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Lymph node evaluation for colon cancer in routine clinical practice: a population-based study

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ABSTRACT

Background Guidelines recommend that 12 or more lymph nodes (LNs) be evaluated during surgical resection of colon cancer. Here, we report LN yield and its association with survival in routine practice.

Methods Electronic records of treatment were linked to the population-based Ontario Cancer Registry to identify all patients with colon cancer treated during 2002–2008. The study population (n = 5508) included a 25% random sample of patients with stage II or III disease. Modified Poisson regression was used to identify factors associated with LN yield; Cox models were used to explore the association between LN yield and overall (OS) and cancer-specific survival (CSS).

Results During 2002–2008, median LN yield increased to 17 from 11 nodes ($p < 0.001$), and the proportion of patients with 12 or more nodes evaluated increased to 86% from 45% ($p < 0.001$). Lymph node positivity did not change over time (to 53% from 54%, $p = 0.357$). Greater LN yield was associated with younger age ($p < 0.001$), less comorbidity ($p = 0.004$), higher socioeconomic status ($p = 0.001$), right-sided tumours ($p < 0.001$), and higher hospital volume ($p < 0.001$). In adjusted analyses, a LN yield of less than 12 nodes was associated with inferior OS and CSS for stages II and III disease [stage II OS hazard ratio (HR): 1.36; 95% confidence interval (CI): 1.19 to 1.56; stage II CSS HR: 1.52; 95% CI: 1.26 to 1.83; and stage III OS HR: 1.45; 95% CI: 1.30 to 1.61; stage III CSS HR: 1.54; 95% CI: 1.36 to 1.75].

Conclusions Despite a temporal increase in LN yield, the proportion of cases with LN positivity has not changed. Lymph node yield is associated with survival in patients with stages II and III colon cancer. The association between LN yield and survival is unlikely to be a result of stage migration.

Key Words Colon cancer, lymph node yield, survival factors, population studies

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INTRODUCTION

The importance of lymph node (LN) yield in surgery for colon cancer lies in the reported association between the number of LNs evaluated and survival[1]. That association is independent of whether the LNs are involved with metastatic disease[2]. Given that association, international guidelines recommend that at least 12 LNs be evaluated with resection of the primary tumour[3–6].

Since the publication of those clinical guidelines in the early 2000s, LN yield has increased in routine practice. In their analysis of data from the Surveillance, Epidemiology, and End Results Program in the United States, Parsons *et al.*[2] reported that the proportion of surgeries in which 12 or more LNs were evaluated increased from 35% in 1988–1990 to 74% in 2006–2008. Similarly, a population-based study from the Netherlands found that the rate of adequate LN yield increased to 59% in 2009–2011 from 13% in 2000–2002[7]. Population-based data from Ontario have shown similar temporal trends: during 1991–1993, 10 or more LNs were resected in only 26% of patients; by 2004, the proportion of resections with more than 12 LNs evaluated had increased to approximately 70%[8,9].

We undertook a population-based study to explore LN yield in a contemporary cohort, to identify factors associated with LN yield, and to evaluate the association between LN yield and survival in routine clinical practice.

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METHODS

Study Design and Population

This population-based retrospective cohort study describes nodal yield and outcomes for patients with stages II and 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 II or III colon cancer in Ontario during 2002–2008.

Using the Ontario Cancer Registry (OCR), we identified a study cohort consisting of all incident patients with colorectal cancer (CRC) diagnosed in Ontario during 2000–2008. We then identified all patients who underwent primary tumour resection within 6 months of diagnosis. The OCR does not capture disease stage for all patients; we therefore obtained surgical pathology reports for a random sample of 25% of the patients. Reports for patients undergoing surgery in 2005 were not available; the study cohort was thus restricted to patients who underwent surgery in 2002–2004 and 2006–2008. Patients with rectal cancer and non-adenocarcinoma histology were excluded, as were patients for whose surgeries the number of LNs was unspecified. The study was approved by the Research Ethics Board of Queen's University.

Data Sources

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information for at least 98% of all incident cases of cancer in the province of Ontario[10]. The OCR also provides information about vital status and cause of death. Records of hospitalization from the Canadian Institute for Health Information provided information about surgical procedures; those records are known to have a very high level of completeness for CRC surgery[11]. Provincial physician billing records from the Ontario Health Insurance Plan, treatment records from regional cancer centres, and provincial records of chemotherapy delivery (New Drug Funding Program and the Ontario Drug Benefit) were used to identify chemotherapy use. The datasets were linked using unique encoded identifiers and were analyzed at the Institute for Clinical Evaluative Sciences. Surgical pathology reports were obtained from the OCR. A team of trained data abstractors reviewed the pathology reports and entered information about extent of disease and LN yield into an electronic database.

Measures and Outcomes

Indicators of the socioeconomic status of the community in which a patient resided at diagnosis were linked as previously described[12]. Quintiles of median household income were based on the household income distribution for the full province of Ontario. Geographic regions reflect the catchment areas for Ontario's regional cancer centres[12]. Comorbidity was classified using the modified Charlson index and was based on all non-cancer diagnoses recorded during any hospital admission within the 5 years preceding surgery[13]. Each patient was assigned a hospital volume index based on the total number of colon cancer resections performed at their respective hospital in the preceding 12 months. We used the same approach to derive a surgeon volume index for each patient. Laparoscopic surgical resections were identified using Ontario Health Insurance Plan physician billing records.

Overall (OS) and cancer-specific survival (CSS) were determined from the date of surgery. To account for the potential of cause-of-death miscoding, CSS included death from any cancer. Complete information about vital status in the OCR was available up to 31 December 2012; cause of death was available up to 31 December 2010.

Statistical Analysis

The chi-square test was used to compare proportions between study groups. Lymph node yield was evaluated as a continuous variable and a categorical variable—that is, 12 or more LNs compared with fewer than 12 LNs, and by quartile. Factors associated with LN yield were evaluated by modified Poisson regression. The associations of patient-, disease-, and treatment-related factors with OS and CSS were evaluated using Cox proportional hazards regression models stratified by disease stage. Results were considered statistically significant at a p value less than 0.05. All analyses were performed using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Study Population

Linked administrative data sets identified 25,613 potentially eligible patients who underwent resection of primary colon cancer during 2002–2008. Surgical pathology reports were reviewed for 7519 randomly selected patients. The age, sex, comorbidity, and survival of the randomly selected patients did not differ substantially from those of the 18,094 unselected cases (Table I). Of the 7519 randomly selected patients, 270 (4%) were excluded. Of the 5519 surgical pathology reports for patients with stage II or III disease, 11 (0.2%) lacked an explicit nodal count and were therefore excluded. Accordingly, the study cohort consisted of 5508 patients. Table II shows the characteristics of the study population. Median age in this cohort was 72 years; 51% of the patients were men; and 47% (n = 2593) had stage II disease.

Practice Patterns and Factors Associated with Nodal Yield

Median LN yield in the study cohort was 15 nodes. In 72% of the patients (n = 3941), 12 or more LNs were evaluated. Figure 1 shows temporal trends for LN yield. Mean and median LN yield increased, respectively, to 20 and 17 from 13 and 11 ($p < 0.001$). The proportion of patients with a LN yield of 12 or more increased to 89% (717 of 809 patients) in 2008 from 48% in 2002 (301 or 623 patients), $p < 0.001$. The proportion of patients with node-positive disease remained stable over the study period (53% in 2008 vs. 54% in 2002, $p = 0.357$).

Table III shows factors associated with LN yield. The factors associated with a LN yield of 12 or more nodes were younger age, higher socioeconomic status, lesser comorbidity, more recent year of surgery, a right-sided tumour, and a higher-volume hospital. Those factors remained

TABLE I Characteristics of 25,613 patients with and without randomly selected pathology reports treated with surgical resection for colon cancer in Ontario, 2002–2008

Characteristic	Pathology report [*n* (%)]	
	Yes (*n*=7,519)	No (*n*=18,094)
Age		
20–49 Years	470 (6)	1,195 (7)
50–59 Years	1,025 (14)	2,724 (15)
60–69 Years	1,804 (24)	4,485 (25)
70–79 Years	2,477 (33)	5,938 (33)
≥80 Years	1,743 (23)	3,752 (21)
Sex		
Men	3,842 (51)	9,403 (52)
Women	3,677 (49)	8,691 (48)
Socioeconomic status[a]		
Quintile 1	1,584 (21)	4,047 (22)
Quintile 2	1,777 (24)	4,123 (23)
Quintile 3	1,627 (22)	3,702 (20)
Quintile 4	1,357 (18)	3,311 (18)
Quintile 5	1,152 (15)	2,835 (16)
Score on the CCI		
0	5,890 (78)	14,330 (79)
1	941 (13)	2,144 (12)
≥2	688 (9)	1,620 (9)

[a] Quintile 1 represents patients from the poorest communities in Ontario. Data were not available for 98 patients (0.4%).
CCI = Charlson comorbidity index.

TABLE II Characteristics of the study population

Characteristic	Patient groups [*n* (%)]		
	All (*n*=5508)	Node-negative (*n*=2593)	Node-positive (*n*=2915)
Patient-related			
Age (years)			
20–49	343 (6)	134 (5)	209 (7)
50–59	744 (14)	300 (12)	444 (15)
60–69	1,309 (24)	565 (22)	744 (26)
70–79	1,787 (32)	881 (34)	906 (31)
≥80	1,325 (24)	713 (27)	612 (21)
Sex			
Men	2,833 (51)	1,314 (51)	1,519 (52)
Women	2,675 (49)	1,279 (49)	1,396 (48)
SES by quintile[a]			
1	1,193 (22)	574 (22)	619 (21)
2	1,304 (24)	621 (24)	683 (23)
3	1,177 (21)	560 (22)	617 (21)
4	977 (18)	455 (18)	522 (18)
5	843 (15)	375 (14)	468 (16)
Score on the CCI			
0	4,340 (79)	2,002 (77)	2,338 (80)
1–2	931 (17)	463 (18)	468 (16)
≥3	237 (4)	128 (5)	109 (4)
Disease-related			
Laterality			
Right	2,742 (50)	1,354 (52)	1,388 (48)
Left	2,478 (45)	1,100 (42)	1,378 (47)
Both or unstated	283 (5)	136 (5)	147 (5)
Histology			
Lymphovascular			
Yes	1,813 (33)	371 (14)	1,442 (49)
No	3,268 (59)	2,023 (78)	1,245 (43)
Not available	427 (8)	199 (8)	228 (8)
T Stage[b]			
T≤1	44 (1)	—	44 (2)
T2	181 (3)	—	181 (6)
T3	4,092 (74)	2,168 (84)	1,924 (66)
T4	1,191 (22)	425 (16)	766 (26)
Lymph nodes			
Mean	16.7	16.4	16.8
Median	15	15	15
≥12	3,941 (72)	1,822 (70)	2,119 (73)
<12	1,567 (28)	771 (30)	796 (27)
Treatment-related			
Adjuvant chemotherapy			
Yes	2,317 (42)	460 (18)	1,857 (64)
No	3,191 (58)	2,133 (82)	1,058 (36)
Region			
A	2,539 (46)	1,170 (45)	1,369 (47)
B	787 (14)	409 (16)	378 (13)
C	433 (8)	212 (8)	221 (8)
D	349 (6)	164 (6)	185 (6)
E	120 (2)	69 (3)	51 (2)
F	161 (3)	65 (3)	96 (3)
G	372 (7)	184 (7)	188 (6)
H	745 (14)	318 (12)	427 (15)
Study period			
2002–2004	2,693 (49)	1,261 (49)	1,432 (49)
2006–2008	2,815 (51)	1,332 (51)	1,483 (51)
Surgical procedure			
Open	4,656 (85)	2,179 (84)	2,477 (85)
Laparoscopic	852 (15)	414 (16)	438 (15)

[a] Quintile 1 represents the communities where the poorest 20% of the Ontario population resides. Data were not available for 14 patients.
[b] T≤1 = pTX, pT0, pTis, or pT1.
SES = socioeconomic status; CCI = Charlson comorbidity index.

significant when LN yield was analyzed as a continuous variable; however, in the model, female sex, higher T stage, and laparoscopic resection were also associated with a greater LN yield. Surgeon volume was not associated with LN yield in either model.

Factors Associated with Survival

For stage II patients, the 5-year OS and CSS were 70% (95% CI: 68% to 71%) and 79% (95% CI: 77% to 81%) respectively; for stage III patients, they were 47% (95% CI: 45% and 48%) and 52% (95% CI: 50% to 54%). Tables IV and V show factors associated with survival in those patient groups. In stage II and stage III colon cancer, LN yield (as a categorical variable

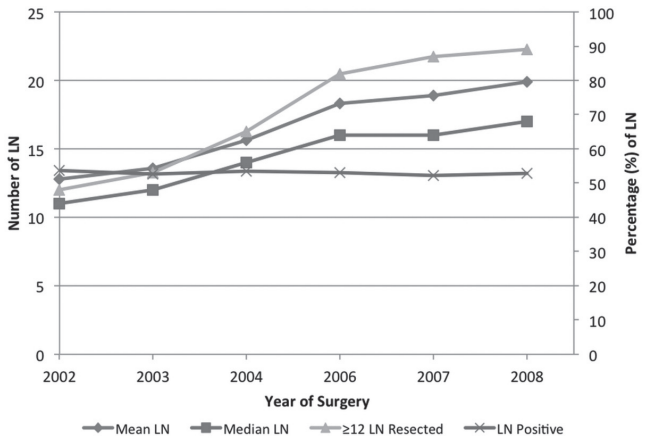

FIGURE 1 Temporal trends in lymph node (LN) evaluation for 5508 patients with stage II and stage III colon cancer in Ontario, 2002–2008.

by quartile) was associated with OS and CSS: the stage II lowest-quartile HR was 1.53 for OS (95% CI: 1.26 to 1.86) and 1.84 for CSS (95% CI: 1.40 to 2.42); the stage III lowest-quartile HR was 1.79 for OS (95% CI: 1.54 to 2.08) and 1.95 for CSS (95% CI: 1.64 to 2.32). In both stage II and stage III, a stepwise decrease in the risk of death by LN quartile was observed. The association between LN yield and survival was also evident when the Cox model was repeated with LN yield dichotomized as 12 or more LNs compared with fewer than 12 LNs: the stage II <12 LN HR was 1.36 for OS (95% CI: 1.09 to 1.65) and 1.44 for CSS (95% CI: 1.06 to 1.96); the stage III <12 LN HR was 1.45 for OS (95% CI: 1.30 to 1.61) and 1.54 for CSS (95% CI: 1.36 to 1.75).

DISCUSSION

In this population-based study, we described LN yield for patients with colon cancer in routine clinical practice in the contemporary era. Several important findings emerged. First, LN yield increased substantially over the study period. Second, despite the increase in LN yield, the proportion of patients with node-positive disease did not change. Third, we found that age, socioeconomic status, comorbidity, year of surgery, laterality, and hospital volume were associated with LN yield. Surgeon volume was not associated with LN yield. Finally, our data demonstrated a substantial association between LN yield and survival for both stage II and stage III colon cancer in the general population.

Ontario data from the early 1990s revealed that, in 74% of patients, fewer than 10 nodes were resected[8]; by the late 1990s, fewer than 12 LNs were being evaluated in 73% of patients with stage II disease[9]. After a multifaceted knowledge translation intervention study designed by Wright *et al.* in 2004[14], the proportion of patients having 12 or more LNs resected increased to 76%. Our study demonstrates that, in 2006–2008, more than 12 LNs were being evaluated in more than 80% of patients; that finding is comparable with nodal yield data in the United States during 2006–2009, as reported by Parsons *et al.*[15].

Our study also provides insight into factors that are associated with LN yield. Understanding the factors that affect LN yield is important if optimizing yield has the potential to improve patient outcomes. The association between LN yield and survival has been established in numerous studies. A large systematic review by Chang *et al.*[1] that included seventeen studies and 61,371 patients reported a consistent association between LN count and survival for both stage II and III CRC. The existing literature has identified three broad factors that are associated with nodal yield: the operating characteristics of the surgeon, the facilitating techniques of the pathologist, and patient-related factors[16]. The former two factors are "modifiable" in the sense that interventions to alter LN yield can be established; in contrast, patient- and disease-related factors are not modifiable.

With respect to modifiable factors, our study reveals that hospital volume is associated with LN yield, but that surgeon volume is not. Those two modifiable factors have had inconsistent associations with LN yield in the literature[17–24]. Nevertheless, although variations in hospital-associated LN yield are larger than those for individual pathologists and surgeons, patient-related variations are largest[18]. Of the non-modifiable patient factors, senescence has consistently been shown to be associated with lower LN yield[18,20,22,24–26]. That observation might reflect decreased immune response with aging[27] and comorbidity[28]. Right-sided tumours are also known to be associated with higher LN counts[18–22,24–26,29], likely a result of a larger mesenteric surface and the presence of multiple vascular trunks[30].

It must be emphasized that this retrospective study confirms the known association between LN yield and survival; it does not establish causality. The current debate is focused on the mechanism behind the association: whether LN yield itself leads to improved survival (for example, because of a direct therapeutic effect or appropriate stage classification) or whether it is a surrogate for other factors associated with outcome, such as quality of care or variation in host or tumour biology.

At present, studies have failed to establish that a more extensive LN dissection confers a direct therapeutic benefit by removal of occult micrometastases[31,32]. Studies have also refuted what is perhaps the most debated mechanism: stage migration, whereby detection of node positivity "migrates" a patient from a lower stage to a higher one, transforming that patient from a "high-risk" stage II individual to a "low-risk" stage III individual, thereby spuriously improving survival in both groups[33]. The largest retrospective data collections in both the United States and Europe have shown that, despite increases in LN yield over time, and increased survival with increased LN yield, the yield of positive LNs has not increased[2,7,34]. Our results are consistent with that finding. Moreover, stage migration would not explain the observed association between LN yield and survival of patients with stage III disease.

Finally, the literature does not support the assertion that LN yield is a marker for quality care. There is no association between patients who receive an adequate LN yield and guideline-recommended postsurgical CRC care[35]. There is also a strong association between LN yield and outcome in single centres, where provider factors would be held constant[36].

Some of the factors that we found to be associated with a higher LN yield—younger age, lower comorbidity,

TABLE III Factors associated with lymph node yield in 5508 patients with stage II and stage III colon cancer resected in Ontario, 2002–2008

Factor	Patients		Multivariate analyses					
	(*n*)	≥12 nodes resected (%)	At least 12 nodes resected[a]			Nodes as continuous variable[b]		
			RR	95% CI	*p* Value	RR	95% CI	*p* Value
Age group					<0.001			<0.001
20 to 49 Years	343	78		Reference			Reference	
50 to 59 Years	744	75	0.96	0.90 to 1.03		0.87	0.85 to 0.90	
60 to 69 Years	1309	74	0.95	0.89 to 1.01		0.80	0.78 to 0.82	
70 to 79 Years	1787	68	0.90	0.84 to 0.95		0.75	0.73 to 0.77	
≥80 Years	1325	69	0.88	0.82 to 0.94		0.72	0.70 to 0.74	
Sex					0.328			<0.001
Men	2833	71		Reference			Reference	
Women	2675	72	1.02	0.98 to 1.05		1.04	1.03 to 1.06	
SES quintile[c]					0.001			<0.001
1	1193	68	0.90	0.85 to 0.94		0.89	0.87 to 0.91	
2	1304	71	0.95	0.90 to 1.00		0.94	0.92 to 0.96	
3	1177	71	0.93	0.88 to 0.98		0.92	0.90 to 0.94	
4	977	71	0.94	0.89 to 0.99		0.94	0.92 to 0.97	
5	843	78		Reference			Reference	
Score on the CCI					0.004			<0.001
0	4340	73		Reference			Reference	
1 to 2	931	69	0.96	0.92 to 1.01		0.96	0.94 to 0.97	
≥3	237	63	0.87	0.79 to 0.95		0.88	0.85 to 0.91	
Year					<0.001			<0.001
2002	623	48		Reference			Reference	
2003	971	53	1.07	0.97 to 1.18		1.06	1.03 to 1.09	
2004	1099	65	1.30	1.19 to 1.43		1.23	1.20 to 1.26	
2006	978	82	1.64	1.50 to 1.79		1.45	1.41 to 1.49	
2007	1028	87	1.70	1.56 to 1.85		1.47	1.43 to 1.51	
2008	809	89	1.77	1.62 to 1.92		1.58	1.54 to 1.63	
Laterality[d]					<0.001			<0.001
Left	2478	66		Reference			Reference	
Right	2742	77	1.17	1.13 to 1.21		1.19	1.18 to 1.21	
T stage					0.128			0.002
≤T1	44	59	0.91	0.82 to 1.01		0.93	0.86 to 1.01	
T2	181	67	0.98	0.94 to 1.02		0.93	0.89 to 0.97	
T3	4092	72	0.84	0.67 to 1.06		1.00	0.98 to 1.01	
T4	1191	73		Reference			Reference	
Hospital volume[e]					<0.001			<0.001
Q1	1375	63	0.90	0.86 to 0.95		0.92	0.91 to 0.94	
Q2	1350	71	0.97	0.92 to 1.01		0.95	0.93 to 0.97	
Q3	1430	75	0.99	0.95 to 1.03		1.03	1.01 to 1.05	
Q4	1353	76		Reference			Reference	
Surgeon volume[e]					0.280			0.112
Q1	1270	71	1.00	0.95 to 1.04		0.98	0.97 to 1.00	
Q2	1364	68	0.96	0.91 to 1.00		0.98	0.96 to 1.00	
Q3	1390	71	0.99	0.95 to 1.04		1.00	0.98 to 1.02	
Q4	1382	76		Reference			Reference	
Surgical procedure					0.269			<0.001
Open	4656	70		Reference			Reference	
Laparoscopic	852	80	0.98	0.94 to 1.02		0.92	0.90 to 0.93	

[a] Relative risk was estimated using modified Poisson regression.
[b] Number of nodes was modelled as a continuous variable using zero-truncated Poisson regression.
[c] Socioeconomic status quintile 1 represents the lowest socioeconomic status. Data were not available for 14 patients.
[d] Patients with "both" or unstated laterality (*n* = 288) were removed from the analyses.
[e] Q1 represents the lowest volume. Data were not available for 102 patients.
RR = relative risk; CI = confidence interval; SES = socioeconomic status; CCI = Charlson comorbidity index.

right-sided colectomies—raise the question of whether LN yield might reflect prognosis rather than drive it. Patients with histologic evidence of a more vigorous immune response experience improved outcomes[37,38]. Similarly, patients with a depleted or under-stimulated lymphocytic response to their CRC, either within their lymphatics[39] or at the tumour edge[40], have a relatively unfavourable prognosis. Galon *et al.*[41] coined the term "immune contexture" to describe the effect of the local host immune reaction in CRC. There is a negative association between senescence and decreased nodal count[27], and possibly a stronger association between comorbidity and diminished immunity[28]; also, patients with CRCs that genomically harbour microsatellite instability have a propensity

TABLE IV Factors associated with survival for 2593 patients with stage II colon cancer resected in Ontario, 2002–2008

Covariate	Overall survival				Cancer-specific survival			
	5-Year (%)	Multivariate analysis			5-Year (%)	Multivariate analysis		
		HR	95% CI	*p* Trend		HR	95% CI	*p* Trend
Age				<0.001				<0.001
<65 Years	83		Reference		86		Reference	
65 to 74 Years	73	1.72	1.38 to 2.14		80	1.50	1.14 to 1.97	
≥75 Years	59	2.99	2.44 to 3.66		74	1.96	1.51 to 2.53	
SES quintile[a]				0.029				0.426
Q1	65	1.11	0.89 to 1.38		75	0.98	0.73 to 1.32	
Q2	66	1.06	0.85 to 1.33		77	0.95	0.71 to 1.29	
Q3	72	0.86	0.68 to 1.08		82	0.81	0.59 to 1.11	
Q4	73	0.87	0.68 to 1.11		81	0.81	0.59 to 1.13	
Q5	74		Reference		80		Reference	
Score on the CCI				<0.001				0.032
0	74		Reference		80		Reference	
1–2	59	1.59	1.36 to 1.86		75	1.21	0.96 to 1.53	
≥3	37	3.09	2.46 to 3.87		71	1.58	1.06 to 2.35	
T Stage				<0.001				<0.001
T3	73		Reference		82		Reference	
T4	55	1.74	1.49 to 2.04		63	2.40	1.96 to 2.93	
Adjuvant chemotherapy				0.411				0.637
Yes	75	0.92	0.75 to 1.12		78	1.06	0.83 to 1.36	
No	69		Reference		79		Reference	
Number of nodes				<0.001				<0.001
Q1 (≤10 nodes)	60	1.53	1.26 to 1.86		71	1.84	1.40 to 2.42	
Q2 (11–14 nodes)	68	1.25	1.02 to 1.52		77	1.41	1.05 to 1.87	
Q3 (15–20 nodes)	75	1.07	0.87 to 1.31		84	1.11	0.83 to 1.50	
Q4 (≥21 nodes)	76		Reference		85		Reference	
Surgical approach				0.004				0.019
Open	68	1.35	1.10 to 1.66		78	1.45	1.06 to 1.97	
Laparoscopic	78		Reference		85		Reference	
Laterality[b]				0.208				0.232
Right	70		Reference		81		Reference	
Left	70	1.09	0.95 to 1.24		78	1.12	0.93 to 1.34	
Hospital volume				0.592				0.565
Q1	69	1.08	0.90 to 1.30		78	1.02	0.79 to 1.32	
Q2	70	1.11	0.92 to 1.33		80	0.95	0.73 to 1.23	
Q3	69	1.13	0.94 to 1.36		79	1.14	0.88 to 1.46	
Q4	71		Reference		80		Reference	

[a] Quintile 1 represents the lowest socioeconomic status. Data were not available for 8 patients.
[b] The analysis excluded 139 patients for "both" or unstated laterality.
HR = hazard ratio; CI = confidence interval; SES = socioeconomic status; CCI = Charlson comorbidity index.

for right-sided malignancies[42], higher LN yields[43], and better overall prognosis[44]. Given those findings, it is entirely plausible that LN yield is the surrogate marker for an immune response that reflects inherent prognosis.

Although our study provides detailed data about LN yield in early-stage colon cancer in a contemporary population-based cohort, several methodology limitations merit comment. The study population was identified using linked administrative health databases. Although the OCR and the Canadian Institute for Health Information dataset are known to be consistent and complete, it is possible that our results might be biased by misclassification. As with

TABLE V Factors associated with survival in 2915 patients with stage III colon cancer resected in Ontario, 2002–2008

Covariate	Overall survival				Cancer-specific survival			
	5-Year (%)	Multivariate analysis			5-Year (%)	Multivariate analysis		
		HR	95% CI	*p* Trend		HR	95% CI	*p* Trend
Age group				<0.001				0.711
<65 Years	57		Reference		59		Reference	
65 to 74 Years	51	1.09	0.96 to 1.25		54	1.06	0.91 to 1.23	
≥75 Years	33	1.30	1.14 to 1.48		43	1.06	0.91 to 1.23	
SES qunitile[a]				0.147				0.115
Q1	45	0.99	0.84 to 1.17		51	1.00	0.82 to 1.21	
Q2	41	1.14	0.97 to 1.34		47	1.18	0.98 to 1.43	
Q3	48	0.96	0.81 to 1.14		53	0.97	0.79 to 1.17	
Q4	50	0.98	0.82 to 1.17		54	1.00	0.82 to 1.22	
Q5	52		Reference		56		Reference	
Score on the CCI				<0.001				0.596
0	50		Reference		54		Reference	
1 to 2	36	1.23	1.08 to 1.40		44	1.08	0.93 to 1.27	
≥3	22	1.46	1.17 to 1.83		41	1.02	0.76 to 1.37	
T stage				<0.001				<0.001
≤T1	73		Reference		77		Reference	
T2	75	0.80	0.46 to 1.39		83	0.63	0.30 to 1.30	
T3	50	1.69	1.03 to 2.77		56	2.03	1.09 to 3.80	
T4	30	2.91	1.77 to 4.80		33	3.88	2.07 to 7.28	
Adjuvant chemotherapy				<0.001				<0.001
Yes	58	0.45	0.40 to 0.50		61	0.45	0.39 to 0.51	
No	27		Reference		36		Reference	
Number of nodes				<0.001				<0.001
Q1 (≤10 nodes)	38	1.79	1.54 to 2.08		44	1.95	1.64 to 2.32	
Q2 (11 to 14 nodes)	45	1.38	1.19 to 1.60		50	1.51	1.27 to 1.79	
Q3 (15 to 20 nodes)	47	1.29	1.12 to 1.49		52	1.36	1.15 to 1.61	
Q4 (≥21 nodes)	56		Reference		62		Reference	
Surgical approach				0.002				0.001
Open	45	1.26	1.09 to 1.46		51	1.34	1.12 to 1.60	
Laparoscopic	55		Reference		60		Reference	
Laterality[b]				0.002				<0.001
Right	43		Reference		48		Reference	
Left	51	0.85	0.77 to 0.94		56	0.78	0.69 to 0.88	
Hospital volume				0.016				0.036
Q1	45	1.08	0.93 to 1.25		52	0.96	0.81 to 1.14	
Q2	44	1.23	1.07 to 1.42		48	1.19	1.01 to 1.40	
Q3	47	1.19	1.03 to 1.37		53	1.12	0.95 to 1.32	
Q4	51		Reference		54		Reference	

[a] Quintile 1 represents the lowest socioeconomic status. Data were not available for 6 patients.
[b] The analysis excluded 147 patients for "both" or unstated laterality.

any retrospective cohort study, the observed association between LN yield and survival is vulnerable to confounding by incompletely controlled differences between patient groups. For example, our results suggest inferior outcomes for patients treated with open surgery rather than with laparoscopic surgery. It is highly likely that that observation is itself driven by residual confounding rather than by a true difference in outcome.

Our study population was identified from the OCR and is, therefore, unselected and includes patients of all ages. Because of the work required to manually review surgical pathology reports, our study population consists of a random sample of approximately 25% of all cases treated in Ontario during the study time period. No substantial differences were observed between the randomly selected patients and those not included in the study cohort (Table I). We did not obtain pathology reports for patients who underwent surgery in 2005; we feel that this omission is unlikely to bias our results in any significant way. Finally, our study does not establish whether there is a causal relationship between LN yield and outcome, or whether LN yield is a surrogate for other elements of care or for variation in host–tumour biology.

CONCLUSIONS

In this contemporary population-based study, we found that, despite international guidelines and numerous knowledge translation initiatives, fewer than 12 LNS are resected in one quarter of patients with stages II and III colon cancer. Lymph node yield is associated with age, comorbidity, socioeconomic status, tumour laterality, and hospital volume. Greater LN yield is associated with improved survival in routine clinical practice and is unlikely to be explained by stage migration. Future work should further explore the extent to which this survival benefit is driven by the complex relationship between tumour biology and host response.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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