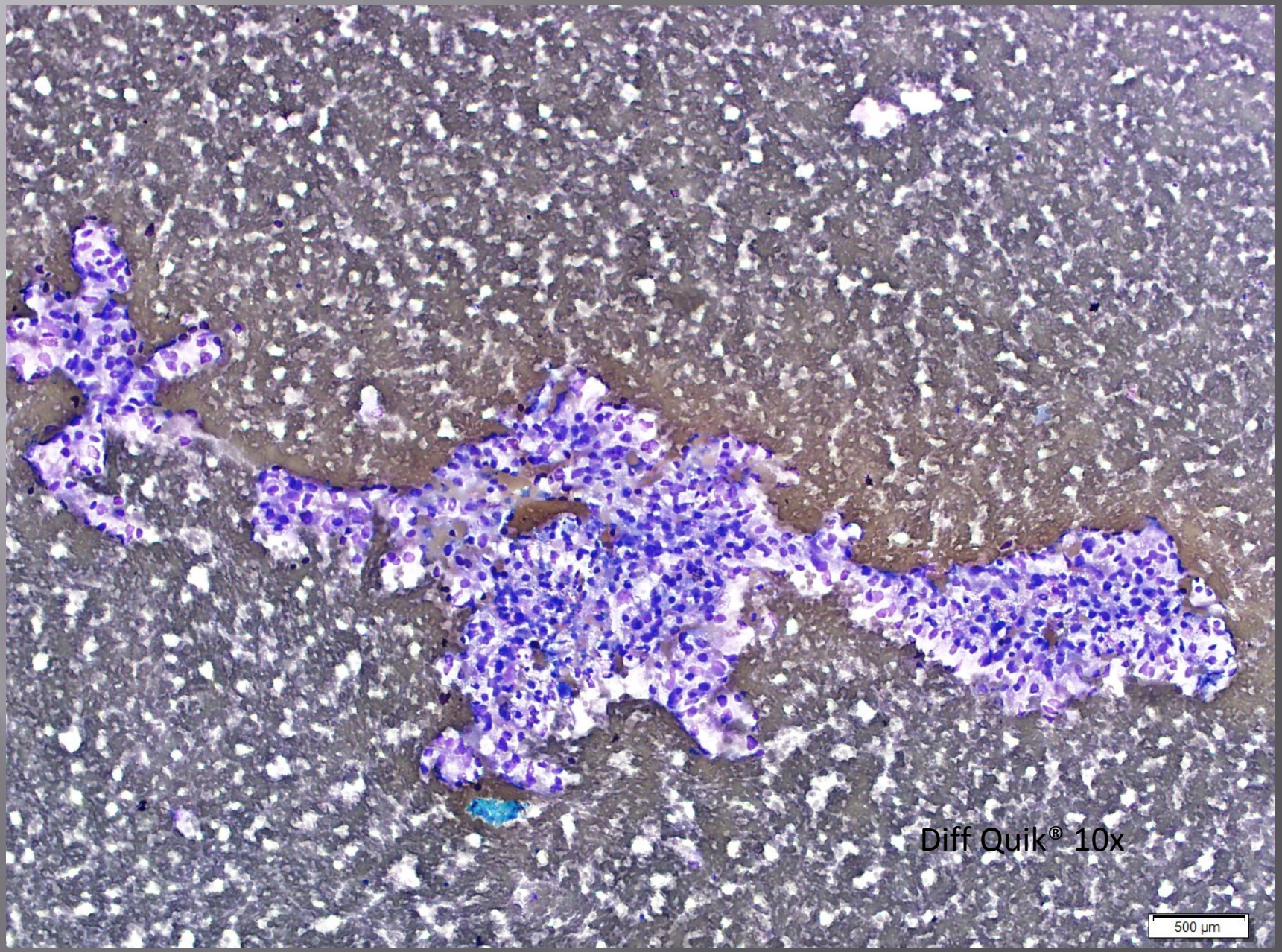
Conclusions of ROSE Impact on EUS-Guided Pancreatic FNA

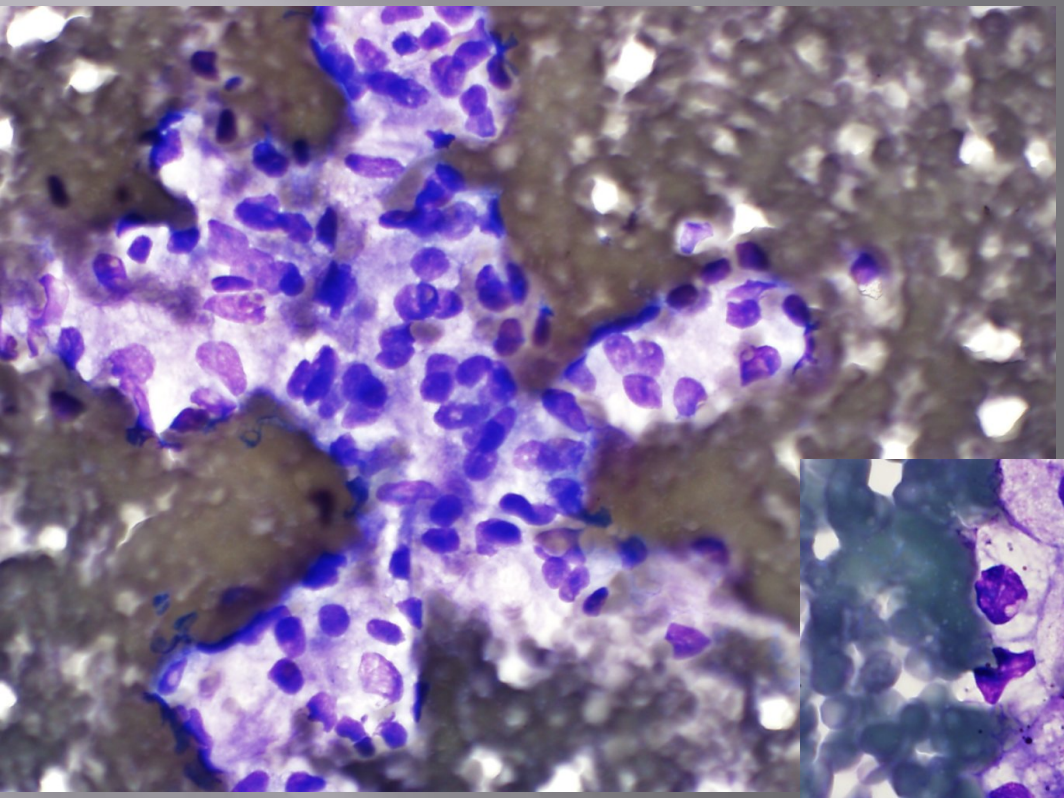
- ROSE frequently can have a statistically significant impact on adequacy rates when implemented at locations where the per-case adequacy rate without ROSE is low (<90%)
- About half of sites appear to have non-ROSE adequacy rates below 90%
- ROSE is associated with small but clinically insignificant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

Case 1

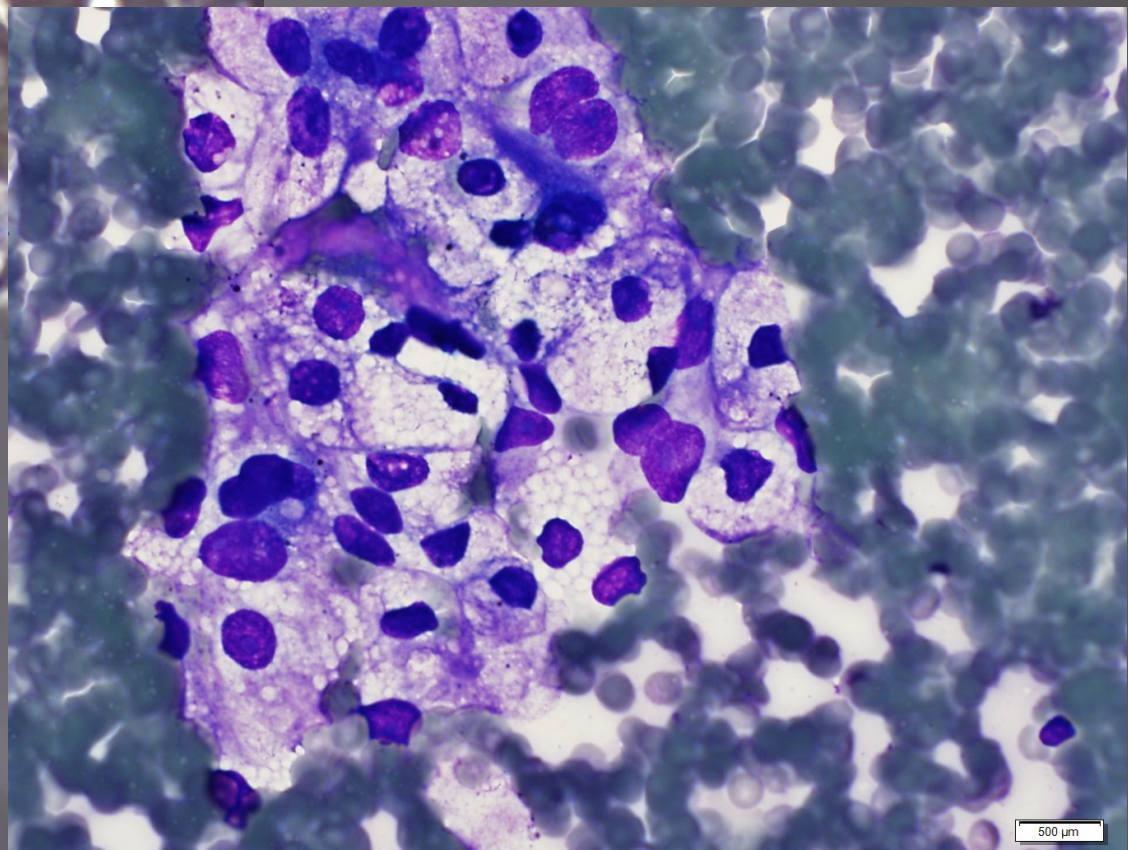
- 60 year-old male with a pancreatic mass
- One pass made
- A single Diff-Quik® slide prepared on site


ALOKA
HUNTSMAN CANCER CENTER
:No ID
12:44:40
52Hz
F13
7.5M 5.0 R03 G51 C5
2:EUS Linear
MI =0.52 DVA: 70%
TIS< 0.4


Diff Quik® 10x
500 µm



Diff Quik® 40x



Diff Quik® 60x

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.

Layfield et al. Diagn Cytopathol. 2012;40(3):228-33

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

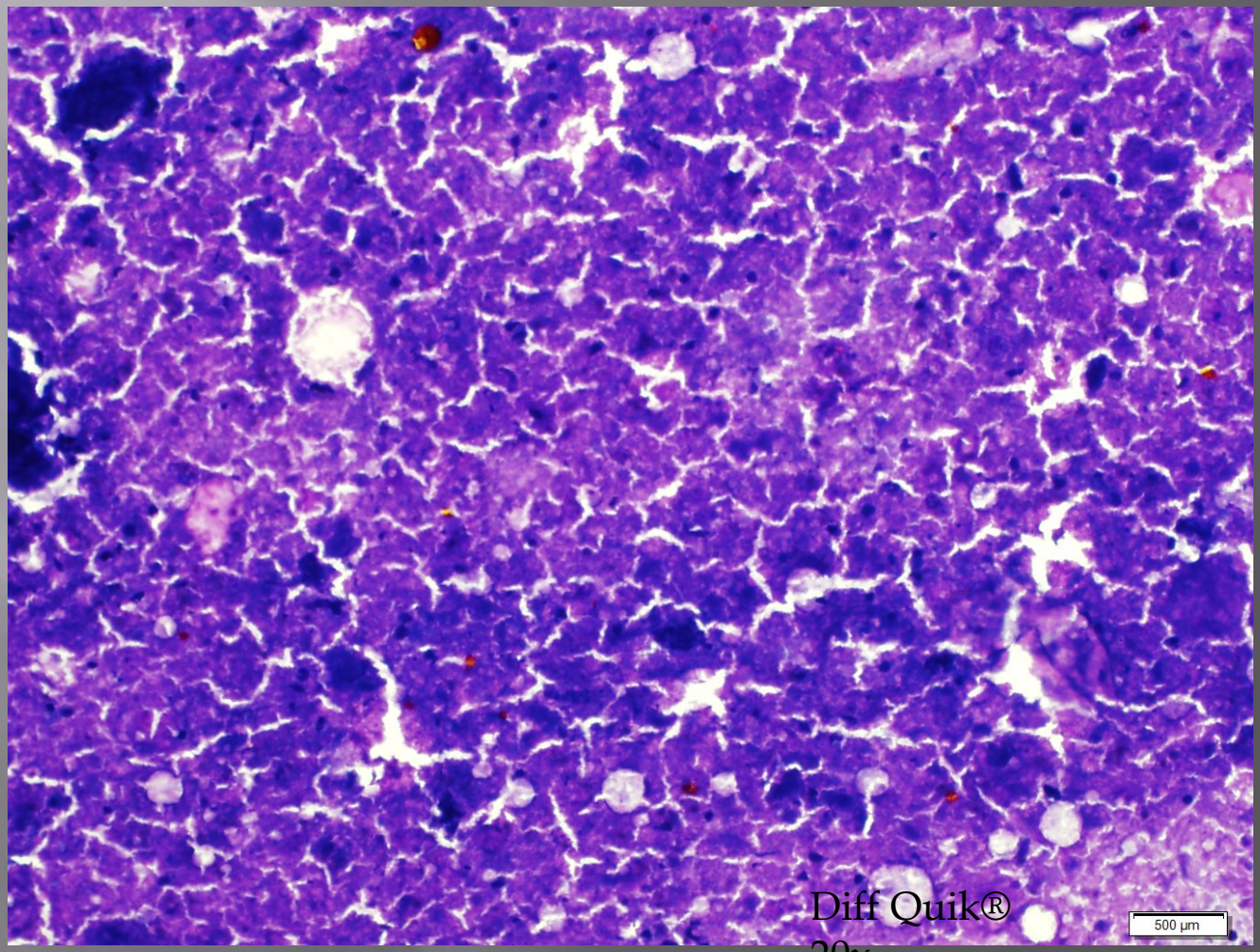
Case 2

- 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


ALOKA
HUNTSMAN CANCER CENTER
:No ID
15:56:55
52Hz
F13
7.5M 5.0 R05 G60 C5
2:EUS Linear
MI =0.53 DVA: 70%
TIS< 0.4

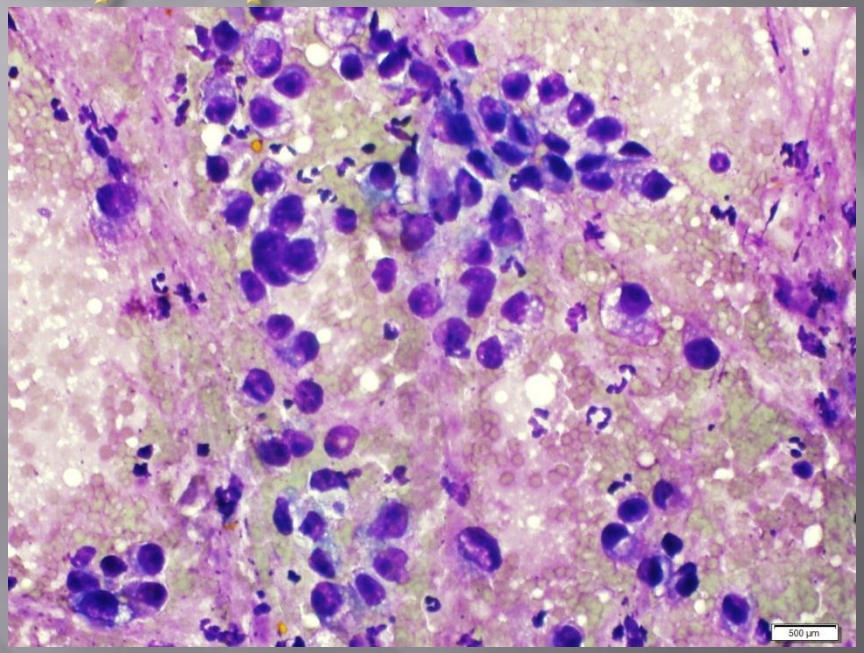

ALOKA
No ID
12:29:31
52Hz
F18
7.5M 5.0 R03 G60 C5
2:EUS Linear
MI =0.52 DVA: 70%
TIS< 0.4

Pass #1: From Pancreatic Head Mass

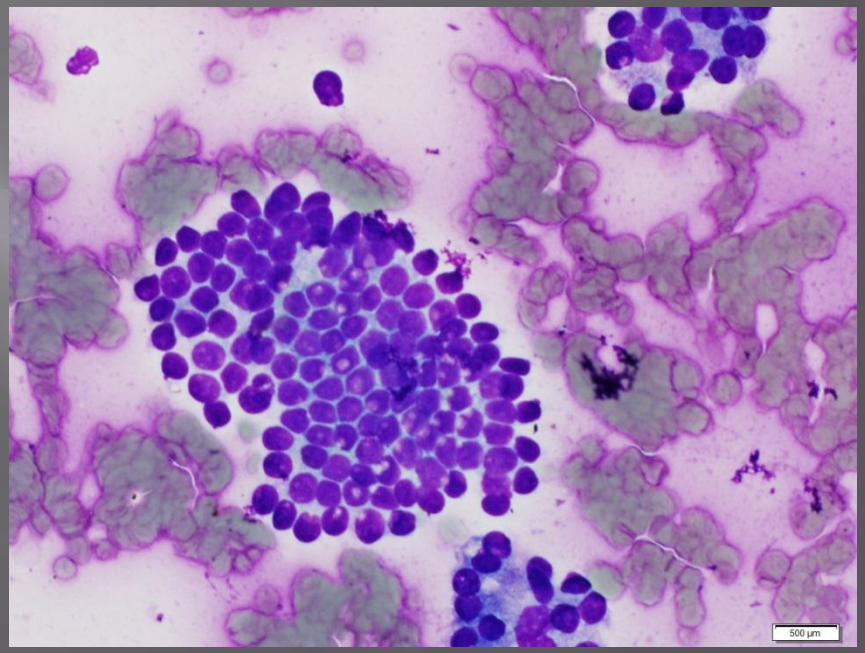


Diff Quik®
20x

Pass #2: From Peripancreatic Lymph Node

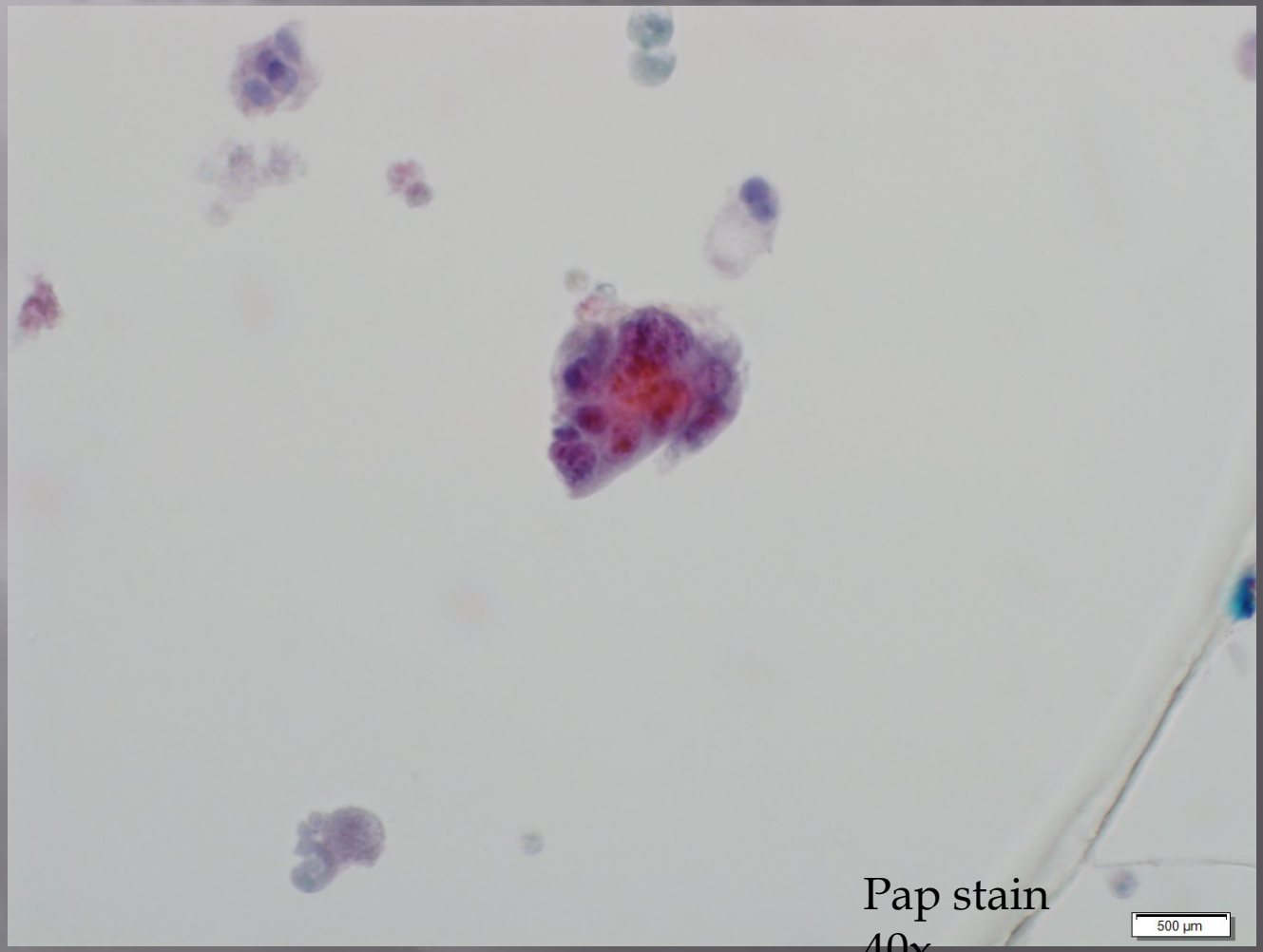


Diff Quik® 40x: Lesional cells



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

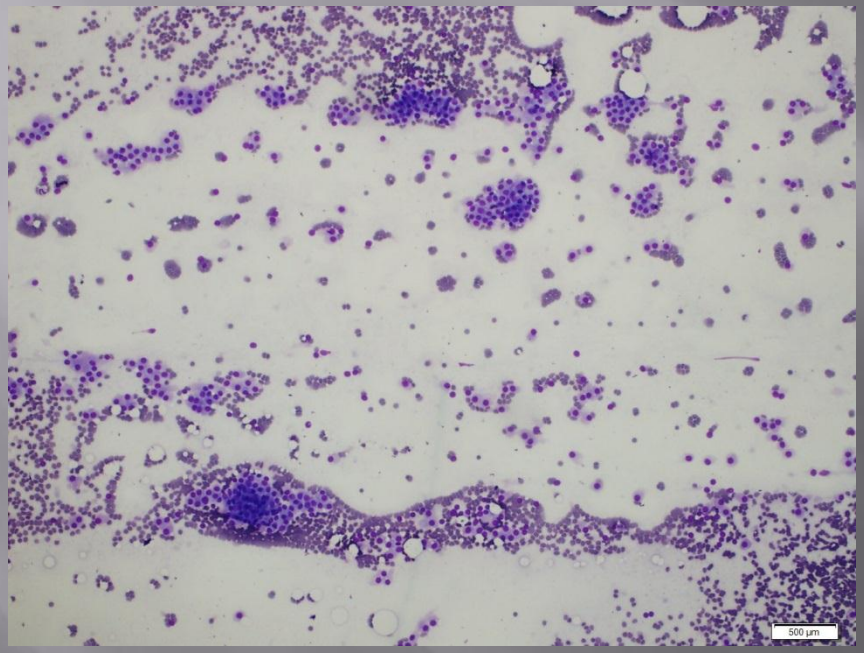
- Communicating lack of viability at initial sampling site prompted endoscopist to change targets
- Viable and diagnostic cells were obtained from the second site

Case 3

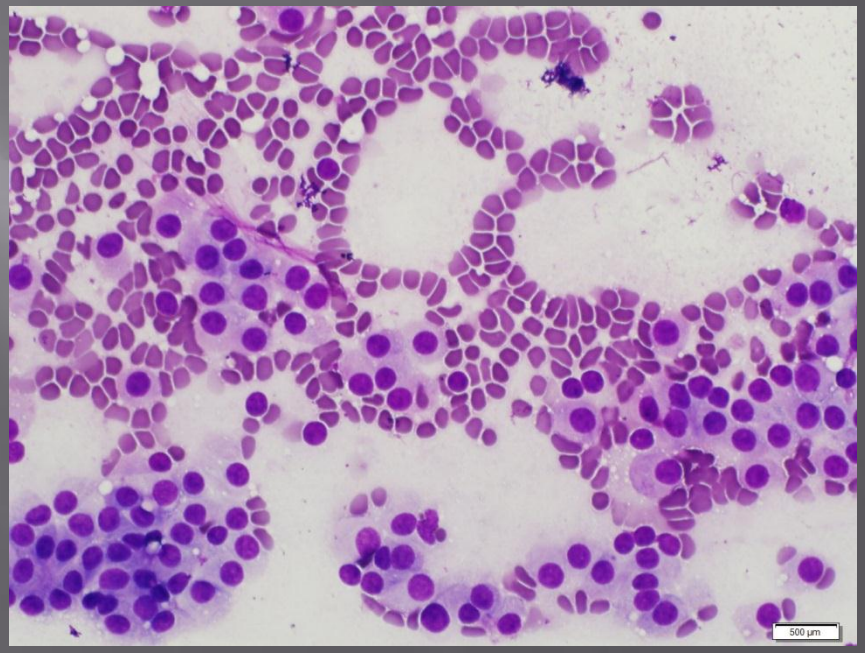
- 39 year-old female with large pancreatic tail mass identified incidentally on abdominal CT performed for trauma


ALOKA
No ID
11:43:49
52Hz
F13
7.5M 5.0 R06 G60 C5
2:EUS Linear
MI =0.58 DVA: 70%
TIS< 0.4

Pass #2: From Pancreatic Tail Mass

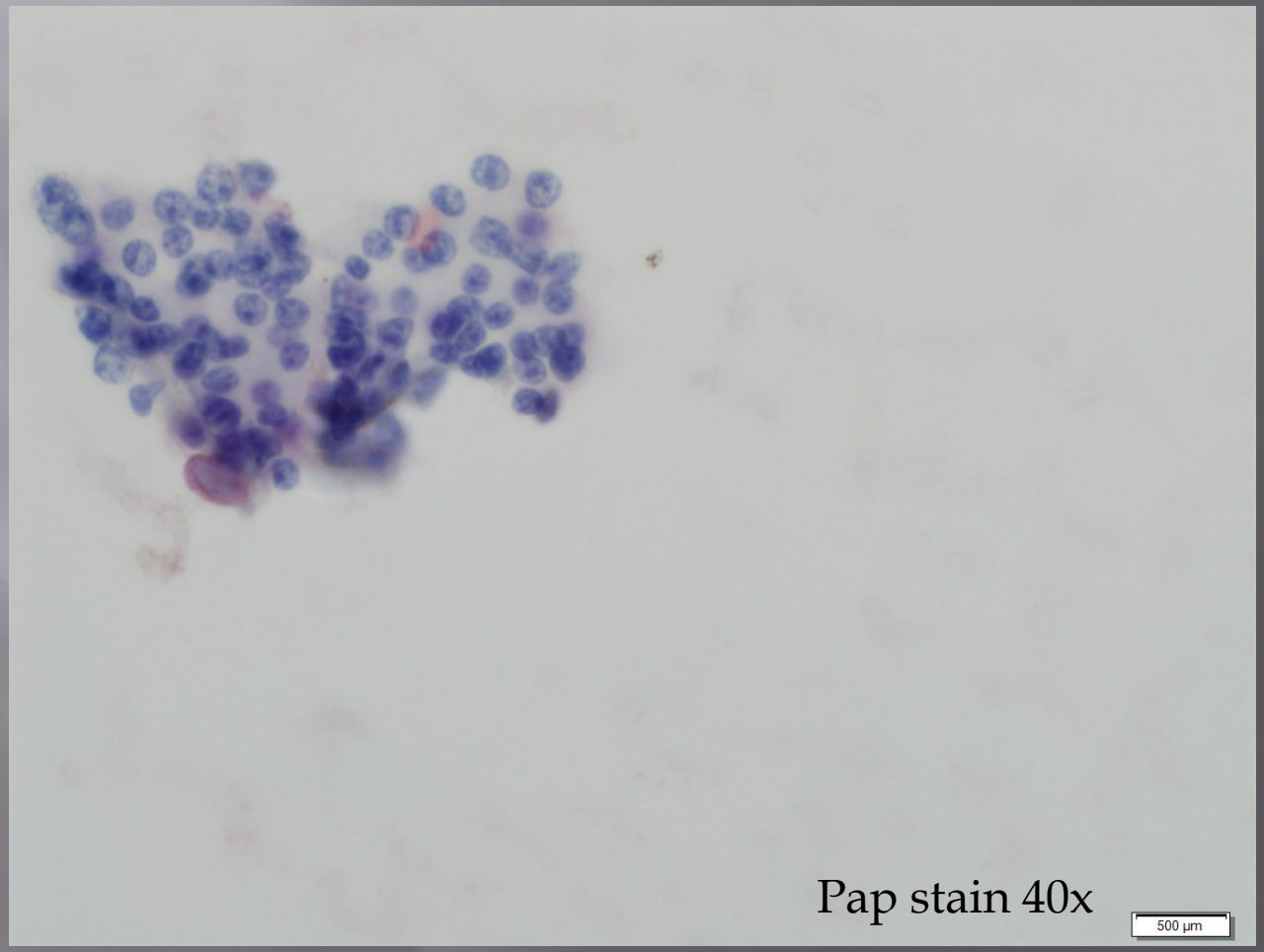


Diff Quik® 10x



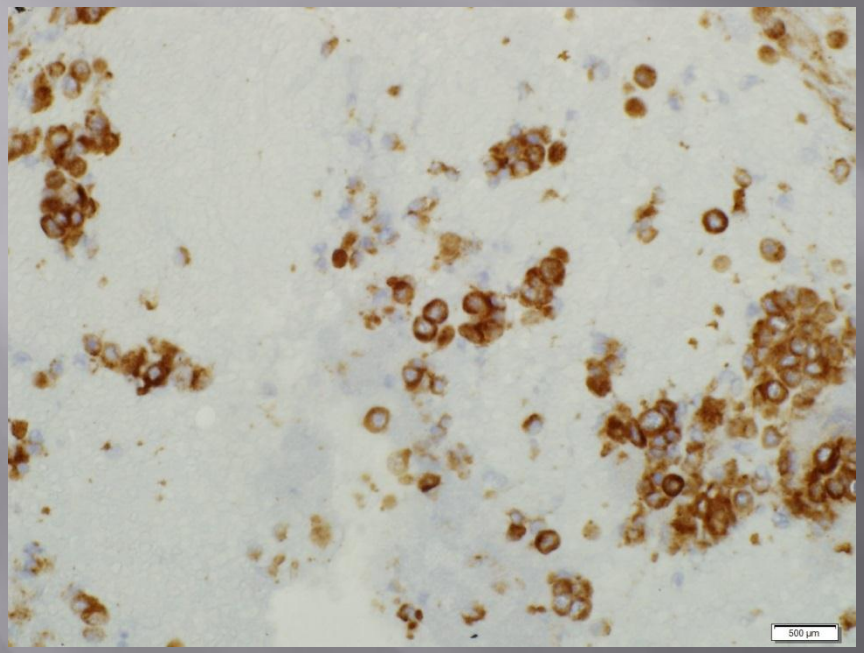
Diff Quik® 40x

Pass #2: Alcohol-Fixed Slide

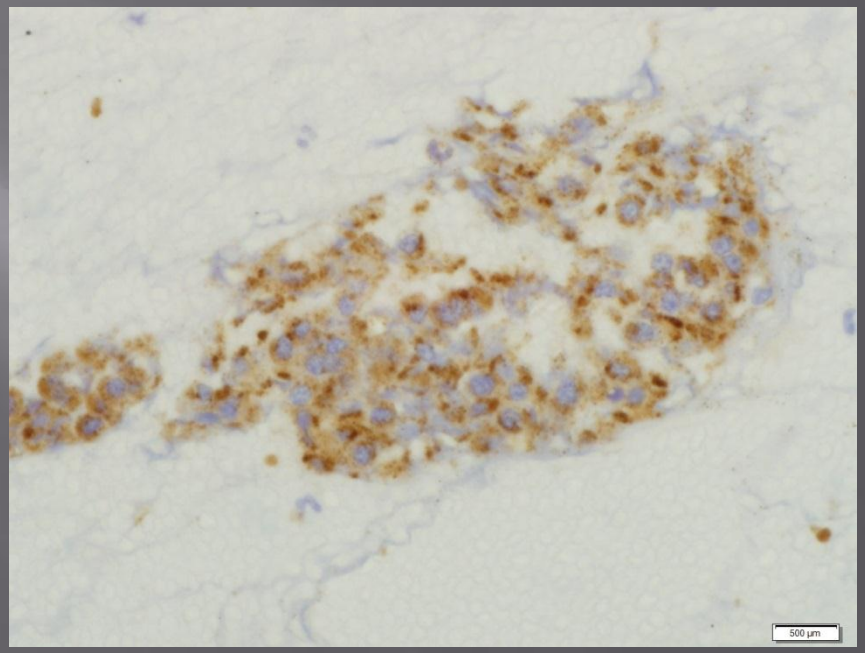


Pap stain 40x

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

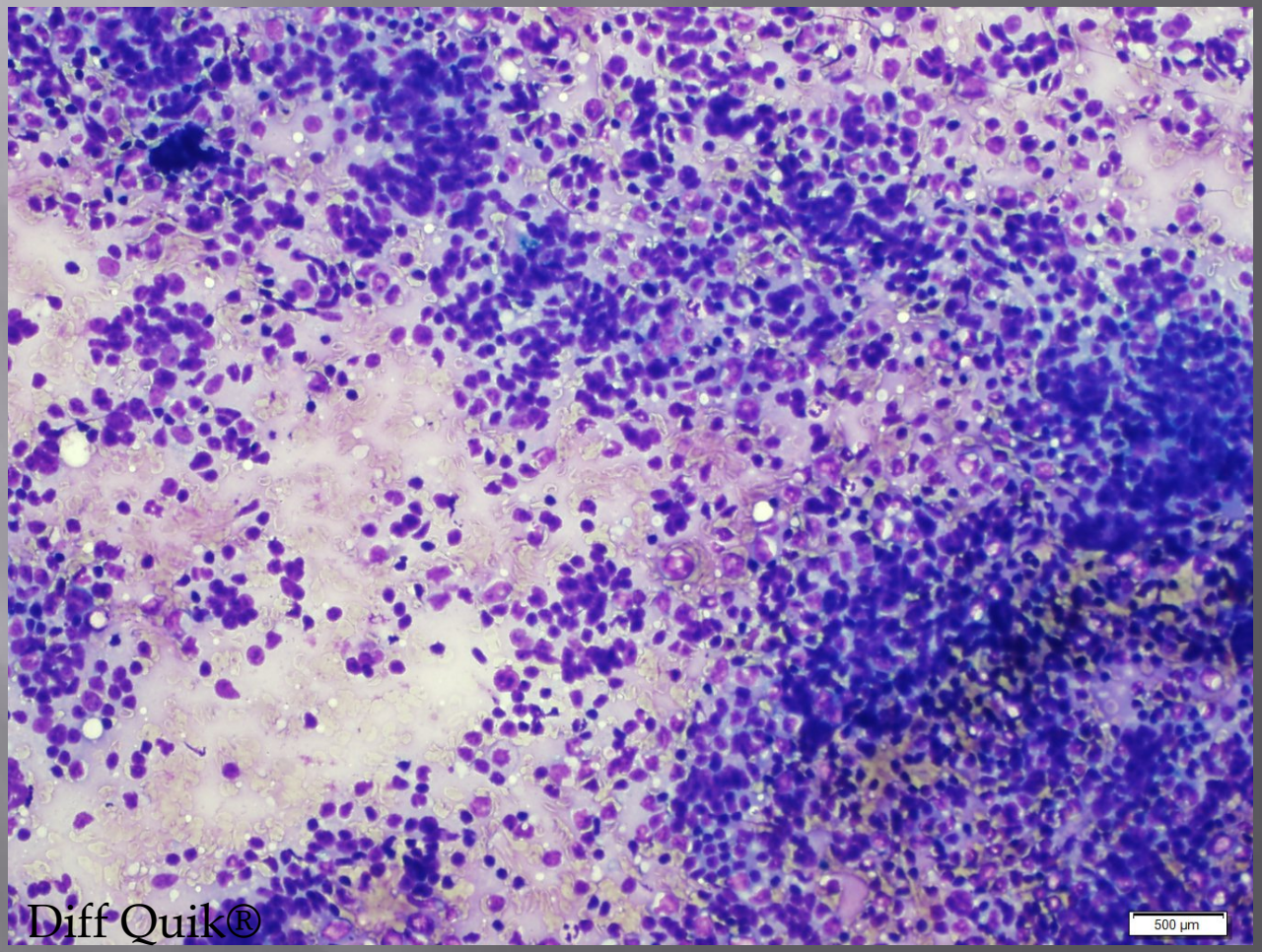
- Based on ROSE interpretation (an entity with a differential diagnosis), further passes were requested and triaged into a cell block
- Immunostains allowed for a definitive diagnostic interpretation

Case 4

- 75 year-old male with a pancreatic head mass and peripancreatic lymphadenopathy
- EUS FNA was performed

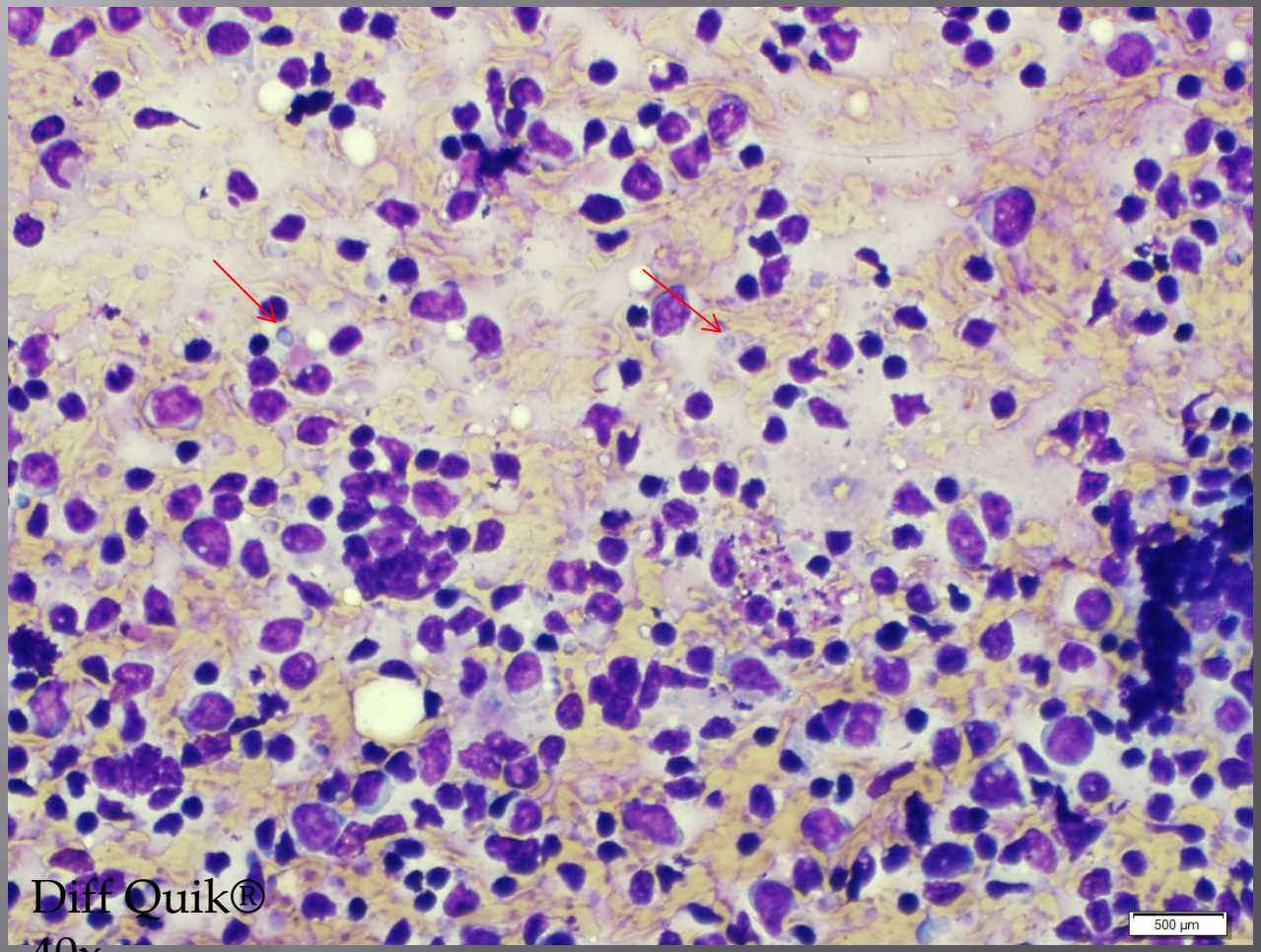

ALOKA
HUNTSMAN CANCER CENTER
12:15:15
52Hz
F13
7.5M 5.0 R04 G60 C5
2:EUS Linear
MI =0.53 DVA: 70%
TIS< 0.4


ALOKA
CENTER
12:17:35
52Hz
F13
7.5M 5.0 R03 G60 C5
2:EUS Linear
MI =0.53 DVA: 70%
TIS< 0.4



Diff Quik®

20x



Diff Quik®
40x

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

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.