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Apical lymphadenectomy during low ligation of the IMA during rectosigmoid resection for cancer☆

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ABSTRACT

Background: Low ligation of the inferior mesenteric artery with preservation of the left colic artery may decrease the risk of colorectal anastomotic ischemia compared to high ligation at its origin. Low ligation leaves apical nodes in situ and is therefore paired with apical lymphadenectomy. We sought to compare relevant oncologic outcomes between high ligation and low ligation plus apical lymphadenectomy in rectosigmoid resection for colorectal cancer.

Methods: We conducted a retrospective cohort study. Patients receiving a rectosigmoid resection for cancer between January 2012 and July 2018 were included. Patients with metastatic disease and those who underwent low ligation without apical lymphadenectomy were excluded. Our primary outcome was nodal yield/metastasis. Secondary outcomes included perioperative complications, local recurrence, and overall survival.

Results: Eighty-four patients underwent high ligation and 89 low ligation plus apical lymphadenectomy (median follow-up 20 months). In the low-ligation group, a median of 2 (interquartile range = 1–3) apical nodes was resected; 4.1% were malignant, increasing pathologic stage in 25% of these patients. There were no differences in nodal yield, complications, anastomotic leak, local recurrence, or overall survival.

Conclusion: No differences were identified between high ligation and low ligation plus apical lymphadenectomy with respect to relevant clinical outcomes. Prospective trial data are needed to robustly establish the oncologic benefit and safety of the low ligation plus apical lymphadenectomy technique.

Standard current surgical management of rectosigmoid colorectal cancer involves an anterior resection, including a wide lymph node harvest to ensure that accurate staging is possible. This operation is classically performed using a "high-ligation" (HL) technique, whereby the inferior mesenteric artery (IMA) is ligated at its origin from the aorta. This ensures that all lymph nodes draining the region of colon containing the tumor are resected. The ostensible trade-off is that this approach ligates the left colic artery and compromises the perfusion to the colorectal anastomosis. As a result of this concern, the "low-ligation" (LL) technique was developed, wherein the left colic artery is left intact and the superior rectal and sigmoid arterial branches of the IMA are ligated. This LL technique was paired with an "apical lymphadenectomy" (AL) of the proximal lymph nodes to ensure complete nodal harvest compared with traditional HL techniques [1–3].

Many studies have compared HL and LL without AL; meta-analyses on this topic have shown no differences between groups with respect to key clinical outcomes including anastomotic leak, lymph node yield, and 5-year survival [4,5]. These studies do not take the AL into account however, and numerous studies have identified IMA nodal metastasis as a significant prognostic factor [6,7]. The literature remains divided on which technique is more appropriate, with studies often arriving at contrary conclusions [8–10]. In addition, the role of AL in the context of LL is not well established.

Many studies have suggested that an LL + AL approach is superior to HL with respect to complication profile and functional outcomes. Some studies show increased rates of mesenteric ischemia, colon/stoma necrosis, and anastomotic leak and worse functional and intraoperative outcomes in patients undergoing a HL [11–15].

All published meta-analyses on the topic emphasize the need for randomized controlled studies to address this question in an appropriate

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fashion. At the time of writing, one Chinese RCT has been completed and reports similar rates of anastomotic leak between HL and LL + AL groups, but these results have not been published in a peer-reviewed journal [16]. Five registered RCTs are currently in progress according to clinicaltrials.gov [17]. Our objective with this study was to investigate the differences between HL and LL + AL with respect to oncologic outcomes and lymph node outcomes and specifically to assess the importance of AL when an LL is completed; we hypothesized that no differences would be found between HL and LL + AL groups with respect to these outcomes.

MATERIAL AND METHODS

A retrospective cohort study was performed using prospectively collected data from an institutional database (derived from patient chart review). All patients receiving a rectosigmoid resection for cancer (ie, for a tumor located 10–15 cm from the anal verge) between January 2012 (when LL + AL began being performed at our institution) and July 2018 were included in the initial cohort. Exclusion criteria included metastatic disease at any time and low ligation with 0 apical node resected (per final pathology report). Patients were divided into 2 groups based upon their surgeon (ie, one surgeon exclusively performed HL and the other exclusively performed LL + AL): HL ($n = 84$) and LL + AL ($n = 89$). LL + AL was conducted according to our previously described methods wherein apical nodes were specifically dissected and sent as separate specimens for pathologic analysis [18]. Briefly, HL of the IMA was performed at the bifurcation of the IMA from the aorta, and LL was performed just below the bifurcation of the left colic artery. Apical nodes were defined as those overlying the remnant IMA between the branch from the aorta and the left colic artery. Apical nodes were not sent as separate specimens when HL was performed except in cases where suspicious nodes were identified intraoperatively proximal to the level of ligation. Cases where LL was conducted but no apical nodes were reported by pathology were excluded from this analysis. Descriptive statistics consisting of means (SD) were reported for continuous variables, while proportions were used for categorical variables. Baseline characteristics between HL and LL groups were compared using the χ^2 and t tests for categorical and continuous variables, respectively. Patients were observed until death, loss to follow-up, or July 2018, when data were censored. Overall survival (OS) was compared between ligation groups using a Cox proportional hazard model to calculate the hazard ratio and 95% confidence interval and illustrated using a Kaplan–Meier curve. Mantell–Cox log-rank test was used to compare survival for various medically important predictors of survival. The number of events limited the use of the multivariable Cox regression model.

This study was approved by the Institutional Research Ethics Board. Written consent was not required for this study because of its retrospective nature.

RESULTS

Thirty-seven patients were excluded because of the presence of distant metastases, and 24 patients (21.2%) in the LL group were found to have 0 apical node resected; these patients were excluded from the final analysis (Fig 1). Baseline characteristics (Table 1) were not different for sex, primary tumor site, T-stage, N-stage, and neoadjuvant therapy receipt. Patients undergoing HL were older (67 vs 63 years, $P = .047$) and more likely to have an open approach (29.8% vs 5.6%, $P < .0001$), whereas more LL + AL than HL underwent laparoscopic/robotic approaches (68.5% vs 57.1% and 25.8% vs 10.7%, respectively, $P < .0001$). There was no difference between the HL and LL + AL groups for the following outcomes: total number of lymph nodes resected, total number of positive nodes, any complication, major complication, minor complication, anastomotic leak, reoperation due to leak, abscess, ileus, and local recurrence.

The mean number of apical nodes resected in the LL + AL group was 2.19; 4.1% of resected apical nodes were positive for malignancy. Three patients in the HL group had apical nodes submitted for pathology separately, one of which was positive for malignancy. A breakdown of apical node status is shown in Table 2. All patients with positive apical lymph nodes also had positive lymph nodes in the primary specimen. Two patients' N-stage was increased by apical node positivity, and 1 patient's prognostic stage was increased by apical node positivity (Table 3).

Median follow-up time was 19.8 months (interquartile range 10.5–37.4 months). Median survival was not achieved (insufficient patient mortality). There was no difference in survival between the ligation groups, with a mortality of 8.3% of the HL vs 4.5% of the LL + AL group at the end of the study, hazard ratio (HR) = 0.55 (0.164–1.91, $P = .35$) (Fig 2 and Table 4). Univariate analysis for overall survival demonstrated an increased risk of death in patients with hypertension (HR = 5.09, $P = .04$), with higher T-stage (T3 or T4) tumors (HR = 8.68, $P = .04$), with major complications (HR = 6.34, $P < .01$), and with minor complications (HR = 3.92, $P = .03$). No associations existed between overall survival and any other patient or tumor variables investigated (Table 5). There was no difference in the number of apical nodes positive for malignancy when comparing patients who had neoadjuvant therapy to those who did not ($P = .40$). Several variables could not be included in this analysis because of low numbers of events: emergency case, chronic obstructive pulmonary disease, chronic kidney disease, steroid use, 30-day anastomotic leak, and reoperation due to leak.

DISCUSSION

The question of high vs low ligation of the IMA during rectosigmoid resection for colorectal cancer has been asked historically, but the initial studies used patients undergoing heterogeneous operations and with variable or no AL. The modern version of this question has been asked recently with specific focus on minimally invasive techniques and a careful AL; however, the specific role of AL remains poorly explored. Our study sought to compare the outcomes of patients undergoing HL with those undergoing LL + AL to investigate the oncologic adequacy of the LL + AL approach and, secondarily, the effect of HL vs LL on perioperative outcomes. For this reason, we excluded patients who underwent LL without AL from our analysis.

We found that the 21% of patients undergoing LL had zero apical lymph node reported by pathology. We propose several compatible explanations for this observation. Firstly, this may be an artifactual finding resulting from the apical nodes not being sent to pathology as a separately labeled specimen; however, our institutional practice of submitting separate surgical specimens is quite robust, and we do not believe this accounts for a significant proportion of these patients. Instead, we suggest that the patients with zero apical node had a complete dissection of the tissue around the IMA but that this tissue turned out not to contain lymphatic tissue. This is feasible as both a variant of normal anatomy and a response to neoadjuvant therapy (received by ~32% of those undergoing LL).

The baseline characteristic comparison showing a statistically significant difference in age between the groups seems to be coincidental. The surgeons involved in the study were asked about this finding and suggested that these differences were due to differences in referral patterns. The differences in surgical approach between the 2 groups likely reflect access to the surgical robot platform, although it is interesting that significantly more HL cases were done with an open approach. This may suggest that the delicate apical lymphadenectomy is more difficult to perform in an open fashion; however, a larger study would be required to directly assess this implication.

The outcome findings presented here support previous studies that show no significant differences in the rates of relevant clinical outcomes, including perioperative complication, anastomotic leak, reoperation for leak, recurrence, or survival, although follow-up time for this study was limited [4–6,8,9]. We were not able to corroborate studies that report differences in lymph node harvest, complication rate, leak rate, survival, or recurrence [9–12,14,15]. There may be differences

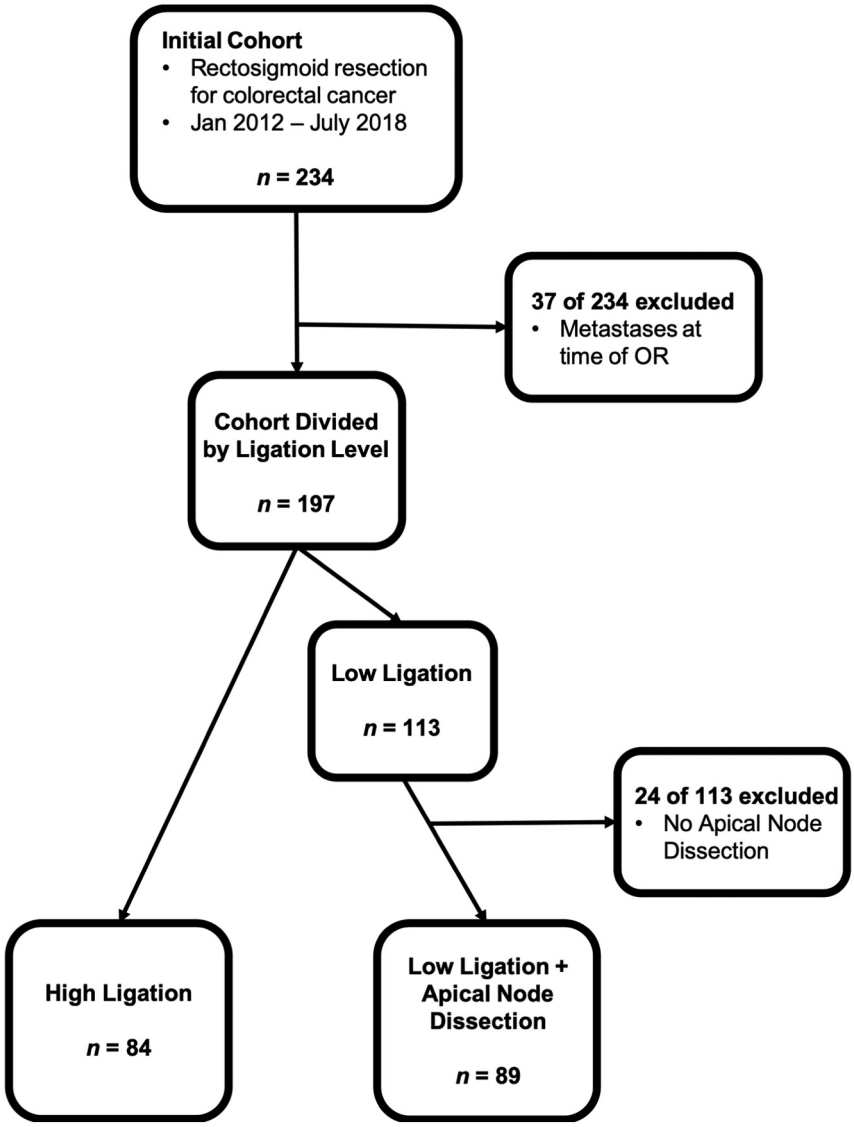

Fig 1. Cohort flow diagram.

within a subset of patients with cardiovascular disease, as shown previously, but we were unable to investigate this question for reasons of statistical power [19]. The univariate analysis performed here demonstrated that patients with hypertension, increased T-stage, and major or minor complications were at increased risk of death. Unfortunately, further analysis was limited by the low event rate occurring in this cohort.

Perhaps the most interesting and unique findings that our study presents relate to the AL. Although our study showed a relatively low rate of apical node metastasis (~4%), other studies have seen rates up to 22% and demonstrated that apical node metastasis carries significant implications regarding cancer-specific death, 5-year survival, and overall survival [20–23]. Accurate AL does not only confer benefits from a prognostic perspective; removal of malignant nodes may also confer a survival benefit [24]. This study supports the importance of apical node resection both to achieve an R0 resection and for staging purposes [7]. The AJCC nodal stage of 2 patients with positive apical lymph nodes increased as a result of this analysis. One of those patient's (of 4 with positive apical nodes) overall prognostic stage increased as a result of the analysis of apical nodes. While the change from stage IIIB to IIIC in this patient would not necessarily change ultimate chemotherapeutic treatment, this finding suggests that apical node analysis can change the pathologic stage of a colorectal cancer and therefore informs future treatment decisions. It is, therefore, vitally important that this information be as accurate as possible.

Although no difference was seen in these important clinical outcomes, several studies have demonstrated superior functional outcomes in patients who underwent LL + AL compared with HL [13,14,25]. We did not investigate functional outcomes in this study, but this represents an attractive line of inquiry, offering the opportunity to conduct a prospective trial comparing LL + AL with nerve-sparing HL.

This study is limited by the retrospective nature of its analysis, despite the data being prospectively recorded, and by the institutional nature of the database. In some cases, certain variables (like body mass index) could not be obtained because of incomplete records. The study may also be affected by the fact that nearly all of the HL operations were performed by one surgeon and nearly all of the LL + AL operations were performed by a second. It is possible that this low sample size of surgeons affects the conclusions that can be drawn with respect to clinical outcomes given that any techniques specific to these surgeons are not necessarily generalizable to all surgeons. This can also be considered a strength, however, because it minimizes the variation in the execution of the techniques. In addition, our findings concerning the overall survival of our cohort may be affected by the receipt or nonreceipt of adjuvant chemotherapy (a parameter not captured in our data set). Finally, we were unable to obtain detailed data on whether or not any of

Table 1
Descriptive statistics for baseline characteristics and outcomes, high ligation vs low ligation + apical lymphadenectomy

	High ligation (n = *84*)	*Low ligation + apical lymph node dissection* (n = *89*)	P *value*
Female sex, *n (%)*	38 (45.2)	40 (44.9)	1.00
Age at surgery, mean (SD)	67.4 (12.5)	63.4 (13.8)	.047
Site of primary tumor			.627
Sigmoid colon, *n (%)*	23 (27.4)	22 (24.7)	
Rectosigmoid colon, *n (%)*	20 (23.8)	27 (30.3)	
Rectum, *n (%)*	41 (48.8)	40 (44.9)	
Neoadjuvant therapy received, *n (%)*	25 (29.8)	29 (32.6)	.813
Pathologic T-stage, *n (%)*			.462
0	4 (4.8)	6 (6.7)	
1	14 (16.7)	16 (18.0)	
2	12 (14.3)	19 (21.3)	
3	40 (47.6)	40 (44.9)	
4	14 (16.7)	8 (9.0)	
Pathologic N-stage, *n (%)*			.21
0	64 (76.2)	58 (65.2)	
1	15 (17.9)	20 (22.5)	
2	5 (6.0)	11 (12.4)	
Surgical approach			<.0001
Unknown	2 (2.4)	0 (0.0)	
Open	25 (29.8)	5 (5.6)	
Laparoscopic	48 (57.1)	61 (68.5)	
Robotic	9 (10.7)	23 (25.8)	
Number of lymph nodes resected, mean (SD)	17.1 (8.2)	19.4 (8.0)	.063
Total positive lymph nodes, mean (%)	0.8 (20.2)	1.1 (30.3)	.486
Apical nodes resected, mean (SD)	0.04 (0.2)	2.2 (1.5)	<.001
Positive apical nodes, mean (%)	0.01 (33.3)	0.09 (4.5)	.208
Any complication, *n (%)*	25 (29.8)	34 (38.2)	.313
Major complications, *n (%)*	8 (9.5)	8 (9.0)	1.000
Minor complications, *n (%)*	21 (25.0)	31 (34.8)	.214
Anastomotic leak, *n (%)*	2 (3.1)	4 (4.5)	.967
Reoperation (due to leak), *n (%)*	0 (0.0)	1 (25.0)	1.000
Abscess, *n (%)*	4 (4.8)	3 (3.4)	.938
Ileus, *n (%)*	5 (6.0)	6 (6.7)	1.000
Local recurrence, *n (%)*	6 (7.1)	2 (2.2)	.242

Table 2
Apical node characterization, high ligation vs low ligation + apical lymphadenectomy

	High ligation (n = *84*)	*Low ligation* (n = *89*)
Patients with >0 apical node resected, *n (%)*	3 (3.6)	89 (100.00)
Apical nodes resected, *n*	3	195
Positive apical nodes, *n* (% of apical nodes resected)	1 (33.3)	8 (4.1)
Patients with positive apical nodes, of total patients, *n (%)*	1 (1.2)	4 (4.5)
Patients with positive apical nodes, of patients with >0 apical node resected, *n (%)*	1 (33.3)	4 (4.5)

these patients eventually suffered from IMA nodal recurrence, although we recognize that such information would be extremely valuable to our research question. We hope to include such information in future studies.

There is no difference in relevant clinical outcomes between HL and LL + AL. Contrary to previous studies, HL does not seem to confer an

Table 3
Staging changes in patients with positive apical lymph nodes [26].

Patient #	*T*	N_0	N_1	*Prognostic stage*$_0$	*Prognostic stage*$_1$	*Upstaged?*
1	3	1a	2a	IIIB	IIIB	No
2	3	2a	2a	IIIB	IIIB	No
3	3	2a	2b	IIIB	IIIC	Yes
4	3	2b	2b	IIIC	IIIC	No

[0] Category without apical nodes considered.
[1] Category with apical nodes considered.

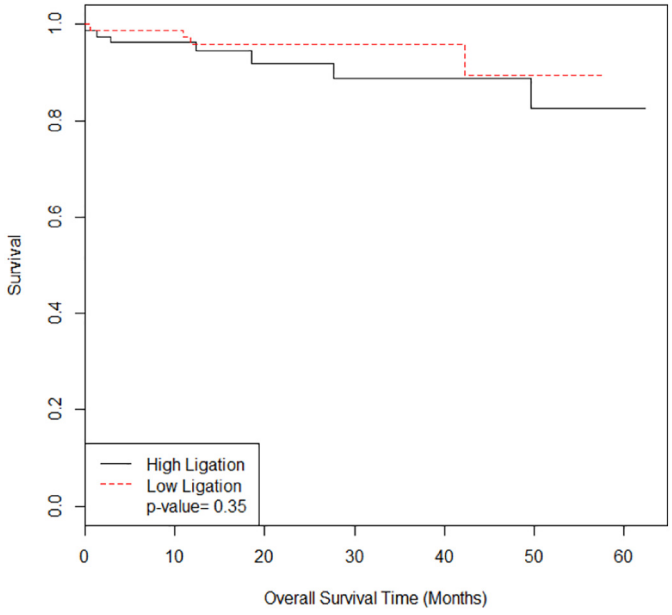

Fig 2. Kaplan–Meier curve for overall survival.

increased risk of complication, anastomotic leak, recurrence, or survival in our cohort; nor does LL + AL result in reduced lymph node yield. However, our study supports the feasibility and safety of AL as part of an LL technique to ensure the accurate assessment of the apical lymph node basin largely for prognostic purposes and decision-making purposes (ie, regarding adjuvant therapy). A randomized, controlled trial in a North American population is needed to more definitively answer this clinical question, and ideally, such a trial would also measure functional outcomes and compare LL + AL with nerve-sparing HL. Until such a trial is complete, surgeons must rely on their comfort with each operation and clinical judgment to decide which of these operations to offer.

In conclusion, apical lymphadenectomy is feasible and appears to be safe to conduct during low ligation of the IMA. Approximately 1 in 20

Table 4
Survival by ligation level

	High ligation, n = *84*	*Low ligation*, n = *89*
Alive, *n* = 162 (93.6%)	77 (91.7%)	85 (95.5%)
Dead, *n* = 11 (6.4%)	7 (8.3%)	4 (4.5%)

Table 5
Univariate analysis for overall survival with respect to patient and tumor characteristics

Variable	*Reference*	*Experimental*	*HR (95% CI)*	P *value*
Ligation level	High	Low	0.55 (0.16–1.91)	.35
Age (y)	N/A	N/A	1.05 (0.99–1.11)	.05
Sex	Male	Female	0.36 (0.09–1.38)	.14
Primary tumor site	Sigmoid	Rectosigmoid	0.61 (0.14–2.76)	.52
		Rectal	0.46 (0.11–1.83)	.27
ASA class	I–III	IV–V	6.51 (0.80–53.26)	.08
CAD	Absent	Present	1.64 (0.43–6.25)	.47
HTN	Absent	Present	5.09 (1.09–23.73)	.04
T2DM	Absent	Present	1.66 (0.49–5.68)	.42
Neoadjuvant therapy	Absent	Present	0.82 (0.22–3.11)	.78
Pathologic T-stage	T0–T2	T3–T4	8.68 (1.11–68.10)	.04
Pathologic N-stage	N0	N1–N2	1.47 (0.43–5.03)	.54
Pathologic prognostic stage	Stage I–II	Stage III	1.46 (0.42–4.99)	.54
Any complication	Absent	Present	3.36 (0.98–11.52)	.05
Major complication	Absent	Present	6.34 (1.62–24.8)	<.01
Minor complication	Absent	Present	3.92 (1.15–13.41)	.03

HR, hazard ratio; *CI*, confidence interval; *ASA*, American Society of Anesthesiologists; *CAD*, coronary artery disease; *HTN*, hypertension; *T2DM*, type II diabetes mellitus.

patients who undergo a low-ligation procedure without apical lymphadenectomy will have malignant lymph nodes left in situ. If included in the resection, these nodes may result in disease upstaging. More robust evidence is required before firm conclusions can be drawn regarding the oncologic benefit and safety of a low ligation with apical lymphadenectomy technique.

Conflict of Interest

Dr Fayez Quereshy has received consulting and speaking honoraria from Minogue Medical and Medtronic.

Dr Sami Chadi has received consulting and speaking honoraria from Stryker Endoscopy.

Dr Andrea Covelli has no conflicts of interest to declare.

Dr Tyler Chesney has no conflicts of interest to declare.

Dr Arman Draginov has no conflicts of interest to declare.

Dr Keegan Guidolin has no conflicts of interest to declare.

Author Contribution

Keegan Guidolin collected and cleaned the data, interpreted the analysis, and drafted the manuscript. Arman Draginov assisted in data collection and manuscript review. Andrea Covelli, Tyler Chesney, Sami Chadi, and Fayez Quereshy assisted with data interpretation and manuscript review.

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