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3rd Annual NorCal Carcinet Community/ UCSF Patient Education Conference

Surgery for NETs

Eric K. Nakakura
Berkeley, CA

January 19, 2014

Surgery for NETs

Overview

- **Surgery**
 - A member of the multidisciplinary team
- **Focus on a very confusing issue in NETs**
 - NETs of Unknown Primary
- **It's not so confusing after all**
- **History and experience have shone us the light**
- **Seeing is believing**



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Neuroendocrine Tumors of Unknown Primary:

*Is the Primary Tumor
Site Really Not Known?*

Eric K. Nakakura
Berkeley, CA

January 19, 2014

NETs of Unknown Primary

What does “unknown primary” mean?

NETs of Unknown Primary

What does “unknown primary” mean?

- **The location where the NET originated is not known.**

NETs of Unknown Primary

What does “unknown primary” mean?

- **The location where the NET originated is not known**
- **Possible primary sites:**
 - **Small intestine (ileum, jejunum, duodenum)**
 - **Pancreas**
 - **Colon/rectum**
 - **Bronchopulmonary**
 - **Stomach...**

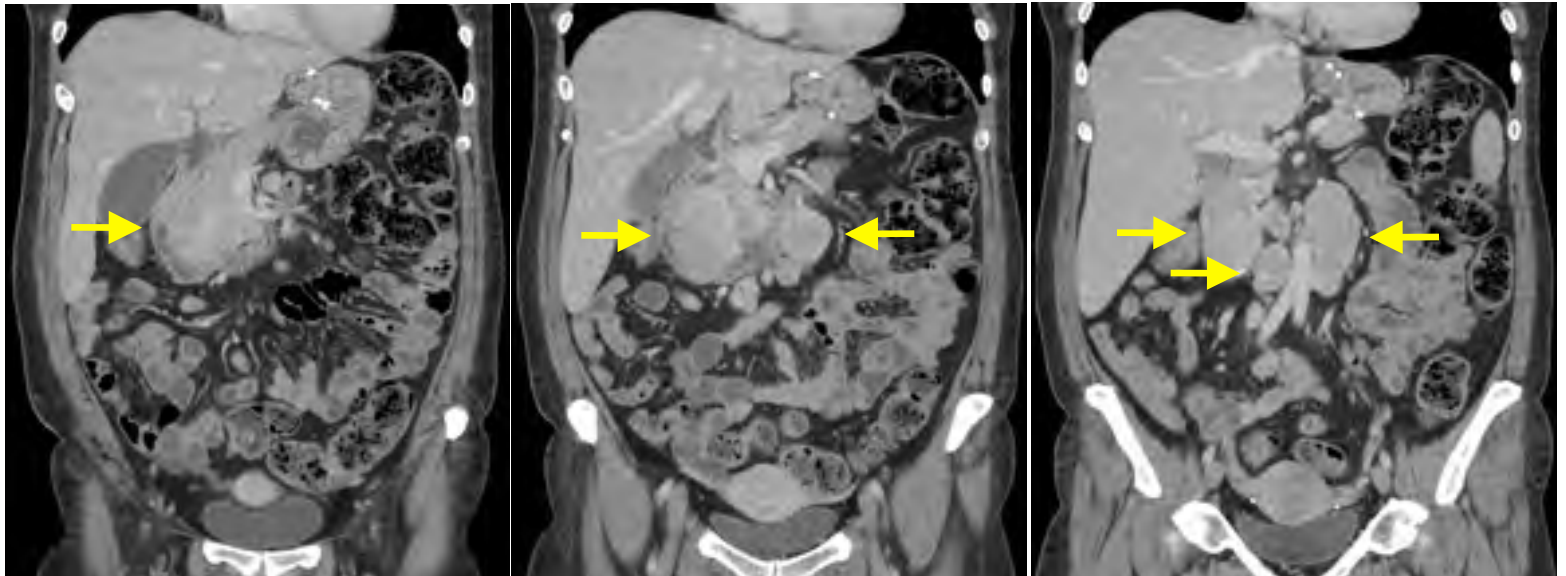
NETs of Unknown Primary

Patient example

- **A 44-year-old obese woman**
- **Underwent a laparoscopic R-Y gastric bypass**
- **Six months later, she developed dull constant right flank pain and lost 60 pounds**

NETs of Unknown Primary

Patient example



- **Retroperitoneal masses**
- **Core needle biopsy: CgA +, Syn +**
- **Well-differentiated NET**
- ***Unknown primary site***

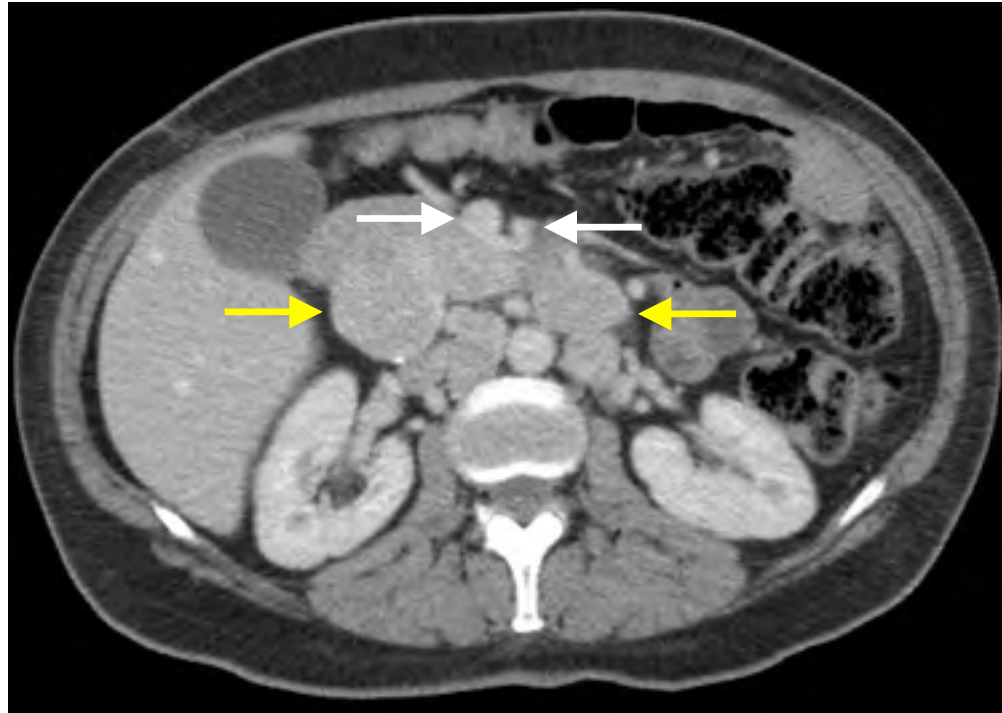
NETs of Unknown Primary

Patient example

- **Is the primary site really unknown?**

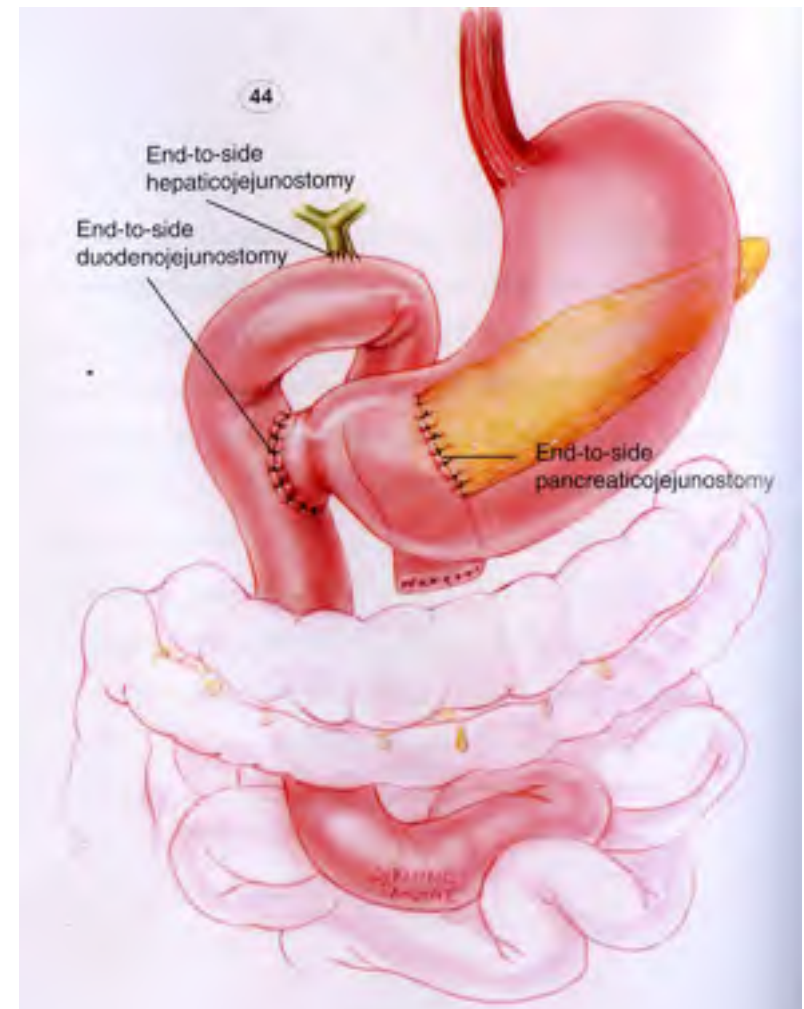
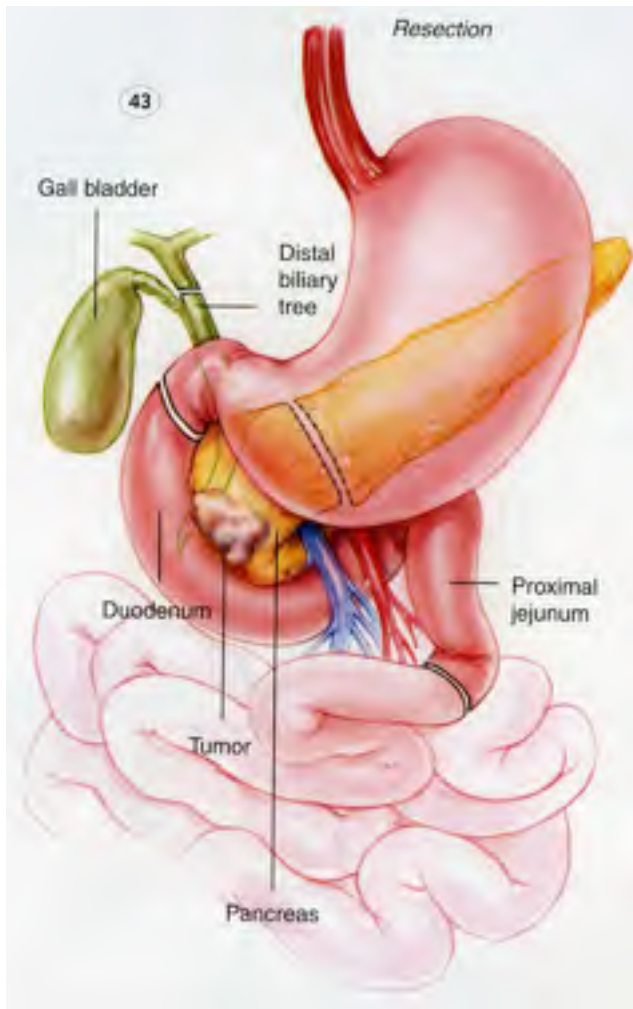
NETs of Unknown Primary

Patient example



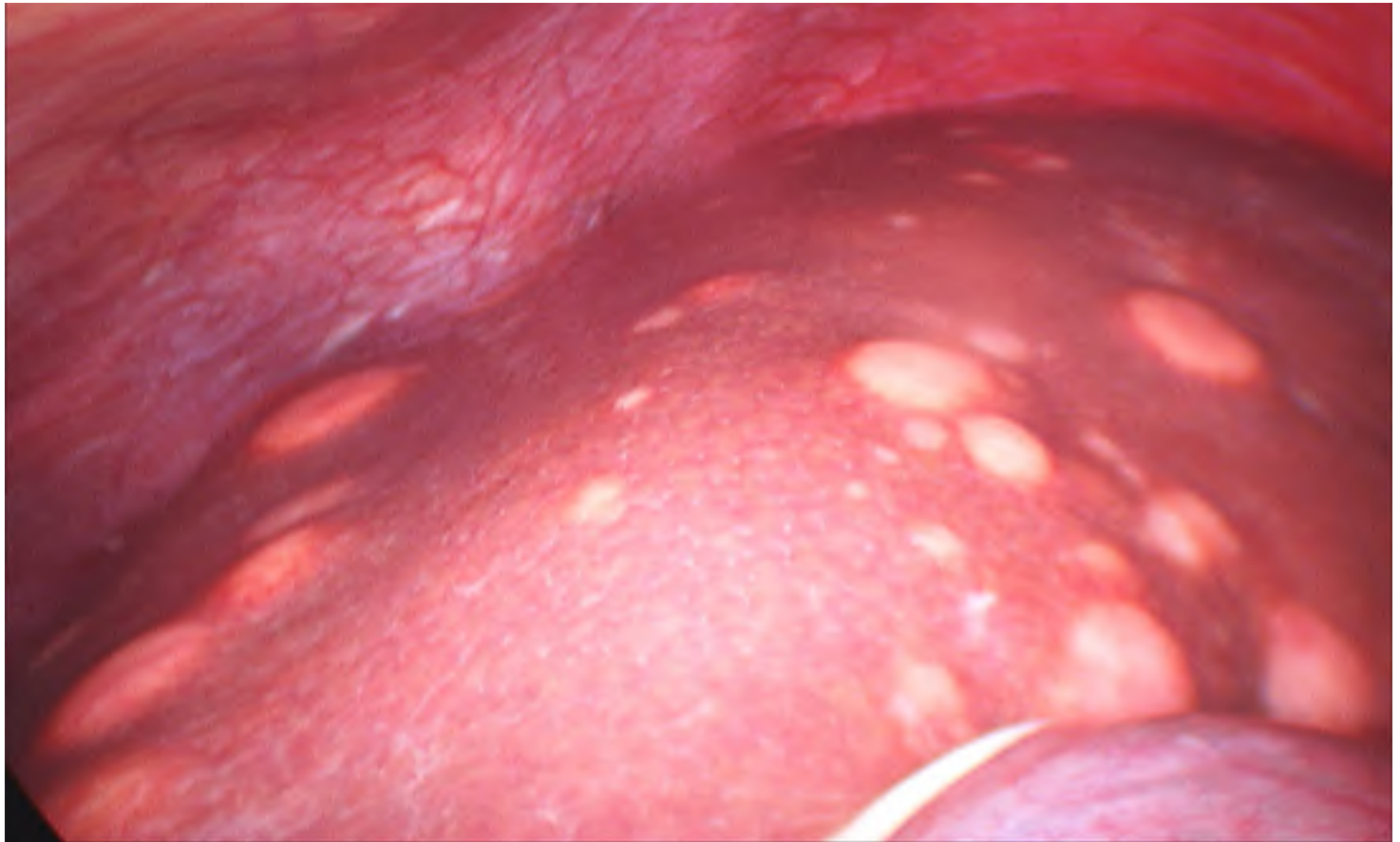
- On our review, there appears to be a primary tumor arising from the pancreas.

Whipple Procedure



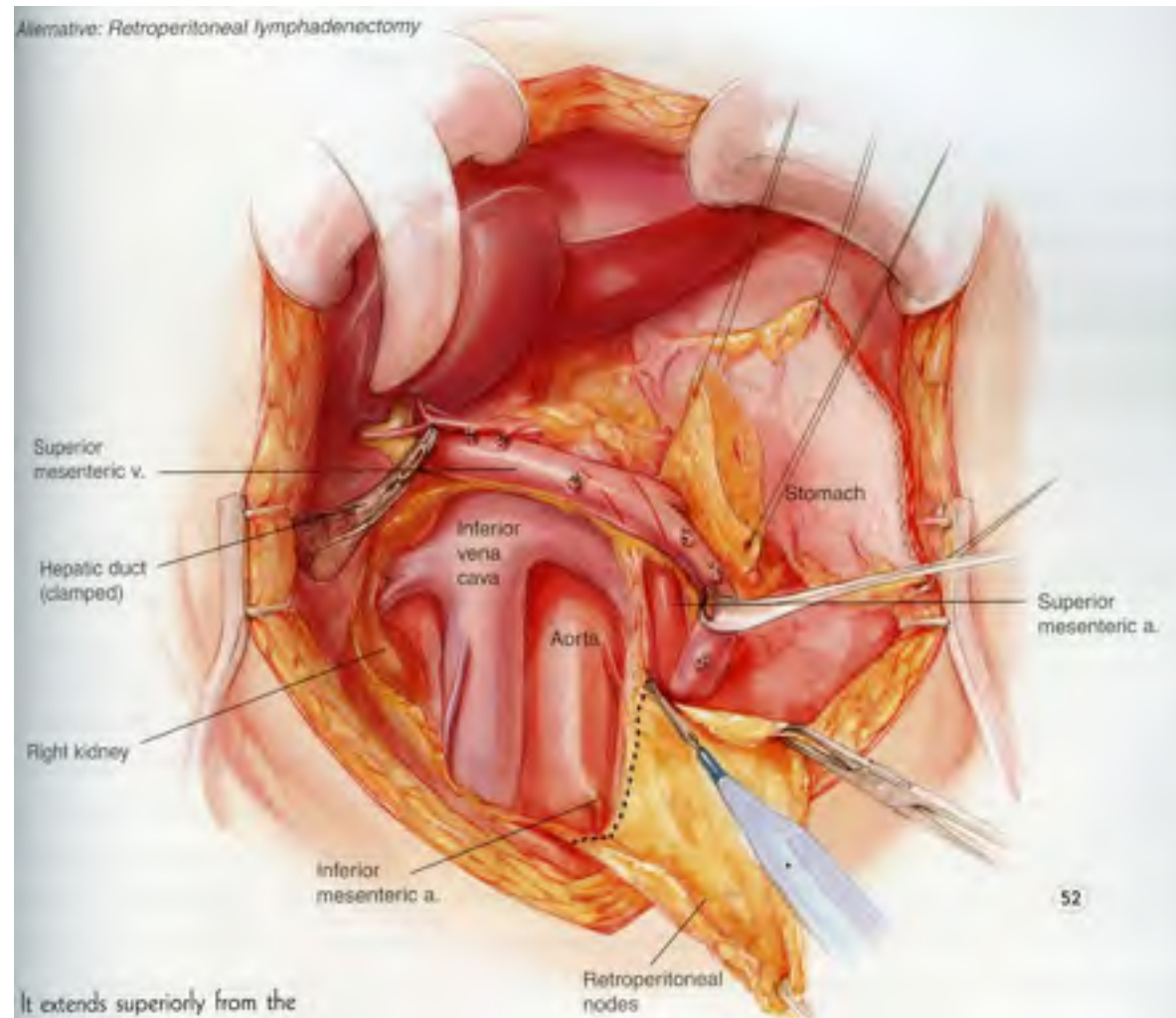
Cameron and Sardone. Atlas of GI Surg 2007.

NETs of Unknown Primary



- **Diffuse, bilobar liver masses**
- ***Where did the tumor originate?***

Retroperitoneal Lymphadenectomy



Cameron and Sardone. Atlas of GI Surg 2007.

NETs of Unknown Primary

Patient example

- **She underwent a Whipple procedure and extensive retroperitoneal lymphadenectomy**
- **all gross disease removed**
- **Pathology: 8 cm, well-differentiated PNET, G1, < 2 mitoses/10 hpf, 47/49 LNs +**

NETs of Unknown Primary

Does finding the primary tumor matter?

NETs of Unknown Primary

Reasons for finding the primary tumor

- **Symptoms**
 - **Abdominal pain, weight loss**
- **Asymptomatic**
 - **Resect the primary as part of surgery to remove all gross disease**
 - **Prevent bowel obstruction**
 - **Prevent ischemia**
 - **Improve outcome?**

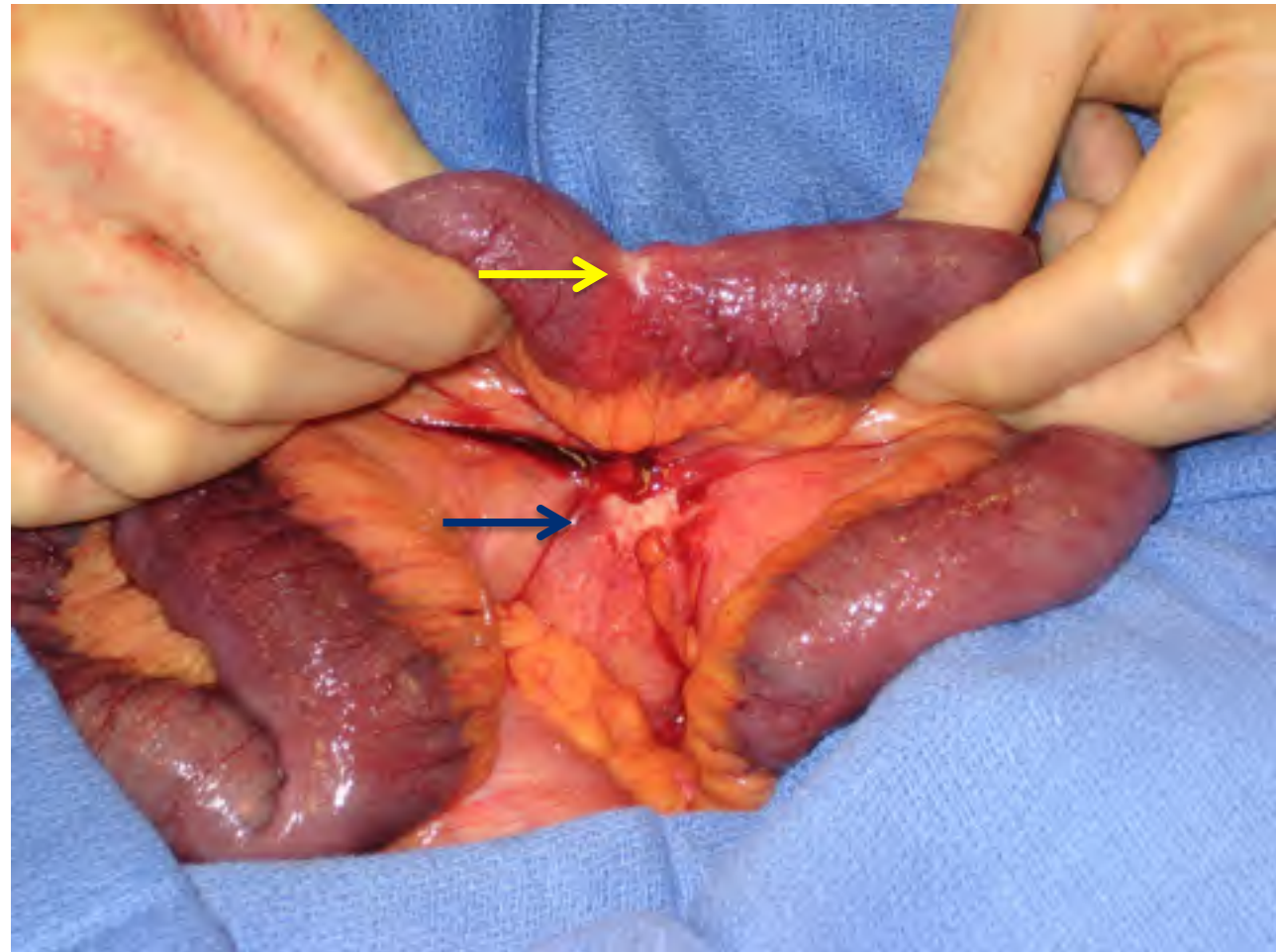
Hellman et al. World J Surg 2002

Boudreaux et al. Ann Surg 2005

Givi et al. Surgery 2006

Small intestine (ileum) NET

Intestinal ischemia



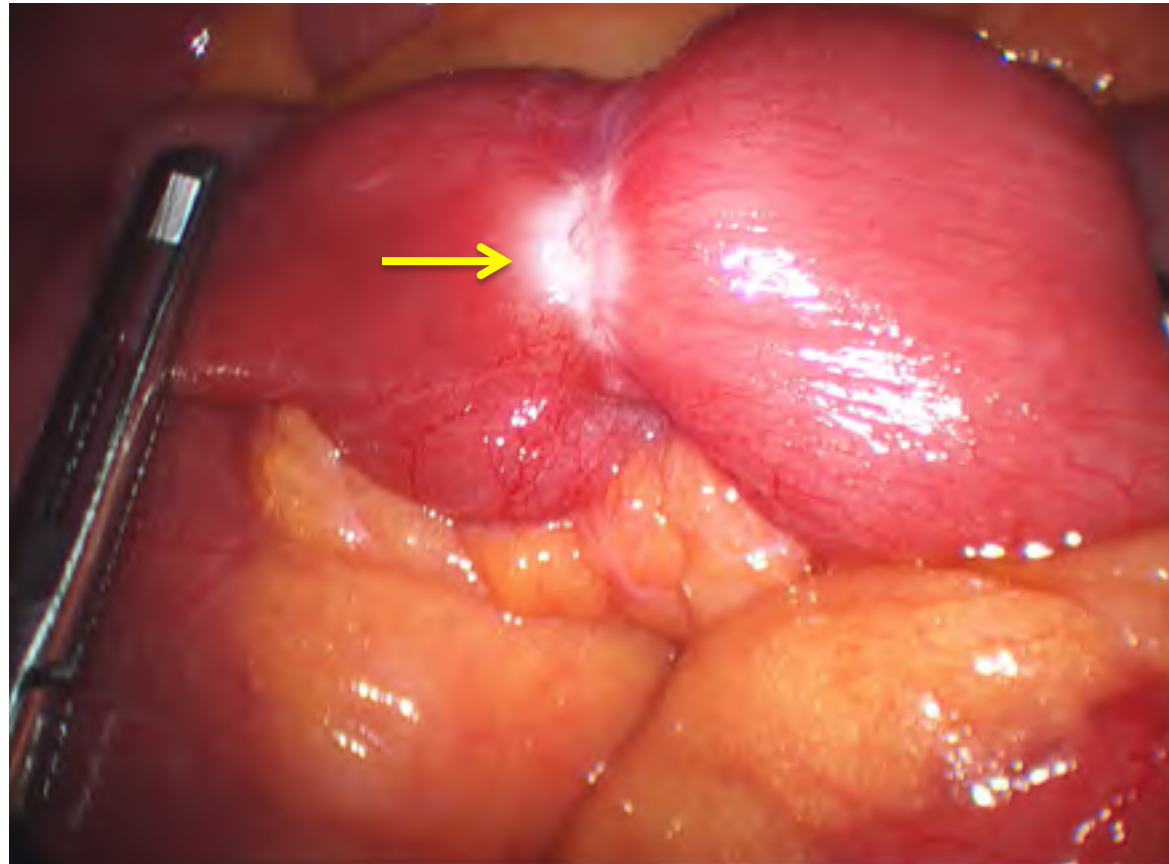
Small intestine (ileum) NET

Intestinal ischemia



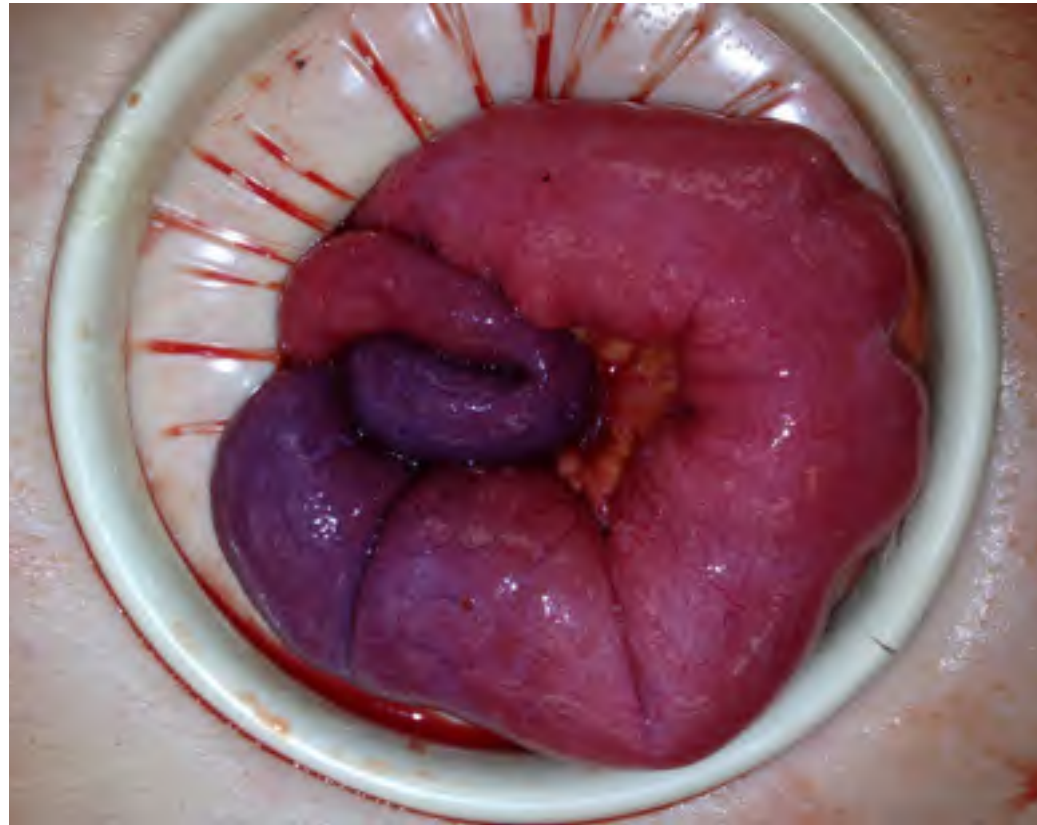
Small intestine (ileum) NET

Intestinal obstruction



Small intestine (ileum) NET

Intestinal ischemia and obstruction



NETs of Unknown Primary

Reasons for finding the primary tumor

- **Treatment increasingly depends on site**
 - **Everolimus, sunitinib for pancreatic NETs**
 - **Octreotide for midgut NETs**
 - **Systemic chemotherapy for pancreatic NETs**
 - **Participation in clinical trials**

NETs of Unknown Primary

What tests should be done to find it?

NETs of Unknown Primary

What tests should be done to find it?

- **Currently, there is no consensus on what minimum tests should be done before the primary site is considered *unknown***

NETs of Unknown Primary

What tests should be done to find it?

- **CT?**
- **MRI?**
- **OctreoScan?**
- **^{68}Ga -DOTA-TATE or ^{68}Ga -DOTA-NOC PET-CT**
- **Upper/lower endoscopy?**
- **Endoscopic ultrasound?**
- **Enteroclysis?**
- **Capsule endoscopy?**
- **Double-balloon enteroscopy?**
- **Gene expression profiling?**

NETs of Unknown Primary

UCSF study

- **Study design: Pathology database (1993-2008)**
- **Setting: UCSF**
- **Patients: 123 patients with NET liver metastases**
- **Outcomes: 1) Detection of primary tumor preop
2) Laparoscopic or open surgery to find and remove an unknown primary tumor**

Wang et al. Arch Surg 2010

NETs of Unknown Primary

UCSF study

Table 2. Sensitivity of Diagnostic Methods for Locating Neuroendocrine Tumors in the Gastrointestinal Tract

Diagnostic Method	No. of Studies	Primary Identified (Sensitivity), No. (%)
Computed tomography	78	27 (34.6)
Magnetic resonance imaging	3	0
Somatostatin receptor scintigraphy	42	11 (26.2)
PET scan	8	2 (25.0)
Upper endoscopy		
Total	21	1 (4.8)
Stomach NET	1	1 (100.0)
Lower endoscopy		
Total	42	20 (47.6)
All colon/ileum NET	33	20 (60.6)
Colon/rectum NET	15	13 (86.7)
Ileum NET	18	7 (38.9)
Capsule endoscopy	1	0
Small-bowel series	1	1 (100.0)
Ultrasonography	3	0

- **Despite extensive evaluation, 13.8% had occult primary tumors.**

NETs of Unknown Primary

Where is the primary site likely to be?

Siegfried Oberndorfer



- 1907: Pathological Institute of Geneva
 - 1) multiple tumors in submucosa of ileum
 - 2) slow growth
 - 3) borders sharply circumscribed
 - 4 (do not metastasize)
- Karzinoide: “carcinoma-like”
- 1929: He recognized potential to metastasize

Modlin et al. Hum Path 2004

Gastrointestinal NETs Epidemiology

Carcinoid site (no islet cell)	(1950-1971) n = 2425 %	(1973-1999) n = 6996 %
Stomach	2.5	7
Small intestine	25	44
Appendix	48	7
Colon	8	13
Rectum	17	24

NETs of Unknown Primary

UCSF study results

- **Primary site found in 13/15 patients (87%) by surgery**
- **All primary tumors in small intestine (12 ileum, 1 jejunum)**
- **Primary tumors small (1.4 cm) and often multifocal (54%)**
- **Careful palpation of small intestine is essential**

NETs of Unknown Primary

Multicenter results

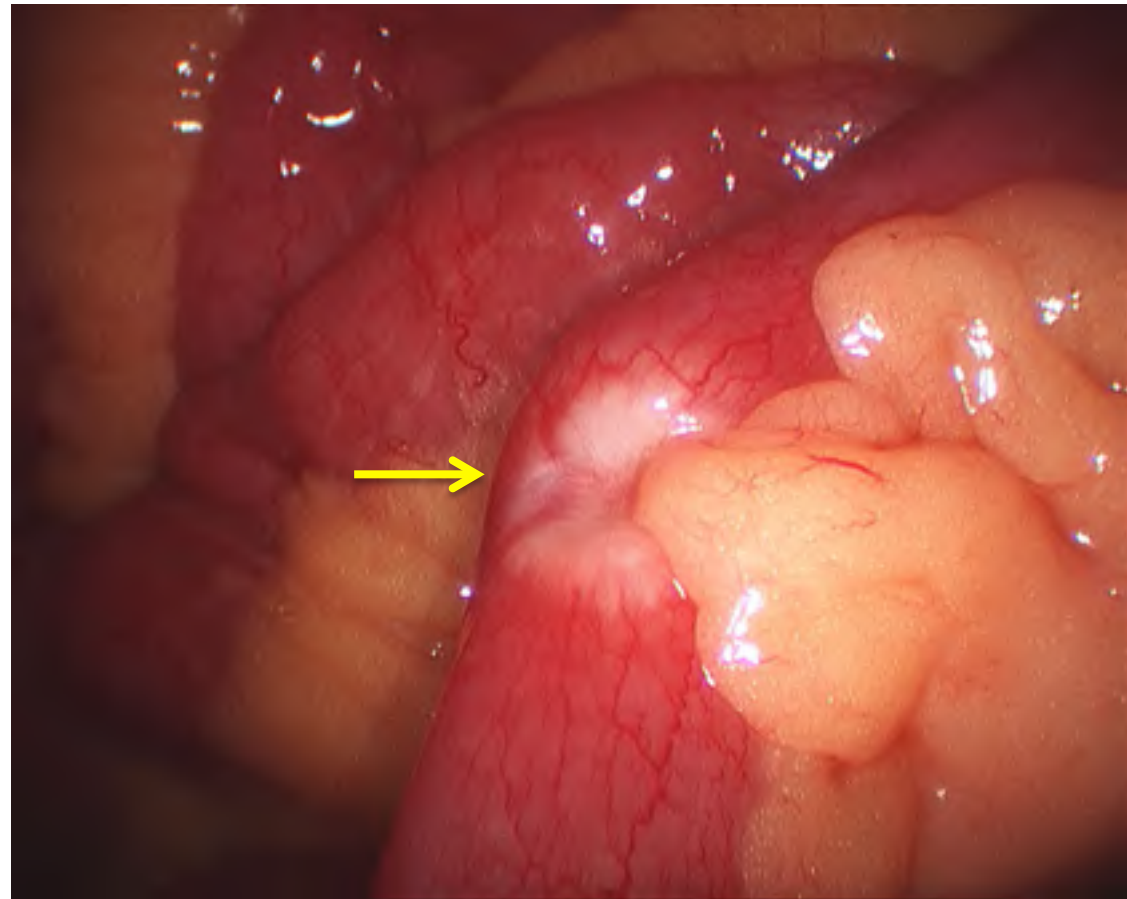
Table 1. Success of Identifying the Primary Tumor by Surgical Exploration

Institution	Year	No. of Unknown Primary	Primary Identified No. (%)	Location of Primary
Louisiana State University Health Sciences Center	2005	22	17 (77.3)	Not specified
University of California San Francisco	2010	15	13 (86.7)	12 ileum, 1 jejunum
Oregon Health and Science University	2012	52	39 (75.0)	Most in small intestine
University of Pennsylvania	2013	28	25 (89.3)	10 terminal ileum, 12 other small intestine
Louisiana State University Health Sciences Center	2013	26	26 (100.0)	23 ileum, 3 pancreas
Total		143	120 (83.9)	

~ 84% success in finding primary

NETs of Unknown Primary

Laparoscopic identification of tumor in ileum



Wang et al. Arch Surg 2010

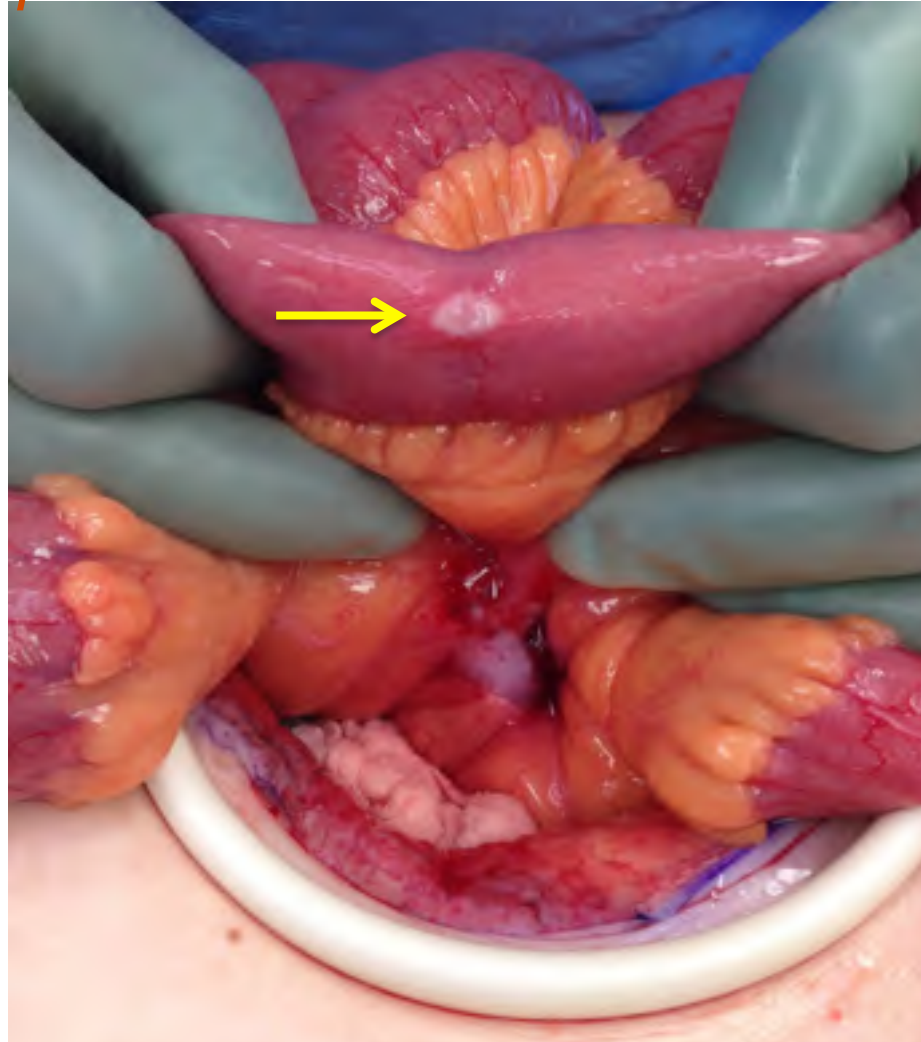
Karnovsky Memorial Lecture

An Odyssey in the Land of Small Tumors

- **Small intestine NETs**
 - Most (193/209; 92%) arise from ileum
 - Multifocal (46/183; 25%)
- **Primary tumors small, deep mucosal site of origin**
- **Nature of spread**
 - First invades muscle layer → serosa → mesentery (outward spread)
- **Nature of obstruction**
 - Fibroblastic reaction in mesentery → buckling of bowel wall → kinking of bowel wall (like an accordion)

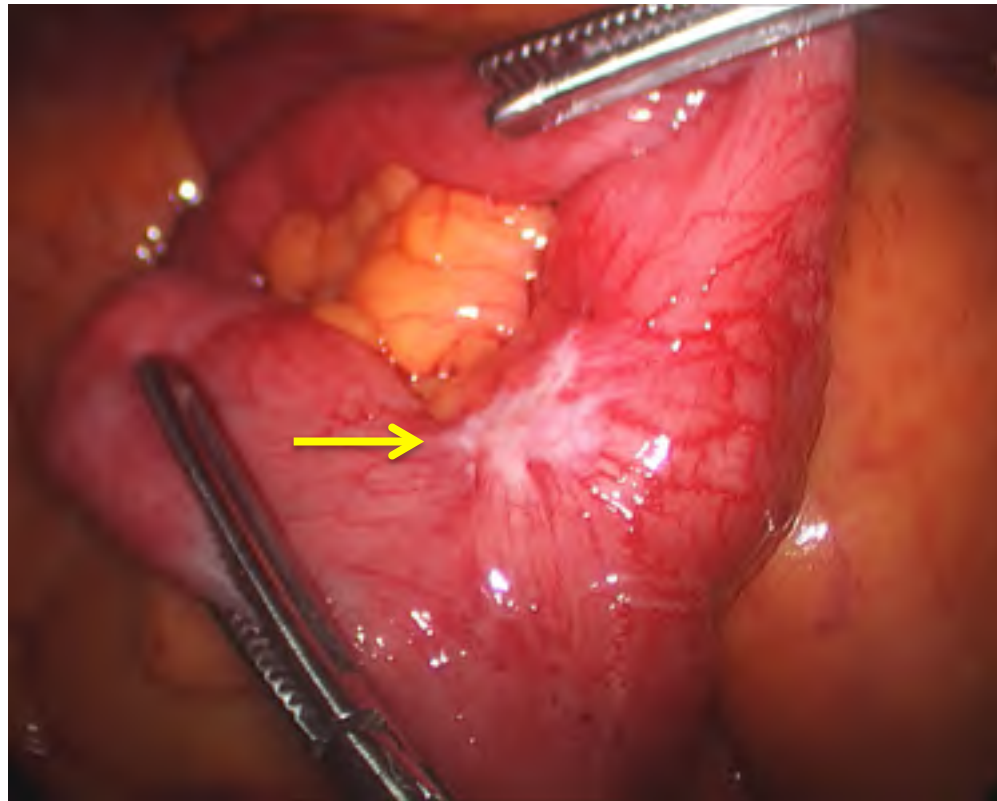
NETs of Unknown Primary

Laparoscopic identification of tumor in ileum



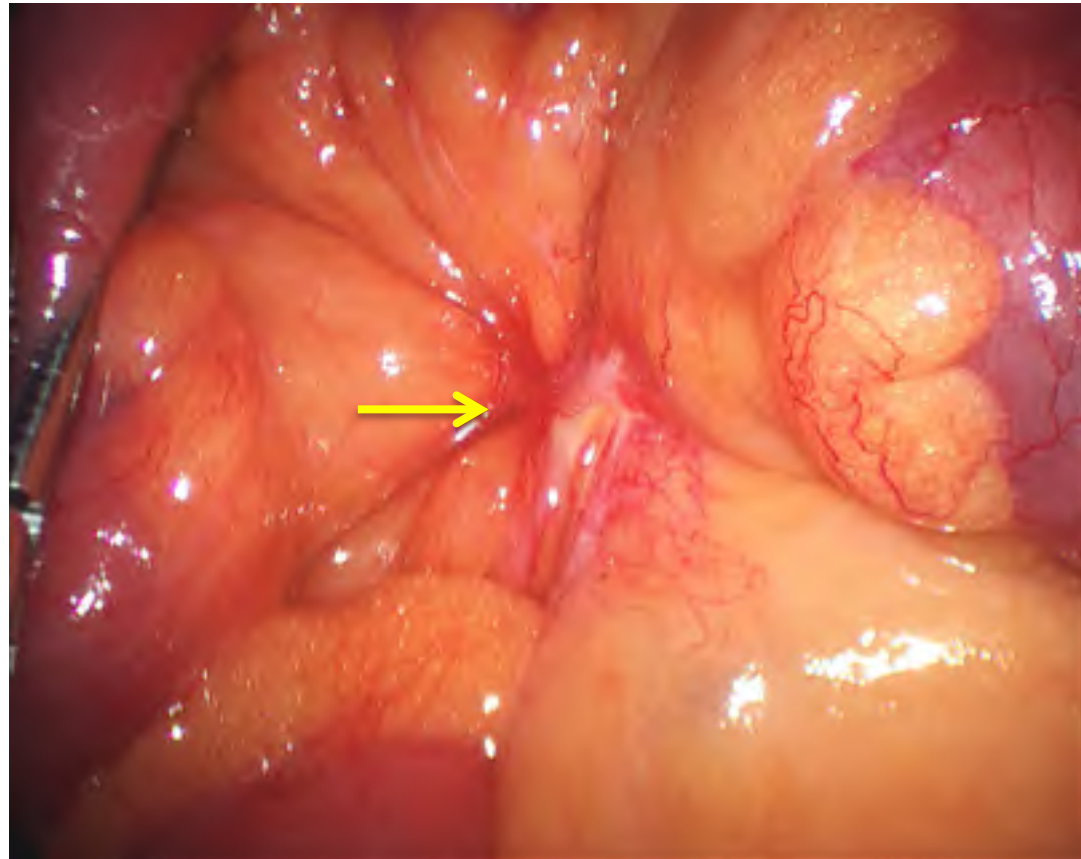
NETs of Unknown Primary

Laparoscopic identification of tumor in ileum with Meckel's diverticulum



NETs of Unknown Primary

Laparoscopic identification of tumor in ileum with regional adenopathy



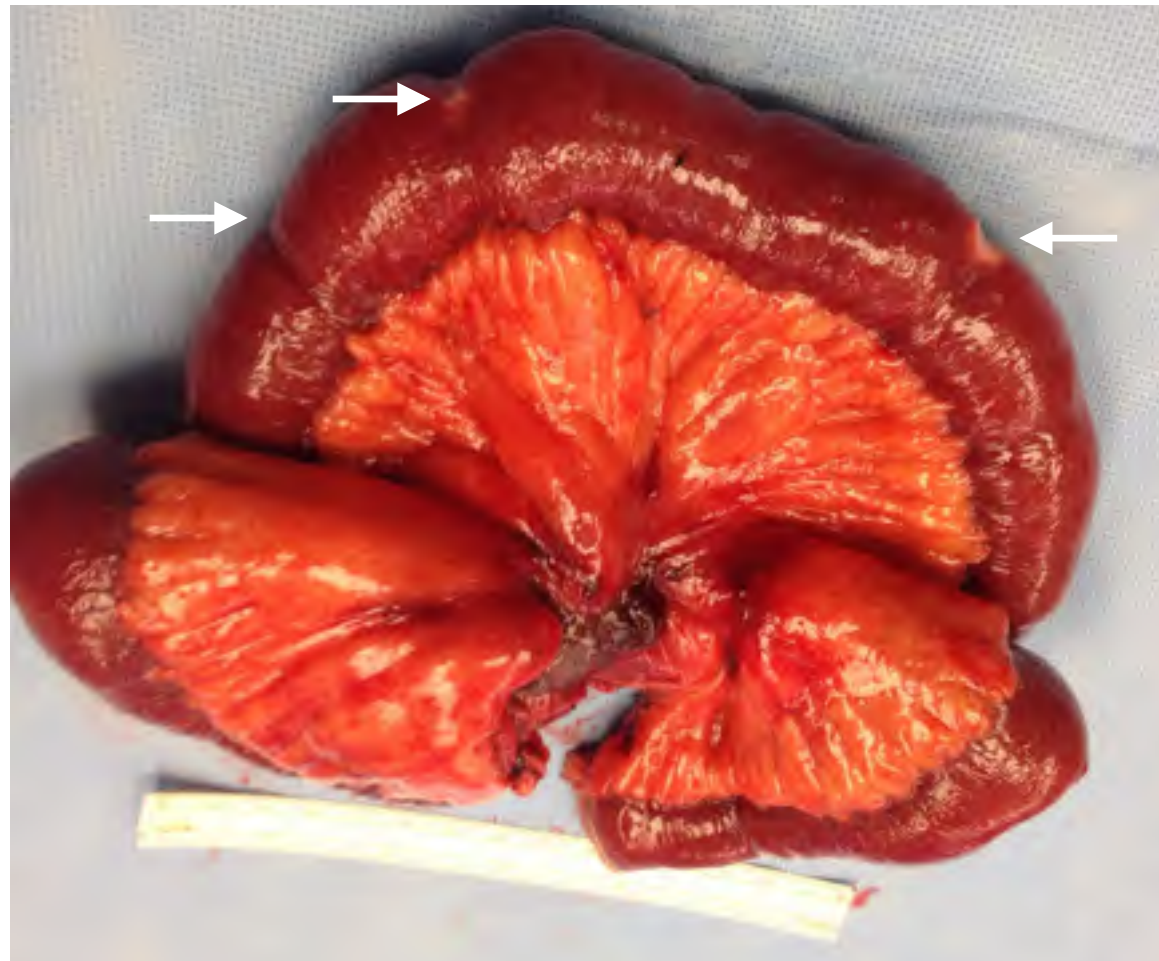
NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum



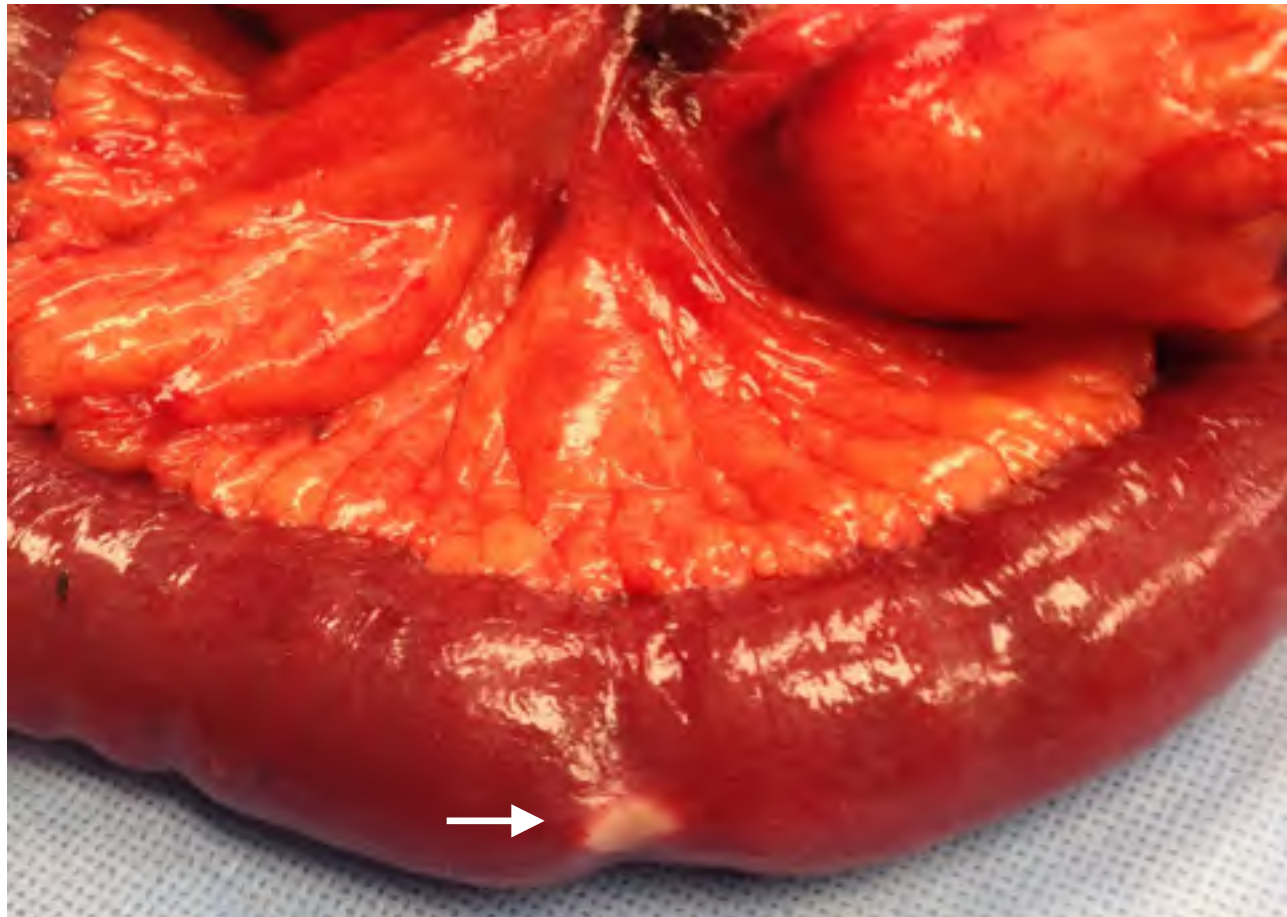
NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum



NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum



NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum (#2)



NETs of Unknown Primary

Multifocal primary tumors (N = 11) in ileum (#2)



NETs of Unknown Primary

What tests should be done to find it?

- **CT scan: chest, abdomen/pelvis (multiphase, thin slice)**
- **Somatostatin receptor scintigraphy (OctreoScan)**
- **Urine 24-h 5-HIAA**
- **Upper and lower endoscopy**
- **Immunohistochemical markers (TTF-1, CDX2, PAX8, Islet 1)**
- **Careful review by multidisciplinary team**

Finding the Primary Tumor

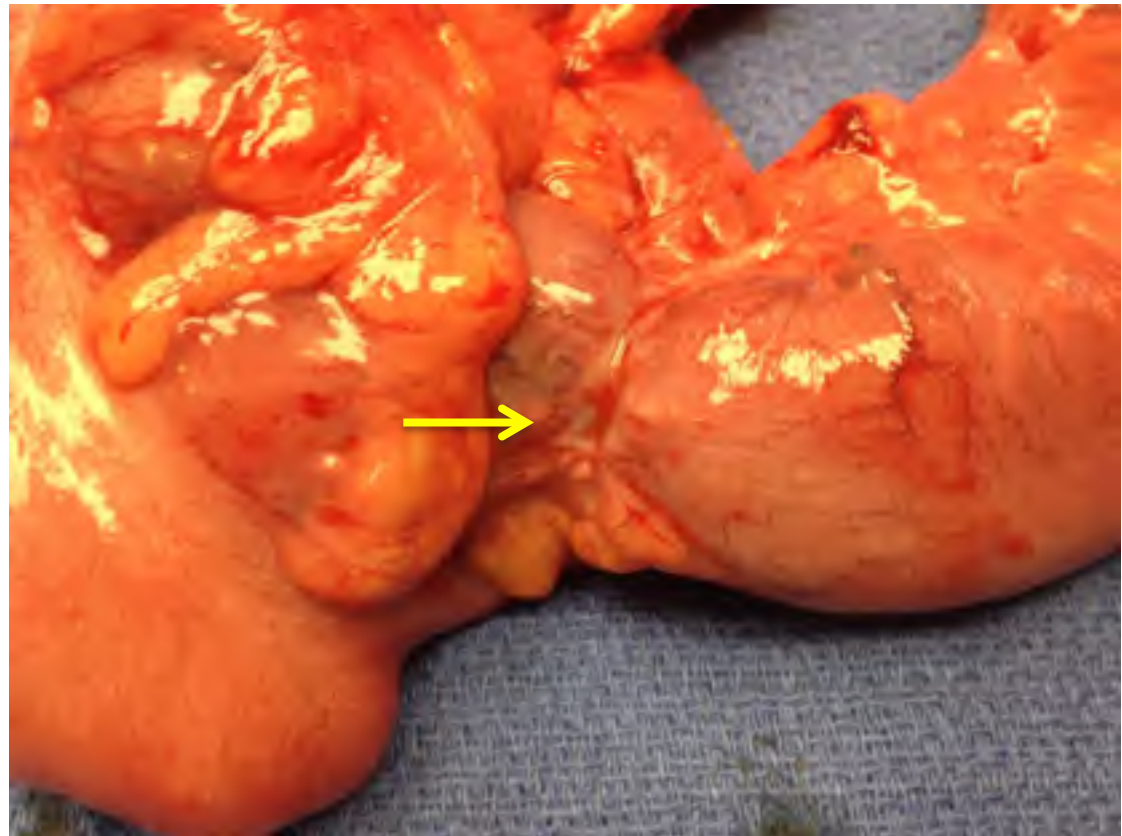
Potentially seen on colonoscopy



- **WDNET** of the terminal ileum.

Finding the Primary Tumor

Potentially seen on colonoscopy



- **WDNET** of the terminal ileum.

NETs of Unknown Primary

Take home points

- For most patients with WDNETs and *unknown primary* the primary site is most likely in the small intestine, in particular, the ileum
- If surgery planned, appropriate preoperative tests should be done
- Many other tests (enteroclysis, capsule endoscopy, double-balloon enteroscopy, and endoscopic ultrasound) unnecessary since will not affect patient care and only delay treatment
- Multidisciplinary assessment essential

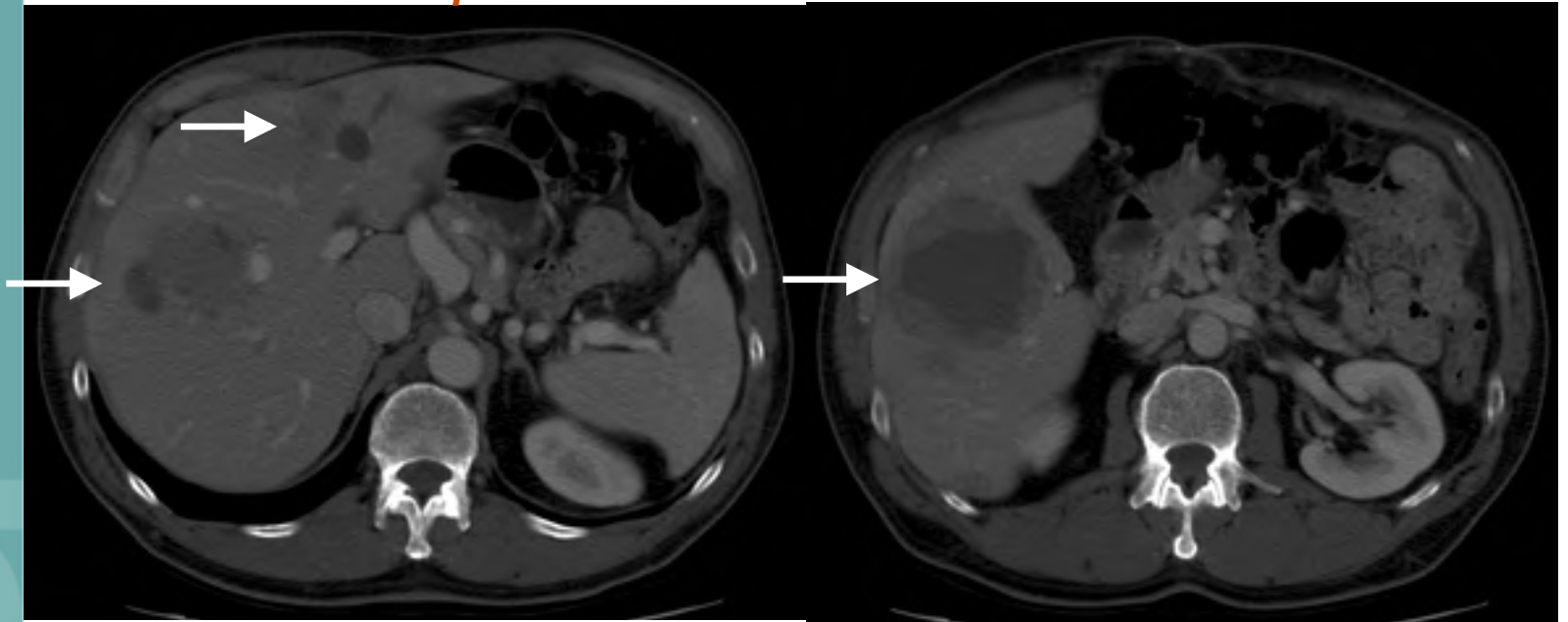
NETs of Unknown Primary

Patient example

- **A 60-year-old man**
- **Fall 2008: abdominal pain**
- **Evaluated at a local hospital**

NETs of Unknown Primary

Patient example



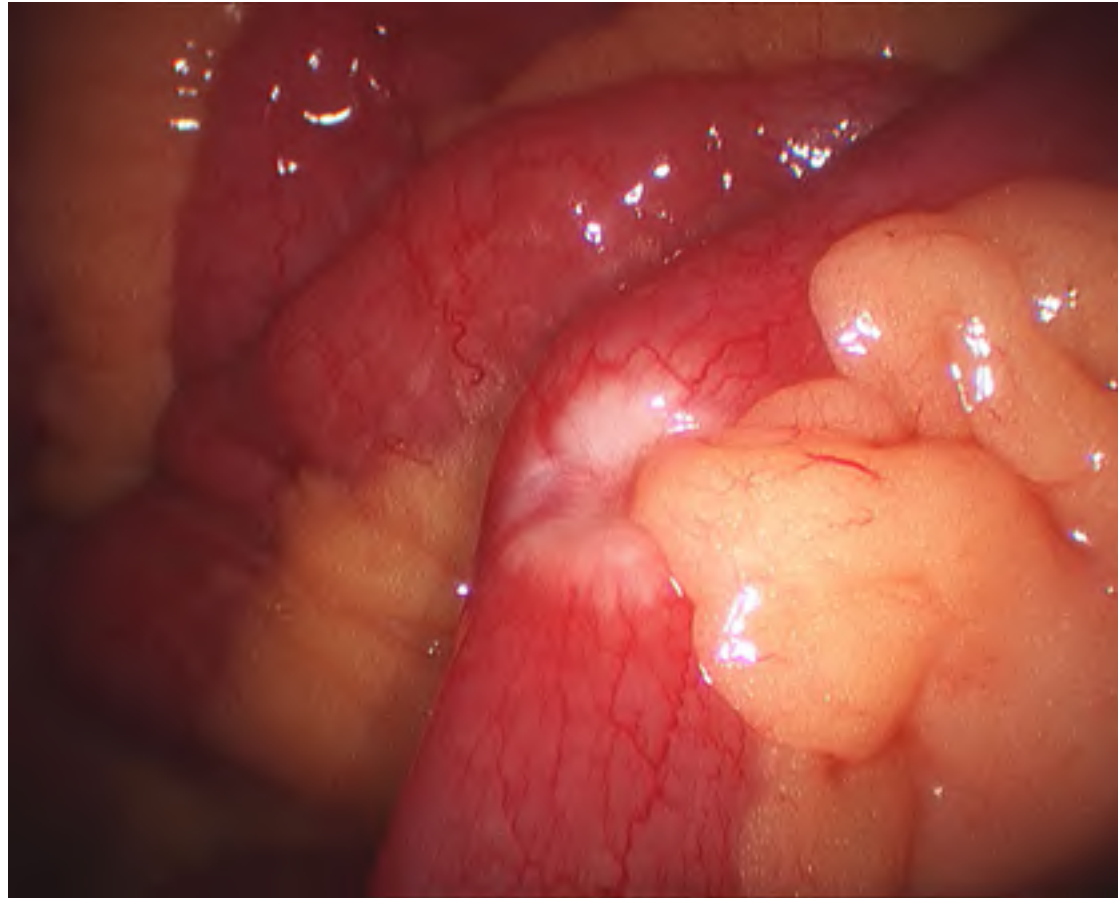
- **Bilobar liver masses**
- **Core needle biopsy: CgA +, Syn +**
- **Well-differentiated NET**
- ***Unknown primary site***

NETs of Unknown Primary

Patient example

- A 60-year-old man with NET liver metastases and unknown primary
- Fall 2008: Started Sandostatin
- Patient informed his disease was inoperable
- UCSF for second opinion by multidisciplinary GI oncology group

NETs of Unknown Primary



- Winter 2008:
- **Laparoscopic identification and resection of ileum primary tumor**

Wang et al. Arch Surg 2010

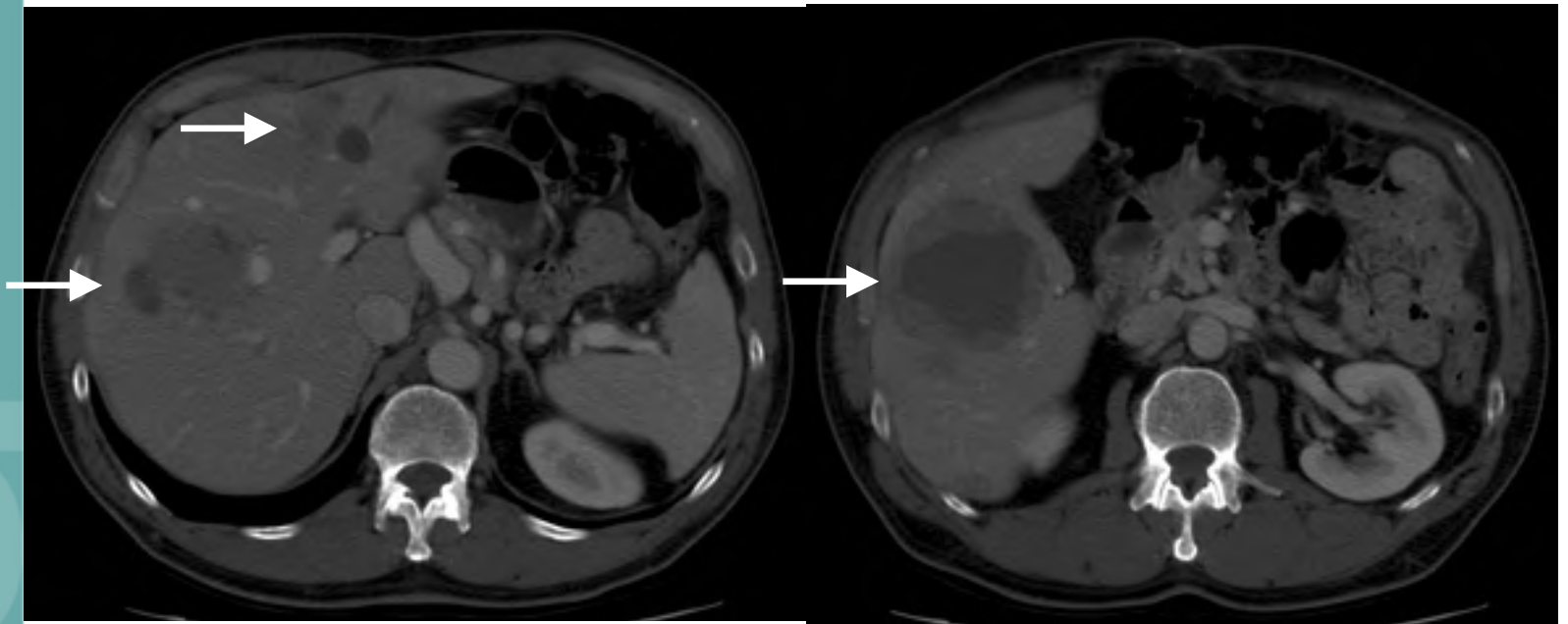
NETs of Unknown Primary

Patient example

- A 60-year-old man with NET liver metastases and unknown primary
- Fall 2008: Started Sandostatin
- Winter 2008: Primary found and removed
- Fall 2009: Carcinoid syndrome
Liver metastases stable

NETs of Unknown Primary

Patient example



- Winter 2009:
- Right hepatectomy and microwave ablation of two left lobe tumors
- Carcinoid syndrome resolved

NETs of Unknown Primary

Patient example

- A 60-year-old man with NET liver metastases and unknown primary
- Fall 2008: Started Sandostatin
- Winter 2008: Primary found and removed
- Winter 2009: Resection/ablation of liver mets
- Jan. 2014: No evidence of disease

NETs of Unknown Primary



NET(s) arising from the ileum



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