

Update in the management of colorectal cancer

HOT SPOT

By Yoo-Joung Ko, MD, MMSc, SM, FRCPC

Background

- Second leading cause of cancer death in Ontario
- Third most common cancer in Canada
- 70% of cancers are in the colon, 30% in the rectum
- More than 50% of patients present with stage III or IV disease

Adjuvant therapy for stage II colon cancer

- Recommendation remains against routine use of adjuvant chemotherapy in stage II disease

- Those with high-risk features, T4 disease, perforation, or clinical bowel obstruction and stage II disease may benefit from adjuvant therapy
- MOSAIC study demonstrated a trend toward improved disease-free survival in high-risk patients (see Table One)
- Other features such as fewer than 12 lymph nodes dissected, lymphovascular invasion and microsatellite instability remain undefined in predicting benefit from chemotherapy

| Table One. MOSAIC study: Disease-free survival | | | | |
|--|--------------|--------|------------------|---------|
| | 5-year DFS % | | HR [95% CI] | p-value |
| | FOLFOX4 | LV5FU2 | | |
| ITT (overall population) | 73.3 | 67.4 | 0.80 [0.68–0.93] | 0.003 |
| Stage III | 66.4 | 58.9 | 0.78 [0.65–0.93] | 0.005 |
| Stage II | 83.7 | 79.9 | 0.84 [0.62–1.14] | 0.258 |
| High-risk stage II n=576 | 82.1 | 74.9 | 0.74 [0.52–1.06] | – |
| Low-risk stage II n=323 | 86.3 | 89.1 | 1.22 [0.66–2.26] | – |

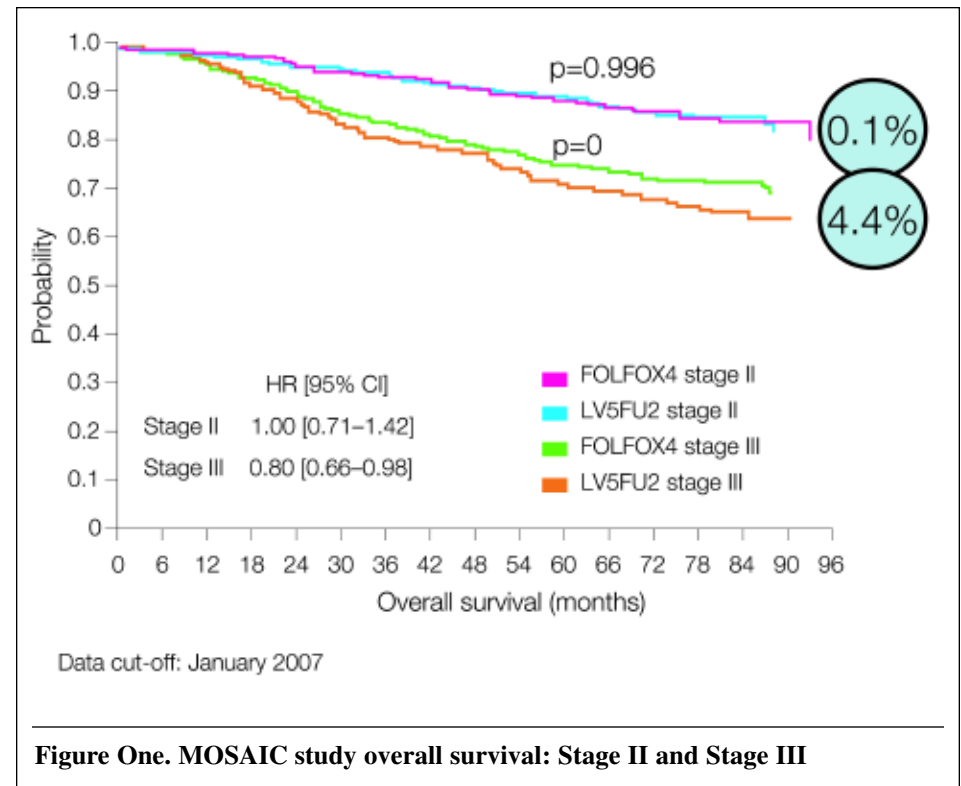
Data cut-off: June 2006

Adjuvant therapy for stage III colon cancer

- Capecitabine (1250 mg/m² po bid on days 1-14 every 21 days) equivalent to bolus fluorouracil and leucovorin (Mayo Regimen)
- MOSAIC study demonstrated an advantage for overall survival in favour

of FOLFOX-4 (HR 0.80 CI 0.66,0.98) (Figure One)

- Increased treatment-related toxicity in terms of grade 3/4 neutropenia and neurotoxicity (0.5% grade 3 toxicity persisting after one year)
- Role of bevacizumab and cetuximab currently being evaluated (see Table Two)



(Neo)adjuvant therapy for rectal cancer

- Neoadjuvant therapy with concurrent 5-FU and radiation therapy has been adopted by many centres for clinical stage II and III disease
- Lower risk of local recurrence with preoperative versus postoperative therapy
- Twice the rate of sphincter-sparing operations with preoperative therapy
- Extrapolation from colon cancer studies to recommend oxaliplatin-based regimens for postoperative adjuvant chemotherapy for stage II and III patients (8 to 12 cycles)

Chemotherapy for metastatic colorectal cancer

- Response rates, progression-free and overall survival better when oxaliplatin or irinotecan is added to 5-FU and leucovorin
- Median overall survival near 20 to 24 months
- Similar response rates between FOLFOX and FOLFIRI
- Monotherapy with capecitabine similar to Mayo regimen

- Addition of bevacizumab to either first line XELOX or FOLFOX did not lead to higher response rates, but did lead to a modest improved OS
- Addition of bevacizumab to second line FOLFOX leads to better progression-free survival and overall survival
- Single agent cetuximab is associated with better survival when compared with best supportive care in the third line setting (overall survival of 6.1 months versus 4.6 months) in those with EGFR positive tumours

Neoadjuvant therapy for liver metastasis

- Almost half of all patients will develop liver metastasis
- Only a minority will be eligible for surgical resection
- EPOC study randomized patients with resectable disease to six cycles of FOLFOX pre- and post-liver resection or to surgical resection alone
- Three-year progression-free survival advantage for neoadjuvant therapy (HR 0.77, P=0.041)

- Longer duration of chemotherapy pre-operatively may lead to damage to normal liver parenchyma
- Those who are initially unresectable but become resectable with chemotherapy have similar outcomes as those who are initially resectable
- Role of postoperative “pseudoadjuvant” chemotherapy remains undefined

Unanswered questions

- Role of dual biologic agents
- Role of biologic agent in the adjuvant setting
- Role of “chemotherapy holiday” (Table Two)

| Trial/Sponsor | Stage | Regimen | Number of Patients |
|------------------|--------------------------------------|--------------------------------|--------------------|
| ECOG/Intergroup | Stage II High High vs low MSI status | mFOLFOX6 ± bevacizumab | 3610 |
| NSABP C-08 | Stage II/III | mFOLFOX6 ± bevacizumab | 2714 |
| AVANT | Stage II/III | FOLFOX4 or XELOX ± bevacizumab | 3450 |
| NCCTG/Intergroup | Stage III | mFOLFOX6 ± cetuximab | 2300 |

Supported by an unrestricted educational grant from Sanofi-Aventis Canada Inc.

