Reports from the Canadian Association of Medical Oncologists Annual Meeting

**Treatment outcomes**

**IMPROVEMENT IN TREATMENT OUTCOMES IN COLORECTAL CANCER**

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**TRIAL SUMMARY: Time to adjuvant chemotherapy**

Parimi S, Kumar A, Batuyong E and Easaw J. A retrospective analysis on the effect of time to adjuvant chemotherapy (TTAC) from surgery in stage III colon cancer. 2015 meeting of the Canadian Association of Medical Oncologists, Abstract 25.

Adjuvant chemotherapy (AC) has conventionally been initiated within 8 weeks post surgery in colon cancer. This study evaluated the impact of delaying administration of modern AC regimens on disease-free survival (DFS) and overall survival (OS) for stage III colon cancer. A retrospective analysis was performed on patients receiving AC for stage III colon cancer at the Tom Baker Cancer Centre between 2007 and 2012. Kaplan-Meier methods and Cox regression that accounted for known prognostic factors were used to evaluate the impact of time to adjuvant chemotherapy (TTAC) on DFS and OS. TTAC was categorized into >8 vs <8 weeks and >12 vs <12 weeks. The study included 296 patients with a median age of 62.5 years. Capecitabine was the most frequently used AC (45.6%), followed by FOLFOX (leucovorin/5-fluorouracil/oxaliplatin; 43.2%), CAPOX (capecitabin/oxaliplatin; 8.5%), and 5FU (5-fluorouracil; 2.7%); 67.2% of patients started AC within 8 weeks and 81.1% started within 12 weeks.

**Results:** On univariate analysis, there was no significant difference in DFS or OS regardless of whether chemotherapy was initiated before or after 8 weeks. The same held true for the 12-week cutoff. Multivariate analyses controlling for gender, age, tumour location, T stage, N stage and chemotherapy regimen, showed that TTAC had no significant impact on DFS or OS at the 8-week cutoff point (DFS hazard ratio [HR] 1.03, 95% CI 0.64–1.66, p=0.89; OS HR 1.01, 95% CI 0.56–1.83, p=0.96), nor at the 12-week cutoff (DFS HR 1.10, 95% CI 0.64–1.87, p=0.73; OS HR 1.34, 95% CI 0.71–2.53, p=0.37). The authors found that delaying AC in stage III colon cancer beyond 8 and 12 weeks did not have an effect on DFS or OS.

**TRIAL SUMMARY: Improving prognostication models**


Cancer staging systems convey valuable prognostic information to both clinicians and patients. Currently, colon cancer is staged according to the American Joint Committee on Cancer (AJCC) TNM classification system. However, survival estimates for patients with the same stage of colon cancer may vary considerably due to other factors including age, sex, grade and number of lymph nodes sampled. This study aimed to 1) assess the accuracy of the 7th edition of the TNM classification system in predicting survival of patients with primary colon cancer after curative-intent surgery, and 2) evaluate the utility of incorporating additional demographic and tumour variables beyond TNM staging to improve prognostic accuracy. Patients with curative-intent resection of a first primary adenocarcinoma of the colon at the time of referral to the Cross Cancer Institute between 2004 and 2007 were identified from the Alberta Cancer Registry. Three multivariate Cox’s proportional hazard models were developed to explore the effect on predicting overall survival (OS) of supplementing TNM staging with additional demographic and tumour variables.

**Results:** The authors identified 559 consecutive patients with complete chart records; 52% (n=290) were male and the median age was 74. In the first model, based only on T and N elements, N2 disease was correlated with increased mortality (HR 2.546; p<0.0001). When the number of lymph nodes examined (HR 0.980; p=0.034) and number of metastatic lymph nodes detected (HR 1.094; p<0.0001) were substituted for the N-staging element, both variables correlated positively and negatively with outcome, respectively. Finally, when tumour grade, sex and age were incorporated into the model, the number of examined lymph nodes (HR 0.980; p=0.029) and number of nodes containing tumour (HR 1.093; p<0.0001) remained independent predictors of
Incorporating readily available demographic and tumour variables, such as age, sex and number of lymph nodes examined, can enhance the current TNM staging system and improve prognostication in early-stage colon cancer.

**COMMENTARY:** Colorectal cancer (CRC) is the third most commonly diagnosed cancer in Canada and second-leading cause of cancer death. Improving patient outcomes is thus of primary importance, particularly in patients undergoing curative resection for localized disease. Optimizing cancer staging to better define prognosis can help identify which patients will benefit from systemic therapy, while a better understanding of optimal chemotherapy scheduling is needed to ensure best outcomes.

The most widely used CRC staging system is the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC)/TNM system, which incorporates tumour extent (T), lymph node involvement (N) and presence of metastatic sites (M). Presence of metastases in regional lymph nodes is second in importance only to the presence of distant metastases as a prognostic factor in resected colorectal cancer. The number of lymph nodes involved with malignancy also directly influences risk of disease recurrence. Other prognostic determinants include the local depth of tumour penetration, the presence of vascular invasion or residual tumour, preoperative carcinoembryonic antigen (CEA) level, and the presence of bowel obstruction. Patient age and gender have also been noted to impact survival, as has tumour grade, despite issues of interobserver variability and intratumour heterogeneity.

In their study, Dr. Ho and colleagues examined the accuracy of the 7th edition of the TNM classification system at predicting survival in a cohort of curatively resected CRC patients identified from the Alberta Cancer Registry. They also evaluated the impact of incorporating additional variables into three constructed hazard models, using variables such as age, gender, tumour grade, number of lymph nodes examined (LNE) and number of lymph nodes involved with metastases (LNM). Noting the value of LNE and LNM as independent predictors of survival, the authors concluded that patient demographics and tumour variables may enhance current staging and improve prognostication in resected CRC patients. These results are in keeping with other attempts that have shown the LNM/LNE ratio to have good predictive power. While a prognostic signal was noted in the hazard models constructed by Dr. Ho’s group, further prospective validation of these markers is required.

In addition to being a strong prognosticator, the metastatic involvement of regional lymph nodes is an indication for adjuvant chemotherapy in resected CRC. Adjuvant chemotherapy is usually initiated 6–8 weeks after surgery, allowing the patient to recover from surgery. In the MOSAIC trial, adjuvant FOLFOX4 demonstrated significant benefit in disease-free survival over the previous standard of 5FU/LV (5-fluorouracil/leucovorin). Patients enrolled in the MOSAIC trial were required to initiate chemotherapy within 7 weeks of surgery. Other trials evaluating oxaliplatin-containing regimens also required eligible patients to commence treatment within 6 to 8 weeks of resection. Guidelines from Cancer Care Ontario support recommendations to initiate adjuvant treatment within 8 weeks post resection. A meta-analysis further investigating the impact of adjuvant chemotherapy delay post resection noted poorer survival and disease-relapse outcomes for every 4 weeks of delay post op. However, a majority of the patients included in the meta-analysis were treated with 5FU-based chemotherapy without oxaliplatin.

Dr. Parimi and his colleagues retrospectively analyzed patients treated with adjuvant chemotherapy for resected CRC at the Tom Baker Cancer Centre from 2007–2012, specifically investigating the effect of time to adjuvant chemotherapy from surgery in stage III CRC. Many patients analyzed were treated with oxaliplatin-containing regimens. The authors noted no significant difference on overall or disease-free survival when adjuvant chemotherapy was initiated within 8 weeks, within 12 weeks or beyond. Although these results seem to contradict earlier studies, at least one other retrospective review came to a similar conclusion. Nevertheless, the meta-analysis investigating a predominantly 5FU/LV-treated population still represents the more robust level of evidence in this matter. Dr. Parimi’s study suggests less impact of starting chemotherapy beyond 8 or 12 weeks in the setting of dual 5FU/LV and oxaliplatin use, however further study is required to validate these findings.

**Already known**
- Many current guidelines state that time to adjuvant chemotherapy (AC) should not exceed 8 weeks following resection of colorectal cancer.
- Assessment of prognosis following resection of colorectal cancer currently employs the American Joint Committee on Cancer TNM classification system.

**What these studies showed**
- Delaying AC after 8 and even 12 weeks following resection had no impact on disease-free survival (DFS) or overall survival (OS) in a group of patient treated mostly with oxaliplatin-containing regimens.
- Demographic and tumour variables such as age, sex and number of lymph nodes examined can enhance the current TNM staging system and improve prognostication in early stage colon cancer.

**Next steps**
- Validate findings that delays of over 12 weeks do not impact DFS or OS before possibly reexamining guidelines.
- Perform further studies to confirm the value of adding number of lymph nodes with metastases and number of lymph nodes examined to TNM staging for prognosis.
findings. Therefore, treatment initiation within 8 weeks post resection should remain the aim in clinical practice.

References