Reduced Duration of Adjuvant FOLFOX in Stage III Colon Cancer - A Bright IDEA?

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Objectives:
1. Describe the role of adjuvant chemotherapy in colon cancer
2. List the adverse effects limiting adjuvant chemotherapy completion and advantages of reduced duration of adjuvant chemotherapy in colon cancer
3. Summarize current guideline recommendations and results of recent literature describing adjuvant chemotherapy duration in colon cancer
4. Recommend or refute reduced adjuvant chemotherapy duration in colon cancer
Colorectal Cancer (CRC)

I. Epidemiology
   A. Incidence\(^1\)\(^\text{-}^2\)
      i. Third most common cancer with an estimated 1.2 million new cases per year
      ii. Estimated 95,520 new cases of colon cancer in the United States (US) per year
      iii. Lifetime risk of developing CRC is approximately 1 in 21 men (4.7%) and 1 in 23 women (4.4%)
   B. Prognosis\(^1\)\(^\text{-}^3\)
      i. Stage at diagnosis is the most important prognostic factor, with the following 5-year relative survival estimates:
         a. Localized disease: 90.1%
         b. Regional tumor spread: 69.2%
         c. Distant tumor spread: 11.7%
      ii. Despite curative resection, nearly half of all patients will die from metastatic disease originating from residual microscopic disease not evident at the time of surgery
   C. Survival\(^1\)\(^\text{-}^5\)
      i. CRC is the third leading cause of cancer-related death in men and women in the US
      ii. CRC is the fourth leading cause of cancer-related death globally with an expected 50,250 deaths from CRC in the US in 2017
      iii. Five-year relative survival is nearly 65% in high-income countries, but remains less than 50% in low-income countries
      iv. Incidence stabilization and death reduction likely due to improved screening and polyp removal in the US
   D. Risk factors\(^1\)\(^\text{-}^2\)\(^,^6\)\(^\text{-}^7\)
      i. Older age – incidence strongly increases with age, with a median age of diagnosis of 70 years in developed countries
      ii. Male gender
      iii. Race – incidence of CRC is 12.3% higher in African Americans compared to Caucasians
      iv. Family history of CRC or polyps - an estimated 35% of CRC risk may be contributed to heritable factors
      v. Inflammatory bowel disease – chronic ulcerative colitis or Crohn’s colitis leading to dysplasia and genetic mutations associated with cell injury or cell repair
      vi. Smoking – carcinogens found in cigarettes
      vii. Excessive consumption of alcohol, red meat, and processed meat
      viii. Obesity – increased risk of CRC due to carcinogens found in unhealthy diets
      ix. Diabetes – CRC is hypothesized to be linked with diabetes induced intestinal or colonic structural and biomechanical remodeling, leading to diabetes complications such as diarrhea, constipation, gastroparesis, and microbiotic changes
      x. Infection – *Helicobacter pylori*, human papilloma virus, and JC virus have been associated with CRC due to disruption of microflora in the gut
      xi. Geography
         a. The highest incidence of CRC is reported in Europe, North America, and Oceania, with the lowest incidence reported in South Asia, Central Asia, and Africa
         b. Highly associated with “western diet” rich in saturated fats

II. Pathophysiology
   A. Polyps, or issue growths from the inner lining of the colon into the lumen, may be considered precancerous and transform into malignant growths
i. Adenoma – carcinoma pathway\(^1,3,8-10\)
   a. Characterized by the slow development of dysplastic adenoma premalignant lesions, often over more than 7 years
   b. Adenomas may be classified as tubular or villous
   c. Genetic mutations
      1. Adenomatous polyposis coli (APC) – inactivated gene in more than 70% of colorectal adenomas leading to deactivation of tumor suppression
      2. KRAS – activated oncogene in the adenoma-carcinoma sequence found in 50% of colon cancers that leads to colonocyte replication and reduces the efficacy of anti-EGFR monotherapy to nearly 0%
      3. P53 – tumor suppressor gene that is inactive in the adenoma-carcinoma sequence

ii. Serrated adenoma – carcinoma pathway\(^1,3,8-11\)
   a. Characterized by moderate development of hyperplastic, sessile, often flat lesions over approximately 3 to 5 years
   b. Characterized by high microsatellite instability (MSI-H), which is found in approximately 15% of sporadic colon cancer
   c. Genetic mutations
      1. BRAF – mutation almost exclusive to sporadic MSI-H type and therefore useful in tumor characterization
      2. CpG island methylator phenotype (CIMP) – mutation leading to global genome hypermethylation, resulting in tumor suppressor gene inactivation
      3. hMLH1 – DNA mismatch repair gene inactivated by DNA methylation
   d. MSI-H and wild type KRAS/BRAF status are associated with improved prognosis

Figure 1. Progression from polyp to cancer

B. Syndromic colon cancer\(^1,3,9\)
   i. Familial adenomatous polyposis (FAP)
      a. Characterized by hundreds to thousands of adenomatous colonic polyps
      b. Transformation into carcinoma is inevitable without colectomy
      c. Caused by inherited single autosomal dominant mutation of the APC gene located on chromosome 5q
ii. Hereditary nonpolyposis colon cancer (HNPCC)
   a. Characterized by few colonic polyps
   b. Genetic etiology associated with genetic mutations of mismatch repair genes
   c. Prevention of repairs to spontaneous DNA errors leads to progressively accumulating mutations in oncogenes and tumor suppressor genes

III. Screening and prevention
   A. Screening\textsuperscript{1,12}
      i. American College of Gastroenterology – colonoscopy every 10 years beginning age 50
         a. Screening in African Americans should begin at age 45
         b. Earlier screening recommended in patients with increased risk of CRC
      ii. CRC prevention alternatives should be offered when colonoscopy is not feasible
         a. Flexible sigmoidoscopy every 5 to 10 years
         b. Computed tomography (CT) colonography every 5 years
      iii. CRC detection tests should be offered when colonoscopy is not feasible
         a. Fecal immunochemical test (FIT) annually
         b. Fecal DNA testing very 3 years
   B. Chemoprevention
      i. Aspirin\textsuperscript{1,13-14}
         a. Clinical trial and observational data suggest reduction of CRC risk with doses as low as 325 mg daily
         b. Secondary analyses of cardiovascular trials suggest that doses as low as 81 mg daily may be effective in CRC risk reduction
         c. Benefits of aspirin for CRC risk reduction are counterbalanced by the risk of gastrointestinal adverse effects
         d. The United States Preventative Service Task Force (USPSTF) recommends low-dose aspirin for primary prevention of CRC in adults with all of the following:
            1. Ages 50 to 59
            2. With $\geq$10% cardiovascular disease risk
            3. Not at an increased risk for bleeding
            4. With life expectancy of at least 10 years
            5. Willing to take low-dose aspirin daily for at least 10 years
      ii. Vitamin D\textsuperscript{1,3,10,15}
         a. Binds to receptors found in colon cancer cell-lines to activate or repress gene expression, leading to antineoplastic properties
         b. Meta-analyses have shown an inverse linear relationship between vitamin D levels and CRC mortality
         c. Current National Comprehensive Cancer Network (NCCN) guidelines do not recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with CRC
   C. Lifestyle modification\textsuperscript{1}
      i. Prevention of modifiable risk factors such as obesity
      ii. Reduction or cessation of modifiable risk factors such as smoking and alcohol consumption

IV. Signs and symptoms\textsuperscript{16}
   A. Changes in bowel habits
   B. Dark or bloody stool
   C. Rectal bleeding
   D. Abdominal pain
   E. Weight loss
   F. Weakness and fatigue
   G. Intestinal obstruction or perforation
V. Diagnosis and staging\textsuperscript{1,3}
   A. Diagnosis is determined histologically by biopsy sample taken during endoscopy
      i. Complete colonoscopy or CT colonography is required to detect any synchronous cancers
      ii. Additional imaging is required to rule out distant metastases, which is found in approximately 20% of newly diagnosed cases of CRC
         a. The liver is the most common site of metastasis
         b. Routine imaging for lung metastases is also recommended
   B. TNM classification (Appendix A)
      i. T = local invasion depth
      ii. N = lymph node involvement
      iii. M = distant metastases
   C. Stage III is indicative of locally advanced disease while stage IV is indicative of metastatic disease

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Treatment of Colon Cancer

VI. Surgery – cornerstone of resectable CRC treatment\textsuperscript{1,3,10}
   A. Resection of affected segment of bowel, adjacent mesentery, and draining lymph nodes
   B. Open vs. laparoscopic colectomy approach
      i. Laparoscopic colectomy is non-inferior to open colectomy with similar rates of intraoperative complications and postoperative mortality
      ii. Laparoscopic colectomy is associated with shorter perioperative recovery, hospital stay, and duration of narcotic and analgesic use
      iii. Open colectomy recommended over laparoscopic colectomy in complicated disease (acute obstruction, acute perforation, or locally invasive disease into surrounding structures)
   C. Anastomosis vs. colostomy\textsuperscript{17-18}
      i. Despite a goal of tension-free primary anastomosis during colectomy, colostomy may be required in complicated cases of colonic perforation or obstruction
      ii. Primary anastomosis cannot be performed in the setting of:
         a. Diffuse peritonitis
         b. Free perforation – spilling of bowel contents freely into the abdominal cavity leading to diffuse peritonitis
         c. Obstructing left-sided colon cancer – high bacterial counts in the feces-containing left colon may lead to increased rates of sepsis
   D. Timing of ostomy closure\textsuperscript{19}
      i. Stoma closure typically occurs 6 to 12 weeks after initial surgery, but timing is dependent on resolution of contributing indications for colostomy
      ii. When indicated, adjuvant chemotherapy should be completed before ostomy closure to prevent delays in chemotherapy treatment due to surgical complications

VII. Adjuvant therapy – treatment after surgical tumor resection\textsuperscript{1,3,10}
   A. Risk for relapse exists after surgical resection of macroscopic disease
      iii. Stage III colon cancer recurrence risk is estimated to range between 15% and 50%
      iv. Adjuvant therapy can reduce risk of recurrence by 40% to 50% in high-risk patients
      v. Six months of adjuvant chemotherapy is recommended for all patients with stage III colon cancer without contraindications after curative resection
      vi. Adjuvant therapy may be considered in high-risk stage II colon cancer
Table 1. Adjuvant Chemotherapy Treatment Options in Colon Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Components</th>
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</table>
| mFOLFOX6 – every 2 weeks x 24 weeks (12 cycles) | • Oxaliplatin 85 mg/m² IV on day 1  
• Leucovorin 400 mg/m² IV on day 1  
• 5-FU 400 mg IV bolus then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46-48 hours) continuous IV infusion |
| CapeOx – every 3 weeks x 24 weeks (8 cycles) | • Oxaliplatin 130 mg/m² IV on day 1  
• Capecitabine 1000 mg/m² PO twice daily on days 1-14 |
| FLOX – every 8 weeks x 24 weeks (3 cycles) | • 5-FU 500 mg/m² IV bolus weekly x 6 weeks  
• Leucovorin 500 mg/m² IV weekly x 6 weeks  
• Oxaliplatin 85 mg/m² IV on weeks 1, 3, and 5 |
| 5-fluorouracil/leucovorin (5-FU/LV) – every 8 weeks x 24 weeks (4 cycles) or every 2 weeks (12 cycles) | • Leucovorin 500 mg/m² IV over 2 hours weekly x 6 weeks  
• 5-FU 500 mg/m² IV over 1 hour after start of leucovorin weekly x 6 weeks  
• Simplified biweekly regimen:  
  • Leucovorin 400 mg/m² IV on day 1  
  • 5-FU bolus 400 mg/m² then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46-48 hours) continuous IV infusion |
| Capecitabine – every 3 weeks x 24 weeks (8 cycles) | • Capecitabine 1000-1250 mg/m² PO twice daily on days 1-14 |

B. Landmark trials
1. Several trials have established the efficacy of 6 months of 5-fluorouracil and leucovorin (5-FU/LV) adjuvant treatment in stage III colon cancer
2. MOSAIC – demonstrated superiority of 6 months of FOLFOX adjuvant therapy over 5-FU/LV alone and established FOLFOX as the standard of care in stage III colon cancer
3. XELOXA – established superiority of 6 months of CapeOx adjuvant therapy over 5-FU/LV alone and established CapeOx as the standard of care in stage III colon cancer

Table 2. Landmark Trials for Adjuvant Chemotherapy in Colon Cancer

<table>
<thead>
<tr>
<th>Landmark trial</th>
<th>Outcomes</th>
<th>Results</th>
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</table>
| MOSAIC²³ | **Primary**: 5-year disease-free survival (DFS)  
**Secondary**: adverse effects, 6-year overall survival (OS) | **Primary**:  
- Stage II and III: 66.4% vs. 58.9%; HR 0.78; 95%CI 0.65 to 0.93; p=0.005  
**Secondary**:  
- Grade 3 peripheral sensory neuropathy: 12.5% vs. 0.2%  
- Secondary cancers: 5.5% vs. 6.1%  
- **Overall 6-year survival in stage II and III disease**: 72.9% vs. 68.7% (HR 0.80; 95%CI 0.65 to 0.97; p=0.023) |
| FOLFOX4 vs. 5-FU/LV | N=1,123 patients with stage II/III colon cancer | **Primary**:  
- DFS: 68.7% vs. 62.5%; HR 0.8 (95%CI 0.69 to 0.93, p = 0.0045)  
- 5-year DFS: 66.1% (95%CI 62.9% to 69.4%) vs. 59.8 (95%CI 56.4% to 63.1%)  
**Secondary**:  
- OS after median 57 months: 79.1% vs. 77.1%; HR 0.87 (95%CI 0.72 to 1.05, p=0.1486)  
- DFS: 68.7% vs. 62.5%; HR 0.8 (95%CI 0.69 to 0.93, p = 0.0045)  
- Grade 3 or 4 adverse events: 55% vs. 47%  
- Grade 3 or 4 neurosensory toxicity: 11% vs. <1% |
| XELOXA²⁴ | CapeOx vs. bolus 5-FU/LV | **Primary**:  
- DFS: 68.7% vs. 62.5%; HR 0.8 (95%CI 0.69 to 0.93, p = 0.0045)  
- 5-year DFS: 66.1% (95%CI 62.9% to 69.4%) vs. 59.8 (95%CI 56.4% to 63.1%)  
**Secondary**:  
- OS after median 57 months: 79.1% vs. 77.1%; HR 0.87 (95%CI 0.72 to 1.05, p=0.1486)  
- DFS: 68.7% vs. 62.5%; HR 0.8 (95%CI 0.69 to 0.93, p = 0.0045)  
- Grade 3 or 4 adverse events: 55% vs. 47%  
- Grade 3 or 4 neurosensory toxicity: 11% vs. <1% |
VIII.  Current guidelines recommendations
   A.  NCCN guidelines\textsuperscript{10}
      i.  FOLFOX or CapeOx recommended over 5-FU/LV in stage III colon cancer
         a.  FLOX is acceptable alternative to FOLFOX, but requires weekly administration
         b.  Capecitabine is considered equivalent to 5-FU/LV in stage III colon cancer
      ii.  Duration of adjuvant treatment is 6 months
         a.  FOLFOX – every 2 weeks for 12 cycles
         b.  FLOX – 8-week cycles for 3 cycles
         c.  CapeOx – every 3 weeks for 8 cycles
      iii.  Benefit of oxaliplatin in combination with 5-FU/LV in patients ages \(\geq 70\) years is not established due to exclusion of this population in landmark trials
   B.  Oxaliplatin tolerability
      i.  Common adverse effects\textsuperscript{23,25}
         a.  Fatigue
         b.  Myelosuppression
         c.  Diarrhea
         d.  Renal toxicity
         e.  Peripheral neuropathy (Appendix B)
            1.  Reported in 92.1\% of all patients in the MOSAIC trial
            2.  Grade 3 neurotoxicity occurred in 12\% of patients in the MOSAIC trial
            3.  Grade 1 or 2 neurotoxicity occurred in approximately 50\% of patients during the second post-treatment year in the MOSAIC trial
   C.  Considerations
      i.  Suboptimal completion rates\textsuperscript{23,26}
         a.  In the MOSAIC trial, 25.3\% of patients did not complete the full 12 cycles of FOLFOX, with a median oxaliplatin dose of 810 mg/m\textsuperscript{2} (9.5 cycles)
         b.  In the XELOXA trial, 31\% of patients did not complete the planned number of cycles
         c.  Abrams et al. described a 26.9\% discontinuation rate of FOLFOX or CapeOx after < 3 months in a population-based cohort study of 1,842 patients
            1.  Median duration of oxaliplatin based therapy was 5.6 months
            2.  Patients receiving CapeOx were nearly twice as likely to discontinue adjuvant therapy (OR 1.94, 95\%CI 1.38 to 2.71)
      ii.  Average wholesale price (AWP) based on average body surface area of 1.9 m\textsuperscript{2} per cycle\textsuperscript{27}
         a.  Oxaliplatin
            1.  Based on mFOLFOX6 requirements of 85 mg/m\textsuperscript{2}/cycle: $329.46
            2.  Based on CapeOx requirements of 130 mg/m\textsuperscript{2}/cycle: $503.88
         b.  5-FU - based on mFOLFOX6 requirements of 2800 mg/m\textsuperscript{2}/cycle (bolus plus continuous infusion): $32.76
         c.  Capecitabine - based on CapeOx requirements of 28,000 mg/m\textsuperscript{2}/cycle: $4,381.29
         d.  Leucovorin - based on mFOLFOX6 requirements of 400 mg/m\textsuperscript{2}/cycle: $57.60
         e.  Estimated cost of FOLFOX per cycle: $419.82
         f.  Estimated cost of CapeOx per cycle: $5304.99
      iii.  Other Costs\textsuperscript{28}
         a.  Sterile compounding cost
         b.  Infusion room costs
         c.  Continuous infusion pump costs
         d.  Follow-up cost
      iv.  Treatment duration reduction has the potential to proportionally decrease all costs
IX. Clinical Question

A. Does reduced oxaliplatin-based adjuvant therapy duration result in worsened patient outcomes for stage III colon cancer patients?

B. What is the optimal treatment duration of adjuvant therapy in stage III colon cancer?

Literature Review


Objective

- Determine effect of FOLFOX completion on overall survival (OS) and DFS
- Determine predictive factors of therapy completion
- Characterize FOLFOX completion rates

Study Design

Retrospective population-based analysis of patients receiving adjuvant FOLFOX for stage III colon cancer from the British Columbia Cancer Agency

Enrollment

Inclusion:
- Curative resection for stage III colon cancer between 2006 to 2010
- Started at least one cycle of FOLFOX within 12 weeks of surgery
- Managed at one of five British Columbia Cancer Agency comprehensive cancer centers

Exclusion:
- Patients initiating FOLFOX beyond 12 weeks from surgery
- Synchronous or previous colon cancer
- Histological diagnosis other than adenocarcinoma
- Treatment with neoadjuvant therapy

Interventions

- Completion or incompletion of adjuvant FOLFOX (>10 or <10 cycles of treatment after curative resection, respectively)

Endpoints

Covariates evaluated:
- Patient demographic
- Clinical tumor characteristics
- Pathological tumor characteristics
- Timing of adjuvant chemotherapy initiation after surgery
- Length of postoperative hospitalization

Primary outcomes:
- OS, defined as time interval between date of colon cancer diagnosis and date of death from any cause
- DFS, defined as time interval between date of colon cancer diagnosis and date of recurrence or death due to colon cancer

Study Sample

- Median age – 62 years; IQR 26 to 80 years
- Median follow up – 4.2 years
- Median number of cycles in <10 cycles group: 7 cycles

Table 3. Demographic information

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>&lt;10 cycles</th>
<th>&gt;10 cycles</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total – n (%)</td>
<td>616</td>
<td>183 (29.7)</td>
<td>433 (70.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>295 (47.9)</td>
<td>72 (24.4)</td>
<td>223 (75.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>Male</td>
<td>321 (52.1)</td>
<td>111 (34.6)</td>
<td>210 (65.4)</td>
<td></td>
</tr>
<tr>
<td>Obstruction/Perforation – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>530 (86.4)</td>
<td>149 (28.1)</td>
<td>381 (71.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Yes</td>
<td>86 (14)</td>
<td>34 (39.5)</td>
<td>52 (60.5)</td>
<td></td>
</tr>
<tr>
<td>Nodal Stage – n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>522 (84.7)</td>
<td>97 (26.1)</td>
<td>274 (73.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>N2</td>
<td>94 (15.3)</td>
<td>86 (35.1)</td>
<td>159 (64.9)</td>
<td></td>
</tr>
</tbody>
</table>
Statistics
- Chi-square and Fisher’s exact tests for differences in baseline parameters
- Kaplan-Meier method for OS and DFS estimation
- Multivariate Cox proportional hazard regression models for relationship between chemotherapy cycles received and survival outcomes
- Multivariate logistic regression models to find predictors of treatment completion

Results
- No difference in 3-year DFS (77% vs. 78%, p=0.99) or 5-year OS (81% vs. 81%, p=0.995)

Table 4. Multivariate Logistic Regression Predicting for >10 Cycles of Treatment
<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (OR)</th>
<th>95%CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Female vs. Male</td>
<td>1.61</td>
<td>1.12-2.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Performance Status, 0-1 vs. 2-3</td>
<td>1.10</td>
<td>0.50-2.28</td>
<td>0.81</td>
</tr>
<tr>
<td>Obstruction/Perforation, No vs. Yes</td>
<td>1.82</td>
<td>1.08-3.05</td>
<td>0.02</td>
</tr>
<tr>
<td>T Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs. T1/T2</td>
<td>0.91</td>
<td>0.52-1.62</td>
<td>0.73</td>
</tr>
<tr>
<td>T4 vs. T1/T2</td>
<td>0.74</td>
<td>0.37-1.48</td>
<td>0.39</td>
</tr>
<tr>
<td>N Stage, N1 vs. N2</td>
<td>1.46</td>
<td>1.01-2.13</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 5. Multivariate Cox Regression for Overall and Disease-Free Survival
<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Survival</th>
<th>Disease-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>HR [95%CI]</td>
<td>p</td>
</tr>
<tr>
<td>Cycles of FOLFOX, &gt;10 vs. &lt;10</td>
<td>1.07 [0.7-1.61]</td>
<td>0.76</td>
</tr>
<tr>
<td>Age, &gt;70 vs. &lt;70</td>
<td>1.46 [1.00-2.15]</td>
<td>0.05</td>
</tr>
<tr>
<td>Site of Disease, left vs. right</td>
<td>1.33 [0.9-1.97]</td>
<td>0.15</td>
</tr>
<tr>
<td>Obstruction/perforation</td>
<td>1.47 [0.9-2.42]</td>
<td>0.13</td>
</tr>
<tr>
<td>T Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 vs. T1/T2</td>
<td>2.20 [0.87-5.51]</td>
<td>0.09</td>
</tr>
<tr>
<td>T4 vs. T1/T2</td>
<td>4.44 [1.69-11.65]</td>
<td>0.002</td>
</tr>
<tr>
<td>N stage, N2 vs. N1</td>
<td>1.84 [1.24-2.72]</td>
<td>0.002</td>
</tr>
<tr>
<td>Postoperative stay, &gt;7 vs. &lt;7</td>
<td>1.19 [0.73-1.95]</td>
<td>0.49</td>
</tr>
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Author’s Conclusions
- Most stage III colon cancer patients completed ≥10 cycles of adjuvant FOLFOX chemotherapy after curative resection
- Female patients and those without obstruction or perforation were significantly more likely to complete planned treatment
- Less nodal burden demonstrated a trend for higher likelihood of completing treatment
- No difference in DFS or OS for patients who did and did not complete adjuvant therapy

Critique
Strengths
- Real-world population-based analysis of FOLFOX tolerability and outcomes
- Similar rate of FOLFOX incompletion as MOSAIC trial (29.7% vs. 25.3%)

Limitations
- Retrospective, nonrandomized design and unequally distributed groups, with more patients receiving ≥10 cycles
- Does not evaluate outcome differences between the guideline-recommended 12 cycles vs. <12 cycles due to a median of 10 cycles administered in previous trials
- Inability to measure dose reductions or delays

Application
- Treatment durations less than the standard 12 cycles may not affect patient outcomes
- A median number of 7 cycles appears to yield no difference in outcomes

**Objective**
To determine the appropriate number of adjuvant FOLFOX treatment cycles needed to reduce adverse effects and cost while maintaining efficacy for the treatment of stage III colon cancer.

**Study Design**
Retrospective observational stratified cohort study at Taipei Veterans General Hospital

**Enrollment**

**Inclusion:**
- Treated for stage III colon cancer between June 2005 and June 2012
- History of curative resection and at least one cycle of adjuvant FOLFOX chemotherapy

**Exclusion:**
- Cases with rectum and recto-sigmoid junction primary colon tumor sites

**Interventions**
- mFOLFOX6 every 2 weeks

**Endpoints**

**Primary outcomes:**
- OS, defined as time interval between date of operation to date of death from any cause
- DFS, defined as time interval between date of operation to date of either colon cancer recurrence or death

**Study Sample**
- Total of 213 cases included out of 692 cases in patient database of stage III CRC
  - 210 cases excluded for inadequate data or lack of follow up
  - 49 cases excluded for not receiving chemotherapy
  - 220 cases excluded for receiving chemotherapy other than FOLFOX
- Median age – 61.7 years old; range 29-88
- Median follow up – 54 months
- No patients received neoadjuvant chemotherapy or radiotherapy

<table>
<thead>
<tr>
<th>Table 6. Demographic Information</th>
<th>Variable (n=213)</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Age – n (%)</td>
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</tr>
<tr>
<td>&lt;70 years</td>
<td>152 (71.4)</td>
<td></td>
</tr>
<tr>
<td>≥70 years</td>
<td>61 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>114 (54.5)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>99 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes harvested – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes &lt;12</td>
<td>19 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes ≥12</td>
<td>194 (91.1)</td>
<td></td>
</tr>
<tr>
<td>T Stage – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-3</td>
<td>193 (90.6)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>20 (9.4)</td>
<td></td>
</tr>
<tr>
<td>Nodal Stage – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>128 (60.1)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>85 (39.9)</td>
<td></td>
</tr>
<tr>
<td>Time to treatment – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤8 weeks</td>
<td>203 (95.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;8 weeks</td>
<td>10 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Obstruction/perforation – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35 (16.4)</td>
<td></td>
</tr>
<tr>
<td>Performance Status – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>193 (90.6)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17 (8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Maintenance treatment - %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Statistics**
- Kaplan-Meier method and stratified two-sided log-rank test were used to determine significance for survival analyses with each cycle number
- Univariate Cox regression analyses for every demographic factor if a difference was reached
- Multivariate Cox regression performed for all factors resulting in p-value <0.2 to determine if the number of cycles received was an independent prognostic factor

**Results**
- 5-year overall survival rate: 77.9%
- 5-year cancer specific survival rate: 82.2%
- 3-year disease free survival: 76.7%
- Recurrence rate: 26.3%
Reasons for oxaliplatin discontinuation included intolerance of adverse effects (AE) (50.5%), avoidance of future AE (23.3%), disease progression (16.8%), and unknown reasons (9.5%).

Table 7. Survival Analysis Based on FOLFOX Cycle Completion

<table>
<thead>
<tr>
<th>FOLFOX cycles</th>
<th>N (total =213)</th>
<th>%</th>
<th>Cumulative percentage (%)</th>
<th>OS p-value</th>
<th>DFS p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>29</td>
<td>13.6</td>
<td>29.1</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>2.3</td>
<td>31.5</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
<td>4.2</td>
<td>35.7</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>3.3</td>
<td>39.0</td>
<td>0.07</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>4.7</td>
<td>43.7</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>0.9</td>
<td>44.6</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>12</td>
<td>118</td>
<td>55.4</td>
<td>100</td>
<td>0.06</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 8. Multivariate Survival Analysis Stratified by 8 Cycles for Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate COX regression</th>
<th>Multivariate logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95%CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>T stage, 4 vs. 1-3</td>
<td>1.77 [0.79-3.97]</td>
<td>0.17</td>
</tr>
<tr>
<td>Performance Status, 1-2 vs. 0</td>
<td>2.08 [0.93-4.66]</td>
<td>0.08</td>
</tr>
<tr>
<td>Cycles of FOLFOX, &gt;8 vs. &lt;8</td>
<td>0.54 [0.3-0.99]</td>
<td>0.043</td>
</tr>
<tr>
<td>Lymph nodes, &gt;12 vs. &lt;12</td>
<td>3.1 [0.75-12.89]</td>
<td>0.12</td>
</tr>
<tr>
<td>Obstruction/perforation, yes vs. no</td>
<td>1.92 [0.99-3.73]</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Table 9. Multivariate Survival Analysis Stratified by 7 Cycles for Disease-Free Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate COX regression</th>
<th>Multivariate logistic regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [95%CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>T stage, 4 vs. 1-3</td>
<td>1.63 [0.7-3.81]</td>
<td>0.26</td>
</tr>
<tr>
<td>Performance Status, 1-2 vs. 0</td>
<td>1.07 [0.43-0.68]</td>
<td>0.89</td>
</tr>
<tr>
<td>Cycles of FOLFOX, &gt;7 vs. &lt;7</td>
<td>0.56 [0.32-0.97]</td>
<td>0.04</td>
</tr>
<tr>
<td>Lymph nodes, &gt;12 vs. &lt;12</td>
<td>0.67 [0.3-1.48]</td>
<td>0.32</td>
</tr>
<tr>
<td>Time to treatment, &gt;8 vs. &lt;8 weeks</td>
<td>2.22 [0.03-6.15]</td>
<td>0.12</td>
</tr>
<tr>
<td>Obstruction/perforation, yes vs. no</td>
<td>1.52 [0.78-2.96]</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Author’s Conclusions

- OS survival benefits were significantly different with at least 8 cycles of adjuvant FOLFOX therapy, but this difference was not consistent with each subsequent cycle.
- DFS survival benefits were consistently different from 7 to 12 cycles of adjuvant FOLFOX therapy.
- Cycle number is an independent prognostic factor of overall survival (8 cycles) and disease-free survival (7 cycles).

Critique

- Analysis performed at each cycle number to determine optimal cycle requirements.
- Reported 6-year OS rate (72.6%) and 3-year DFS (75.6%) were similar to the OS and DFS in the MOSAIC trial (72.9 and 78.2%, respectively).
Critique (cont.)

Limitations

- The 55.4% completion rate of 12 cycles of FOLFOX is higher than rates observed in previous studies, but lower than the 74.7% observed in the MOSAIC trial.\(^{23,31}\)
- Lack of head-to-head comparison between cycle numbers to determine survival benefit
- Limited statistical power due to unequal patient distribution in each cycle number stratum
- Maintenance with 5-FU based treatments to finish 6 months of therapy by >90% of patients after oxaliplatin disruption may confound results
- Inability to measure dose reductions or delays

Application

At least 7 cycles of adjuvant FOLFOX should be administered for similar survival benefits seen in landmark trials

Pending Literature

X. International Duration Evaluation of Adjuvant Chemotherapy (IDEA) Collaboration\(^{32-35}\)

A. Publicly-funded international initiative comprised of six independently conducted trials designed to answer the clinical question of reduced adjuvant therapy duration in stage III colon cancer

B. Abstracts for TOSCA, SCOT, IDEA France, and IDEA pooled analysis presented at ASCO Meeting 2017

Table 10. IDEA Collaboration Trial Details\(^{33}\)

<table>
<thead>
<tr>
<th>Trial name – location</th>
<th>Treatment regimens used</th>
<th>Stage III colon cancer patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA – Italy</td>
<td>CapeOx or FOLFOX4</td>
<td>2402</td>
</tr>
<tr>
<td>SCOT – United Kingdom, Denmark, Spain, Australia, Sweden, New Zealand</td>
<td>CapeOx or mFOLFOX6</td>
<td>3983</td>
</tr>
<tr>
<td>IDEA France – France</td>
<td>CapeOx or mFOLFOX6</td>
<td>2010</td>
</tr>
<tr>
<td>CALGB/SWOG – United States, Canada</td>
<td>mFOLFOX6</td>
<td>2440</td>
</tr>
<tr>
<td>HORG – Greece</td>
<td>CapeOx or FOLFOX4</td>
<td>708</td>
</tr>
<tr>
<td>ACHIEVE – Japan</td>
<td>CapeOx or mFOLFOX6</td>
<td>1291</td>
</tr>
</tbody>
</table>

XI. Abbreviated Abstract Review


Objective

To determine whether 3 month adjuvant oxaliplatin-based in high risk stage II/stage III colon cancer is as effective as 6 months of treatment

Study Design

Non-inferiority prospective randomized study

Interventions

3 vs. 6 months of mFOLFOX6 or CapeOx

Endpoints

3-year DFS

Study Sample

- N = 6088 patients with stage III/high risk stage II colon cancer
  - FOLFOX – 1981 patients (32.5%)
  - CapeOx – 4107 patients (67.5%)
  - Males – 3653 patients (60%)
  - Median age – 65

Statistics

- Noninferiority defined as ≤2.5% fall in 3-year DFS in the 3 month arm vs. 6 months arm
- Hazard ratio upper limit of 1.13 for noninferiority
- 90% power at the 2.5% 1-sided level of statistical significance with goal of 9500 patients and 2750 DFS events
- Cox model analysis adjusted for study minimization
Results

- Study power of 66% based on 1469 DFS events
- Per test for heterogeneity, results between CapeOx and FOLFOX groups were similar (p=0.059), although a trend for improved outcomes with CapeOx was suggested

Table 11. Study Outcomes

<table>
<thead>
<tr>
<th></th>
<th>3 month treatment</th>
<th>6 month treatment</th>
<th>HR [95%CI, p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS event, no.</td>
<td>734</td>
<td>735</td>
<td>--</td>
</tr>
<tr>
<td>3-year DFS, %</td>
<td>76.8</td>
<td>77.4</td>
<td><strong>1.008 [0.910 – 1.117, 0.014]</strong></td>
</tr>
</tbody>
</table>

Author’s Conclusions

3 months of adjuvant oxaliplatin based therapy is noninferior to 6 months of treatment

Critique

- Large sample size, with majority treated with CapeOx
- Underpowered at 66% but still found noninferiority of 3 vs. 6 months of adjuvant treatment
- Included rectal cancer patients, in which treatment strategy differs from CRC
- Inclusion of high risk stage II colon cancer patients in addition to stage III colon cancer

Application

3 months of oxaliplatin-based adjuvant therapy (primarily FOLFOX) is non-inferior to 6 months of adjuvant therapy high-risk stage II/stage III colorectal patients


Objective

To determine whether 3 month adjuvant oxaliplatin-based in high-risk stage II/stage III colon cancer is as effective as 6 months of treatment

Study Design

Open label, phase III, multicenter, non-inferiority trial

Interventions

3 vs. 6 months of FOLFOX4 or CapeOx

Endpoints

Relapse free survival (RFS)

Study Sample

- N = 3759 patients with high risk stage II/stage III colon cancer
  - 64% and 36% of patients received FOLFOX4 and CapeOx, respectively
  - 65.3% of patients with stage III disease

Statistics

- Analysis performed with 82% of planned events, with power of 72%
- Noninferiority confidence interval upper limit of 1.2

Results

- Total of 772 RFS events observed
- Median DFS follow up: 62 months
- 8-year RFS rate: 75%
- 3 month vs. 6 month RFS event HR: 1.14 (95%CI 0.99-1.31, p=0.253)
- Completion rate (including dose reductions and delays): 52% vs. 44% for 3 vs. 6 months

Author’s Conclusions

- Noninferiority of 3 months of oxaliplatin-based adjuvant treatment compared to 6 months was not demonstrated
- Reported small absolute difference in RFS (<3% at 5 years) warrants risk/benefit analysis for 6 months vs. 3 months of adjuvant treatment

Critique

- Large sample size, with majority treated with FOLFOX
- Long follow-up period (8 years)
- Limited power <80%
- Accounted for dose reduction and delays, but resulted in low completion rates
- Inclusion of high-risk stage II colon cancer patients

Application

3 months of oxaliplatin-based adjuvant therapy (primarily FOLFOX) may not be equivalent to 6 months of adjuvant therapy high-risk stage II/stage III colon cancer

**Objective**
To determine whether 3 month adjuvant oxaliplatin-based in stage III colon cancer is as effective as 6 months of treatment

**Study Design**
Prospective randomized cohort study

**Interventions**
3 vs. 6 months of mFOLFOX6 or CapeOx

**Endpoints**
DFS

**Study Sample**
- N = 2022 patients with stage III colon cancer
  - 2010 patients received oxaliplatin based therapy, with 90% and 10% receiving mFOLFOX6 and CapeOx, respectively
  - 49.9% and 50.1% of patients received 3 and 6 months of therapy, respectively
  - 99.5% of patients with stage III disease
    - N1: 74.9%
    - N2: 25.2%
  - Median age 63.9 years

**Statistics**
- Kaplan-Meier method for 3-year DFS estimation and analysis

**Results**
- Total 578 DFS events
- Median follow up: 50.2 months

**Table 12. Study Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>3 months (N=1003)</th>
<th>6 months (N=1007)</th>
<th>HR [95%CI, p-value]</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS event, no.</td>
<td>314</td>
<td>264</td>
<td>--</td>
</tr>
<tr>
<td>3-year DFS, %</td>
<td>72.1</td>
<td>75.7</td>
<td>1.24 [95%CI 1.05-1.46, 0.0069]</td>
</tr>
<tr>
<td>mFOLFOX6, 3-year DFS, %</td>
<td>72</td>
<td>76.3</td>
<td>1.27 [95%CI 1.07-1.51, 0.0069]</td>
</tr>
<tr>
<td>Median oxaliplatin dose intensity, % (mg/m2)</td>
<td>96.9 (495)</td>
<td>72.1 (735.1)</td>
<td>--</td>
</tr>
<tr>
<td>Completion rate, %</td>
<td>94.2</td>
<td>78</td>
<td>--</td>
</tr>
<tr>
<td>Max neuropathy grade, %3-4</td>
<td>7.9</td>
<td>25.3</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

**Author's Conclusions**
6 months of adjuvant treatment with oxaliplatin based therapy in stage III colon cancer is superior to 3 months of adjuvant treatment

**Critique**
- Large sample size, with majority treated with FOLFOX
- Evaluated stage III colon cancer patients only

**Application**
6 months of adjuvant treatment with oxaliplatin based therapy in stage III colon cancer is superior to 3 months of adjuvant treatment at the cost of increased neuropathy

Shi Q, Sobrero AF, Shields AF, et al. Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration. Paper presented at: 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2017; Chicago, IL.

**Objective**
To evaluate non-inferiority of 3 months compared with 6 months of adjuvant oxaliplatin-based treatment in stage III colon cancer

**Study Design**
Prospective, non-inferiority, pooled analysis of individual patient data from six concurrently conducted phase III randomized trials

**Interventions**
3 vs. 6 months of FOLFOX or CapeOx
**Endpoints**

DFS, defined as time from date of randomization to earliest date of relapse, secondary colorectal primary tumor, or death from all causes

**Study Sample**

- N = 12,834 patients with stage III colon cancer

**Table 13. Study Characteristics**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>T4 disease (%)</th>
<th>Median follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>SCOT</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td>IDEA France</td>
<td>18</td>
<td>51</td>
</tr>
<tr>
<td>CALGB/SWOG</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>HORG</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>ACHIEVE</td>
<td>28</td>
<td>37</td>
</tr>
</tbody>
</table>

**Table 14. Demographic Information**

<table>
<thead>
<tr>
<th>Variable (n=12,834)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total DFS events</td>
<td>3263 (96% of planned)</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
</tr>
<tr>
<td>ECOG 0/1</td>
<td>79/21</td>
</tr>
<tr>
<td>Nodal Involvement</td>
<td></td>
</tr>
<tr>
<td>N1/N2</td>
<td>72/28</td>
</tr>
<tr>
<td>T Stage</td>
<td></td>
</tr>
<tr>
<td>T1-2/T3/T4</td>
<td>13/66/21</td>
</tr>
<tr>
<td>Treatment regimen</td>
<td></td>
</tr>
<tr>
<td>FOLFOX/ CapeOx</td>
<td>60/40</td>
</tr>
</tbody>
</table>

**Statistics**

- HR and two-sided 95% CI estimated by Cox model, with an initial HR noninferiority upper limit of 1.10 and 4,700 planned DFS events
- Modification of target noninferiority margin to 1.12 due to inadequate DFS events at preplanned interim analysis
- 90% power at the 2.5% 1-sided level of statistical significance with 3,400 planned DFS events
- Preplanned subgroup analyses: regimen and risk group (T/N stage)

**Results**

- 3-year DFS for 3 vs. 6 months treatment: 74.6% vs. 75.5% (HR 1.07, 95% CI 1.00 to 1.15)

**Table 15. Study Outcomes**

<table>
<thead>
<tr>
<th>Efficacy Outcome 3 vs. 6 months</th>
<th>HR [95%CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS by risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-3 N1</td>
<td>1.01 [0.9 to 1.12]</td>
<td>0.11</td>
</tr>
<tr>
<td>T4 or N2</td>
<td>1.12 [1.03 to 1.23]</td>
<td></td>
</tr>
<tr>
<td>DFS by regimen</td>
<td></td>
<td>0.0051</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>1.16 [1.06 to 1.26]</td>
<td></td>
</tr>
<tr>
<td>CapeOx</td>
<td>0.95 [0.85 to 1.06]</td>
<td></td>
</tr>
<tr>
<td>DFS by risk group and regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-3N1, FOLFOX</td>
<td>1.10 [0.96 to 1.26]</td>
<td></td>
</tr>
<tr>
<td>T1-3N1, CapeOx</td>
<td>0.85 [0.71 to 1.01]</td>
<td></td>
</tr>
<tr>
<td>T4 or N2, FOLFOX</td>
<td>1.20 [1.07 to 1.25]</td>
<td></td>
</tr>
<tr>
<td>T4 or N2, CapeOx</td>
<td>1.02 [0.89 to 1.17]</td>
<td></td>
</tr>
</tbody>
</table>

**Table 16. Safety Outcomes**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>FOLFOX</th>
<th>CapeOx</th>
<th>p-value</th>
<th>FOLFOX</th>
<th>CapeOx</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>3 months</td>
<td>6 months</td>
<td>3 months</td>
<td>6 months</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Overall adverse events grade, %</td>
<td>2</td>
<td>32</td>
<td>32</td>
<td>&lt;0.001</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Neurotoxicity grade, %</td>
<td>2</td>
<td>14</td>
<td>32</td>
<td>&lt;0.001</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>3-4</td>
<td>38</td>
<td>57</td>
<td></td>
<td>24</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>
Table 17. Compliance Outcomes

<table>
<thead>
<tr>
<th>Duration</th>
<th>FOLFOX</th>
<th>CapeOx</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months (N=3870)</td>
<td>6 months (N=3893)</td>
<td>3 months (N=2554)</td>
</tr>
<tr>
<td>6 months (N=2517)</td>
<td>69.3 (28.3)</td>
<td>69.3 (28.3)</td>
</tr>
<tr>
<td>Mean oxaliplatin dose intensity, % (SD)</td>
<td>91.4 (19.9)</td>
<td>72.8 (25.6)</td>
</tr>
<tr>
<td>Completion rate, %</td>
<td>90</td>
<td>71</td>
</tr>
<tr>
<td>86</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Author’s Conclusions

- 3 months of adjuvant treatment is associated with greater treatment compliance and lower neurotoxicity compared to 6 months
- DFS non-inferiority of 3 months compared to 6 months with adjuvant therapy could not be established in stage III colon cancer
- DFS subanalyses suggest non-inferiority in DFS with 3 months compared to 6 months of treatment in patients with T1-3 N1 disease, patients treated with CapeOx, and patients with T1-3 N1 disease treated with CapeOx
- A 0.9% absolute reduction of DFS benefit must be weighed against greater than twice the risk of neurotoxicity

Critique

- Individual studies contained varying proportions of patients treated with CapeOx, introducing potential for heterogeneity in outcomes and selection bias
- Study was not powered for DFS analysis stratified by regimen or disease staging
- Noninferiority margin modification due to inadequate DFS events may confound results

Application

- In stage III colon cancer patients, 3 months of FOLFOX or CapeOx adjuvant chemotherapy does not demonstrate DFS non-inferiority compared to 6 months

Recommendations

XII. Recommendations

A. A shortened treatment duration of 3 months should not be recommended over 6 months of adjuvant oxaliplatin-based therapy
B. Shortened treatment duration should ultimately be dictated by tolerability or patient preference
C. Shortened treatment may be more appropriately considered in patients with T1-3 N1 disease
D. A goal of at least 7 cycles of FOLFOX may be associated with similar survival outcomes\textsuperscript{29-30}

Conclusion

XIII. Future Directions

A. Pending full IDEA, TOSCA, SCOT and IDEA France publications
B. Pending other IDEA collaboration individual trial abstracts and publications
C. Pending long-term OS data from individual trials and overall IDEA collaboration pooled analysis
D. Individual IDEA collaboration study data may better describe patient populations and identify those that would most benefit from 3-month adjuvant therapy
E. Further trials are needed to investigate a suggested difference in outcomes between various risk groups and regimens (T1-3 N1 and T4 or N2 disease; FOLFOX and CapeOx)

XIV. Summary

A. Adjuvant therapy is crucial in delaying recurrence and extending OS in stage III colon cancer\textsuperscript{10}
B. Current guidelines recommend six months of oxaliplatin-based adjuvant therapy in high-risk stage II and stage III colon cancers\textsuperscript{10}
C. Oxaliplatin-based adjuvant chemotherapy regimens are not well tolerated or completed by many patients, primarily due to neurological adverse effects\textsuperscript{23,25-26}
Available retrospective and prospective data suggest that a complete 6 months of adjuvant therapy is not necessary for sustained survival benefit.\(^{29-30,35-36}\)

Prospective trials failed to establish non-inferiority of 3 months compared to 6 months of oxaliplatin-based adjuvant therapy in stage III colon cancer.\(^{33}\)

Decisions to shorten the duration of adjuvant oxaliplatin-based therapy in stage III colon cancer should be dictated by drug intolerability or patient preference and consider the value of decreased neurotoxicity at the cost of decreased DFS.

### References


Table 18. Classification of colorectal cancer per TNM classification system

<table>
<thead>
<tr>
<th>T Stage – local invasion depth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>No information about local tumor infiltration available</td>
</tr>
<tr>
<td>Tis</td>
<td>Tumor restricted to mucosa, no infiltration of lamina muscularis mucosa</td>
</tr>
<tr>
<td>T1</td>
<td>Infiltration of lamina muscularis mucosa into submucosa, no infiltration of lamina muscularis propria</td>
</tr>
<tr>
<td>T2</td>
<td>Infiltration into, but not beyond, lamina muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Infiltration into subserosa or non-peritonealised pericolic or perirectal tissue, or both; no infiltration of serosa or neighboring organs</td>
</tr>
<tr>
<td>T4a</td>
<td>Infiltration of the serosa</td>
</tr>
<tr>
<td>T4b</td>
<td>Infiltration of neighboring tissues or organs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N Stage – lymph node involvement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>No information about lymph node involvement available</td>
</tr>
<tr>
<td>N0</td>
<td>No lymph node involvement</td>
</tr>
<tr>
<td>N1a</td>
<td>Cancer cells detectable in 1 regional lymph node</td>
</tr>
<tr>
<td>N1b</td>
<td>Cancer cells detectable in 2–3 regional lymph nodes</td>
</tr>
<tr>
<td>N1c</td>
<td>Tumor satellites in subserosa or pericolic or perirectal fat tissue, regional lymph nodes not involved</td>
</tr>
<tr>
<td>N2a</td>
<td>Cancer cells detectable in 4–6 regional lymph nodes</td>
</tr>
<tr>
<td>N2b</td>
<td>Cancer cells detectable in 7 or greater regional lymph nodes</td>
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</table>

<table>
<thead>
<tr>
<th>M stage – presence of distant metastases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>No information about distant metastases available</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases detectable</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis to 1 distant organ or distant lymph nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis to more than 1 distant organ or set of distant lymph nodes or peritoneal metastasis</td>
</tr>
</tbody>
</table>
### Table 19. Union Internationale Contre le Cancer/American Joint Committee on Cancer Stage Classification of Colorectal Cancers

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>I</td>
<td>T1/T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T3/T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Any</td>
<td>N+</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1-T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3-T4a</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2-T3</td>
<td>N2a</td>
<td>M0</td>
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<tr>
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<td>T1-T2</td>
<td>N2b</td>
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</tr>
<tr>
<td>IIIC</td>
<td>T4a</td>
<td>N2a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3-T4a</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>N1-N2</td>
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</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>M+</td>
</tr>
<tr>
<td>IVA</td>
<td>Any</td>
<td>Any</td>
<td>M1a</td>
</tr>
<tr>
<td>IVB</td>
<td>Any</td>
<td>Any</td>
<td>M2b</td>
</tr>
</tbody>
</table>

### Appendix B. Peripheral Motor Neuropathy Severity

Table 20. Common Terminology Criteria for Adverse Events (CTCAE) peripheral motor neuropathy grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Moderate symptoms; limiting instrumental activities of daily living (ADL)</td>
</tr>
<tr>
<td>3</td>
<td>Severe symptoms; limiting self-care ADL; assistive device indicated</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>