Carcinoid Tumors: The Beginning and End

Surgical Oncology Update 2011

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BC Cancer Agency, CSI

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- 1st described by Oberndofer(1907)
- “Karzinoide”= “cancer like”
- Arise from neuroendocrine cells
- Most organs of the body
- Clinical and pathologic characteristics both similar to the organ of origin, but also attributes shared by all NET’s

Klimstra, Pancreas, 2010

- **Distributed in the lung, thymus, GIT**
  - **Lung/Bronchi - 25%**
- **65% from GIT**
  - **Rectum - 18%**
  - **Small Bowel - 17%**
  - **Colon - 10%**
  - **Pancreas - 7%**
  - **Stomach - 6%**
  - **Appendix - 4%**

Lawrence, Endo Met Cl NA,2011

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GEP-Carcinoids

- **Increasing incidence**
  - **1 - 3.6 /100,000**
  - **APC 7% / year for gastric and rectum**
- **68% overall 5 YS (38 - 89%)**
- **1% increase survival / year**

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Carcinoid

- Various nomenclature and classifications
- Variability in grading and staging
- Certain common themes
- “Carcinoid” is controversial

Klimstra, NANETS, Pancreas, 2010

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TABLE 3. Systems of Nomenclature for Neuroendocrine Tumors

Grade	Lung and Thymus (WHO)[34]	GEP-NETs (ENETS)[28,29]	GEP-NETs (WHO 2010)[3]	Lung and Thymus (Moran et al)[23]	Pancreas (Hochwald et al)[14]
Low grade	Carcinoid tumor	Neuroendocrine tumor, grade 1 (G1)	Neuroendocrine neoplasm, grade 1	Neuroendocrine carcinoma, grade 1	Well-differentiated pancreatic endocrine neoplasm, low grade
Intermediate grade	Atypical carcinoid tumor	Neuroendocrine tumor, grade 2 (G2)	Neuroendocrine neoplasm, grade 2	Neuroendocrine carcinoma, grade 2	Well-differentiated pancreatic endocrine neoplasm, intermediate grade
High grade	Small cell carcinoma	Neuroendocrine carcinoma, grade 3 (G3), small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell carcinoma	Poorly differentiated pancreatic endocrine carcinoma, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine	Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma	Poorly differentiated pancreatic endocrine carcinoma, large cell neuroendocrine carcinoma

The grade of the tumor MUST be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as *neuroendocrine tumor* or *neuroendocrine carcinoma* without reference to grade do not provide adequate pathology information.

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TABLE 4. Grading Systems for Neuroendocrine Tumors

Grade	Lung and Thymus (WHO)[34]	GEP-NETs (ENETS, WHO)[3,28,29]	Lung and Thymus (Moran et al)[23]	Pancreas (Hochwald et al)[14]
Low grade	<2 mitoses / 10 hpf AND no necrosis	<2 mitoses / 10 hpf AND <3% Ki67 index	≤3 mitoses / 10 hpf AND no necrosis	<2 mitoses / 50 hpf AND no necrosis
Intermediate grade	2–10 mitoses / 10 hpf OR foci of necrosis	2–20 mitoses / 10 hpf OR 3%–20% Ki67 index	4–10 mitoses / 10 hpf OR foci of necrosis	2–50 mitoses / 50 hpf OR foci of necrosis
High grade	>10 mitoses / 10 hpf	>20 mitoses / 10 hpf OR >20% Ki67 index	>10 mitoses / 10 hpf, Necrosis present	>50 mitoses / 50 hpf

In the pathology report, the actual proliferative rate (mitotic count and/or Ki67 index) should be specified, and a grade should be provided, with the specific grading system used to be specified in the report.

Several Classification Systems

- **WHO(2010)**
  - **Well differentiated NET**
    - **G1 and G2**
  - **Poorly differentiated NE Carcinomas**
    - **Small and large cell(G3)**

Staging

- **TNM staging classification**
  - **Subdivided by organ of origin**
- **Influenced by :**
  - **Differentiation**
  - **Grading**
    - **Mitotic index**
    - **Ki-67**

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Presentation

- **Foregut**
  - **incidental, functioning tumor, obstruction**
- **Midgut**
  - **carcinoid syndrome, obstruction**
- **Hindgut**
  - **obstruction, bleeding, screening**

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Work-up

- Imaging
  - CT+/- MRI
  - Endoscopy +/- EUS
  - Octreotide scan
- Endocrine
  - Subtype specific for pancreas
  - Chromogranin A
  - 5-HIAA for midgut

Gastric NET

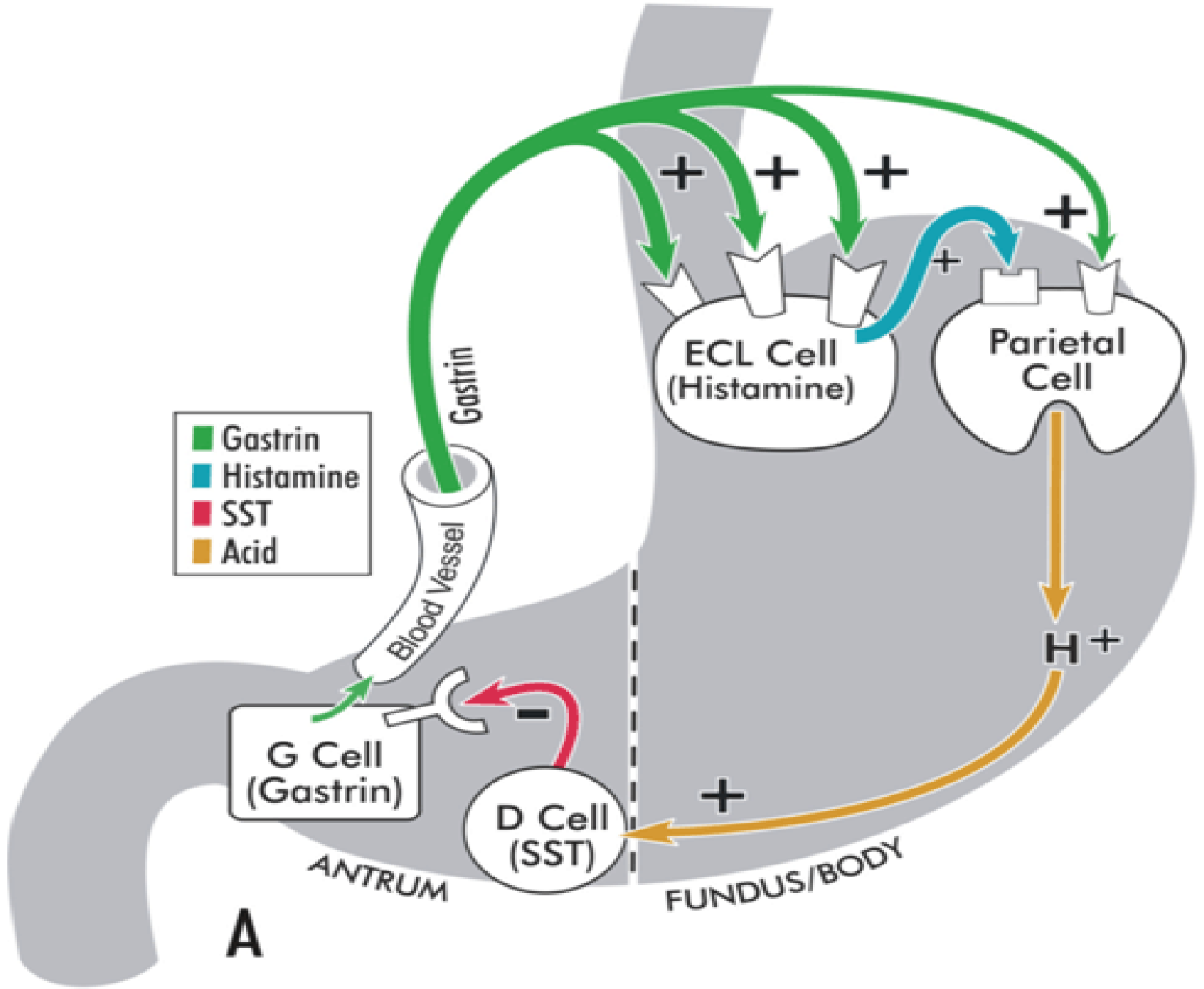
- First reported in 1923(Askanazy)
- Incidence increasing
- 8.7% of NET's (1997 SEER)
  - 2% in 1969
- 1.77% of gastric malignancies

Modlin, Am J Gastroenterol, 2004

Gastric NET

- Stomach has at least 5 endocrine cells
  - 2% of mucosal cells
- Enterochromaffin-like (ECL) derived
  - 80% of oxyntic endocrine cells
- 4 subtypes

Lawrence, Curr Gastroent Rep, 2011

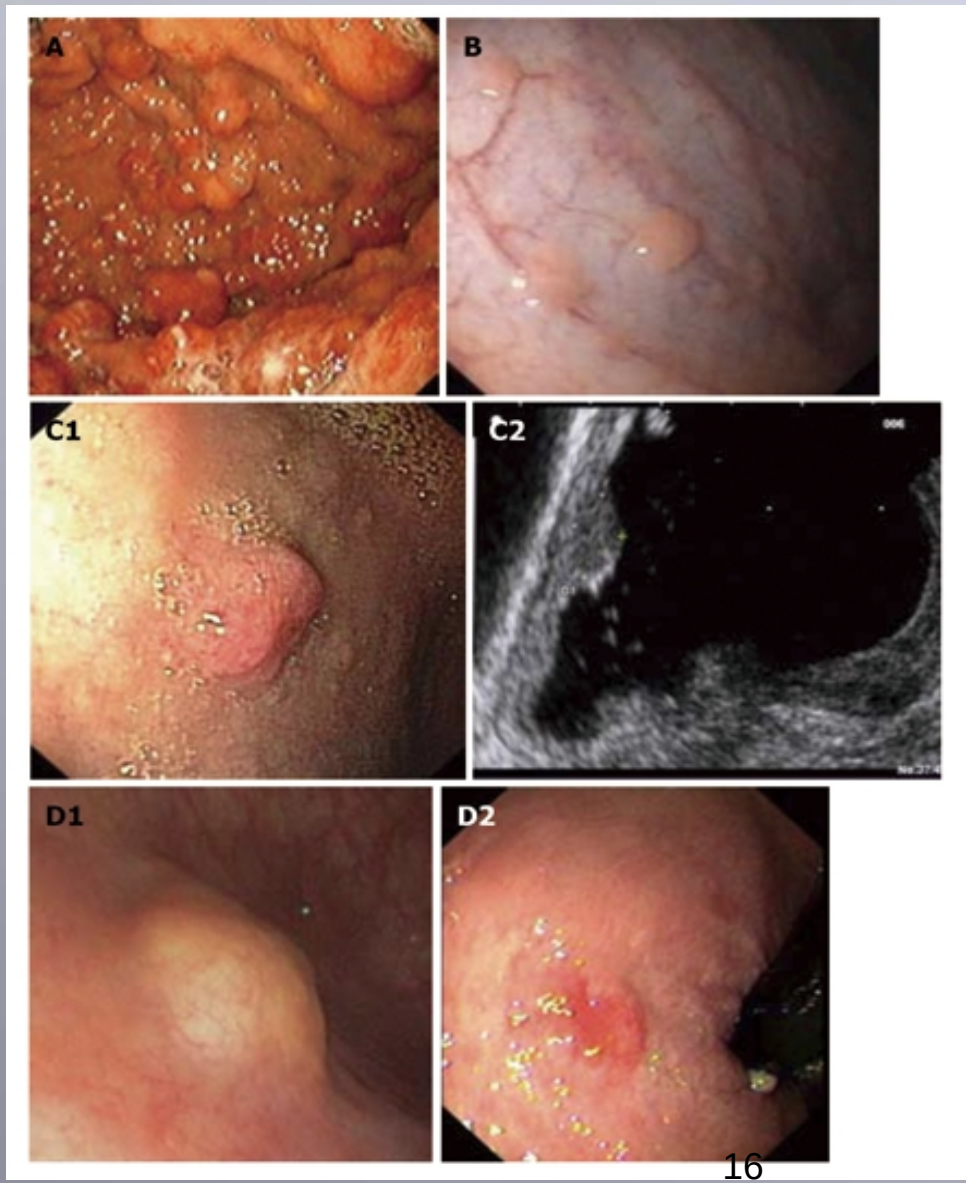

Gastrin
Histamine
SST
Acid
Gastrin
Blood Vessel
ECL Cell
(Histamine)
Parietal
Cell
H+
G Cell
(Gastrin)
D Cell
(SST)
ANTRUM
FUNDUS/BODY
A

Type 1 Gastric NET

- 80%
- Atrophic gastritis and pernicious anemia
- Hypergastrinemia
- Hypochlorhydria
- Excellent prognosis

Scherubl, Endoscopy,2010

- **Fundus/body**
- **2/3 multiple**



Type 2 Gastric NET

- 5%
- Hypergastrinemia
- Hyperchlorhydria
- ZES with MEN-1
- Modest chance of metastasis

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Pathogenesis

- Gastrin the most important growth factor in Type 1 and 2
- Other growth factors ?
- Antrectomy may reverse changes in Type 1
- ZES without MEN-1 rarely a cause of Type 2

- **Type 3**
  - **15-20%**
  - **Sporadic**
  - **No other mucosal abnormalities**
- **Type 4**
  - **Poorly differentiated neuroendocrine carcinomas**

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Table 3 Clinicopathological characteristics of gastric neuroendocrine neoplasms[4,23-26]

	Gastric NETs/carcinoids			Gastric NECs (poorly differentiated NENs)
	Type 1	Type 2	Type 3	Type 4
Relative frequency	70%-80%	5%-6%	14%-25%	6%-8%
Features	Mostly small (< 1-2 cm) and multiple	Mostly small (< 1-2 cm) and multiple	Solitary often > 2 cm	Solitary mostly exulcerated, > 2 cm
Associated conditions	CAG	MEN1/ZES	No	No
Histology	Well differentiated G1	Well differentiated G1	Well/moderate differentiated* G2*	Poorly differentiated G3
Serum gastrin	(Very) high	(Very) high	Normal	(Mostly) normal
Gastric pH	Anacidic	Hyperacidic	Normal	(Mostly) normal
Metastases	< 10%	10%-30%	50%-100%	80%-100%
Tumor-related deaths	no	< 10%	25%-30%	≥ 50%

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; CAG: Chronic atrophic gastritis, due to pernicious anemia or Helicobacter pylori infection; MEN1: Multiple endocrine neoplasia type1; ZES: Zollinger-Ellison syndrome; MEN1/ZES: ZES associated with MEN1; G1-3 histological differentiation: see Table 2; ENETS and NANETS nomenclature are identical for G1 and G3 grading: G1: Well differentiated; G3: Poorly differentiated. For G2 grading ENETS and NANETS nomenclature differ: *ENETS-nomenclature: G2: Well-differentiated; *NANETS-nomenclature: G2: Moderate differentiated (modified from Scherübl *et al*[13])

Scherubl, WJGE, 2011

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Gastric NET

- 63% 5YS 1990's
  - 51% in 1970's
  - 71% in recent SEER
- Metastasis:
  - Type 1 – 2-5%
  - Type 2 – 30%
  - Type 3 – 70%

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Gastric NET

- Incidental finding in most
- Symptomatic occasionally
- Carcinoid or atypical carcinoid rare

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Work-up

- Endoscopy (EUS?)
- CT
- Consider Octreotide scan
- Fasting serum Gastrin
- Chromogranin A
- 5-HIAA ?

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Options

- Surveillance
- Limited resection
- Antrectomy
  - 70-85% success (Zhang, WJS, 2011)
- Major Resection
- Somatostatin

Population Based Study

- N=984 gastric carcinoids
- Age, size, depth significant survival
- 2% LN mets if <1cm (6.4%)
  - 32% if > 2cm

Saund, ASO, 2011

- **3.4% LN mets if < 1cm/SM**
- **No LN mets in tumors < 2cm/IE**
- **Other subgroups 8 - 86%**
- **Selected patients appropriate for EMR**
- **Subtypes may be important(Landry,2009)**
  - **Multiple lesions > Solitary lesions**
  - **84 vs 68% 5YS**

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Institutional Experience

- **N=65**
- **51 type 1**
- **Symptoms primarily not related to tumors**
  - **19 with atrophic gastritis**
- **Tumor type correlated with size/depth**
  - **42/51 Type 1 into submucosa**
- **48/51 had treatment per protocol**
  - **30 ES**
  - 10 antrectomy and 8 radical resections

Borch, Ann Surg, 2005

- **4/51 Type 1 had LN(3) or distant mets(1)**
- **1 known NET death in Type 1**
- **96% 5YS and 74% 10YS**
  - **Same as general population**
  - **33% 5YS in type 4**
- **No difference in survival between ES and Sx**
- **Trend to improved survival in those tumor free**

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Type 1 Gastric NET

- 37% tumors > 1cm (vs 4%)
- Median 1.3 cm (vs 0.5 cm)
- 3/19 surgically treated patients had LN mets
- 100% survival overall
  - 10/99 LN mets in surgical literature
- No type 1 deaths in those with LN mets

Gladdy, ASO, 2009

TABLE 4 Treatment and outcome in type I gastric carcinoid

Study (institution)	No. of type I GC patients	No. of patients treated with SR	Mean follow-up (months)	Incidence of carcinoid mets in SR patients	DSS
Present (MSKCC)	65	19	42	3/19	100%
Borch* (24 institutions)	51	22	95	4/22	98% (5-year OS, w/o mets) 75% (5-year OS, w/mets)
Dakin (Cornell)	18	10	NR	NR	NR
Jordan (Baylor)	18	10	72	3/10	100%
Schindl (Vienna)	16	7	70	0/7	100%
Rindi (four institutions)	152	NR	53	2/41	100%

SR surgical resection, *DSS* disease-specific survival, *OS* overall survival, *NR* not reported, *mets* metastatic disease in either lymph nodes or liver, *NR* not reported

* DSS not reported

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Non-interventional Rx ?

- N=11 patients with small carcinoids
- Follow-up 54 months (median)
- Progression in number/size in 4 (36%)
- None progressed to 1 cm

Ravizza, Dig Liv Dis, 2007

ESR	Low risk	Low risk	High Risk*
Size	< 1.0 cm	1 – 2 cm	Any size
Type 1	ESR or Observe	ESR	Surgery
Type 2	Observe / ESR / SS	ESR or Observe	Surgery
Type 3	ESR	Surgery	Surgery
Type 4			Surgery

Scherubl, WorldJGastrointestEndosc, 2011

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Rectal NET's

- Age adjusted incidence 1 / 100,000
- Increase 10x last 35 years
- 50% incidental
- Prevalence in screening pop'n 0.05%

Scherubl, Endoscopy, 2009

Rectal NET

- 89% 5 YS
- 82% localized at Dx (median 6 mm)
- Incidence of LN metastasis similar to adenocarcinoma
  - Small, low grade – 99% 5YS
  - LN mets – 54-73% 5YS
  - Metastatic – 15-30% 5YS

Rectal NET

- **Population based**
  - **65-80% < 1cm**
  - **10-20% 1-2 cm**
  - **10-15% > 2cm**
- **Screening studies**
  - **95% < 1cm**
  - **4% 1-2 cm**
  - **1% > 2 cm**

Scherubl, Endoscopy, 2009

- **Rectal NET's < 1cm**
  - **LN mets in 3 - 10%**
  - **amenable to local excision**
  - **Pre-op EUS**
    - **Improve Resectability(ESR)**
    - **R0 in 95% vs 20 - 80%**

- **Rectal NET > 2cm**
  - **Metastasis in 60 - 80%**
  - **Formal resection preferred**
- **Rectal NET 1 - 2 cm**
  - **LN mets in 17- 81%**

	Low risk	Low risk	High risk
Grade/Size	< 1.0 cm	1 – 2 cm	Any size
G1	ESR	Surgery or ESR*	Surgery
G2	ESR or surgery	Surgery	Surgery
G3			Surgery

Scherubl, WJGE, 2011

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Conclusions

- Rising incidence of NET's
- Greatest in gastric and rectal sites
- Survival quite variable
- Outcome in early (<2cm) excellent
- Amenable to endoscopic measures
- Subclassification of type in gastric

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Thank You

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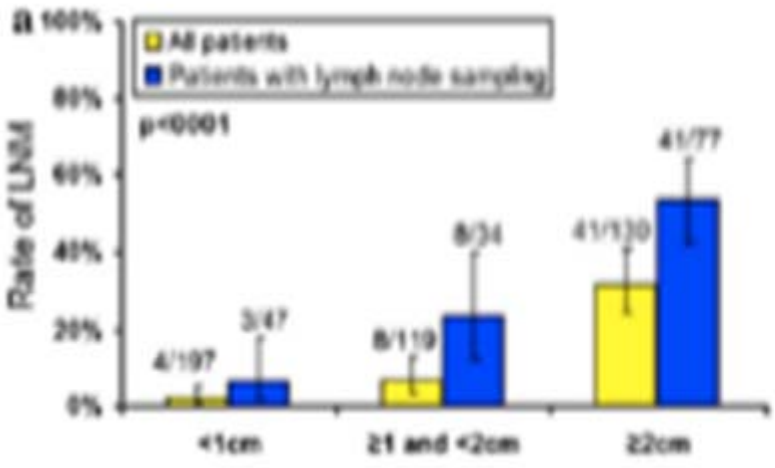

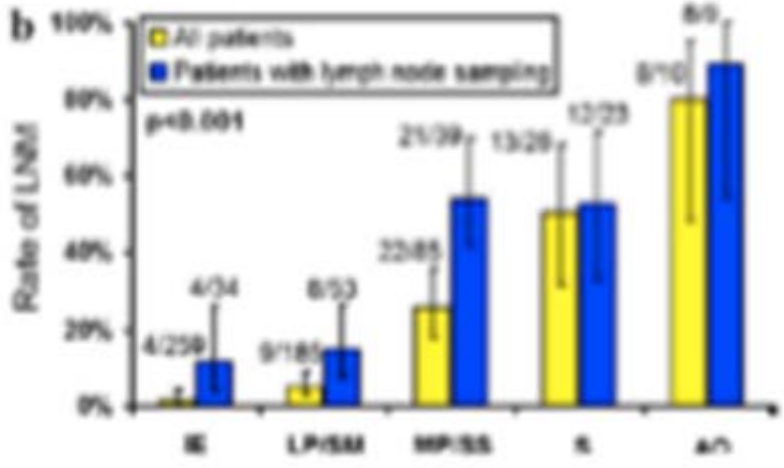

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TABLE 3 Rate of lymph node metastasis by size and depth groupings in the entire patient population

	Depth of penetration				
	Intraepithelial	Lamina propria or submucosa	Muscularis propria or subserosa	Serosa	Adjacent organ
Size					
<1 cm	0/89 (0)	2/59 (3.4%)	2/5 (40%)	0	0
1–2 cm	0/23 (0)	5/47 (11%)	2/25 (8.0%)	0	1/1 (100%)
≥2 cm	3/20 (15%)	2/27 (7.4%)	15/37 (41%)	12/25 (48%)	6/7 (86%)