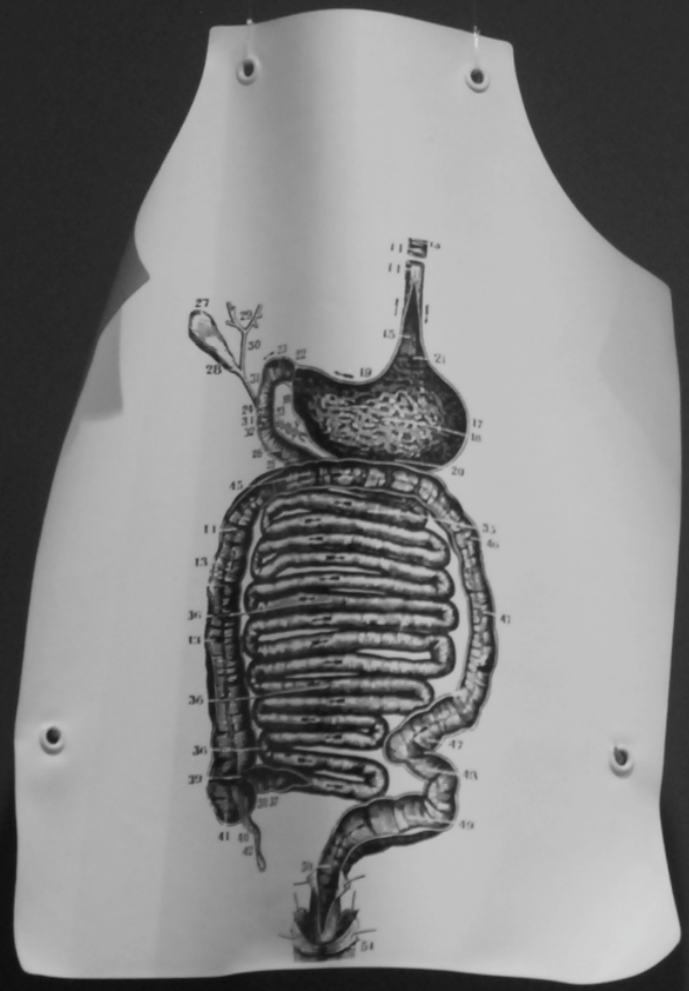
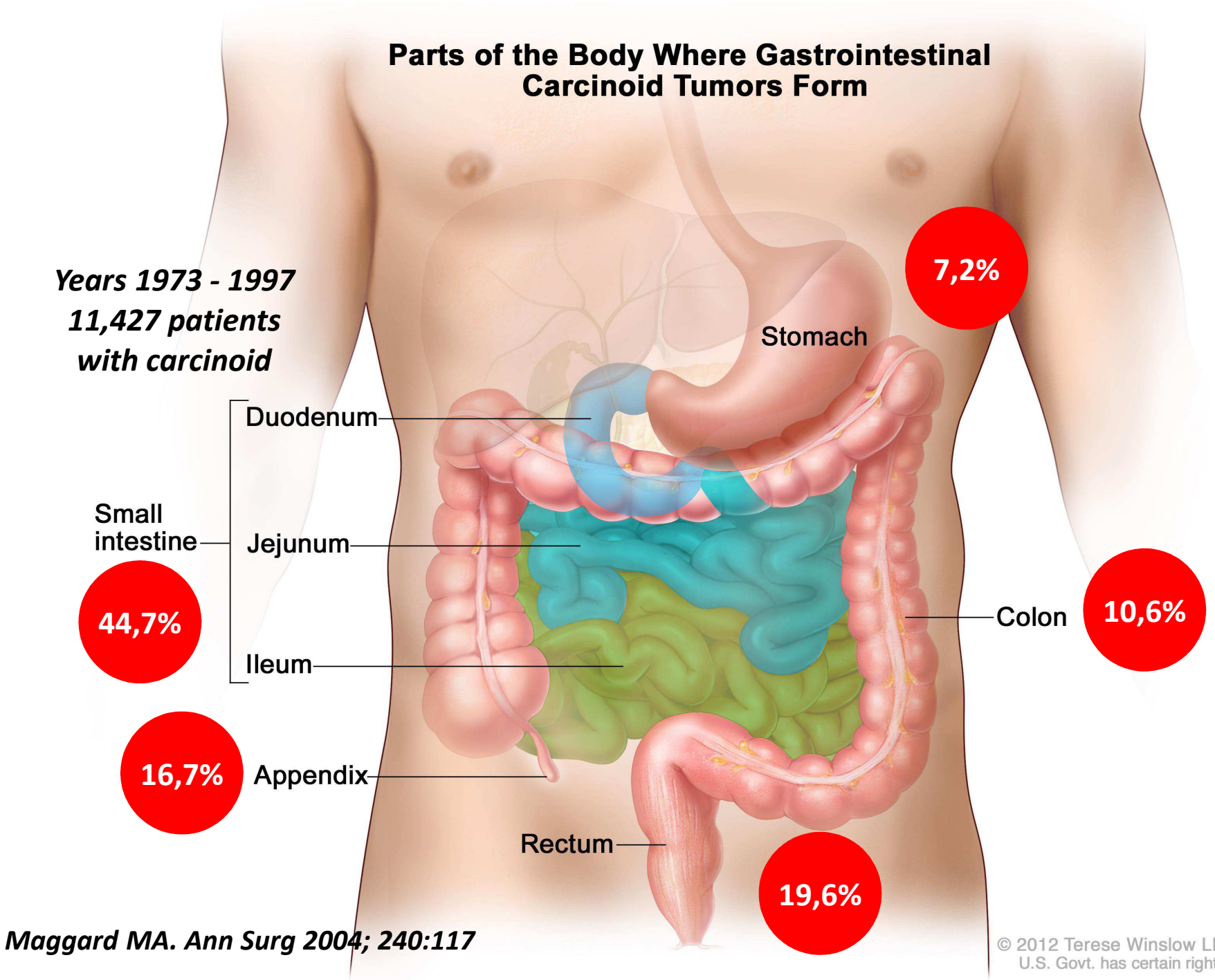
IL PERCORSO DEL PAZIENTE CON NEOPLASIA NEUROENDOCRINA NELLA PROVINCIA DI FERRARA



MoMA – New York 2009

Gli approcci chirurgici su piccolo e grande intestino

MATTIA **PORTINARI**


Parts of the Body Where Gastrointestinal Carcinoid Tumors Form
Years 1973 - 1997
11,427 patients
with carcinoid
7,2%
Stomach
Duodenum
Small intestine
Jejunum
44,7%
Ileum
Colon
10,6%
16,7%
Appendix
Rectum
19,6%
Maggard MA. Ann Surg 2004; 240:117
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Epidemiology

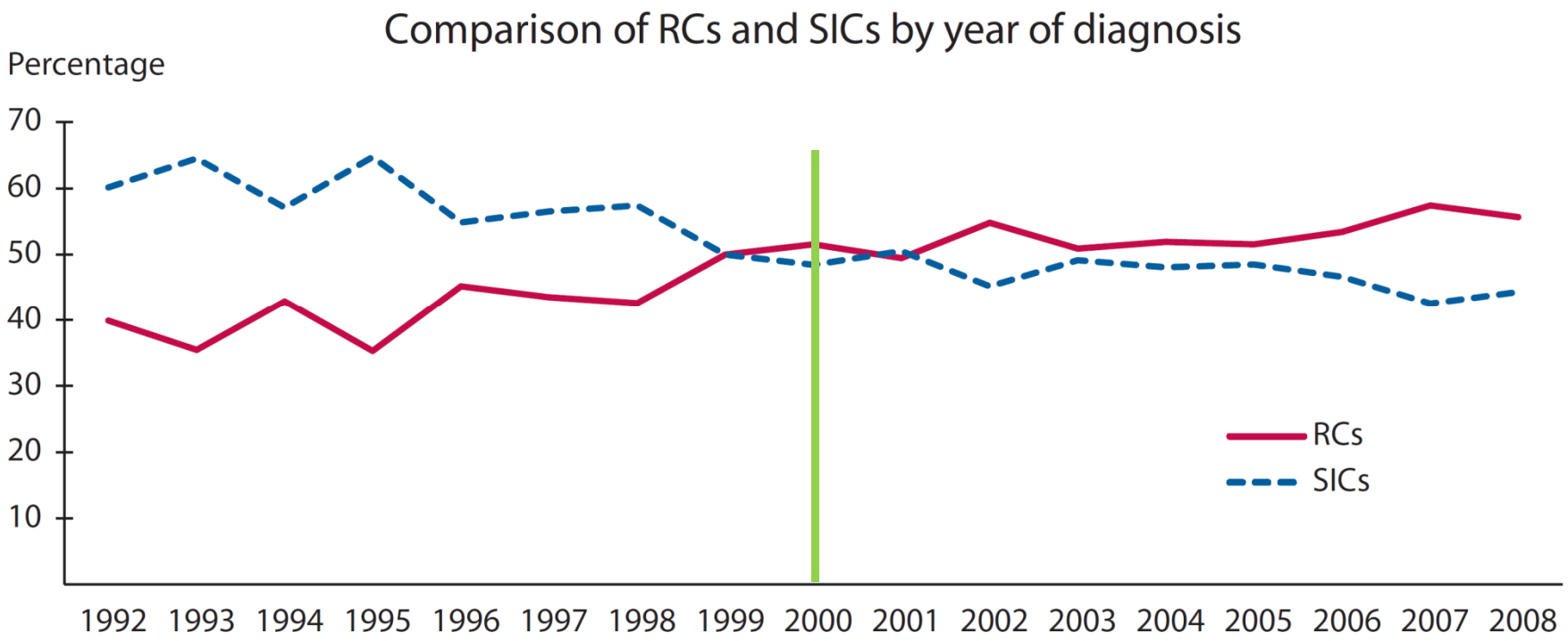

FIGURE 1. Comparison of rectal carcinoids (RC) and small intestinal carcinoids (SIC) during the study period.

Taghavi S, Dis Colon Rectum 2013; 56:952

Surgery

The treatment of choice for a patient who has a **localized well-differentiated gastrointestinal tract neuroendocrine (carcinoid) tumors** (NET) is usually surgery.

The **extent of the surgical resection** depends on the **site** of origin and **size** of the primary tumor

Prognosis

TABLE II. Incidence of Metastases Related to the Size of the Primary Carcinoid Tumor

Size (cm)	Total patient numbers	Nodal metastases patient numbers (%)	Distant metastases patient numbers (%)
Small Intestine [2,21,22]			
≤1	43	5 (12)	2 (5)
1.1–1.9	83	58 (70)	16 (19)
≥2	59	50 (85)	28 (47)
Appendix [2,21,26–29]			
≤1	431	0	0
1.1–1.9	53	4 (7.5)	2 (4)
≥2	33	11 (33)	4 (2)
Colon [2,30,31]			
<2	11	2	2
≥2	62	34 (55)	24 (39)
Rectum [2,21,32–35]			
≤1	176	2 (1)	0
1.1–1.9	39	2 (5)	2 (5)
≥2	42	26 (62)	17 (40)

1032 out of 13053 patients

Rorstad O. J. Surg. Oncol. 2005;89:151–160

Prognosis

The anatomical site of carcinoids and the tumor stage are known to be important factors in determining prognosis and survival

TABLE 4. 5-Year Survival Rates by Carcinoid Location (1973–1997)

Site	All Stages	Local Stage	Regional Stage	Distant Stage
Stomach	75.1%/55.3%	90.2%/69.6%	40.4%/27.2%	18.0%/9.0%
Small bowel	76.1%/54.6%	94.5%/70.4%	84.4%/64.1%	51.2%/32.4%
Appendix	76.3%/65.0%	95.6%/87.8%	80.0%/67.6%	37.5%/26.8%
Colon	69.5%/41.8%	94.1%/77.1%	72.5%/35.3%	27.8%/4.1%
Rectum	87.5%/77.8%	94.9%/86.2%	53.7%/42.1%	14.6%/13.1%

*Cancer-specific survival/relative overall survival.
Survival rates are all age-adjusted to standard 2000 population.

Maggard MA. Ann Surg 2004; 240:117

Appendix

The **majority** of appendiceal NETs are found **incidentally** at the time of appendectomy

70-75% Well differentiated NET

The reported incidence of appendiceal NETs is

1 NET in every 150 to 300 appendectomies

Sandor A. Am J Gastroenterol 1998; 93:422.
Mullen JT. J Surg Oncol 2011; 104:41.
Goede AC. Br J Surg 2003; 90:1317.

Most are **submucosal** and in the **distal one-third**

The **prognosis** of appendiceal NETs and **type of surgery** are best predicted by **tumor size**.

Appendix

In many series, **tumors <2 cm** in diameter
(found in approximately 95% of patients)
have a **low likelihood of metastases at diagnosis**.

There is general agreement that tumors **<1 cm R0** can usually be treated by **simple appendectomy**

A **right hemicolectomy** has been recommended for:

- **tumors >2 cm**
- **tumors <2 cm** and **meso-appendiceal invasion or positive or unclear margins, higher proliferative rate, angioinvasion, mixed histology (goblet cell carcinoid, adenocarcinoid)**

Appendix

Comparison of management strategies for neuroendocrine appendix tumors according to different published guidelines

	<1 cm	1 to 2 cm	>2 cm
TNCD[1]	***Cured by appendectomy if:*** ▪ R0 (no tumor on margin) ▪ Grade 1 ***Right hemicolectomy if:*** ▪ Base or R1 ***No recommendation for tumor <1 cm, but grade 2***	***Right hemicolectomy if:*** ▪ Base or R1 or lymph node involvement ▪ Lymphovascular involvement ▪ Invasion of the mesoappendix >3 mm ▪ Grade 2	Right hemicolectomy
ENETS[2]	***Cured by appendectomy if:*** ▪ Tip/body and R0 ***Right hemicolectomy if:*** ▪ Base or R1 ***Discuss right hemicolectomy if:*** ▪ Mesoappendix invasion >3 mm	***Right hemicolectomy if:*** ▪ Base or R1 ***Discuss right hemicolectomy if:*** ▪ Tip/middle and R0, but with risk factors (lymphatic invasion, grade 2, or invasion of the mesoappendix >3 mm)	Right hemicolectomy
UKINETS[3]	Cured by appendectomy	***Right hemicolectomy if:*** ▪ Serosal breach by tumor ▪ Cellular atypia ▪ Mesoappendix invasion >3 mm ▪ Base (perforation of the appendix) (lymphovascular and perineural invasion)	Right hemicolectomy
NCCN[4]	***Cured by appendectomy if:*** ▪ Confined to the appendix (complete resection: nodes, margins)		Right hemicolectomy
NANETS[5]	***Cured by appendectomy if:*** ▪ Tip ▪ Complete tumor resection ▪ No lymphovascular involvement ▪ No invasion of the mesoappendix	***Right hemicolectomy if:*** ▪ Base ▪ Incomplete tumor resection ▪ Lymphovascular invasion ▪ Mesoappendix invasion ▪ Intermediate- to high-grade tumor ▪ Mesenteric nodal involvement	Right hemicolectomy

TNCD: Thésaurus National de Cancérologie Digestive; R0: indicates negative surgical margin; R1: indicates positive surgical margin; ENETS: European Neuroendocrine Tumor Society; UKINETS: United Kingdom and Ireland Neuroendocrine Tumour Society; NCCN: National Comprehensive Cancer Network; NANETS: North American Neuroendocrine Tumor Society.

References:

1. *Cadiot G, Baudin E, Coriat R, et al. Tumeurs neuro-endocrine. In: Thésaurus National de Cancérologie Digestive, Société Nationale Française de Gastro-Entérologie, 2017.*
2. *Pape UF, Niederle B, Costa F, et al. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). Neuroendocrinology 2016; 103:144.*
3. *Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61:6.*
4. *National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2016: Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors). Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site (Accessed 2016).*
5. *Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas 2010; 39:753.*

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DOI: 10.1002/jso.24714

RESEARCH ARTICLE

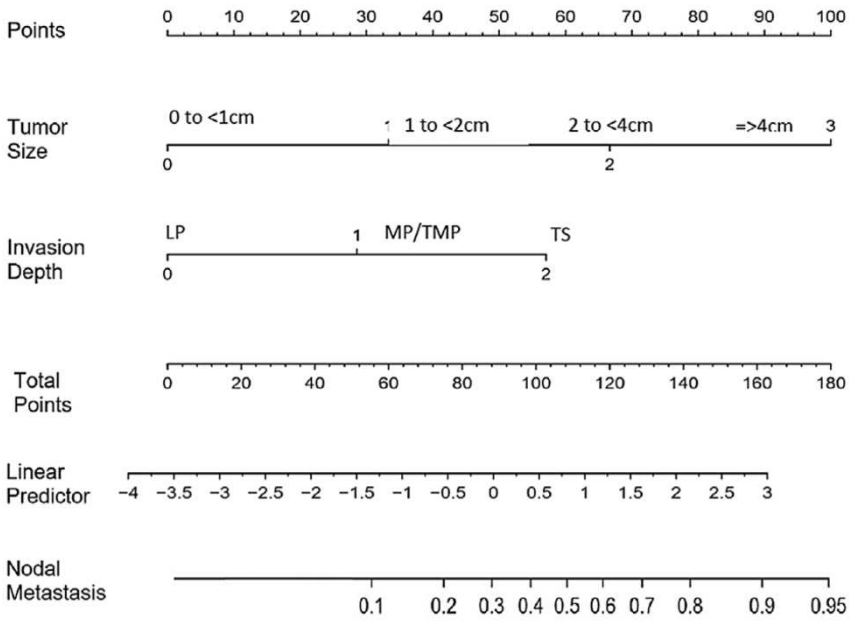
WILEY Journal of SURGICAL ONCOLOGY

PROGNOSIS

Novel nomogram combining depth of invasion and size can accurately predict the risk for regional nodal metastases for appendiceal neuroendocrine tumors (A-NET)

Catalina Mosquera MD[1] | Timothy L. Fitzgerald MD[2] | Haily Vora MPH[3] | Marysia Grzybowski PhD, MPH[4]

Lamina Propria (LP)
Muscularis Propria (MP)
Through the Serosa (TS)



The model predicted the likelihood of nodal metastasis, with an AUC of 0.89

FIGURE 2 Nomogram

Small intestine

Jejuno-ileal

"running the bowel"

60 cm

NETs of the small intestine are most **commonly found in the ileum within 60 cm of the ileocecal valve**

25%

Of patients will have more than one small bowel NET at the time of discovery.

40%

Of patients with midgut NETs have a **second gastrointestinal tract malignancy**.

Small intestine

Jejuno-ileal

Due to the **significant metastatic potential**, any locoregional small bowel NET should be **resected en bloc with its lymphatic drainage field, including the mesentery**

Retrieval of **at least 8 lymph nodes** appears to be optimal to achieve **accurate staging**

Palliative resection of the primary tumor may be advised **even in patients** with known **distant metastases** in order **to reduce** the potential for **bowel obstruction or bleeding**, or to **palliate abdominal pain** related to the primary tumor.

ENETS Consensus Guidelines - Neuroendocrinology 2016;103:125–138
Pancreas 2017;46: 715–731

Small intestine

ENETS Consensus Guidelines
Neuroendocrinology
2016;103:125–138

GUIDELINE

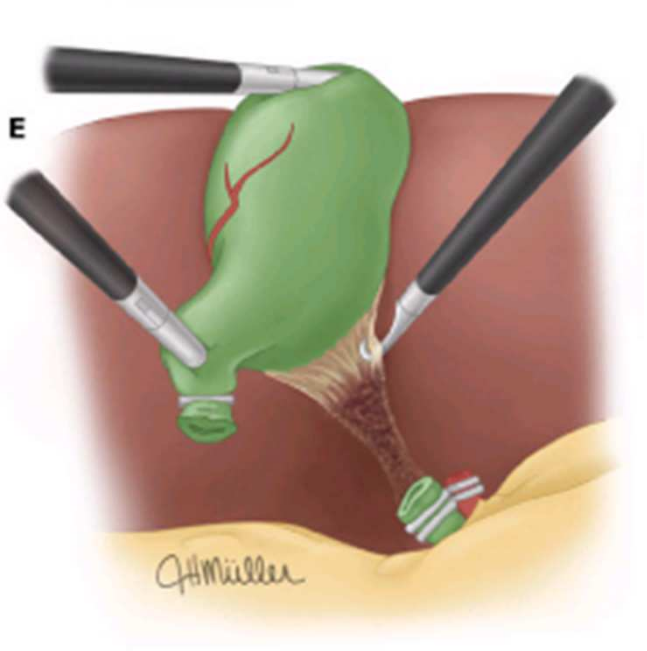
Disease	Localized	Regional	Distant		
Stage	**I/II**	**III**	**IV**		
TNM	T1–3N0M0	T4N0M0 T1–4N1M0		TxNxM1 **Unresectable metastatic disease**	
Surgical treatment	**Radical** resection		**Radical** resection **with curative intent**	**Palliative** resection	**No** resection
At least 8 lymph nodes for accurate staging	Local radical open (or in selected pts) laparoscopic resection* of • primary tumor(s)** • lymph nodes (dissection along the superior mesenteric root) **Absence of diffuse bilobar liver involvement, compromised liver function, or Grade 3 tumor (neuroendocrine carcinoma).**		Local radical open resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root) in combination with: • mets (liver)	Local radical open (in selected pts) laparoscopic resection of • primary tumor(s) • lymph nodes (dissection along the superior mesenteric root)	Due to: • local inoperability • comorbidity
Aim	Free from tumor **R0**		20% **Peritoneal metastases** Free from tumor **R0**	• To avoid local complications (obstruction, bleeding etc.) • To possibly improve prognosis*	

Cytoreductive surgery → impact on survival

Fig. 2. Therapeutic algorithm for Si-NENs. Pts = Patients; mets = metastasis. *For details, see the text. **Caution: multiple primaries.

Small intestine

If there is a high likelihood that the patient will require **long-term treatment with a somatostatine analogue** (i.e. liver metastases, peritoneal disease, or significant nodal involvement), a **prophylactic cholecystectomy can be considered** due to the risk of gallstones development

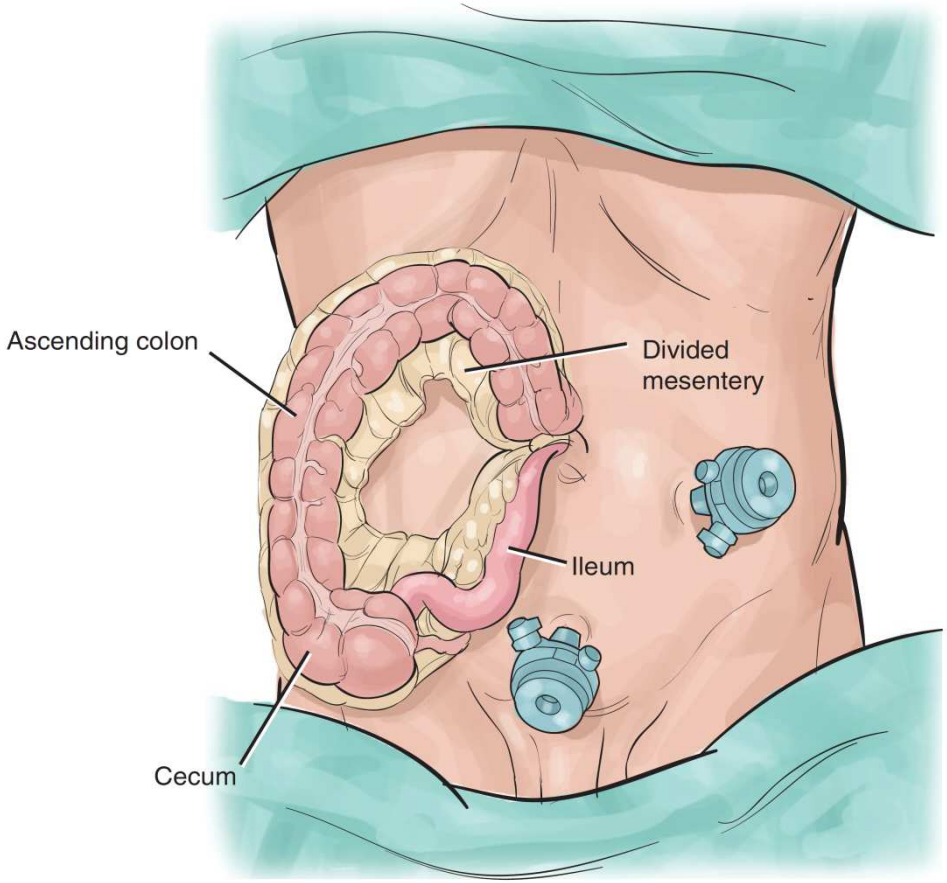


ENETS Consensus Guidelines - Neuroendocrinology 2016;103:125–138
Pancreas 2017;46: 715–731

Colon

The majority of colonic NETs are located in the right colon, particularly in the cecum

Colonic NETs, for the most part, are **treated like adenocarcinoma**.



Colonic NETs < 2 cm

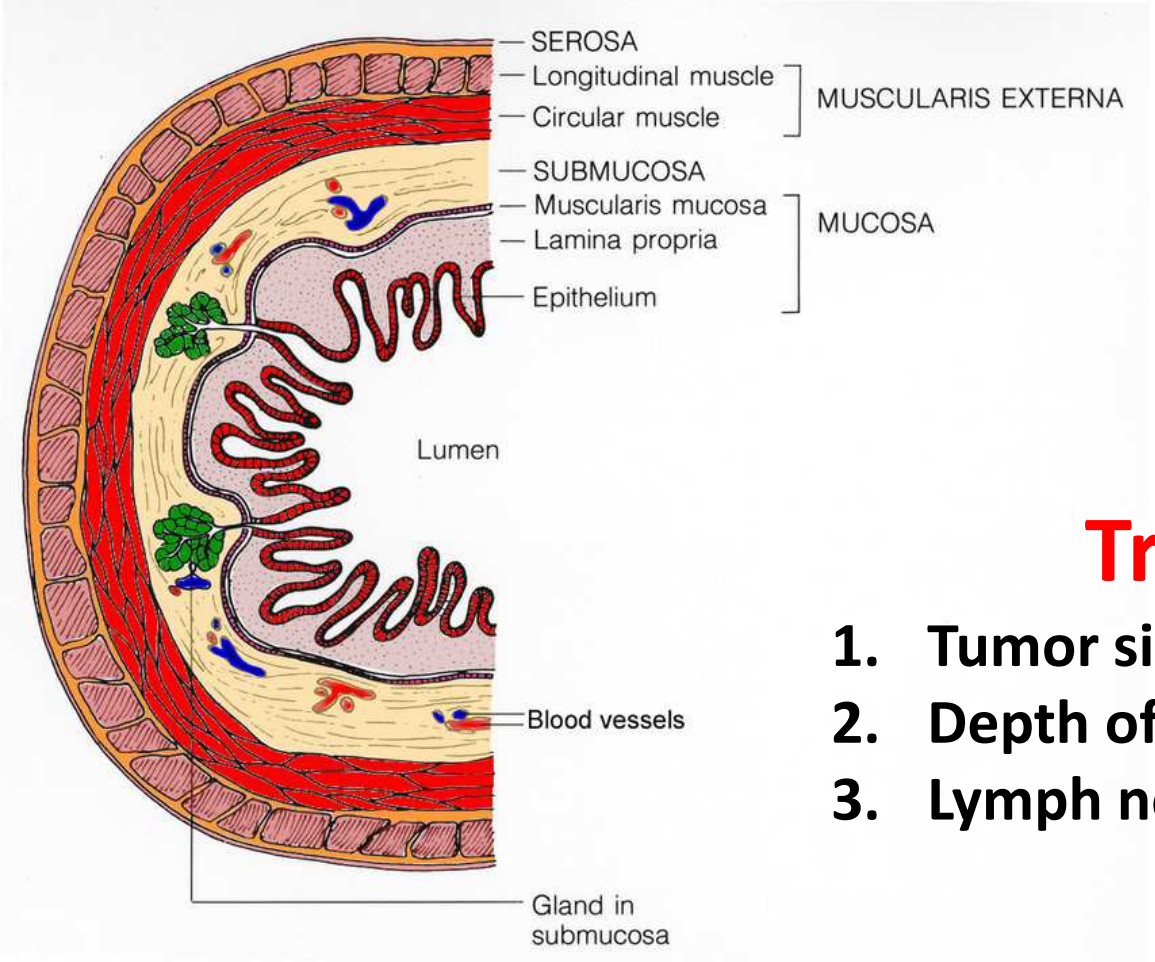
may be **resected endoscopically**, but an oncologic resection is required if the lesion is incompletely excised, or if the tumor is high grade.

Colonic NETs >2 cm with invasion of the muscularis propria

endoscopic resection alone is not appropriate for the majority of colonic NETs. An **oncologic resection with colectomy and resection of the associated lymph drainage is required**.

Rectum

Most rectal NETs are small, localized, and **mucosal or submucosal** in location



A **full colonoscopy** should be performed, if not already done at the time of initial diagnosis to evaluate **for synchronous lesions**.

Treatment

1. **Tumor size**
2. **Depth of invasion**
3. **Lymph node involvement**

Clin Colon Rectal Surg 2018;31:301–308

Rectum

Rectal NETs <1 cm and confined to the mucosa or submucosa (T1) can generally be treated by **standard endoscopic resection or endoscopic mucosal resection** particularly if they lack other risk factors (i.e. mitotic rate >2 per 10 high-power fields or lymphovascular invasion)

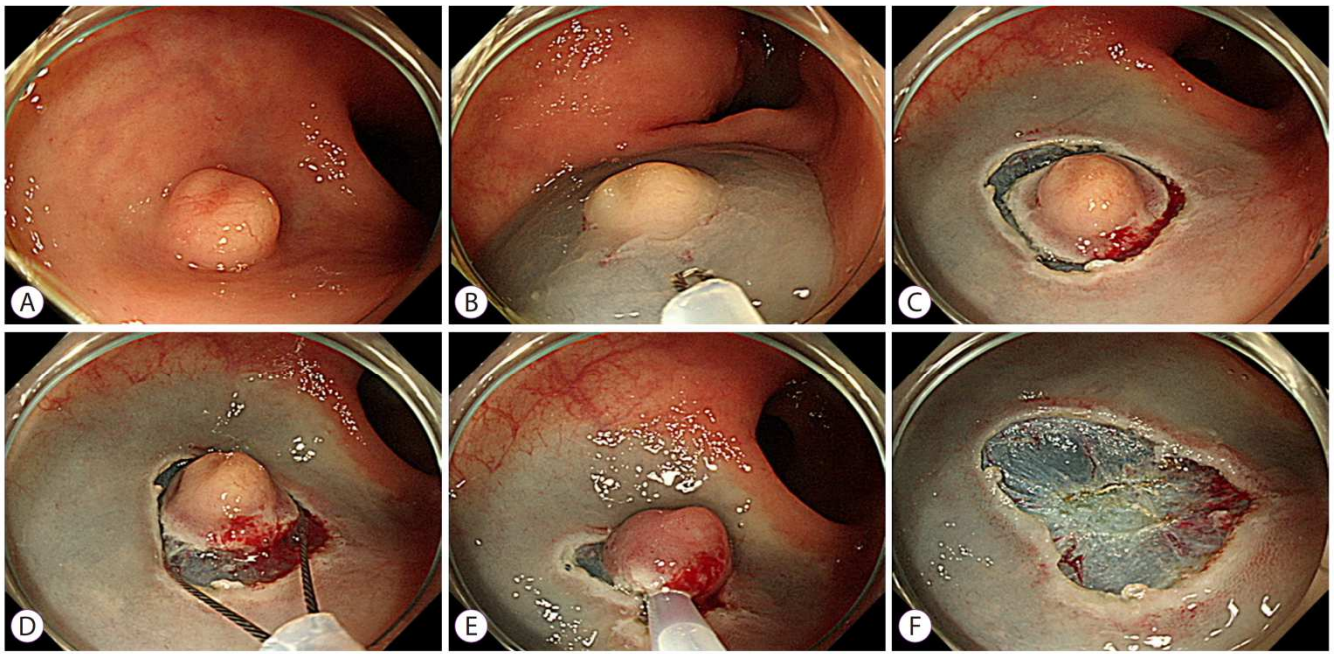
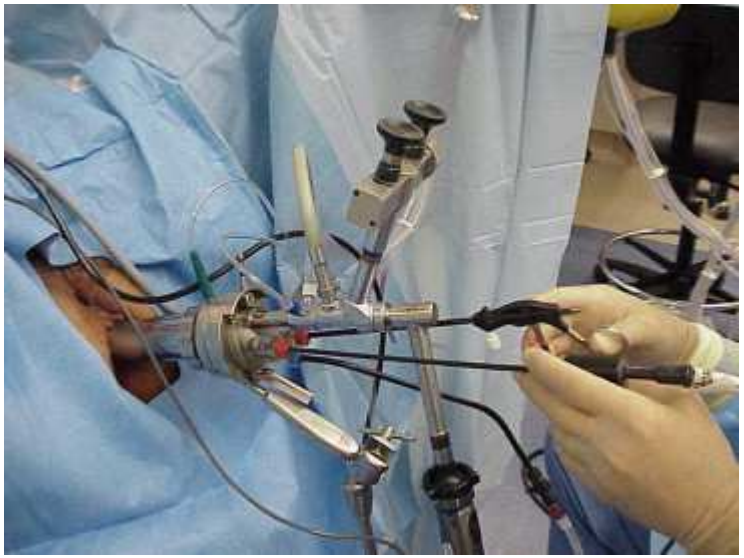


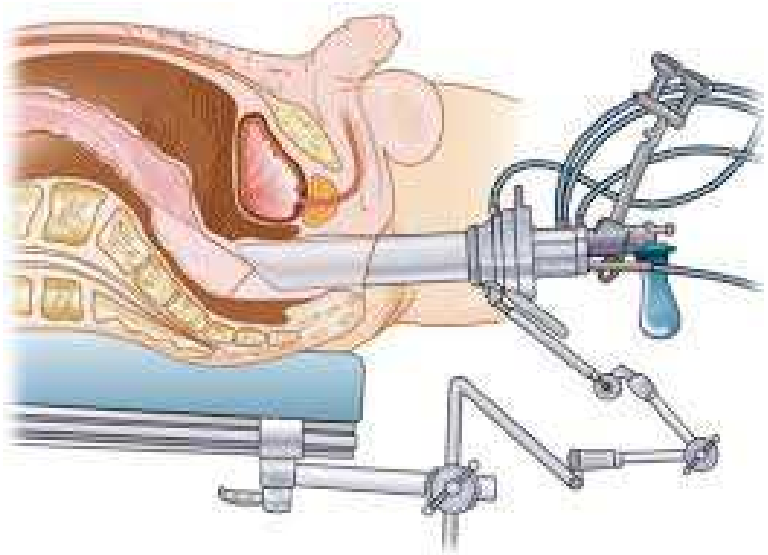
Fig. 1. Precut endoscopic mucosal resection of a rectal neuroendocrine tumor (NET). (A) A 9 mm sized rectal NET. (B) Following submucosal injection into the tumor, the tip of the snare is introduced for circumferential incision/precutting. (C) Precutting around the tumor. (D, E) Secure snaring in the precut mucosal groove. (F) A clear post-resection ulcer base is seen.

ENETS Consensus Guidelines
Neuroendocrinology 2016;103:139–143
Clin Endosc 2017;50:585-591

Rectum

The management of intermediate-sized tumors (1 to 2 cm confined to mucosa or submucosa) is somewhat controversial

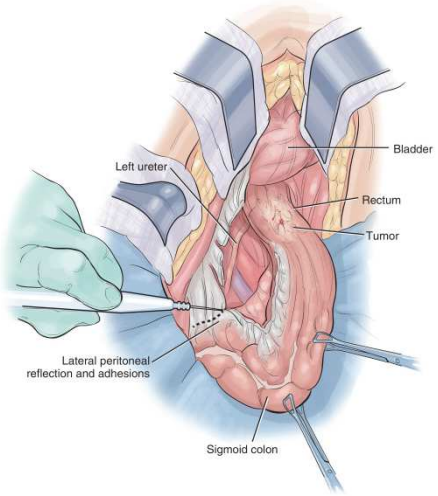


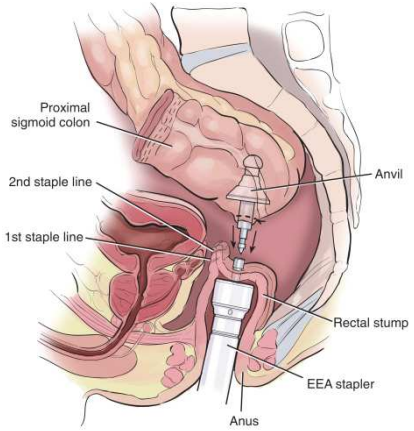


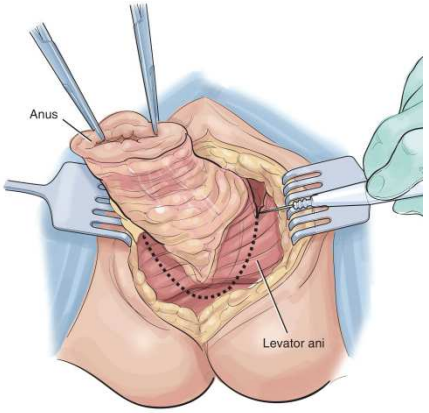
Transanal Endoscopic Microsurgery [TEM],

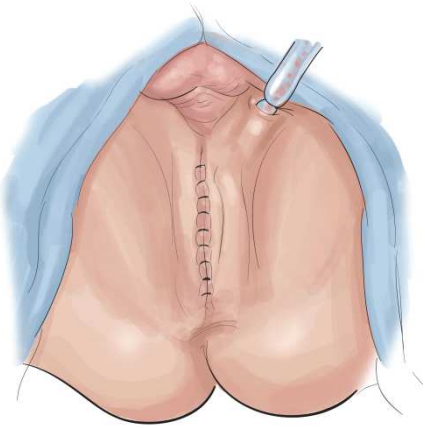
Transanal resection or advanced **endoscopic resection techniques** (such as TEM) may be appropriate **for tumors lacking risk factors**, whereas **radical resection** may be more appropriate for tumors with risk factors such as **elevated mitotic rate (or Ki-67 index), lymphovascular invasion, or size >1.5 cm**

Rectum









Low anterior resection - Total Mesorectal Excision

Abdominoperineal resection

Rectal NETs >2 cm or those that invade the muscularis propria (T2) without metastasis (M0) should generally be treated with **radical surgical resection**.

Rectal NETs >2 cm with metastasis Palliative resection or stent for bleeding or obstruction

Rectum

Carcinoid of the Rectum Risk Stratification (CaRRs): A Strategy for Preoperative Outcome Assessment (5-year recurrence-free survival)

TABLE 6. *CaRRS: carcinoid of the rectum risk stratification*

Points	Size (cm)	Depth	Lymphovascular invasion	Mitotic rate (HPF)
0	<1	Mucosa/submucosa	No	<2/50
1	1–1.9	Muscularis or deeper	Yes	≥2/50
2	≥2			

To obtain CaRRS, add patients associated with each clinicopathologic feature.

Low risk = 0 points, intermediate risk = 1–2 points, high risk = ≥3 points.

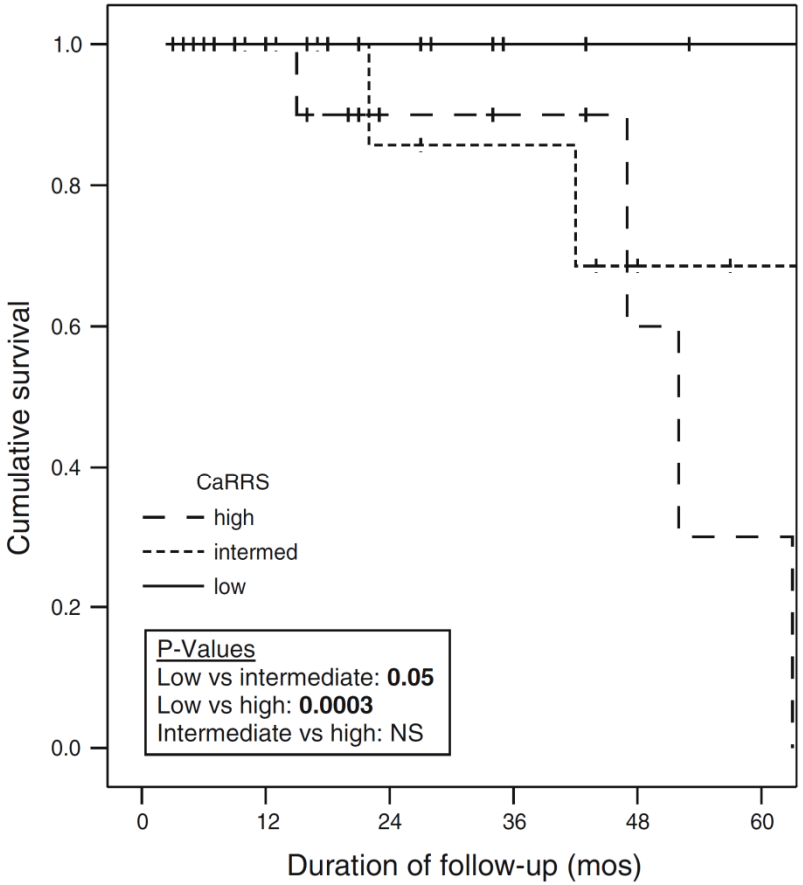
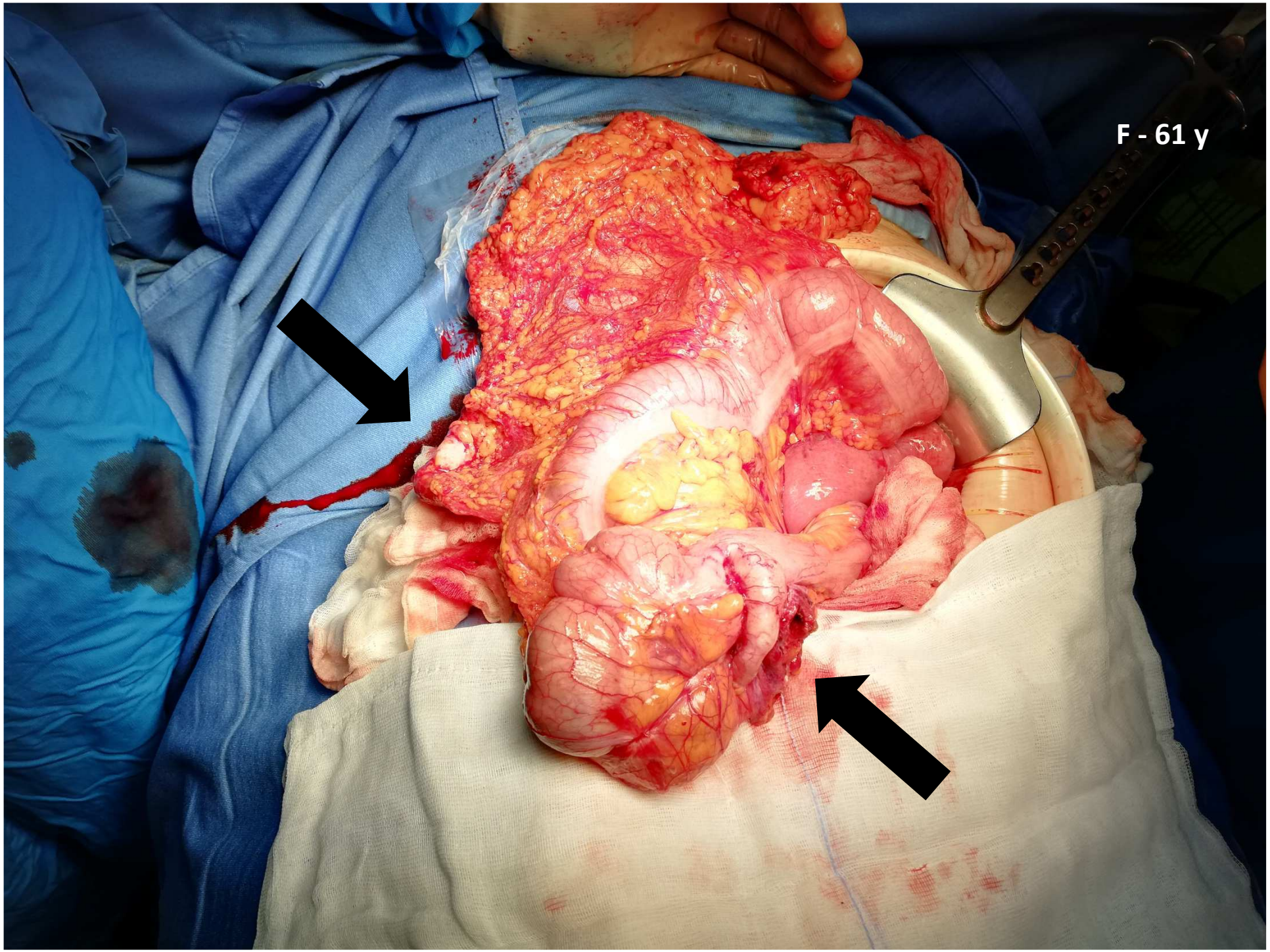


FIG. 2. Recurrence-free survival for patients based upon carcinoid of the rectum risk stratification (CaRRS) scores.

Ann Surg Oncol. 2007 May;14(5):1735-43


F - 61 y

2010 ENETS/WHO nomenclature and classification for neuroendocrine neoplasms arising in the gastrointestinal (GI) tract

Differentiation	Grade	Mitotic count *	Ki-67 index ¶	Traditional	ENETS, WHO
Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3 to 20%	Carcinoid, atypical carcinoid Δ, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, G3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, G3, large cell

ENETS: European Neuroendocrine Tumor Society; WHO: World Health Organization; HPF: high-power fields.

* Counted in 10 HPF; 10 HPF = 2 mm^2, at least 40 fields (at 400x magnification) evaluated in areas of highest mitotic density. Cut-offs per American Joint Commission on Cancer Staging Manual, 8th edition.

¶ Ki-67 index as assessed by MIB1 antibody staining: percent positive after count of 2000 cells in area of highest nuclear labeling. Cut-offs per American Joint Commission on Cancer Staging Manual, 8th edition.

Δ The term "atypical carcinoid" only applies to intermediate-grade neuroendocrine tumors of the lung.

Graphic 60365 Version 14.0