

# The Quality of Lymph Node Harvests in Extralevator Abdominoperineal Excisions

Ben Liu (✉ [Ben.Liu@nhs.net](mailto:Ben.Liu@nhs.net))

Royal Wolverhampton Hospitals NHS Trust <https://orcid.org/0000-0002-4406-5012>

Ja'Quay Farquharson

Royal Wolverhampton Hospitals NHS Trust

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## Research article

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# Abstract

## Background:

Lymph node (LN) harvest in colorectal cancer resections is a well-recognised prognostic factor for disease staging and determining survival, particularly for node-negative (N0) diseases.

Extralevator abdominoperineal excisions (ELAPE) aim to prevent “waisting” that occurs during conventional abdominoperineal resections (APR) for low rectal cancers, and reducing circumferential resection margin (CRM) infiltration rate. Our study investigates whether ELAPE may also improve the quality of LN harvests, addressing gaps in the literature.

## Methods:

This retrospective observational study reviewed 2 sets of 30 consecutive APRs before and after the adoption of ELAPE in our unit.

The primary outcomes are the total LN count and rates of meeting the standard of 12-minimum, particularly for those with node-negative disease. The secondary outcomes are the CRM involvement rates.

Baseline characteristic including age, sex, laparoscopic or open surgery and neoadjuvant chemoradiotherapy were accounted for in our analyses.

## Results:

Median LN counts were slightly higher in the ELAPE group (16.5 vs. 15). Specimens failing the minimum 12-LN requirements were almost significantly fewer in the ELAPE group (OR=0.456). Among node-negative rectal cancers, significantly fewer resections failed the 12-LN standard in the ELAPE group than APR group (OR=0.211,  $p=0.044$ ). ELAPE led to a near-significant decrease in CRM involvement (OR=0.365). These improvements were persistently observed after taking into account baselines and potential confounders in regression analyses.

## Conclusion

ELAPE provides higher quality of LN harvests that meet the 12-minimal requirements than conventional APR, particularly in node-negative rectal cancers. The superiority is independent of potential confounding factors and may implicate better clinical outcomes.

## Background

An abdominoperineal Resections (APR) includes the resection of the sigmoid colon, rectum, and anus and the construction of a permanent end colostomy. It is the established curative surgical treatment for low-lying rectal cancers within 4 cm from the anal verge or those involving anal sphincter complexes [1].

However, a high rate of intraoperative bowel perforation (IBP) and risks of positive circumferential resection margin (CRM), both strong predictors of survival [2] had been reported to be as high as 30.4% in the Dutch TME trial [3] and 30.2% in the MERCURY trial [4]. These have subsequently been correlated with higher recurrence rates and reduced survival after APR [5]. Extralevator Abdominoperineal Excision (ELAPE) had been described to standardise a cylindrical specimen without a “waist” in order to minimise the risk of CRM involvement, and early outcomes have been favourable [6–8]

In addition to CRM, the identification of lymph node (LN) metastases following surgical resection for colon and rectal cancer is well recognised as a key prognostic factor[9], and is a pre-requisite in accurate cancer staging [10]. Established evidence had demonstrated strong association between higher total LN counts and improved disease survival [11, 12] particularly for node negative colorectal cancers [12, 13]. This is because in clinical practice, the presence of LN metastasis determines those patients most likely to benefit from adjuvant therapies as shown in multiple key phase III trials such as the MOSAIC trial [14]. Although there are still debates regarding the optimal number of LNs required for adequate staging [15], the evaluation of at least 12 LNs following colorectal resection is widely recommended in most clinical guidelines [16, 17]

Although the rationale and outcomes relating to CRM clearance associated with ELAPE are well documented, there are gaps in the literature regarding the quality of lymph node harvests between the traditional APR technique and ELAPE, and how that may have an impact on recurrences and disease survival. The aim of our observational study is to investigate the number of lymph nodes yielded from ELAPE compared with conventional APR. As evidence had shown diminishing returns from excessive lymph node dissection beyond the recommended 12 lymph nodes [18], our study hence focuses on whether ELAPE may be superior at meeting the 12 LN minimal requirement.

## Methods

### Study objectives and hypothesis

The primary objective of this observational study is to determine if ELAPE improves the absolute number of LN yield and the rate of meeting the 12LN minimal requirement, compared with standard APR. The secondary objective is to assess the CRM involvement rates and determining whether the known advantages of ELAPE can be reproduced in a district general hospital setting.

The null hypothesis is finding no differences in the pathological outcomes between the two groups (ELAPE vs. APR) of patients. If there are significant differences, we evaluate whether they are independent of patients’ baseline characteristics and other cofounders including the use of open / laparoscopic surgery and neoadjuvant chemoradiotherapy.

## Endpoints

The primary endpoints are:

Absolute number of lymph node yields

Failure rates to meet the 12 LN nodes pathological requirement

Failure rates to meet the 12 LN pathological requirement in node-negative (N0) subgroups

The secondary endpoint is

The rates of CRM involvement

## Inclusion and exclusion criteria

Our colorectal unit in The Royal Wolverhampton Hospital NHS Trust adopted ELAPE as a standard procedure for low rectal cancer in 2014. From the register of this single centre, we included patients who underwent the two methods of abdominoperineal resections for rectal cancer (i.e. adenocarcinoma) over a 10 year period between 2009 and 2019.

Patients undergoing revisional or completion procedures or procedures for non-adenocarcinomas were excluded.

## Data Collection

Two groups of 30 consecutive cases were sampled over three years period before and after our adoption of ELAPE. Case notes were retrospectively reviewed for baseline characteristics including patient age and sex. The operation notes were reviewed to determine the techniques employed and type of access (open or laparoscopic). The uses of any neoadjuvant therapies were documented.

## Statistics

Data from the United Kingdom National Bowel Cancer Audit [17] showed a median of 15.1 LN harvested from rectal resections and 78.6% of them achieved 12 LN minimum. Shen et al. [19] in 2009 noted the mean number of LN ranges from 13.6 to 19 depending on factors such as age, sex, tumour grade, stage and surgical techniques; the standard deviation was 10.5. Based on this, at the power of 80% the minimum sample size for capturing a 5% difference between the two groups was calculated to be 60.

As the data is not normally distributed, the median number of lymph node yields was recorded. Between the two groups (ELAPE vs. Conventional APR) Mann-Whitney U Test was used to detect any significant differences in the absolute LN yield. Odds ratios were used for differences in the rate of specimens failing the minimum 12-LN requirement, and in analysing differences in the nodal-negative subgroups. The same is applied to differences in the rates of CRM involvement. Regression calculations were performed

to analyse the differences between the two groups independently of potential confounders (baseline characteristics, laparoscopic/open surgery and the use of neoadjuvant therapies).

## Results

After excluding 7 patients from the APR group and 3 patients from the ELAPE group, there are 30 patients per study group included in the analyses. The exclusions are described in the flow diagram (Fig. 1).

## Baseline Characteristics

The baseline characteristics are shown in Table 1. There is no statistical difference in the genders of patients between the two groups – 22 male: 8 female in the conventional APR group and 17 male: 13 female in the ELAPE group ( $p = 0.176$ ). No significant differences ( $P = 0.930$ ) were observed between the mean age of the APR group (67.8) and the ELAPE group (68.0). Significantly fewer traditional APR cases (4 out of 30) were performed laparoscopically contrary to 11 out 30 in the ELAPE group ( $P = 0.037$ ). 14/30 patients in the traditional APR group received neoadjuvant chemoradiotherapy, not significantly different ( $P = 0.606$ ) to the 16/30 in the ELAPE group.

Table 1  
Baseline characteristics of the ELAPE and APR groups.

	Conventional APR	ELAPE	P value
Male: Female	22 : 8	17 : 13	0.176
Age	67.8	68.0	0.930
Laparoscopic : Open surgery	4:26	11:19	<b>0.037</b>
Neoadjuvant chemoradiotherapy	14/30	16/30	0.606

## Lymph Node Counts

The median number of lymph node harvested from conventional APR and ELAPE specimens were 15 and 16.5 respectively (Shown in Table 2) without a significant difference ( $P = 0.181$ ). The ELAPE group has lower rates of lymph node harvests failing the minimum 12-LN requirement (7/30) compared with the conventional APR group (13/30) with odds ratio of 0.456 which almost reached statistical significance ( $p = 0.085$ ). In those patients with negative nodal metastases status (N0), the rate of failing the 12-LN requirement is significantly reduced (3/19) in the ELAPE group compared with the APR group (8/17) with odds ratio of 0.211 ( $P = 0.025$ ). When contrasting the rates of pathological CRM involvement in the specimens, ELAPE (3/30) outperforms conventional APR (7/30) with odds ratio of 0.365, which almost reached statistical significance ( $p = 0.088$ ).

# Regression Analyses

There were no significant independent differences between the two groups in median lymph node counts ( $p = 0.224$ ), rate of failure to reach 12 LN ( $p = 0.129$ ) and the rates of CRM involvement ( $p = 0.099$ ). However in those with nodal negative status (N0), significantly lower failure rates of harvesting 12 LN were persistently observed ( $p = 0.044$ ) in the ELAPE group, suggesting independence from the potential aforementioned confounders.

Table 2  
Comparisons of pathological results between the ELAPE group and APR group.

	Median Total Lymph nodes (LN)	Below 12 LN requirement	Node negative (N0), < 12 LN requirement	CRM involvement	Total number of cases
ELAPE	16.5	7/30	3/19	3/30	30
Conventional APE	15	12/30	8/17	7/30	30
Statistical tests and significance	Mann-Whitney U Test (P = 0.181)	Odds ratio (OR) = 0.456 (P = 0.085)	OR = 0.211, P = 0.025	OR = 0.365, P = 0.088	60
Regression analysis (including age, sex, lap/open, neoadjuvants )	$p = 0.224$	$P = 0.129$	$P = 0.044$	$P = 0.099$	60

## Discussion

In this study we have investigated the differences in the number of lymph nodes harvested between ELAPE and conventional APR. The median number of LN yielded from conventional APR is 15. Authors such as Shen et al. 2009 [19] retrospectively inspected 69 cases and had reported the same median number of 15. The absolute LN count in our ELAPE group is higher but not significantly compared to the APR group, and is comparable to the 13.7 nodes from the ELAPE results in the large scale ( $n = 519$ ) Swedish population study [20]. Neither our study nor the Swedish cohorts found significant differences between APR and ELAPE groups. However, reported number of LN harvest from APEs in literature varies greatly. In general LN counts for abdominoperineal excisions are lower than other type of colorectal resections, and can be as low as 9 LN [21]. Though comparable, the number of lymph nodes harvested at our unit appears higher compared to the reported literature. This may be explained by the contemporaneousness of our data and higher proportion of laparoscopic surgery in our study compared with established evidence. Dolan et al. [22], in a prospective study of 896 patients spanning 20 years

(1997–2016), had found significant independent correlation between later operative date, increasing prevalence of laparoscopic surgery and higher lymph node harvests.

## 12-LN minimal requirement

Secondly, we have found a reduction in the rate of resections failing to meet the 12-LN minimal requirement under the ELAPE technique compared with traditional APR. The differences are considerable and almost statistically significant. Hitherto; there has been a lack of evidence comparing quality of LN harvests between the two techniques despite emphases of its importance by many authors [13, 23–25] and guidelines including the National Cancer Institute [16]. A minimum of 12 lymph nodes was recommended [23] as below this cut-off value there is a high risk of false-negatives in reporting lymph node metastases due to inadequate sampling [25]. The 12-node standard has been endorsed by other researches for reasons of “diminishing returns” beyond the examination of 12–17 nodes [18]. In our study, 60% and 77% of specimens in the APR and ELAPE groups respectively met this standard. When compared with known literature from authors who specifically investigated the 12-LN criteria among rectal cancers, our cohort of patients have achieved higher rates in general. Field et al. [21] reported 50%, while Gurawalia et al. [26] achieved 52%, and Baxter et al. [27] had a 46.4% attainment rate. Our higher success rate could be explained again by the contemporaneousness of our cases, and a higher prevalence of laparoscopic surgery in our cohort, both considered to be independent determinant of meeting the 12-LN standard as found by Dolan et al. [22]

## Node Negative Disease

The British reviewers Ong and Schofield [28] have summarised that node-negative colorectal cancer patients have a 5-year survival rate of 70%-80% in contrast to 30%-60% for their nodal-positive counterparts. Survival can be improved in the latter group by adjuvant chemotherapy [14]. The 20%-30% disease recurrence in apparently completely excised tumours without lymph node metastases is thought to be due to occult lymph node disease [29]. If this subset of patients could be identified by better lymph node staging, they might also benefit from adjuvant chemotherapy. Nodal-positive resections, irrespective of the number of LN harvested, would indicate adjuvant chemotherapy. Therefore substantial researches have investigated how the number of LN examined affects the accuracy of colorectal cancer staging and prognosis among node-negative individuals [12, 30, 31]. As aforementioned, Fielding et al. [23] advocated a minimum of 12 lymph nodes since below this cut-off value there is a high risk of false-negative reporting of lymph node involvement due to inadequate sampling. Based on this evidence, we have conducted a separate analysis of nodal-negative cases investigating whether the minimum 12-LN standard has been met in this subset. We have found significantly lower rates of failures in meeting the 12-LN requirement with ELAPE when compared to APEs. This suggests that ELAPE may be superior at staging rectal cancers, minimising false-negatives in apparently negative nodal disease, leading to more appropriate decision-making on adjuvant treatments. The mechanism underlying the observed

improvement with ELAPE is not entirely understood, since anatomically the mesorectum tapers as it adjoins the pelvic floor. However as Holms et al. eluded to in their research [6], while other techniques (e.g. intersphincteric, extrasphincteric dissections) are available, ELAPE offers a standardised approach for surgeons to perform abdominoperineal excisions, leading to more consistent quality of resections which in turn reduces the rates of sub-standard TMEs.

## CRM Involvement

The overall CRM rate of our cohort is 16.7%, which is relatively high but comparable with published data of 16.6% from Great Britain [32] and 16.7% from Canada [33]. Our study has showed a decreased rate of CRM involvement among the ELAPE group compared with conventional APR, though not quite to a statistically significant level. Most of the studies [20, 34, 35] have also failed to show statistically significant superiority of ELAPE in CRM clearance. However the Danish study [35] suggests a magnitude of reduction (OR 0.386) that is considerable and comparable to our data (OR of 0.365). The more recent, yet small (n = 34) randomised controlled trial, nevertheless, demonstrated a significantly improved CRM and zero intraoperative perforations in their ELAPE arm of patients [36]. Our investigation suggests that the apparent benefit of ELAPE may be reproducible in a district general hospital setting among 8 different local colorectal surgeons who have performed these procedures at our unit.

## Potential Confounders

It is established that the quality of surgery and pathologic examination are both major determinants of LN harvests [37, 38]. However, multiple clinicopathologic factors may also affect the number of lymph node retrievals. In particular, a significant reduction in the mean LN yield was found in patients who received neoadjuvant chemoradiotherapy, from 17 to 13 [39], and from an average of 19 to 16 [40]. Other authors such as Field et al. [21] have also found that young, female patients and higher T stages of cancers to be correlated with higher LN yield. There was also significant link between laparoscopic surgery and higher rate of attaining the 12-LN standard [22]. On this basis, we have conducted regression analyses taking into account the above predictors of LN yield as potential confounders. This has not changed the correlations found in our results. The rate of failure to achieving 12LN standard is significantly lower in the ELAPE group among the nodal negative cohorts. The reduction in CRM involvement is still present but not significant. Our analyses have demonstrated superiority of ELAPE in these pathological aspects independently of other influencing factors.

## Limitations

As a retrospective observational study, our investigation is subject to the usual limitations of selection and recall biases. The aim of our research was to establish whether ELAPE leads to a better pathological outcome. Although our results have suggested it, there remains uncertainty whether this would

necessarily translate to an improvement in clinical outcomes i.e. local recurrence rate (LR) and disease survival. Several systematic reviews found no differences in either CRM or LR with ELAPE [34, 41]. Some meta-analyses [42] showed that despite ELAPE significantly lowering the rates of CRM involvement, there has been no benefit in the LR, while others [43], did demonstrate a significant reduction in LR (OR 0.30,  $P < 0.01$ ). Even if the LR were found to be improved with ELAPE, some authors have found no difference in overall survival, disease free survival or disease progression in a prospective controlled study [44], and from a randomised controlled trial with median follow-up of 20 months [45]. However these studies have been marred by their small recruitment numbers ( $n = 69$  and  $n = 67$  respectively) and short follow-up periods.

It is less disputable, nevertheless, that the retrieval and analysis of a larger number of lymph nodes result in a survival advantage [30]. This was initially thought to be due to upstaging of “missed” positive lymph nodes. However, more recent studies suggest that this phenomenon cannot be attributed to staging migration alone. A systematic review [18] found improved survivals correlating with higher lymph node harvests in stage III (4 of 6 studies) as well as stage II (16 of 17 studies) diseases. Furthermore, lymph node sampling past a certain point does not appear to improve disease staging [46]. Interestingly Joseph et al.[47] Found that improvement in colorectal cancer survival was associated with greater LN harvest irrespective of patients’ nodal statuses (N1 or N0). Tumour-host interactions may be a plausible explanation for this, as higher LN yield may reflect a stronger host immune response[48].

Among other factors that could have influenced our results was the lack of pathological reporting of the lengths of our specimens. This may be because there has not been a standardised length of resection for APEs in general. The amount of mesentery associated with specimen length undoubtedly correlates with the number of LNs found [19].

Secondly, authors such as Dolan et al. [22] have noticed greater number of LN yield to be associated with more contemporaneous operations when comparing cases before and after year 2007. Since our study design is based on the adoption before and after the adoption of ELAPE in year 2014, the latter date of the surgery in the ELAPE group may be a potential bias. Are we simply becoming better surgeons and pathologists as a whole rather than observing improvement due to the merits of the new technique?

Despite our effort to improve LN harvests, no internationally recognised standards of practice have been developed for the histopathological processing of lymph nodes in specimens [49]. A notable Canadian study showed that only 58% of pathologists were aware of current guidelines and that only 25% recognized that a minimum of 12 LNs was necessary for accurate designation of node negativity [50]. On the other hand, the concern with rigidly fixing a recommended number (i.e. 12) is that once this figure is met, the lab search for LNs may end at that point regardless of how many potentially positive nodes are left in the sample [27].

The apparent advantages of ELAPE also need to be balanced with the morbidity this new technique brings. Some authors have reported significantly more post-operative wound infections after ELAPE (20.5%) than for APR (12%) [20]. A prospective multicentred trial [51] also suggested higher rates of

sexual dysfunction, urinary retention, and perineal complications including chronic perineal pain associated with ELAPE. However, a meta-analysis [52] found no differences in complication rates between the two techniques, and some of these potential complications can be mitigated with reconstructions using meshes or plastic surgery. Our enthusiasm for ELAPE should nevertheless be tempered with caution and consideration of its potentially higher complexity and morbidity.

## Abbreviations

APR

Abdominoperineal Resections

CRM

Circumferential Resection Margin

ELAPE

Extralevator Abdominoperineal Excisions

IBP

Intraoperative Bowel Perforation

LN

Lymph Node

LR

Local Recurrence

## Declarations

### Ethics approval and consent to participate

Written informed consents have been obtained from the study subjects. Data were collected, processed and stored in accordance with the Data Protection Act. The study protocol was submitted and approved by Research Ethics Committee via Health Research Authority (UK) IRAS reference ID: 282958

### Consent for publication

Not applicable

# Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

# Competing Interests

The authors declare that they have no competing interests

# Funding Sources

No additional source of funding was sought or given.

# Author Contributions

Ben Liu: Chief Investigator, case identification, data collection, data analyses, main author

Ja'Quay Farquharson: Sub-investigator, data collection, data analyses, co-author

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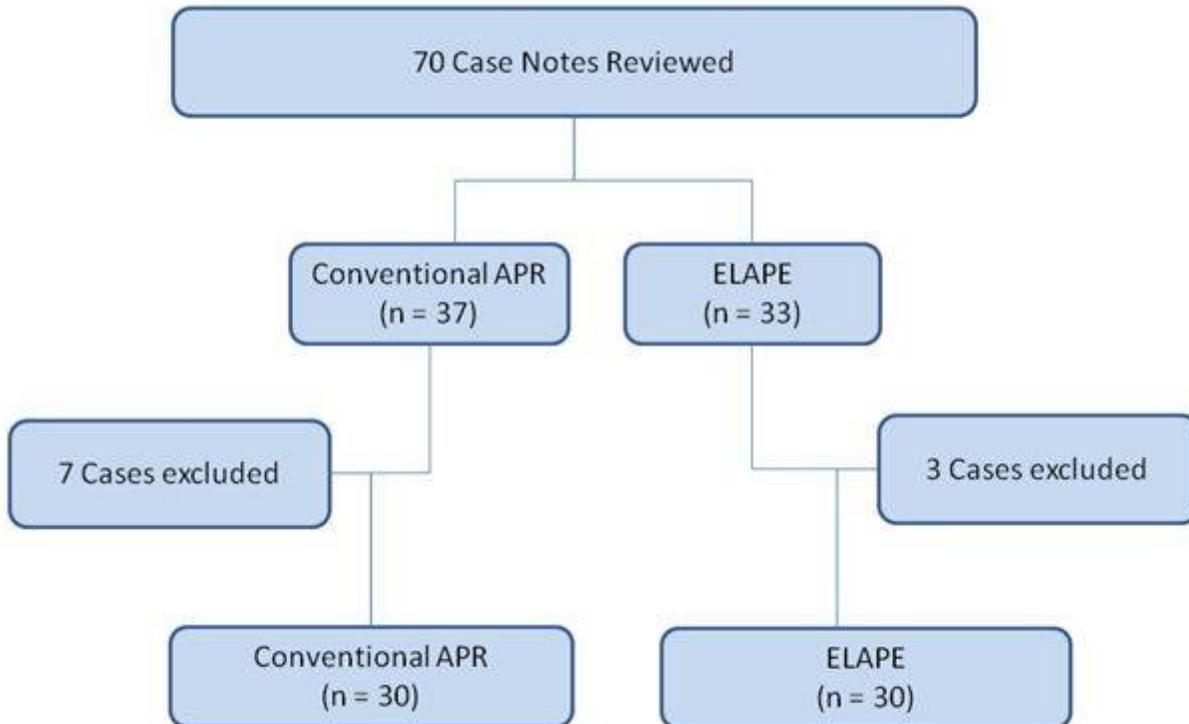
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## Figures



**Figure 1**

Flow chart of case selection for the ELAPE and APR groups