Received: 9 March 2022 | Accepted: 23 April 2022

DOI: 10.1002/jso.26913

RESEARCH ARTICLE

Journal of SURGICAL ONCOLOGY WILEY

Is increasing nodal count associated with improved recurrence-free and overall survival following standard right hemicolectomy for colon cancer?

Ian P. Hayes MBBS, MS, MEpi, FRCS(Gen-Surg), FR[1,2] | Elasma Milanzi PhD, MBiostats[3,4] | Peter Gibbs MBBS, MD, FRACP[5,6,7] | Ian Faragher FRACS[8] | Jeanette C. Reece PhD, MPH[3,9]

[1]Colorectal Surgery Unit, Royal Melbourne Hospital, Melbourne, Victoria, Australia

[2]Department of Surgery, The University of Melbourne, Melbourne, Victoria, Australia

[3]Neuroepidemiology Unit, Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics, The University of Melbourne, Carlton, Victoria, Australia

[4]Australasian Kidney Trials Network, University of Queensland, Brisbane, Queensland, Australia

[5]Personalised Oncology Division, The Walter and Eliza Hall Institute of Medical Research, Melbourne, Victoria, Australia

[6]Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, Victoria, Australia

[7]Department of Medical Oncology, Western Health, Melbourne, Victoria, Australia

[8]Department of Colorectal Surgery, Western Health, Melbourne, Victoria, Australia

[9]The University of Melbourne Centre for Cancer Research, The University of Melbourne, Melbourne, Victoria, Australia

Correspondence

Jeanette C. Reece, PhD, MPH, Neuroepidemiology Unit, Melbourne School of Population and Global Health, Centre for Epidemiology and Biostatistics, The University of Melbourne, Level 3 207 Bouverie St, Melbourne, VIC 3010, Australia.
Email: jreece@unimelb.edu.au

Abstract

Background and Objectives: Increasing lymph node harvest for right-sided colon cancer is associated with improved overall survival (OS), but most relevant studies failed to report the extent of resection. We examined the association between increasing lymph node count with standard right hemicolectomy according to nodal status and prognostic outcomes in right-sided tumors.

Methods: Retrospective analysis of prospectively collected clinical data from patients with proximal colonic adenocarcinomas ($n = 1390$) following right hemicolectomy. Associations between lymph node counts (0–12 vs. 13–15, 16–20, and >20) and recurrence-free survival (RFS) and OS were examined using multivariate Cox modeling adjusted for confounders.

Results: We found no association between increasing nodal count and RFS, regardless of nodal status. In the absence of nodal metastases, increasing nodal count (16–20 and >20 vs. 0–12 nodes) was associated with 57% (95% confidence interval [CI]: 0.21–0.89) and 52% (95% CI: 0.24–0.95) improved OS, respectively. In the presence of nodal metastases, increasing nodal count was not associated with OS. Adjuvant chemotherapy did not modify this effect.

Conclusion: Increasing nodal count (>15 nodes) with right hemicolectomy was not associated with improved RFS. Improved OS was only found for node-negative tumors, casting some doubt on the benefits of resecting more lymph nodes in the presence of nodal metastases.

KEYWORDS

nodal count, overall survival, proximal colon cancer, recurrence-free survival, right hemicolectomy

1 | INTRODUCTION

Standard treatment for right-sided colon cancer comprises resection of the primary tumor and associated tumor-draining lymph nodes. Previous studies found increasing nodal count is associated with improved recurrence-free survival (RFS),[1–3] and survival outcomes.[2,4–6] Further, two large National Cancer Database studies recently found yields of ≥22[7] and ≥24 nodes,[8] respectively, had the highest overall survival (OS). Similarly, studies have found more extensive surgery for proximal tumors (complete mesocolic excision [CME] with central vascular ligation or extended lymph node dissection [D3 lymphadenectomy]), resulting in higher lymph node yields, is associated with superior prognostic outcomes compared with less extensive surgery (non-CME and D2).[6,7,9–11]

Studies stratifying by nodal status have also found increasing numbers of *negative* nodes harvested were associated with improved RFS,[3,5] disease-specific survival,[12] and OS.[5] A further substudy of 3648 participants enrolled in a multicenter adjuvant trial in Italy by Prandi et al.[2] found increasing numbers of *positive* nodes harvested was not associated with improved disease-free survival or OS using univariate analysis.

However, evidence for the positive association between increasing node yields and improved prognostic outcomes in right-sided colon cancers is compromised due to limitations of previous studies. Several studies, especially those utilizing large national databases, provided little or no information regarding the extent of resection.[2,3,6–8,11] Also statistical shortcomings were often present as potential confounders, including adjuvant chemotherapy use, tumor characteristics, or DNA mismatch repair (MMR) status were not adjusted for in multivariate analyses,[8,12] or only univariate analyses were performed.[2,13] Further, most studies only examined one outcome (survival),[6–8,14,15] with few assessing both recurrence and survival,[2,9] and only a handful of studies examined the status of retrieved nodes.[2,3,5,12]

In the present study, we aimed to clarify the association between increasing nodal count for cecal and ascending colon tumors and prognostic outcomes compared with lower nodal count. The limitations of heterogeneity of surgical resection in prior related studies were overcome by analyzing data following one surgical procedure, standard (D2) right hemicolectomy, using data from a large comprehensive multicentre clinical database. The association between categories of increasing numbers of lymph nodes and two prognostic outcomes, RFS and OS, was examined using multivariate analysis adjusted for confounders, including adjuvant chemotherapy use and tumor characteristics and MMR status. Additionally, we examined associations between increasing nodal count and prognostic outcomes in both the presence and absence of involved nodes. The findings of this study will help clarify the association between the number of lymph nodes harvested and oncological outcomes for right-sided colon cancer following standard right hemicolectomy surgery. The potential oncological effect of increasing nodal count is also relevant to current surgical interest in extended lymphadenectomy.

2 | MATERIALS AND METHODS

2.1 | Data

A retrospective analysis of data from the BioGrid ACCORD clinical colorectal cancer database was conducted.[16] Biogrid comprises prospectively collected data from all colorectal cancer patients admitted to seven tertiary-referral hospitals with specialist colorectal surgery services in Melbourne, Australia (four public, three private) via clinical notes, supported by radiology and histopathology reports. Biogrid was demonstrated to perform well in a validation study.[17] The selected sample satisfied the following inclusion and exclusion criteria; tumor site: ascending colon or cecum; microscopic type: adenocarcinoma; surgery method: laparoscopic or open standard right hemicolectomy (operative title was defined by the title used in clinical notes); time period: between 1990 and 2018; no synchronous or distant metastatic tumor; no preoperative chemotherapy or radiotherapy or postoperative radiotherapy; and no previous history of any cancer. Extended resections including extended right hemicolectomy, subtotal and total colectomy were excluded. Right hemicolectomy, as performed by the contributing surgeons, routinely involved resection of the distal 5 cm ileum and right colon to approximately the junction of proximal and middle third of the transverse colon. The ileocolic pedicle was routinely ligated 1–2 cm distal to the junction of ileocolic and superior mesenteric arteries. High ligation of the middle colic pedicle was not routinely performed. However, resected length of colon, extent of lymphadenectomy, and completeness of mesocolic excision were not recorded in the database. This resulted in a sample size of 1390. Figure 1 shows the selected sample after applying the inclusion and exclusion criteria.

2.2 | Primary outcome

The primary outcome of interest was RFS, defined as the time from right hemicolectomy surgery to first recurrence at any site. Those who had not experienced recurrence at the time the data were extracted, who died or were lost to follow-up before recurrence, were censored. Censoring occurred at either the date of the last recorded visit or the date of death.

2.3 | Secondary outcomes

Secondary outcomes included OS and loco-regional recurrence-free survival (LRRFS). OS was defined as time from surgery to death. Patients were censored if they were still alive at the time of data extraction or were lost to follow-up. For LRRFS, the event of interest was restricted to first recurrence, classified as loco-regional recurrence. Those who experienced other forms of recurrence or did not experience any form of recurrence while under observation were censored on their last observed date.

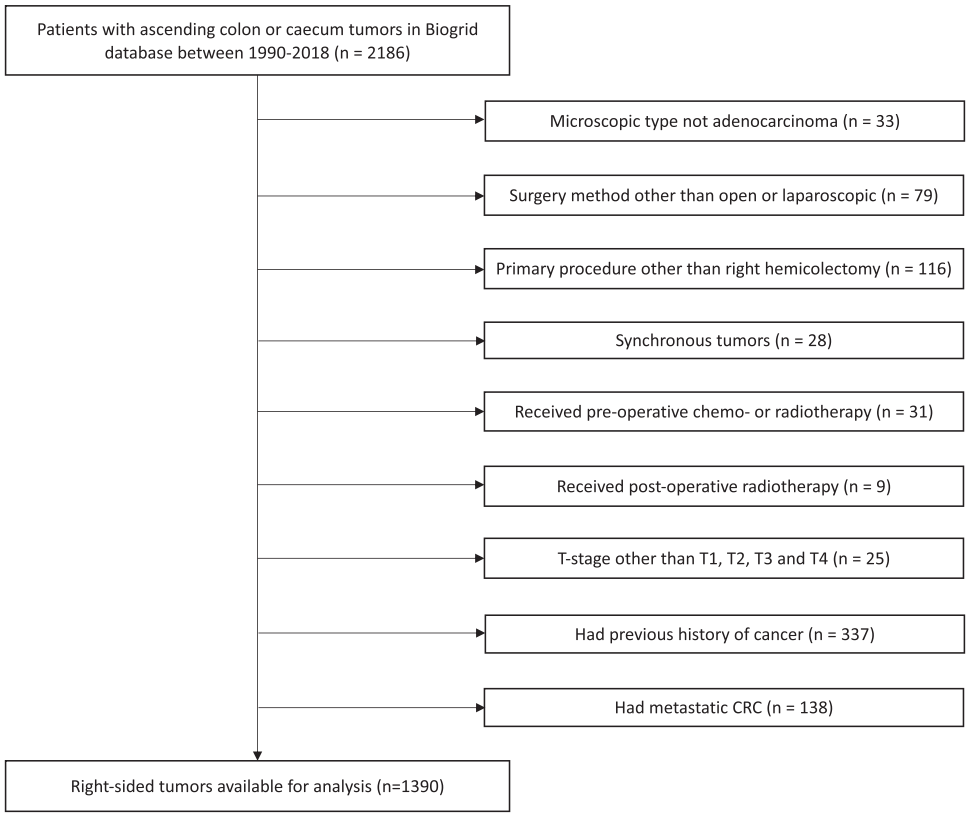

FIGURE 1 Flow chart of patient selection. CRC, colorectal carcinoma.

2.4 | Exposure

The exposure of interest was increasing nodal count (as a categorical variable). Total lymph nodes examined (positive and negative combined) were categorized as 0–12, 13–15, 16–20, and >20 nodal counts. We used 12 resected lymph nodes as the control group in analyses as studies indicate histological evaluation of 12 nodes identifies 90% of positive nodes and the College of American Pathologists Consensus Statement recommends at least 12 nodes be removed for reliable nodal status classification.[18–20] Categories >12 nodes were selected to ensure the relative numbers in each categorical group were comparable and to identify any potential trends in the association between increasing nodal counts and prognostic outcomes.

Covariables (and how they were categorized) are listed in Table 1.

2.5 | Statistical methods

Descriptive statistics (frequencies and percentages) were used to summarize patient and tumor characteristics. Pearson correlation was used to measure the correlation between total number of lymph nodes examined and count of positive nodes. Kaplan Meier (KM) curves based on cumulative incidence were used to visualize survival relationships in unadjusted analyses (recurrence and mortality).

The main analysis for RFS and OS was multivariate Cox proportional hazards (PH) modeling adjusting for potential confounders, consistent with several prior studies examining nodal yields and prognostic outcomes.[1,4,7,8,10,16,21] Results of analyses are reported as hazard ratios (HRs) and 95% confidence intervals (CIs) representing the hazard of tumor recurrence and mortality, respectively. Potential confounders with p values ≤0.15 in univariate modeling were included in multivariate models. The PH assumption of the Cox model was checked using the Schoenfeld residuals test.[22]

We noted that a competing risk approach should be considered when death can prevent observing recurrence. Mortality cumulative incidence for the different levels of the number of lymph nodes examined was assessed (Figure 1) and found to be similar. Therefore, we assumed that any differences in RFS would not be due to differential prevention of observing recurrence due to death.

2.6 | Effect modifiers

Effect modifiers are variables that are assumed to modify the association between the exposure and the outcomes, such that the association varies for different levels of the effect modifiers. Nodal stage (N-stage) was considered an effect modifier in addressing the objective as to whether the relationship between the number of lymph nodes examined and outcomes (RFS and OS) depended on nodal metastases. For meaningful interpretation, N-stage was categorized as N0, N1, and N2 based on the AJCC 8th edition.

TABLE 1 Baseline characteristics of the full data set (patients with right-sided colon cancers who underwent right hemicolectomy between 1990 and 2018) and cumulative 5-year recurrence

		No. of participants		Recurrence				Death				5-year
Covariate	Categories	*n*	%	Yes (*n*)	Yes (%)	No (*n*)	No (%)	Yes (*n*)	Yes (%)	No (*n*)	No (%)	recurrence
No. of lymph nodes examined	0–12	259	20%	57	22	202	78	71	27	188	73	26
	13–15	284	22%	45	16	239	84	56	20	228	80	18
	16–20	334	26%	52	16	282	84	64	19	270	81	18
	>20	423	33%	60	14	363	86	55	13	368	87	17
	Missing	15	15	3	20	12	80	4	27	11	73	NA
N stage	N0	814	62%	61	8	753	93	102	13	712	88	9
	N1	300	23%	72	24	228	76	70	23	230	77	27
	N2	191	15%	84	44	107	56	77	40	114	60	50
	Missing	10	10	0	0	10	100	1	10	9	90	NA
Age	<55	89	9%	20	23	69	78	15	17	74	83	26
	≥55	875	91%	141	16	734	84	170	19	705	81	19%
	Missing	351	351	56	16	295	84	65	19	286	82%	18
Sex	F	672	51%	104	16	568	85	118	18	554	82	18
	M	643	49%	113	18	530	82	132	21	511	80	21
Surgical method	Laparoscopic	902	69%	109	12	793	88	108	12	794	88	13
	Open	413	31%	108	26	305	74	142	34	271	66	30
Year of surgery	1990–1999	66	5%	23	35	43	65	30	46	36	55	39
	2000–2004	110	8%	28	26	82	75	45	41	65	59	27
	2005–2009	259	20%	48	19	211	82	74	29	185	71	20
	2010–2014	434	33%	71	16	363	84	81	19	353	81	17
	≥2015	446	34%	47	11	399	90	20	5	426	96	NA
Type of hospital	Private	337	26%	39	12	298	88	32	10	305	91	13
	Public	978	74%	178	18	800	82	218	22	760	78	21
Admission type	Elective	1125	86%	152	14	973	87	187	17	938	83	15
	Emergency	184	14%	64	35	120	65	63	34	121	66	44
	Missing	6	6	1	17	5	83	0	0	6	100	20
Diabetes	No	979	76%	161	16	818	84	174	18	805	82	19
	Yes	306	24%	55	18	251	82	73	24	233	76	21
	Missing	30	30	1	3	29	97	3	10	27	90	5
ASA comorbidity[a]	<3	799	61%	147	18	652	82	137	17	662	83	21
	3+	516	39%	70	14	446	86	113	22	403	78	15
Adjuvant chemotherapy	No	917	70%	116	13	801	87	169	18	748	82	15
	Yes	398	30%	101	25	297	75	81	20	317	80	27
BMI	Normal/Under weight	743	73%	128	17	615	83	138	19	605	81	19
	Overweight/Obese	279	27%	42	15	237	85	40	14	239	86	16
	Missing	293	293	47	16	246	84	72	25	221	75	21
Margins	Involved	4	0%	2	50	2	50	2	50	2	50	NA
	Not involved	1275	100%	208	16	1067	84	242	19	1033	81	19
	Missing	36	36	7	19	29	81	6	17	30	83	26

TABLE 1 (Continued)

Covariate	Categories	No. of participants		Recurrence				Death				5-year recurrence
		n	%	Yes (*n*)	Yes (%)	No (*n*)	No (%)	Yes (*n*)	Yes (%)	No (*n*)	No (%)	
Tumor characteristics												
Braf	Mutated	61	5%	9	15	52	85	7	12	54	89	15
	Wild type	81	6%	42	52	39	48	19	24	62	77	61
	Not done	1173	89%	166	14	1007	86	224	19	949	81	17
Kras	Mutated	51	4%	47	92	4	8	27	53	24	47	96
	Wild type	39	3%	24	62	15	39	15	39	24	62	64
	Not done	1225	93%	146	12	1079	88	208	17	1017	83	14
Differentiation	Poor	367	28%	82	22	285	78	108	29	259	71	27
	Moderate/well	910	69%	125	14	785	86	135	15	775	85	16
	Not reported	38	3%	10	26	28	74	7	18	31	82	32
DNA mismatch repair status	MSI-H/abnormal IHC	254	19%	15	6	239	94	28	11	226	89	7
	MSI-stable/ normal IHC	625	48%	114	18	511	82	89	14	536	86	20
	Not done	436	33%	88	20	348	80	133	31	303	70	23
Inflammatory infiltrate	Absent	499	38%	87	17	412	83	75	15	424	85	21
	Present	344	26%	37	11	307	89	44	13	300	87	12
	Not reported	472	36%	93	20	379	80	131	28	341	72	22
Lymphovascular invasion	No	805	61%	80	10	725	90	110	14	695	86	11
	Yes	408	31%	122	30	286	70	117	29	291	71	36
	Not reported	102	8%	15	15	87	85	23	23	79	78	18
Mucinous histology	No	618	47%	96	16	522	85	81	13	537	87	18
	Yes	430	33%	70	16	360	84	93	22	337	78	19
	Not reported	267	20%	51	19	216	81	76	29	191	72	21
T-stage	T1	114	9%	5	4	109	96	6	5	108	95	5
	T2	191	15%	9	5	182	95	20	11	171	90	6
	T3	769	59%	106	14	663	86	139	18	630	82	16
	T4	230	18%	97	42	133	58	84	37	146	64	49
	Missing	11	11	0	0	11	100	1	9	10	91	NA

Abbreviations: IHC, immunohistochemistry; MSI-H, microsatellite instability high; NA, not available.

[a]American Society of Anesthesiologists physical status classification system used to assess patient's preanesthesia medical comorbidities.

To assess whether the association between increasing nodal count in patients with N-stage 1–2 and recurrence and OS depended on whether the patient received postoperative adjuvant chemotherapy, a subanalysis was performed where postoperative adjuvant chemotherapy was considered an effect modifier.

2.7 | Potential confounders

To minimize bias in estimating the association between increasing nodal count and outcomes (RFS and OS), we adjusted analyses for potential confounders (Supporting Information: Tables 1 and 2, covariates with p values ≤ 0.15 in univariate modeling).

3 | RESULTS

In all, 1390 patients with right-sided stage 1–3 colon cancer who had right hemicolectomy within the study period were eligible for study inclusion (Figure 1). Patient baseline characteristics and tumor characteristics are shown in Table 1. Over 90% of patients were ≥55 years. Most surgeries were elective (86%), laparoscopic (69%), and performed in

public hospitals (74%). The percentage of patients who had 0–12, 13–15, 16–20, and ≥20 nodes examined was 20%, 22%, 26% and 33%, respectively. In total, 62%, 23%, and 15% were N0, N1, and N2, respectively. There were no involved margins. Five-year cumulative incidence for recurrence was highest for 0–12 nodes at 26%.

The median follow-up time for RFS and OS ranged from 2.1 to 3.0 and 2.3 to 3.5 years, respectively (Supporting Information: Table 3).

Estimated Spearman's correlation between number of nodes harvested and number of positive nodes was 0.11, suggesting that examining a greater number of nodes does not necessarily lead to finding more positive nodes.

3.1 | Lymph nodes examined and RFS

KM plots of unadjusted analyses suggested increasing nodal count was associated with improved RFS (Figure 2A).

In univariate analysis (Supporting Information: Table 1), surgery method (laparoscopic vs. open), tumor differentiation (poor, well, not reported), Kras status (mutated, wild type, not done), Braf status (mutated, wild type, not done), inflammatory infiltrate (absent, present, not reported), DNA MMR status (MSI high or abnormal HC phenotype, MSI stable or normal IHC, not done), lymphovascular invasion (yes, no, not reported), ASA comorbidity category (<3 vs. 3+), N stage (N0, N1, N2), admission type (elective, emergency), hospital type (public vs. private), surgery period (1990–1999, 2000–2004, 2005–2009, 2010–2014, 2015+), and T-stage (T1, T2, T3, T4) had p values ≤ 0.15 and were adjusted for in multivariate analysis.

Multivariate analysis examining the association between the number of nodes examined, with N-stage as an effect modifier and adjusting for confounders, found no clear trend in the relationship of RFS and nodes examined (Table 2). For N0 stage tumors, the hazard of recurrence was reduced by 29% and 24% when >15 nodes were examined compared to examining ≤12 nodes. For N1 stage tumors, examining >12 nodes reduced the hazard of recurrence by at least 35%. On the other hand, for N2 stage tumors, harvesting 16–20 nodes increased the hazard of recurrence by 93% compared to ≤12. However, all p values associated with these analyses were much higher than 0.05, indicating no statistical evidence of an association between increased nodal count and RFS, regardless of nodal stage.

The hazard of recurrence was 3.1 times higher in tumors that were MSI stable or had normal IHC compared to tumors with MSI-high or had abnormal IHC. Increased hazard of recurrence was also found in patients that had lymphovascular invasion, T4 tumors, or emergency surgery. Notably, surgeries performed after 2005 were associated with remarkedly improved recurrence outcomes compared with surgeries between 1990 and 1999.

An additional univariate analysis examining number of nodes harvested and LRRFS found no association between increasing nodes harvested and loco-regional recurrence (Supporting Information: Table 4).

3.2 | Lymph nodes examined and OS

KM plots of unadjusted analyses suggested superior OS with increasing number of nodes examined (Figure 2B). In univariate analysis (Supporting Information: Table 2), the same covariates for

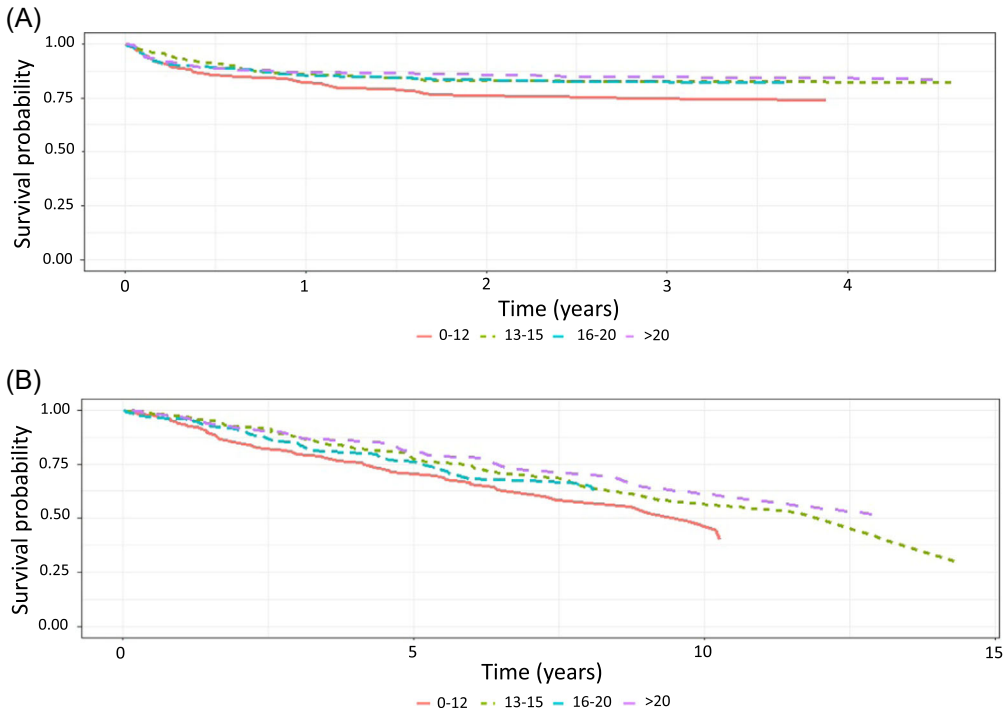

FIGURE 2 Kaplan Meier curves of recurrence (A) and overall survival (B) based on lymph nodes examined using Cox PH regression.

TABLE 2 Multivariate analysis examining number of harvested lymph nodes and recurrence-free survival with N-stage as an effect modifier

Covariate	Category	Nodal status	No. of nodes harvested	Adjusted hazard ratio (95% CI)	*p* value
		N0	≤12	1	
		N0	13–15	1.152 (0.560, 2.369)	0.7
		N0	16–20	0.709 (0.331, 1.518)	0.376
		N0	>20	0.737 (0.357, 1.521)	0.409
		N1	≤12	1	
		N1	13–15	0.652 (0.245, 1.737)	0.783
		N1	16–20	0.543 (0.222, 1.330)	0.338
		N1	>20	0.645 (0.279, 1.491)	0.624
		N2	≤12	1	
		N2	13–15	1.041 (0.402, 2.695)	1
		N2	16–20	1.927 (0.802, 4.628)	0.243
		N2	>20	0.847 (0.342, 2.095)	0.996
ASA comorbidity[a]	<3			1	
	≥3			1.019 (0.745, 1.393)	0.907
Surgery method	Laproscopic			1	
	Open			0.945 (0.641, 1.392)	0.774
Admission type	Elective			1	
	Emergency			1.488 (1.028, 2.155)	0.035**
Hospital type	Private			1	
	Public			1.32 (0.896, 1.945)	0.16
Year of surgery	1990–1999			1	
	2000–2004			0.654 (0.356, 1.203)	0.172
	2005–2009			0.364 (0.193, 0.685)	0.002**
	2010–2014			0.259 (0.125, 0.537)	<0.001**
	≥2015			0.254 (0.117, 0.55)	0.001**
Adjuvant chemotherapy	No			1	
	Yes			0.815 (0.583, 1.139)	0.231
Tumor characteristics					
T-stage	T1			1	
	T2			1.297 (0.393, 4.275)	0.669
	T3			2.501 (0.893, 7.002)	0.081
	T4			5.437 (1.902, 15.542)	0.002**
Differentiation	Not reported			1	
	Poor			0.555 (0.216, 1.424)	0.22
	Moderate/well			0.491 (0.194, 1.24)	0.132
Lymphovascular invasion	No			1	
	Not reported			0.504 (0.244, 1.039)	0.063
	Yes			1.483 (1.048, 2.098)	0.026**
Inflammatory infiltrate	Absent			1	
	Not reported			1.284 (0.914, 1.805)	0.15

(Continues)

TABLE 2 (Continued)

Covariate	Category	Nodal status	No. of nodes harvested	Adjusted hazard ratio (95% CI)	*p* value
	Present			0.809 (0.54, 1.212)	0.303
Braf	Mutated			1	
	Not done			0.84 (0.34, 2.072)	0.705
	Wild-type			0.856 (0.353, 2.075)	0.73
Kras	Mutated			1	
	Not done			0.065 (0.038, 0.113)	<0.001**
	Wild type			0.753 (0.407, 1.394)	0.367
DNA mismatch repair status	MSI high or abnormal IHC			1	
	MSI stable or normal IHC			3.124 (1.625, 6.005)	0.001**
	Not done			1.83 (0.905, 3.703)	0.093

Note: Multivariate analysis adjusted for ASA, surgery method, patient type, hospital type, year of surgery, adjuvant chemotherapy, and tumor characteristics (T-stage, differentiation, lymphovascular invasion, inflammatory infiltrate, Kras, Braf, immune history).

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability.

[a]American Society of Anesthesiologists physical status classification system used to assess patient's preanesthesia medical co-morbidities.

**$p < 0.05$.

recurrence were associated with OS except adjuvant chemotherapy use. Additionally, sex (female, male) and mucinous histology (no, not reported, Yes), BMI (normal/underweight, overweight/obese), and diabetes (no, yes) were included in the multivariate analysis.

Multivariate analysis examining the association between the number of nodes examined, with N-stage as an effect modifier and adjusting for confounders, found for N0 stage tumors, 16–20 and >20 nodes examined was associated with 57% and 52% decreased hazard of death, respectively (Table 3; 95% CI: 0.21%–0.89% and 95% CI: 0.24–0.95, respectively), with evidence of a statistical difference ($p < 0.05$). However, for N1 and N2 stage tumors, there was no evidence of association between increasing nodal count and OS.

Consistent with recurrence, OS was higher in surgeries performed after 2005 compared with surgeries between 1990 and 1999. Stage T4 tumors, emergency procedures, and higher ASA score were associated with reduced OS.

3.3 | Subanalysis with postoperative chemotherapy as an effect modifier

In the subanalysis of patients with nodal metastases (N1, N2) to assess whether the association between increased nodal count and oncological outcomes depended on whether the patient received postoperative adjuvant chemotherapy, multivariate analysis with postoperative adjuvant chemotherapy as an effect modifier found no evidence that increasing nodal count was associated with decreased hazard of recurrence or death (Supporting Information: Tables 5 and 6).

4 | DISCUSSION

The present study aimed to determine whether increased nodal count was associated with improved prognostic outcomes in a large cohort of patients with right-sided colon cancer. To the authors' knowledge this is the first study to investigate the association between nodal count controlling for N-stage following standard right hemicolectomy and examining both recurrence and survival outcomes. In multivariate analysis with N-stage as an effect modifier, we found no evidence of association between increasing nodal count and RFS, regardless of N-stage. However, increasing nodal count (16–20 and >20 nodes) was associated with 57% and 52% improved OS, respectively, compared with 0–12 nodes but only in the absence of involved nodes, with no evidence of a trend between increasing nodal count categories and OS. Therefore, increasing nodal count may only result in marginal clinical benefit in this better prognosis group. In the presence of involved nodes, increasing nodal count was not associated with improved OS.

Previous studies have also found an association between increasing nodes harvested and survival for stage II or III colon cancers. The single-center prospective Norwegian study by Sjo et al.[4] found examining ≥12 nodes versus <8 nodes was associated with improved OS for both stage II and III colon cancer in multivariate analysis. Similarly, Prandi et al.[2] found greater nodal yields (≥7 vs. <7 nodes) in stage II cancers were associated with improved OS in univariate analysis. A large study of T3N0 tumor data from the National Cancer Database by Swanson et al.[1] also found increasing nodes examined (8–12 or ≥13 versus 1–7 nodes) reduced the hazard of recurrence by 19% (95% CI: 0.77–0.84) and 32% (95% CI: 0.65–0.71), respectively, using multivariate analysis. However, these

TABLE 3 Multivariate analysis examining number of harvested lymph nodes and overall survival with N-stage as an effect modifier.

Covariate	Category	Nodal status	No. of nodes harvested	Adjusted hazard ratio (95% CI)	*p* value
		N0	≤12	1	
		N0	13–15	0.817 (0.438, 1.525)	0.526
		N0	16–20	0.429 (0.207, 0.887)	0.023**
		N0	>20	0.48 (0.244, 0.948)	0.034**
		N1	≤12	1	
		N1	13–15	0.569 (0.192, 1.691)	0.636
		N1	16–20	0.536 (0.2, 1.439)	0.422
		N1	>20	0.555 (0.195, 1.575)	0.545
		N2	≤12	1	
		N2	13–15	1.028 (0.312, 3.392)	1
		N2	16–20	1.823 (0.6, 5.541)	0.593
		N2	>20	1.204 (0.395, 3.675)	0.998
Sex	Female			1	
	Male			0.994 (0.715, 1.382)	0.971
ASA comorbidity[a]	<3			1	
	≥3			1.961 (1.404, 2.74)	<0.001**
BMI	Normal/underweight			1	
	Overweight/obese			0.81 (0.554, 1.186)	0.279
Diabetes	No			1	
	Yes			1.399 (0.987, 1.983)	0.059
Surgery method	Laproscopic			1	
	Open			0.902 (0.591, 1.375)	0.631
Admission type	Elective			1	
	Emergency			1.887 (1.201, 2.963)	0.006**
Hospital type	Private			1	
	Public			1.399 (0.84, 2.331)	0.198
Year of surgery	1990–1999			1	
	2000–2004			0.83 (0.35, 1.967)	0.673
	2005–2009			0.547 (0.229, 1.307)	0.175
	2010–2014			0.556 (0.215, 1.441)	0.227
	≥2015			0.369 (0.126, 1.084)	0.07
Tumor characteristics					
T-stage	T1			1	
	T2			0.706 (0.253, 1.966)	0.505
	T3			1.705 (0.715, 4.067)	0.229
	T4			3.37 (1.353, 8.39)	0.009**
Differentiation	Not reported			1	
	Poor			0.917 (0.269, 3.129)	0.891
	Moderate/well			0.575 (0.167, 1.972)	0.379
Lymphovascular invasion	No			1	

(Continues)

TABLE 3 (Continued)

Covariate	Category	Nodal status	No. of nodes harvested	Adjusted hazard ratio (95% CI)	*p* value
	Not reported			0.837 (0.368, 1.908)	0.673
	Yes			1.097 (0.751, 1.602)	0.632
Inflammatory infiltrate	Absent			1	
	Not reported			1.737 (1.162, 2.595)	0.007**
	Present			0.906 (0.572, 1.433)	0.672
Braf	Mutated			1	
	Not done			0.793 (0.297, 2.115)	0.643
	Wild-type			0.81 (0.28, 2.347)	0.698
Kras	Mutated			1	
	Not done			0.31 (0.156, 0.613)	0.001**
	Wild type			0.884 (0.384, 2.032)	0.771
DNA mismatch repair status	MSI high or abnormal IHC			1	
	MSI stable or normal IHC			1.169 (0.645, 2.119)	0.606
	Not done			1.433 (0.77, 2.669)	0.256
Mucinous histology	No			1	
	Not reported			0.804 (0.498, 1.299)	0.373
	Yes			0.974 (0.663, 1.432)	0.894

Note: Multivariate analysis adjusted for sex, ASA, BMI, diabetes, surgery method, hospital type, patient type, year of surgery, and tumor characteristics (T-stage, differentiation, lymphovascular invasion, inflammatory infiltrate, Kras, Braf, immune history, mucinous).

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability.

[a]American Society of Anesthesiologists physical status classification system used to assess patient's preanesthesia medical comorbidities.

**$p < 0.05$.

studies did not control for nodal status and/or information regarding the type of surgical procedure performed was not specified.[1,2,4]

Studies that stratified for nodal status found there was an association between increasing yields of negative nodes and improved survival but these studies were also limited due to the limited details on surgical procedures provided.[5,12] The large study of stage III colon cancer data from the US SEER data set by Johnson et al. found ≥13 negative nodes were associated with improved disease-specific survival after controlling for the number of positive nodes; however, adjuvant chemotherapy data were not included in multivariate analyses.[12] Similarly, Le Voyer et al.[5] found increasing negative node yields were associated with improved RFS and OS in stage II and III patients in multivariate analysis, after controlling for the number of positive nodes,[5] consistent with the study by Zafar et al.[3] where negative node yields (≥12 versus <12) were associated with less recurrence in multivariate analysis (hazard ratio = 0.98; 95% CI: 0.97–0.99).[3]

Notably, we did not subcategorize nodal count beyond >20 so were unable to determine whether there was a threshold nodal count above which outcomes plateaued, a concept demonstrated by two recent National Cancer Database studies. In these studies, Trepanier et al.[8] found survival outcomes plateaued at 24 nodes and harvesting ≥24 nodes did not improve survival, with Lee et al. reporting >22 node yields had the highest OS (HR = 0.71; 95% CI: 0.68–0.75). When taking into account nodal status, Del Paggio et al.[15] found improved survival outcomes (and the ability to identify positive nodes) plateaued after examining 12-14 negative nodes, whereas Renshaw et al.[23] found the majority of positive nodes were identified in yields ≤40 nodes, with >40 nodes yields only increasing the ability to identify further positive nodes by <1% (1/378 cases).

While we found no association between increasing nodes and improved prognostic outcomes in the presence of positive nodes, these findings support emerging evidence that the process of lymph node metastases represents a complex process where nodal metastases may not necessarily be the precursors of distant metastases.[24] Although the metastatic process is thought to occur early via lymphatic and vascular systems, a recent study by Naxerova et al.[25] examined the genetic origins of lymphatic and distant colorectal carcinoma metastases and found in only 35% of cases, nodal and distant metastases had the same subclonal origin as the primary tumor. That is, two-thirds of distant metastases had a different subclonal origin to the primary tumor, indicating distant metastases arose via a mechanism independent of nodal metastases.[26] Consequently, resection of higher yields of metastatic nodes may not result in less recurrence or improved survival outcomes.

Lymph node metastases have important implications for prognosis,[19] and for determining whether a patient will have postoperative

adjuvant chemotherapy.[27] However, the potential for postoperative adjuvant chemotherapy to influence prognostic outcomes in our study findings was overcome by performing multivariate subanalyses of tumors with positive lymph nodes and RFS and OS with adjuvant chemotherapy use as an effect modifier.

Of note, nodal count does not always relate to the extent of surgery performed. While we restricted our analysis to patients undergoing standard right hemicolectomy to limit heterogeneity of extent of surgical resection, there may have been cases where more extensive/careful resection or more extended lymphadenectomy was performed that were not captured in the Biogrid database. However, examining the association between nodal yields and prognostic outcomes in the present study is an important starting premise to justify the current interest in more extensive lymphadenectomy, with the results of our subgroup analysis finding no evidence of an association between increasing nodal counts and either local-regional or distant recurrence.

While younger age is related to the presence of more nodes,[15] we adjusted for age in multivariate analyses. Increased nodal count may be impacted by greater diligence by the pathologist:[28] confounding factors we could not adjust for. A higher nodal count may also reflect a stronger immune response,[15] which could lead to improved outcomes. Further, a higher nodal count could be a surrogate measure of quality in a healthcare system where the outcome gains are system based rather than directly related to the nodal resection. However, this was unlikely to be a factor in the present study as all data were abstracted from tertiary-referral hospitals with specialist colorectal surgery services, and no differences in outcomes were found between private and public hospitals.

Strengths of the present study include a large study size and robust multivariate survival methodology, consistent with methods employed by previous studies examining the association between nodal yields and prognostic outcomes.[1,4,7,8,10,16,21] Further, the Biogrid database contains prospectively collected data on several clinical variables including surgery type and date, exact tumor location, tumor characteristics, precise adjuvant chemotherapy regimens (type, dose, and timing), and outcomes (recurrence and mortality), data often not available in studies of data from large national cancer databases. This comprehensive data also allowed several relevant confounders to be adjusted for in multivariate analyses.

5 | CONCLUSIONS

We found no evidence that increasing nodal count (>12 nodes) was associated with improved RFS in patients having right hemicolectomy for cecal and ascending colon cancer. Nodal count >15 was associated with improved OS for patients without nodal metastases, but no evidence of improved OS was found for those with nodal metastases. This suggests resecting greater numbers of lymph nodes may not improve oncological outcomes in right colon cancer and resecting more nodes may only result in marginal clinical benefit in the group of patients already aligned with a better prognosis (i.e., no nodal metastases). These findings are relevant in the context of current interest in the utility of extended lymphadenectomy for colon cancer with the results of forthcoming randomized controlled trials comparing standard resection with extended lymphadenectomy awaited with interest.

AUTHOR CONTRIBUTIONS

Ian P. Hayes, Elasma Milanzi, and Jeanette C. Reece were responsible for the concept and study design and for writing the report. Ian P. Hayes, Elasma Milanzi, Peter Gibbs, and Jeanette C. Reece were responsible for the interpretation of the results. Elasma Milanzi was responsible for the statistical analysis. Ian P. Hayes, Elasma Milanzi, Peter Gibbs, Ian Faragher, and Jeanette C. Reece were responsible for intellectual content and approving the final draft of the manuscript.

ACKNOWLEDGMENTS

We would like to acknowledge Biogrid Australia for providing the data for this study. Open access publishing facilitated by The University of Melbourne, as part of the Wiley – The University of Melbourne agreement via the Council of Australian University Librarians

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY

The reidentifiable data used in the study are derived from Biogrid Australia https://www.biogrid.org.au/. Biogrid has not verified and is not responsible for the statistical methodology employed, or the conclusions drawn by the investigators using these data.

ETHICS STATEMENT

Biogrid data were collected from patients' clinical notes, supported by radiology and histopathology reports. Study ethics approval was obtained from Melbourne Health/Biogrid HREC, no. BG-201905/8. This study was performed in accordance with the Declaration of Helsinki.

ORCID

Elasma Milanzi https://orcid.org/0000-0003-1164-2298
Peter Gibbs https://orcid.org/0000-0003-1423-4484
Jeanette C. Reece https://orcid.org/0000-0003-2897-0271

REFERENCES

1. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol*. 2003;10(1):65-71.
2. Prandi M, Lionetto R, Bini A, et al. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: results of a secondary analysis of a large scale adjuvant trial. *Ann Surg*. 2002;235(4):458-463.

3. Zafar SN, Hu CY, Snyder RA, et al. Predicting risk of recurrence after colorectal cancer surgery in the United States: an analysis of a special commission on cancer national study. *Ann Surg Oncol*. 2020; 27(8):2740-2749.
4. Sjo OH, Merok MA, Svindland A, Nesbakken A. Prognostic impact of lymph node harvest and lymph node ratio in patients with colon cancer. *Dis Colon Rectum*. 2012;55(3):307-315.
5. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol*. 2003; 21(15):2912-2919.
6. Chen SL, Bilchik AJ. More extensive nodal dissection improves survival for stages I to III of colon cancer: a population-based study. *Ann Surg*. 2006;244(4):602-610.
7. Lee L, Erkan A, Alhassan N, et al. Lower survival after right-sided versus left-sided colon cancers: is an extended lymphadenectomy the answer? *Surg Oncol*. 2018;27(3):449-455.
8. Trepanier M, Erkan A, Kouyoumdjian A, et al. Examining the relationship between lymph node harvest and survival in patients undergoing colectomy for colon adenocarcinoma. *Surgery*. 2019; 166(4):639-647.
9. Kotake K, Mizuguchi T, Moritani K, et al. Impact of D3 lymph node dissection on survival for patients with T3 and T4 colon cancer. *Int J Colorectal Dis*. 2014;29(7):847-852.
10. Galizia G, Lieto E, De Vita F, et al. Is complete mesocolic excision with central vascular ligation safe and effective in the surgical treatment of right-sided colon cancers? A prospective study. *Int J Colorectal Dis*. 2014;29(1):89-97.
11. West NP, Hohenberger W, Weber K, Perrakis A, Finan PJ, Quirke P. Complete mesocolic excision with central vascular ligation produces an oncologically superior specimen compared with standard surgery for carcinoma of the colon. *J Clin Oncol*. 2010;28(2):272-278.
12. Johnson PM, Porter GA, Ricciardi R, Baxter NN. Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol*. 2006; 24(22):3570-3575.
13. Ouyang M, Luo Z, Wu J, et al. Comparison of outcomes of complete mesocolic excision with conventional radical resection performed by laparoscopic approach for right colon cancer. *Cancer Manag Res*. 2019;11:8647-8656.
14. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007;99(6):433-441.
15. Del Paggio JC, Peng Y, Wei X, et al. Population-based study to re-evaluate optimal lymph node yield in colonic cancer. *Br J Surg*. 2017; 104(8):1087-1096.
16. Bertelsen CA, Neuenschwander AU, Jansen JE, et al. 5-year outcome after complete mesocolic excision for right-sided colon cancer: a population-based cohort study. *Lancet Oncol*. 2019;20(11): 1556-1565.
17. Field K, Kosmider S, Johns J, et al. Linking data from hospital and cancer registry databases: should this be standard practice? *Intern Med J*. 2010;40(8):566-573.
18. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Colon Cancer, Rectal Cancer*. Version 1. 2014.
19. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*. 2000;124(7):979-994.
20. Nelson H, Petrelli N, Carlin A, et al., National Cancer Institute Expert Panel. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001;93(8):583-596.
21. Balciscueta Z, Balciscueta I, Uribe N, et al. D3-lymphadenectomy enhances oncological clearance in patients with right colon cancer. Results of a meta-analysis. *Eur J Surg Oncol*. 2021;47(7):1541-1551.
22. Pettitt AN, Bin Daud I. Investigating time dependence in Cox's proportional hazards model. *Appl Stat*. 1990;39:313-329.
23. Renshaw AA, Gould EW. How many lymph nodes are enough in a colorectal resection? *Am J Surg Pathol*. 2020;44(9):1290-1292.
24. Sleeman JP, Cady B, Pantel K. The connectivity of lymphogenous and hematogenous tumor cell dissemination: biological insights and clinical implications. *Clin Exp Metastasis*. 2012;29(7):737-746.
25. Naxerova K, Reiter JG, Brachtel E, et al. Origins of lymphatic and distant metastases in human colorectal cancer. *Science*. 2017; 357(6346):55-60.
26. Cady B. Lymph node metastases. Indicators, but not governors of survival. *Arch Surg*. 1984;119(9):1067-1072.
27. Chau I, Cunningham D. Adjuvant therapy in colon cancer--what, when and how? *Ann Oncol*. 2006;17(9):1347-1359.
28. Field K, Platell C, Rieger N, et al. Lymph node yield following colorectal cancer surgery. *ANZ J Surg*. 2011;81(4):266-271.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Hayes IP, Milanzi E, Gibbs P, Faragher I, Reece JC. Is increasing nodal count associated with improved recurrence-free and overall survival following standard right hemicolectomy for colon cancer? *J Surg Oncol*. 2022;126:523-534. doi:10.1002/jso.26913