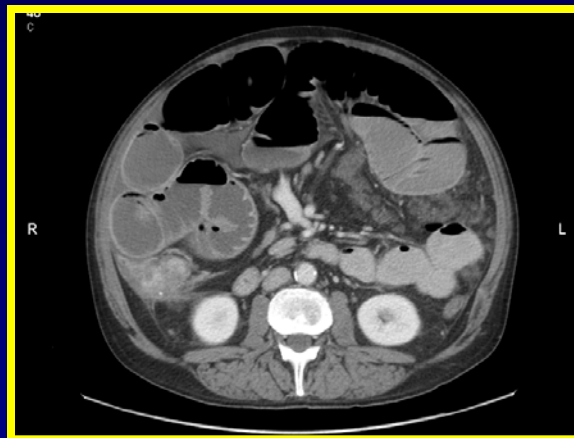


Trends and Comparative Effectiveness in Treatment of Stage IV Colorectal Adenocarcinoma



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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%

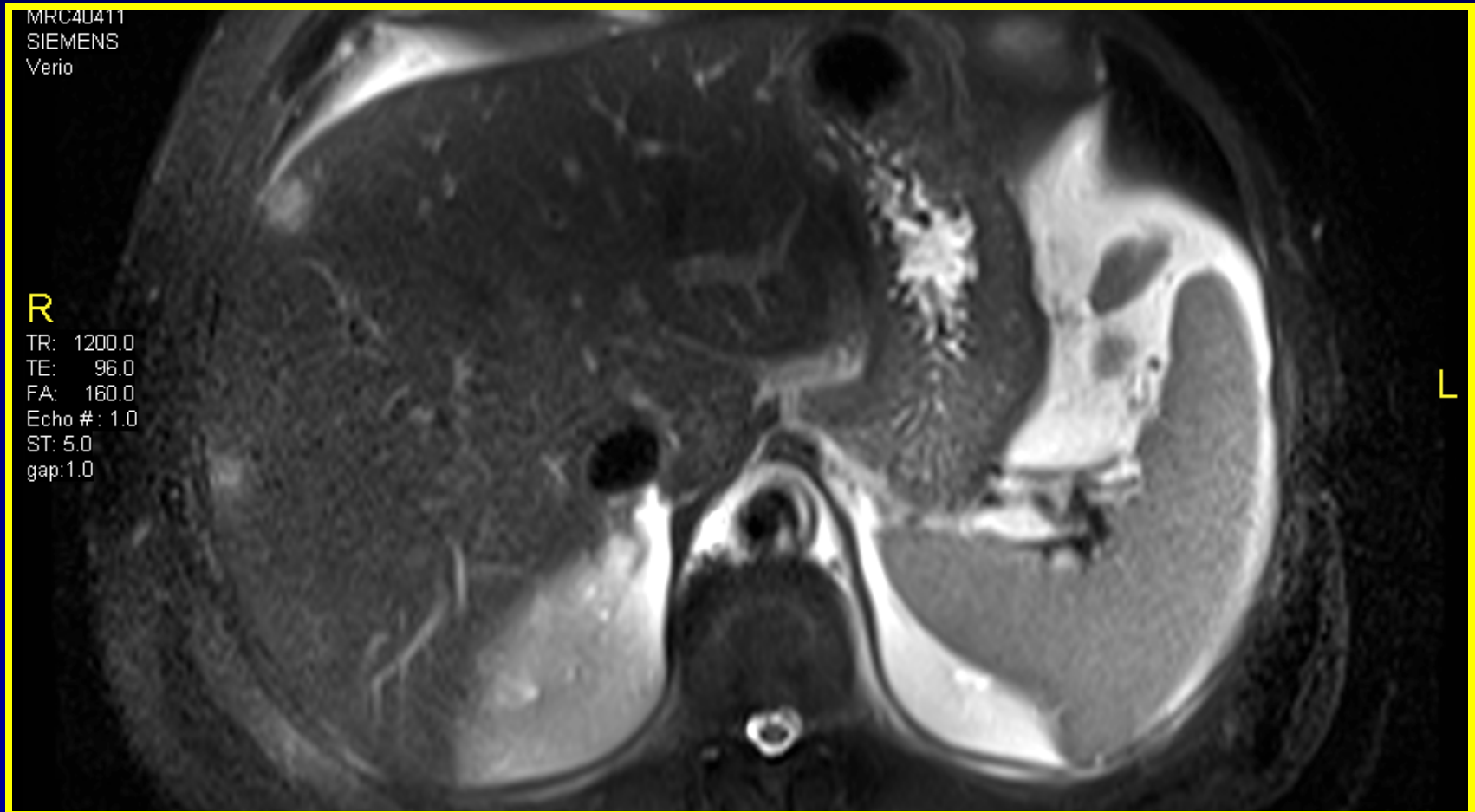
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SITES OF METASTASES

- Common sites of metastatic disease
 - Liver
 - Lungs
 - Carcinomatosis
 - Distant nodal metastases
- Uncommon
 - Brain
 - Bone

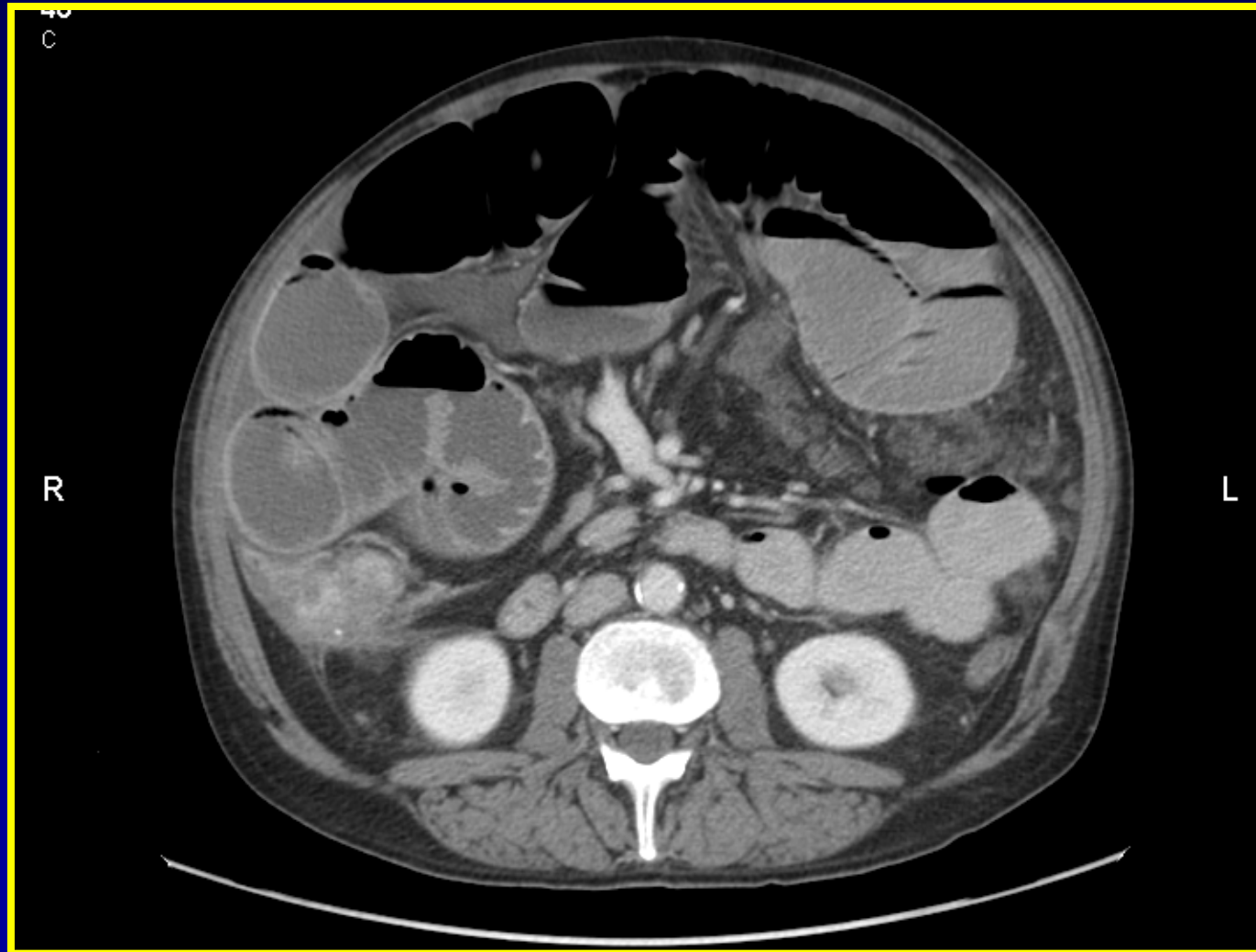
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LIVER METASTASES



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CARCINOMATOSIS



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CHEMOTHERAPY

- 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

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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

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TIMING OF RESECTION AND CHEMO

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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

- Analysis of SEER data (1988-2000)
 - 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

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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
- Analysis of SEER data (1988-2000)

Trends in Management of Stage IV Colon Cancer

OBJECTIVE

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.

Trends in Management of Stage IV Colon Cancer

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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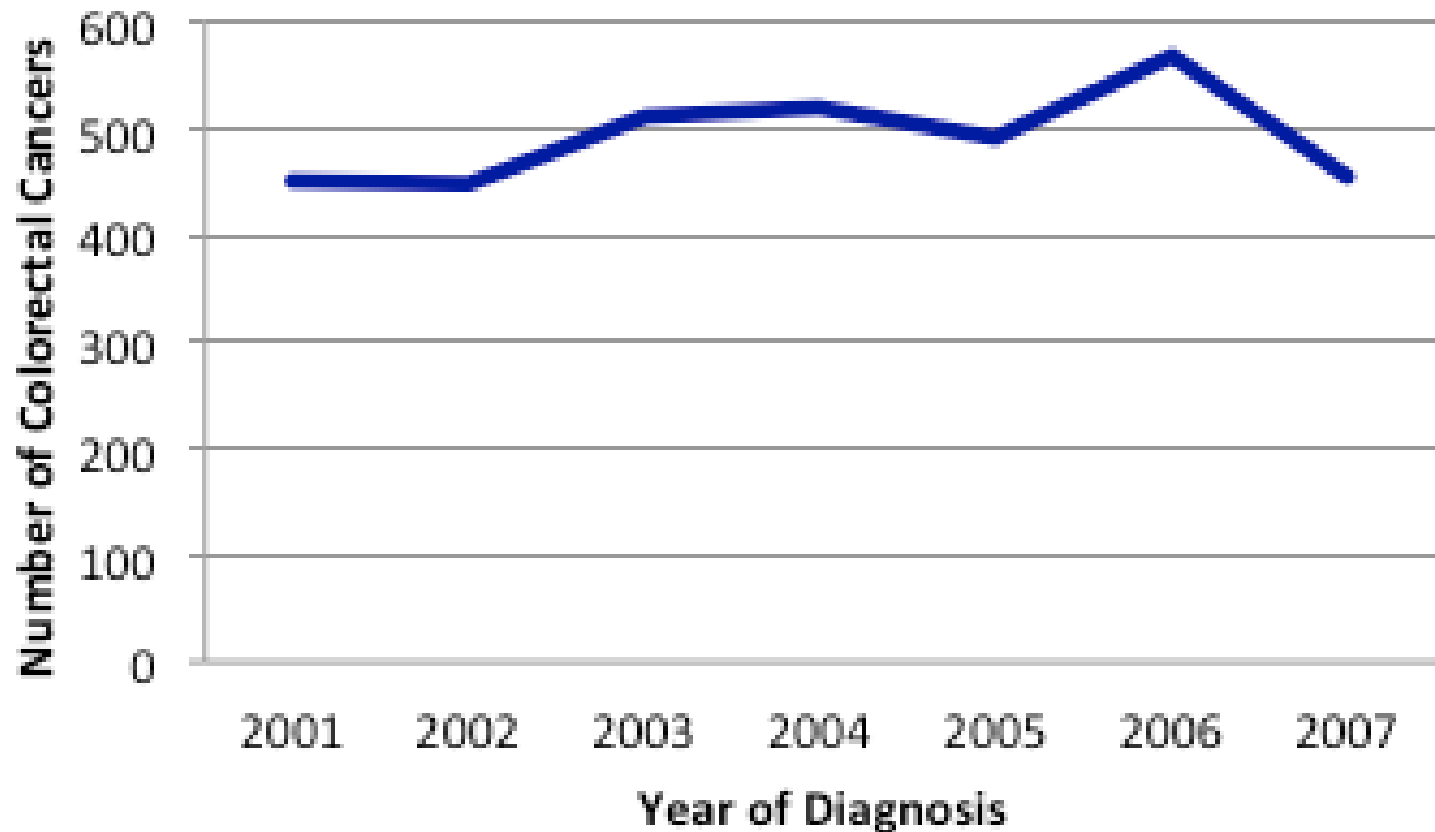
METHODS

- TCR-Medicare
 - Colon or rectal cancer 2001-2007 (claims 2000-2009)
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COLORECTAL CANCERS BY YEAR

N = 3,343



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DEMOGRAPHICS

| | |
|--------------|--------------------|
| Mean age | 76.9 +/- 7.2 years |
| Age group | |
| 66-69 | 17.8% |
| 70-74 | 24.0% |
| 75-79 | 23.7% |
| 80-84 | 18.4% |
| 85+ | 16.1% |
| Gender | 46.7% male |
| Race | |
| White | 80.9% |
| Black | 12.8% |
| Hispanic | 4.2% |
| Other | 2.1% |
| Charlson = 0 | 62.4% |

Trends in Management of Stage IV Colon Cancer

TUMOR CHARACTERISTICS

| | |
|--------------------------------|-------|
| Colon | 87.8% |
| Right | 36.3% |
| Transverse | 4.2% |
| Left | 36.1% |
| Indeterminate | 11.1% |
| Rectum | 12.2% |
| Differentiation | |
| Well/moderate | 50.5% |
| Poor | 25.7% |
| Unknown | 23.8% |
| Positive nodes (N=1931) | 78.8% |

Trends in Management of Stage IV Colon Cancer

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?

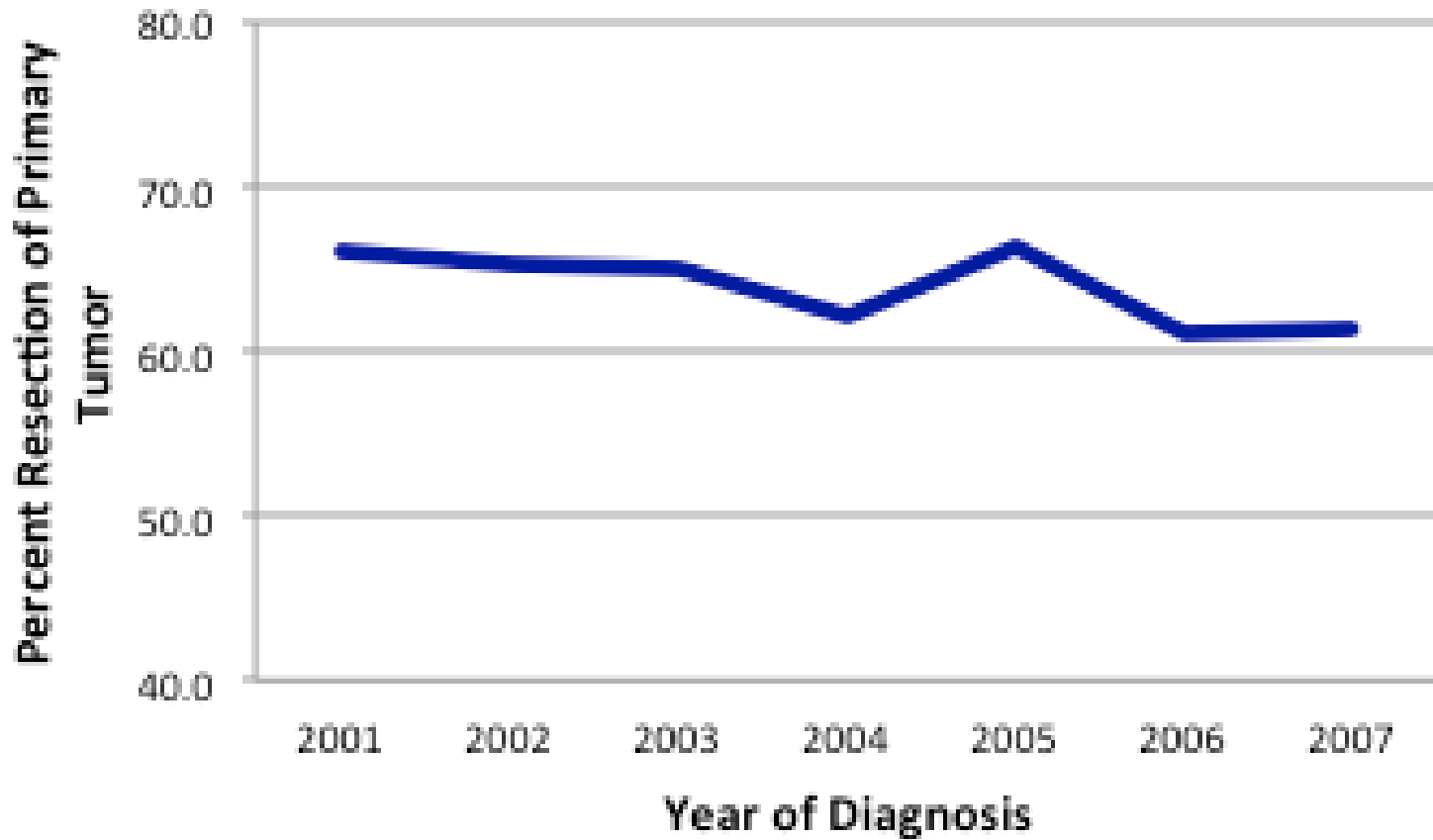
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SITES OF METASTATIC DISEASE

| | |
|---------------------------------|-------|
| Liver | 73.1% |
| Liver mets only | 20.4% |
| Lung | 32.4% |
| Carcinomatosis | 36.4% |
| Distant nodal metastases | 38.9% |
| Brain | 4.7% |

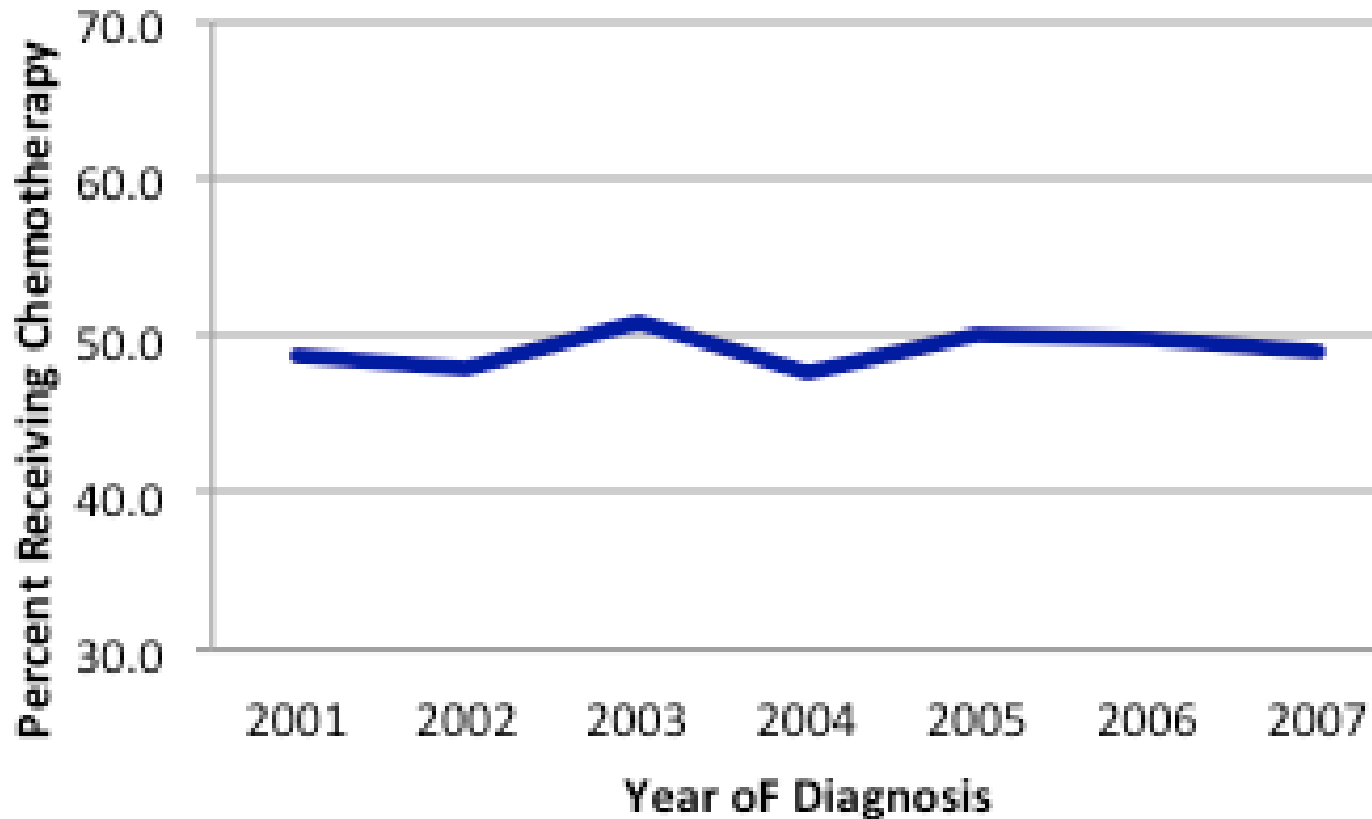
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RESECTION OF PRIMARY TUMOR



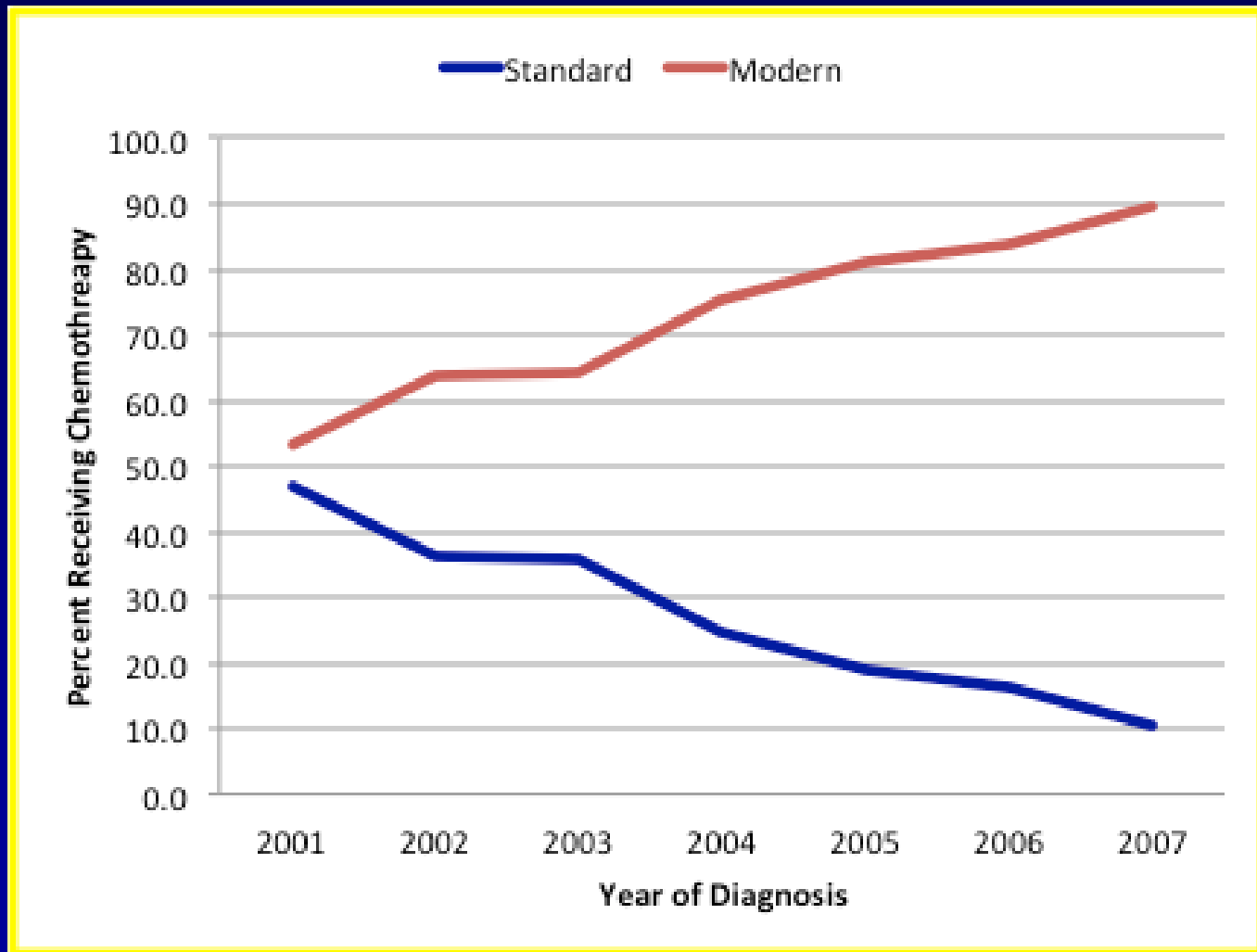
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CHEMOTHERAPY



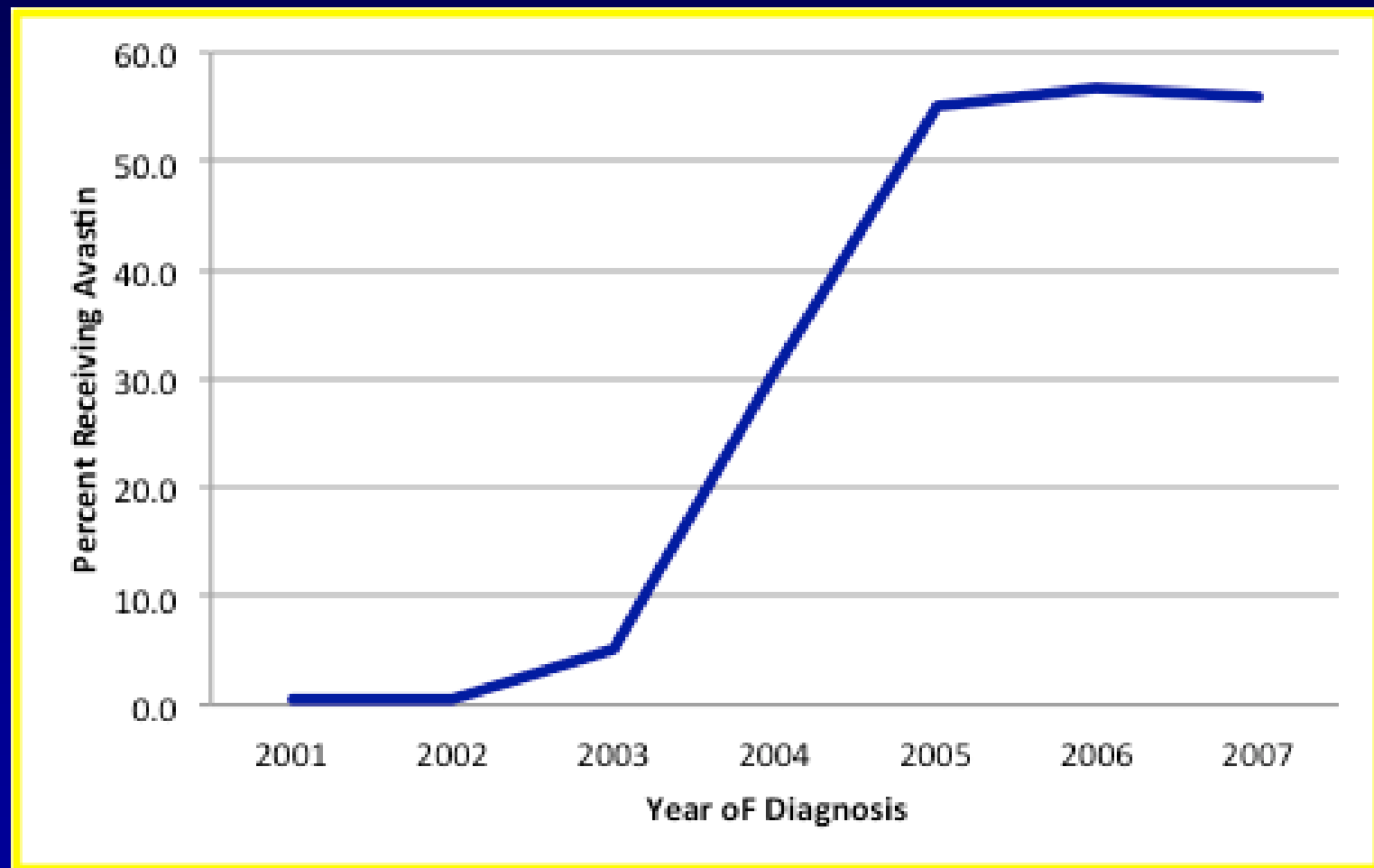
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STANDARD VS. MODERN



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AVASTIN



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RESECTION AND CHEMO

| | |
|---------------------------------|-------|
| Resection only | 26.4% |
| Chemotherapy only | 11.8% |
| Resection + chemotherapy | 37.4% |
| Surgery first | 89.1% |
| Emergent | 19.3% |
| Chemotherapy first | 10.9% |
| No treatment | 24.4% |

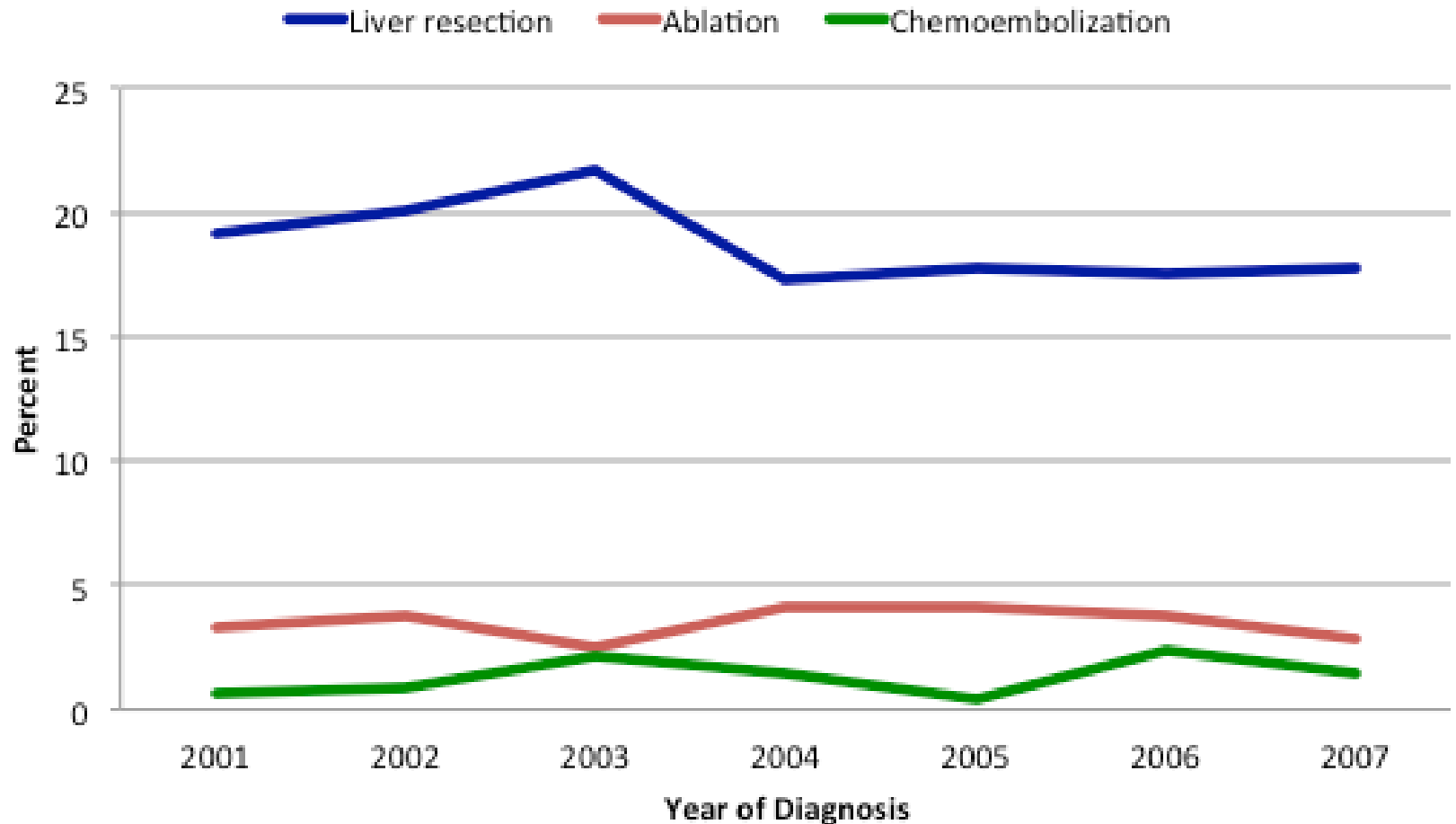
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MANAGEMENT OF LIVER METS

- 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



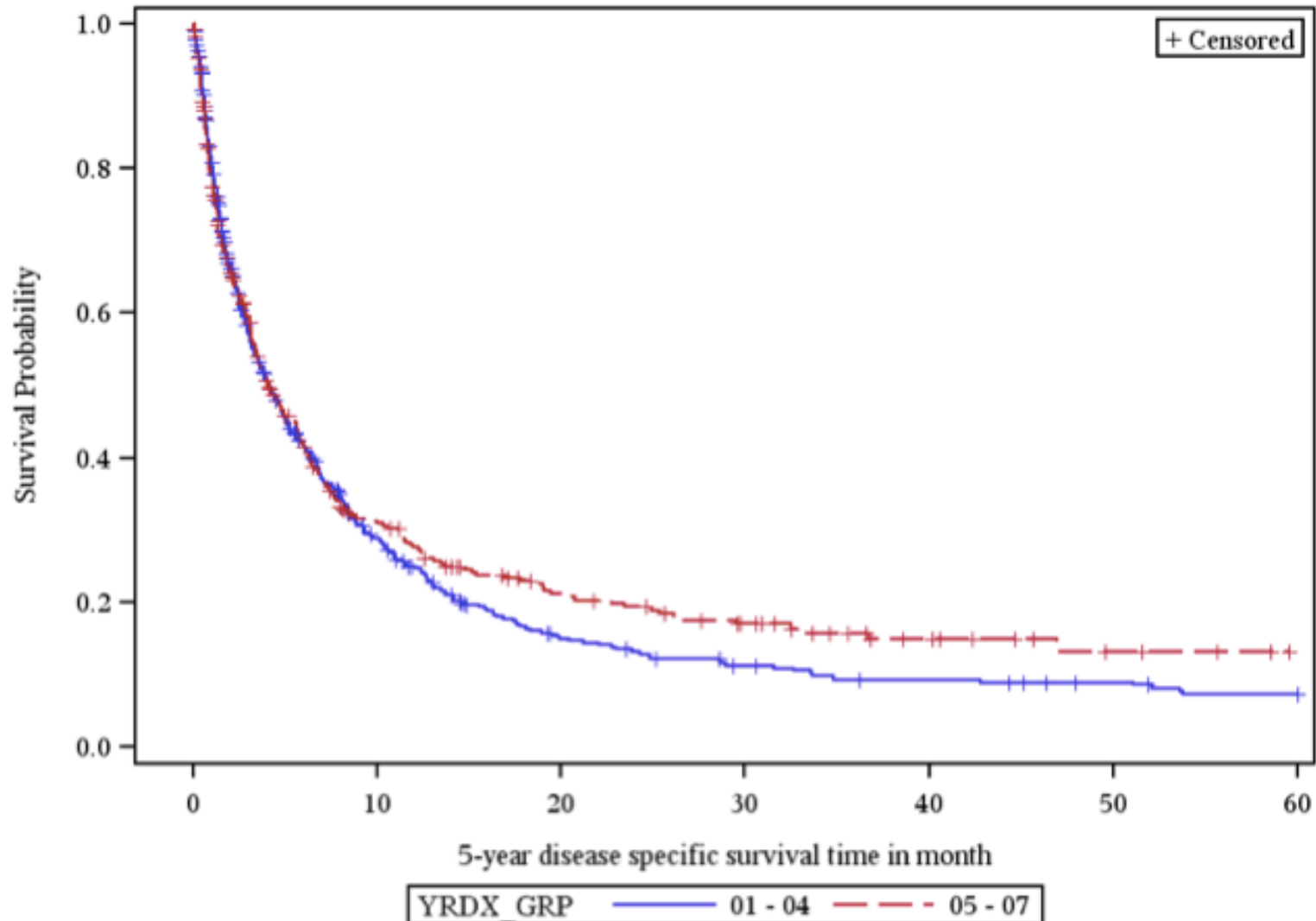
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SURVIVAL

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

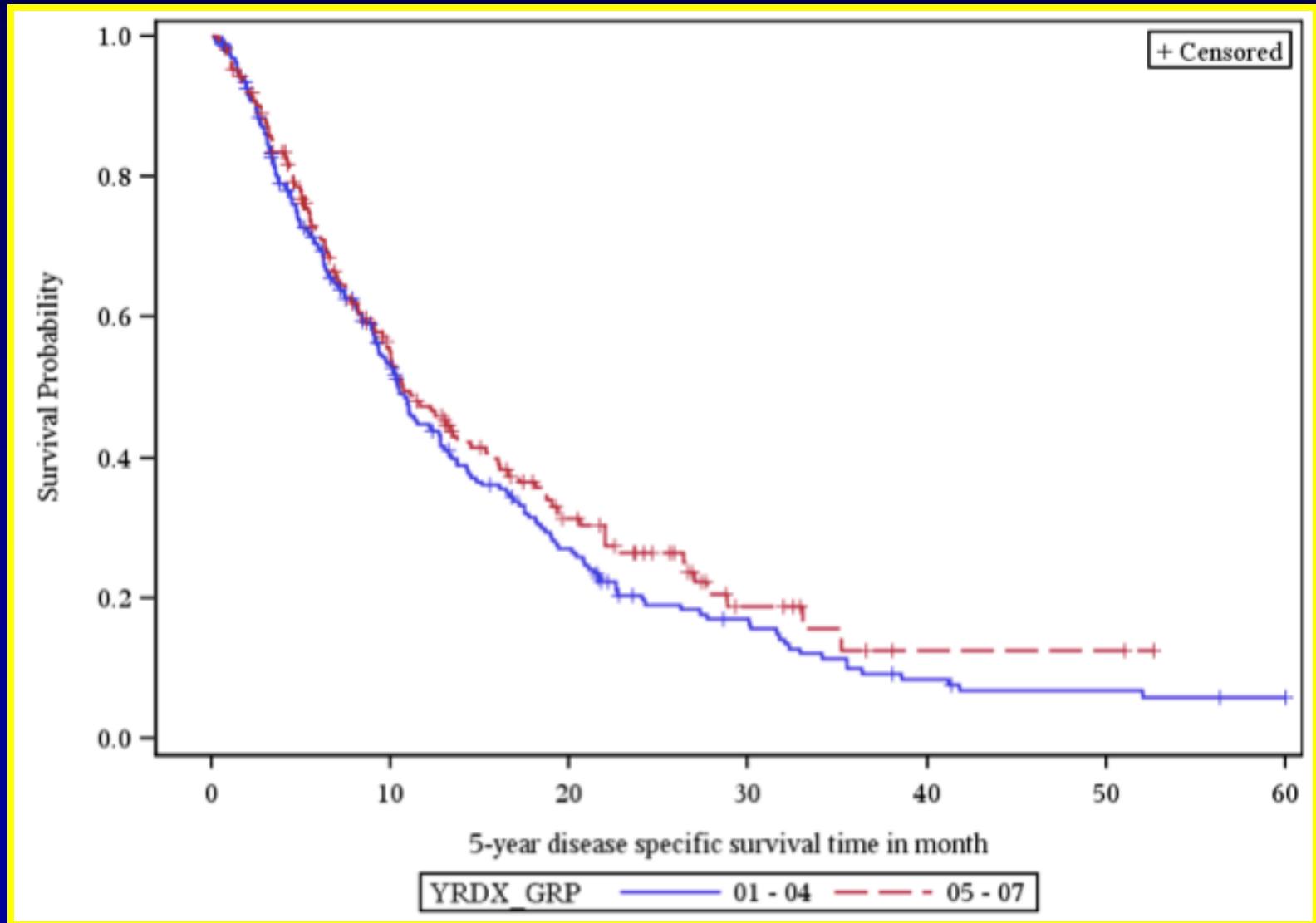
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SURVIVAL – RESECTION ONLY



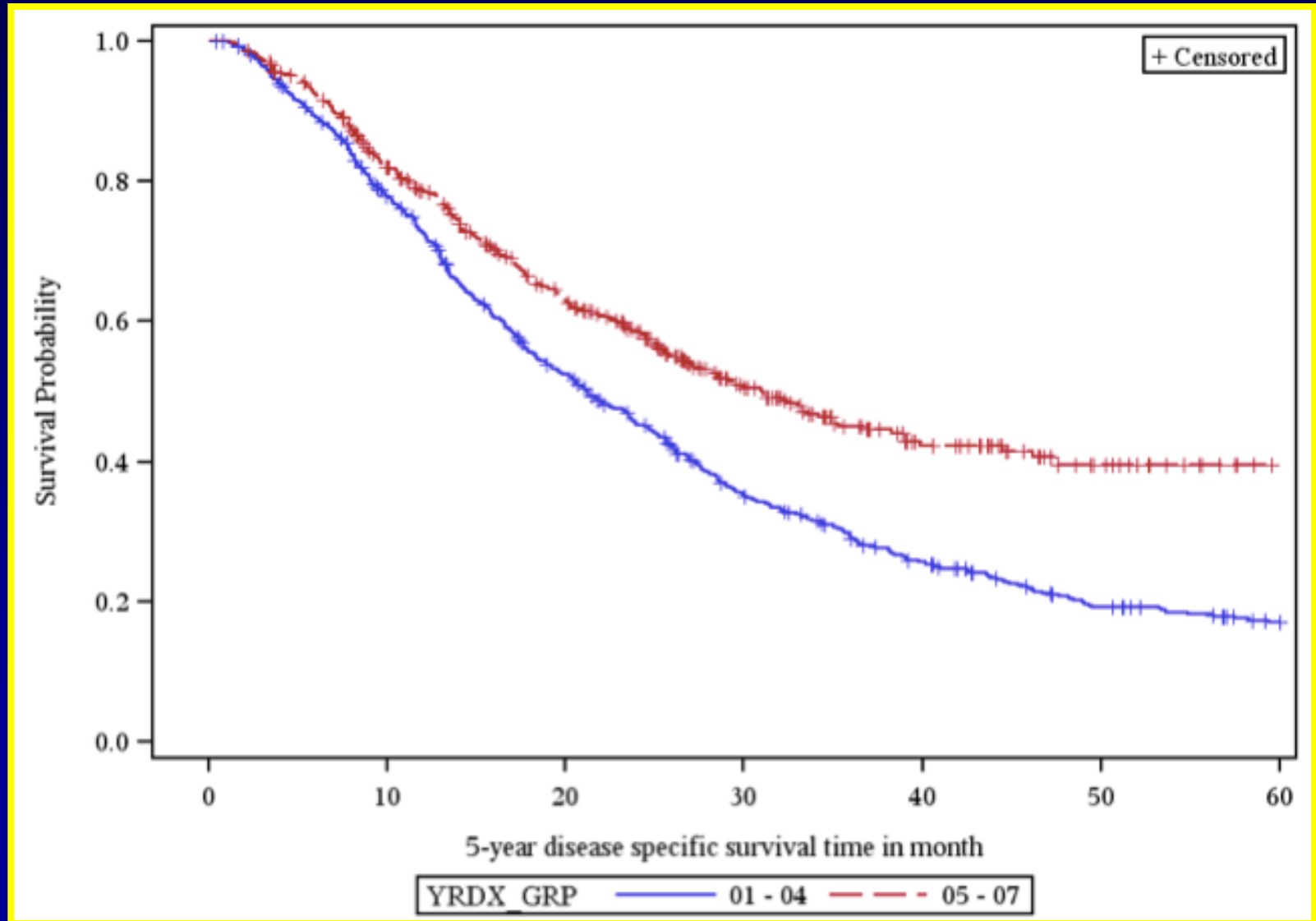
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SURVIVAL – CHEMO ONLY



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SURVIVAL – RESECTION + CHEMO



Trends in Management of Stage IV Colon Cancer

SURVIVAL – RESECTION ONLY

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

*Model controls for age, gender, race, comorbidity, SES, as well as factors shown above. If not shown, factor is not significant.

Trends in Management of Stage IV Colon Cancer

SURVIVAL – CHEMO ONLY

| Factor (REF) | OR and 95% CI |
|--------------------------------|----------------------|
| Modern chemotherapy (standard) | 0.61 (0.44, 0.83) |
| Black (white) | 0.99 (0.66, 1.50) |
| Hispanic (white) | 2.42 (1.15, 5.12) |
| Rectum (colon) | 0.88 (0.63, 1.22) |
| Liver metastases (no) | 1.36 (0.90, 2.04) |
| Lung metastases (no) | 0.89 (0.67, 1.19) |
| Carcinomatosis (no) | 1.04 (0.79, 1.39) |
| 2005-2007 (2001-2004) | 1.01 (0.75, 1.36) |

*Model controls for age, gender, race, comorbidity, SES, as well as factors shown above. If not shown, factor is not significant.

Trends in Management of Stage IV Colon Cancer

SURVIVAL – RESECTION + CHEMO

| Factor (REF) | OR and 95% CI |
|--------------------------------|-------------------|
| Modern chemotherapy (standard) | 1.03 (0.86, 1.23) |
| 66-69 years (85+) | 0.60 (0.40, 0.89) |
| 70-74 years | 0.64 (0.43, 0.95) |
| 75-79 years | 0.69 (0.47, 1.03) |
| 80-85 years | 0.91 (0.60, 1.39) |
| Rectum (colon) | 0.84 (0.64, 1.09) |
| Liver metastases (no) | 1.25 (1.02, 1.53) |
| Lung metastases (no) | 0.93 (0.80, 1.09) |
| Carcinomatosis (no) | 1.35 (1.15, 1.57) |
| 2005-2007 (2001-2004) | 0.60 (0.51, 0.72) |

*Model controls for age, gender, race, comorbidity, SES, as well as factors shown above. If not shown, factor is not significant.

Trends in Management of Stage IV Colon Cancer

SURVIVAL – NO TREATMENT

| Factor (REF) | OR and 95% CI |
|-----------------------|----------------------|
| Black (white) | 0.94 (0.75, 1.18) |
| Hispanic (white) | 0.69 (0.45, 1.08) |
| Rectum (colon) | 0.89 (0.70, 1.12) |
| Liver metastases (no) | 1.36 (1.14, 1.63) |
| Lung metastases (no) | 0.74 (0.60, 0.92) |
| Carcinomatosis (no) | 1.35 (1.11, 1.64) |
| 2005-2007 (2001-2004) | 0.95 (0.80, 1.12) |

*Model controls for age, gender, race, comorbidity, SES, as well as factors shown above. If not shown, factor is not significant.

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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

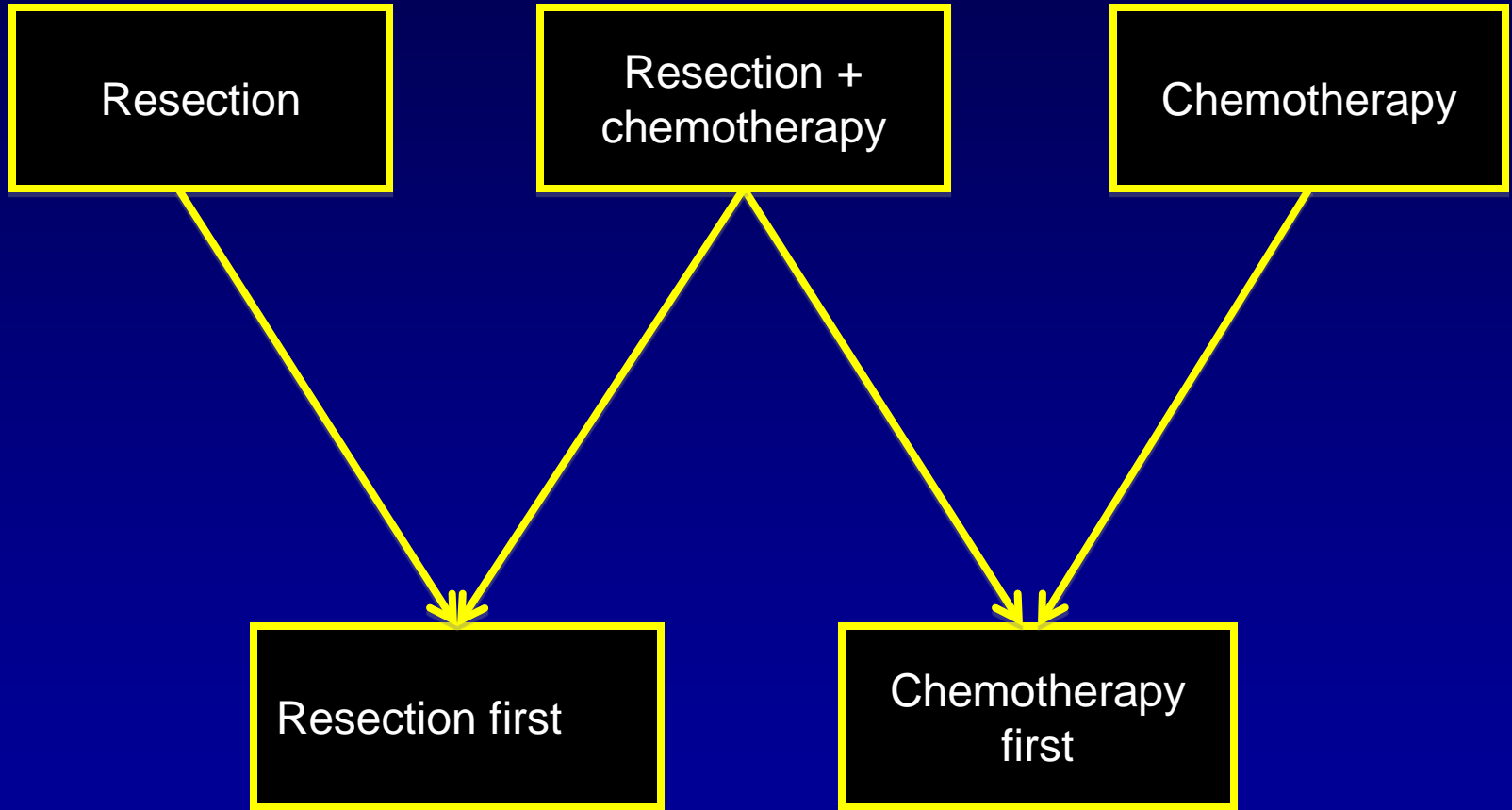
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METHODS

- 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



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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

Trends in Management of Stage IV Colon Cancer

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)