

Concordance with clinical practice guidelines for adjuvant chemotherapy in patients with stage I–III colon cancer: experience in 2 Canadian provinces

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Background: Clinical practice guidelines (CPGs) for the adjuvant treatment of colorectal cancer were published by the National Institutes of Health in 1991. The American Society of Clinical Oncology and Cancer Care Ontario have recommended adjuvant chemotherapy for patients with high-risk stage II colon cancer. We evaluated differences in concordance with guidelines in the treatment of patients with stage I–III colon cancer in the Canadian provinces of Newfoundland and Labrador and Ontario.

Methods: We assessed clinical data and treatment from January 1999 to December 2000 for 130 patients from Newfoundland and Labrador and 315 patients from Ontario who had stage I–III colon cancer. The primary outcome was concordance with guidelines for adjuvant treatment. We evaluated factors affecting the use of chemotherapy in patients with stage II disease.

Results: No patients received adjuvant therapy for stage I disease. Forty-five of 52 patients (87%) in Newfoundland and Labrador and 108 of 115 patients (94%) in Ontario received adjuvant chemotherapy for stage III colon cancer. Twenty of 55 patients (36%) in Newfoundland and Labrador and 44 of 116 patients (38%) in Ontario received adjuvant therapy for stage II disease. Eighteen of 41 patients (44%) in Newfoundland and Labrador and 30 of 53 patients (57%) in Ontario with high-risk features received adjuvant treatment, which was significantly higher than patients without high-risk features. There was a strong trend toward using chemotherapy in patients with stage II disease who were 50 years or younger, independent of high-risk status.

Conclusion: Concordance with CPGs for adjuvant chemotherapy in patients with stage II colon cancer was not optimal. This may reflect selection bias among referring surgeons, a paucity of level-I evidence and the belief that other factors such as age may play a role in predicting outcome.

Contexte : Les National Institutes of Health ont publié en 1991 leurs lignes directrices sur le traitement adjuvant du cancer colorectal. L'American Society of Clinical Oncology et Action Cancer Ontario ont recommandé la chimiothérapie adjuvante aux patients atteints d'un cancer du côlon de stade II à haut risque. Nous avons mesuré les différences en ce qui a trait au respect des lignes directrices dans le traitement des patients atteints d'un cancer du côlon de stade I à III dans les provinces canadiennes de Terre-Neuve-et-Labrador et de l'Ontario.

Méthodes : Nous avons analysé, pour la période allant de janvier 1999 à décembre 2000, les données cliniques et les traitements relatifs à 130 patients de Terre-Neuve-et-Labrador et de 315 patients de l'Ontario atteints d'un cancer du côlon de stade I à III. Le paramètre principal était la fidélité aux lignes directrices pour le traitement adjuvant. Nous avons examiné les facteurs affectant l'utilisation de la chimiothérapie chez les patients atteints d'un cancer de stade II.

Résultats : Aucun patient n'a reçu de traitement adjuvant pour un cancer de stade I. Quarante-cinq patients sur 52 (87 %) de Terre-Neuve-et-Labrador et 108 patients sur 115 (94 %) de l'Ontario ont reçu une chimiothérapie adjuvante pour un cancer du côlon de stade III. Vingt patients sur 55 (36 %) de T-N-L et 44 patients sur 116 (38 %) de l'Ontario ont reçu un traitement adjuvant pour un cancer de stade II. Dix-huit patients sur 41 (44 %) de T-N-L et 30 patients sur 53 (57 %) de l'Ontario présentant des caractéristiques de risque élevé ont reçu un traitement adjuvant, soit un nombre significativement plus élevé que chez les patients ne présentant pas ces caractéristiques. On a noté une forte tendance à l'utilisation de la chimiothérapie chez les patients atteints d'un cancer de stade II âgés de 50 ans ou moins, indépendamment du degré de risque.

Conclusion : La fidélité aux lignes directrices en matière de chimiothérapie adjuvante dans le cancer du côlon de stade II n'a pas été jugée optimale. Ce phénomène pourrait résulter d'un biais de sélection de la part des chirurgiens référents, d'un manque de preuves de niveau 1 et de la perception que d'autres facteurs, comme l'âge, peuvent jouer un rôle dans le pronostic.

Colorectal cancer is the third most common cancer in Canada.¹ Although screening has been shown to improve survival,²⁻⁴ almost 50% of patients in North America present with either stage III or IV disease.⁵

Clinical practice guidelines (CPGs) are “systematically developed statements to assist both practitioner and patient decisions about appropriate health care for specific clinical circumstances.”⁶ When based on high-quality evidence, CPGs should assist in clinical decision-making, improve health care delivery and decrease ineffective costs.^{7,8} Although CPGs represent the best available evidence, concordance with guidelines is voluntary.

In 1991, the National Institutes of Health (NIH; National Cancer Institute, United States) published the first evidence-based guidelines for the use of adjuvant therapy in patients with colorectal cancer.⁹ The expert panel concluded that patients with stage III colon cancer benefit from adjuvant fluorouracil (5-FU)-based chemotherapy. No adjuvant therapy was recommended for patients with stage I or II colon cancer. Although systematic review does not support the routine use of adjuvant chemotherapy after curative resection in patients with stage II colon cancer,^{10,11} it should be considered in patients with poor prognostic factors.¹²⁻¹⁴ Such factors include malignant bowel obstruction, perforation at the tumour site, the presence of lymphatic and/or vascular invasion and tumour aneuploidy. Although molecular features such as tumour microsatellite instability status may be important, these have not been emphasized in currently accepted guidelines. Although the approach to the treatment of stage II colon cancer is evolving, adjuvant treatment is currently recommended for high-risk patients with stage II disease and all patients with stage III disease, as per the NIH, American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO) guidelines.^{9,13,14} Concordance with these guidelines has not been systematically evaluated in Canada. Factors that influence the decision to administer adjuvant chemotherapy in patients with stage II colon cancer after curative resection have not previously been addressed in the English literature.

The Colorectal Cancer Interdisciplinary Health Research Team was initiated in 2000 as a joint effort by a multidisciplinary team of investigators in Newfoundland and Labrador and Ontario to study incident cases of colorectal cancer in the 2 Canadian provinces. Newfoundland and Labrador has a population of about 505 000¹⁵ and 1 regional cancer centre. Peripheral clinics are staffed by oncologists from the regional centre. Conversely, Ontario

has a population of 12 160 000¹⁵ and 9 cancer centres that provide comprehensive cancer services. The purpose of our study was to evaluate concordance with NIH, ASCO and CCO guidelines for the administration of adjuvant chemotherapy in patients with stage I-III colon cancer and to explore whether differences exist between the 2 provinces.

METHODS

In Newfoundland and Labrador, we reviewed all incident cases of colon cancer diagnosed between Jan. 1, 1999, and Dec. 31, 2000 in patients aged 20-74 years. The Newfoundland and Labrador Familial Colorectal Cancer Registry (NFCCR) is a true population-based registry that collected information on patients aged 20-74 years who received diagnoses of colorectal cancer between 1999 and 2003. The Newfoundland Cancer Treatment and Research Centre (NCTRC) identified each patient with an International Classification of Diseases (ICD-10) code to indicate colon (153) or rectal (154) cancer. The team pathologist retrieved and reviewed pathology reports to ensure a diagnosis of adenocarcinoma, signet ring carcinoma or pseudomyxoma accompanied by adenocarcinoma. We forwarded a letter to the attending physicians of all patients with a diagnosis of colon cancer (153) describing the study and providing details on who the patients should contact if they were interested in participating. If a patient was deceased, we identified the next of kin by several methods, including through family physicians and nursing clinics. We then contacted the next of kin in the same manner as the patients, asking for consent to a review of the patients' medical records (proxy consent). Patients or the next of kin consented to the completion of a family history and dietary questionnaire and to the extraction of information pertaining to the diagnosis and treatment of their diseases from their medical records.

In Ontario, we asked patients enrolled in the Ontario Familial Colorectal Cancer Registry (OFCCR), a National Cancer Institute-funded consortium for the study of the genetic epidemiology of colorectal cancer, to participate in our study. The OFCCR is 1 of 6 international sites participating in the Cooperative Familial Registry for Colorectal Studies established by the NCI. We used the population-based Ontario Cancer Registry (OCR) to identify all cases of invasive colon cancer diagnosed between Jan. 1, 1999, and Jun. 30, 2000, among residents of Ontario aged 18-74 years. Patients were recruited into the OFCCR by mechanisms previously outlined in detail.¹⁶ Briefly, all

high- or intermediate-risk patients and a 25% random sample of low-risk patients were recruited into the OFCCR. Patients enrolled in our study consented to the completion of a family history and dietary questionnaire and to the extraction of information pertaining to the diagnosis and treatment of their diseases from their medical records. We did not seek proxy consent in Ontario.

After obtaining informed consent, trained health record technicians or research nurses retrospectively reviewed medical records and extracted the relevant data, including information on patient demographics, diagnosis (symptoms, location of diagnosis, site of cancer and date of diagnosis), surgical intervention (date, type of surgery, operative findings, hospital/surgeon), pathology (stage, number of lymph nodes, tumour differentiation/cell type, margins, perineural/lymphovascular invasion), adjuvant treatment (start date, type of chemotherapy), follow-up (metachronous primary, first documented locoregional and/or distant recurrence and treatment), time to last follow-up and/or death and cause of death.

To verify the accuracy of the data, 2 of us (D.W. and L.M.) randomly reviewed about one-half of the charts. We reviewed all records for participants with stage III disease who did not receive adjuvant chemotherapy ($n = 14$). We assessed the charts of patients with stage II disease to determine the presence or absence of high-risk features (i.e., clinical obstruction or tumour perforation at presentation, T4 lesion, poor differentiation, lymphatic invasion, perineural invasion, vascular invasion or mucin production) and whether these features were used to guide chemotherapy recommendations. We excluded patients with stage IV disease from this analysis. The local institutional review boards and the advisory committee of the NIH Cooperative Family Registries for Colorectal Cancer Studies approved all study procedures.

We used descriptive statistics where appropriate. We performed multivariate analysis to determine factors associated with the administration of chemotherapy in patients with stage II disease.

RESULTS

Study population

In Newfoundland and Labrador, there were 274 incident cases of colon cancer diagnosed between Jan. 1, 1999, and Dec. 31, 2000; 191 patients (70%) or their appropriate proxies consented to participate. Of these, we included 130 patients (68%) with stage I–III disease in our study.

There were 2464 patients with colon cancer diagnosed between Jan. 1, 1999, and Jun. 30, 2000, in the OCR. Of these, 1031 (42%) completed a family history questionnaire and were recruited into the OFCCR. We deemed all patients who reported a high-risk family history (28) or an intermediate-risk family history (331) to be eligible for

inclusion in our study. In addition, we also deemed a 25% random sample of patients who reported a low-risk family history (155/508) to be eligible for inclusion in this study (514/2464, 21%). In total, 364 of 514 patients (71%) consented to participate. Of these, we included 315 patients (87%) with stage I–III disease in our study.

Treatment at stage I

No adjuvant chemotherapy recommended in CPGs

Of the 21 patients in Newfoundland and Labrador with stage I disease and the 60 patients in Ontario with stage I disease, none received adjuvant chemotherapy (Table 1).

Treatment at stage II

Chemotherapy as a function of risk status, Newfoundland and Labrador

Of 55 patients with stage II colon cancer in Newfoundland and Labrador (Fig. 1A), 41 (75%) had at least 1 high-risk feature. Twenty-nine of the 41 patients (71%) considered to be high-risk were referred to medical oncology. Of these, 18 patients (62%) received adjuvant chemotherapy (44% of the high-risk cohort). Of the 11 high-risk patients who were referred to medical oncology but did not receive chemotherapy, 1 was felt to be medically unfit, 1 did not have the issue revisited after work-up for a benign liver lesion, 4 were noted to have high-risk features for which adjuvant chemotherapy showed no definitive benefit and 5 were felt to have no high-risk features, although at least 1 was noted in the standardized tumour pathology summary.

Fourteen of 55 patients (25%) in Newfoundland and Labrador with stage II disease were classified as low-risk. Of these, 11 (73%) were assessed by medical oncology. Three of 11 patients (27%) who were assessed received adjuvant therapy (21% of the low-risk cohort). This was based solely on the presence of tumour ulceration. We did not consider tumour ulceration to be a high-risk feature for the purposes of our study because it is not identified in the CCO and ASCO guidelines.

Chemotherapy as a function of risk status, Ontario

Adequate information was available for 116 of 132 patients (88%) with stage II disease in Ontario to classify these patients as either high- (53) or low-risk (63)

Table 1. Adjuvant chemotherapy by stage

Stage at diagnosis	Province; no. (%) of patients		
	Newfoundland and Labrador	Ontario	Total
Stage I	0/21	0/60	0/81
Stage II	20/55 (36)	44/116 (38)	64/171 (37)
Stage III	45/52 (87)	108/115 (94)	153/167 (92)

(Fig. 1B). The absence of standardized pathology reporting for the remaining 16 patients (12%) made this determination impossible.

Fifty-three of 116 patients (46%) were considered to be high-risk; of these, 36 (68%) were referred to medical oncology and 17 (32%) were not. Thirty of 36 patients (83%) referred received adjuvant chemotherapy. We were unable to determine from an assessment of the initial medical oncology consultations why the other 6 patients were not offered adjuvant chemotherapy.

Sixty-three of 116 patients (54%) in Ontario with stage II disease were classified as low-risk. Of these, 22 patients (35%) were assessed by medical oncology. Fourteen of the 22 patients (64%) who were assessed received adjuvant chemotherapy (22% of the low-risk cohort). The reasons for this were not stated. The receipt of adjuvant chemotherapy differed significantly as a function of risk status ($\chi^2_1 = 14.0, p < 0.001$).

As the proportion of low- and high-risk patients who received adjuvant chemotherapy (low-risk = 21% in Newfoundland and Labrador and 22% in Ontario; high-risk = 44% in Newfoundland and Labrador and 57% in Ontario) did not differ significantly as a function of province, we combined data from the 2 provinces for further analysis.

We performed multivariate logistic regression to identify independent predictors of those who received chemotherapy. Variables included in the model were high-risk status (odds ratio [OR] 3.82, 95% confidence interval [CI] 1.87–7.81), province (not significant) and age 50 years or less at diagnosis (OR 0.38, 95% CI 0.14–1.03). The proportion of those who received chemotherapy was 68% in those aged 50 years or less and 36% in those older than 50 years. There was a strong trend toward using chemotherapy in the younger group, independent of high-risk status.

Treatment at stage III

Adjuvant chemotherapy recommended by CPGs

Most patients with stage III colon cancer received adjuvant chemotherapy (Table 1). In Newfoundland and Labrador, 45 of 52 (87%) patients with stage III colon cancer received adjuvant chemotherapy. Of the 7 who did not, 3 patients died postoperatively, 1 had a delayed postoperative course following an anastomotic leak, 1 was treated for a synchronous retroperitoneal lymphoma and 3 were not referred (no reason given). In Ontario, 108 of 115 (94%) received adjuvant chemotherapy. There was no information available for 4 patients, 1 patient refused therapy, 1 had metastatic breast cancer and there was no reason given for 1 patient.

DISCUSSION

In 1991, the NIH published the first evidence-based guidelines for the use of adjuvant therapy in patients with colon cancer.⁹ Although systematic review does not support the routine use of adjuvant chemotherapy in patients with stage II disease, it should be considered in patients with high-risk features,^{12–14} including malignant bowel obstruction or perforation at the time of presentation, T4 disease, perineural/lymphovascular invasion or aneuploidy.

The results of our study show that patients with stage I and III colon cancer were managed according to current recommendations in both provinces. Clearly, guidelines supported by adequate level-I evidence have been acknowledged by the appropriate target audience, including surgeons and medical oncologists, resulting in successful implementation.

Although patients with high-risk stage II disease were

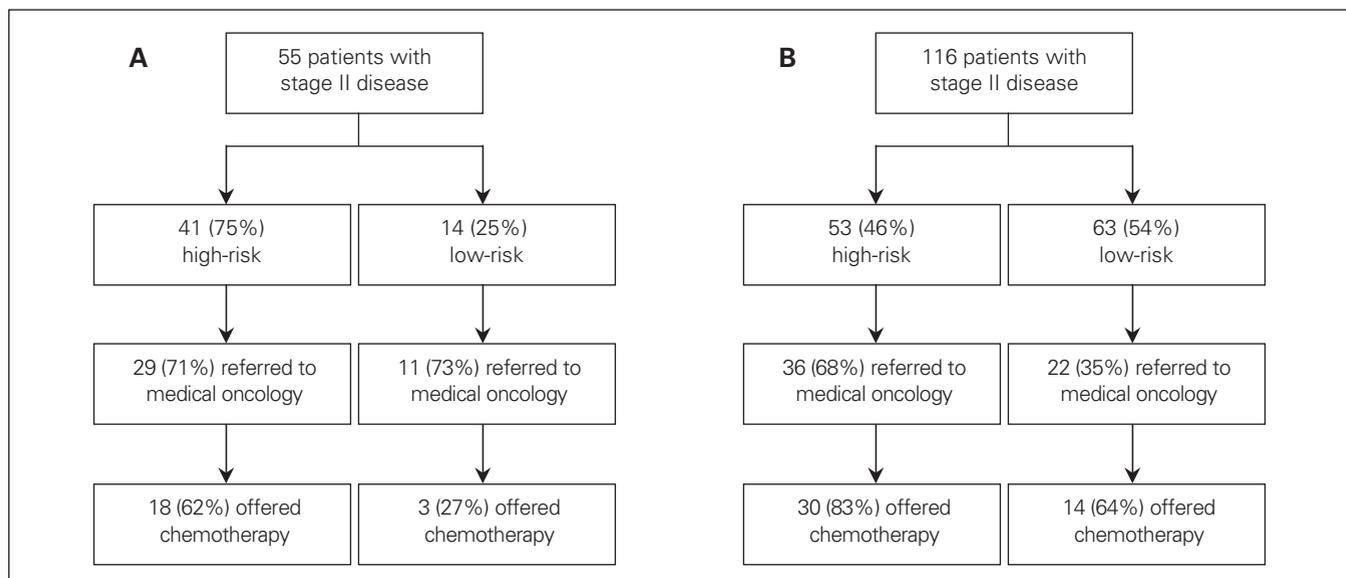


Fig. 1. Receipt of adjuvant chemotherapy (stage II) as a function of risk status in (A) Newfoundland and Labrador and (B) Ontario.

significantly more likely to receive chemotherapy than patients with low-risk stage II disease, our data suggest that other information was used in the decision to administer adjuvant chemotherapy in patients with stage II disease. This may reflect a paucity of level-I evidence. It appears that patient age influenced the decision to offer adjuvant chemotherapy in that there was a strong trend in favour of chemotherapy in patients aged 50 years or younger who had stage II disease, independent of high-risk status. This requires further study as younger age tends to be correlated with high-frequency microsatellite instability tumours.^{17,18} There is evidence that patients with this type of tumour may not derive the same benefit from 5-FU-based chemotherapy.¹⁹ Thus the use of age alone as an adverse prognostic factor in the decision to administer 5-FU-based adjuvant chemotherapy may not be sound.

Only 71% of patients with high-risk stage II disease in Newfoundland and Labrador and 68% of these patients in Ontario were referred to medical oncology. It has previously been shown that patients with stage II colon cancer were less likely to be referred for consideration of adjuvant chemotherapy (76% for stage II colon cancer, 92% for stage III colon cancer).²⁰ We cannot comment on whether this reflects a lack of knowledge on the part of surgeons as to the potential benefit for high-risk patients, whether surgeons do not feel that the evidence is strong enough to warrant referral for patients with stage II disease, or whether other factors such as resource allocation are at play. It has been shown that concordance with guidelines develops along a continuum from awareness to acceptance to ability to enforce to successful implementation.²¹⁻²³ The target audience may be unaware of the existence of the information. Surgeons may be aware of the original guideline that recommended no chemotherapy for patients with stage I and II colon cancer after curative resection. Further refinements, based on less compelling data, may not have been as widely disseminated. Furthermore, even once the recommendation is known, surgeons may not accept the validity of the guideline. Even if surgeons and medical oncologists support the guidelines, local factors such as resource allocation and access to treatment may influence the ability to enforce guidelines. Medical oncology resources may be such that treatment is only readily available where there is good level-I evidence.

This complex process of guideline implementation demands a multidisciplinary focus.²⁴ It has been shown that concordance with guidelines is enhanced when members of the target audience are actively recruited to participate in guideline development and dissemination.²¹⁻²⁴ To this end, it would be important to ensure that surgeons become involved in the creation of guidelines. This would apply not only to surgeons in academic centres, but also to community surgeons and other health care workers who are seen to be local opinion leaders.²⁴ These individuals could determine what guidelines are necessary, the best means to

make surgeons within their communities aware of and accepting of the guidelines and, most importantly, the resource limitations that might impede the implementation of important guidelines. It has been well documented that CPGs without coordinated dissemination strategies rarely result in consistent changes in physician performance and/or behaviour.²⁵⁻²⁷

It will become increasingly important to establish successful multifaceted approaches that provide sound rationale for the delivery of adjuvant therapy in the treatment of colorectal and other cancers as the use of molecular markers and microarray analyses²⁸ come to the forefront. The rise of increasingly expensive therapies such as cetuximab²⁹ and bevacizumab³⁰ in the adjuvant setting will require sophisticated targeting strategies to ensure their efficacious, efficient and cost-effective use.

In our study, selection bias may have been introduced as a result of the differing sampling techniques in the 2 provinces and the need to obtain consent. We used medical record audit, rather than patient recall or the use of administrative data, as an objective measure of compliance with CPGs. This method has been shown to result in higher levels of concordance in a recently reported study that evaluated the receipt of recommended adjuvant therapy among patients with stage II and III colon and rectal cancer in the Veterans Affairs setting; 87% of patients with stage II and 71% of patients with stage III colon cancer received the recommended therapy.²⁰ However, we have no reason to suspect that the main outcome measure (receipt of recommended adjuvant chemotherapy) was correlated with participation in the study. Owing to the retrospective nature of our study, we are unable to comment on whether the decision to refer patients to medical oncology or offer adjuvant chemotherapy was influenced by socioeconomic status or proximity to a treatment centre. High concordance with guidelines for stage III disease in both provinces would suggest that guidelines that are developed with strong input from the target audience and on the basis of good level-I evidence will lead to more equitable and standardized treatment protocols, at least in Canada.

In conclusion, it appears that among doctors treating colon cancer there is not universal agreement with and belief in an improved outcome following implementation of the ASCO and CCO recommendations for the adjuvant treatment of stage II colon cancer. Concordance could be improved by multi-faceted approaches that incorporate surgeons, who are members of the target audience and the first point of patient contact, in all aspects of the development and implementation of important CPGs.

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