Use and Effectiveness of Adjuvant Chemotherapy for Stage III Colon Cancer: A Population-Based Study

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Abstract

Background: International guidelines recommend adjuvant chemotherapy (ACT) for patients with stage III colon cancer. Whether efficacy observed in clinical trials translates to effectiveness in routine practice is less well understood. Here we describe use and outcomes of ACT in routine practice. **Methods:** All cases of colon cancer treated with surgery in Ontario 2002–2008 were identified using the population-based Ontario Cancer Registry. Linked electronic records of treatment identified surgery and ACT use. Pathology reports were obtained for a random 25% sample of all cases; patients with stage III disease were included in the study population. Modified Poisson regression was used to evaluate factors associated with ACT. Cox proportional hazards model and propensity score analysis were used to explore the association between ACT and cancer-specific survival (CSS) and overall survival (OS). **Results:** The study population included 2,801 patients with stage III colon cancer; 66% (n=1,861) received ACT. ACT use rates varied substantially across age groups; 90% among patients aged 20 to 49 years versus 68% among those aged 70 to 79 years (*P*<.001). ACT use was inversely associated with comorbidity (*P*<.001) and socioeconomic status (*P*=.049). In adjusted analyses advanced age is associated with inferior CSS and OS. Use of ACT was associated with decreased risk of death from cancer (hazard ratio [HR], 0.63; 95% CI, 0.54–0.73) and decreased risk of death from any cause (HR, 0.63; 95% CI, 0.55–0.71). This result was consistent in the propensity score analysis. **Conclusions:** One-third of patients with stage III colon cancer in the general population do not receive ACT. Use of ACT in routine practice is associated with a substantial improvement in CSS and OS.
J Natl Comp Canc Netw 2016;14(1):47–56

Background

International treatment guidelines have recommended 5-fluorouracil (FU)–based adjuvant chemotherapy (ACT) for patients with stage III colon cancer since the 1990s.[1] This is based on a series of randomized controlled trials (RCTs) showing a 30% reduction in death with a course of 5-FU, translating into an absolute improvement in 5-year overall survival (OS) of approximately 15%.[2] In 2004, a pivotal RCT demonstrated a further 4% improvement in 5 year OS with the addition of oxaliplatin to 5-FU (FOLFOX).[3] Another landmark RCT in 2005 showed that oral capecitabine chemotherapy could be substituted for 5-FU.[4] Accordingly, standard of care for patients with stage III colon cancer includes ACT with 5-FU/capecitabine with or without oxaliplatin.[5–7]

It is well-known that results reported from clinical trials may not be realized in the general population.[8–10]

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Submitted September 15, 2015; accepted for publication November 30, 2015.

The authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors. Dr. Booth is supported as a Canada Research Chair in Population Cancer Care. This work was also supported by the Canada Foundation for Innovation and the Canadian Institutes of Health Research.

Parts of this material are based on data and information provided by Cancer Care Ontario. However, the analysis, conclusions, opinions and statements expressed herein are those of the authors and not necessarily those of Cancer Care Ontario.

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

Dr. Booth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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This may relate to suboptimal adoption of new therapies in clinical practice. It may also relate to the fact that patients, providers, and health systems differ considerably between high-volume specialized centers and routine practice.[11] Accordingly, it may be misleading to assume that outcomes achieved in routine practice are comparable to those reported in the published literature. Population-based outcome studies are useful to describe practices and outcomes achieved in routine practice.[12,13] Although a number of studies have previously reported rates of use of ACT for stage III colon cancer in routine clinical practice,[14–21] limited literature has evaluated whether the efficacy of ACT observed in RCTs translates into effectiveness in the general population. To our knowledge, only 5 population-based reports have evaluated the effectiveness of ACT in stage III colon cancer. All of these reports are from the United States, 4 studies are restricted to elderly patients (>65 years of age), and 4 reports describe outcomes achieved in the 1990s.[14–16,19,22] We undertook a population-based study with the following objectives: to describe the use of ACT for stage III colon cancer in routine practice and to evaluate the effectiveness of ACT in the general population.

Methods

Study Design and Population

This is a population-based, retrospective cohort study to describe management and outcome of resected stage III colon cancer in the Canadian province of Ontario. Ontario has a population of approximately 13.5 million people and a single-payer universal health insurance program. The study population included patients who underwent resection of stage III colon cancer in Ontario between 2002 and 2008. To identify the study cohort, we used the Ontario Cancer Registry (OCR) to identify all incident cases of colorectal cancer in Ontario diagnosed during 2000–2008. The OCR does not capture stage of disease for all patients; therefore, we obtained surgical pathology reports for a random sample of 25% of cases. Reports were not available for patients with surgery in 2005; therefore, the study cohort is restricted to patients who had surgery in 2002–2004 and 2006–2008. The study was approved by the Research Ethics Board of Queen's University.

Data Sources and Linkage

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario.[23] The OCR also provides information about vital status and cause of death. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical procedures; these records are known to have a very high level of completeness for colorectal cancer surgery.[24] Provincial physician billing records from the Ontario Health Insurance Plan, treatment records from regional cancer centers, and provincial records of chemotherapy delivery were used to identify chemotherapy use. A team of trained data abstractors reviewed the pathology reports and entered information about disease extent into an electronic database.

Measures and Outcomes

Indicators of the socioeconomic status (SES) of the community in which patients resided at diagnosis were linked as described previously.[25] Quintiles (Q) of the median household income were based on the household income distribution for the full province of Ontario. Q1 represents the communities where the poorest 20% of the Ontario population resided. Geographic regions reflect the catchment areas for Ontario's regional cancer centers.[25] Comorbidity was classified using the Charlson Comorbidity Index modified for administrative data based on all noncancer diagnoses recorded during any hospital admission within 5 years before surgery.[26] A surgical hospital was identified for each case included in the study population. Each case was assigned a hospital volume index based on the total number of colon cancer resections performed (ie, all colon cancer resections identified and not just those eligible cases with stage III disease) in the 12 months before the surgical date. The hospitals were divided into quartiles of annual hospital volume. We used the same approach to derive a surgeon volume index for each patient.

ACT was defined as chemotherapy initiated within 16 weeks after surgery; neoadjuvant chemotherapy was defined as treatment given within 16 weeks before surgery.

OS and cancer-specific survival (CSS) were determined from date of primary tumour resection. To account for possible cause of death miscoding, CSS included death from any cancer. Complete informa-

tion about vital status in the OCR was available up to December 31, 2012; cause of death was available up to December 31, 2010. The primary outcome end point was CSS. CSS was prioritized over OS because it was believed likely to be less vulnerable to bias from unmeasured prognostic factors. Because the survival measure began before the chemotherapy exposure window ended (ie, at 16 weeks), our results were vulnerable to immortal person-time bias, whereby patients dying during the exposure window have a lower chance of receiving treatment; this would artificially worsen survival of the no-ACT group.[19] Accordingly, we excluded patients dying within 16 weeks of surgery from all survival analyses.

Statistical Analysis

Comparisons of proportions between study groups were made using the chi square test. Survival was determined from date of surgery using the Kaplan-Meier technique, and comparisons between groups were made using the log-rank test. Factors associated with treatment practices were evaluated by modified Poisson regression. The association between patient-, disease-, and treatment-related factors with OS/CSS was evaluated using the Cox proportional hazards regression model. To control for confounding variables when exploring the association between ACT and survival, we also used the propensity score technique in the Cox proportional hazards model. The propensity scores allowed us to create 5 propensity strata with balanced confounding variables between patients who did and did not receive ACT. Survival of patients treated with ACT was compared with those without ACT within each stratum using a Cox proportional hazards model; a summary hazard ratio (HR) combining the results across quintiles was calculated.[27] Results were considered statistically significant at a *P* value of less than .05. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Study Population

Linked administrative data sets identified 25,613 potentially eligible patients who underwent resection of primary colon cancer in 2002–2008 (Figure 1). Surgical pathology reports were reviewed for 7,519 randomly selected cases. The age, sex, comorbidity, and survival of these randomly selected cases

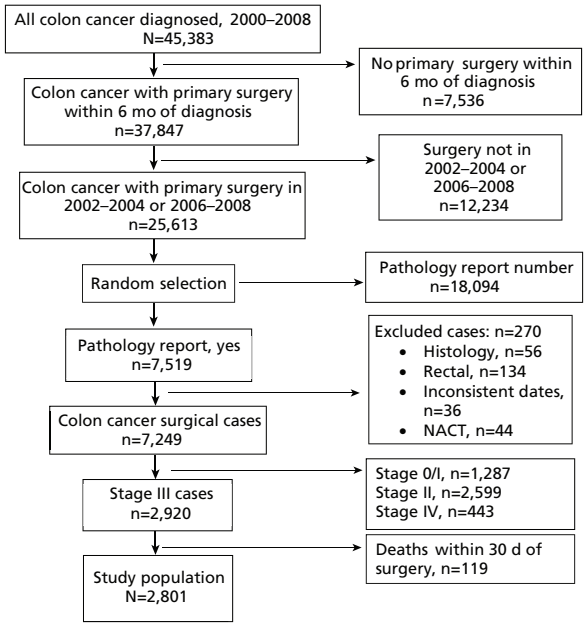

Figure 1. Identification of study population.
Abbreviation: NACT, neoadjuvant chemotherapy.

did not differ substantially from those of the 18,094 unselected cases (see supplemental eTable 1 and eFigure 1, available with this article at JNCCN.org). Among the 7,519 randomly selected cases, 270 (4%) were excluded (Figure 1). Among 2,920 patients with stage III disease, 119 (4%) died within 30 days. Accordingly, the study population included 2,801 patients; survival analyses are restricted to the 2,650 patients alive 16 weeks after surgery. Characteristics of the study population are shown in Table 1. The median age was 70 years and 52% were male.

Use of ACT

ACT was delivered to 66% (1,861/2,801) of the study population. Use rates remained stable throughout the study period (range, 64%–70%; *P*=.421). Specific regimens were identified for 69% (1,282/1,861) of ACT cases. Among these cases, 27% (343/1,282) received 5-FU alone, 19% (243/1,282) received capecitabine, 38% (487/1,282) received FOLFOX, and 16% (209/1,282) received FOLFIRI. Patients with advanced age, greater comorbidity, and/or lower SES were substantially less likely to receive ACT (Table 2). Increased postoperative length of stay was associated with lower use of ACT. There was no significant variation in use of ACT by geographic region, hospital volume, or surgeon volume.

Table 1. Characteristics of Patients With Stage III Colon Cancer Treated With Surgical Resection in Ontario 2002–2008 (n=2,801)

Characteristic		n (%)
Patient-related		
Age, y		
	20–49	207 (7%)
	50–59	437 (16%)
	60–69	727 (26%)
	70–79	872 (31%)
	>80	558 (20%)
Sex		
	Male	1,462 (52%)
	Female	1,339 (48%)
SES by quintile[a]		
	1	595 (21%)
	2	648 (23%)
	3	590 (21%)
	4	509 (18%)
	5	453 (16%)
Charlson comorbidity score		
	0	2,267 (81%)
	1	313 (11%)
	≥2	221 (8%)
Disease-related		
Grade		
	Well–moderately differentiated	2,141 (76%)
	Poorly differentiated	610 (22%)
	Unstated	50 (2%)
Lymphovascular invasion		
	Yes	1,378 (49%)
	No	1,209 (43%)
	NA	214 (8%)
T stage		
	≤T1	43 (2%)
	T2	180 (6%)
	T3	1,854 (66%)
	T4	724 (26%)
N stage		
	N1	1,663 (59%)
	N2	1,138 (41%)
Lymph nodes harvest[b]		
	Mean	16.9
	Median	15
	≥12	2,051 (73%)
	<12	745 (27%)

Abbreviations: NA, not applicable; SES, socioeconomic status.
[a]Quintile 1 represents the communities where the poorest 20% of the Ontario population resided. SES data were not available for 6 patients.
[b]Node count data were not available for <6 patients.

Effectiveness of ACT

Five-year CSS and OS rates for all patients were 56% (95% CI, 54%–59%) and 51% (95% CI, 49%–53%), respectively. Among ACT-treated cases, unadjusted CSS and OS rates at 5 years were 62% (95% CI, 59%–64%) and 59% (95% CI, 56%–61%), respectively. In adjusted analyses, greater age is associated with inferior CSS and OS (Table 3). Comorbidity is associated with OS but not CSS. Disease-related characteristics (T stage, N stage, lymphovascular invasion, and grade) are all associated with CSS and OS. After controlling for relevant patient-, disease-, and system-related characteristics, use of ACT was associated with a decreased risk of death from cancer (HR, 0.63; 95% CI, 0.54–0.73) and decreased risk of death from any cause (HR, 0.62; 95% CI, 0.55–0.71) (Figure 2). This result was consistent in the propensity score analysis (HR for CSS, 0.63; 95% CI, 0.54–0.73; HR for OS, 0.63; 95% CI, 0.55–0.71) (supplemental eTable 2).

Discussion

This report describes the use and effectiveness of ACT for stage III colon cancer in the general population. Several important findings have emerged. First, one-third of patients with stage III colon cancer were not treated with ACT. Second, the most significant predictor of ACT use was patient age; treatment rates decreased markedly with advanced age. Third, long-term survival after ACT in the general population is substantially lower than outcomes reported in the relevant clinical trials. Finally, use of ACT in routine practice is associated with a substantial reduction in the risk of death.

It is useful to consider our study results in light of the existing literature. Although a number of studies have described use rates of ACT for stage III colon cancer in routine practice, many of them are restricted to patients older than 65 years of age treated in the United States; ACT use rates in these US studies range from 42% through 75%.[14,15,19,28,29] In a recent study of patients aged 20 years or older randomly selected from the SEER database, Murphy et al[21] found that ACT treatment rates for stage III colon cancer peaked at 72% in 2005 and declined slightly to 66% in 2010. They found that advanced age and greater comorbidity was associated with lower rates of ACT. Two studies using the US National Cancer Data Base (NCDB)[16,17] during 1998–2007 reported ACT rates of 71% to 74%. Lindskog et al[20] used the Swedish Colorectal Cancer Registry to identify 3,485 patients with stage III colon cancer treated in 2002–2005; ACT was delivered to 84% of patients. In the largest Canadian study of ACT

Table 2. Factors Associated With Use of Adjuvant Chemotherapy Among Patients With Stage III Colon Cancer in Ontario 2002–2008 (n=2,801)

Characteristic	Proportion Receiving Adjuvant Chemotherapy	Multivariate Analysis RR (95% CI)[a]	*P* Value
Patient-related			
Age, y			<.001
20–49	90%	Ref	
50–59	83%	0.92 (0.86–0.98)	
60–69	81%	0.92 (0.87–0.98)	
70–79	68%	0.82 (0.77–0.88)	
≥80	24%	0.30 (0.26–0.35)	
Sex			.919
Male	63%	Ref	
Female	69%	1.00 (0.96–1.05)	
Socioeconomic status, quintile[b]			.049
1	60%	0.92 (0.85–1.00)	
2	63%	0.93 (0.87–1.01)	
3	67%	0.98 (0.91–1.06)	
4	72%	1.02 (0.95–1.09)	
5	74%	Ref	
Charlson comorbidity score			<.001
0	71%	Ref	
1	57%	0.93 (0.85–1.02)	
2	38%	0.67 (0.58–0.78)	
Length of hospital stay, d			<.001
<7	79%	Ref	
7–10	73%	0.97 (0.93–1.02)	
>10	50%	0.74 (0.69–0.79)	
Disease-related			
T stage			.806
<T3	70%	Ref	
T3	67%	0.98 (0.91–1.06)	
T4	65%	0.97 (0.89–1.06)	
N stage			.424
N1	65%	Ref	
N2	69%	1.02 (0.97–1.07)	
Lymphovascular invasion			.381
No	66%	Ref	
Yes	67%	1.00 (0.95–1.05)	
NA	65%	0.94 (0.85–1.03)	
Grade			.973
Well–moderately differentiated	67%	Ref	
Poorly differentiated	65%	0.99 (0.94–1.05)	
Unstated	70%	1.01 (0.86–1.18)	
System-related			
Region			.103
A	67%	Ref	
B	67%	1.04 (0.96–1.11)	
C	64%	0.99 (0.90–1.08)	
D	67%	1.08 (0.98–1.19)	
E	78%	1.26 (1.10–1.45)	
F	62%	1.00 (0.87–1.15)	
G	63%	0.99 (0.89–1.10)	
H	66%	1.05 (0.97–1.13)	
Surgeon volume			.695
Q1 (low volume)	63%	0.97 (0.91–1.04)	
Q2	66%	0.99 (0.93–1.06)	
Q3	68%	1.01 (0.95–1.08)	
Q4 (high volume)	68%	Ref	
Hospital volume			.729
Q1 (low volume)	67%	1.00 (0.93–1.08)	
Q2	67%	0.97 (0.91–1.04)	
Q3	66%	0.97 (0.91–1.04)	
Q4 (high volume)	66%	Ref	

A total of 55 cases were excluded from analysis because of unavailable data (socioeconomic status, region, surgeon volume).
Abbreviations: NA, not applicable; Ref, referent; RR, relative risk.
[a]Modified Poisson regression was used to estimate the relative risks.
[b]Quintile 1 represents the communities where the poorest 20% of the Ontario population.

Table 3. Factors Associated With Cancer-Specific and Overall Survival Among Patients With Stage III Colon Cancer in Ontario 2002–2008 (n=2,650)

		Cancer-Specific Survival[a]			Overall Survival[a]		
			Multivariate Analysis			Multivariate Analysis	
Characteristic		5-Year CSS	HR (95% CI)	*P* Value	5-Year OS	HR (95% CI)	*P* Value
Patient-related							
Age, y				.008			<.001
	20–49	66%	Ref		64%	Ref	
	50–59	63%	1.28 (0.95–1.72)		61%	1.33 (1.01–1.74)	
	60–69	59%	1.34 (1.01–1.77)		57%	1.41 (1.09–1.81)	
	70–79	52%	1.58 (1.20–2.08)		48%	1.65 (1.28–2.11)	
	≥80	49%	1.55 (1.15–2.09)		35%	2.07 (1.59–2.70)	
Sex				.053			.002
	Male	55%	Ref		51%	Ref	
	Female	58%	0.88 (0.78–1.00)		52%	0.84 (0.76–0.94)	
Socioeconomic status, quintile[b]				.308			.389
	1	56%	1.06 (0.85–1.32)		56%	1.02 (0.84–1.22)	
	2	52%	1.20 (0.97–1.48)		52%	1.15 (0.96–1.37)	
	3	58%	1.03 (0.83–1.28)		58%	1.01 (0.84–1.21)	
	4	57%	1.15 (0.92–1.43)		57%	1.08 (0.90–1.30)	
	5	60%	Ref		60%	Ref	
Charlson comorbidity score				.375			<.001
	0	58%	Ref		54%	Ref	
	1	48%	1.13 (0.94–1.37)		41%	1.27 (1.09–1.49)	
	2	49%	1.09 (0.86–1.37)		33%	1.47 (1.23–1.75)	
Length of hospital stay, d				<.001			<.001
	<7	63%	Ref		63%	Ref	
	7–10	55%	1.17 (0.99–1.38)		55%	1.16 (1.00–1.34)	
	>10	37%	1.56 (1.32–1.85)		37%	1.60 (1.39–1.85)	
Disease-related							
T stage				<.001			<.001
	<T3	84%	Ref		77%	Ref	
	T3	59%	2.19 (1.55–3.08)		54%	1.57 (1.23–1.99)	
	T4	38%	3.65 (2.57–5.19)		35%	2.33 (1.81–3.01)	
N status				<.001			<.001
	N1	65%	Ref		59%	Ref	
	N2	43%	2.03 (1.79–2.31)		40%	1.73 (1.55–1.93)	
Lymphovascular invasion				<.001			<.001
	No	66%	Ref		59%	Ref	
	Yes	49%	1.30 (1.14–1.50)		44%	1.28 (1.14–1.44)	
	NA	54%	1.43 (1.13–1.81)		50%	1.30 (1.06–1.59)	

(continued)

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; NA, not applicable; OS, overall survival; Ref, referent.
[a]51 cases were excluded from analysis because of unavailable data (socioeconomic status, region, surgeon volume).
[b]Quintile 1 represents the communities where the poorest 20% of the Ontario population resided.

Table 3. Factors Associated With Cancer-Specific and Overall Survival Among Patients With Stage III Colon Cancer in Ontario 2002–2008 (n=2,650) (cont.)

		Cancer-Specific Survival[a]			Overall Survival[a]		
			Multivariate Analysis			Multivariate Analysis	
Characteristic		5-Year CSS	HR (95% CI)	*P* Value	5-Year OS	HR (95% CI)	*P* Value
Disease-related (cont.)							
Grade				.001			.034
	Well–moderately differentiated	59%	Ref		53%	Ref	
	Poorly differentiated	46%	1.29 (1.12–1.49)		43%	1.18 (1.04–1.34)	
	Unstated	67%	0.80 (0.48–1.35)		57%	0.98 (0.66–1.45)	
System-related							
Region				.031			.034
	A	59%	Ref		55%	Ref	
	B	52%	1.25 (1.03–1.51)		48%	1.19 (1.01–1.41)	
	C	54%	1.28 (1.01–1.61)		49%	1.14 (0.93–1.41)	
	D	51%	1.29 (1.00–1.68)		44%	1.35 (1.08–1.69)	
	E	62%	0.92 (0.55–1.55)		51%	1.11 (0.74–1.66)	
	F	55%	1.01 (0.71–1.43)		44%	1.09 (0.82–1.45)	
	G	50%	1.25 (0.97–1.63)		45%	1.29 (1.04–1.61)	
	H	58%	0.93 (0.76–1.13)		52%	0.98 (0.83–1.15)	
Surgeon volume				.613			.535
	Q1 (low volume)	54%	1.11 (0.93–1.33)		48%	1.12 (0.96–1.31)	
	Q2	59%	1.06 (0.88–1.28)		53%	1.07 (0.92–1.26)	
	Q3	53%	1.11 (0.93–1.33)		49%	1.08 (0.93–1.26)	
	Q4 (high volume)	58%	Ref		55%	Ref	
Hospital volume				.069			.039
	Q1 (low volume)	57%	0.98 (0.81–1.19)		50%	1.07 (0.90–1.26)	
	Q2	52%	1.20 (1.00–1.43)		48%	1.23 (1.06–1.43)	
	Q3	57%	1.01 (0.84–1.21)		52%	1.06 (0.90–1.24)	
	Q4 (high volume)	59%	Ref		56%	Ref	
Adjuvant chemotherapy				<.001			<.001
	Yes	62%	0.63 (0.54–0.73)		59%	0.63 (0.55–0.71)	
	No	44%	Ref		35%	Ref	

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; NA, not applicable; OS, overall survival; Ref, referent.
[a]51 cases were excluded from analysis because of unavailable data (socioeconomic status, region, surgeon volume).
[b]Quintile 1 represents the communities where the poorest 20% of the Ontario population resided.

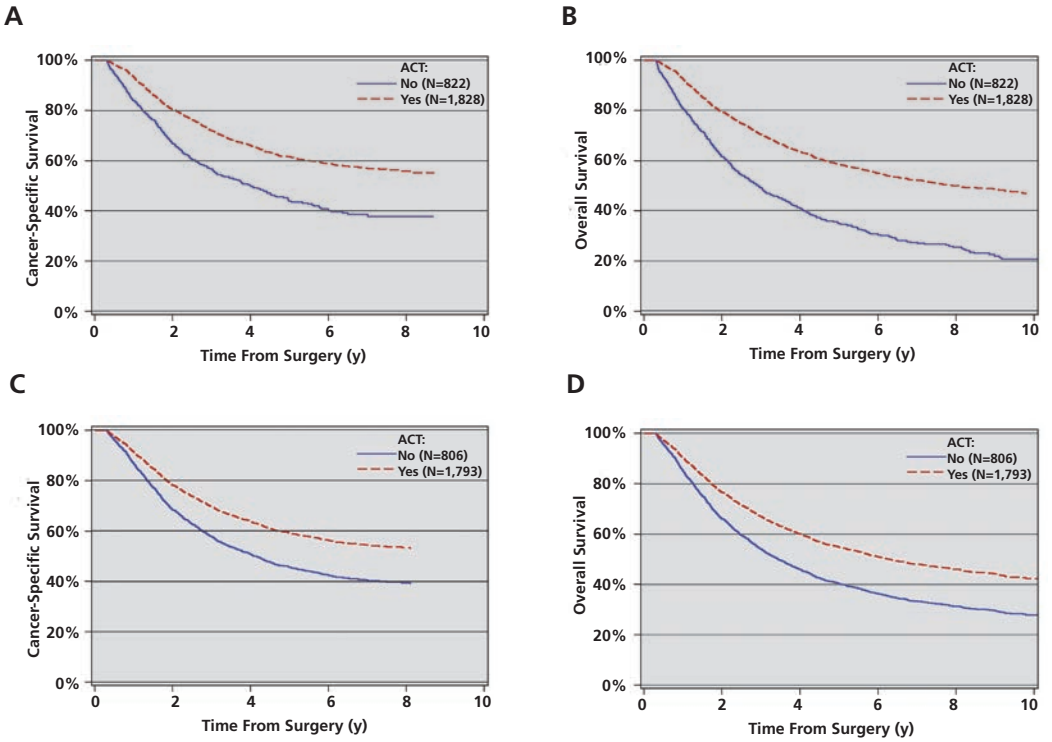

Figure 2. Survival curves for all patients with stage III colon cancer in Ontario 2002–2008 by adjuvant chemotherapy (ACT). (A) Unadjusted cancer-specific (CSS) survival. (B) Unadjusted overall (OS) survival. (C) Adjusted CSS[a]. (D) Adjusted OS[a].
[a]Covariates adjusted include: age, sex, socioeconomic status, Charlson comorbidity score, length of hospital stay, T stage, N status, lymphovascular invasion, grade, region, surgeon volume, and hospital volume.

use, Winget et al[18] identified 772 patients with stage III colon cancer diagnosed in Alberta during 2002–2005. ACT was delivered to 50% of patients. Age, comorbidity, and SES were associated with use of ACT. They also observed significant geographic variation in treatment rates. Two smaller Canadian studies have reported similar rates of ACT use (53% and 55%).[30,31] Our observed ACT use rate of 66% in Ontario during 2002–2008 is greater than reported in earlier Canadian studies, yet remains substantially lower than found in other population-based reports from the United States and Sweden.

Our results also provide insight into whether the efficacy of ACT observed in RCTs translates into effectiveness in routine practice. Five-year OS of patients treated with ACT in the contemporary MOSAIC (The Maudsley Outpatient Study of Treatments for Anorexia Nervosa and Related Conditions) and X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) RCTs was in the range of 68% to 76%.[32,33] To our knowledge, only 2 population-based studies report long-term survival of patients with stage III colon cancer treated with ACT, both of which use US SEER data and are restricted to patients aged 65 years or older.[14,22] In both studies, the 5-year OS of patients treated with ACT was approximately 55%. In our study, the 5-year OS of all patients was 51%, and was 46% among patients aged 65 years or older. These data suggest that the survival of patients with stage III colon cancer treated with ACT in routine practice is considerably lower than that reported in RCTs. This highlights the fact that patients in clinical trials may be very different from patients seen in routine practice.

In the IMPACT (International Multicentre Pooled Analysis of Colon Cancer Trials) meta-analysis,[2] 5-FU–based ACT was associated with a 30% reduction in the risk of death. The observed treatment effect of ACT in our study (HR for OS, 0.63; 95% CI, 0.55–0.71) is comparable to relevant RCTs and other population-based analyses. Four studies have used SEER data to evaluate the effectiveness of ACT compared with surgery in elderly patients with stage III colon cancer; ACT was associated with improved survival in each of these studies (HR for OS range, 0.51–0.73).[14,15,19,22] In the most recent of these reports, Sanoff et al[19] used SEER data to evaluate ACT effectiveness in a cohort of patients older than 75 years

treated during 2004–2007. They found that ACT was associated with a 40% reduction in the risk of death (HR, 0.60; 95% CI, 0.53–0.85). To our knowledge, Boland et al[16] reported the only study that evaluated the effectiveness of ACT in a population of all ages. Using the NCDB, the authors identified 48,758 patients treated during 1998–2002. Cases with surgery and ACT were classified as being adherent to guidelines. In propensity score adjusted analyses, they found improved OS for cases with guideline-adherent care (HR, 0.53; 95% CI, 0.51–0.55).

Our study provides detailed data regarding the use of ACT and outcomes of patients with stage III colon cancer in a contemporary population-based cohort; however, several methodologic limitations merit comment. The study population was identified using linked administrative health databases. Although the OCR and the Canadian Institute for Health Information data sets are known to be consistent and complete,[23,24,34] it is possible that our results may be biased by misclassification. Although the electronic data sources used in this study describe general aspects of disease, treatment, and outcome for all patients in the province, detailed information related to stage carcinoembryonic antigen level, chemotherapy dose/cycles, treatment toxicity, and performance status is not available, and this limits our ability to evaluate the appropriateness of case selection for ACT.

It is possible that other unmeasured confounders may have contributed to the observed survival benefit with ACT. As with any retrospective cohort study, the finding that treatment is associated with improved outcome may reflect unmeasured differences (ie, comorbidity) between patients who were treated and those who were not. Confounding could have accounted for the observed association only if an unmeasured confounder was extremely unequally distributed between treated and untreated groups and was associated with a large increase in risk of death. Even in the setting of persistent residual confounding, the observed effect size is large enough that we believe the study results demonstrate the effectiveness of ACT in routine practice. We believe our results are made more convincing based on the fact that we observe a large treatment effect for CSS, which may be less prone to the effect of additional comorbidity than OS. Moreover, in a separate analysis of patients with stage II colon cancer, we did not observe any benefit to ACT (data not shown). If residual confounding explains the ACT treatment effect in stage III colon cancer, one might expect to see a similar phenomenon in patients with stage II disease. The results of our Cox model analysis were consistent using propensity score methodology, which may further reduce bias from unmeasured confounders.[35]

Our study population was identified from the OCR and is therefore unselected, and, unlike most of the existing literature, includes patients of all ages. Because of the work required to manually review surgical pathology reports, our study population is a random sample of approximately 25% of all cases treated in Ontario during the study period. There were no substantial differences in demographic characteristics, ACT treatment rates, and survival outcomes between the randomly selected cases and the cases not included in our study population (supplemental eTable 1 and eFigure 1). We did not obtain pathology reports for cases that involved surgery in 2005. We believe it is very unlikely that this would bias our results in any significant way, because there were no observed temporal trends in practice or outcome between 2002 and 2008. During the study period, adjuvant oxaliplatin was not readily available in Ontario; for that reason, our results do not provide insight into the differential effect of oxaliplatin-containing ACT and therefore may be less generalizable to contemporary practice.

A total of 16% of patients in our study received FOLFIRI (irinotecan, 5-FU, leucovorin), which is not a standard adjuvant regimen. We believe that this reflects 2 groups of patients. First, most of these patients were treated with ACT in the early years before the negative trials of adjuvant FOLFIRI were reported, and therefore reflect true ACT (either on-study or off-study). Second, it is possible that some of these cases were found to have metastatic disease within 16 weeks after surgery and were therefore started on palliative FOLFIRI chemotherapy.

Conclusions

In this contemporary population-based study of stage III colon cancer, one-third of patients did not receive ACT. We observed large differences in ACT use across age groups. Our data demonstrate that ACT for stage III colon cancer is associated with a substantial survival benefit in routine clinical practice.

Acknowledgments

The authors gratefully acknowledge the contributions of Tina Dyer, Susan Rohland, Sarah Pickett, and Lois Bulch in the conduct of this study.

References

1. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 1990;264:1444–1450.
2. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Lancet 1995;345:939–944.
3. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–2351.
4. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696–2704.
5. Benson AB, Venook AP, Bekaii-Saab T, et al. NCCN Clinical Practice Guidelines in Oncology for Colon Cancer. Version 1.2015. Available at: NCCN.org. Accessed September 14, 2015. To view the most recent version of these guidelines, visit NCCN.org.
6. Schmoll HJ, Van CE, Stein A, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. Ann Oncol 2012;23:2479–2516.
7. Jonker DJ, Spithoff K, Maroun J. Adjuvant systemic chemotherapy for stage II and III colon cancer after complete resection. Clin Oncol (R Coll Radiol) 2011;23:314–322.
8. Peppercorn JM, Weeks JC, Cook EF, et al. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 2004;363:263–270.
9. Templeton AJ, Vera-Badillo FE, Wang L, et al. Translating clinical trials to clinical practice: outcomes of men with metastatic castration resistant prostate cancer treated with docetaxel and prednisone in and out of clinical trials. Ann Oncol 2013;24:2972–2977.
10. Booth CM, Siemens DR, Li G, et al. Perioperative chemotherapy for muscle-invasive bladder cancer: a population-based outcomes study. Cancer 2014;120:1630–1638.
11. Meyer RM. Generalizing the results of cancer clinical trials. J Clin Oncol 2010;28:187–189.
12. Booth CM, Mackillop WJ. Translating new medical therapies into societal benefit: the role of population-based outcome studies. JAMA 2008;300:2177–2179.
13. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. Br J Cancer 2014;110:551–555.
14. Sundararajan V, Mitra N, Jacobson JS, et al. Survival associated with 5-fluorouracil–based adjuvant chemotherapy among elderly patients with node-positive colon cancer. Ann Intern Med 2002;136:349–357.
15. Zuckerman IH, Rapp T, Onukwugha E, et al. Effect of age on survival benefit of adjuvant chemotherapy in elderly patients with stage III colon cancer. J Am Geriatr Soc 2009;57:1403–1410.
16. Boland GM, Chang GJ, Haynes AB, et al. Association between adherence to National Comprehensive Cancer Network treatment guidelines and improved survival in patients with colon cancer. Cancer 2013;119:1593–1601.
17. Chagpar R, Xing Y, Chiang YJ, et al. Adherence to stage-specific treatment guidelines for patients with colon cancer. J Clin Oncol 2012;30:972–979.
18. Winget M, Hossain S, Yasui Y, et al. Characteristics of patients with stage III colon adenocarcinoma who fail to receive guideline-recommended treatment. Cancer 2010;116:4849–4856.
19. Sanoff HK, Carpenter WR, Sturmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. J Clin Oncol 2012;30:2624–2634.
20. Lindskog EB, Gunnarsdottir KA, Derwinger K, et al. A population-based cohort study on adherence to practice guidelines for adjuvant chemotherapy in colorectal cancer. BMC Cancer 2014;14:948.
21. Murphy CC, Harlan LC, Lund JL, et al. Patterns of colorectal cancer care in the United States: 1990–2010. J Natl Cancer Inst 2015;107:djv198.
22. Iwashyna TJ, Lamont EB. Effectiveness of adjuvant fluorouracil in clinical practice: a population-based cohort study of elderly patients with stage III colon cancer. J Clin Oncol 2002;20:3992–3998.
23. Clarke EA, Marrett LD, Krieger N. Cancer registration in Ontario: a computer approach. In: Jenson OM, Parkin DM, MacLennan R, eds. Cancer Registration Principles and Methods. Lyon, France: IARC; 1991:246–257.
24. Li X, King C, deGara C, et al. Validation of colorectal cancer surgery data from administrative data sources. BMC Med Res Methodol 2012;12:97.
25. Mackillop WJ, Zhang-Salomons J, Groome PA, et al. Socioeconomic status and cancer survival in Ontario. J Clin Oncol 1997;15:1680–1689.
26. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.
27. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–763.
28. Sanoff HK, Carpenter WR, Martin CF, et al. Comparative effectiveness of oxaliplatin vs non-oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. J Natl Cancer Inst 2012;104:211–227.
29. Schrag D, Cramer LD, Bach PB, et al. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. J Natl Cancer Inst 2001;93:850–857.
30. Cree M, Tonita J, Turner D, et al. Comparison of treatment received versus long-standing guidelines for stage III colon and stage II/III rectal cancer patients diagnosed in Alberta, Saskatchewan, and Manitoba in 2004. Clin Colorectal Cancer 2009;8:141–145.
31. Rayson D, Urquhart R, Cox M, et al. Adherence to clinical practice guidelines for adjuvant chemotherapy for colorectal cancer in a Canadian province: a population-based analysis. J Oncol Pract 2012;8:253–259.
32. Twelves C, Scheithauer W, McKendrick J, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol 2012;23:1190–1197.
33. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 2009;27:3109–3116.
34. Williams J, Young W. A summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams JI, Anderson GM, et al, eds. Patterns of Health Care in Ontario: The ICES Practice Atlas, 2nd ed. Ottawa, Canada: Canadian Medical Association; 1996:339–345.
35. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46:399–424.

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JNCCN
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Supplemental online content for:

Use and Effectiveness of Adjuvant Chemotherapy for Stage III Colon Cancer: A Population-Based Study

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J Natl Compr Canc Netw 2015;14(1):47–56

- **eTable 1:** Characteristics of Patients Treated With Surgical Resection for Colon Cancer in Ontario 2002–2008 With and Without Randomly Selected Pathology Reports
- **eTable 2:** Propensity Score Analysis Evaluating the Effect of Adjuvant Chemotherapy Compared With No Adjuvant Chemotherapy on Overall and Cancer-Specific Survival Among 2650 Stage III Colon Cancer Patients in Ontario 2002–2008
- **eFigure 1:** Cancer-Specific Survival Curves of Patients Treated With Surgical Resection for Colon Cancer in Ontario 2002–2008 With and Without Randomly Selected Pathology Reports

eTable 1. Characteristics of Patients Treated With Surgical Resection for Colon Cancer in Ontario 2002–2008 With and Without Randomly Selected Pathology Reports

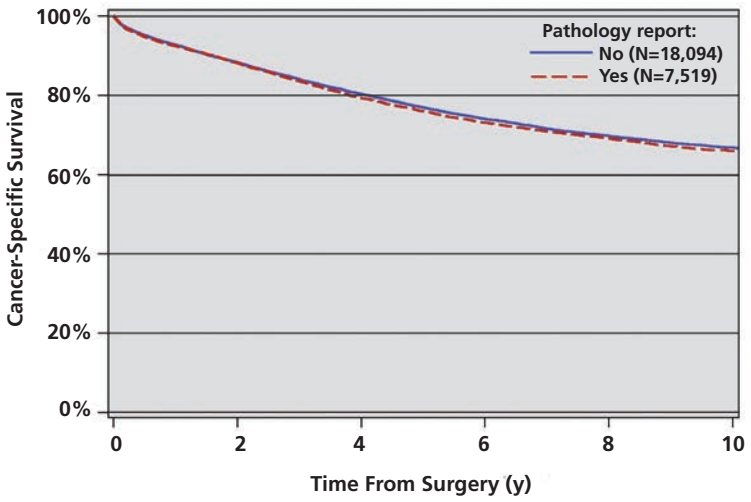
		Pathology Report: Yes n (%) N=7,519	Pathology Report: No n (%) N=18,094
Age, y			
	20–49	470 (6%)	1,195 (7%)
	50–59	1,025 (14%)	2,724 (15%)
	60–69	1,804 (24%)	4,485 (25%)
	70–79	2,477 (33%)	5,938 (33%)
	≥80	1,743 (23%)	3,752 (21%)
Sex			
	Male	3,842 (51%)	9,403 (52%)
	Female	3,677 (49%)	8,691 (48%)
SES by quintile[a]			
	1	1,584 (21%)	4,047 (22%)
	2	1,777 (24%)	4,123 (23%)
	3	1,627 (22%)	3,702 (20%)
	4	1,357 (18%)	3,311 (18%)
	5	1,152 (15%)	2,835 (16%)
Charlson comorbidity score			
	0	5,890 (78%)	14,330 (79%)
	1	941 (13%)	2,144 (12%)
	≥2	688 (9%)	1,620 (9%)

Abbreviations: NA, not applicable; SES, socioeconomic status.
[a]Quintile 1 represents the communities where the poorest 20% of the Ontario population resided. SES data were not available for 98 of 25,613 (0.4%) patients.

eTable 2. Propensity Score Analysis Evaluating the Effect of Adjuvant Chemotherapy Compared With No Adjuvant Chemotherapy on Overall and Cancer-Specific Survival Among 2,650 Patients With Stage III Colon Cancer in Ontario 2002–2008

			Cancer-Specific Survival		Overall Survival	
Quintile	Cases Without ACT	Cases With ACT	Adjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Quintile 1[a] (n=519)	387	132	0.78 (0.57–1.09)	.146	0.76 (0.59–0.98)	.036
Quintile 2 (n=520)	192	328	0.61 (0.47–0.79)	<.001	0.62 (0.49–0.77)	<.001
Quintile 3 (n=520)	107	413	0.73 (0.53–1.01)	.060	0.65 (0.49–0.87)	.003
Quintile 4 (n=520)	72	448	0.41 (0.28–0.60)	<.001	0.45 (0.31–0.64)	<.001
Quintile 5 (n=520)	48	472	0.50 (0.31–0.82)	.006	0.51 (0.33–0.78)	.002
Combined HR across quintiles 1–5			**0.63 (0.54–0.73)**	**<.001**	**0.63 (0.55–0.71)**	**<.001**

51 of 2,650 (2%) cases were not included in the propensity score analysis because of missing data.
Abbreviations: ACT, adjuvant chemotherapy; HR, hazard ratio.
[a]Quintile 1 reflects the 20% of patients with the lowest propensity to have ACT.



eFigure 1. Cancer-specific survival curves of patients treated with surgical resection for colon cancer in Ontario 2002–2008 with and without randomly selected pathology reports.