The Use of PET and PET/CT in the Management of Metastatic Colorectal Cancer

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Metastatic Colorectal Cancer

• Colorectal cancer (CRC) is the 3rd most common cancer worldwide and in the U.S.

• 3rd most common cause of cancer-related death for both U.S. men and women

• The liver and the lung are the most common sites of metastases

• 40-50% of patients will develop liver metastases during their disease course

The WHO. Cancer Fact Sheet No 297, 2013.
Vibert, Canedo, Adam. Semin Oncol 2005
Metastatic Colorectal Cancer

• Liver metastases are the most common cause of death

• Liver resection offers the possibility of long-term cure

• 20-30% of patients are ultimately able to undergo resection with resulting 5-year survival rates of 40-55%

The Clinical Problem

• Patients with more than limited resectable extrahepatic metastases are not candidates for resection of liver mets

• Additional occult liver mets may also prevent curative resection

• A nontherapeutic laparotomy necessitates about 6 weeks off chemotherapy

• Potential for negative impact on quality of life
Research Question

Is there a role for PET or PET/CT in improving outcomes for patients with colorectal cancer liver metastases?
Existing Evidence

• A systematic review and 2 meta-analyses have failed to reach agreement on the imaging modality of choice (CT, MRI, PET or PET/CT) for detecting CRC metastases.

Patel et al., Ann Surg 2011
Niekel, Bipat, and Stoker, Radiology 2010
RCT: Detection of Extrahepatic Disease

- CT-staged patients with potentially resectable CRC liver metastases: **PET (not PET/CT) vs. no further imaging**
- Disease recurrence within 6 months post-op was counted as “futile laparotomy”
- 38% RR reduction (95% CI 4-60%), 17% AR reduction in “futile laparotomy,” NNT=6 with PET
- No significant difference in actuarial OS or DFS

Limitations of PET/CT

• Detection threshold of 5 mm
• Low sensitivity in patients treated with neoadjuvant chemotherapy
• False positive rate?
  – Inflammation
• Cost – CT < MRI < PET

Synchronous Metastases

- PET-CT scan only if potentially surgically curable M1 disease
- Including a surgeon experienced in the resection of hepatobiliary and lung metastases
Metachronous Metastases
Clinical Relevance

• SEER-Medicare trends in PET use for CRC liver mets
  – 1996-2000=<2%, 2001-2002=<3%, 2003-2006=5.5%

• No known survival benefit

• Minimal benefit after chemotherapy

• Does avoidance of nontherapeutic laparotomy outweigh increased cost?

Study Aims

1. To identify trends in the use of PET and PET/CT in the management of patients with potentially resectable liver metastases from colorectal cancer

2. Evaluate the comparative effectiveness of PET/PET CT in the management of colorectal cancer metastatic to the liver
Aim 1

• To identify trends in the use of PET and PET/CT in the management of patients with potentially resectable liver metastases from colorectal cancer
  – Overall use
  – Use in patients receiving chemo
Cohort Selection

• TCR/SEER data from 2000-2009
  – Age ≥66
  – Colon or rectal cancer based on TCR site and ICD histology codes
    • TCR site codes
      • 15=cecum
      • 17=ascending colon
      • 18=hepatic flexure
      • 19=transverse colon
      • 20=splenic flexure
      • 21=descending colon
      • 22=sigmoid colon
      • 23=large intestine NOS
      • 25=rectosigmoid junction
      • 26=rectum
    • ICD-9 codes
      • 153.4
      • 153.6
      • 153.0
      • 153.1
      • 153.7
      • 153.2
      • 153.3
      • 153.9
      • 154.0
      • 154.1
• ICD Histology codes
  – 8000-malignant neoplasm NOS
  – 8010-carcinoma NOS
  – 8140-adenocarcinoma NOS
  – 8141-scirrhous adenocarcinoma
  – 8143-superficial spreading adenocarcinoma
  – 8144-adenocarcinoma intestinal type
  – 8145-diffuse adenocarcinoma
  – 8210-adenocarcinoma in adenomatous polyp
  – 8211-tubular adenocarcinoma
  – 8220-adenocarcinoma in APC
  – 8221-adenocarcinoma in multiple adenomatous polyps
  – 8230-solid carcinoma NOS
  – 8260-papillary adenocarcinoma NOS
  – 8261-adenocarcinoma in a villous adenoma
  – 8262-villous adenocarcinoma
  – 8263-adenocarcinoma in tubulovillous adenoma
  – 8490-signet ring cell adenocarcinoma
Study Design

• Synchronous (simultaneous primary and metastatic disease) patients:
  • Code for colorectal adenocarcinoma
  • Code for stage IV disease
  • Code for liver metastases

• Metachronous (metastatic disease develops after treatment of the primary) patients:
  – Previously defined algorithm
    • Patients with prior diagnosis of colorectal cancer
    • Treatment with resection
All pts w/ primary diagnosis of colorectal cancer

Select pts with diagnosis of CRC liver mets (CPT, ICD-9)

Exclude pts w/ primary diagnosis of liver cancer

Include only pts who underwent surgery

Select pts with adenocarcinoma histology

Select pts w/ cancer-directed operation for primary

Select only completely staged pts

Study Design

• Synchronous disease
  – Time 0=day 15 of month/year of diagnosis

• Metachronous
  – Time 0=date of 1<sup>st</sup> code for liver metastases (197.7=secondary malignancy of liver) or liver resection
Cohort Selection (con’t)

- Patients with synchronous or metachronous liver metastases from colorectal cancer from 2001-2009
  - Using claims 1 year before and 3 years after
  - Medicare part A&B 1 year before and 3 years after diagnosis or until death
- First cancer diagnosis
- Exclusions:
  - Unstaged disease
  - Carcinoma in situ
  - Anal cancers
  - Enrollment in Medicare for ESRD or chronic disability
  - Patients not living in Texas (TCR cohort) or in SEER regions (SEER cohort)
# Population Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synchronous</th>
<th>Metachronous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7889 (53.8%)</td>
<td>4443 (51.1%)</td>
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<tr>
<td>Male</td>
<td>6784 (46.2%)</td>
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<td><strong>Race/Ethnicity</strong></td>
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<tr>
<td>White</td>
<td>12156 (82.9%)</td>
<td>7293 (83.9%)</td>
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<tr>
<td>Black</td>
<td>1579 (10.8%)</td>
<td>789 (9.1%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>293 (2.0%)</td>
<td>210 (2.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>621 (4.2%)</td>
<td>391 (4.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>24 (0.2%)</td>
<td>10 (0.1%)</td>
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</table>
# Population Baseline Characteristics

<table>
<thead>
<tr>
<th>Comorbidity Index</th>
<th>Synchronous</th>
<th>Metachronous</th>
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<tbody>
<tr>
<td>0</td>
<td>8437 (57.5%)</td>
<td>4913 (56.5%)</td>
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<td>1</td>
<td>3526 (24.0%)</td>
<td>2254 (25.9%)</td>
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<td>2</td>
<td>1552 (10.6%)</td>
<td>914 (10.5%)</td>
</tr>
<tr>
<td>≥3</td>
<td>1158 (7.9%)</td>
<td>612 (7.0%)</td>
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## Population Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synchronous</th>
<th>Metachronous</th>
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<tbody>
<tr>
<td><strong>Site of Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>12250 (83.5%)</td>
<td>6944 (79.9%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>2423 (16.5%)</td>
<td>1749 (20.1%)</td>
</tr>
<tr>
<td><strong>Tumor Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well/moderately differentiated</td>
<td>7395 (50.4%)</td>
<td>6442 (74.1%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>3552 (24.2%)</td>
<td>1829 (21.0%)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>189 (1.3%)</td>
<td>73 (0.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3537 (24.1%)</td>
<td>349 (4.0%)</td>
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<tr>
<td><strong>Stage (TCR)</strong></td>
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<tr>
<td>Local</td>
<td>0 (0%)</td>
<td>3030 (34.9%)</td>
</tr>
<tr>
<td>Regional</td>
<td>0 (0%)</td>
<td>5663 (65.1%)</td>
</tr>
<tr>
<td>Distant</td>
<td>14673 (100%)</td>
<td>0 (0%)</td>
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</tbody>
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Analysis

• Time trends in use of any PET/PET CT
  – CPT PET
    • Limited area 78811
    • Skull base to mid-thigh 78812
    • Whole body 78813
  – PET/CT
    • Limited area 78814
    • Skull base to mid-thigh 78815
    • Whole body 78816
  – ICD-9: GI scan and radioisotope function study 92.04, Total body radioisotope scan 92.18
Aim 2

• Evaluate the comparative effectiveness of PET/PET CT in the management of colorectal cancer metastatic to the liver
CE - Question 1

• Are rates of negative exploratory laparotomy different between patients with and without a preoperative PET/CT?

• Negative laparotomy
  – Exploratory laparotomy without liver resection or ablation
  – Were all done with the intent to resect liver mets?
  – Eliminate emergent exploratory laparotomy?
CE - Question 1

• Identify all patients with metastatic colorectal cancer who underwent
  – Exploratory laparotomy (alone)
  – Heptatectomy
  – Hepatic ablation (operative)
• Exclude patients with preoperative chemotherapy?
Laparotomy/Hepatectomy CPT codes

- Exploratory laparotomy: 49000  ICD-9: 54.1, 54.11
- Diagnostic laparoscopy: 49320, 49321, 49329;  54.21
- Liver biopsy, wedge: 47100  ICD-9: 50.12 (open), 50.19 (lap)
- Partial lobectomy/wedge: 47120  ICD-9: 50.22
- Trisegmentectomy: 47122
- Left lobectomy: 47125
- Right lobectomy: 47130
- Lobectomy (either or NOS): 47125, 47130 ICD-9: 50.3
- Unlisted laparoscopic liver procedure 47379
Hepatic Ablation

• Open 50.23
  – Radiofrequency ablation (RFA) 47380
  – Cryosurgical 47381

• Laparoscopic 50.25
  – RFA 47370
  – Cryosurgical 47371
Which Patients Underwent Exploration?

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<tr>
<th>Explored</th>
<th>Synchronous</th>
<th>Metachronous</th>
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<tbody>
<tr>
<td>No</td>
<td>5244 (35.7%)</td>
<td>6456 (74.3%)</td>
</tr>
<tr>
<td>Yes</td>
<td>9429 (64.3%)</td>
<td>2237 (25.7%)</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>9253 (98.1%)</td>
<td>2169 (97.0%)</td>
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</table>
Definition of Therapeutic Laparotomy

• Liver Resection
• Lymphadenectomy
• Bile Duct Excision
• Hepaticojejunostomy
• Hepatic Ablation
• Primary Colorectal Resection-synchronous disease only
## Population Demographic Characteristics-Explored Patients

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<tr>
<th>Characteristic</th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
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</tr>
<tr>
<td>Female</td>
<td>5088 (54.0%)</td>
<td>1150 (51.4%)</td>
</tr>
<tr>
<td>Male</td>
<td>4341 (46.0%)</td>
<td>1087 (48.6%)</td>
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<td><strong>Race/Ethnicity</strong></td>
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<tr>
<td>White</td>
<td>7913 (83.9%)</td>
<td>1909 (85.3%)</td>
</tr>
<tr>
<td>Black</td>
<td>893 (9.5%)</td>
<td>185 (8.3%)</td>
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<tr>
<td>Hispanic</td>
<td>193 (2.0%)</td>
<td>49 (2.2%)</td>
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<tr>
<td>Other</td>
<td>305 (3.2%)</td>
<td>91 (4.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (0.2%)</td>
<td>3 (0.1%)</td>
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<tr>
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<tr>
<td>0</td>
<td>5537 (58.7%)</td>
<td>1291 (57.7%)</td>
</tr>
<tr>
<td>1</td>
<td>2321 (24.6%)</td>
<td>573 (25.6%)</td>
</tr>
<tr>
<td>2</td>
<td>946 (10.0%)</td>
<td>229 (10.2%)</td>
</tr>
<tr>
<td>≥3</td>
<td>625 (6.6%)</td>
<td>144 (6.4%)</td>
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## Population Tumor Characteristics

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<tr>
<td>Colon</td>
<td>8060 (85.5%)</td>
<td>1864 (83.3%)</td>
</tr>
<tr>
<td>Rectum</td>
<td>1369 (14.5%)</td>
<td>373 (16.7%)</td>
</tr>
<tr>
<td><strong>Tumor Grade</strong></td>
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</tr>
<tr>
<td>Well/moderately differentiated</td>
<td>5690 (60.3%)</td>
<td>1691 (75.6%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>2888 (30.6%)</td>
<td>442 (19.8%)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>153 (1.6%)</td>
<td>21 (0.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>698 (7.4%)</td>
<td>83 (3.7%)</td>
</tr>
<tr>
<td><strong>Stage (TCR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>0 (0%)</td>
<td>812 (36.3%)</td>
</tr>
<tr>
<td>Regional</td>
<td>0 (0%)</td>
<td>1425 (63.7%)</td>
</tr>
<tr>
<td>Distant</td>
<td>9429 (100%)</td>
<td>0 (0%)</td>
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# Imaging of Explored Patients

<table>
<thead>
<tr>
<th>Imaging Study</th>
<th>Synchronous</th>
<th>Metachronous</th>
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</thead>
<tbody>
<tr>
<td>CT/MRI/US</td>
<td>6315 (67.0%)</td>
<td>1074 (48.0%)</td>
</tr>
</tbody>
</table>
Why are so many patients missing imaging codes?

• Missing codes?
• Inappropriate time frame?
  – 3 months before or any time after diagnosis of mets, but prior to exploration
• Other suggestions?
Pts explored w/ CRC liver mets
N=11666

Synchronous
N=9429
 Therapeutic
N=9253
 PET/CT
N=478
 No PET/CT
N=8775
 Non-therapeutic
N=176
 PET/CT
N=6
 No PET/CT
N=170

Metachronous
N=2237
 Therapeutic
N=2169
 PET/CT
N=684
 No PET/CT
N=1485
 Non-therapeutic
N=68
 PET/CT
N=33
 No PET/CT
N=35

5.2% 3.4% 31.5% 48.5%

In PET/CT group 98.8% of patients had a therapeutic laparotomy vs. 98.1% of patients without a PET/CT

In PET/CT group 95.4% of patients had a therapeutic laparotomy vs. 97.7% of patients without a PET/CT
CE – Question 2

• Are rates of ANY laparotomy (with or without liver resection) different for all patients presenting with metastatic disease with or without PET/PET CT?

• How would we do this?
  – Exclude patients with laparotomy + bowel resection unless liver resection is also done?
  – Comparison of laparotomy vs. laparoscopy rates?
CRC liver mets

Synchronous
N=14673
- Exploration
  N=9429
    - Therapeutic
      N=9253
      98.1%
    - Non-therapeutic
      N=176
      97.0%
  - No exploration
    N=5244

Metachronous
N=8693
- Exploration
  N=2237
- No exploration
  N=6456

Stratify by PET use?
Graph the trend of PET use with rates of exploration?
CE – Question 3

• Is survival better with or without PET/PET CT?
  – For overall cohort
    • Better selection of patients who will benefit from laparotomy and resection?
    • Potential reduction of time off chemotherapy for unresectable patients if nontherapeutic laparotomy is avoided
    • Potential to identify metastatic disease sooner → initiate chemo sooner
CE-Question 4

• Is PET/CT cost-effective for patients with liver metastases from CRC?
  – If there is a reduction in non-therapeutic laparotomy rates, does it offset the increased cost of PET?
  – What is the cost of any potential improvement in survival?
Study Limitations

• Inability to determine if operation was changed to a more extensive resection based on PET or PET/CT results

• Pre-test probability cannot be determined

• Are we actually answering our study question?
Other Potential Directions

• Trending the use of various imaging modalities over time: CT, MRI, and PET

• Looking at the cost associated with these trends
Questions?

Suggestions?