

2021 NET Lecture

# 神經內分泌腫瘤的內視鏡 診斷與治療

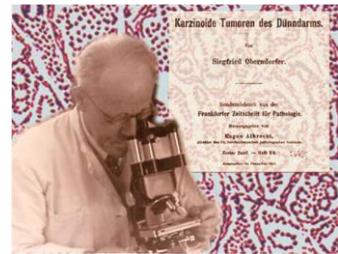
鄭祖耀醫師

臺大醫院癌醫中心分院

2021/11/13

NTU CANCER CENTER  
台大癌醫中心

## 類癌



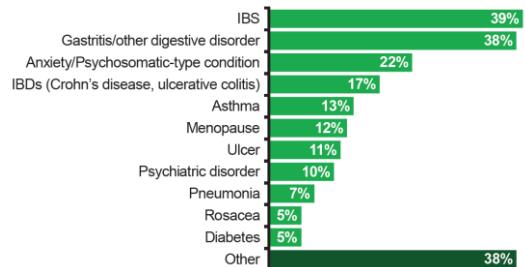
- In 1907, Siegfried Oberndorfer described 6 autopsy cases with multiple small ileal tumors that grew extremely slowly and did not appear to metastasize. He ascribed a new name, *karzinoid* (carcinoma-like), to describe the nature of these tumors.

-Modlin IM, et al. Arch Surg. 2007;142:187-97

## 有症狀/功能性神經內分泌腫瘤

- Well-differentiated NETs arising in the GI system have traditionally been referred to as **carcinoid tumors** or **pancreatic NETs**
  - Carcinoid tumors may arise from **GI tracts** and **lungs**
  - Pancreatic NETs arise from the **pancreas** and rarely within the **duodenal wall**
- Symptomatic/ functional GEP-NETs , associated with a hormonal syndrome
  - GI NETs (carcinoid tumors)**
    - carcinoid syndrome rarely developed without **liver metastases** (due to liver clearance effects)
  - Pancreatic NETs**
    - About 25-50% of are functional
- Symptoms of NETs are **nonspecific** and may resemble other conditions

## 神經內分泌腫瘤正式診斷前的臆斷



-Pavel M, et al. Neuroendocrinology 2015;102:160

## 神經內分泌腫瘤有症狀到診斷的時間差

	Don't know/ NA	<6 months	6 months – 2 years	2 – 5 years	>5 years	Mean (months)
Total sample (N = 1926)	9%	20%	18%	19%	29%	52.0
Diagnosed <5 years ago (n = 1154)	9%	23%	18%	18%	26%	48.2
Diagnosed >5 years ago (n = 774)	7%	16%	18%	21%	33%	57.5
GI NET	8%	17%	18%	21%	31%	54.4
pNET	9%	27%	16%	18%	24%	47.5
Lung NET	8%	21%	15%	21%	29%	56.9

-Pavel M, et al. Neuroendocrinology 2015;102:160

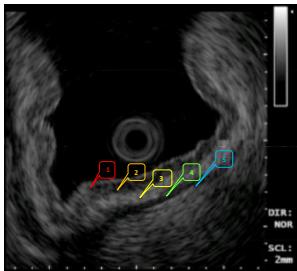
## 腸胃道神經內分泌腫瘤的評估

- Colonoscopy as appropriate for colonic NETs
- Small bowel imaging with CT enterography or capsule endoscopy as appropriate for jejunal and ileal NETs
- EUS** and/or EGD as appropriate for **duodenal** and **gastric** NETs
- Proctoscopic examination for rectal NETs



National Comprehensive Cancer Network®

## 內視鏡超音波(EUS)評估腸胃道壁的分層



- Layer 1 : interface of luminal fluid and mucosa
- Layer 2 : deep mucosa
- Layer 3 : submucosa + interface
- Layer 4 : the muscularis propria - interface
- Layer 5 : adventitia or serosa + adjacent fatty or fibrous tissue

-Hwang JH, et al. Gastroenterology. 2006;130:2217-28

## 胃黏膜下腫瘤的EUS特徵

Subepithelial lesion	EUS layer*	Echogenicity
Benign		
Leiomyoma	2, 3 or 4	Hypoechoic
Neural origin tumors		
Schwanoma	3 or 4	Hypoechoic
Neurofibroma		
Lipoma	3	Intensely hypoechoic
Duplication cyst	Any or extramural	Anechoic
Pancreatic rest	2 or 3	Hypoechoic
Inflammatory fibroid polyp	3 or 4	Hyperechoic
Granular cell tumor	2 or 3	Hypoechoic
Varices	2 or 3	Anechoic
Malignant or with malignant potential	4 (rarely 2 or 3)	Hypoechoic
GIST		
Metastasis	Any	hypoechoic
Carcinoma		
Gliomas tumor	3 or 4	Hypoechoic

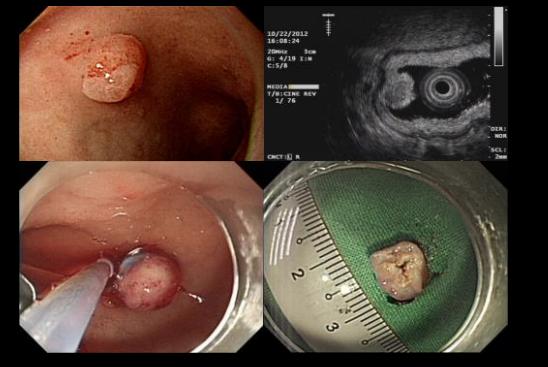
胃神經內分泌腫瘤 2 or 3 低回音性

-Hwang JH, et al. Gastroenterology. 2006;130:2217-28

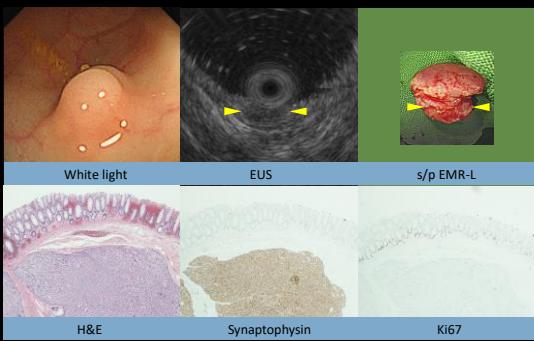
## 胃神經內分泌腫瘤的EUS影像



## 十二指腸神經內分泌腫瘤的EUS影像



## 直腸神經內分泌腫瘤的EUS影像



## 胰神經內分泌腫瘤的診斷

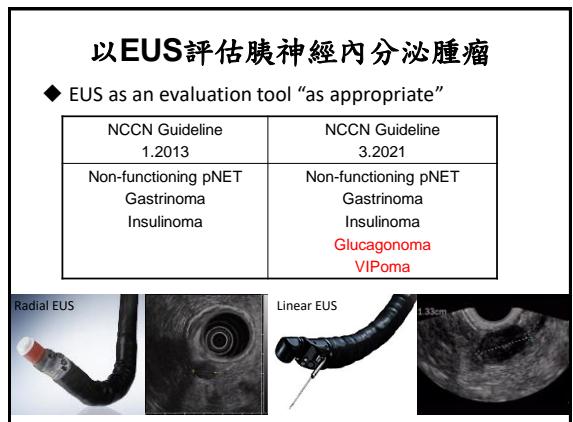
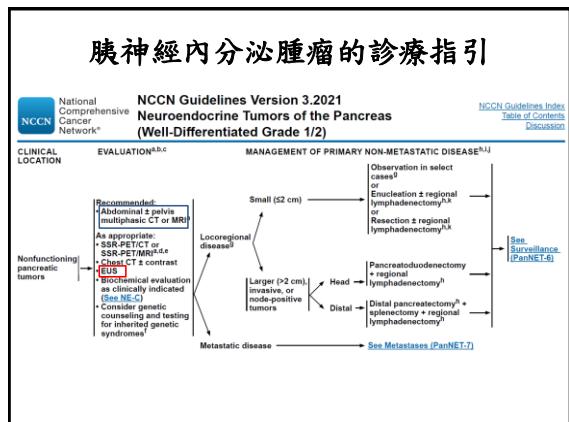
- Diagnosing a functioning pancreatic NET is based on the presence or absence of **clinical syndromes** resulting from **inappropriate hormone secretion**
- A pancreatic NET should not be considered as functioning if the characteristic clinical syndrome is absent
- Confirmation of a functioning pancreatic NET requires the **corresponding hormone test**

**胰神經內分泌腫瘤的診斷**

- Cross-sectional imaging via **contrast-enhanced CT** and/or **MRI** is necessary to detect and establish the extent of the primary tumor and/or metastatic disease.
- SRS/ octreoscan is suggested at the time of diagnostic workup and/or preoperatively if available

**胰神經內分泌腫瘤的診斷**

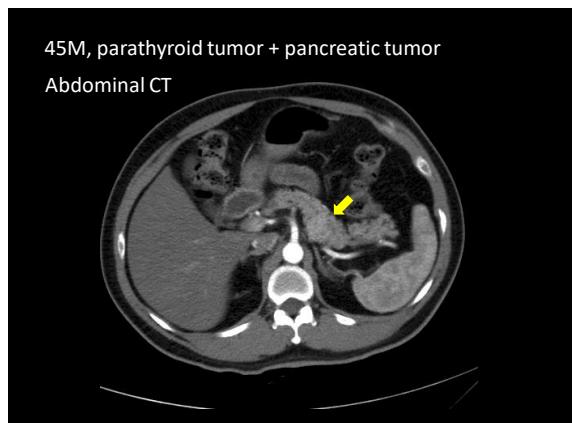
- EUS is effective in detecting sub-centimeter pancreatic NETs and should be performed for diagnostic purposes even if no primary tumor identified on cross- sectional imaging.
- EUS with FNA** is a preferred route for a diagnostic biopsy of a pancreatic NET.
- Peri-pancreatic lymphadenopathy** may be sampled at the same time on pancreatic EUS-FNA for preoperative evaluation.

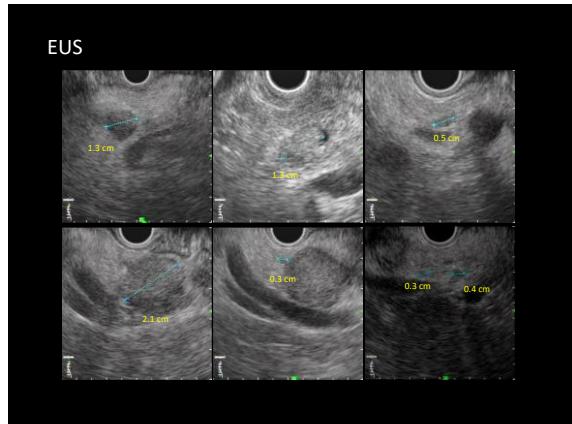
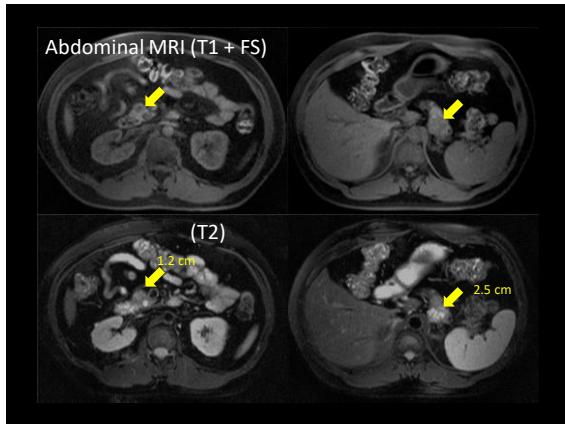


**胰神經內分泌腫瘤的診斷工具**

Author	Publication year	n	Insulinoma (%)	NF-NET (%)	Mean Size (mm)	Size < 20 mm (%)	CT (%)	EUS (%)	MRI (%)	SRS (%)
Rosch, et al	1992	37	80	0	14	95	(all CT-negative)	82	-	-
Palazzo, et al	1993	13	100	0	-	-	14	79	-	-
Zimmer, et al	1996	20	50	0	18	82	25	86	18	50
Ueno, et al	1996	7	71	29	-	86	57	100	-	-
de Angelis, et al	1999	23	52	9	7-35	83	30	87	25	15
Anderson, et al	2000	54	61	0	15	71	-	93	-	-
Gines, et al	2002	10	40	0	12	90	30	100	-	66
Gouya, et al	2003	30	100	0	20	-	72	94	-	-
*IDPCT: Dual Phase helical CT with thin section (IDPCT: 94%)										
Ardenh, et al	2004	23	52	30	20	83	61	100	24	-
Alshabani, et al	2008	14	-	-	4-25	93	77	100	67	50
Khashab, et al	2011	60	32	58	-	68	63	92	-	-

-Khashab MA et al. Gastrointest Endosc 2011;73:691-6

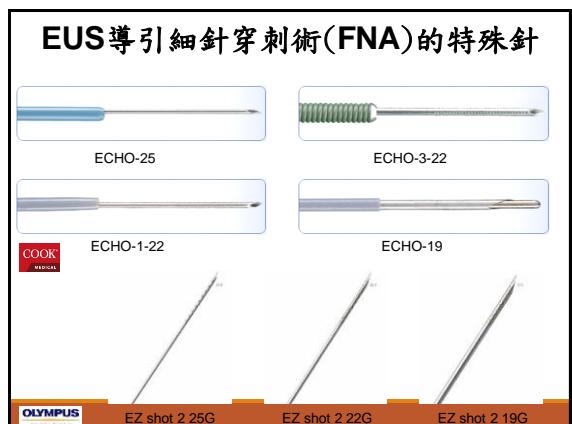
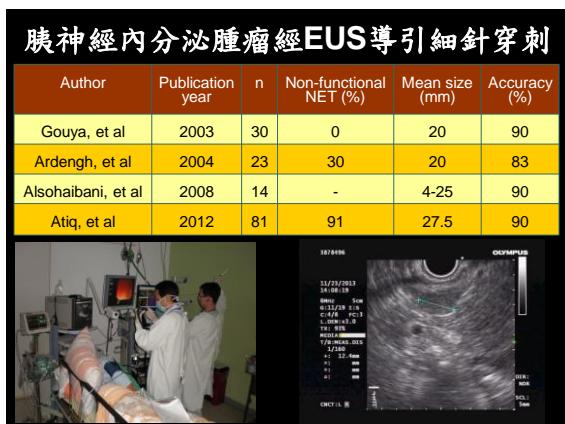


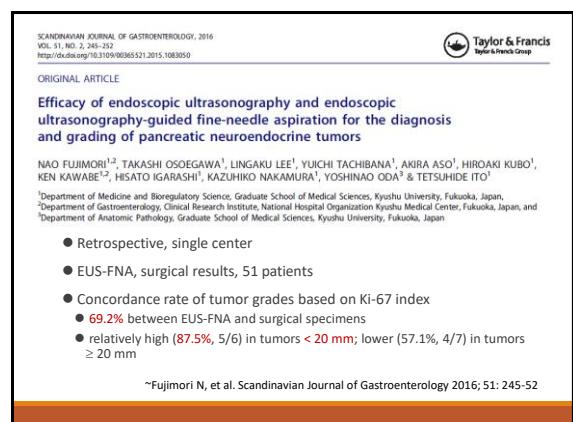
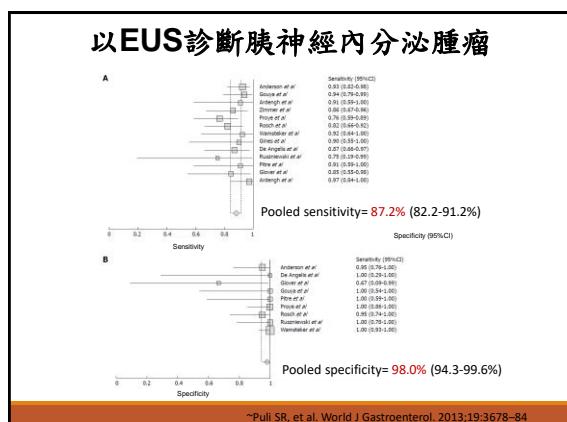
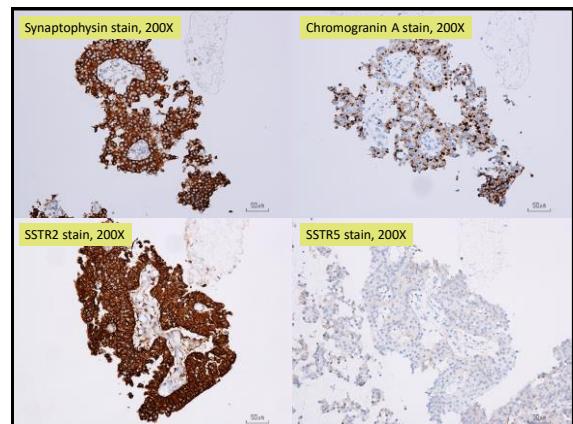
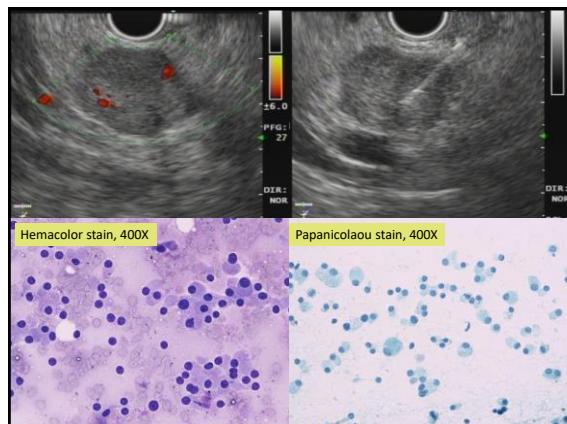
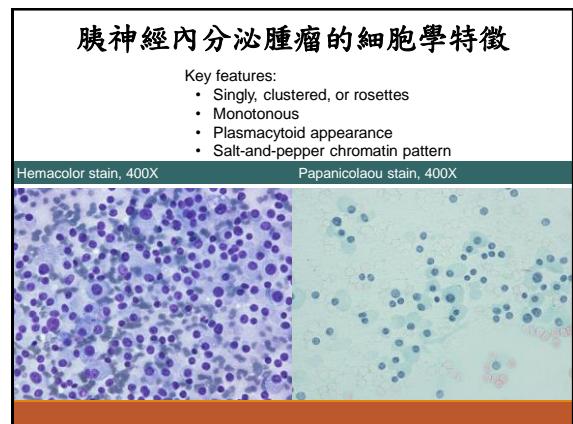


### 胰神經內分泌腫瘤的EUS特徵

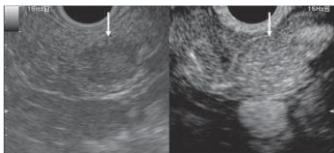
	Adeno-carcinoma	Neuroendo-crine tumors	Pseudotumoral pancreatitis	Lymphoma
EUS findings	<ul style="list-style-type: none"> <li>Hypoechoic</li> <li>Poorly vascularized</li> <li>Lobulated margin</li> <li>Dilated MPD</li> <li>Vascular infiltration</li> </ul>	<ul style="list-style-type: none"> <li>Hypoechoic</li> <li>Highly vascularized</li> <li>Lobulated margin</li> <li>Sharply delineated round margin</li> </ul>	<ul style="list-style-type: none"> <li>Hypoechoic</li> <li>Hypo-vascularized</li> <li>Lobulated margin</li> <li>Califications</li> <li>Necrotic areas</li> </ul>	<ul style="list-style-type: none"> <li>Hypoechoic</li> <li>Differently vascularized</li> <li>Sharply delineated round margin</li> </ul>
Cytology features	<ul style="list-style-type: none"> <li>Disorderly groups of ductal cells</li> <li>Pleiomorphism</li> <li>Increased N/C</li> <li>Nuclear atypia (enlargement, irregular nuclear membranes)</li> </ul>	<ul style="list-style-type: none"> <li>Singly clustered, or rosettes</li> <li>Monotonous</li> <li>Plasmacytoid appearance</li> <li>Salt-and-pepper chromatin pattern</li> </ul>	<ul style="list-style-type: none"> <li>Ductal hypertrophy</li> <li>Inflammatory background (lymphocytes, plasma cells)</li> </ul>	<ul style="list-style-type: none"> <li>Singly</li> <li>Monotonous</li> <li>Increased N/C</li> <li>Nuclear indentation</li> <li>Lymphoglandular bodies in the background</li> </ul>

-鄭祖耀，台灣消化系醫學會第39屆教育研討會講義，2015





## 對比劑增強EUS (CEH-EUS)



- NETs are hypervascular with **strong arterial hyperenhancement** under CEH-EUS
- CEH-EUS-depicted hypervascular enhancement diagnosed neuroendocrine tumors with a sensitivity of **78.9%** (95% CI, 61.4%-89.7%) and specificity of **98.7%** (95% CI, 96.7%-98.8%),
- CEH-EUS + EUS-FNA, sensitivity of EUS-FNA increased from 92.2% to **100%**

~ Kitano M, et al. Am J Gastroenterol. 2012;107:303-10

## 胰神經內分泌腫瘤與 多發性內分泌腫瘤第一型(MEN-1)

- A clinical diagnosis for MEN1 includes two or more MEN1-associated tumors
  - Parathyroid** hyperplasia
  - Pancreatic NETs**
  - Pituitary** tumors
- Patients with MEN1 are more likely to have **multiple** pancreatic NETs than those with sporadic tumors
  - 44% of the sporadic pancreatic NETs had somatic inactivating mutations in *MEN1* gene
  - 25~30% MEN1 patients have ZES (Zollinger-Ellison syndrome)

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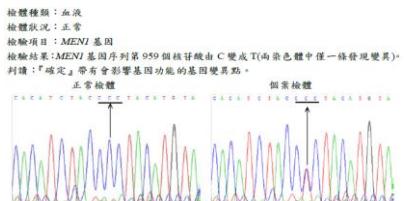


## 胰神經內分泌腫瘤與 多發性內分泌腫瘤第一型(MEN-1)

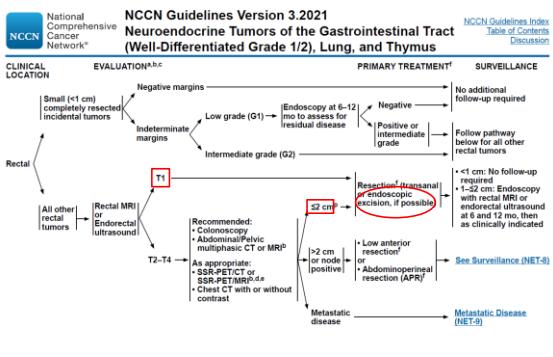
- Genetic testing for MEN-1 is recommended in **all young patients with gastrinoma or insulinoma**, any patient with a **family or personal history of other endocrinopathies** (esp. hyperparathyroidism) or **multiple pancreatic NETs** on EUS studies
- Plasma calcium, iPTH, prolactin, IGF-1 and pituitary gland MRI should be examined in patients with MEN-1.

## MEN1 Gene Analysis

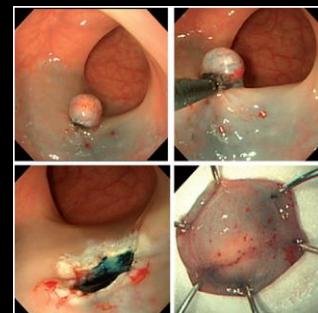
臺大醫院基因醫學部報告



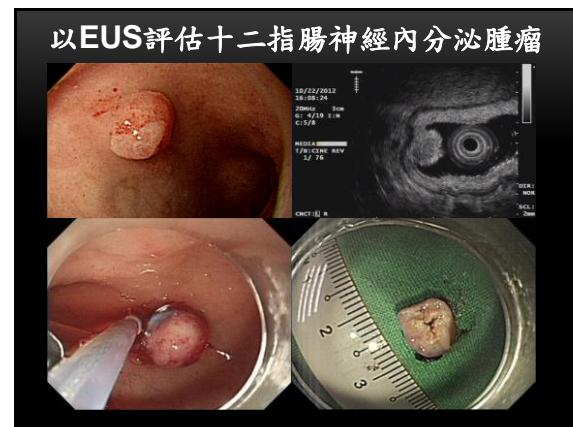
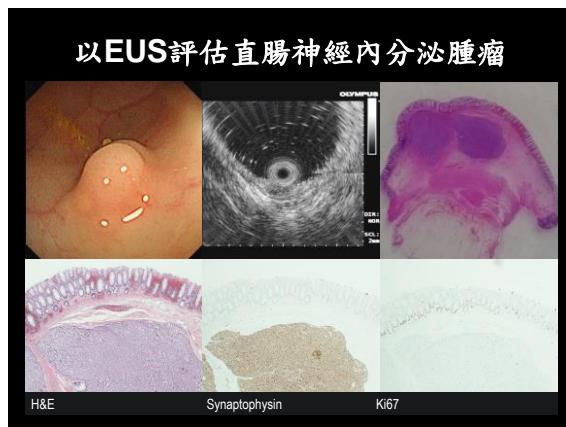
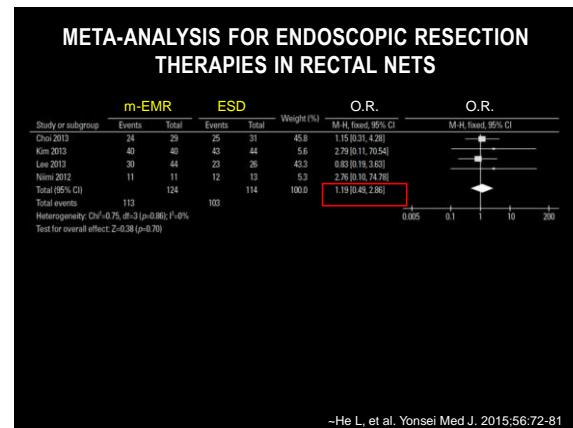
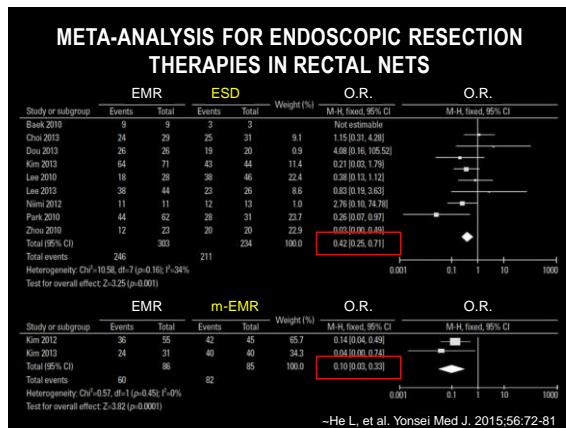
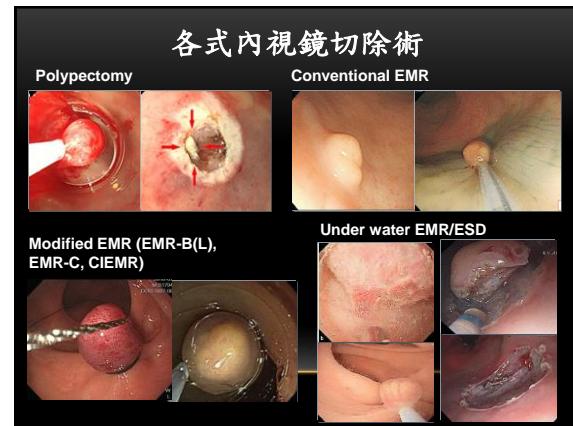
## 直腸神經內分泌腫瘤的診療指引

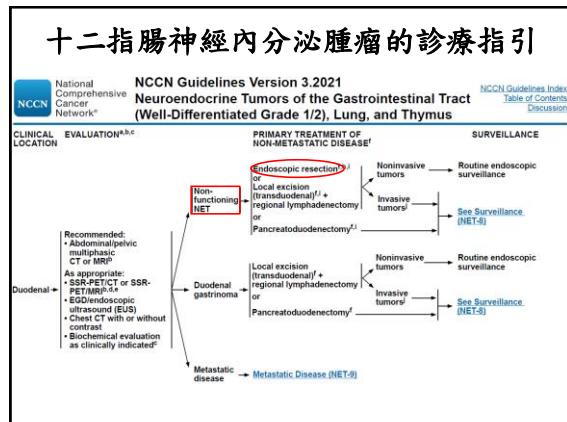


## 綁紮式內視鏡黏膜切除術 (EMR-L)



-Kaneko H, et al. Scand J Gastroenterol. 2016;51:1489-1494





## 以EMR治療小型十二指腸神經內分泌腫瘤

\* ASSOCIATED WITH SIGNIFICANT MORBIDITY, DIFFICULT IN RO RESECTION AND RISK OF LAPS

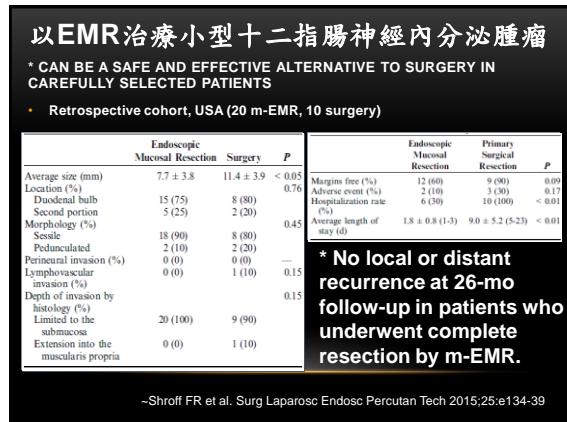
### 29 patients with 32 duodenal NETs

Tumor size, mean(range), mm	8.9 (3-17)
Tumor location, n(%)	
1 <sup>st</sup> portion duodenum	18 (56)
2 <sup>nd</sup> portion duodenum	7 (22)
Major papilla	7 (22)
Resection, n(%) (19 EMR, 13 EMR-C)	
En-bloc	30 (94)
Piecemeal	2 (6)
WHO 2010, n(%)	
G1	27 (84)
G2	5 (16)
Microscopic margin, n(%)	
R0	16 (50)
R1	14 (44)
Rx	2 (6)

**Overall survival:**  
100% at 1 year  
80% at 5 years  
55% at 10 years

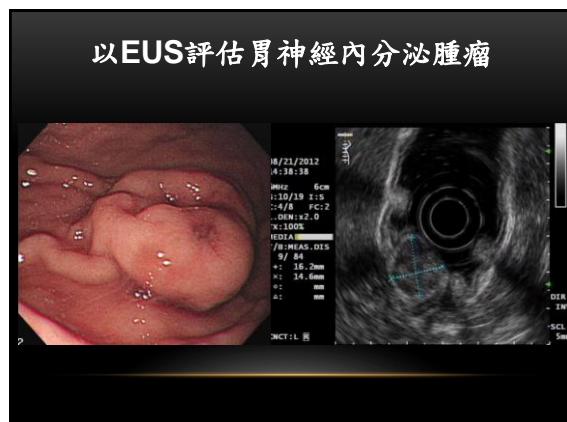
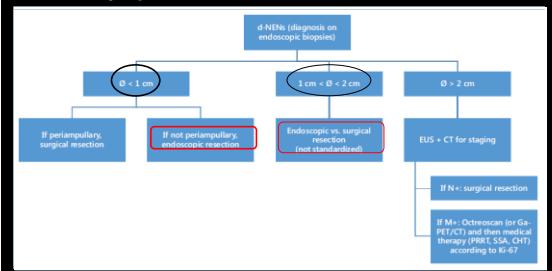
**Disease-free survival:**  
100% at 1 year  
88% at 5 and 10 years

-Gincul R et al. Endoscopy 2016; 48: 979-986



## 十二指腸神經內分泌腫瘤的診療指引 (ENET 2016)

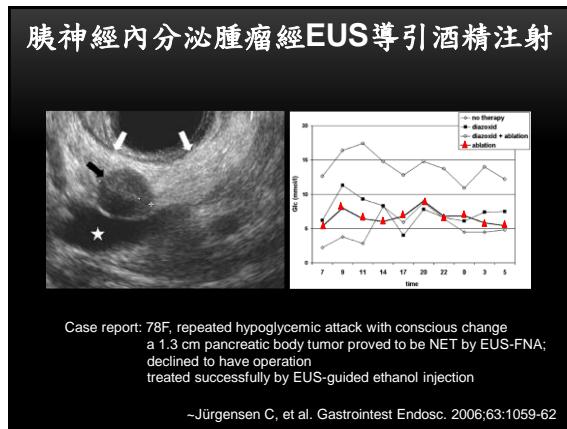
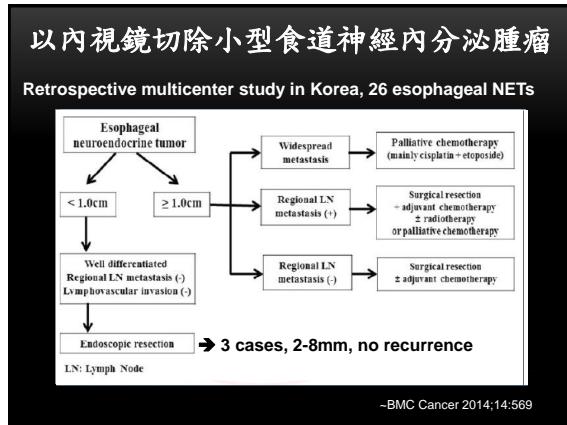
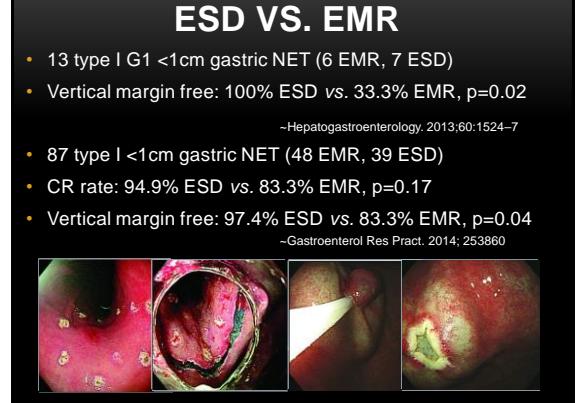
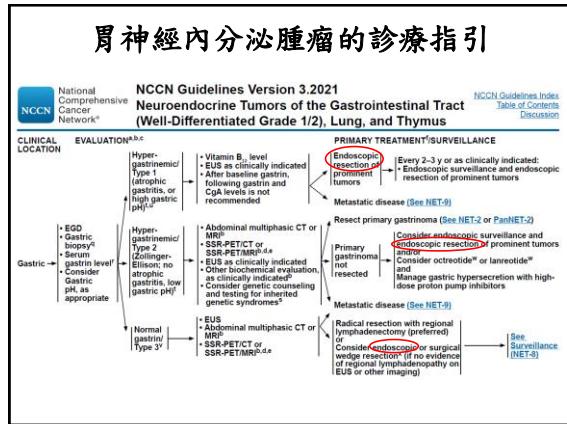
Endoscopic management for lesions ≤ 10 mm in size, **not peripancreatic**, confined to the **M/SM** layer, without lymph node or distant metastasis



**胃神經內分泌腫瘤的特徵**

Characteristic	Type I GNETs	Type II GNETs	Type III GNETs
<b>Proportion</b>	70~80%	5~10%	10~15%
<b>Associated dx</b>	CAG	MEN I <sup>(13%)</sup> <b>ZES</b>	None
<b>Gender</b>	F>M	F=M	F<M
<b>Tumor No.</b>	>1	>1	1
<b>Tumor size</b>	<10~20mm	<10~20mm	>20mm
<b>Location</b>	Fundus/corpus	Fundus/corpus	Any region
<b>Histology</b>	WD (G1~2)	WD (G1~2)	WD to PD (G1~3)
<b>Invasion depth</b>	M/SM	M/SM	Any depth
<b>Serum gastrin</b>	High	High	Normal
<b>Gastric pH</b>	High	Low	Normal
<b>Metastasis</b>	2~5%	10~30%	>50%
<b>Tumor related death</b>	0%	<10%	25~30%

-Dig Surg 2012; 29:331. -World J Gastrointest Endosc 2015 April 16; 7(4): 346-353.  
-Neuroendocrinology 2016;103:119-124



## 胰神經內分泌腫瘤經EUS導引酒精注射

Ref.	n	Max. diameter (mm)	Ethanol (%)	Volume (mL)	Complications
Jurgensen et al.	1	13	95	8.0	Localized pain in the upper abdomen; a mild increase of serum lipase
Muscatiello et al.	1	11 & 7 (*MEN-1 with VIPoma)	40	2.0	A small pancreatic necrotic lesion treated with laparoscopic necrosectomy
Deprez et al.	1		98	3.5	A mild/asymptomatic elevation of pancreatic enzymes; hematoma and ulceration of the duodenal wall
Vleughaar et al.	1	9.5	96	0.3	None
Levy et al.	5	18	95	0.12, 0.38, 0.12	None
		20	98	0.12, 0.25	None
		21	98	0.95, 0.28	None
		8	98	3.0, 1.5	None
		16	99	0.7, 1.0	None

~ Zhang WY et al. World J Gastroenterol 2013; 19: 3397-3403

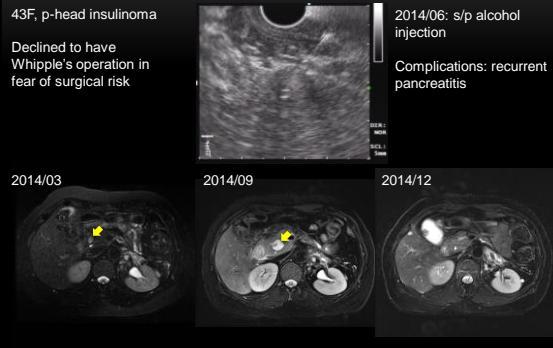
## 胰島素瘤經EUS導引酒精注射

Ref.	n	Max. diameter (mm)	Ethanol (%)	Volume (mL)	Complications
Qin et al.	4	10	95	0.5	None
		5.4	95	0.25	None
		11.8	95	0.5	None
		10.0	95	0.3	None
Yang et al.	4	22	98	1.8	None
		26 (MEN-1)	98	3.8	None
		15	98	2.5, 7.0	None
		11	98	0.5	None

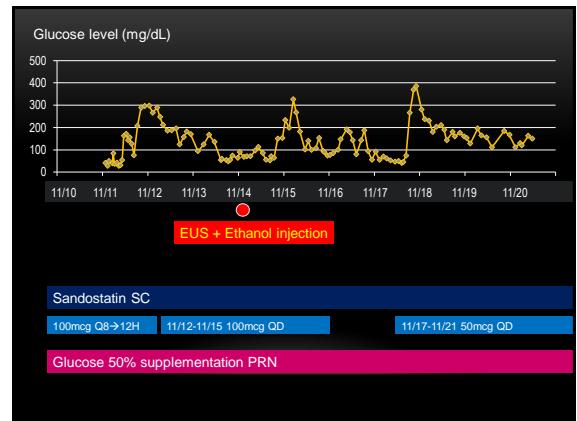
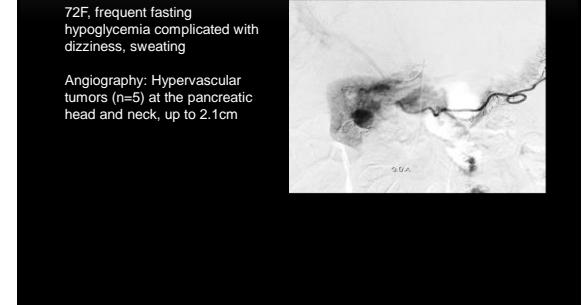
~ Qin SY, et al. Medicine. 2014;93:e85

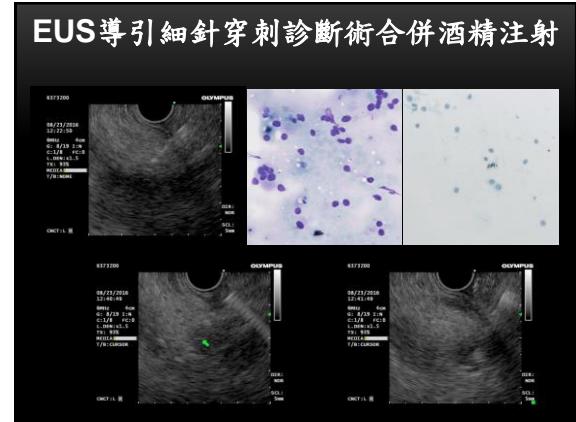
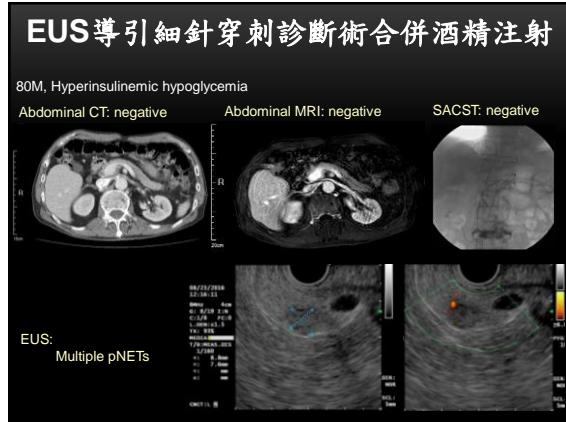
~ Yang D, et al. Gastrointest Endosc. 2015;82:1127

## 胰神經內分泌腫瘤經EUS導引酒精注射



## 胰神經內分泌腫瘤經EUS導引酒精注射





**小型胰神經內分泌腫瘤經EUS導引酒精注射待解決的問題**

- optimal type of injection needle with spray side holes?
- optimal size of injection needle 22G alone?
- safe target area within tumor mass regarding alcohol spreading feeding artery ablation?
- adequate amount of alcohol to achieve successful ablation without causing significant pancreatitis

-Seo DW. Gut Liver. 2010;4 Suppl 1:S76-81

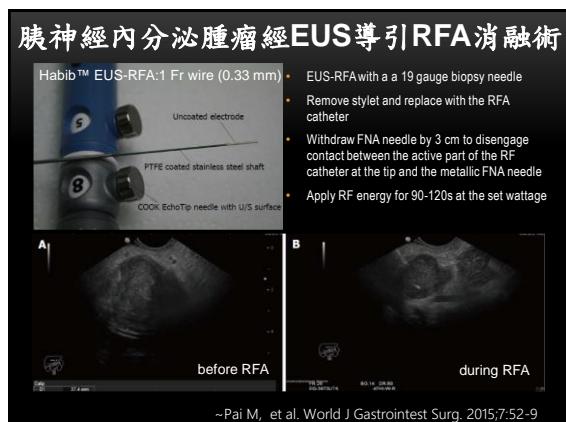
**胰神經內分泌腫瘤經EUS導引RFA消融術**

Clinical Trials Study  
**Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors**

Madhava Pai, Nagy Habib, Hakan Senturk, Sundeep Lakhtakia, Nageshwar Reddy, Vito R Cicinatti, Iyad Kaba, Susanne Beckebaum, Panagiotis Drymousis, Michel Kahaleh, William Brugge

- Prospective, multi-center, pilot safety feasibility study
- EUS-RFA, 2 pancreatic head NETs (6 cystic tumors)
- Post-RFA evaluation with cross sectional images
  - a change in vascularity (15 mm tumor), and central necrosis about 15 mm (40 mm tumor)
- complications: mild abdominal pain resolved in 3 days

~Pai M, et al. World J Gastrointest Surg. 2015;7:52-9



## 總結

- EUS as a good and accurate tool for diagnosing NETs
- EUS along with EUS-FNA/B helpful for diagnosing pancreatic NETs, even for the small ones ( $\leq 2$  cm)
- Development of adjunctive techniques with EUS, such as CEH-EUS, can further increase potential detection of small lesions
- Tumor grade may be evaluated with EUS-FNA/B for those smaller NETs ( $< 2$  cm)
  - the tumor response to biological therapy based on FNA/B specimen is to be evaluated

## 總結

- Endoscopic resection of rectal NETs with ESD or modified EMR is superior to EMR
  - the efficacy of modified EMR is equivalent to ESD
- EUS-guided ethanol injection with 40-99% ethanol for small pancreatic neuroendocrine tumors has been attempted with good resolution and few complications
- EUS-guided tumor ablation strategies for small pancreatic tumors offers a minimally invasive access for local treatment, and may become an alternative choice of surgical resection

謝謝聆聽！

