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ORIGINAL ARTICLE

Factors associated with delayed time to adjuvant chemotherapy in stage III colon cancer

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ABSTRACT

Background

Adjuvant chemotherapy started more than 56 days after colon cancer resection has been associated with lesser overall survival among patients with stage III colon cancer. The objective of the present population-based study was to determine, in referred patients with resected stage III colon cancer, factors associated with delayed time to adjuvant chemotherapy (TTAC), defined as more than 56 days from the date of surgery.

Methods

Eligible patients had been diagnosed with stage III colon cancer and had received at least 1 cycle of adjuvant chemotherapy at one of the four regional cancer treatment sites during 2008–2009. Prognostic and treatment information was prospectively collected through the BC Cancer Agency's GI Cancers Outcomes Unit, and Charlson comorbidity score was retrospectively determined by chart review. Chi-square and Wilcoxon rank-sum tests were used to measure associations between the timing of adjuvant chemotherapy and select prognostic and treatment variables.

Results

Median TTAC from surgery for the 395 included patients was 58 days, with 54% of the patients receiving adjuvant chemotherapy beyond the recommended 56 days. On multivariate analysis, only treatment at the highest-volume site was independently associated with delayed TTAC. Comorbidity index, age, performance status, T stage, tumour location, and oral chemotherapy (compared with intravenous) were not independently associated with delayed TTAC. Delays were observed during each interval associated with the patient's transition from surgery to first cycle of adjuvant chemotherapy.

Conclusions

More than half the patients failed to receive adjuvant chemotherapy within the recommended TTAC of 56 days. Delayed TTAC was associated with process-related delays rather than with patient- or disease-related factors. Efforts to improve timely referral, triage of consultations, and chemotherapy wait lists are required.

KEY WORDS

Colon cancer, stage III, delay, adjuvant therapy

1. INTRODUCTION

Colon cancer is responsible for 8900 deaths annually in Canada and represents the 2nd most common cause of cancer-related morbidity and mortality[1]. The use of adjuvant chemotherapy for resected stage III colon cancer has been shown to significantly lower recurrence rates and to improve overall survival[2]. The current standard of treatment includes 5-fluorouracil (5FU)–based chemotherapy with any of 5FU–leucovorin[3,4], 5FU–oxaliplatin[5,6], and capecitabine[7].

In clinical trials, adjuvant chemotherapy is typically initiated within 6–8 weeks after surgery, but it has been shown that, outside of the clinical trial setting, up to 19% of patients do not receive adjuvant therapy within that period[8]. Several recent meta-analyses have confirmed that delayed administration of adjuvant chemotherapy after curative surgery is associated with significantly lesser overall survival[9,10].

In the present study, we used a contemporary population-based patient cohort in the province of British Columbia to ascertain the temporal factors and patient characteristics associated with delayed delivery of adjuvant chemotherapy in referred patients with resected stage III colon cancer.

2. METHODS

2.1 Data Source

Patients with resected stage III colon cancer who were referred to the BC Cancer Agency (BCCA) were identified in the GI Cancers Outcomes Unit database. The BCCA is a provincial cancer agency responsible for treatment policy and funding of all systemic therapy in a province of 4.4 million.

Of all patients with a diagnosis of colon cancer, 65% are referred to one of five treatment centres. Data relating to receipt of chemotherapy is captured in the provincial pharmacy database. For the purposes of the present analysis, two of the cancer centres were considered together ("centre C") because of low patient volumes at the most newly opened cancer centre.

Provincial treatment guidelines during the study period recommended that adjuvant chemotherapy be initiated within 8 weeks of definitive surgery. For eligible patients with stage III colon cancer, the recommended regimen is 6 months of modified FOLFOX6 (leucovorin, 5-fluorouracil, oxaliplatin); adjuvant capecitabine is recommended for patients deemed to be ineligible for FOLFOX6.

2.2 Patient Selection

Patients with resected stage III colon cancer referred to the BCCA between January 1, 2008, and December 31, 2009, and treated with at least 1 cycle of adjuvant chemotherapy were included. Patients were excluded if they had previously been diagnosed with a colon cancer, if any portion of their colon cancer treatment (including surgery or chemotherapy) was performed outside of British Columbia, or if the referral was for a second opinion. The study was approved by the University of British Columbia Research Ethics Board.

2.3 Data Collection

Patient data collected included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (as reported by the treating physician at consultation), type of chemotherapy, and regional treatment centre. Disease factor data—including tumour location, T stage, N stage, histology, and grade—were abstracted from the GI Cancers Outcomes Unit database. Comorbidities, scored using the Charlson comorbidity index, were determined from a retrospective chart review.

The time from curative surgery to initiation of adjuvant chemotherapy (TTAC) was recorded, as were the intervals between the times of surgery, hospital discharge, referral to BCCA, first medical oncology consultation, and first cycle of adjuvant chemotherapy. Delayed TTAC was defined as initiation of chemotherapy more than 56 days after surgery.

2.4 Statistical Analysis

Chi-square and Wilcoxon rank-sum tests were used to assess differences in characteristics and time intervals for patients who received delayed and timely adjuvant chemotherapy. Multivariate analysis with logistic regression was used to investigate independent patient and tumour characteristics predictive of delayed chemotherapy.

3. RESULTS

Of 395 referred patients with resected stage III colon cancer who met the inclusion criteria over the 2-year study period, 54% also met the definition for delayed TTAC. Median time from surgery to adjuvant chemotherapy was 58 days.

Table I presents the characteristics of the full cohort and of the timely and delayed therapy groups. Median age at diagnosis was 65 years, and 52% of patients were men. By entry criteria, all patients had node-positive disease (63%, N1 disease; the remainder, N2 disease). Most patients had T3 tumours located in the proximal colon. No significant differences in age or sex were observed between the timely and delayed chemotherapy groups. Also, no significant differences were observed in nodal status, tumour stage, or location of the primary tumour. Oral adjuvant capecitabine was given to 40% of the patients, but the proportion of patients receiving oral capecitabine compared with intravenous FOLFOX6 was not different between the delayed and timely groups. Most patients had a Charlson comorbidity index of 0–1 and an ECOG performance of 0–1.

On univariate analysis (Table I), an ECOG performance status of 2 or more was associated with a significant delay in adjuvant chemotherapy; a higher score on the Charlson comorbidity index was not. However, in multivariate analysis (Table II), performance status did not retain a significant association with delayed chemotherapy ($p = 0.079$).

Patients were well distributed across health regions, with the most urban centre (centre A) receiving the highest percentage of referrals overall. Compared with the other centres, centre A had a significantly higher proportion of patients who received delayed chemotherapy, and centre was the only factor to retain significance in the multivariate analysis ($p = 0.0004$).

The most common sequence of events was surgery, hospital discharge, referral to BCCA, medical oncology consultation, and initiation of adjuvant chemotherapy. That sequence occurred in 69% of cases. As seen in Table III, significant temporal differences between the timely and delayed chemotherapy groups were identified in all intervals. Overall, the average time from surgery to referral was 15 days; from referral to medical oncology consultation, 21 days; and from medical oncology consultation to initiation of chemotherapy, 20 days. All of those intervals were

TABLE I Patient and tumour characteristics by time to adjuvant chemotherapy

Variable	*Time to adjuvant chemotherapy*			p *Value*[a]
	Overall	*≤56 Days*	*>56 Days*	
Patients (*n*)	395	182	213	
Age at diagnosis (years)				
Median	65	66	65	0.8119
Interquartile range	57–72	57–72	58–72	
Sex [*n* (%)]				
Women	188 (48)	92 (50)	96 (45)	0.2771
Men	207 (52)	90 (50)	117 (55)	
N Stage [*n* (%)]				
N1	249 (63)	119 (65)	130 (61)	0.3718
N2	146 (37)	63 (35)	83 (39)	
Pathologic T stage [*n* (%)]				
T1/2	49 (12)	24 (13)	25 (12)	0.2370
T3	276 (70)	132 (73)	144 (68)	
T4	68 (17)	25 (14)	43 (20)	
TX	2 (1)	1 (1)	1 (1)	
Tumour location [*n* (%)]				
Proximal	226 (57)	103 (57)	123 (58)	0.7755
Distal	168 (43)	79 (43)	89 (42)	
Colon NOS	1 (0)	0 (0)	1 (1)	
CCI score [*n* (%)]				
0	287 (73)	128 (70)	159 (75)	0.5802
1	72 (18)	35 (19)	37 (17)	
2	29 (7)	16 (9)	13 (6)	
3	5 (1)	2 (1)	3 (1)	
4	2 (1)	1 (1)	1 (1)	
Unknown	0 (0)	0 (0)	0 (0)	
ECOG PS [*n* (%)]				
0	101 (26)	44 (24)	57 (27)	0.0257
1	93 (24)	49 (27)	44 (21)	
2	22 (6)	5 (3)	17 (8)	
3	1 (0)	0 (0)	1 (1)	
Unknown	178 (45)	84 (46)	94 (44)	
Centre [*n* (%)]				
A	124 (31)	42 (23)	82 (39)	0.0002
B	79 (20)	31 (17)	48 (23)	
C	110 (28)	58 (32)	52 (24)	
D	82 (21)	51 (28)	31 (15)	
Chemotherapy type [*n* (%)]				
Intravenous 5FU ± oxaliplatin	235 (60)	104 (57)	131 (62)	0.3790
Oral capecitabine monotherapy	160 (40)	78 (43)	82 (39)	

[a] Unknown, TX, and colon NOS were removed before statistical testing was performed. Scores of 2 or 3 on the ECOG PS and scores 2, 3, or 4 on the CCI were pooled for statistical testing.

NOS = not otherwise specified; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; 5FU = 5-fluorouracil.

TABLE II Multivariate model for predictors of delayed adjuvant chemotherapy

Variable	*Type III* p *value*[a]	*Comparison*	*OR*	*95% CL*	p *Value*[a]
Age at diagnosis	0.7320	Per year	1	0.97, 1.02	0.7320
Sex	0.2664	Men vs. women	1.27	0.83, 1.95	0.2664
N Stage	0.5219	N2 vs. N1	1.16	0.74, 1.82	0.5219
Pathologic T stage	0.1888	T3 vs. T1/T2	1.04	0.54, 2.02	0.9006
		T4 vs. T1/T2	1.76	0.79, 3.93	0.1690
Tumour location	0.6174	Distal vs. proximal	0.9	0.58, 1.38	0.6174
CCI score	0.8270	1 vs. 0	0.9	0.52, 1.57	0.7107
		2+ vs. 0	0.81	0.39, 1.71	0.5850
ECOG PS	0.0789	1 vs. 0	0.8	0.44, 1.46	0.4632
		2 and 3 vs. 0	3.47	1.14, 10.51	0.0279
		Unknown vs. 0	1.04	0.6, 1.8	0.8990
Centre	0.0004	B vs. A	0.68	0.36, 1.28	0.2269
		C vs. A	0.42	0.24, 0.74	0.0027
		D vs. A	0.28	0.15, 0.54	0.0001
Chemotherapy type	0.7238	Capecitabine vs. FOLFOX	1.1	0.65, 1.85	0.7238

[a] The type III *p* value column represents the variable's overall contribution to the model; the *p* value column represents the specific comparison ("Comparison" column) involving the variable.

OR = odds ratio; CL = confidence limits; CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFOX = leucovorin–5-fluorouracil–oxaliplatin.

TABLE III Differences in process time intervals between timely and delayed adjuvant chemotherapy

Variable	*Time to adjuvant chemotherapy*			p *Value*
	Overall	*≤56 Days*	*>56 Days*	
Surgery to referral (days)	(*n*=370)	(*n*=164)	(*n*=206)	
Median	15	12	18	<0.0001
Interquartile range	10–22	9–17	12–27	
Range	1–106	2–41	1–106	
Referral to medical oncology consultation (days)	(*n*=349)	(*n*=156)	(*n*=193)	
Median	21	17	23	<0.0001
Interquartile range	14–27	12–22	17–31	
Range	0–55	0–40	0–55	
Medical oncology consultation to chemotherapy (days)	(*n*=395)	(*n*=182)	(*n*=213)	
Median	20	14	26	<0.0001
Interquartile range	12–28	7–21	15–36	
Range	0–121	0–48	0–121	

significantly increased in the delayed TTAC cohort. On average, the delayed cohort commenced adjuvant chemotherapy 67 days after surgery; the timely cohort started adjuvant chemotherapy an average of 43 days after surgery.

4. DISCUSSION

In this population-based analysis examining the factors associated with TTAC, more than half the patients referred with resected stage III colon cancer (54%) received delayed adjuvant chemotherapy. This real-world pattern has previously been reported in the published literature; however, the rates in British Columbia are higher than those reported in other provinces in Canada[8,9]. Comparing retrospective studies is difficult, but the proportion of patients with delayed chemotherapy ranges from 26% in Alberta[11] to 32% in Winnipeg[12] and 35% in Saskatchewan[13]. Although the definition of delayed chemotherapy varies, most studies have accepted fewer than 56 days as the standard against which to judge delay.

In univariate analysis in the present study, poor ECOG performance status and treatment at the most

urban cancer centre in the province were the only characteristics significantly associated with delayed chemotherapy. It is not surprising that ECOG status might result in delayed initiation of chemotherapy: it represents a functional status that might change, especially in the postoperative period. In contrast to previously published meta-analyses, in which the effect of timing was based on clinical trials, our study had a referred population with relatively poorer ECOG scores, highlighting some of the phenotypic differences between trial-eligible and real-world patients. However, a higher score on the Charlson comorbidity index was not associated with delayed treatment. That finding might be explained by the strict criteria defining comorbidities in the Charlson index, which might not significantly change in the perioperative period.

On multivariate analysis, treatment at the most urban health centre remained the only significant independent factor associated with delayed chemotherapy. It might be postulated that the difference is a function of centre-specific referral and triage processes, workload and patient volumes, and chemotherapy administration resources. Interestingly, oral compared with intravenous chemotherapy was not associated with timeliness of adjuvant therapy. The reasons for that lack of an association are unclear, but might be related to a confounding effect of patient selection. For example, patients selected to receive capecitabine monotherapy as adjuvant chemotherapy for stage III disease might have had factors related to patient preference, personal supports, or frailty that were associated with delayed initiation of chemotherapy and yet were not captured in our retrospective analysis.

Ultimately, delayed TTAC appears to be more process-related than patient-related, with all intervals (surgery to referral, referral to medical oncology consultation, and medical oncology consultation to chemotherapy) being significantly prolonged.

Given that logistics factors rather than intrinsic patient factors are driving the delay in chemotherapy, we are encouraged that those factors can be remedied. Our findings highlight the need to address process-related delays at each step, including timely referral, medical oncology consultation triage, and management of chemotherapy wait lists. The referring community has to be educated about the importance of timely referral for adjuvant chemotherapy, which typically can be initiated in the immediate postoperative period. Attempts to reduce chemotherapy wait times also need to be considered, including prioritization for patients requiring curative-intent adjuvant chemotherapy and greater utilization of oral fluoropyrimidine–oxaliplatin combinations (XELOX, CAPOX), which might mitigate delays related to infusional 5FU therapy and implantation of vascular access devices[14].

We acknowledge the limitations associated with the retrospective nature of our study. First, although most patient demographics were prospectively recorded, comorbidities and ECOG performance status were retrospectively abstracted in a chart review. We were therefore unable to confirm the ECOG performance status in 45% of cases. Whether the presence of those performance status data would have remained a significant patient factor between the timely and delayed chemotherapy groups is unclear. Second, specific dates were not available to calculate time from surgery to medical oncology referral for 20 patients or time from BCCA referral to medical oncology consultation appointment for 46 patients. However, those patients represent a very small proportion of the 395 in the cohort, and their missing data are unlikely to have significantly altered the results.

5. SUMMARY

More than half the referred patients with stage III colon cancer attending four B.C. cancer centres experienced delayed initiation of adjuvant chemotherapy after surgical resection. Factors associated with delayed chemotherapy included being treated at the most urban provincial centre. Temporal delays occurred in all intervals (surgery to time of medical oncology consultation to time of chemotherapy initiation). Recognizing that delayed TTAC is associated with a detrimental effect on survival, efforts must be made to address the delays, potentially including improved education, referral and triage guidelines, and expanded resources.

6. CONFLICT OF INTEREST DISCLOSURES

The authors report that there are no financial conflicts related to this paper.

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