The American Journal of Surgery 218 (2019) 113–118

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Predictors of adequate lymph node harvest during colectomy for colon cancer☆

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ARTICLE INFO

Article history:
Received 6 April 2018
Received in revised form
17 June 2018
Accepted 26 August 2018

Meeting Presentation: This abstract was a poster presentation at the meeting of The American Society of Colon and Rectal Surgeons, Seattle, WA, June 10–14, 2017

Keywords:
Colon cancer
Surgical quality
Outcomes
Lymph node harvest
Colectomy

ABSTRACT

Background: Consensus guidelines recommend a yield of 12 lymph nodes in resections for colon cancer. Factors affecting this yield are not well defined.
Methods: Retrospective study using the colectomy-targeted American College of Surgeons National Surgical Quality Improvement Program for years 2014–2016. Primary outcome was resection of at least 12 nodes. Univariate and multivariate analyses determined factors associated with ≥12 LN yield.
Results: 17,612 colectomies for colon cancer were extracted from the NSQIP database. 7.26% of cases did not reach a 12 LN harvest. Harvesting ≥12 LN was 74% more likely ($p = 0.001$) if the resection was laparoscopic and 72% more likely ($p < 0.0001$) if hand-assisted. Advanced T and N stage had a higher likelihood of reaching 12 LN harvest. Older age, female gender and smoking history decreased the likelihood of ≥12 LN harvest.
Conclusions: Laparoscopic and robotic colectomies were 1.5–2.5 times more likely to achieve adequate LN harvest compared to open surgery. Several non-modifiable patient and disease related factors may render adequate LN yield challenging.

Introduction

With the implementation of quality driven initiatives such as the Center for Medicare and Medicaid Services' (CMS) pay for performance strategies,[1] discussions involving surgical quality have become more prevalent. The search for appropriate metrics to objectively evaluate surgical quality becomes a challenging but crucial element in the equation.

Colorectal surgery as a field has been well involved in the field of quality improvement, as exemplified by many national and global initiatives such as those aimed at decreasing surgical site infections, developing enhanced recovery protocols, improving rectal cancer care, amongst others.[2–6]

When performing oncologic resections for colorectal cancer, the adequacy of lymph node (LN) harvest has been used as a prognostic tool, associated with survival, as well as a tool that guides treatment and the necessity for adjuvant chemotherapy.[7,8] Furthermore, LN harvest has also been evaluated as an important metric to assess quality in colorectal resections for cancer.[9,10] Most consensus guidelines, such as those issued by the National Cancer Institute (NCI) and American Joint Committee of Cancer (AJCC) agree that the harvest of at least 12 lymph nodes is required for proper staging of colorectal cancer and has become standard of care.[11–14]

Factors affecting LN yield in colectomies have been studied, but research is limited to institutional experiences.[15,16] Further, there is scarce data on the effect of surgical approach on LN yield. Using the multi-institutional, national database ACS-NSQIP, we explore factors that influence LN yield in colectomies for colon cancer, including surgical approach.

☆ All three authors were involved in the design, acquisition, analysis, and interpretation of the data, as well as the writing and revisions of the manuscript and its tables.

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https://doi.org/10.1016/j.amjsurg.2018.08.020
0002-9610/

Methods

Data source

We used the 2014–2016 American College of Surgeons National Surgical Quality & Safety Improvement Program (NSQIP) procedure targeted Participant Use Data File (PUF). The NSQIP colectomy targeted PUF provides patient-level data from over 250 participating sites for investigators studying the safety and quality of surgical care.[17] The ACS NSQIP includes over 150 variables, including preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes for major surgical procedures, both inpatient and outpatient.[18]

Patient population

Using the colectomy-targeted PUF, we identified 32,576 patients who underwent colon resection for an indication of colon cancer between 2014 and 2016, as 2014 was the first year when lymph node data were reported by NSQIP. Patients undergoing emergent resection (n = 1136), those without lymph node data (n = 1020), those receiving adjuvant chemotherapy (n = 2325), and T0 patients (n = 883) were excluded.

We included several patient characteristics in our analysis. Demographic variables included age (≤49, 50–64, ≥65, categorized similar to prior studies[19,20]), sex, and race (categorized as white, black, Asian, and other). Clinical measures included body mass index, BMI (classified as normal if 18.5 to less than 25 kg/m^2, underweight if less than 18.5 kg/m^2, overweight if 25 to less than 30 kg/m^2, and obese if 30 kg/m^2 and greater), American Society of Anesthesiologists (ASA) class categorized between 1 and 5, and several pre-operative conditions. Preoperative conditions were all dichotomized, based on the presence or absences of the condition: pre-operative steroid use, smoking history, diabetes, congestive heart failure, chronic obstructive lung disease, hypertension, dialysis, chemotherapy received within 90 days, and greater than 10% weight loss in the last six months.

The following cancer characteristics were also considered in the study: T stage (categorized as T1, T2, T3, T4, except T0 which was excluded), N stage (categorized as N0, N1, N2), and location of malignancy based on post-operative *International Classification of Diseases* (ICD)*, Ninth* and *Tenth Revisions,* diagnoses and *Current Procedural Terminology* (CPT) codes. Right-sided colon cancers were identified using ICD-9 codes 153.0, 153.4, 153.5, 153.6; ICD-10 codes C18.0, C18.1, C18.2, C18.3; and CPT codes 44160, 44205. Left-sided colon cancers were identified using ICD-9 codes 153.2, 153.3, 153.7; ICD-10 codes C18.5, C18.6, C18.7; and CPT codes 44143, 44145, 44146, 44147, 44206, 44207, 44208. Transverse colon cancers were identified using the ICD-9 code 153.1 and the ICD-10 code C18.4. We also considered surgical approach in the analysis, which is directly reported in the colectomy-targeted database: open, laparoscopic, laparoscopic with hand-assist, laparoscopic with conversion to open, robotic, robotic with conversion to open, and single incision laparoscopic surgery (SILS).

The final analytic cohort excluding patients with missing data was 17,612.

Outcome definition

Our primary outcome was adequate lymph node resection, defined as resection of at least 12 nodes, based on consensus guidelines from the National Comprehensive Cancer Network.[11–14]

Statistical analysis

We investigated the unadjusted association of adequate lymph node resection with patient and cancer characteristics, as well as surgical approach, using Pearson's χ^2 for categorical variables. We used analysis of variance (ANOVA) to test the difference in mean lymph nodes resected by surgical approach and location. We used multivariate logistic regression to determine the association of surgical approach with adequate lymph node resection, controlling for patient and cancer characteristics. Likelihood ratio tests were used to determine statistical evidence for interaction between approach and location. Data were analyzed used STATA IC 12.1.

Results

Characteristics of patient, tumor and surgical approach (Table 1)

17, 612 patients who had undergone resection for colon cancer were extracted from the NSQIP data base. 92.74% of the patient population had ≥12 LN harvested, while 7.26% of the population did not reach this benchmark. Younger, lower ASA, and male patients were more likely to reach a ≥12 LN harvest, while race and BMI class did not have a significant association.

HTN, CHF and CKD on dialysis, were associated with a lower likelihood of adequate lymph node harvest, while a >10% weight loss before surgery trended towards better harvest. Preoperative steroid use did not have a significant effect.

Right-sided cancers were more likely to achieve 12 or more lymph nodes when compared to left-sided and transverse tumors. More advanced tumors, with higher T and N stages correlated significantly with ≥12 LN harvest.

The dataset also demonstrates that nationally, 23.13% of colon resections are done in an open approach, 29.73% are done laparoscopically, 29.51% are hand-assisted laparoscopic resections, and 9.71% of cases are done robotically. All minimally invasive approaches were more likely to achieve 12 lymph nodes when compared to an open approach.

Mean lymph node harvest (Table 2)

For patients who did not reach the quality benchmark, the mean LN harvested was 7.68, while those attaining the metric had a mean of 22.99 LN harvested ($p < 0.001$). Interestingly, the mean number of LN harvested did not correlate with the surgical approaches used ($p = 0.29$). However, tumor location, did affect mean LN harvest, with the highest mean (22.78) being for right sided tumors.

Tumor location and surgical approach (Table 3)

Based on the dataset, tumor location did influence the surgical approach used $p < 0.0001$. Most right sided tumors were resected laparoscopically, while transverse and left sided tumors trended towards laparoscopic assist. Of note, a higher percentage of left sided tumors were resected robotically compared to right and transverse tumors.

Multivariate logistic regression model (Table 4)

When applying the variables into a regression model, females were less likely to have a ≥12 LN harvest, OR = 0.87 ($p = 0.024$).

Using open resection as the reference surgical approach, harvesting ≥12 LN was 74% more likely ($p = 0.001$) if the resection was carried laparoscopically and 72% more likely ($p < 0.0001$) if the resection was carried in a laparoscopic assisted fashion. Of note

Table 1
Characteristics of patient, tumor and surgical approach.

	Total n (%)	<12 lymph nodes n (%)	≥12 lymph nodes n (%)	p value
Total cases	17, 612 (100)	1, 279 (7.26)	16, 333 (92.74)	
Age				
<50	1, 769 (10.04)	84 (6.57)	1, 685 (10.32)	P < 0.0001
50–64	5, 562 (31.58)	414 (32.37)	5, 148 (31.52)	
65–79	6, 899 (39.17)	504 (39.41)	6, 395 (39.15)	
>79	3, 382 (19.20)	277 (21.66)	3, 105 (19.01)	
Gender				0.022
Male	8, 821 (50.09)	680 (53.17)	8, 141 (49.84)	
Female	8, 791 (49.91)	599 (46.83)	8, 192 (50.16)	
Race				0.176
White	14, 572 (82.74)	1, 065 (83.27)	13, 507 (82.70)	
Black	2, 038 (11.57)	158 (12.35)	1, 880 (11.51)	
Asian	875 (4.97)	49 (3.83)	826 (5.06)	
Other	127 (0.72)	7 (0.55)	120 (0.73)	
BMI Class				0.563
Normal	4, 494 (25.52)	305 (23.85)	4, 189 (25.65)	
Underweight	19 (1.49)	239 (1.46)	258 (1.46)	
Overweight	5, 913 (33.57)	437 (34. 17)	5, 476 (33.53)	
Obese	6, 947 (39.44)	518 (40.50)	6, 429 (39.36)	
ASA Class				P < 0.0001
ASA Class 1	263 (1.49)	13 (1.02)	250 (1.53)	
ASA Class 2	6, 278 (35.65)	378 (29.55)	5, 900 (36.12)	
ASA Class 3	9, 988 (56.71)	798 (62.39)	9, 190 (56.27)	
ASA Class 4	1, 083 (6.15)	90 (7.04)	993 (6.08)	
Preoperative Conditions				
Preoperative Steroid use	528 (3.00)	45 (3.52)	483 (2.96)	0.257
Smoking history	2, 150 (12.21)	17 (13.84)	1, 973 (12.08)	0.064
Diabetes	3, 606 (20.47)	262 (20.48)	3, 344 (20.47)	0.993
CHF	282 (1.60)	30 (2.35)	252 (1.54)	0.028
COPD	985 (5.59)	85 (6.65)	900 (5.51)	0.089
HTN	9, 890 (56.15)	763 (59.66)	9, 127 (55.88)	0.009
Dialysis	113 (0.64)	14 (1.09)	99 (0.61)	0.035
>10% weight loss	870 (4.94)	45 (3.52)	825 (5.05)	0.015
Location				<0.0001
Right	9, 219 (52.34)	444 (34.71)	8, 775 (53.73)	
Left	7, 377 (41.89)	724 (56.61)	6, 653 (40.73)	
Transverse	1, 016 (5.77)	111 (8.68)	905 (5.54)	
T stage				p < 0.0001
T1	2, 313 (13.13)	294 (22.99)	2, 019 (12.36)	
T2	3, 258 (18.50)	265 (20.72)	2, 993 (18.32)	
T3	9, 283 (52.71)	537 (41.99)	8, 746 (53.55)	
T4	2, 758 (15.66)	183 (14.31)	2, 575 (15.77)	
N stage				p < 0.0001
N0	10, 517 (59.71)	807 (63.10)	9, 710 (59.45)	
N1	4, 733 (26.87)	359 (28.07)	4, 374 (26.78)	
N2	2, 362 (13.41)	113 (8.84)	2, 249 (13.77)	
Approach				p < 0.0001
Open	4, 073 (23.13)	399 (31.20)	3, 674 (22.94)	
Laparoscopic	5, 236 (29.73)	327 (25.57)	4, 909 (30.06)	
Laparoscopic with assist	5, 198 (29.51)	326 (25.49)	4, 872 (29.83)	
Laparoscopic with conversion to open	1, 242 (7.05)	95 (7.43)	1, 147 (7.02)	
Robotic	1, 711 (9.71)	126 (9.85)	1, 585 (9.70)	
Robotic with conversion to open	94 (0.53)	4 (0.31)	90 (0.55)	
SILS	58 (0.33)	2 (0.16)	56 (0.34)	

robotic resections 1.48 times more likely to reach ≥12 LN compared to open ($p < 0.0001$).

Furthermore, left sided and transverse tumors were 41% and 55% less likely to attain ≥12 LN than right sided resection, respectively ($p < 0.0001$).

Advanced tumor burden maintained its effect on LN harvest; compared to T1 tumor, T3 tumors and T4 tumors were 2.59 and 2.32 times more likely respectively to reach the ≥12 LN benchmark ($p > 0.001$). Furthermore, compared to N0 disease, N2 disease was 1.28 times more likely to harvest ≥12 LN ($p = 0.024$).

Some preoperative conditions also influenced LN harvest; smoking history decreased the likelihood of ≥12 LN, OR = 0.75 ($p = 0.031$) while interestingly, > 10% weight loss preoperatively increased the likelihood of ≥12 LN harvest by 47% ($p = 0.012$).

Discussion

Adequate lymphadenectomy remains a fundamental surgical principle in the resection for colon cancer; it influences prognosis and guides further treatment. With many national and international efforts encouraging a more quality conscious surgical mindset, the search for appropriate metrics to evaluate surgical quality, such as quality of colon resections for colon cancer, becomes crucial. LN harvest is an objective quantifiable marker that can serve such a task. Nevertheless, several factors, including patient, disease and technique specific, may influence this outcome. This study is a multi-institutional database study that identifies important factors that influence LN harvest, in hopes to better understand the variations that affect this metric. The harvest of ≥12

Table 2
Mean lymph nodes harvest.

	Mean lymph nodes	SD	
Adequacy of lymph nodes			p < 0.0001
<12 Lymph nodes	7.68	2.99	
>12 lymph nodes	22.99	10.71	
Approach			0.29
Open	21.61	11.62	
Laparoscopic	22.04	11.01	
Laparoscopic with assist	21.73	10.50	
Laparoscopic with conversion to open	22.13	11.75	
Robotic	22.26	11.22	
Robotic with conversion to open	22.48	12.70	
SILS	22.00	8.36	
Location			p < 0.0001
Right	22.87	10.97	
Left	20.76	10.76	
Transverse	20.94	13.33	

LN, agreed by general consensus and current guidelines, is considered to satisfy the quality benchmark.[11–14]

Reassuringly, we found that most patients (92.74%) had 12 LN harvested at time of resection. This reflects a growing understanding of the importance of this metric as an essential principle of oncologic resection for colon cancer, with efforts led by both surgeons performing the colectomies and pathologist evaluating the surgical specimen. However, 7.26% of patients did not reach this benchmark, having a mean of only 7.68 LN harvested. This has important implications as some organizations such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) recommend adjuvant chemotherapy to patients for whom the LN study proved insufficient.[14,21] This means that a subset of patients, who might actually be node negative, might end up unnecessarily receiving adjuvant chemotherapy due to inadequate lymph node harvest at the time of their surgery. The harvest of <12 LN is also an independent risk factor associated with decreased survival.[7]

As supported by literature,[22–24] our findings also show that the mean number of lymph nodes did not differ based on approach of the resection, whether it was done open, laparoscopic, or robotically. However, when compared to open surgery, all minimally invasive approaches had a significantly higher likelihood of achieving $\geq$12 LN, but there was no significant variation between different minimally invasive techniques. Conversion to open surgery was not associated with a decrease in LN harvest. Laparoscopic and robotic colectomies were 30–150% more likely to achieve adequate LN harvest of $\geq$12 LN compared to open surgery, while still accounting for patient and disease related factors in our regression model. The fact that laparoscopic and robotic approaches improved likelihood of $\geq$12 LN harvest, but not the mean LN harvested, independent of disease and patient factors, could imply that surgeons performing laparoscopic/robotic resection are more cognizant and capable of reaching this benchmark, compared to the open technique. This dataset is recent, and it could be that with the more proficient use of laparoscopy as well as the advent of high definition cameras, surgeons improved on their laparoscopic manipulation of the mesentery and subsequently developed a more facile high ligation of the arterial pedicle leading to better lymph node harvest. Although early randomized controlled trials that compared laparoscopic versus open resection did not show a difference between the approaches in terms of lymph node harvest, the trials are more than a decade old[25–27] and could suffer from early surgeon learning curves for laparoscopy as well as earlier generation laparoscopic technology.

Surgeon experience and specialty have been associated with improved lymph node harvest,[28–30] and overall outcomes in colorectal cancer, favor management by colorectal specialists.[31,32] Surgeon experience and specialty also correlate with more frequent and efficient use of laparoscopy in colon resection with less conversions and complications.[33–35] Surgeon experience and specialization in the colorectal field could explain the improved harvest rates of lymph nodes when laparoscopy and robotic surgery are employed rather than open surgery. Additionally, it is possible that there were patient and tumor factors not adequately captured by the NSQIP database that led to the choice of employing an open approach, and simultaneously impacting the ability to obtain an adequate number of lymph nodes.

Patient and tumor behavior also have important repercussions on lymph node harvest. Patient factors such as age and gender affected LN harvest. Also, more advanced disease implied by progressed T and N stages increased the likelihood of LN harvest, a finding concordant with current literature.[29,36–38] This is thought to be related to an increased immunological defense elicited by the host in response to more aggressive tumors.[39] One could also argue that a more pronounced immune response and lymph node involvement could make for an easier pick up by the pathologist evaluating the surgical specimen.

Table 3
Tumor location and surgical approach.

Approach	Location n (%)			
	Right	Left	Transverse	p < 0.0001
Open	2, 129 (23.09)	1, 663 (22.54)	281 (27.66)	
Laparoscopic	3, 003 (32.57)	1, 948 (26.41)	285 (28.05)	
Laparoscopic with assist	2, 726 (29.57)	2, 163 (29.32)	309 (30.41)	
Laparoscopic with conversion to open	615 (6.67)	542 (7.35)	85 (8.37)	
Robotic	664 (7.20)	993 (13.46)	54 (5.31)	
Robotic with conversion to open	37 (0.40)	56 (0.76)	1 (0.10)	
SILS	45 (0.49)	12 (0.16)	1 (0.10)	
Total	**9, 219**	**7, 377**	**1, 016**	

Table 4
Multivariate logistic regression model.

	Odds Ratio (95% CI)	P value
Approach		
Open	Reference	
Laparoscopic	1.74 (1.49–2.04)	p < 0.0001
Laparoscopic with assist	1.72 (1.47–2.02)	p < 0.0001
Laparoscopic with conversion to open	1.34 (1.06–1.70)	0.014
Robotic	1.48 (1.20–1.84)	p < 0.0001
Robotic with conversion to open	2.58 (1.20–5.84)	0.029
SILS	3.40 (0.83–14.43)	0.086
Location		
Right	Reference	
Left	0.41 (0.32–0.50)	p < 0.0001
Transverse	0.55 (0.45–0.69)	p < 0.0001
Mean Age (SD)		
<50	Reference	
50–64	0.69 (0.54–0.88)	0.003
65–79	0.70 (0.55–0.90)	0.005
>79	0.61 (0.46–0.80)	p < 0.0001
Gender		
Male	Reference	
Female	0.87 (0.78–0.98)	0.024
Race		
White	Reference	
Black	0.94 (0.78–1.20)	0.468
Asian	1.19 (0.88–1.60)	0.261
Other	1.24 (0.58–2.69)	0.55
BMI Class		
Normal	Reference	
Underweight	0.91 (0.56–1.48)	0.705
Overweight	0.96 (0.82–1.12)	0.566
Obese	0.97 (0.83–1.13)	0.683
ASA Class		
ASA Class 1	Reference	
ASA Class 2	0.85 (0.47–1.51)	0.580
ASA Class 3	0.66 (.37–1.17)	0.154
ASA Class 4	0.69 (0.37–1.30)	0.253
Preoperative Conditions		
Steroid use	0.87 (0.63–1.19)	0.388
Smoking history	0.75 (0.61–0.91)	0.031
Diabetes	1.14 (0.98–1.33)	0.082
CHF	0.7 (0.52–1.15)	0.206
COPD	0.94 (0.76–1.23)	0.767
Hypertension	0.99 (0.87–1.12)	0.848
Dialysis	0.72 (0.40–1.29)	0.273
>10% weight loss	1.49 (1.09–2.04)	0.012
T stage		
T1	Reference	
T2	1.74 (1.46–2.08)	p < 0.0001
T3	2.59 (2.21–3.04)	p < 0.0001
T4	2.32 (1.88–2.89)	p < 0.0001
N stage		
N0	Reference	
N1	0.84 (0.73–0.96)	0.012
N2	1.28 (1.04–1.59)	0.024

Also, concordant with the existing literature is our finding that resection of right sided tumors are 60-60% more likely to reach a ≥12 LN compared to transverse and left sided tumors, typically attributed to the longer size of right sided specimens and thereby a higher LN yield.[16,40,41] It is the authors' experience that high ligation of the ileocolic artery is not as technically challenging as high ligation of the middle colic or inferior mesenteric arteries, and this may also partially explain the discrepancy in lymph node yield.

In their study of the Norwegian colorectal cancer registry evaluating 2879 patients, Nedrebo et al. found that male sex, age >75 years, sigmoid tumors, pT 1–2 tumors were all independent factors for poor lymph node harvest[44]; results that resonate with our findings.

We also found that smoking history decreased the likelihood of ≥12 LN harvest. Therefore, several factors influencing harvest of ≥12 LN can be either be non-modifiable, disease and patient related (tumor stage, location) while others are modifiable, surgeon (approach used) or patient related factors (smoking).

Some of these factors may render adequate LN yield challenging and should then be taken into consideration when evaluating resection specimens for meeting the ≥12 LN metric. Understanding these factors allows for a more meaningful comparison of nodal harvest against national standards. Furthermore, preoperative optimization of modifiable risk factors should also be considered with the goal of an improved oncologic resection. Finally, the use of laparoscopic and robotic surgery should be considered by experienced surgeons when patients present with risk factors that are thought to decrease LN yield.

Although a large database such as ACS-NSQIP offers a sizeable patient population for study that is generalizable across the United States, like any administrative database, it also has limitations. Variables used to study the association with reoperation were selected from the pre-determined ACS–NSQIP catalogue and we could only analyze these pre-set preoperative factors with the outcome of LN harvest in question. The ACS-NSQIP data does not provide information on tumor biology, cycles of chemotherapy, and other tumor-specific factors which could affect colectomy outcomes and lymph node harvest.

One important limitation to our study is that the dataset does not account for the pathologist's impact on lymph node harvest. Expert pathologist examination is a known predictor for adequate lymph node harvest.[40] Although we cannot account for variations among pathologist in analyzing the surgical specimen, it has become standard of care for pathologists to look for at least 12 lymph nodes in colorectal specimen, as stated by the American College of Pathologist, which recommends reexamination of the specimen as well as using special techniques if that number is not reached.[42] We would also hope that the large number of specimen analyzed in the dataset would also translate into a large number of pathologists analyzing the specimen, with overall mean assessment that would mimic real-life outcomes. We also cannot comment on individual surgeon related and hospital related factors which also can affect surgical outcomes and lymph node harvest,[43] variables that are not accounted for in NSQIP. These limitations should be kept in mind while interpreting our paper. However, the aim of our study remains to better elucidate an already set benchmark that can help compare surgical quality and performance across the country. No one benchmark will be absolute, and any will suffer from limitations in its interpretation on a nationwide scale. We nevertheless hope that by using this dataset, we are able to shed light on a better understanding of the harvest of ≥12 LN as a quality measure.

Conclusion

≥12 LN harvest is an important benchmark in evaluation adequacy of oncologic resections for colon cancers. Minimally invasive approaches improve LN yield; laparoscopic and robotic colectomies are 1.5–2.5 times more likely to achieve adequate LN harvest compared to open surgery. Non-modifiable patient and disease related factors (cancer location, gender and age) may render adequate LN yield challenging. Understanding and balancing such factors can give a better understanding of this metric, especially when it is used as a standard for quality assessment.

Funding/Support

None reported. No disclaimers.

Disclosure

The authors have no relevant financial disclosures or other conflicts of interest.

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