

Il Percorso del Paziente con Neoplasia Neuroendocrina nella Provincia di Ferrara

Gli approcci endoscopici

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Introduzione

- ▣ L'incidenza dei tumori neuroendocrini è aumentata nelle ultime decadi
- ▣ L'aumento è in parte dovuto alla maggior frequenza di esami endoscopici
- ▣ L'endoscopia digestiva è fondamentale nella gestione di tali patologie perché permette una diagnosi e un trattamento

Localizzazione gastroenterica dei NET

Table 1

Main indications and utility of EUS and EUS-FNA. This table summarizes the main indications of EUS for the different types of neuroendocrine neoplasms and the future fields of interest of this technique.

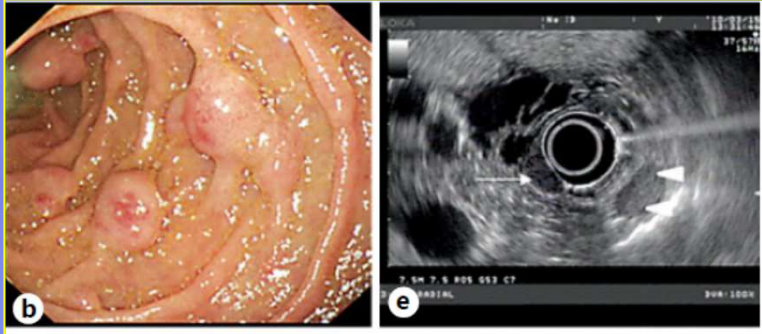
Type of NENs ^a	Indication to EUS ^b	EUS ^b not indicated	Utility of EUS-FNA ^c	Future fields of interest
Gastric NENs	Type 1 and 2 gastric NENs: to evaluate the depth of invasion and indication to endoscopic treatment that is reserved to lesions not infiltrating beyond the muscularis propria. Type 3 gastric NENs: to stage the disease by assessing the presence of regional lymph-node involvement.	EUS is not recommended for very small gastric NENs with diameter <1 cm.	To evaluate the grade of differentiation and thus indication to endoscopic vs. surgical treatment.	
Duodenal NENs	EUS could help to localize small pancreatic gastrinoma. To stage NENs with diameter >2 cm. To exclude loco-regional lymph node metastases and thus indication for endoscopic mucosal resection.	The routine use of EUS for duodenal gastrinoma in MEN-1 ^d remains controversial, since the sensitivity is <50%.	To evaluate the grade of differentiation and thus indication to endoscopic removal, especially for high risk surgical candidates.	Contrast-enhanced EUS could help in localizing small tumors.
Colorectal NENs	To determine the indication of endoscopic removal versus transanal excision or radical surgery, in particular for rectal NENs with diameter >2 cm, by assessing depth of invasion and the presence of lymph node metastases. To follow up patients after resection of rectal NENs.	EUS is not routinely recommended for rectal NENs <5 mm.	To evaluate the grade of differentiation and thus indication to endoscopic removal.	
Pancreatic NENs	To localize small pancreatic NENs, mainly insulinomas or gastrinoma, before surgery, especially if other non-invasive imaging studies are negative. To differentiate pancreatic NENs from adenocarcinoma by using contrast agents, elastography and FNA. To evaluate solid components of cystic lesions. To stage the NEN by evaluating the presence of vascular invasion or loco-regional lymph node. To evaluate the distance between pancreatic lesion and the main pancreatic duct in a pre-operative setting, thus predicting the risk of developing pancreatic fistula. To follow-up patients with small NEN managed with a "wait and watch" approach.	EUS is not recommended as the only method of staging, due to the limited ability to stage distant localizations.	To evaluate the grading of NENs. To differentiate lesions or neoplasms with a EUS patterns mimicking pancreatic NENs. To distinguish pancreatic NENs from pancreatic adenocarcinoma. To sample solid components of cystic lesions.	New EUS needle acquisition may obtain tissue samples for complete histological examination. EUS- FNA tattooing and EUS-guided fiducial implantation of pancreatic lesions may help surgeons to find the neoplasm and avoid demolitive surgery. EUS-guided therapies (i.e. alcohol ablation, radiofrequency ablation), especially in patients unsuitable for surgery, are under investigation.

NET gastrici



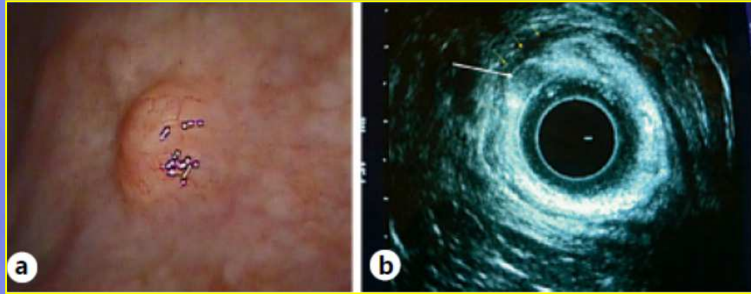
- L'endoscopia permette di identificare queste lesioni, di caratterizzarle ed asportarle
- Le lesioni <1 cm hanno un decorso benigno → Follow-up
- Lesioni 1-2 cm sono passibili di resezione endoscopica se limitate a mucosa o sottomucosa
- Tecnica di EMR o ESD
- Recidiva tra 20 e 60% dei casi

NET duodenali



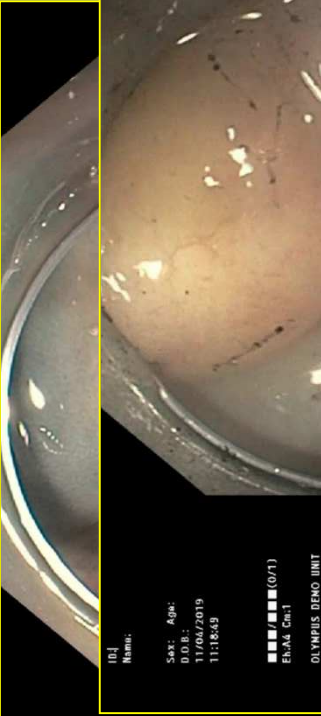
- Gastrinomi sono i più frequenti ma generalmente rari
- L'endoscopia è utile per la diagnosi e la stadiazione
- Le tecniche di resezione endoscopica sono gravate da maggior tasso di complicanze dovute alla sede
- La diagnosi viene agevolata dall'utilizzo combinato di altre indagini quali TC o PET

NET rettali



- Incidenza in notevole aumento e 50% sono scoperti incidentalmente (campagne di screening)
- Localizzati nel retto medio/basso e aspetto di lesione sottomucosa
- Il rischio metastatico è correlato alle dimensioni
- E' possibile la resezione endoscopica (EMR e ESD) ed è possibile la biopsia di linfonodi perirettali dubbi

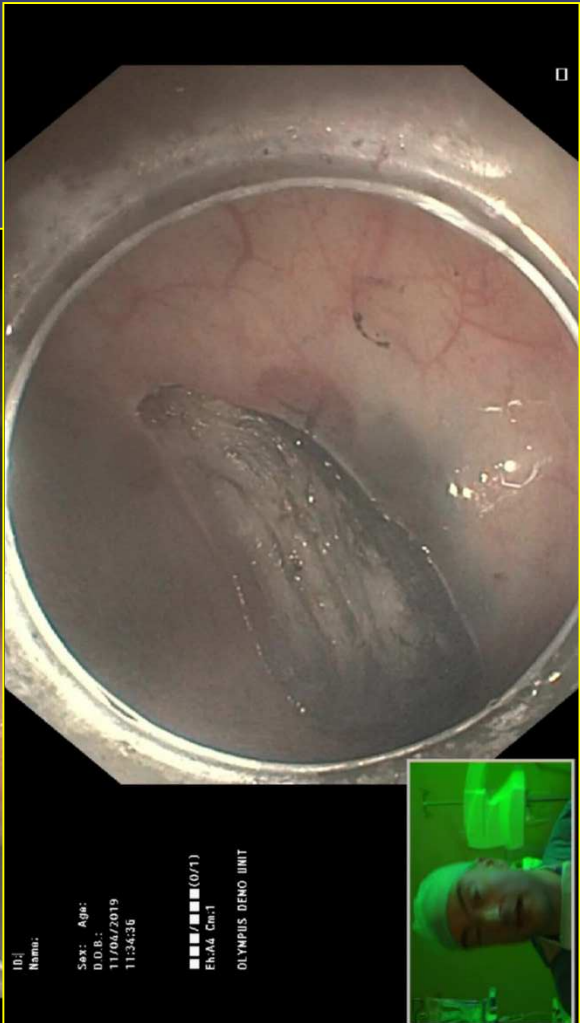
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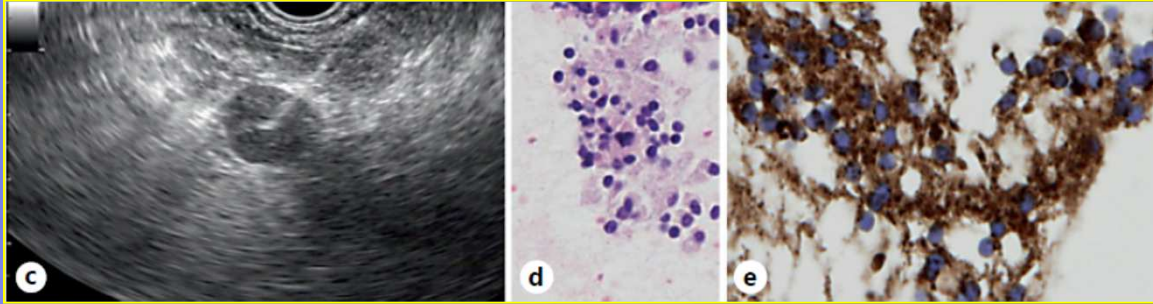
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NET pancreatici



- Incidenza in notevole aumento (1-4/100.000 abitanti)
- Possono essere funzionanti o non funzionanti
- Diagnosi spesso difficile che si avvale di test di laboratorio e di imaging
- L'EUS è strumento fondamentale nella gestione di queste patologie

ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors

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B. Kos-Kudla^g D. Kwekkeboom^h G. Rindiⁱ G. Klöppel^j N. Reed^k R. Kianmanesh^l
R.T. Jensen^m all other Vienna Consensus Conference participants

- Eus metodica di scelta per la diagnosi e la caratterizzazione dei NET dopo la negatività delle altre indagini radiologiche
- Octreoscan e Gallio PET/TC
- RMN e TC



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META-ANALYSIS

Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: A systematic review and meta analysis

Srinivas R Puli, Nikhil Kalva, Matthew L Bechtold, Smitha R Pamulaparthi, Micheal D Cashman, Norman C Estes, Richard H Pearl, Fritz-Henry Volmar, Sonu Dillon, Michael F Shekleton, David Forcione

- Eus per diagnosi di NET: sensibilità 87%, specificità 98%, PPV 11.1, NPV 0.17
- TC sensibilità 73% (range 39-94%)
- RMN sensibilità 73% (range 50-94%)

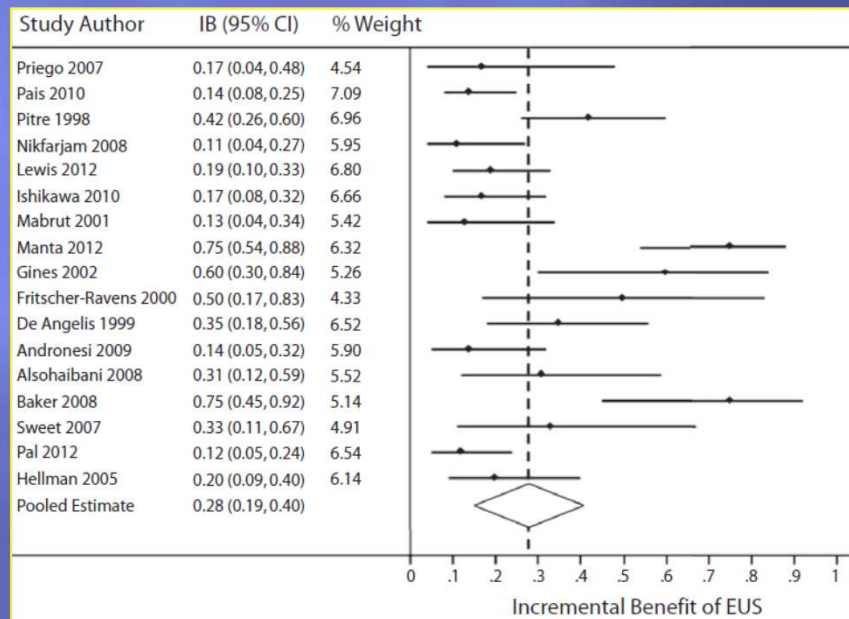
SYSTEMATIC REVIEWS AND META-ANALYSES

Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis

Paul D. James, MSc, MD,^{1,2*} Apostolos V. Tsolakis, PhD, MD,^{2,3,*} Mei Zhang, MSc,³ Paul J. Belletrutti, MD,² Rachid Mohamed, MD,² Derek J. Roberts, MD,⁴ Steven J. Heitman, MSc, MD²

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GIE 2015;81:841-46



- Eus permette di identificare NET pancreatici nel 97%
- Incremental benefit dell'EUS: 28%
- Maggior incremento per le lesioni piccole (<2 cm)

Contrast Harmonic Echo-Endoscopic Ultrasound Improves Accuracy in Diagnosis of Solid Pancreatic Masses

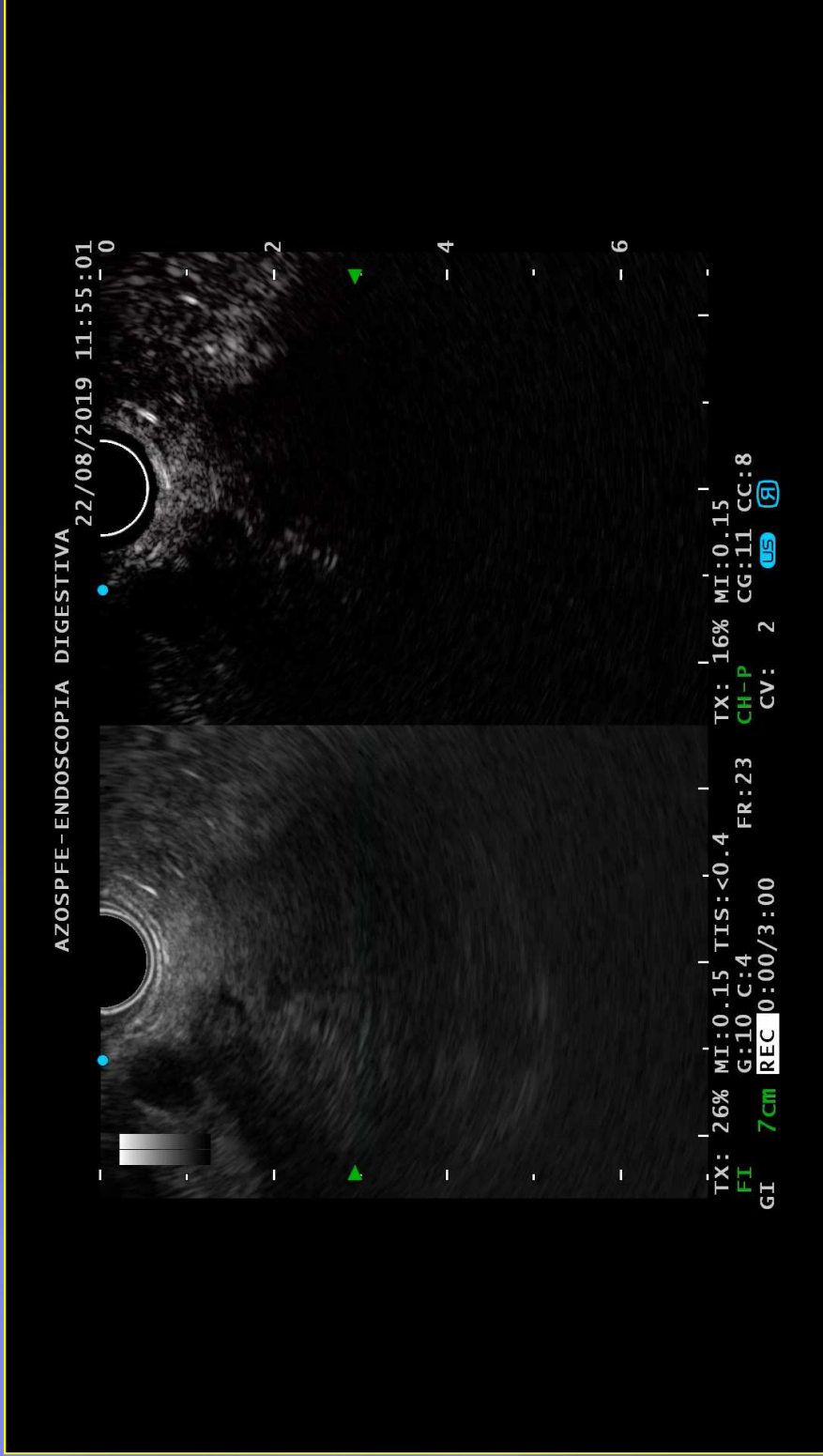
PIETRO FUSAROLI,* ALESSIA SPADA,† MARIA GRAZIA MANCINO,* and GIANCARLO CALETTI*

Table 3. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Standard EUS and CHE-EUS

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Hypoechoic lesion on standard EUS as a predictor of adenocarcinoma	86% (73%–94%)	18% (8%–34%)	58% (47%–69%)	59% (24%–76%)	57% (50%–64%)
Hypoechoic lesion on CHE-EUS as a predictor of adenocarcinoma	96% (85%–99%)	64% (47%–78%)	78% (65%–87%)	93% (74%–99%)	82% (74%–85%)
Hyperenhancing lesion on CHE-EUS as an exclusion sign of adenocarcinoma	39% (30%–41%)	98% (92%–100%)	94% (74%–99%)	68% (63%–69%)	72% (65%–74%)
Hyperenhancing lesion on CHE-EUS as a predictor of NET	69% (46%–86%)	90% (87%–94%)	56% (33%–76%)	95% (87%–98%)	88% (81%–93%)

NOTE. Data in parentheses are 95% confidence intervals.

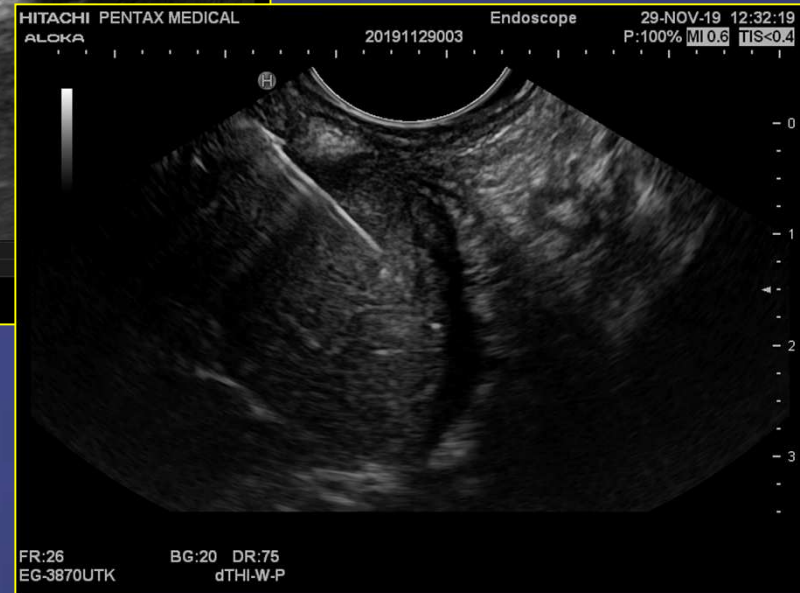
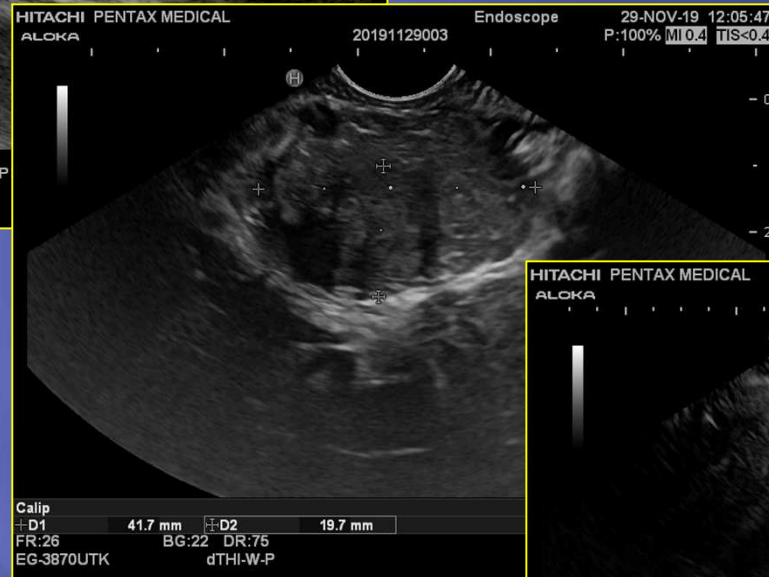
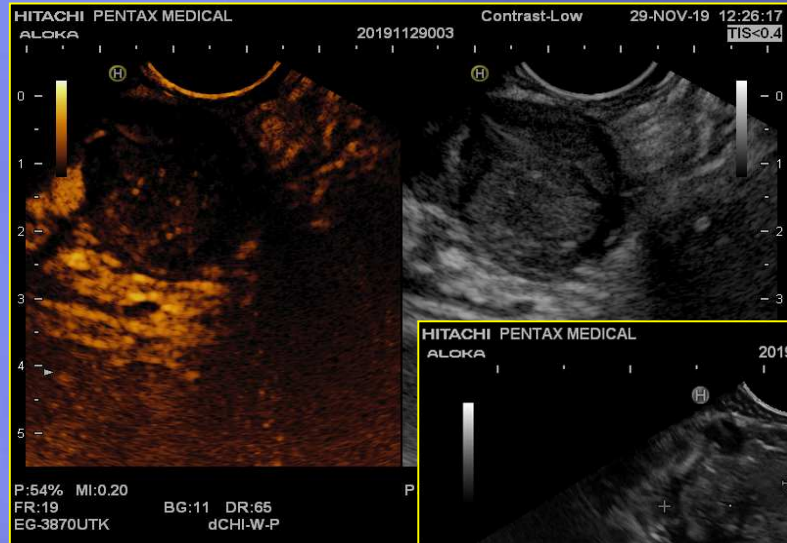
Eus con mdc



Utilità dell'eco-endoscopia per la diagnosi di NET

- L'ecus permette di eseguire FNA/FNB e quindi di caratterizzare istologicamente la lesione
- Il grading istologico (G1-G3, Ki-67 index) hanno valore prognostico ed influenzano la strategia terapeutica

EUS con FNB



Accuratezza dell'EUS/FNA

Table 2. Sensitivity of EUS-FNAB in the detection of pancreatic neuroendocrine tumors

First author and year	Sensitivity, %
Voss [35], 2000	75
Ardengh [36], 2004	83
Figueiredo [37], 2009	90
Atiq [38], 2012	91

Concordance rate between endoscopic ultrasound fine needle aspiration and surgical samples in diagnosing the grading of neuroendocrine neoplasms. This table reports the main studies about the concordance rate between endoscopic ultrasound-guided fine-needle aspiration and surgical samples for the grading of neuroendocrine neoplasms.

Study (period of study)	Concordance rate (%)	Needles used	FNA ^a technique used	Mean number of passes	Mean (range) lesion size, mm	ROSE ^b
Piani et al. [37] (2003–2007)	16/18 (89%)	22 G or 25 G	n.r. ^c	n.r. ^c	30 (10–100)	No
Larghi et al. [32] (2009–2011)	10/12 (83%)	19 G	Application of negative pressure	2.7	16.9 (7–100)	No
Hasegawa et al. [33] (1998–2011)	21/27 (78%)	22 G or 25 G	Fanning method	2.3	28.1 (5–130)	Yes
Unno et al. [34] (2008–2012)	17/19 (90%)	22 G	n.r. ^c	4.1	22.3 (7–100)	No
Sugimoto et al. [38] (2001–2013)	7/8 (88%)	19 G, 22 G or 25 G	Fanning method	3.5	26 (4–40)	Yes
Fujimori et al. [40] (2007–2014)	9/13 (69%)	22 G or 25 G	Fanning method	3.2	21 (8–67)	Yes
Weynand et al. [41] (1996–2010)	21/33 (64%)	22 G	Fanning method	2	33 (2–110)	No
Boutsen et al. [42] (1996–2013)	39/57 (72%)	n.r. ^c	n.r. ^c	n.r. ^c	29 (20–110)	n.r. ^c

1. O'Tool D et al. *Front Horm Res.* 2015, 44, 88–103
2. Zilli A et al *Dig Liv Dis* 2018;50:6-14

Eus FNA/FNB

Table 3

Factors that may reduce the sampling adequacy.

Factors that may reduce the sampling adequacy

Factors related to the characteristics of the lesion

Sub-optimal ultrasound visibility of the lesion

Lesions located in the pancreatic body or tail rather than in the head

Small size of the lesion

Lesions characterized by rich stromal fibrosis

Presence of cystic component in the lesion

Presence of necrotic component in the lesion

Factors related to the EUS-FNA² technique

Use of normal negative-pressure instead of high negative-pressure suction

Use of smaller needles

Factors related to operators

Initial experience of endosonographers and cytopathologists

Absence of rapid on-site evaluation

- Zilli A et al *Dig Liv Dis* 2018;50:6-14

Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer

Paolo Giorgio Arcidiacono, MD,*¹ Silvia Carrara, MD,*¹ Michele Reni, MD,² Maria Chiara Petrone, MD,¹ Stefano Cappio, MD,³ Gianpaolo Balzano, MD,⁴ Cinzia Boemo, MD,¹ Stefano Cereda, MD,² Roberto Nicoletti, MD,³ Markus Dominik Enderle, MD,⁵ Alexander Neugebauer, PhD,⁵ Daniel von Renteln, MD,⁶ Axel Eickhoff, MD,⁶ Pier Alberto Testoni, MD¹

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GIE 2012;76:1142-51

- 22 pz con adenocarcinoma pancreatico localmente avanzato che avevano mostrato progressione di malattia dopo ciclo di chemio e radioterapia
- Nel 76% dei casi (16 pz) è stato possibile eseguire la tecnica
- Complicanze immediate in 3/16 e tardive in 4/16
- In 6/16 la TC ha dimostrato una riduzione della massa neoplastica
- Sopravvivenza media 6 mesi

Conclusioni

- ▣ L'endoscopia gioca un ruolo determinante nella gestione delle neoplasie neuroendocrine del tratto digestivo
- ▣ Alle capacità diagnostiche sono associate capacità terapeutiche (EMR e ESD)
- ▣ Per le lesioni pancreatiche l'eco-endoscopia è considerata la metodica diagnostica più sensibile
- ▣ La possibilità di acquisizione di tessuto è fondamentale per la conferma diagnostica e la strategia terapeutica