Adjuvant Treatment of Stage III Colon Cancer

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Stage III Colon Cancer - TNM

- Node-positive colon cancer
- Duke’s C

http://www.hopkinscoloncancercenter.org
Stage III Colon Cancer - TNM

**N1**  Metastasis in 1-3 regional LNs

- **N1a**  Metastasis in 1 regional LN
- **N1b**  Metastasis in 2-3 regional LNs
- **N1c**  Tumor deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues w/o regional LN metastasis

**N2**  Metastasis in 4 or more regional LNs

- **N2a**  Metastasis in 4-6 regional LNs
- **N2b**  Metastasis in 7 or more regional LNs
## Stage III Colon Cancer - TNM

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<th>Stage</th>
<th>T</th>
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<td>N1 / N1c</td>
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Stage III CRC is an aggressive disease, especially stage IIIB and stage IIIC.

Curiously, stage IIIA CRC has a relatively better prognosis.

Data from the 1973-2005 SEER Database
Historical Perspective - Pre-dawn

- Colon cancer adjuvant scene in the 70s and 80s was fairly sterile

- Early studies showed post-op 5FU did not add benefit

- Hint of something more exciting began emerging in the late 80s, with modulated 5FU regimens

Adjuvant Therapy of ColoRectal Cancer
Why We Still Don't Know
Marc Buyse, MSc, MBA; Anne Zeleniuch-Jacquotte, MD; Thomas C. Chalmers, MD
Historical Perspective - Dawn

- In 1988, NSABP C-01 showed MOF chemotherapy (semustine, vincristine, 5FU) was superior to surgery alone or surgery + BCG in Duke’s B and C patients - surgery alone group had a risk of death 1.31x that of MOF [1]

- In 1995, NCCTG study showed that 5FU + levamisole was superior to surgery alone (40% less relapse and 33% less death) in Duke’s C patients [2]

- 5FU / levamisole subsequently shown to be inferior to 5FU / leucovorin, and levamisole was associated with multifocal cerebral demyelinating syndrome

Historical Perspective - 5FU / LV

- 5FU synergistically interacts with leucovorin (LV)
- 5FU + LV form a stable complex with thymidylate synthetase (TS), thereby allowing 5FU to inactivate TS
- Three pivotal trials established adjuvant role of bolus 5FU/LV:
  
  A. NSABP C-03 showed 5FU/LV > MOF [1]
  
  B. NCCTG showed 5FU/LV (“Mayo regimen”) > observation [2]
  
  C. IMPACT pooled analysis showed 5FU/LV > observation [3]

Further Refinements of 5FU/LV (1)

- **Dose of LV**: LDLV = HDLV

  INT 0089 showed Mayo regimen (LDLV) = Rosewell Park (HDLV) in terms of efficacy, but Mayo regimen was more toxic, especially in women and in older individuals [1]

- **Duration of 5FU/LV**: 6 months probably most appropriate

  Several trials have shown 6 months not inferior to 12 months

  Cochrane review showed 3-6 months not inferior to 9-12 months [2]

Further Refinements of 5FU/LV (2)

- Infusional vs bolus 5FU: Similar efficacy but infusion less toxic

  At least 4 studies have shown the above

  E.g. PETACC-02: Mayo regimen vs 3 different infusional 5FU/LV regimens [1]

  No difference in efficacy

  Infusional regimens had less mucositis and neutropenia, similar rates of diarrhoea, but more HFS

  “de Gramont” infusional 5FU/LV (“LV5FU2”) best toxicity profile

Oral Fluoropyrimidines: Capecitabine

- X-ACT study (European/Canadian) compared Cap (1250 mg/m² BD) vs Mayo regimen [1]
  - 3Y DFS: 64% vs 61%, p = 0.05; 3Y OS: 81% vs 78%, p = 0.07
  - Cap is at least as effective as bolus 5FU/LV as adjuvant therapy
  - 50% of Cap users needed dose reduction
  - Caution: American patients and those with renal impairment
  - More toxicity when crossing over from FU/LV to Cap - mechanism unknown

Oral Fluoropyrimidines: UFT + LV

- **UFT**: 4:1 molar combination of tegafur with uracil; uracil inhibits degradation of FU, resulting in sustained concentrations

- **NSABP C-06** showed similar DFS and OS between 5FU/HDLV and oral UFT + oral LV in stage II and III colon cancer [1]

- Similar results obtained in a Japanese study involving stage III colon cancer patients [2]

**References**

Oral Fluoropyrimidines: S1

- **S1**: tegafur, gimeracil (potent inhibitor of DPD), oteracil (inhibits phosphorylation of intestinal FU)

- 80 mg, 100 mg or 120 mg daily - 4 weeks on, 2 weeks off

- In a Japanese study (**ACTS-CC**), S1 was found to have non-inferior DFS when compared to UFT + LV as adjuvant treatment of stage III colon cancer [1]

FU-Based Adjuvant: Summary

- Mayo bolus regimen most commonly used in trials, but toxic
- Roswell Park bolus regimen better tolerated than Mayo regimen
- Infusional 5FU regimens (e.g. de Gramont schedule) is as least as good as, and less toxic than, bolus 5FU/LV; but more inconvenient because of central venous access
- Oral FP (Capecitabine, UFT + LV, S1) is as good as bolus 5FU/LV; not known if comparable to infusional 5FU regimens

Modern Trial Therapeutic End-points

- Historically, gold standard to define benefit for adjuvant therapy has been improvement in OS.

- Recent analyses have shown that 3Y DFS (time from randomisation to any event, irrespective of the cause) appears to be an acceptable surrogate for 5Y OS, especially for stage III colon cancer.

- However, the duration of follow-up that is required to see DFS benefits translating into prolonged OS may be longer because of the prolongation of median survival with newer treatments for metastatic CRC.

- Significant improvements in 3Y DFS formed the basis for approval of adjuvant FOLFOX in United States.
New Era: Oxaliplatin-based Therapy

- Oxaliplatin + FP = Present standard of care
- “French revolution”: MOSAIC study
- 3 variations:
  1. MOSAIC: Oxaliplatin + infusional 5FU/LV
  2. NSABP C-07: Oxaliplatin + Roswell Park bolus 5FU/LV
  3. CAPOX (XELOX): Oxaliplatin + oral Capecitabine
Oxaliplatin-based Therapy: MOSAIC

• 2246 patients with stage II (40%) and stage III (60%) colon cancers; primary endpoint was DFS [1,2]

• FOLFOX4 (Ox + 48hr infusional FU/LV) vs 48hr infusional FU/LV

• In the 2004 NEJM publication (follow-up 37.9 months) [1]:

  Recurrence: 21.1% vs. 26.1%

  3Y DFS: 78.2% vs 72.9%; HR=0.77; p=0.002

DFS

- FL plus oxaliplatin (237 events, 21.1%)
- FL (293 events, 26.1%)

Probability of Disease-free Survival

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No. at Risk

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<td>981</td>
<td>903</td>
<td>817</td>
<td>619</td>
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P = 0.002
Oxaliplatin-based Therapy: MOSAIC

• In the 2009 update in JCO [1]:

  • 5Y DFS (entire group): 73% vs 67%; HR 0.80; p=0.003

    Stage III: 66% vs 59%; HR 0.78; p=0.005

    Stage II: 84% vs 80%; HR 0.84; p=0.258 #

  • 6Y OS (entire group): 79% vs 76%; HR 0.84; p=0.046

    Stage III: 73% vs 69%; HR 0.80; p=0.023

    Stage II: 87% vs 87%; HR 1.00; p=0.996

# Exploratory analysis: DFS difference larger in high-risk stage II, but still not significant (82% vs 75%; HR 0.72)

Oxaliplatin-based Therapy: MOSAIC

Toxicity with FOLFOX4:

- 1.8% FN
- 10.8% G3/4 diarrhea
- 92% peripheral neuropathy, all grades
  - 13% peripheral neuropathy, grade 3
  - By 48 months: grade 1 (12%), grade 2 (3%), grade 3 (0.7%)

Nowadays, modified FLOFOX6 commonly used
Oxaliplatin-based Therapy: NSABP C-07

- 2407 patients with stage II (29%) and stage III (71%) colon cancers; primary endpoint was DFS [1]

- FLOX (Ox on weeks 1, 3, 5 + b5FU/LV) vs Roswell Park b5FU/LV

- 8 years follow-up

- FLOX was superior to 5FU/LV in DFS: 69% vs 64%, HR 0.82

- But OS not statistically significant: 80% vs 78%, HR 0.88

- FLOX more toxic than FOLFOX

- FLOX inferior to FOLFOX in mCRC [2]

Oxaliplatin-based Therapy: XELOX

• 1886 patients with stage III colon cancers; primary endpoint was DFS [1]

• XELOX (Oxaliplatin at 130 mg/m²) vs 5FU/LV (either Mayo regimen or Roswell Park regimen)

• 57 months of follow-up

• 3Y DFS in favour of XELOX: 71% vs 66%; HR 0.8; p=0.0045

• But OS not statistically significant

• In an updated 7Y follow-up (presentation), both DFS (63% vs 56%) and OS (73% vs 67%) were significant

Oxaliplatin-based Therapy: Summary

- Addition of oxaliplatin to some form of FU (infusional, bolus or oral) is clearly beneficial for stage III colon cancer

- Benefit of oxaliplatin-based adjuvant chemotherapy for unselected stage II colon cancer patients is less clear

- Choice of 5FU backbone depends on many factors, including need for central venous access, 2 weeks vs 3 weeks, different toxicity profile, patient preference and physician preference

- Oxaliplatin + FU for about 6 months (24 weeks) is standard of care for patients with resected stage III colon cancer

- Unclear if shorter duration of chemotherapy is non-inferior
Other Attempts - Irinotecan

Three negative trials:

- **CALGB 89803**: IFL vs FL [1]
  
  G3/4 neutropenia: 43% vs 5%; 2.8% deaths in IFL group

- **PETACC-3**: FOLFIRI vs LV5FU2 [2]

- **ACCORD**: FOLFIRI vs LV5FU2 [3]
  
  FOLFIRI arm fared even worse than LV5FU2 - probably due to significant imbalances between groups for important prognostic factors

Other Attempts - Bevacizumab

Two negative trials:

- **NSABP C-08**: 2672 patients with stage II (25%) and stage III (75%) colon cancers randomised between FOLFOX + Bev (12 months) vs FOLFOX [1]

  Addition of Bev did not confer DFS or OS benefit

- **European AVANT**: FOLFOX4 vs FOLFOX + Bev or XELOX + Bev [2]

  No benefit of adding Bev; suggestion of poorer OS with Bev

Other Attempts - Cetuximab

Two negative trials:

- **N0147**: 1760 patients with stage III (75%) KRAS WT colon cancers randomised between mFOLFOX6 + Cet vs mFOLFOX6 [1]

  Interim analysis showed no benefit of adding cetuximab, leading to premature trial closure

- **PETACC-8** also showed no benefit of adding cetuximab to FOLFOX4 in patients with stage III KRAS exon 2 WT colon cancer [2]

Timing of Adjuvant Therapy

- Clinical trials: typically within 6-8 weeks of resection

- No randomised trials to address this

- Retrospective studies (non-oxaliplatin containing) showed possible detrimental outcomes if delay beyond 8 weeks

- But adjuvant clinical trials that have identified delay as a prognostic factor, delay beyond 6 or 8 weeks has not been associated with inferior outcome

- One meta-analysis showed increased mortality (HR 1.14) and disease relapse (HR 1.14) if there was a 4 weeks delay beyond 8 weeks post-op [1]

- Population-based analysis from database of British Columbia Cancer Agency 2006-2011 (incl Ox): no major difference if delay > 8 weeks [2]

[1] JAMA. 2011;305(22):2335
Role of Radiotherapy

• Adjuvant RT not commonly given in colon cancer

• Retrospective single institution series compared RT for ‘high-risk’ patients vs historical cohort without RT [1]

  LR rates (RT vs no RT): T4N0: 7% vs 31%; T4N+: 28% vs 53%

• INT 0130 randomized 222 patients to RT for ‘high-risk’ patients vs no RT; trial closed early because of poor accrual [2]

  No difference in outcome; but limited statistical power

• Contemporary recommendation: consider RT for ‘high-risk’ patients (LR > 30%): ascending or descending colon cancer with T4 disease or positive resection margin

“Stage III (any T, N1 M0, any T, N2 M0) (old staging: Dukes’ C or MAC C1–C3):
(i) Wide surgical resection and anastomosis;
(ii) following surgery the standard treatment is a doublet schedule with oxaliplatin and 5FU/folinic acid (LV) (FOLFOX4 or FLOX) [I, A]. When oxaliplatin is contraindicated monotherapy with FU/LV, mostly with infusional schedules (DeGramont, AIO regimen), or oral fluoropyrimidines (capecitabine) can be employed) [I, A].”
# NCCN Guidelines

## Colon Cancer

### Pathologic Stage

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<thead>
<tr>
<th>T1-3, N1-2, M0 or T4, N1-2, M0</th>
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### Adjuvant Therapy

- FOLFOX\(^{0,p,r}\) or CapeOx\(^{0,p,r}\)  
  (both category 1 and preferred)
- Other options include:
  - FLOX (category 1)\(^{0,p,r,s}\)
  - Capecitabine\(^{0,p}\)
  - 5-FU/leucovorin\(^{0,p}\)

### Surveillance

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA\(^{w}\) every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT\(^{h}\) annually for up to 5 y
- Colonoscopy\(^{b}\) 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,\(^{w}\) repeat in 3 y, then every 5 y\(^{y}\)
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (COL-G)

If Recurrence, See Workup (COL-9)
Diet and exercise:

• Prospective observational studies suggest that dietary factors may influence outcomes in some patients with CRC

• Mechanism unclear: weight reduction, changes in dietary composition

• Higher levels of physical activity may reduce risk of CRC-specific and overall mortality

• But no randomised controlled trials to confirm these observations

• 2013 ASCO guidelines endorse counselling patients on maintaining a healthy body weight, being physically active and eating a healthy diet
Adjunctive Measures

Aspirin and other NSAIDs:

- Numerous observational and randomised trials [1, 2] have demonstrated the efficacy of aspirin against the development of colorectal adenoma and cancer, through inhibition of COX-2 pathway (over-expressed in 85% of CRC)

Aspirin and other NSAIDs:

- Many but not all observational studies suggest that use of aspirin and other NSAIDs may also improve survival among CRC patients:

  1. Nurses’ Health Study and Health Professionals Follow-up Study, CRC patients who were aspirin users had a significant 29% lower cancer-specific mortality, and 21% lower overall mortality than non-users - irrespective of stage of CRC and adjuvant chemotherapy [1]

  2. Meta-analysis of six cohort studies and one nested case-control study concluded that post-diagnosis use of aspirin significantly improved overall mortality (HR 0.74), but not CRC-specific mortality [2]

- But no randomised trials to confirm benefit of aspirin for routine use

Adjunctive Measures

Aspirin and other NSAIDs:

- It is not clear that all colon cancer patients benefit from aspirin:

  Nurses’ Health Study and Health Professionals Follow-up Study showed that only patients whose tumours harboured mutations in the PIK3CA gene had marked reduction in CRC-specific death (HR 0.18 vs HR 0.96) [1]

  A later analysis showed that regular aspirin use was a/w a lower risk of BRAF WT but not BRAF MT CRC, independent of PIK3CA mutations [2]

- 2013 ASCO guidelines do not endorse routine use of aspirin for CRC patients

- Randomised trials ongoing: celecoxib vs placebo, + FOLFOX, in stage III CRC

- Some oncologists recommend low-dose aspirin to stage III CRC patients

In My Practice…[1]

- Adjuvant chemotherapy recommended to all patients with resected stage III colon cancer

- mFOLFOX6 preferred; 12 cycles = 24 weeks

  No calcium or magnesium

  If unable to continue full 12 doses of oxaliplatin (neuropathy or hypersensitivity reactions), omit oxaliplatin but continue LV5FU2 till #12

- XELOX as an alternative; 8 cycles = 24 weeks; try to keep oxaliplatin dose close to 130 mg/m²

- Oral capecitabine as an alternative to small subset of patients
• Dose the chemotherapy based on actual BSA, without capping it at 2.0 (ASCO guidelines)

• Start chemotherapy 3-4 weeks after resection, ensuring that the patient has adequately recovered from surgery - assessing: wound, general fitness, appetite, amount of food consumed, bowel habit, and laboratory tests

• Refer for adjuvant RT if ascending or descending colon with T4 or positive resection margins

• No routine use of aspirin; look for other good reasons to use aspirin

• Advise: healthy body weight, healthy diet, adequate vitamin D level, and exercise (30 min of moderate to vigorous physical activity at least 5 days a week)
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Hwai-Loong KONG
Remembering
Lee Kuan Yew
1923 - 2015