Update on Surgical Management of Neuroendocrine Tumors

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University of Iowa College of Medicine

Distribution of NETs 2000-2004

<table>
<thead>
<tr>
<th>Primary Tumor Site</th>
<th>2000-2004</th>
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<tbody>
<tr>
<td>Lung</td>
<td>23%</td>
</tr>
<tr>
<td>Stomach</td>
<td>6%</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4%</td>
</tr>
<tr>
<td>Jejunum</td>
<td>3%</td>
</tr>
<tr>
<td>Appendix</td>
<td>3%</td>
</tr>
<tr>
<td>Colon</td>
<td>4%</td>
</tr>
<tr>
<td>Rectum</td>
<td>11%</td>
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Stage at Diagnosis

SEER vs. University of Iowa

<table>
<thead>
<tr>
<th>Primary Tumor Site</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
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<tbody>
<tr>
<td>Lung</td>
<td>49</td>
<td>23</td>
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<tr>
<td>Stomach</td>
<td>21</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Duodenum</td>
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<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Jejunum</td>
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<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Appendix</td>
<td>15</td>
<td>32</td>
<td>12</td>
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<tr>
<td>Colon</td>
<td>45</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Rectum</td>
<td>42</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>


Median Survival by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Median Survival (months)</th>
</tr>
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<tbody>
<tr>
<td>Appendix</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Colon</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Duodenum</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Jejunum</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Liver</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Pancreas</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>&gt;60</td>
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SEER vs. University of Iowa

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<tr>
<td>Duodenum</td>
<td>&gt;60</td>
</tr>
<tr>
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</tr>
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<td>&gt;60</td>
</tr>
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</table>

SEER 88 mos.
10 yr. OS=52.9%
Median 126 mos.
SEER 42 mos.
5 yr. OS=79.9%

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

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Lymphadenopathy

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?

SBNETs with Liver Metastases:
Does Resection of the Primary Improve Survival?

SBNETs with Liver Metastases:
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

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

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

Resection for Symptom Control

Calgary Study 2008
- 66 pts. with Sx and GI NETs
- 52% mesenteric masses, 77% liver
- Primary and nodes removed in 45, debulked in 8
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Resection of the primary tumor improves symptoms in the majority of patients
Update on Surgical Management of NETs

- 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

- 91% nodal, 81% liver mets

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

- Difference of Removing Primary
  - 7.4 yrs. (n=249)
  - 4.0 yrs. (n=63)
  - p<0.001

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

- Resection of Mesenteric Nodes
  - 7.9 yrs. (n=166)
  - 6.2 yrs. (n=83)
  - p<0.001

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

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

Givi et al. Surgery 140:891, 2006

- Survival: Resected vs. Not Resected
  - 159 mos. (n=60)
  - 47 mos. (n=24)
  - 81% 5 yr.
  - 21% 5 yr.

Givi, Pommier et al. Surgery 140:891, 2006

- Survival: Explored vs. Not Explored
  - 108 mos. (n=66)
  - 50 mos. (n=18)

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

Ahmed et al. Endocrine-Related Cancer 16:885, 2009

Midgut neuroendocrine tumours with liver metastases: results of the UKI NETS study

- 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 16:885, 2009

Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative risk (95% CI)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.07 (1.015-1.148)</td>
<td>0.002</td>
</tr>
<tr>
<td>KPS</td>
<td>1.04 (1.002-1.086)</td>
<td>0.033</td>
</tr>
<tr>
<td>Resection of primary</td>
<td>0.39 (0.260-0.777)</td>
<td>0.003</td>
</tr>
<tr>
<td>Liver HbA</td>
<td>0.61 (1.000-1.001)</td>
<td>0.539</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>1.00 (0.000-1.022)</td>
<td>0.983</td>
</tr>
<tr>
<td>Hepatic necrosis</td>
<td>Unavailable to calculate</td>
<td>0.988</td>
</tr>
<tr>
<td>PEr receptor therapy</td>
<td>0.60 (0.220-1.793)</td>
<td>0.240</td>
</tr>
<tr>
<td>Sorafenib analog therapy</td>
<td>0.41 (0.000-3.757)</td>
<td>0.475</td>
</tr>
</tbody>
</table>

Ahmed et al. Endocrine-Related Cancer 16:885, 2009
Update on Surgical Management of NETs

Survival Analysis by Resection

Survival in PNETs

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

When to Resect Pancreatic Primary
- Functional lesions
- >2 cm
- Not < 1 cm
- Controversy in 1-2 cm
- Not high grade, unless isolated
- >2 cm in MEN1
- >3 cm in VHL

Survival Advantage in PNETs

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

CT: Pancreatic Body/Tail Mass

Pathologic Specimen

PNET in Pancreatic Head

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The Role of Laparoscopy for PNETs
- Especially good for small, distal lesions
- Can also enucleate
- Well-suited for pancreatoduodenectomy

What to do with Liver Lesions?
- Embolization
- Radioembolization
- Peptide Receptor Radiotherapy (PRRT)
- Somatostatin analogues
- Systemic therapy
- Resection/Enucleation/Ablation

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

Debulking at same Procedure
- Reduces tumor burden
- Reduces hormone levels
- Improves targeted therapy
- Improves survival

Survival after Hepatic Resection
- 5 yr. Survival: 74%
- SEER
- 5 yr. Survival: 54%
- Recurrence: 94%

Overall Survival-M1 Disease
- Symptomatic vs. Asymptomatic?
- Survival Benefit?
- Only Attempt if Can Get >90%?
- Major Resections vs. Ablations?
- Cutoff for lesion number?
- Cutoff for % hepatic replacement?

Unanswered Questions in Hepatic Cytoreduction
- Cutoff for % hepatic replacement?
Update on Surgical Management of NETs

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

- 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


Primary also resected in 84%


PFS with >70% Cytoreduction

- Median 1.3 yrs.
- Median 3.2 yrs. \(p=0.001\)


OS with >70% Cytoreduction

- Median not reached
- Median 6.5 yrs.


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’Dorisio—Endocrinology
- James Howe—Surgical Oncology
- Sue O’Dorisio—Pediatric Oncology
- Daniel Vavna—Medical Oncology
- Joseph Dillon—Endocrinology
- Andrew Bellizzi—Pathology
- Yusuf Menda, Dave Buchnell—Nuc. Med
- Kim Miller, Kelly Back—Nursing

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