EARLY STAGE COLON CANCER

Executive Summary

Surgical resection, the cornerstone of treatment in early disease, is potentially curative as a single modality therapy in stage I, II and III colorectal cancer. Multiple clinical trials have demonstrated that 5-FU based adjuvant chemotherapy can increase the cure rate of stage III colon cancer and this is an option in countries that have sufficient resources to administer chemotherapy and monitor its side effects. In wealthy countries, the standard of care is the FOLFOX regimen (5-FU, Calcium folinate, and Oxaliplatin) or the Capeox scheme (capecitabine/oxaliplatin). However, in countries that are unable to afford the expense of oxaliplatin, 5-FU/Calcium folinate chemotherapy, possibly administered in bolus fashion, is still an effective regimen.

Public Health Relevance

Colorectal cancer is one of the most common, and deadly, malignancies; it has been estimated that worldwide there are 1.2 million new cases a year [1]. Globally, colorectal cancer is the fourth most common cause of cancer-related deaths in men and third in women, killing an estimated 320,600 men and 288,100 women annually [1].

In the developed world, the death rate from colorectal cancer has been decreasing, largely due to colonoscopy screening, that enable both the removal of precancerous polyps and the detection of early stage, curable disease. Because 90% of colon cancers occur in patients who are at least 50 years-old, in countries that are able to afford colonoscopy screening the recommendation for the general population is to begin at age 50[2].

Because of the expense of colonoscopy, population based screening programs are usually not feasible in many parts of the world. With poor access to health care added to that, colorectal cancer patients in low- and middle-income countries often present with more advanced stages of the disease.

In the United States, 40% of colorectal cancer patients have localized disease (stage I and II) [3], 36% are regionally advanced (stage III) and 20% have metastases at presentation [3].

Requirements for diagnosis, testing, and administration

**Diagnostics:** Localized colorectal cancer often presents with one of the following symptoms: change in bowel habits, blood in the stools, abdominal discomfort, and weight loss. The symptoms of metastatic colorectal cancer depend on the site of metastasis depending on the site
of metastasis (liver: RUQ abdominal pain, jaundice; bone: bone pain; lungs: chest pain, shortness of breath).

The primary mass in colorectal cancer can be diagnosed with a rectal exam, sigmoidoscopy or colonoscopy. During endoscopy a biopsy can be performed so that the diagnosis of cancer is confirmed pathologically.

A critical aspect of the evaluation of a colorectal cancer patient is establishing whether she has metastatic disease. In high resource health systems, computed tomography scan of the Chest, Abdomen and Pelvis is performed routinely. In resource-constrained settings systemic evaluation with abdominal and pelvic ultrasound is a less costly commonly employed option. Preoperative rectal cancer staging, which evaluates the T and N stage of the tumor, is also important in establishing the degree of loco-regional invasiveness of the tumor. Where available, it is performed by either rectal MRI or endoscopic ultrasound, complex and highly specialized have limited availability in resource-constrained settings.

When chemotherapy is employed, laboratory evaluations play an important role in monitoring patient safety. A complete blood count (CBC) with differential assesses whether patients are myelosuppressed and neutropenic. A comprehensive metabolic panel monitors renal and hepatic function as well as electrolyte imbalances.

Administration: Administration requires intravenous infusion capacity and regular access to clinical care. Treatment can be done in an outpatient fashion. In settings where ambulatory infusion of 5FU is not feasible it is common for patients to be treated as inpatients. Anti-emetics need to be available. Monitoring requires laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself. Importantly, in-patient facilities capable of supporting patients with severe infections and dehydration need to be readily available. Social and financial well-being can be impacted by treatment side effects and should be monitored and addressed as well.

There are several regimens of 5-FU/Calcium folinate that have equal efficacy. The modified de Gramont regimen is typically used because of its safety profile, but it requires continuous infusion of 5-FU over 46 hours and hence is more complex to administer. The Roswell Park and Mayo clinic regimens of 5-FU and oral capecitabine are alternatives that do not require infusional 5-FU. The corresponding oxaliplatin-containing regimes are FOLFOX, FLOX and Capeox.

Overview of Regimens

Surgery for Stage I and II Colon Cancer

For stage I and II disease, surgery alone is potentially curative and post-operative chemotherapy does not improve outcome. While there is considerable controversy, 5-FU based chemotherapy may be beneficial in a highly selected patient population with stage
II colon cancer (i.e., T4 tumors; poorly differentiated histology; lymphovascular or perineural invasion; perforated or obstructed lesion; fewer than 12 lymph node in the surgical specimen).

**Surgery and Adjuvant Chemotherapy for Stage III Colon Cancer**

Surgery alone is potentially curative, even without post-operative chemotherapy, and should be utilized even in its absence. The addition of post-operative chemotherapy to surgery improves the likelihood of a patient remaining disease-free and of improving overall survival.

**Standard Regimens for Stage III Colon Cancer**

**Modified FOLFOX6 Regimen (2-week cycle; 12 cycles)**
- Calcium folinate 400 mg/m² IV on Day 1 of each 14-day cycle
- Fluorouracil (5-FU) 400 mg/m² IV bolus on Day 1 of each 14-day cycle
- Fluorouracil (5-FU) 1200mg/m² daily; continuous infusion over 46 hours (day 1 and 2 of each 14-day cycle)
- Oxaliplatin 85mg/m² IV on Day 1 of each 14-day cycle

**CapeOx (3-week cycle; 8 cycles)**
- Capecitabine 1,000 mg/m² PO BID twice daily on Days 1-14 of each 21-day cycle
- Oxaliplatin 130 mg/m² over 2 hours on Day 1 of each 21-day cycle

**FLOX (8-week cycle; 3 cycles)**
- 5-FU 500 mg/m² IV bolus weekly for 8-week cycle
- Calcium folinate 500 mg/m² IV weekly for 6 weeks of each 8-week cycle
- Oxaliplatin 85 mg/m² IV on weeks 1,3,5 of each 8-week cycle

Note: it is acceptable to use low-dose calcium folinate, i.e. 20 mg/m² instead of higher doses.

The following regimes are acceptable where oxaliplatin is not available or when it is contraindicated

**Roswell Park Regimen of adjuvant chemotherapy with 6 cycles of 5-FU and Calcium folinate (6 months)**
- Calcium folinate 500 mg/m² IV bolus on Day 1, 8, and 15 of each 28 day cycle (i.e. week 1, 2, and 3 of each 4 week cycle) Fluorouracil (5-FU) 500 mg/m² IV bolus on Day 1, 8, and 15 of each 28 day cycle (i.e. week 1, 2, and 3 of each 4 week cycle)
Mayo regimen of adjuvant chemotherapy with 6 cycles of 5-FU and Calcium folinate (6 months)
- Calcium folinate 20 mg/m$^2$ IV bolus administered on days 1-5 of each four week cycle
- Fluorouracil (5-FU) 425 mg/m$^2$ on days 1-5 of each four week cycles

Modified de Gramont regimen of adjuvant chemotherapy with 12 cycle of 5-FU and Calcium folinate (6 months)
- Calcium folinate 400 mg/m$^2$ IV on Day 1 of each 14 day cycle
- Fluorouracil (5-FU) 400 mg/m$^2$ IV bolus on Day 1 of each 14 day cycle
- Fluorouracil (5-FU) 1200mg/m$^2$ daily; continuous infusion over 46 hours (day 1 and 2 of each 14 day cycle)

Capecitabine as a single agent
- Capecitabine 1,000-1,250 mg/m$^2$ twice daily for 14 days of each 21 day-cycle for 8 cycles

Note: it is acceptable to use low-dose calcium folinate, i.e. 20 mg/m$^2$ instead of higher doses.

Review of Benefits and Harms

Benefits

Early stage colon cancer is a potentially curable illness. The most critical treatment for patients with early stage colon cancer is surgery. Patients with stage I, stage II and stage III colon cancer can be cured with surgery alone. The survival rates for stage I and stage II colon cancer are so high (the cancer specific 5 year survival for stage I is greater than 95% and for stage II is 71%-87%), that even in developed countries the vast majority of these patients are treated with surgery alone. The benefit and therefore administration of adjuvant chemotherapy in patients with stage II colon cancer remain unclear, although there is a subset of patients with high-risk clinicopathologic features for whom adjuvant chemotherapy is, at a minimum, discussed.

Colon cancers that spread to regional lymph nodes, stage III colon cancers, have a higher risk of recurrence. Multiple clinical trials have demonstrated that adjuvant chemotherapy lowers the risk of cancer of recurrence. Initial adjuvant therapy trials showed that adjuvant 5-FU, combined with either levisamole (an agent no longer used) or calcium folinate, decreased the risk of recurrence by 40% and the risk of death by 35% when compared to no adjuvant treatment [4,5]. In one seminal intergroup trial, Moertel and colleagues demonstrated that colorectal cancer patients with Dukes Class C cancer (i.e. node positive stage III disease) survival at 3.5 years was 55 percent for the observation arm and 71 percent for the 5-FU/levisamole arm[4]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-03 study, an increase in both 3-year disease-free survival (73%, 95% CI 69–77 vs 64%, 60–68) and overall survival (84% vs 77%; p=0.007) was recorded with bolus fluorouracil and calcium folinate compared with lomustine,
vincristine, and fluorouracil. A similar benefit was noted in a study by the North Central Cancer Treatment Group, in which patients were randomly allocated either bolus fluorouracil and calcium folinate or observation, and in the International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) study, in which data were pooled from three separate trials undertaken in Italy, Canada, and France. In these three trials, patients received treatment based on one of two regimens: Roswell Park (RPMI), consisting of 500 mg/m² fluorouracil and 500 mg/m² calcium folinate a week for 6 of 8 weeks; or Mayo, comprising 370–425 mg/m² fluorouracil and 20 or 200 mg/m² calcium folinate daily for 5 days every 28 days. In subsequent trials, comparable clinical benefit has been noted between RPMI and Mayo bolus fluorouracil regimens and between high-dose and low-dose calcium folinate. However, toxic effects differ between the RPMI and Mayo regimens; Mayo is associated with increased neutropenia and stomatitis, whereas RPMI leads to more cases of diarrhea. Based on these differences, the RPMI regimen is generally preferred. One additional advantage of the RPMI regimen is that subsequent weekly doses can be held for severe toxic effects. In addition to bolus regimens, those that include fluorouracil infusions and the oral prodrug capecitabine have been assessed. Findings of several randomized studies show that infusional fluorouracil regimens are not superior to the Mayo fluorouracil and calcium folinate regimen but are less toxic. In a phase 3 trial, capecitabine was noninferior to the Mayo regimen in terms of disease-free survival and had fewer toxic effects. 3-year disease-free survival (64% vs 61%; p=0·05) and overall survival (81% vs 78%; p=0·07) were increased with capecitabine, although the difference was not statistically significant. These results have been corroborated by a recent meta-analysis which confirmed the non-inferiority of capecitabine [12]. In general, bolus and infusional fluorouracil and oral capecitabine are acceptable options, and choice depends on local practices and economic considerations. [13]

The standard of care for adjuvant treatment of stage III colon cancer is now a combination of oxaliplatin and a fluoropyrimidine, such as FOLFOX and FLOX, which contain 5-FU, calcium folinate and oxaliplatin), or Capeox, in which capecitabine, an oral drug, substitutes for 5-FU. The MOSAIC trial compared adjuvant FOLFOX4 to adjuvant 5-FU/Calcium folinate. It demonstrated that in stage III colon cancer FOLFOX4 improved survival by 20% compared to 5-FU/Calcium folinate [6]. The six year survival rate for stage III colon cancer patients treated with FOLFOX was 72.9% compared to 68.7% in patients treated with 5-FU/Calcium folinate [6]. The rates of grade 3 and 4 neutropenia was higher in the FOLFOX4 arm than the 5-FU/Calcium folinate arm (41.1% vs. 4.7%)[7]. The rate of febrile neutropenia was also higher in the FOLFOX4 arm (1.8% verse 0.2%)[7]. Grade 3 neuropathy occurred in 12.4% of the patients treated with FOLFOX4 [7]. For ease of administration, most institutions use the modified FOLFOX6 regimen, in which the bolus of 5-FU on the second day of chemotherapy is eliminated. It is not believed that this would alter the efficacy of the regimen.

The FLOX regimen was compared to 5FU alone in the NSABP C-07 trial. For the intent to treat analysis, with both stage II and III patients included, The HR favoring FLOX was 0.82 and DFS estimates at 5 years were 64.2% for FULV and 69.4%. HR for DFS was 0.78 for stage III patients. OS improvement with FLOX compared with FULV bordered on significance for stage III patients (HR, 0.85; 95% CI, 0.72 to 1.00; P = .052). The 5-year OS estimates were 73.8% for FULV and 76.5% for FLOX.
The Capeox scheme (Capecitabine and Oxaliplatin) utilizes capecitabine, an oral pro-drug that is enzymatically converted to 5-FU. Similar to the results of FOLFOX, the Capeox regimen improved progression free survival compared to 5-FU/Calcium folinate. The 3-year disease free survival rate was 70.9% with Capeox and 66.5% with 5-FU/Calcium folinate [8]. OS at 5 years was 77.6% with oxaliplatin/capecitabine and 74.2% with 5FU, but the difference was not statistically significant, p=0.15. Toxicities associated with capecitabine also vary based on ethnicity and geographic location; while it is generally well-tolerated by Asians, Western Europeans also have improved tolerance compared to North American patients, in terms of reduced incidence of hand-foot syndrome, mucositis and diarrhea. One of advantage of the capecitabine containing-regimen is that it obviates the need for long term intravenous catheter access and the 46-hour infusion associated with the FOLFOX regimen and its variants.

Despite caveats associated with comparisons across phase 3 trials, the bolus fluorouracil and calcium folinate backbone in the NSABP C-07 trial31 seems to be the most toxic. Grade 3–4 diarrhoea was noted in 37% of patients receiving fluorouracil and oxaliplatin (FLOX) versus 32% of those who received bolus fluorouracil and calcium folinate alone. By comparison, grade 3–4 diarrhoea was reported in only 11% of individuals who received FOLFOX30 and 19% of those who received capecitabine plus oxaliplatin (CapeOx). Overall, the FOLFOX and CapeOx regimens seem to have slightly different but comparable toxic effect profiles, as has been noted in the metastatic setting.

FOLFOX or CapeOx are preferred over FLOX because of the poorer toxicity profile seen with FLOX. Patients with resected stage III colon cancer should only receive a fluoropyrimidine alone if they are not candidates for oxaliplatin (for either medical or financial reasons). Either an infusional fluorouracil regimen or an oral fluoropyrimidine such as capecitabine for 6 months are preferred over bolus fluorouracil and calcium folinate because of diminished toxic effects and, possibly, superior efficacy (for capecitabine).

If a bolus fluorouracil and calcium folinate regimen must be chosen for cost or logistical reasons, the regimen RPMI is preferred slightly over Mayo because of its more favourable haematological toxicity profile.

Some health care systems may not be able to afford the expense associated with chemotherapy administration and toxicity monitoring and management. For these countries, it should be emphasized that surgical resection alone is potentially curative for stage I, II, and III colon cancer. Since patients with early stage colon cancer are potentially cured with surgery alone, adjuvant chemotherapy should not be administered unless it can be done safely.

Finally, several studies have demonstrated equivalence between low dose (20 mg/m²) and high-dose (500 mg/m²) calcium folinate when administered with 5-FU. [9]
Harms and Toxicity Considerations

Common
Frequent adverse effects of 5FU/Calcium folinate combination therapy include diarrhea and associated dehydration, neutropenia (uncommonly leading to infection in <2% of patients), anemia, and mucositis.[7,10] Palmar-plantar erythrodysesthesia (hand-foot) syndrome is associated with fluorouracil and capecitabine, with an increased incidence of up to 60% for patients treated with capecitabine. This adverse effect typically resolves following treatment interruption.[11]

Oxaliplatin-containing regimens can lead to sensory neuropathy (24-92% of patients) which is often acute and reversible but may be persistent at high cumulative doses.[6,7,8]

Serious
Diarrhea occurs in up to 50% of patients treated with fluorouracil or capecitabine. Diarrhea can be severe and may require hospital admission for IV fluid replacement, it is often dose-limiting. [7,10]

Systematic Reviews

5-FU-based adjuvant chemotherapy


Purpose: Although it is well-established that fluorouracil- (FU-) based adjuvant therapy improves survival for patients with resected high-risk colon cancer, the magnitude of adjuvant therapy benefit across specific subgroups and for individual patients has been uncertain. Patients and Methods: Using a pooled data set of 3,302 patients with stage II and III colon cancer from seven randomized trials comparing FU + calcium folinate or FU + levamisole to surgery alone, we performed an analysis based on a Cox proportional hazards regression model. Treatment, age, sex, tumor location, T stage, nodal status, and grade were tested for both prognostic and predictive significance. Model derived estimates of 5-year disease-free survival and overall survival (OS) for surgery alone and surgery plus FU-based therapy were calculated for a range of patient subsets. Results: Nodal status, T stage, and grade were the only prognostic factors independently significant for both disease-free survival and OS. Age was significant only for OS. In a multivariate analysis, adjuvant therapy showed a beneficial treatment effect across all subsets. Treatment benefits were consistent across sex, location, age, T-stage, and grade. A significant stage by treatment interaction was present, with treatment benefiting stage III patients to a greater degree than stage II patients. Conclusion: Patients with high-risk resected colon cancer obtain benefit from FU-based therapy across subsets of age, sex, location, T stage, nodal status, and grade. Model estimates of survival stratified by T stage, nodal status, grade, and age
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are available at http://www.mayoclinic.com/calcs. This information may improve patients' and physicians' understanding of the potential benefits of adjuvant therapy.

Addition of oxaliplatin to 5-FU

André T et al. Improved overall survival with oxaliplatin, fluorouracil, and calcium folinate as adjuvant treatment in stage II or III colon cancer in the mosaic trial. Journal of Clinical Oncology 2009;27:3109-3116.

Purpose: Three-year disease-free survival (DFS) was significantly improved in patients who had undergone resection with curative intent for stage II or III colon cancer who received bolus plus continuous-infusion fluorouracil plus calcium folinate (LV5FU2) with the addition of oxaliplatin (FOLFOX4). Final results of the study, including 6-year overall survival (OS) and 5-year updated DFS, are reported. Patients and Methods: A total of 2,246 patients were randomly assigned to receive LV5FU2 or FOLFOX4 for 6 months. The primary end point was DFS. Secondary end points were OS and safety. Results Five-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups, respectively (hazard ratio [HR] = 0.80; 95% CI, 0.68 to 0.93; P = .003). Six-year OS rates were 78.5% and 76.0% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.84; 95% CI, 0.71 to 1.00; P = .046); corresponding 6-year OS rates for patients with stage III disease were 72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97; P = .023). No difference in OS was seen in the stage II population. The incidence of second noncoeloreal cancers was 5.5% and 6.1% in the FOLFOX4 and LV5FU2 groups, respectively. Among patients receiving oxaliplatin, the frequency of grade 3 peripheral sensory neuropathy was 1.3% 12 months after treatment and 0.7% at 48 months. Conclusions: Adding oxaliplatin to LV5FU2 significantly improved 5-year DFS and 6-year OS in the adjuvant treatment of stage II or III colon cancer and should be considered after surgery for patients with stage III disease.

Recommendations

The reviewers recommend the incorporation of early stage colon cancer treatment options into the WHO Model List of Essential Medicines, and recommend specifically that oxaliplatin and capecitabine be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Oxaliplatin
Capecitabine
References


