Treatment of Colon Cancer

A Medical Oncologist’s Perspective

4 FEBRUARY 2009
Contents

Colon Cancer
- Overview

Stage II/III Colon Cancer
- Who needs Adjuvant Chemotherapy
- What is best chemo regimen?
- Adjuvant RT? Who needs it?

Advanced Colon Cancer
- Palliative Chemotherapy
- How do we sequence chemotherapy to obtain best outcomes?

Conclusions
Colorectal Cancers Globally

- 3rd most common cancer in (746,000 cases, 10.0% of the total) and 2nd in women (614,000 cases, 9.2% of the total) worldwide.

- Almost 55% of the cases occur in more developed regions.

- Mortality is lower (694,000 deaths, 8.5% of the total) in developed nations,

- More deaths (52%) in the less developed regions of the world
New cases and Deaths

Table 4: Ten Most Frequent Cancers in Singapore Males, 2006-2010

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No.</th>
<th>%</th>
<th>CR (95% CI)*</th>
<th>ASR (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Colorectum</td>
<td>4,456</td>
<td>17.8</td>
<td>49.3 (47.9-50.9)</td>
<td>39.9 (38.7-41.1)</td>
</tr>
<tr>
<td>2</td>
<td>Lung</td>
<td>4,062</td>
<td>16.2</td>
<td>45.0 (43.5-46.4)</td>
<td>37.3 (36.1-38.4)</td>
</tr>
<tr>
<td>3</td>
<td>Prostate</td>
<td>2,860</td>
<td>11.4</td>
<td>31.7 (30.5-32.8)</td>
<td>27.1 (26.1-28.1)</td>
</tr>
<tr>
<td>4</td>
<td>Liver</td>
<td>1,897</td>
<td>7.6</td>
<td>21.0 (20.1-21.9)</td>
<td>17.0 (16.2-17.8)</td>
</tr>
<tr>
<td>5</td>
<td>Stomach</td>
<td>1,579</td>
<td>6.3</td>
<td>17.5 (16.5-16.3)</td>
<td>15.6 (14.3-16.4)</td>
</tr>
<tr>
<td>6</td>
<td>Skin (incl. Melanoma)</td>
<td>1,404</td>
<td>5.6</td>
<td>15.5 (14.7-16.4)</td>
<td>12.8 (12.1-13.5)</td>
</tr>
<tr>
<td>7</td>
<td>Lymphoma</td>
<td>1,247</td>
<td>5.0</td>
<td>13.8 (13.0-14.6)</td>
<td>11.2 (10.5-11.9)</td>
</tr>
<tr>
<td>8</td>
<td>Nasopharynx</td>
<td>1,158</td>
<td>4.6</td>
<td>12.8 (12.1-13.8)</td>
<td>9.5 (8.9-10.0)</td>
</tr>
<tr>
<td>9</td>
<td>Kidney &amp; Other</td>
<td>821</td>
<td>3.3</td>
<td>9.1 (8.5-9.7)</td>
<td>7.2 (6.7-7.7)</td>
</tr>
<tr>
<td>10</td>
<td>Urinary Bladder</td>
<td>759</td>
<td>3.0</td>
<td>8.4 (7.6-9.0)</td>
<td>6.8 (6.3-7.3)</td>
</tr>
<tr>
<td></td>
<td>All Sites</td>
<td>26,097</td>
<td>100.0</td>
<td>277.8 (274.2-281.2)</td>
<td>229.6 (226.7-232.5)</td>
</tr>
</tbody>
</table>

*CR crude rate per 100,000 per year
** ASR Age-standardized rate per 100,000 per year. ASR derived by the direct method using the “World Population”.

Table 5: Ten Most Frequent Cancers in Singapore Females, 2006-2010

<table>
<thead>
<tr>
<th>Rank</th>
<th>Site</th>
<th>No.</th>
<th>%</th>
<th>CR (95% CI)*</th>
<th>ASR (95% CI)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Breast</td>
<td>7,781</td>
<td>29.3</td>
<td>84.4 (82.5-86.2)</td>
<td>80.7 (78.9-82.0)</td>
</tr>
<tr>
<td>2</td>
<td>Colorectum</td>
<td>3,750</td>
<td>14.1</td>
<td>40.7 (39.4-42.0)</td>
<td>38.2 (37.2-39.1)</td>
</tr>
<tr>
<td>3</td>
<td>Lung</td>
<td>2,057</td>
<td>7.7</td>
<td>22.3 (21.3-23.3)</td>
<td>15.3 (14.6-16.0)</td>
</tr>
<tr>
<td>4</td>
<td>Corpus uteri</td>
<td>1,574</td>
<td>5.9</td>
<td>17.1 (16.2-17.8)</td>
<td>12.4 (11.8-13.0)</td>
</tr>
<tr>
<td>5</td>
<td>Ovary</td>
<td>1,455</td>
<td>5.5</td>
<td>15.6 (15.0-16.8)</td>
<td>12.0 (11.4-12.7)</td>
</tr>
<tr>
<td>6</td>
<td>Skin (incl. Melanoma)</td>
<td>1,136</td>
<td>4.3</td>
<td>12.3 (11.6-13.0)</td>
<td>10.3 (9.7-11.0)</td>
</tr>
<tr>
<td>7</td>
<td>Stomach</td>
<td>1,113</td>
<td>4.2</td>
<td>12.1 (11.4-12.8)</td>
<td>8.0 (7.5-8.7)</td>
</tr>
<tr>
<td>8</td>
<td>Cervix uteri</td>
<td>993</td>
<td>3.7</td>
<td>10.6 (10.1-11.4)</td>
<td>7.2 (6.8-7.7)</td>
</tr>
<tr>
<td>9</td>
<td>Lymphoma</td>
<td>960</td>
<td>3.6</td>
<td>10.4 (9.7-11.1)</td>
<td>7.6 (7.0-8.0)</td>
</tr>
<tr>
<td>10</td>
<td>Thyroid</td>
<td>800</td>
<td>3.0</td>
<td>8.8 (8.2-9.4)</td>
<td>6.6 (6.3-7.2)</td>
</tr>
<tr>
<td></td>
<td>All Sites</td>
<td>26,570</td>
<td>100.0</td>
<td>288.0 (284.6-291.5)</td>
<td>208.0 (205.4-210.6)</td>
</tr>
</tbody>
</table>

*CR crude rate per 100,000 per year
** ASR Age-standardized rate per 100,000 per year. ASR derived by the direct method using the “World Population”.
Colorectal Cancer in Singapore

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Conclusions
Taking Stage 3 CRC as an example
Let’s assume 10 patients receive surgery for stage 3 colorectal cancer…..
Colorectal Cancer: What happens after surgery?

- Abt 50% of patients are cured because of surgery alone
Colorectal Cancer: What’s the benefit of chemo?

- Adjuvant Chemotherapy given to ALL stage 3 patients
- With chemotherapy, an additional 20% of patients will be cured
- Arguably, only 20% of patients receiving adjuvant chemotherapy “benefit” from it.
Stratifying patients better in stage 2 colon cancer

SURGERY alone
Spare unnecessary treatment

Give standard Chemotherapy ONLY in patients who BENEFIT

Identify patients who need better treatments
Rationally develop NOVEL treatment for them
List of chemotherapy drugs for Colon Cancer

Chemotherapy
- 5 Fluorouracil / TS-One / Xeloda
- Oxaliplatin
- Irinotecan

Targeting Blood Vessels (Anti-angiogenic)
- Bevacizumab (Avastin)
- Aflibcept (Zaltrap)

Targeting tumor molecular characteristics (Anti-EGFR)
- Cetuximab (Erbitux)
- Panitumumab (Vectibix)

Targeting both molecular characteristics & blood vessels
- Regorafenib (Stivarga)
The evolution of treatment of early colon cancer

5-FU/Lev better than surgery alone (Moertel et al) 1990

HDLV = LDLV
5-FU/LV better than 5-FU/Lev
6mo = 12mo
Lev unnecessary weekly = monthly 1998

5-FU/LV better than surgery alone (IMPACT) 1994

LV5FU2 = monthly bolus (André et al) 2002

FOLFOX better than LV5FU2 (MOSAIC) 2004/2005
FLOX better than 5-FU/LV (NSABP C-07)

Xeloda non-inferior to 5-FU/LV (X-ACT) 2008
Xelox better than 5-FU (XELOXA) 2012

FU/Lev better than surgery alone (Moertel et al) 1990

FU/LV better than surgery alone (IMPACT) 1994
Adjuvant chemotherapy for Resected Stage III or Stage II High Risk CRC

- Chemo is better than no chemo after curative surgery
- 6 months of chemo is equivalent to 12 months
- CI 5FU has better survival outcome and toxicity profile than bolus 5FU
- Capecitabine (Xeloda) can replace 5FU as equivalent (X-ACT trial)
- FOLFOX has better survival outcomes than infusional 5FU (MOSAIC)
- XELOX is better than 5FU/FA (XELOXA trial)
- Thus, FOLFOX and XELOX are interchangeable. (shown in metastatic CRC)
X-ACT: Randomized, multicenter, phase 3 trial

Chemotherapy-naive patients with Duke’s C colorectal cancer, resection ≤8 weeks
(N = 1987)

Capecitabine twice daily, Days 1-4, every 21 days
1250 mg/m² orally
(n = 1004)

5-FU 425 mg/m² IV bolus +
Leucovorin 20 mg/m² IV
Days 1-5 every 28 days
(n = 983)

24 Weeks

Table 2. Efficacy for the Major End Points over a Median Follow-up Period of 3.8 Years.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Total No. of Patients</th>
<th>No. of Patients with Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Equivalence</th>
<th>P Value for Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1004</td>
<td>348</td>
<td>0.87 (0.75–1.00)</td>
<td>&lt;0.001†</td>
<td>0.05</td>
</tr>
<tr>
<td>Fluorouracil plus leucovorin</td>
<td>983</td>
<td>380</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse-free survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1004</td>
<td>327</td>
<td>0.86 (0.74–0.99)</td>
<td>—</td>
<td>0.04</td>
</tr>
<tr>
<td>Fluorouracil plus leucovorin</td>
<td>983</td>
<td>362</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1004</td>
<td>200</td>
<td>0.84 (0.69–1.01)</td>
<td>&lt;0.001‡</td>
<td>0.07</td>
</tr>
<tr>
<td>Fluorouracil plus leucovorin</td>
<td>983</td>
<td>227</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety Profile

Toxicities
Capecitabine > HFS
5-FU > diarrhea, stomatitis, neutropenia, nausea, vomiting

G3/4

Patients (%)
MOSAIC: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4 (n=1123)</th>
<th>LV5FU2 (n=1123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Male/Female %</td>
<td>56/44</td>
<td>52/48</td>
</tr>
<tr>
<td>KPS 80-100 %</td>
<td>86.2</td>
<td>87.6</td>
</tr>
<tr>
<td>Stage II/III %</td>
<td>40/60</td>
<td>40/60</td>
</tr>
<tr>
<td>Bowel obstruction %</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Perforation %</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Stage 2: 40%
(25% High Risk Stage 2; 15% not)

Stage 3: 60%
Stage 3.1-4 LN: 45%
Stage 3 >=4 LN: 15%

Statistical hypotheses Stage II / III ratio = 40 / 60%
Expected 3-year DFS: 79% vs 73%
HR 0.75
N = 2200 power of 90% (α=0.05)

5 year Disease-Free Survival: Stage II and Stage III Patients

Overall Survival: Stage II and Stage III

<table>
<thead>
<tr>
<th>5 year DFS</th>
<th>6 Year OS</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FOLFOX</td>
<td>5FU</td>
</tr>
<tr>
<td>All patients</td>
<td>73.3%</td>
<td>67.4%</td>
</tr>
<tr>
<td>Stage III</td>
<td>66.4%</td>
<td>58.9%</td>
</tr>
<tr>
<td>Stage II</td>
<td>83.7%</td>
<td>79.9%</td>
</tr>
<tr>
<td>High Risk Stage II</td>
<td>82.3%</td>
<td>74.6%</td>
</tr>
</tbody>
</table>

NB: all patients DFS @ 3 years 72% vs 65% HR 0.76
↑ benefit if ↑ Risk
NSABP C07
RP ± Oxali

Four-year DFS rates
73.2%
67.0%
seven-year median follow-up
DFS
(F=0.0017, HR 0.81)
no statistically significant differences in overall survival (hazard ratio=0.88; 95% CI, 0.76-1.03; P=0.1173)
nor colon-cancer specific mortality (hazard ratio=0.88; 95% CI, 0.74-1.05; P=0.1428)

More toxic than FOLFOX (cross trial)
Grade 3 diarrhea, and dehydration were higher with FLOX than with 5-FU/LV
38% and 32% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV, respectively (P=0.003)

7% bowel wall injury (gut wall edema CT scan) in FLOX

Table 2, Percentage of Patients With Grade 3 or 4 Toxicity by the NCI Common Toxicity Criteria Version 2.0

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>FULV Toxicity Grade 2</th>
<th>FULV Toxicity Grade 3</th>
<th>FULV Toxicity Grade 4</th>
<th>FLOX Toxicity Grade 2</th>
<th>FLOX Toxicity Grade 3</th>
<th>FLOX Toxicity Grade 4</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>31.6</td>
<td>0.6</td>
<td>0.6</td>
<td>36.0</td>
<td>1.1</td>
<td>1.1</td>
<td>.003</td>
</tr>
<tr>
<td>Dehydration</td>
<td>11.3</td>
<td>0.5</td>
<td>0.5</td>
<td>10.1</td>
<td>1.1</td>
<td>1.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11.0</td>
<td>0.0</td>
<td>0.0</td>
<td>15.0</td>
<td>0.0</td>
<td>&lt;.001</td>
<td>.76</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.7</td>
<td>0.7</td>
<td>0.7</td>
<td>12.0</td>
<td>0.7</td>
<td>0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.9</td>
<td>0.7</td>
<td>0.7</td>
<td>4.9</td>
<td>0.4</td>
<td>0.4</td>
<td>.16</td>
</tr>
<tr>
<td>NCI-Sanofi Neurosensory†</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
<td>8.2</td>
<td>0.2</td>
<td>0.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>3.8</td>
<td>1.1</td>
<td>1.1</td>
<td>3.2</td>
<td>1.4</td>
<td>1.4</td>
<td>.76</td>
</tr>
</tbody>
</table>

NOTE. Based on all randomly assigned patients with data: 1,230 patients receiving FULV and 1,234 patients receiving FLOX. NCI-Sanofi Neurosensory toxicity used 1,226 patients receiving FULV and 1,232 patients receiving FLOX.

Abbreviations: NCI, National Cancer Institute; FULV, fluorouracil and leucovorin; FLOX, fluorouracil, leucovorin, and oxaliplatin.

†Fisher’s exact test for difference in rate of grade 3 or 4 toxicity across treatments.
Adjuvant XELOX vs 5-FU/LV: NO16968 (XELOX/A) Phase III trial

Randomisation

n=944

XELOX (6 months)
capecitabine 1000mg/m² bid d1–14
oxaliplatin 130mg/m² d1
q3w
8 cycles

Bolus 5-FU/LV (6 months)
Mayo Clinic [n=664]
or
Roswell Park [n=278]

Primary endpoint: superiority of DFS
Secondary endpoints: RFS, OS, tolerability

Primary tumour (%)
T1 3
T2 8
T3 74
T4 15

Regional lymph nodes (%)
N1 65
N2 35

Number of lymph nodes examined
<8 23
8–12 26
>12 51
Stage II High Risk patients: Adjuvant therapy increases survival—evidence from 20,898 patients

Surgery alone: 66.8%
Surgery + FU-based chemotherapy: 72.2%

Δ=5.4%
p=0.026

Surgery alone: 42.7%
Surgery + FU-based chemotherapy: 53.0%

Δ=10.3%
p<0.0001
IDEA: International Duration Evaluation in Adjuvant colon cancer

Worldwide effort to address duration question of oxaliplatin (3 vs 6 mos)

Common question

What is the optimal duration of adjuvant chemotherapy?

N>10,500 stage III patients receiving oxaliplatin-based adjuvant chemo

Joint analysis of at least 6 trials
Elderly patients still benefit from adjuvant 5FU

Meta-analysis of 7 randomized trials
(n = 3351, 15% > 70 yo, 0% > 80 yo)

Greater toxicities among elderly patients
Patient selection is crucial
Conflicting data for benefit of addition of adjuvant Oxaliplatin in the elderly

### Cross-trial comparison: Age

<table>
<thead>
<tr>
<th></th>
<th>NSABP C-07&lt;sup&gt;1&lt;/sup&gt;</th>
<th>MOSAIC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>NO16968</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FLOX*</td>
<td>FOLFOX*</td>
<td>XELOX*</td>
</tr>
<tr>
<td>Age, years</td>
<td>&lt;70</td>
<td>≥70</td>
<td>&lt;70</td>
</tr>
<tr>
<td>DFS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.66–0.88)</td>
<td>1.03 (0.77–1.36)</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.80 (0.67–0.94)</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.80 (0.68–0.95)</td>
<td>1.18 (0.86–1.62)</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.82 (0.67–1.01)</td>
</tr>
</tbody>
</table>

*Comparison vs 5-FU/LV

na: not available

2. Tournigand et al, JCO 2010;28:15s (abstr 3522)
No role for Adjuvant Irinotecan in resected CRC:

Several trials have shown this
Absolutely NO role for biologics as adjuvant therapy in CRC

FOLFOX/XELOX + Bevacizumab

Vs FOLFOX/XELOX

NSABP C-08 AVANT
All NEGATIVE
QUASAR-2

AVANT trial

NSABP C-08 trial
Allegra CJ et al. JCO 2013;31(3):359
Detrimental effect of adding Cetuximab to adj chemo even if KRAS WT

PETACC-8

Intergroup 0147

NEGATIVE

Disease Free Survival (N=1847)

<table>
<thead>
<tr>
<th>Arm</th>
<th>3 Year Rates (95% CI)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX N=902</td>
<td>75.8% (72.1%-79.6%)</td>
<td>1.2 (0.96-1.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>FOLFOX+Cmab N=945</td>
<td>72.3% (68.5%-76.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjuvant chemotherapy for colon cancers

Recommended for patients with

Stage III colon cancers

High risk Stage II colon cancers

- Clinically obstructed or perforated tumours
- Poorly differentiated histology
- Lymphovascular/perineural invasion histology
- Inadequate lymph nodes sampling (less than 13).
**NCCN Guidelines Version 2.2015**

**Colon Cancer**

### PATHOLOGIC STAGE

- Tis; T1, N0, M0
  - Adjuvant Therapy: None

- T2, N0, M0
  - Observation

- T3, N0, M0
  - Clinical trial
  - Observation
  - Consider capecitabine or 5-FU/leucovorin

- T3, N0, M0 at high risk for systemic recurrence
  - FOLFOX or CapeOx
  - Clinical trial
  - Observation

- T4, N0, M0
  - Clinical trial
  - Observation

### SURVEILLANCE

- Colonoscopy at 1 y
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma, repeat in 3 y, then every 5 y

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT annually for up to 5 y for patients at high risk for recurrence
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo
- If advanced adenoma, repeat in 1 y
- If no advanced adenoma, repeat in 3 y, then every 5 y
- PET-CT scan is not routinely recommended

### Node-positive disease

- See COL-4

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Notes:
- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Summary: Adjuvant therapy for Colon Cancer

FOLFOX was the only real step forward since 5FU/LEV in 1990
Negative Irinotecan studies
Negative Bevacizumab studies
Negative Cetuximab studies

We offer adjuvant chemotherapy to all stage 3 and high-risk stage 3 colorectal cancer patients

For stage 3 CRC, we prefer XELOX or FOLFOX x 6 months

For high risk stage 2 CRC, we prefer Xeloda or 5FU alone x 6 months
Contents

Colorectal Cancer
- Overview

Stage II/III Colorectal Cancer
- Who needs Adjuvant Chemotherapy
- What is best chemo regimen?
- Adjuvant RT? Who needs it?

Advanced Colorectal Cancer
- Resectable metastatic disease
- Palliative Chemotherapy
- How do we sequence chemotherapy to obtain best outcomes?

Conclusions
Metastatic Colorectal Cancer
Low disease burden, generally with a single solitary site of spread

Chemotherapy & Surgical removal of the site of metastasis with the intention of achieving cure
Liver resection improves long-term survival

- 12-month landmark analysis evaluated the impact of liver resection on OS

Liver resection dramatically improves long-term survival and offers a real chance for cure

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Median OS (mo)</th>
<th>5-year OS rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>65.3</td>
<td>55%</td>
</tr>
<tr>
<td>Non resected</td>
<td>26.7</td>
<td>19.5%</td>
</tr>
<tr>
<td>HR</td>
<td>0.35</td>
<td></td>
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</tbody>
</table>

Error bars represent 95% CIs


70% of population included
Collaboration is essential from diagnosis onwards
NCCN Guidelines Version 2.2015
Colon Cancer

RESECTABLE METACHRONOUS METASTASES

**PRIMARY TREATMENT**

- Resection\(^{CC}\)
- Neoadjuvant chemotherapy (2–3 mo)
  - FOLFOX or CapeOx (preferred)
  - FLOX or Capecitabine or 5-FU/leucovorin

**ADJUVANT TREATMENT**

- No growth on neoadjuvant chemotherapy
  - Reinitiate neoadjuvant therapy\(^{hh}\)
    - or FOLFOX
  - Growth on neoadjuvant chemotherapy
    - Active chemotherapy regimen\(^{hh}\)
      - (See COL-C)
      - or Observation

- Observation (preferred for previous oxaliplatin-based therapy)

- Neoadjuvant chemotherapy (2–3 mo) (See COL-C)

- Resection\(^{CC}\)

- No growth on neoadjuvant chemotherapy
  - Reinitiate neoadjuvant therapy\(^{hh}\)
    - or FOLFOX
  - Growth on neoadjuvant chemotherapy
    - Active chemotherapy regimen\(^{hh}\)
      - (See COL-C)
      - or Observation

- Previous chemotherapy

- Neoadjuvant chemotherapy (2–3 mo) (See COL-C)

- Resection\(^{CC}\)

- No growth on neoadjuvant chemotherapy
  - Reinitiate neoadjuvant therapy\(^{hh}\)
    - or FOLFOX
  - Growth on neoadjuvant chemotherapy
    - Active chemotherapy regimen\(^{hh}\)
      - (See COL-C)
      - or Observation

---

\(^{CC}\) Hemic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

\(^{hh}\) Total duration of perioperative chemotherapy should not exceed 6 months.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Stage 4 Colorectal Cancer is a Continuum from curable disease to incurable disease

Curable

- Low disease burden, generally with a single solitary site of spread
- Chemotherapy & Surgical removal of the site of metastasis with the intention of achieving cure

Incurable

- High disease burden with widespread metastatic cancer

1st line Palliative Chemotherapy

2nd line Palliative Chemotherapy

3rd line Palliative Chemotherapy

Experimental therapy or stop all active cancer treatment (@BSC)
Systemic therapy for CRC has improved survival over the years

Treatment Approaches to mCRC

Overall Survival (months)

- **FU/LV bolus**
  - Saltz: 5.0
- **FU/LV infusion**
  - Douillard: 5.0
  - Saltz: 5.0
- **IFL**
  - Douillard: 14.8
  - Goldberg: FOLFOX: 19.5
- **LVFU2/irinotecan**
  - Hurwitz: IFL + bevacizumab: 20.3
  - Falcone: FOLFOX/FOLFIRI: 22.6
- **XELOX/FOLFOX + bevacizumab**
  - Saltz: 21.3
  - Bokemeyer: FOLFOX + cetuximab: 22.8*
- **FOLFIRI + cetuximab**
  - Van Cutsem: FOLFIRI + cetuximab: 23.5*
  - Douillard: FOLFOX + panitumumab: 23.9*
- **FOLFOX + panitumumab**
  - Falcone/Heinemann: FOLFIRI + bevacizumab: 25.0 - 25.8
  - Heinemann: FOLFIRI + cetuximab: 28.8*
  - Falcone: FOLFOXIRI + bevacizumab: 31.0

*KRAS wildtype tumors.

Note: Informal comparison as these are not head-to-head clinical trials.

FOLFOX vs CAPOX

• Lower RR with CAPOX but similar PFS and OS
• FOLFOX less grade 3/4
  – Hand-foot syndrome
  – Thrombocytopenia
  – Diarrhoea
• CAPOX less grade 3/4
  – Neutropenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen*</th>
<th>No. of Patients</th>
<th>RR (%)</th>
<th>Progression Free</th>
<th>Overall</th>
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<td>NO16966*17,18</td>
<td>XELOX, FOLFOX</td>
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<td>46</td>
<td>8.0</td>
<td>19.8</td>
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<td>US TREE, cohort 19</td>
<td>CAPOX, mFOLFOX</td>
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<td>27</td>
<td>5.9</td>
<td>17.2</td>
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<tr>
<td>US TREE, cohort II*19</td>
<td>CAPOX, mFOLFOX</td>
<td>72</td>
<td>46</td>
<td>10.3</td>
<td>24.6</td>
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<tr>
<td>Italian GOAM*20</td>
<td>XELOX</td>
<td>62</td>
<td>43</td>
<td>9.0</td>
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<td>German AIO*21</td>
<td>CAPOX, FUFOX</td>
<td>242</td>
<td>48</td>
<td>7.1</td>
<td>16.8</td>
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<tr>
<td>Spanish TTD*22</td>
<td>XELOX, FUOX</td>
<td>171</td>
<td>37</td>
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<td>18.1</td>
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<tr>
<td>French study*23</td>
<td>XELOX, FOLFOX6</td>
<td>144</td>
<td>42</td>
<td>9.3</td>
<td>19.9</td>
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</tbody>
</table>
FOLFOX vs FOLFIRI
GERCOR (V-308): Overall survival

FOLFOX and FOLFIRI were equivalent (GERCOR)
FOLFOXIRI = 5FU + oxaliplatin + irinotecan

- Triplet chemotherapy resulted in a very high RR and R0 resection rate compared to the standard doublet.
- Triplet chemotherapy also resulted in an improved OS.
- However, triplet chemotherapy is associated with higher toxicities.
- We still don’t know really know whether triplet chemo is superior if compared to sequential FOLFOX/FOLFIRI.
Combination vs sequential therapy

Upfront combination chemotherapy should remain the first choice of treatment for fit patient.

However sequential therapy remains a viable alternative for some patients.

Eventual exposure to all three drugs was associated with a longer OS.
Stop and go strategy

Stop-and-go strategy may provide respite to patients without compromising survival.

Maintenance chemo appeared more favourable than chemo-free interval.

The choice between chemo-free interval or maintenance chemotherapy should be discussed with patients as the difference in outcome is small.
Bevacizumab is useful as 1\textsuperscript{st} line therapy

Bevacizumab + 5FU/irinotecan resulted in improved OS when compared to 5FU/irinotecan in 1\textsuperscript{st} line

Bevacizumab as a single agent has little or no activity. Addition of Bev improves survival of patients previously refractory to chemotherapy.

Bev is useful in 2\textsuperscript{nd} line therapy


FOLFOX/BEV

FOLFOX

BEV

Probability

PFS (months)

A
B
C

Patients At the Heart of Clinical Care
BRiTE study – continuation bevacizumab beyond progression may be beneficial

![Graph showing survival rates](image-url)
Summary

Single agent BEV had little or no activity.

BEV added to combination chemotherapy was superior to chemotherapy alone.

BEV used beyond disease progression could play a role in improving survival.
Cetuximab is useful as single agent

Figure 1. Kaplan–Meier Curves for Overall Survival (Panel A) and Progression-free Survival (Panel B).

1st line: Cetuximab improves survival when added to FOLFIRI in RAS wild type (CRYSTAL trial)

Response rate: 46.9% vs 38.7%, p=0.004
In KRAS WT: 59.3% vs 43.2%, p=0.0025
1\textsuperscript{st} line: Cetuximab with FOLFOX improved survival (OPUS trial)


RR: 61\% vs 37\% in KRAS WT, \( p=0.011 \)
PRIME study: Panitumumab added to FOLFOX improved survival

KRAS WT  

KRAS MUTANT
Cetuximab added to Irinotecan is active in 2\textsuperscript{nd}- and 3\textsuperscript{rd}-line

Cetuximab + IRI improved RR and PFS in pts who failed 1\textsuperscript{st}-line IRI (BOND1)

Cetuximab + IRI improved RR and PFS in pts who failed 1\textsuperscript{st}-line FU/OX (EPIC study)

Cetuximab + IRI resulted in a RR of 25% in pts who failed FU/IRI and FU/OX (Danish study)

\textit{Alberto F. Sobrero, et al. JCO 26: 2311-2319, 2008}
Combining BEV + EGFR inhibitor and chemo results in negative outcome:

CALGB 80405: FOLFOX or FOLFIRI + Bevacizumab vs FOLFOX or FOLFIRI + Cetuximab in KRAS WT CRC
<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>ORR</th>
<th>PFS</th>
<th>PFS HR</th>
<th>OS</th>
<th>OS HR</th>
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<td>AVF2107g</td>
<td>IFL</td>
<td>35%</td>
<td>6.4</td>
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<td>15.6</td>
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<tr>
<td></td>
<td>+ Bevacizumab</td>
<td>45%</td>
<td>10.6</td>
<td><strong>0.54</strong></td>
<td>20.3</td>
<td><strong>0.66</strong></td>
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<td>7.9</td>
<td></td>
<td></td>
<td>20.2</td>
<td></td>
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<tr>
<td></td>
<td>+ panitumumab</td>
<td>10.1</td>
<td></td>
<td><strong>0.72</strong></td>
<td>26</td>
<td><strong>0.72</strong></td>
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<td>FOLFIRI</td>
<td>8.4</td>
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<td></td>
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<tr>
<td></td>
<td>+ Cetuximab</td>
<td>11.4</td>
<td></td>
<td><strong>0.56</strong></td>
<td>28.4</td>
<td><strong>0.69</strong></td>
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<tr>
<td>TRIBE</td>
<td>FOLFIRI/Bev</td>
<td>53%</td>
<td>9.7</td>
<td></td>
<td>25.8</td>
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</tr>
<tr>
<td></td>
<td>FOLFOXIRI/Bev</td>
<td>65%</td>
<td>12.1</td>
<td><strong>0.75</strong></td>
<td>31</td>
<td><strong>0.79</strong></td>
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<td>FIRE3</td>
<td>FOLFIRI/Bev</td>
<td>56%</td>
<td>10.2</td>
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<tr>
<td></td>
<td>FOLFIRI/Cet</td>
<td>71%</td>
<td>10.4</td>
<td><strong>0.93</strong></td>
<td>33.1</td>
<td><strong>0.7</strong></td>
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<tr>
<td>CALGB</td>
<td>Chemo + Bev</td>
<td>57%</td>
<td>11.3</td>
<td></td>
<td>31.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemo + Cet</td>
<td><strong>69%</strong></td>
<td>11.4</td>
<td><strong>1.1</strong></td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>
Summary

Panitumumab or Cetuximab are active as single agents.

Cetuximab added to Irinotecan or oxaliplatin was active in 1\textsuperscript{st}, 2\textsuperscript{nd}- and 3\textsuperscript{rd}-line treatment.

Panitumumab added to irinotecan or oxaliplatin was active in 1\textsuperscript{st} and 2\textsuperscript{nd} line treatment.

Cetuximab and Panitumumab therapy should only be used in patients with extended RAS wild type.
Regorafenib in nth line

An oral multi-kinase inhibitor which inhibits VEGFRs, PDGFR, Ret, Kit and Raf kinases.

**CORRECT study design**

- **Randomization**
  - mCRC after standard therapy
  - 2:1
  - Regorafenib + BSC
    - 160 mg orally once daily
    - 3 weeks on, 1 week off
  - Placebo + BSC
    - 3 weeks on, 1 week off

**Primary Endpoint: OS**
- 90% power to detect 33.3% increase (HR=0.75), with 1-sided overall $\alpha=0.025$

Grothey 2013
Overall survival (primary endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Regorafenib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>6.4 mos</td>
<td>5.0 mos</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9–7.3</td>
<td>4.4–5.8</td>
</tr>
</tbody>
</table>

Hazard ratio: 0.77 (95% CI: 0.64–0.94)
1-sided p-value: 0.0052

Primary endpoint met prespecified stopping criteria at interim analysis
(1-sided p<0.009279 at approximately 74% of events required for final analysis)
TAS 102 in 3\textsuperscript{rd} line:

TAS-102 is an oral combination anticancer drug of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA.

<table>
<thead>
<tr>
<th>RECOREUSE (3\textsuperscript{rd} line)</th>
<th>TAS-102 (n=534)</th>
<th>Placebo (n=266)</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>2.0 mo</td>
<td>1.7</td>
<td>0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median OS</td>
<td>7.1 mo</td>
<td>5.3 mo</td>
<td>0.68</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Ohtsu GI ESMO 2014
Conclusions: Metastatic Colorectal Cancer

Resection of metastases can render cure in selected patients +/- “adjuvant” chemotherapy

Oxaliplatin-based and irinotecan-based chemo with 5FU are interchangeable

Addition of bevacizumab to chemo increases survival

Addition of panitumumab or cetuximab to chemo in RAS WT increases survival.

In RAS WT, bevacizumab + chemo vs cetuximab + chemo are equivalent

Regorafenib is active in heavily pre-treated met CRC
NCCN Guidelines Version 2.2015
Colon Cancer

UNRESECTABLE METACHRONOUS METASTASES

- Previous adjuvant FOLFOX/CapeOx within past 12 months
- Previous adjuvant FOLFOX/CapeOx >12 months
- Previous 5-FU/LV or capecitabine
- No previous chemotherapy

PRIMARY TREATMENT

- FOLFIRI ± bevacizumab
- FOLFIRI ziv-aflibercept
- Irinotecan ± bevacizumab
- Irinotecan ± ziv-aflibercept
- FOLFIRI + (cetuximab or panitumumab)
  (KRAS/NRAS WT gene only)
- FOLFIRI + (Cetuximab or panitumumab)
  (KRAS/NRAS WT gene only)

Re-evaluate for conversion to resectable every 2 mo if conversion to resectability is a reasonable goal

- Converted to resectable
  - Resection (See COL-C)
  - Observation

- Remains unresectable
  - Active chemotherapy regimen (See COL-C)

---

^See Principles of Pathologic Review (COL-A 4 of 5) - KRAS, NRAS and BRAF Mutation Testing.
^See Principles of Surgery (COL-B 2 of 3).
^Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
^Total duration of perioperative chemotherapy should not exceed 6 months.
^Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest a lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SGH Campus

Largest Concentration of Medical Services & Facilities

SingHealth General Hospital

- Beds: 1,637
- Total Doctors: 1,226
- SOC visits: 1,214,878 p.a.
- Surgeries: 116,269 p.a.
- DEM attendances: 144,973 (400/day)

Singapore General Hospital

National Cancer Centre Singapore
National Dental Centre of Singapore
National Heart Centre Singapore
Singapore National Eye Centre
National Neuroscience Institute (SGH Campus)

* Beds in service
Thank you

Questions?