



Portsmouth Regional Hospital
Cancer Care Center

2014 Cancer Report

Adjuvant Chemotherapy in Stage 3 Colon Cancer

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Colorectal cancer is the second most common cause of cancer-related death in the United States. In 2014, approximately 137,000 people will be diagnosed with colon cancer and over 50,000 will die of the disease (SEER). According to the SEER database, the lifetime risk of developing colorectal cancer is approximately 4.8%. However, aggressive screening strategies have reduced both the incidence of invasive disease and mortality rates significantly.

Stages of Colon cancer

Stage 0	Carcinoma in Situ
Stage I	Tumor has spread from mucosa to submucosa
Stage IIA	Tumor has spread through muscular wall to the serosa, no nodal involvement
Stage IIB	Tumor has spread through the serosa ,but has not spread to nearby organs, no nodal involvement
Stage IIC	Spread through serosa of the colon to nearby organs, no nodal involvement

<p>Stage IIIA</p>	<p>Tumor is within the colon wall with lymph node spread (Cancer may have spread through the mucosa of the colon wall to the submucosa and muscle layer, and has spread to one to three nearby lymph nodes or tissues near the lymph nodes. OR, cancer has spread through the mucosa to the submucosa and four to six nearby lymph nodes).</p>
<p>Stage IIIB</p>	<p>Tumors have grown through the colon wall with one to four lymph node spread (Cancer has spread through the muscle layer of the colon wall to the serosa or has spread through the serosa but not to nearby organs; cancer has spread to one to three nearby lymph nodes or to tissues near the lymph nodes. OR, cancer has spread to the muscle layer or to the serosa, and to four to six nearby lymph nodes. OR, cancer has spread through the mucosa to the submucosa and may have spread to the muscle layer; cancer has spread to seven or more nearby lymph nodes.)</p>



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<p>Stage IIIC</p>	<p>Cancer has spread through the serosa of the colon wall but not to nearby organs; cancer has spread to more than four to six nearby lymph nodes. OR, cancer has spread through the muscle layer to the serosa or has spread through the serosa but not to nearby organs; cancer has spread to seven or more nearby lymph nodes. OR, cancer has spread through the serosa to nearby organs and to one or more nearby lymph nodes or to tissues near the lymph nodes.</p>
<p>Stage IV</p>	<p>Colon cancer with distant metastasis</p>

Treatment of stage III colorectal cancer includes surgery, adjuvant chemotherapy and in patients with rectal cancer neoadjuvant chemoradiotherapy in selected patients. The definite treatment of localized colon cancer is resection. Recurrence, which is predominantly metastatic in character, is thought to be due to occult micro metastasis present at the time of the surgery. The goal of adjuvant therapy is to eradicate these micro-metastasis. A landmark meta-analysis of 7 Phase III trials showed improved overall survival as well as improved time to tumor recurrence with adjuvant chemotherapy. Specifically, 5 year OS rate was 71% for the adjuvant chemotherapy group and 64 % for who did not have chemotherapy. (Marshall, Gastrointest Cancer Research 2007). The benefit of adjuvant chemotherapy was clearly demonstrated in stage III disease, although more controversial with stage II disease.

Specifically, the first large scale study was done by National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01. They randomly assigned 1166 patients with Duke B or C colon cancer to surgery alone or chemotherapy with BCG or MOF. MOF was significantly associated with improved 5 year overall survival compared to surgery alone or BCG. The next important study in the field was North Central Cancer Treatment Group (NCCTG) which studied the combination of 5 FU and levamisole in Duke B and C colon cancer. However, due to the reports of multifocal cerebral demyelinating syndrome with levamisole and inferiority of 5 FU/levamisole combination this combination is no longer in practice.

The current NCCN recommendation for stage III colon cancer is adjuvant chemotherapy with an oxaliplatin-based regimen, in general FOLFOX. This should be started within 6-8 weeks post operatively ideally. While FOLFOX 4 was used in most of the adjuvant registration trials, modified FOLFOX 6 is most commonly used in this population. The benefit of adding oxaliplatin to 5 FU/LV was studied in MOSAIC trial. After 82 months, 5 year DFS was significantly higher with FOLFOX than 5-FU and leucovorin alone. In patients with contraindication to oxaliplatin such as pre-existing significant neuropathy, 5-FU/LV is an acceptable option.

Oxaliplatin and oral capecitabine known as XELOX regimen is another alternative but potentially more toxic than FOLFOX. The combination was compared to 5 FU/LV in a

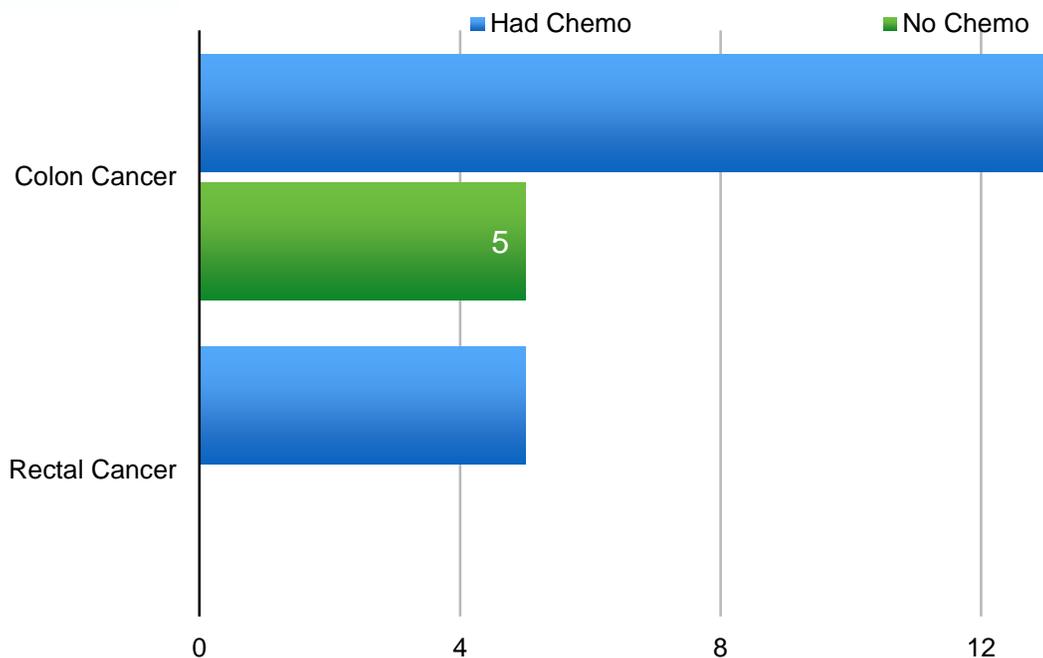


phase III clinical trial which demonstrated clearly superior DFS in XELOX group than 5-FU/LV. XELOX had less neutropenia but caused more neurotoxicity and thrombocytopenia.

Finally, patients with T3, T4 or N1-3 rectal tumors should ideally receive neoadjuvant chemoradiotherapy followed by resection followed by adjuvant therapy with regimens identical to colon cancer. This leads to significant improvement in local control. It is not uncommon to offer an attenuated course of adjuvant therapy to patients with rectal cancer who receive neoadjuvant chemoradiotherapy.

The purpose of our study was to examine the use of adjuvant, and where appropriate neoadjuvant therapy, in patient with stage III colorectal cancer at Portsmouth Regional Hospital. The inclusion criteria for the study was a confirmed diagnosis of stage III colorectal adenocarcinoma with first contact year between 2007-2012. We reviewed total of 30 cases listed in the registry as stage III. Diagnostic evaluations and staging were reviewed and felt to be adequate. Out of these, 3 cases were excluded due to metastases at time of diagnosis, a fourth case was excluded as squamous cell carcinoma of the anal region, and a fifth was excluded as a colon lymphoma. This left 25 cases included in the final review.

Of the 20 cases of colon cancer, 15 received adjuvant chemotherapy. Two patients declined recommended chemotherapy and were lost to f/u, two patients were not considered candidates for chemotherapy due to co-morbidities, and one patient was lost to follow-up after one cycle of XELOX. All 5 patients with rectal cancer received appropriate neoadjuvant chemoradiotherapy and adjuvant chemotherapy. Of the 15 patients receiving adjuvant therapy, four did not receive oxaliplatin. Patient ages were 89, 79, 54 and 52. Note was made of severe underlying peripheral neuropathy in the 54 year-old patient as the reason oxaliplatin was not given. It is unclear why the other three patients did not receive oxaliplatin, although over age 75 it is common to give 5-FU based therapy alone.



We have follow-up data for 23 of the 25 patients. One patient who received adjuvant FOLFOX was lost to follow-up at 3 years, but was in remission at that point. The second patient lost to follow-up received one cycle of XELOX and then abstained from further clinical contact at PRH. Of the remaining 23 patients, 17 are alive and disease-free. Of these, two patients did not receive adjuvant therapy – one due to comorbidities and one who declined recommended therapy. Three patients who received therapy are alive with metastatic disease, and the second patient who declined therapy died of metastatic disease.

Overall we did well in the recommended adjuvant chemotherapy in stage III colon Cancer. Two areas identified for improvement include 1) increasing the use of oxaliplatin-containing regimens in patients who are appropriate candidates, and 2) designing an effective follow up system with patient and PCPs when recommended treatment is declined or when patients do not follow up as anticipated. Perhaps with greater monitoring and support we can help these patients receive appropriate therapy, or at least receive appropriate post-surgical monitoring if they decline adjuvant chemotherapy. Many patients may be overwhelmed with the diagnosis and may decide against chemotherapy in the short term, but we may be able to improve outcomes with continues support. Additionally, timely counseling about the proven benefit of adjuvant chemotherapy may increase the treatment rate.

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