Trends and Comparative Effectiveness in Treatment of Stage IV Colorectal Adenocarcinoma

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Trends in Management of Stage IV Colon Cancer

INTRODUCTION

• Second leading cause of cancer death

• In 2012:
  – 143,460 cases of colorectal cancer
  – 51,690 deaths

• Approximately 20% present with distant metastases

• Majority are unresectable at the time of presentation

• Overall 5-year survival for stage IV disease: 10-15%
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SITES OF METASTASES

• Common sites of metastatic disease
  – Liver
  – Lungs
  – Carcinomatosis
  – Distant nodal metastases

• Uncommon
  – Brain
  – Bone
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LIVER METASTASES
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CARCINOMATOSIS
Chemotherapy is the primary treatment.

Before 2000 (standard chemotherapy):
- 5-FU
- Leucovorin

Phase III studies in 2000:
- Oxaliplatin (FULFOX)
- Irinotecan (FULFIRI)

FULFOX and FULFIRI now first line regimens (modern chemotherapy)
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CHEMOTHERAPY

• Newer agents:
  – Bevacizumab (avastin)
    • Monoconal Ab against VEGF-A
    • Angiogenesis inhibitor
    • Approved in 2004 for metastatic colon cancer
  – Cetuximab
    • Monoclonal Ab against EGFR
    • Used in $k$-ras wild type colon cancers
    • Approved in 2008 for colon cancer
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RESECTION OF PRIMARY TUMOR

• Done to prevent tumor complications
  – Bleeding
  – Obstruction
  – Perforation

• May improve survival but studies done are subject to significant selection bias
TIMING OF RESECTION AND CHEMO

• Historically done BEFORE initiation of chemotherapy
  – Prevent complications requiring surgery during chemotherapy/immunosuppression

• Now controversial
  – New techniques for palliation
  – Improved tumor response with modern chemotherapy
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TIMING OF RESECTION AND CHEMO

• Historically done BEFORE initiation of chemotherapy
  – Prevent complications requiring surgery during chemotherapy/immunosuppression

• Now controversial
  – New techniques for palliation
  – Improved tumor response with modern chemotherapy
TIMING OF RESECTION AND CHEMO

• Proponents of immediate resection
  – Prevents tumor related complications
  – Allows for accurate abdominal staging
  – Potentially improves the efficacy of chemotherapy by decreasing tumor burden
  – May improve survival
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TIMING OF RESECTION AND CHEMO

• Opponents of immediate resection
  – High morbidity and mortality rates
  – May delay onset or preclude receipt of chemotherapy
  – Chemotherapy first may prevent unnecessary resection in patients with rapid disease progression
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MANAGEMENT OF LIVER METS

• Modalities have evolved over the last decade

• For resectable disease in good surgical candidates
  – Resection preferred
  – Concurrent or sequential with resection of primary tumor

• When resection not possible
  – Ablation (thermal, radiofrequency, chemoembolization)
  – Hepatic arterial infusion chemotherapy
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PREVIOUS SEER STUDIES

  - 27,654 patients with stage IV colon cancer
  - 66% underwent resection of primary tumor
    - Younger
    - Right-sided tumors
  - Survival better in resected patients
  - No attempt to control for selection bias

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PREVIOUS SEER STUDIES

• 2004 – “role of surgery to remove primary tumor is controversial”
• SEER: 9,011 beneficiaries with stage IV colorectal cancer
• 72% underwent CDS (excluded diverting colostomy)
• 3.9% underwent metastectomy
• Conclude that practice patterns needs to be re-evaluated, given the improvement in the efficacy of chemotherapy

CURRENT TRENDS

- Little is known regarding current trends in the management of stage IV colorectal cancer
  - Use of resection
  - Timing of resection relative to chemotherapy
  - Management of liver mets
Used Texas Cancer Registry and linked Medicare claims data to:

• Describe patterns and trends in the management of stage IV colorectal cancer including:
  – Resection of the primary tumor
  – Receipt/type of chemotherapy
  – Management of hepatic metastases.
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**COHORT**

- TCR-Medicare
  - Colon or rectal cancer 2001-2007 (claims 2000-2009)
  - Aged 66 and older
  - Stage IV disease based on SEER historic stage
  - First primary cancer only
  - Not diagnosed on autopsy or death certificate
  - Part A and B coverage one year before and two years after diagnosis
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METHODS

• TCR-Medicare
  - Colon or rectal cancer 2001-2007 (claims 2000-2009)
  - Aged 66 and older
  - Stage IV disease based on SEER historic stage
  - First primary cancer only
  - Not diagnosed on autopsy or death certificate
  - Part A and B coverage one year before and two years after diagnosis
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COLORECTAL CANCERS BY YEAR

N = 3,343
<table>
<thead>
<tr>
<th>DEMOGRAPHICS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>76.9 +/- 7.2 years</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>66-69</td>
<td>17.8%</td>
</tr>
<tr>
<td>70-74</td>
<td>24.0%</td>
</tr>
<tr>
<td>75-79</td>
<td>23.7%</td>
</tr>
<tr>
<td>80-84</td>
<td>18.4%</td>
</tr>
<tr>
<td>85+</td>
<td>16.1%</td>
</tr>
<tr>
<td>Gender</td>
<td>46.7% male</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80.9%</td>
</tr>
<tr>
<td>Black</td>
<td>12.8%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.2%</td>
</tr>
<tr>
<td>Other</td>
<td>2.1%</td>
</tr>
<tr>
<td>Charlson = 0</td>
<td>62.4%</td>
</tr>
</tbody>
</table>
# Trends in Management of Stage IV Colon Cancer

## Tumor Characteristics

<table>
<thead>
<tr>
<th>Location</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>87.8%</td>
</tr>
<tr>
<td>Right</td>
<td>36.3%</td>
</tr>
<tr>
<td>Transverse</td>
<td>4.2%</td>
</tr>
<tr>
<td>Left</td>
<td>36.1%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>11.1%</td>
</tr>
<tr>
<td>Rectum</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

**Differentiation**

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well/moderate</td>
<td>50.5%</td>
</tr>
<tr>
<td>Poor</td>
<td>25.7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>23.8%</td>
</tr>
</tbody>
</table>

**Positive nodes (N=1931)** 78.8%
SITES OF METASTATIC DISEASE

- ICD-9 codes in Medicare claims to identify:
  - Liver mets: Secondary neoplasm of liver OR liver resection
  - Lung mets: Secondary neoplasm of lung, pleura, mediastinum OR lung resection
  - Carcinomatosis: Carcinomatosis OR secondary neoplasm of retroperitoneum, small bowel, other digestive organs
  - Brain: Secondary neoplasm of brain, spinal cord, or meninges

- Previous studies suggest that Medicare claims alone not accurate in identifying stage

- Good PPV in the subset of stage IV cancers identified in TCR?
## Trends in Management of Stage IV Colon Cancer

### SITES OF METASTATIC DISEASE

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>73.1%</td>
</tr>
<tr>
<td>Liver mets only</td>
<td>20.4%</td>
</tr>
<tr>
<td>Lung</td>
<td>32.4%</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>36.4%</td>
</tr>
<tr>
<td>Distant nodal metastases</td>
<td>38.9%</td>
</tr>
<tr>
<td>Brain</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
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RESECTION OF PRIMARY TUMOR

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Graph showing the percentage of resection of primary tumor over the years of diagnosis from 2001 to 2007. The line graph indicates a slight decrease in the percentage of resections over time.
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CHEMOTHERAPY
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STANDARD VS. MODERN
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AVASTIN
## Trends in Management of Stage IV Colon Cancer

### RESECTION AND CHEMO

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection only</td>
<td>26.4%</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>11.8%</td>
</tr>
<tr>
<td>Resection + chemotherapy</td>
<td>37.4%</td>
</tr>
<tr>
<td>Surgery first</td>
<td>89.1%</td>
</tr>
<tr>
<td>Emergent</td>
<td>19.3%</td>
</tr>
<tr>
<td>Chemotherapy first</td>
<td>10.9%</td>
</tr>
<tr>
<td>No treatment</td>
<td>24.4%</td>
</tr>
</tbody>
</table>
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MANAGEMENT OF LIVER METS

• All patients with stage IV colon cancer:
  – 19.7% liver resection
  – 3.5% ablation
  – 1.4% chemoembolization

• 73.1% of patients had documented liver mets (N=2,444)

• Of 2,444 with documented liver mets:
  – 25.7% liver resection
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MANAGEMENT OF LIVER METS

![Graph showing trends in management of liver metastases for liver resection, ablation, and chemoembolization from 2001 to 2007. The graph indicates a decrease in liver resection and an increase in ablation and chemoembolization over time.]
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SURVIVAL

- 30-day operative mortality = 13.5%
- 291 deaths in 5-year follow-up period
- 103 censored before 5-years
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SURVIVAL – RESECTION ONLY
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SURVIVAL – CHEMO ONLY

Graph showing survival probability over 5-year disease-specific survival time in months for two different years (01-04 and 05-07).
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SURVIVAL – RESECTION + CHEMO

[Graph showing survival probability over 5-year disease specific survival time in months, with different markers for different groups and time periods.]
## Trends in Management of Stage IV Colon Cancer

### SURVIVAL – RESECTION ONLY

<table>
<thead>
<tr>
<th>Factor (REF)</th>
<th>OR and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black (white)</td>
<td>0.84 (0.67, 1.08)</td>
</tr>
<tr>
<td>Hispanic (white)</td>
<td>1.11 (0.77, 1.63)</td>
</tr>
<tr>
<td>Rectum (colon)</td>
<td>1.11 (0.79, 1.57)</td>
</tr>
<tr>
<td>Liver metastases (no)</td>
<td>1.99 (1.62, 2.40)</td>
</tr>
<tr>
<td>Lung metastases (no)</td>
<td>0.94 (0.78, 1.14)</td>
</tr>
<tr>
<td>Carcinomatosis (no)</td>
<td>1.21 (1.03, 1.42)</td>
</tr>
<tr>
<td>2005-2007 (2001-2004)</td>
<td>0.96 (0.82, 1.12)</td>
</tr>
<tr>
<td>Liver resection</td>
<td>0.89 (0.74, 1.08)</td>
</tr>
</tbody>
</table>

*Model controls for age, gender, race, comorbidity, SES, as well as factors shown above. If not shown, factor is not significant.*
<table>
<thead>
<tr>
<th>Factor (REF)</th>
<th>OR and 95% CI</th>
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<tr>
<td>Modern chemotherapy (standard)</td>
<td>0.61 (0.44, 0.83)</td>
</tr>
<tr>
<td>Black (white)</td>
<td>0.99 (0.66, 1.50)</td>
</tr>
<tr>
<td>Hispanic (white)</td>
<td>2.42 (1.15, 5.12)</td>
</tr>
<tr>
<td>Rectum (colon)</td>
<td>0.88 (0.63, 1.22)</td>
</tr>
<tr>
<td>Liver metastases (no)</td>
<td>1.36 (0.90, 2.04)</td>
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<td>Carcinomatosis (no)</td>
<td>1.04 (0.79, 1.39)</td>
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<td>2005-2007 (2001-2004)</td>
<td>1.01 (0.75, 1.36)</td>
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### SURVIVAL – RESECTION + CHEMO

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<tr>
<td>Modern chemotherapy (standard)</td>
<td>1.03 (0.86, 1.23)</td>
</tr>
<tr>
<td>66-69 years (85+)</td>
<td>0.60 (0.40, 0.89)</td>
</tr>
<tr>
<td>70-74 years</td>
<td>0.64 (0.43, 0.95)</td>
</tr>
<tr>
<td>75-79 years</td>
<td>0.69 (0.47, 1.03)</td>
</tr>
<tr>
<td>80-85 years</td>
<td>0.91 (0.60, 1.39)</td>
</tr>
<tr>
<td>Rectum (colon)</td>
<td>0.84 (0.64, 1.09)</td>
</tr>
<tr>
<td>Liver metastases (no)</td>
<td>1.25 (1.02, 1.53)</td>
</tr>
<tr>
<td>Lung metastases (no)</td>
<td>0.93 (0.80, 1.09)</td>
</tr>
<tr>
<td>Carcinomatosis (no)</td>
<td>1.35 (1.15, 1.57)</td>
</tr>
<tr>
<td>2005-2007 (2001-2004)</td>
<td>0.60 (0.51, 0.72)</td>
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### Trends in Management of Stage IV Colon Cancer

**SURVIVAL – NO TREATMENT**

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<td>0.69 (0.45, 1.08)</td>
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</tr>
<tr>
<td>Liver metastases (no)</td>
<td>1.36 (1.14, 1.63)</td>
</tr>
<tr>
<td>Lung metastases (no)</td>
<td>0.74 (0.60, 0.92)</td>
</tr>
<tr>
<td>Carcinomatosis (no)</td>
<td>1.35 (1.11, 1.64)</td>
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OBJECTIVE

• Evaluate the comparative effectiveness of timing of surgery and resection of the primary tumor
  – Resection before chemotherapy
  – Chemotherapy before resection
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METHODS

• Identify a group of “treated” patients
  – Resection of primary tumor OR
  – Chemotherapy

• Exclude patients who underwent emergent colectomy/diverting colostomy
  – 18.7% emergent surgery
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ASSUMPTIONS

- Resection
- Resection + chemotherapy
- Chemotherapy

- Resection first
- Chemotherapy first
OUTCOMES

• Overall survival

• Disease-specific survival

• Need for emergent surgery
  – Complications after original elective operation
  – Surgery done <4 weeks after completion of a course of chemotherapy or mid-cycle

• Completion of chemotherapy
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SELECTION BIAS

• Stratify
  – Surgery and chemotherapy only group?
  – Patients with carcinomatosis?
  – Liver mets?

• Propensity score analysis with inverse probability of treatment weighting?

• IV?

• Link to MDS
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NURSING HOME PATIENTS

• Link to TCR or SEER-Medicare to MDS
  – Provides serial detailed cognitive and functional assessments

• Describe current treatment patterns in colon cancer

• Evaluate factors predicting resection and/or chemotherapy

• Evaluate hospital days, ICU days, overall survival, and functional decline with various treatment strategies
  – Stratified by life expectancy using modified mortality risk index (uses MDS data)