CONVEGNO DI ENDOSCOPIA DIGESTIVA

"Endoscopic update live in Ferrara"



Aula magna / Sala endoscopica Ospedale Sant'Anna Cona ,Ferrara 11 apríle 2019



La diagnosi isto-citologica in ecoendoscopia: FNA, FNB, ROSE

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Trends in Pancreatic Pathology Practice Before and After Implementation of Endoscopic Ultrasound-Guided Fine-Needle Aspiration



Isam A. Eltoum, MD, MBA; Evans A. Alston, MD; Janie Roberson, CT(ASCP)



Arch Pathol Lab Med-Vol 136, April 2012











Quality Indicators for EUS

 Diagnostic rate and sensitivity for malignancy in patients undergoing EUS-FNA of pancreatic masses ≥ 85%



Wani S et al. Am J Gastroenetrol 2015 Wani S et al. Gastrointest Endosc 2015





Key performance	Tissue sampling during EUS
Description	Frequency of obtaining a diagnostic tissue sample in EUS-FNA or FNB of solid lesions
Domain	procedure
Rationale	Improve technical success of EUS FNA/FNB
Standard	Minimum standard: 85% Target standard: 90%
Consensus agreement for performance measure	90%
Evidence grading	Very low quality evidence







Endoscopic ultrasonography-guided fine needle aspiration: Relatively low sensitivity in the endosonographer population



Jean-Marc Dumonceau, Thibaud Koessler, Jeanin E van Hooft, Paul Fockens

World J Gastroenterol 2012





Optimasing EUS-guided tissue sampling: KEY POINTS



- ✓ Endopoints of EUS-Tissue Acquisition: adequate sample, accurate diagnosis
- ✓ Most important pitfall: low diagnostic yield

Endosonographer experience

Needles and techniques Pathologist experience









Guidelines for privileging, credentialing, and proctoring to perform GI endoscopy ASGE Standard Practice Committe. Gastrointest Endosc 2017

Procedure	Minimum number to be performed before assessment of competency	Quality of evidence
Moderate sedation	20	⊕000
Upper endoscopy	130	0000
Colonoscopy	275	$\oplus \oplus \oplus \bigcirc$
Flexible sigmoidoscopy	30	0000
ERCP	200	$\oplus \oplus \oplus \odot$
Capsule endoscopy	20	0000
DE, lower	20	⊕000
DE, upper	10	000€
EMR (upper GI)	20	@@ 00
Endoscopic submucosal dissection, stomach	30	000€
Ablation, Barrett's esophagus	30	0000
Enteral stent placement	10	000€
Enteral feeding tube placement	20	⊕000
EUS	225	$\oplus \oplus \oplus \odot$

Variation in Aptitude of Trainees in Endoscopic Ultrasonography, Based on Cumulative Sum Analysis







The EUS and ERCP Skills Assessment Tool (TEESAT)

ANCHORS

1(novice) = unable to complete requiring trainer to take over 2(intermediate) = achieves with multiple verbal instruction or hands on assistance 3(advanced) = achieves with minimal verbal instruction 4 (superior) = achieves independently N/T = not attempted for reasons other than trainee skill N/A = not applicable

EUS: Cognitive Aspects

Identify lesion of interest or appropriately ruled out	1	2	3	4	N/T	N/A
Appropriate TNM stage	1	2	3	4	N/T	N/A
Characterize subepitheial lesion (wall layers)	1	2	3	4	N/T	N/A
Appropriate differential diagnosis	1	2	3	4	N/T	N/A
Appropriate management plan (FNA, refer to surgery, surveillance or no surveillance)	1	2	3	4	N/T	N/A

Global Overall Assessment:

Mild

Immediate

Cardiopulmonary complications

Bleeding

Other:

Perforation

Moderate

Delayed

Severe

in possible, trainee to receive one minute per station	19. 	Global Ov	erall Asse	essment (subjective)			
Intubation	1 2 3 4 N/T I	N/A	1	2		3	4
AP window	1 2 3 4 N/T I	N/A	Novice: Learning basic technical &	Acquired technical &		Able to perform independently with	Competent to perform procedure
Body of pancreas	1 2 3 4 N/T I	N/A	cognitive aspects,	skills but r	2001 CONTRACTOR - 10	limited coaching	independently
Tail of pancreas	1 2 3 4 N/T I	N/A	requires significant assistance & coaching	limited ha assistance		and/or requires additional time to	
Head/neck of pancreas	1 2 3 4 N/T	N/A	-	significant of	coaching	complete	
Uncinate	1 2 3 4 N/T	N/A	-				
Ampulla	1 2 3 4 N/T	N/A	- 	mmediate P	ost-Proc	edure Complications	<u>11</u>
Gallbladder	1 2 3 4 N/T I	N/A					
CBD/CHD (Trace CBD from hilum to ampulla)	1 2 3 4 N/T	N/A	Procedure done in ambula	atory setting?	□Yes □N	No	
Portosplenic confluence	1 2 3 4 N/T	N/A	Patient admitted post-proc	edure?	Yes	No	
Celiac axis	1 2 3 4 N/T I	N/A			f yes , ⊡Pain requi	ring hospitalization	
					Pancreatit	is	

EUS: Technical Aspects:

Achieve FNA	1	2	3	4	N/T	N/A
Achieve celiac plexus block/ neurolysis	1	2	3	4	N/T	N/A

Wani S et al. Gastrointest Endosc 2018

ANCH

Radial Linear Both

<u>EUS</u>

Indication for EUS (mark all that apply):

Pancreatic Mass
Possible subepithelial lesion
Luminal GI cancer staging
Rule Out CBD Stones
Other:

Biliary dilation
 Pancreatic Cyst
 Mediastinal mass
 Rule Out Chronic Pancreatitis

Abdominal/Mediastinal lymphadenopathy
 Pancreatic Duct Dilation
 Abdominal pain

ANCHORS

1(novice) = unable to complete requiring trainer to take over 2(intermediate) = achieves with multiple verbal instruction or hands on assistance 3(advanced) = achieves with minimal verbal instruction 4 (superior) = achieves independently N/T = not attempted for reasons other than trainee skill N/A = not applicable

EUS: Technical Aspects: If possible, trainee to receive one minute per station prior to first verbal instruction.

Optimasing EUS-guided tissue sampling: KEY POINTS

Endosonographer experience

Needles and techniques Pathologist experience





Interobserver agreement among cytopathologists in the evaluation of pancreatic endoscopic ultrasoundguided fine needle aspiration cytology specimens^{*}

- ✓ IOA among cytopathologists in assessing EUS-FNA cytology specimens of solid pancreatic lesions
- ✓ Standardized scoring system
- ✓ Tertiary referral centre
- ✓ 4 blinded cytopathologists
 - Final diagnosis
 - Qualitative parameters (blood, inflammation/necrosis, artifacts)
 - Quantitative parameters (n° of diagnostic cells)



Mounzer R et al. Endoscopy International Open 2016





Interobserver agreement among cytopathologists in the evaluation of pancreatic endoscopic ultrasoundguided fine needle aspiration cytology specimens^{*}



99 pts included

IOA for final diagnosis was moderate k=0.45, 95% (CI) 0.4-0.49

IOA slight to fair (K=0.04 – 0.32) for individual cytologic parameter



Parameter	Kappa (95 %CI)	Standard Error	Strength of agreement
Final cytologic diagnosis	\bigcirc		
Overall diagnosis	0.45 (0.4 0-0.49)	0.02	Moderate
Overall diagnosis combining suspicious and malignant	0.54 (0.49-0.60)	0.03	Moderate
Quantity measures			
Number of nucleated cells/slide	0.31	0.03	Fair
Number of diagnostic cells/slide	0.32	0.03	Fair
Quality measures			
Amount of blood	0.14 (0.08-0.20)	0.03	Slight
Degree of inflammation/necrosis	0.21 (0.14-0.28)	0.04	Fair
Amount of gastrointestinal contaminants	0.14 (0.08-0.20)	0.03	Slight
Quality of slide preparation/staining	0.04 (-0.04 to 0.11)	0.04	Slight

Mounzer R et al. Endoscopy International Open 2016

Suboptimal Agreement Among Cytopathologists in Diagnosis of Malignancy Based on Endoscopic Ultrasound Needle Aspirates of Solid Pancreatic Lesions: A Validation Study

Marshall C et al. Clinical Gastroenterol Hepatol 2018

- ✓ Validation prospective study
- ✓ IOA among cytopathologists in assessing EUS-FNA cytology specimens of solid pancreatic lesions
- ✓ Standardized scoring system
- ✓ 5 Tertiary referral centre
- ✓ 11 blinded cytopathologists
 - Final diagnosis
 - Qualitative parameters (blood, inflammation/necrosis, artifacts)
 - Quantitative parameters (n° of diagnostic cells)

IOA for final diagnosis was moderate k=0.56; 95% Cl, 0-43-0.70

IOA was slight to moderate for individual quantitative (k=0.007; 95% CI, -0.03 to 0.04) and qualitative parameters (k=0.5; 95%CI, 0.47-0.53)

Needles and techniques









Mapping international practice patterns in EUS-guided tissue sampling: outcome of a global survey



United States , Europe, Asia

Online questionnaire sent to 400 endosonographers (29% USA, 46% Europe, 25% Asia)







Van Riet PA et al, Endoscopy Int Open 2016

Author and Year	Study design	No. of patients 22-g/25-g	Sensitivity (95% CI) 22-g	Sensitivity (95% Cl) 25-g
Imazu et al (2009)	Prospective	12/12	0.83 (0.36-1.00)	1.00 (0.54-1.00)
Lee et al (2009)	Prospective	10/10	1.00 (0.72-1.00)	1.00 (0.72-1.00)
Siddiqui et al (2009)	RCT	64/67	0.88 (0.77-0.94)	0.96 (0.87-0.99)
Yusuf et al (2009)	Retrospective	540/302	0.84 (0.80-0.88)	0.92 (0.87-0.95)
Siddiqui et al (2010)	Retrospective	26/17	0.85 (0.62-0.97)	0.91 (0.59-1.00)
Camellini et al (2011)	RCT	43/41	0.86 (0.70-0.95)	0.89 (0.75-0.97)
Uehara et al (2011)	Retrospective	54/66	0.88 (0.74-0.96)	1.00 (0.91-1.00)
Fabbri et al (2011)	Prospective	50/50	0.85 (0.71-0.94)	0.94 (0.82-0.99)







Choice of needle

RECOMMENDATION

For routine EUS-guided sampling of solid masses and lymph nodes (LNs) ESGE recommends 25G or 22G needles (high quality evidence, strong recommendation);







FNA VS FNB



- Potential advantages of FNB
- ✓ Larger specimens
- ✓ Improving diagnostic yield especially for non-pancreatic lesions
- ✓ Assessment of tissue architecture
- ✓ Perform ancillary studies (IHC)
- ✓ May obviate need for on-site cytopathologist
- ✓ Achieve the end-point with fewer passes







FNB NEEDLES



- Designs:
- ✓ Fork shaped Tip: cutting needle with a fork shape distal tip including 6 cutting edges and an opposing bevel (SharkCore – 19G, 22G, 25G, Medtronic)
- <u>Reverse bevel</u>: modified Menghini type needle with a beveled side slot near needle tip (ProCore 19G, 22G, 25G, Cook)
- ✓ <u>Anterograde core trap</u>: modified Menghini type needle with a beveled side slot near needle tip (ProCore 20G, Cook)
- ✓ <u>Franseen tip geometry</u>: endo cutting needle with a crown shaped distal tip (Acquire, 25G, 22G, Boston Scientific)



FNA vs. FNB



- Outcomes from 2 meta-analysis:
- ✓ No difference between FNA and FNB regarding rate of sample adequacy for pathologic examination
- ✓ No difference in rate of histologic core tissue procurement (overall, solid masses including pancreatic masses and LNs)
- ✓ FNB associated with a lower number of needle passes
 - No difference in adverse events or technical failure rates

PANCREAS Translational and Clinical Research Center

Bang JY et al, Endoscopy 2016 Oh HC et al, Korean J Intern Med 2016

FNA vs. FNB









A multicenter randomized trial comparing a 25-gauge EUS fine-needle aspiration device with a 20-gauge EUS fine-needle biopsy device (ME) Van Riet P et al, Gastrointest Endosc 2019



612 patients randomized



FNB had a higher diagnostic accuracy for malignancy 87% vs 78% (p=0.002)





FNA vs. FNB



RCT comparing EUS- TA

EUS-FNB (Franseen biopsy needle) vs EUS-FNA, 22G needle (N=46)

✓ Primary outcome: compare median areas of total tissue and tumor, presence of desmoplastic fibrosis and retention of tissue architecture

- ✓ Secondary outcome: compare rates of diagnostic cell block
- ✓ A specialized software for histological assessment



Bang JY et al. GUT 2017



FNA vs. FNB



		FNB	FNA	p-value
Total tissue area (mm²):	Mean (SD)	11.1 (26.6)	0.9 (1.9)	
	Median	6.1	0.28	< 0.0001
	IQR	2.2 - 9.9	0.045 - 0.93	
	Range	0.025 - 181.1	0 - 11.7	
Total tumor area (mm ²):	Mean (SD)	1.7 (2.3)	0.50 (1.86)	
	Median	0.68	0.099	< 0.0001
	IQR	0.23 - 2.8	0.0044 - 0.30	
	Range	0 - 12.4	0 - 11.6	
Desmoplastic fibrosis present: n (%)		33 <mark>(</mark> 84.6)	13 (33.3)	< 0.0001
Area of desmoplastic fibrosis (mm ²):	Mean (SD)	9.8 (28.4)	0.14 (0.45)	
	Median	3.9	0	< 0.0001
	IQR	0.5 - 8.2	0 - 0.11	
	Range	0 - 178.3	0 - 2.7	
Architecture retained: n (%)		43 (93.5)	9 (19.6)	< 0.0001
Suitable for immunohistochemistry stud	ies: n (%)*	41 (100)	28 (68.3)	< 0.0001





Choice of needle

RECOMMENDATION

For routine EUS-guided sampling of solid masses and lymph nodes (LNs) ESGE recommends 25G or 22G needles (high quality evidence, strong recommendation); fine needle aspiration (FNA) and fine needle biopsy (FNB) needles are equally recommended (high quality evience, strong recommendation).





SEUS GUIDED TISSUE ACQUISITION TECHNIQUE

- ✓ Use of suction (low pressure, high pressure, wet, dry, no suction)
- ✓ Use of a stylet
- ✓ Fanning technique
- ✓ Capillary technique





Role of suction



Author and year	Study design
Wallace 2001	RCT
Puri 2009	RCT
Lee 2013	RCT
Tarantino I 2014	RCT

The use of suction

RECOMMENDATION

ESGE recommends using 10-mL syringe suction for EUSguided sampling of solid masses and LNs with 25G or 22G FNA needles (high quality evidence, strong recommendation) and other types of needles (low quality evidence, weak recommendation).





Accepted Manuscript

Endoscopic Ultrasound-guided Specimen Collection and Evaluation Techniques Affect Diagnostic Accuracy

Ji Young Bang, MBBS MPH, Udayakumar Navaneethan, MD, Muhammad K. Hasan, MD, Robert Hawes, MD, Shyam Varadarajulu, MD

Original article

🏽 Thieme

Comparison of endoscopic ultrasound-guided fine-needle aspiration by capillary action, suction, and no suction methods: a randomized blinded study

Endoscopy International Open 2017; 05: E980–E984

©€≶∋

Authors

Rinkesh K. Bansal¹, Narendra S. Choudhary¹, Rajesh Puri¹, Saurabh K. Patle¹, Suraj Bhagat¹, Mukesh Nasa¹, Amit Bhasin¹, Haimanti Sarin², Mridula Guleria², Randhir Sud¹

ORIGINAL ARTICLE

Retrospective Study

Slow-pull and different conventional suction techniques in endoscopic ultrasound-guided fine-needle aspiration of pancreatic solid lesions using 22-gauge needles Stylet slow-pull versus standard suction for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic lesions: a multicenter randomized trial

Thieme

Gut and Liver, Published online February 8, 2018

Authors

Payal Saxena^{1,2}, Mohamad El Zein¹, Tyler Stevens², Ahmed Abdelgelil¹, Sepideh Besharati¹, Ahmed Messallam¹, Vivek Kumbhari¹, Alba Azola¹, Jennifer Brainard^{3,4}, Eun Ji Shin¹, Anne Marie Lennon¹, Marcia I. Canto¹, Vikesh K. Singh¹, Mouen A. Khashab¹

ORIGINALARTICLE

Slow-Pull Using a Fanning Technique Is More Useful Than the Standard Suction Technique in EUS-Guided Fine Needle Aspiration in Pancreatic Masses

Jae Min Lee, Hong Sik Lee, Jong Jin Hyun, Jung Min Lee, In Kyung Yoo, Seung Han Kim, Hyuk Soon Choi, Eun Sun Kim, Bora Keum, Yeon Seok Seo, Yoon Tae Jeen, Hoon Jai Chun, Soon Ho Um, and Chang Duck Kim



Author, year	Study design	N of pts	technique	aim	P value
Saxena P 2018	RCT, needle 22G	121	Suction vs slow- pull	Diagnostic accuracy 70% vs 80%	NS
Lee JM 2018	Prospective, needle 22G	48	Suction vs slow- pull blood	Diagnostic accuracy 71% vs 88% 44% vs 23%	p= 0.04 p= 0.04
Bansal RK 2017	7 RCT, needle 22G	300 (pancreas + lymphnodes)	Capillary vs suction vs no suction	Diagnostic accuracy 91% vs 91%	NS
Bang JY 2018	RCT, needle 22G	352	Suction vs NO suction	Number of passes Diagnostic accuracy from duodenum 89% vs 100% Blood	p= 0.03 p=0.04 p=0.01
ANCREAS anslational and Clinical esearch Center					Unise Unise Unise Unise



Funning technique



RECOMMENDATION

ESGE suggests fanning the needle throughout the lesion when sampling solid masses and LNs (moderate quality evidence, weak recommendation).









- ✓ Real time feedback regarding the content and adequacy
- ✓ Make a diagnosis with minimum number of passes
- Appropriate triage of limited specimens (IHC, special stains, molecular studies)





2 RCT (both pancreatic masses, fixed number 7 passes vs ROSE, diagnostic accuracy and sample adequacy NS)

4 meta analyses (2 pros, 2 Cons)

On-site cytologic evaluation

RECOMMENDATION

ESGE equally recommends EUS-guided sampling with or without on-site cytologic evaluation (moderate quality evidence, strong recommendation).







FNA with ROSE vs. FNB

- ✓ Meta-analysis: 15 studies 1024 pts
- ✓ Overall, no difference in diagnostic adequacy
- ✓ For solid pancreatic lesions, in the absence of ROSE, FNB was associated with better diagnostic adequacy p=0.02



- No significant difference in the diagnostic yield between FNA and FNB, when FNA is with ROSE

- In the absence of ROSE, FNB has a relatively better diagnostic adequacy in solid pancreatic lesions

Ali khan et al. Endoscopy 2017







Number of needle passes in the absence of on-site evaluation

RECOMMENDATION

When on-site cytologic evaluation is unavailable, ESGE suggests performance of three to four needle passes with an FNA needle or two to three passes with an FNB needle (low quality evidence, weak recommendation).








Review your sensitivity for malignancy diagnosis

If less than 85%: modify your practice

Close collaboration with the pathologist is crucial!

choose needle and technique considering the experience of your pathologist (cytologist or histology? Smear or microcore?)

After that: ask for help







Repeat Endoscopic Ultrasound-Guided Fine Needle Aspiration for Solid Pancreatic Lesions at a Tertiary Referral Center will Alter the Initial Inconclusive Result Bhutani MS et al.



Table III. Diagnostic accuracy of repeated EUS-FNA (n=80)	
Sensitivity (%)	95.7 (69/72)
Specificity (%)	100 (8/8)
PPV (%)	100 (69/69)
NPV (%)	72.7 (8/11)
Accuracy (%)	96.3 (77/80)

EUS-FNA: endoscopic ultrasound-guided fine needle aspiration, PPV: positive predictive value, NPV: negative predictive value



J Gastrointestin Liver Dis, June 2013 Vol. 22 No 2: 183-187







Thank you !

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EUS-TA and PERSONALIZED MEDICINE



- ✓ Next Generation Sequencing
- ✓ RNA and microRNA analyses
- ✓ Creation of human pancreatic organoids from malignant pancreatic tissue









www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 34 Research Paper Targeted next generation sequencing of endoscopic ultrasound acquired cytology from ampullary and pancreatic adenocarcinoma has the potential to aid patient stratification for optimal therapy selection Ferga C. Gleeson¹, Sarah E. Kerr², Benjamin R. Kipp², Jesse S. Voss², Douglas M. Minot², Zheng Jin Tu³, Michael R. Henry², Rondell P. Graham², George Vasmatzis⁴, John C. Cheville⁴, Konstantinos N. Lazaridis^{1,4}, Michael J. Levy¹

29 pts, ampullary cancer or PDAC Cytology smears (FNA) – NGS with a panel of 160 cancer genes

83 pathogenic alteration in 21 genes – Complete concordance with pathology specimen



Transcriptomic Analysis Predicts Survival and Sensitivity to Anticancer Drugs of Patients with a Pancreatic Adenocarcinoma



hypothesis: the variable sensitivity observed in patients with PDAC is mainly due to the intrinsic molecular characteristics of the cancer cells.

17 samples of human PDAC were collected by EUS-FNA Each sample otained from EUS-FNA was mixed with 100 mL of Matrigel (BD Biosciences, Franklin Lakes, NJ) and was injected in the upper right flank of a nude mouse

When the tumors reached 1 cm³ mice were sacrified and tumors removed

transcriptomic analysis was perfomed: significant heterogeinity in the RNA expression profile of tumors

Duconseil P, Am J Pathol 2015

Primary culture of cells allowed to analyze their relative sensitivity to drugs, using Chemogram: INDIVIDUAL PROFILE OF DRUG SENSITIVITY



- \checkmark The response was patient dipendent
- ✓ Correlation between transcriptome and drug response

Duconseil P, Am J Pathol 2015



Correlation between transcriptome and drug response

4 most resistant and 4 most sensitive cultures → heat map analysis of the transcriptome: sets of genes were identified as specifically over or under expressed in resistant and sensitive cells

Duconseil P, Am J Pathol 2015







- Transcriptomic analysis of PDAC seems to be a promising strategy
- to reveal the molecular phenotype of the disease
- Transcriptomic analysis could predict the sensitivity to anticancer drugs
- and clinical outcome of pts with PC
- EUS-FNA biopsy
- To get diagnosis
- To characterize the molecular phenotype







Organoids simulate the full spectrum of a patients tumor, they can be Used for testing personalized treatment strategies

Aim: to generate human PDAC organoids by mean of EUS-FNB in pts with solid pancreatic masses

29 pts underwent EUS FNA with 22G needle Successful organoids isolation in 85% in 2 weeks

3 pts with organoids created from FNB samples had successful In vitro drug sensitivity testing

Conclusion: pancreatic cancer organoids can be successfully and rapid created based on sample obtained by EUS-FNA



IN THE NEAR FUTURE











Thank you !

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