

Update on Surgical Management of NETs

Update on Surgical Management of Neuroendocrine Tumors

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Distribution of NETs 2000-2004

Primary tumor site	Relative frequency	Percentage
Lung	1.35	27%
Thymus	0.02	---
Stomach	0.30	6%
Duodenum	0.19	4%
Jejunum/Ileum	0.67	13%
Cecum	0.16	3%
Appendix	0.15	3%
Colon	0.20	4%
Rectum	0.86	17%
Pancreas	0.32	6%
Liver	0.04	1%
Other/unknown	0.74	15%

Yao et al. J. Clin. Oncology 26:3063, 2008

Stage at Diagnosis

SEER vs. University of Iowa

Primary tumor site	Localized	Regional	Distant
Lung	49	23	28
Thymus	28	41	31
Stomach	76	9	15
Duodenum	81	10	9
Jejunum/Ileum	29	85% nodes	77% liver
Cecum	14	42	44
Appendix	60	28	12
Colon	45	23	32
Rectum	92	4	5
Pancreas	14	51% nodes	37% liver
Liver	45	27	28

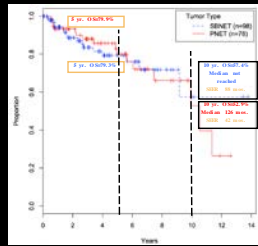
Yao et al. J. Clin. Oncology 26:3063, 2008

Median Survival by Site

Color	Site	Localized	Regional	Distant
Appendix	>360	>360	27	
Cecum	135	107	41	
Colon	261	36	5	
Duodenum	107	101	57	
Gastric	154	71	13	
Liver	50	14	12	
Lung	227	154	16	
Pancreas	136	77	24	
Rectum	290	90	22	
Small bowel	111	105	56	
Thymus	110	68	40	

Yao et al. J. Clin. Oncology 26:3063, 2008

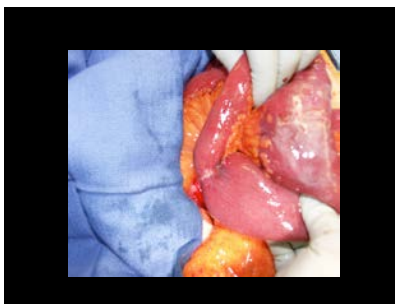
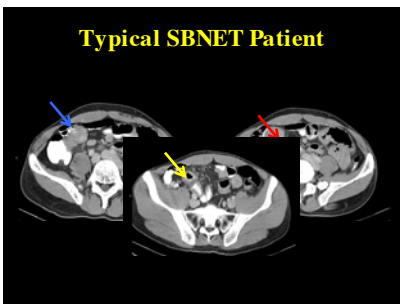
Overall Survival



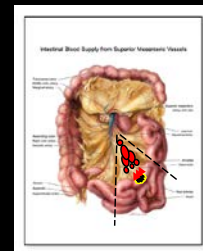
Small Bowel Primaries (SBNETs)

- Most common GI site
- Incidence 7 per million
- 30% multicentric
- Well-differentiated
- Indolent but present late

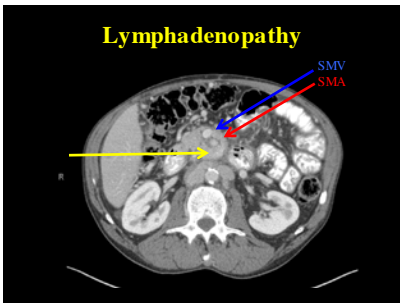
Typical SBNET Patient



Resecting Mesentery



Update on Surgical Management of NETs



Benefits to Resection of Primary

- Prevents future metastases
- Prevents obstruction
- Prevents bleeding
- Prevents peritoneal seeding
- May reduce hormone levels
- Improves Survival

Cholecystectomy at Exploration

- Eliminates problems of biliary colic or gallstones
- Prevents GB necrosis after hepatic embolization

SBNETs with Liver Metastases:

Does Resection of the Primary Improve Symptoms?

Progression of Metastases and Symptom Improvement from Laparotomy in Midgut Carcinoid Tumors

Charlie Makridis, M.D.,¹ Jonas Rastad, M.D.,² Kjell Öberg, M.D.,³ Göran Åkerström, M.D.³

- Uppsala Study 1996
- ◆ 121 pts. with midgut carcinoids
- ◆ 93% with mets
- ◆ 158 laparotomies in 107 pts.

Makridis et al. World J. Surg. 20:900,1996

Resection for Symptom Control

Table 2. Frequency of symptoms at study inclusion in patients with (n = 50) or without (n = 63) resected primaries.

Symptoms	Frequency (%)	
	Carcinoid resected	Without evidence
Diarrhea	43	15
Flush	36	6
Dyspepsia, palpitation	26	14
Nonrecumbent	41	14
Abdominal pain	26	3
Weight loss	23	3
Fever	50	52
Hypertensive/lower abdominal mass	5	52
Acute abdominal episode	5	52

Table 4. Symptom response rates to primary operation and rate response to octreotide and elective procedures for midgut carcinoid tumors.

Response	Primary operation		First reoperation		All operations (n = 129)
	Acute (n = 54)	Elective (n = 49)	Acute (n = 23)	Elective (n = 30)	
Complete (%)	85	53	52	60	54
Partial (%)	4	28	24	30	18
None (%)	4	27	24	30	18

Makridis et al. World J. Surg. 20:900,1996

The palliative benefit of aggressive surgical intervention for both hepatic and mesenteric metastases from neuroendocrine tumors

Stephen J. Chambers, MB, FRACS^{1,2,3,4}, Justin J. Parake, MB, FRACS, FRCS^{1,2,3,4}

1. St. Vincent's Hospital, Sydney, NSW, Australia; 2. St. George's Hospital, Sydney, NSW, Australia; 3. St. George's Hospital, Sydney, NSW, Australia; 4. St. George's Hospital, Sydney, NSW, Australia

- Calgary Study 2008
- ◆ 66 pts. with Sx and GI NETs
- ◆ 52% mesenteric masses, 77% liver
- ◆ Primary and nodes removed in 45, debulked in 8
- ◆ Complete relief of obstruction, ischemia, 75% carcinoid syndrome

Chambers et al. Surgery 144:645,2008

Resection of the primary tumor improves symptoms *in the majority of patients*

SBNETs with Liver Metastases:

Does Resection of the Primary Improve Survival?

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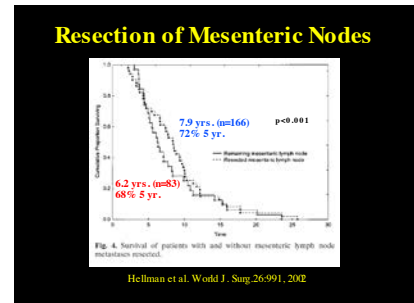
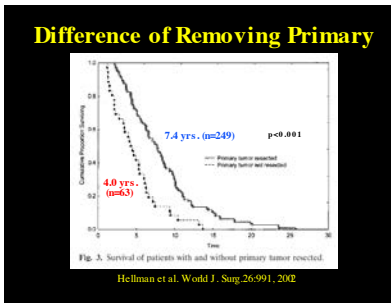
Effect of Surgery on the Outcome of Midgut Carcinoid Disease with Lymph Node and Liver Metastases

Per Hellman, M.D., Ph.D.,¹ Tobias Lindström, M.D.,¹ Ulf Östervik, M.D., Ph.D.,² Barbro Eriksson, M.D., Ph.D.,³ Britt Skjerve, M.D., Ph.D.,⁴ Kjell Öberg, M.D., Ph.D.,⁵ Eva Teunen-Jaana, M.D., Ph.D.,⁶ Göran Akerman, M.D., Ph.D.⁷

Department of Surgery, University Hospital, SE-761 08 Örebro, Sweden

- 314 pts. with midgut carcinoids
- 262 explored, 52 not explored
- 91% nodal, 81% liver mets
- Primary resected in 249 (of 262)
- Primary and LNs removed in 166

Hellman et al. World J. Surg. 26:991, 2002

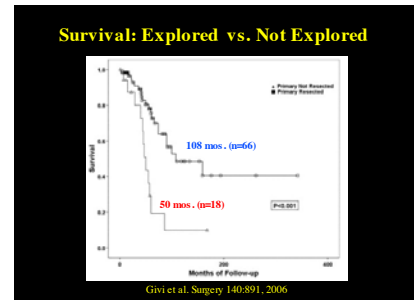
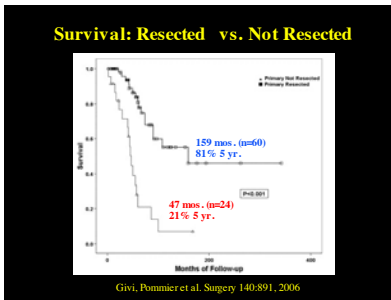


Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival

Rahab Givi, MD,¹ Saïden J. Pommier, PhD,² Abira K. Thompson, MD,³ Brian S. Diggs, PhD,⁴ and Rodney F. Pommier, MD,⁵ *Portland, Ore.*

- Patients with unresectable carcinoid liver mets.
- 84 pts.
- 60 resected, 24 not
- Similar groups

Givi et al. Surgery 140:891, 2006



OHSU Conclusions

- Resection of primary beneficial
- Due to difference in PFS
- Not selection bias
- Removal of metastatic source
- Decrease in circulating amines
- Deprivation of growth factors for liver tumors

Midgut neuroendocrine tumours with liver metastases: results of the UKINETS study

A Ahmed^{1,2}, G Turner³, B King⁴, L Jones⁵, D Culliford⁶, D McCance⁷, J Ardill⁸, B T Johnston⁹, G Poston¹⁰, M Rees¹¹, M Buxton-Thomas¹², M Caplin¹³ and J K Flanagan¹⁴

- 5 centers in UK/Ireland
- Pts with SBNETS/Liver mets
- 360 pts., 209 resected
- 12 bypassed, 17 unresectable, 80 not explored

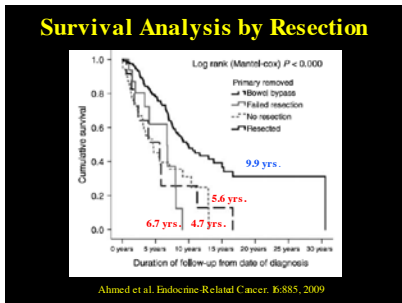
Ahmed et al. Endocrine-Related Cancer. 6:885, 2009

Multivariate Analysis

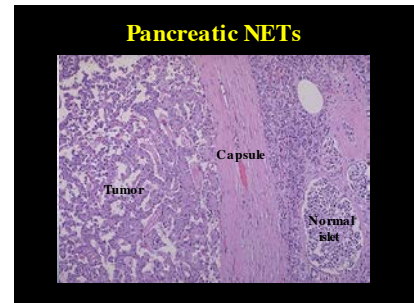
Variable	Relative risk (95% CI)	P
Age at diagnosis	1.07 (1.015–1.146)	0.014
Ki67	1.04 (1.002–1.086)	0.039
Resection of primary	0.26 (0.092–0.777)	0.015
Urinary HIAA	1.00 (1.000–1.001)	0.236
Serum chromogranin A	1.00 (0.998–1.002)	0.923
Hepatic resection	Unable to calculate	0.988
Peptide receptor therapy	0.63 (0.227–1.793)	0.340
Somatostatin analogue therapy	0.41 (0.045–3.737)	0.478

Ahmed et al. Endocrine-Related Cancer. 6:885, 2009

Update on Surgical Management of NETs



Resection of the primary tumor improves patient survival

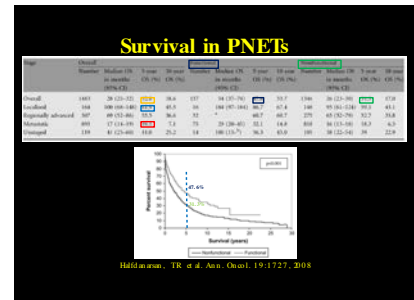


- ### Pancreatic NETs
- Non-functional
 - Insulinoma
 - Gastrinoma
 - VIPoma
 - Glucagonoma
 - Somatostatinoma
 - PPoma

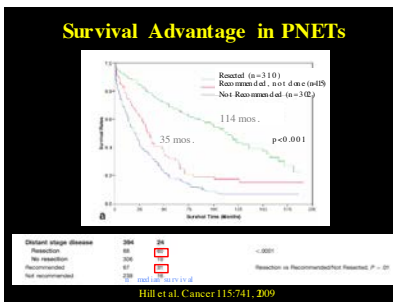
General Facts About PNETs

Characteristic	Value
Age (yr) patients	48.5 (16-85)
Sex	50% M, 50% F
Race	95% W, 5% B
Site	90% P, 10% D
Grade	60% G1, 40% G2, 0% G3
Size (cm)	2.5 (0.5-10)
Number of patients	1000
Number of sites	1000
Number of sites per patient	1.0
Number of sites per site	1.0
Number of sites per patient per site	1.0
Number of sites per patient per site per patient	1.0

Hall et al. Ann. Oncol. 19:1727, 2008

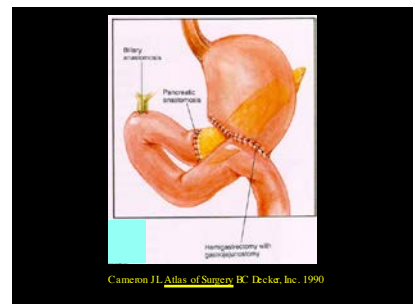
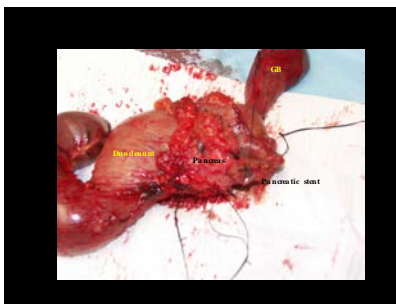
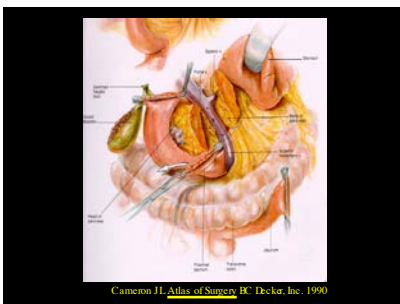
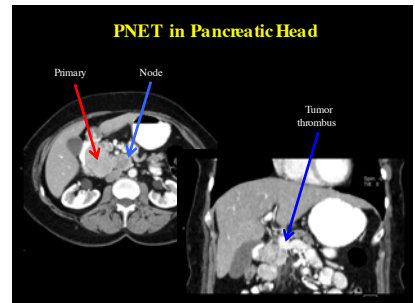
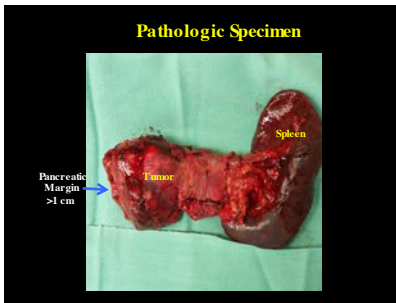
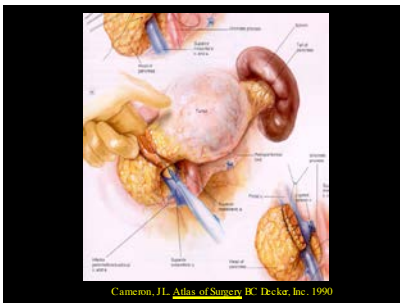
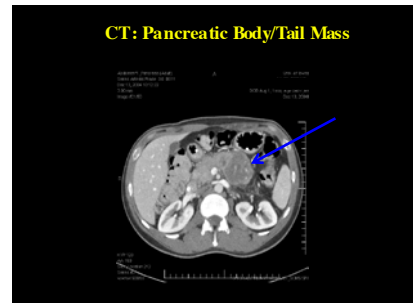
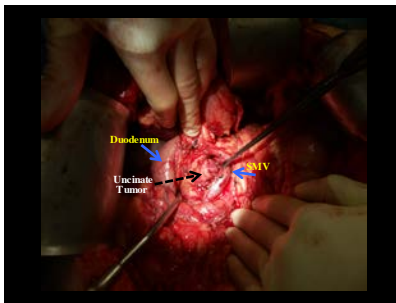
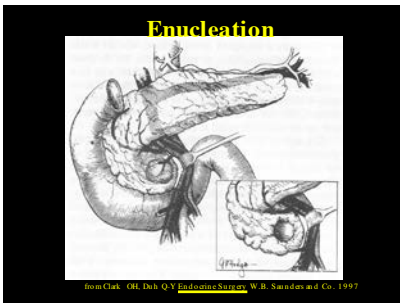


- ### When to Resect Pancreatic Primary
- Functional lesions
 - >2 cm
 - Not < 1 cm
 - Controversy in 1-2 cm¹⁻³
 - Not high grade, unless isolated
 - >2 cm in MEN1⁴
 - >3 cm in VHL⁵
1. LC. Lee et al. Surgery 152:965, 2012
 2. EJ. Kuo et al. Ann. Surg. Onc. 20:2815, 2013
 3. S.M. Sharpe et al. J. Gastrointest. Surg. 19:117, 2015
 4. F. Taponez et al. Ann. Surg. 243:26, 2006
 5. S.K. Libutti et al. Surgery 124:1153, 1998



- ### Surgical Treatment Options
- Enucleation
 - Distal Pancreatectomy
 - Pancreaticoduodenectomy
 - Laparoscopic distal pancreatectomy

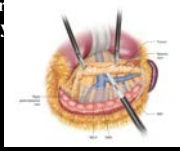
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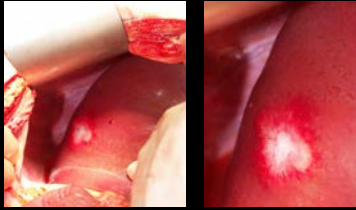
The Role of Laparoscopy for PNETs

- Especially good for small, distal lesions
- Can also enucleate
- Well-suited for pancreatic resection



J. Howe, et al. *Ann. Surg.* 2010; 251: 101-107

What to do with Liver Lesions?

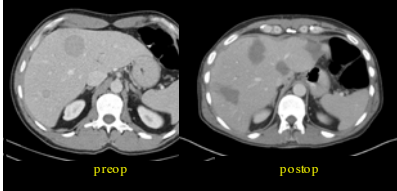


Options for Liver Metastases

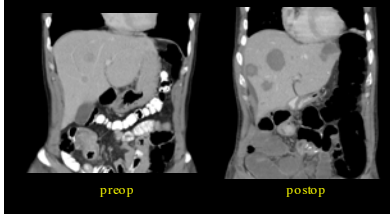
- Embolization
- Radioembolization
- Peptide Receptor Radiotherapy (PRRT)
- Somatostatin analogues
- Systemic therapy
- Resection/Enucleation/Ablation

Approach to Multiple Liver Lesions

Ablation of Liver Lesions
Cholecystectomy



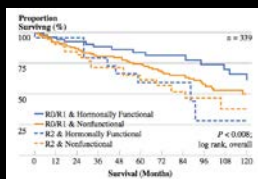
Ablation of Liver Lesions



Debulking at same Procedure

- Reduces tumor burden
- Reduces hormone levels
- Improves targeted therapy
- Improves survival

Survival after Hepatic Resection



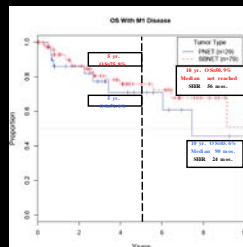
Med. Survival: 125 mos.
5 yr. Survival: 74%

SEER
Med. Survival: 56 mos.
5 yr. Survival: 54%

Recurrence: 94%

Mayo et al. *Ann. Surg. Oncol.* 17:3129, 2010

Overall Survival-M1 Disease



SK Steiman et al. *Ann. Surg. Oncol.* 21:2973, 2014

Unanswered Questions in Hepatic Cytoreduction

- Symptomatic vs. Asymptomatic?
- Survival Benefit?
- Only Attempt if Can Get >90%?
- Major Resections vs. Ablations?
- Cutoff for lesion number?
- Cutoff for % hepatic replacement?

Update on Surgical Management of NETs

Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy?

Janica E. Maxwell, MD, MBA,* Scott R. Sherman, MD,* Thomas M. O'Doriso, MD,* Andrew M. Bellizzi, MD,* and James R. Howe, MD,* Iowa City, IA

- 108/142 pts. liver directed surgery
- 80 SBNETs, 28 PNETs
- Primary also resected in 84%
- 64% pts. had 70% cytoreduction
- Median 10 lesions, 10-19% replacement

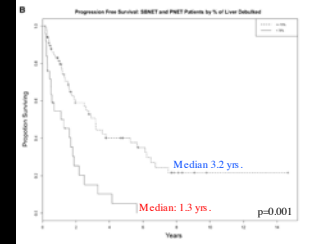
Maxwell et al. Surgery 159:320-2016

Table 10. Survival analyses in PNEs, SBNETs, and the combined group

Surgical parameter	Median PFS, yr		P value	Median OS, yr		P value
	Events	95% CI		Events	95% CI	
PNET and SBNET						
Primary resection by intent	23	7.7	0.02	20	NA	.01
No	76	3.0		4	0.1	
Hepatic replacement by intent	42	3.0	0.01	12	NA	.00
No	37	2.0		12	0.1	
No. hepatocellular carcinoma	54	1.0	0.02	8	NA	.05
No	40	0.2		10	0.1	
No. nonhepatic carcinoma	30	2.7	0.01	11	NA	.01
No	33	1.3		13	0.3	
% Hepatic tumor burden						
<25%	35	3.7	0.01	11	0.3	0.00
≥25%	40	0.9		13	NA	
% Hepatic tumor burden						
<25%	32	3.0	0.01	13	0.3	.02
≥25%	42	2.3		9	NA	
CA, PNET, SBNET response to						
Cytoreduction	89	1.0	0.01	4	NA	.20
No response	14	1.0		4	NA	
Hepatocellular carcinoma	7	0.6	0.01	13	NA	

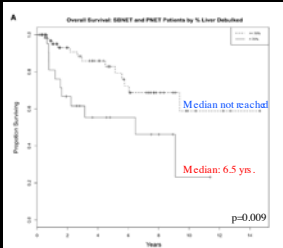
Maxwell et al. Surgery 159:320-2016

PFS with >70% Cytoreduction



Maxwell et al. Surgery 159:320-2016

OS with >70% Cytoreduction



Maxwell et al. Surgery 159:320-2016

Answers to Questions Regarding Hepatic Cytoreduction

- Can be Asymptomatic
- Survival Benefit—Yes!
- >70% Cytoreduction target
- Parenchymal Sparing reasonable
- <10 lesions do better
- <25% replacement do better

Summary: Metastatic NETs

- Remove the primary
- Resect the nodes
- Debulk peritoneal disease
- Cytoreduce liver metastases
- Use Somatostatin analogues
- Use systemic therapy*

*when other options not feasible or at progression

University of Iowa NeuroEndocrine Cancer Clinic

- Thomas O'Doriso-Endocrinology
- James Howe-Surgical Oncology
- Sue O'Doriso-Pediatric Oncology
- Daniel Vaena-Medical Oncology
- Joseph Dillon-Endocrinology
- Andrew Bellizzi-Pathology
- Yusuf Menda, Dave Bushnell-Nuc. Med.
- Kim Miller, Kelly Buck-Nursing