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

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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) and survival outcomes. Further, two national cancer database studies recently found yields of ≥22 and ≥24 nodes, 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 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. 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, or only univariate analyses were performed. Further, most studies only examined one outcome (survival) with few assessing both recurrence and survival, and only a handful of studies examined the status of retrieved nodes.

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 surgery 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. 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. 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.
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. 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.

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. 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.

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.

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

| Covariate                        | Categories | No. of participants | Recurrence                      | Death                         |
|----------------------------------|------------|---------------------|---------------------------------|-------------------------------|
|                                  |            | n | % | Yes (n) | Yes (%) | No (n) | No (%) | Yes (n) | Yes (%) | No (n) | No (%) | 5-year 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 | 35% | 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 | 29% | 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 |
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
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 at least 35%. On the other hand, for N2 stage tumors, harvesting 16–20 nodes increased the hazard of recurrence by at least 35%. 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 remarkably 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](image-url)  Kaplan Meier curves of recurrence (A) and overall survival (B) based on lymph nodes examined using Cox PH regression.
| 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 comorbiditya   | <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 | 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)
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. 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. 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. 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
| Covariate | Category | Nodal status | No. of nodes harvested | Adjusted hazard ratio (95% CI) | p value |
|-----------|----------|--------------|------------------------|-------------------------------|---------|
| Sex       | Female   |              | 1                      |                               |         |
|           | Male     |              | 0.994 (0.715, 1.382)   | 0.971                         |         |
| ASA comorbidity | <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 | 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)
studies did not control for nodal status and/or information regarding the type of surgical procedure performed was not specified.\textsuperscript{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.\textsuperscript{5,12} The large study of stage III colon cancer data from the US SEER data by John et al. found \( \geq 13 \) 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.\textsuperscript{12} Similarly, Le Voyer et al.\textsuperscript{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,\textsuperscript{5} consistent with the study by Zafar et al.\textsuperscript{3} where negative node yields (\( \geq 12 \) versus <12) were associated with less recurrence in multivariate analysis (hazard ratio = 0.98; 95% CI: 0.97–0.99).\textsuperscript{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, Trepnier et al.\textsuperscript{8} found survival outcomes plateaued at 24 nodes and harvesting \( \geq 24 \) 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.\textsuperscript{15} found improved survival outcomes (and the ability to identify positive nodes) plateaued after examining 12–14 negative nodes, whereas Renshaw et al.\textsuperscript{23} found the majority of positive nodes were identified in yields \( \leq 40 \) 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.\textsuperscript{24} Although the metastatic process is thought to occur early via lymphatic and vascular systems, a recent study by Naxerova et al.\textsuperscript{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.\textsuperscript{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,\textsuperscript{19} and for determining whether a patient will have postoperative

| 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.

\( *\)American Society of Anesthesiologists physical status classification system used to assess patient's preanesthesia medical comorbidities.

\( **\)\( p < 0.05.\)
resecting more nodes may only result in marginal clinical benefit in metastases. This suggests resecting greater numbers of lymph nodes but no evidence of improved OS was found for those with 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.

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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.

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

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