Timing of Chemotherapy and Primary Tumor Resection in Older Patients with Stage IV Colorectal Cancer

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COLORECTAL CANCER

Estimated New Cases*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>238,590</td>
<td>232,340</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>118,080</td>
<td>110,110</td>
</tr>
<tr>
<td>Colorectum</td>
<td>73,680</td>
<td>69,140</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>54,610</td>
<td>49,560</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>45,060</td>
<td>45,310</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40,430</td>
<td>32,140</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>37,600</td>
<td>31,630</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>29,620</td>
<td>24,720</td>
</tr>
<tr>
<td>Leukemia</td>
<td>27,680</td>
<td>22,480</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,740</td>
<td>22,240</td>
</tr>
<tr>
<td>All Sites</td>
<td>854,790</td>
<td>805,500</td>
</tr>
</tbody>
</table>

COLORECTAL CANCER

• Colorectal cancer is primarily a disease of the elderly
  – 60% of new cases occur in persons 65 years or older

INTRODUCTION

- 20-30% of patients with colorectal cancer present with stage IV disease
- Traditional management:
  - Surgical resection of the primary tumor
  - Systemic chemotherapy
    - 5-fluorouracil and leucovorin (5-FU/LV)
COLORECTAL CANCER COMPLICATIONS
Colon Cancer

**Clinical Presentation**
- Suspected or proven metastatic adenocarcinoma from large bowel (Any T, any N, M1)

**Work-up**
- Colonoscopy
- Chest x-ray
- Abdominal/pelvic CT
- CBC, platelets, chemistry profile
- CEA
- Needle biopsy if clinically indicated
- If liver only, the following as clinically indicated:
  - Spiro CT
  - Portography
  - MRI
  - Laparoscopy
  - Angiogram
  - PET
  - Intraoperative ultrasound (IOUS)

**Findings**
- Liver metastases
  - Resectable (1-3 discrete lesions)
  - Unresectable
- Lung metastases
  - Resectable (1-3 nodules)
  - Unresectable (multiple)
- Abdominal metastases
  - Resectable
  - Unresectable
- Impending obstruction

**Surgery**
- Colectomy with en bloc removal of regional lymph nodes, IOUS, synchronous liver resection ± cryosurgery or Colectomy with en bloc removal of lymph nodes + 6 wk later: liver resection, IOUS ± cryosurgery
- Right colon, asymptomatic → Salvage
- Limited colon resection
- Left colon or Obstructive symptoms → Consider colectomy with en bloc removal of nodes followed by resection of pulmonary nodules
- Limited bowel resection or Diverting colostomy
- Consider limited bowel resection

**Postoperative Treatment**
- Hepatic artery Infusion therapy ± 5-FU/leucovorin or continuous IV 5-FU or 5-FU/leucovorin or Continuous IV 5-FU
- Salvage
- Observe or 5-FU/leucovorin or 5-FU/leucovorin or Continuous IV 5-FU
- Salvage
- Salvage
ADVANCES IN CHEMOTHERAPY

• In 2000, oxaliplatin or irinotecan in combination with 5-FU/LV are approved by FDA
  – First line chemotherapy for advanced colorectal cancer


ENDOSCOPIC ADVANCES

• Stents
• Ablative techniques
  – Laser
Length of hospital stay

COLORECTAL CANCER SURGERY IN THE ELDERLY

30 day mortality

- Operative mortality increased with advancing age*
  - 65-74 yrs: 1.8x higher
  - 75-84 yrs: 3.2x higher
  - 85+ yrs: 6.2x higher

*compared to patients < 65 years old
CONTROVERSY

- Mortality of cancer-directed surgery in older patients 10-18%
- In asymptomatic patients at presentation, incidence of tumor related complications is low
- With more effective chemotherapy, the role and timing of elective resection in asymptomatic patients is controversial
- No RCTs comparing chemotherapy-first vs. surgery-first

**NCCN GUIDELINES**

**Colon Cancer**

**FINDINGS**
- Synchronous liver metastases
- Unresectable

**SURGERY**
- Neoadjuvant therapy (FOLFIRI or FOLFOX + bevacizumab) followed by synchronous or staged colectomy ± liver resection (category 2B)
- Colectomy, with synchronous or subsequent liver resection
- Colectomy with neoadjuvant chemotherapy (category 2B) (FOLFIRI or FOLFOX + bevacizumab) and staged liver resection

**ADJUVANT THERAPY**
- Active chemotherapy regimen for advanced disease (See Chemotherapy for Advanced or Metastatic Disease (COL-C)) (category 2B)
- Hepatic artery infusion therapy ± systemic 5-FU/leucovorin (category 2B) or continuous IV 5-FU
- Consider observation or shortened course of chemotherapy, if patient received neoadjuvant therapy

**Resectable**
- Converted to Resectable
- Resection

**Unresectable**
- Systemic therapy (FOLFIRI or FOLFOX + bevacizumab)
- Consider colon resection if imminent risk of obstruction and/or if liver burden low ± ablative therapy (category 2B)

**Remains unresectable**
- See Chemotherapy for Advanced or Metastatic Disease (COL-C)
ARGUMENTS FOR CHEMOTHERAPY-FIRST

- Delivery of chemotherapy to a tumor with an intact blood supply
- Ability to assess tumor’s response to treatment
- Avoidance of morbidity associated with surgical resection in patients with early disease progression
- No delay in administering systemic therapy
HYPOTHESIS

• A chemotherapy-first approach would allow clinicians to select the subset of patients most likely to benefit from resection of the primary tumor and result in improved survival
OBJECTIVES

• Evaluate trends in:
  – Receipt of chemotherapy
  – Resection of the primary tumor

• Evaluate the timing of chemotherapy and resection of the primary tumor

• Compare disease-specific survival based on initial treatment modality
METHODS

- Data source (2000-2009)
  - Texas Cancer Registry (TCR)-Medicare linked data
  - Surveillance Epidemiology and End Results (SEER)-Medicare linked data
Stage IV colon or rectal cancer diagnosed in 2001-2007
N=31,273

Exclude ESRD, diagnosis at autopsy only, no histologic confirmation

Patients treated with chemotherapy and/or resection of the primary tumor

Part A/B without HMO 1 yr before and 2 yrs after diagnosis

Exclude patients requiring emergency resection

N=7,738
METHODS

- Identified claims for:
  - Elective resection of the primary tumor
  - Receipt of chemotherapy

- Specific agents identified in 82% of patients

  • Leucovorin
  • 5-FU
  • Oxaliplatin
  • Irinotecan
  • Bevacizumab

“Standard”

“Modern”
TREATMENT

• Patients were categorized in two groups based on their initial treatment modality
  – Resection of primary tumor
  – Chemotherapy

• Regardless of whether they received the other modality
TREATMENT CLASSIFICATION

- **Chemotherapy and/or Resection**
  - N=7,738
    - Chemotherapy only
      - N=1,792
    - Chemotherapy and Resection
      - N=1,511
    - Resection only
      - N=4,435
    - Chemotherapy BEFORE resection
      - N=484
    - Resection BEFORE chemotherapy
      - N=1,027

CHEMOTHERAPY GROUP
- N=2,276

RESECTION GROUP
- N=5,462
TREATMENT

CHEMOTHERAPY GROUP
N=2,276

78.7% did not undergo resection of the primary tumor

RESECTION GROUP
N=5,462

81.2% did not receive chemotherapy
## PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=7,738</th>
</tr>
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<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>77.7 ± 7.2</td>
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<tr>
<td>Female gender</td>
<td>4,164 (53.8%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
<td>6,482 (83.9%)</td>
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<tr>
<td>Black</td>
<td>750 (9.7%)</td>
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<tr>
<td>Hispanic</td>
<td>155 (2.0%)</td>
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<tr>
<td>Other</td>
<td>338 (4.4%)</td>
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<tr>
<td>Charlson Comorbidity Score</td>
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</tr>
<tr>
<td>0</td>
<td>4,482 (57.9%)</td>
</tr>
<tr>
<td>1</td>
<td>1,849 (23.9%)</td>
</tr>
<tr>
<td>2</td>
<td>812 (10.5%)</td>
</tr>
<tr>
<td>3</td>
<td>595 (7.7%)</td>
</tr>
<tr>
<td>Operative mortality</td>
<td>N=1,256/5,462 (23.1%)</td>
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</table>
# PATIENT AND TUMOR CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Resection of Primary Tumor</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>Patient Demographics</strong></td>
<td>N=2,276</td>
<td>N=5,462</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>74.8 ± 6.0</td>
<td>78.9 ± 7.3</td>
<td>&lt;.0001</td>
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<tr>
<td>Charlson Comorbidity Score</td>
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<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>0</td>
<td>1,460 (64.2%)</td>
<td>3,022 (55.3%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>505 (22.2%)</td>
<td>1,344 (24.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>190 (8.4%)</td>
<td>622 (11.4%)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>121 (5.3%)</td>
<td>474 (8.7%)</td>
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<tr>
<td><strong>Tumor Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td></td>
<td></td>
<td>&lt;.0001</td>
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<tr>
<td>Colon cancer</td>
<td>1,450 (63.7%)</td>
<td>4,847 (88.7%)</td>
<td></td>
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<tr>
<td>Rectal cancer</td>
<td>826 (36.3%)</td>
<td>615 (11.3%)</td>
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<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td>NS</td>
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<tr>
<td>Standard</td>
<td>609 (34.1%)</td>
<td>292 (32.2%)</td>
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<tr>
<td>Modern</td>
<td>1,177 (65.9%)</td>
<td>614 (67.8%)</td>
<td></td>
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<tr>
<td>Metastasectomy (yes)</td>
<td>194 (8.5%)</td>
<td>1,365 (25.0%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
TIME TRENDS IN USE OF MODERN CHEMOTHERAPY

Graph showing trends in use of modern and standard chemotherapy from 2001 to 2007.
TIME TRENDS: CHEMOTHERAPY AS FIRST TREATMENT MODALITY
3-YEAR DISEASE SPECIFIC SURVIVAL BY INITIAL TREATMENT MODALITY

All Patients
3-YEAR DISEASE SPECIFIC SURVIVAL BY INITIAL TREATMENT MODALITY

Resection & Chemotherapy (N=1,511)
## COX PROPORTIONAL HAZARDS
### ALL PATIENTS

<table>
<thead>
<tr>
<th>Factor (REF)*</th>
<th>Hazard Ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>First treatment modality (Resection)</td>
<td>0.89 (0.83-0.95)</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>0.95 (0.94-0.96)</td>
</tr>
<tr>
<td>Age (66-69 yrs)</td>
<td></td>
</tr>
<tr>
<td>70-74 yrs</td>
<td>1.20 (1.10-1.31)</td>
</tr>
<tr>
<td>75-79 yrs</td>
<td>1.26 (1.15-1.37)</td>
</tr>
<tr>
<td>80-84 yrs</td>
<td>1.38 (1.26-1.51)</td>
</tr>
<tr>
<td>≥ 85 yrs</td>
<td>1.61 (1.46-1.77)</td>
</tr>
<tr>
<td>Charlson Comorbidity Score (0)</td>
<td></td>
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<tr>
<td>1</td>
<td>1.04 (0.97-1.10)</td>
</tr>
<tr>
<td>2</td>
<td>1.09 (0.99-1.19)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1.29 (1.17-1.44)</td>
</tr>
<tr>
<td>Cancer type (Rectal)</td>
<td>1.16 (1.09-1.24)</td>
</tr>
<tr>
<td>Metastasectomy</td>
<td>1.05 (0.98-1.12)</td>
</tr>
</tbody>
</table>

*Model also controlled for sex, race, and tumor differentiation
LIMITATIONS

- Inability to determine intent of treatment
- Selection bias
SUMMARY

• Resection of the primary tumor was the initial treatment modality in 70% of patients

• The use of chemotherapy as the first treatment modality increased over time

• Three-year disease-specific survival was equivalent between the two treatment groups
CONCLUSIONS

- Resection of the primary tumor in stage IV disease is associated with significant mortality.
- Survival is better with chemotherapy as the initial treatment modality.
- Our data support the use of chemotherapy as the initial treatment modality in patients presenting with stage IV colon cancer.
- Resection can then be performed in patients most likely to benefit.
NEXT STEPS

• RCT trial
• Decision-making in colorectal cancer
  – Literature is limited
  • No studies evaluating quality of life
  • Few studies evaluating patient preferences in treatment
EXPLORING SHARED DECISION-MAKING

• What sort of treatment and care choices do people with colorectal cancer perceive they are presented with?
• What are patient preferences for participation in different types of treatment and care decisions?
• What are the factors that prevent and enable patient participation in decision-making?
TREATMENT DECISIONS

• Patients perceived that they had been presented with few choices
• The need for surgical intervention easily understood
• More opportunity for participation in decision making in adjuvant therapy
  – Complexity of treatment limited ability to make decision

Patient – ‘I suppose, you know, with the surgery as an emergency, you got to have it done... they had to do it. There are no decisions there you know. If they say something then they’re going to do it, because they have to, you know.’ (ID209)

Patient – ‘But I think it’s too involved I think. Too involved for the layman. They come out with these long words you know the drugs, you know, the names they’re about that long and you think what the hell am I on this for? I think it could take a lot of the time up as well. I think there’s the doctors time and they’re pushed enough as it is ... if they did go into great detail I wouldn’t really understand it.’ (ID202)
TREATMENT DECISIONS

• The majority of patients reported that they would NOT wish to make treatment decisions

• Want to be informed and involved
  – Being kept up to date with what was happening and what was planned

Patient – ‘I wouldn’t like to be too involved about the treatment. I think if they say that treatment is beneficial to you that means you should accept that treatment, you know. I think you should accept the doctor’s (pause). I mean that’s what they’re there for. They know what’s best.’ (ID207)
QUESTIONS?