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# Linking surgical specimen length and examined lymph nodes in colorectal cancer patients

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## Abstract

*Aim*: The number of examined lymph nodes (NLN) was associated with survival of stages II and III colorectal cancer (CRC) patients. Guidelines recommend examining at least 12 lymph nodes. This study investigated the influence of surgical specimen length on lymph node harvest and compliance with international guidelines.

*Materials and methods*: This population-based study included 4,724 cases of surgically treated CRC that were diagnosed from 2002 to 2008. Multivariate analyses were performed for the main study variables (age, gender, diagnosis at screening or in symptomatic patients, cancer site, staging, grading, number of positive nodes, neo-adjuvant treatment for rectal cancer, hospital were surgery was performed). Fractional polynomial models investigated the relationship between continuous variables and outcomes.

*Results*: The NLN increased over time reaching ≥12 NLN in 64% of cases at the end of the study period. More NLN were associated with young age, right colon cancer, pT3–T4 disease, stages II and III and high grade. Fewer NLN were associated with short surgical specimen length and neo-adjuvant treatment in rectal cancer patients. Use of laparoscopy increased sharply over time.

*Conclusions*: NLN increased over time in accordance with international guidelines. Surgical specimen length correlated with NLN which may determine therapeutic choices, particularly in stage II colon cancer. When harvested lymph nodes are under 10 in number and all are negative, chemotherapy is always recommended. As specimen lengths <20 cm were associated with a high risk of inadequate NLN counts, patients are at risk of over-treatment.



*Keywords:* Digestive system surgical procedures; Colorectal tumours; Lymph nodes; Laparoscopy; Guidelines adherence

## Introduction

In non-metastatic colorectal cancer (CRC), one of the main prognostic factor is the number of examined lymph nodes (NLN)[1] which, whether positive or negative, correlated with survival[1] and indeed, since the 1990s, guidelines have recommended a cut-off of 12 harvested lymph nodes.[2–6] More accurate identification of positive cases (i.e. stage migration) was linked to more appropriate patient selection for chemotherapy (i.e. real survival benefit) and increased stage-specific survival.[1,7] Even though more lymph nodes were examined over the years, population studies did not show a rise in the rate of node positive cases,[8] probably because organized screening programs contributed to diagnosis at early-stage. Moreover, lymph node yield in CRC patients is influenced by, for example, age, cancer site, disease stage, type of surgery, expertise of surgeon and pathologist, pathological features and surgical resection length.[1,7,9–11]

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In the present study we explored links between type of surgery (laparotomy *vs* laparoscopy), surgical specimen length, number of examined lymph nodes (NLN) and compliance with the ≥12 node cut-off over time to determine whether a longer specimen was associated with a greater lymph node harvest and better disease staging. Our population-based study was conducted in Umbria, an Italian region with a population of about 900,000, with 24% aged 65 years or more in 2012, ranking it among the oldest in the world. CRC is still a major health problem with 2008–2010 standardized (European population) incidence rates of 73.5 per 100,000 inhabitants per year in males and 41.8 in females despite an organized screening program using the fecal immunochemical test (FIT) which was started in 2006. According to the Umbria Regional cancer registry, an average of 845 new CRC cases were diagnosed per year from 2002 to 2008, the period we analysed in the present study.

## Materials and methods

Retrieved CRC cases from the regional cancer registry had been registered according to international standards for cancer registries. Data were of high quality as, for example, no "cause of death certification only" (DCO), which is an indicator of incomplete cancer registry data, was present in our dataset even though many cases were very old. Since cancer registries do not record clinical details of diagnosis, staging and treatment, details of diagnosis were accessed in the regional database belonging to all seven regional pathology units. Full data on staging and treatment were retrospectively obtained from Regional Health Service hospital archives in all medical and radiation oncology, surgery and gastroenterology centers.[12] Quality control of medical archives was satisfactory as few data were missing.

During the study period, patients received surgery in 20 centres, with over 70% being operated in the four main regional hospitals of Umbria. Surgical specimens were examined in seven regional pathology laboratories which did not follow any standardized regional protocol for lymph node examination. Lymph nodes were usually examined by haematoxylin and eosin staining and at least 3 slices were made.

A trained pathologist (SL) reviewed and coded staging information. Personal data was strictly confidential and was not released outside the cancer registry. Anonymization techniques were used for data management within the registry. No further ethical approval was sought.

Of 5,885 first primary CRCs, 4,724 cases underwent surgery in Umbria and were included in the analysis. Exclusion criteria were no surgery (708 cases); endoscopic surgery only (196 cases); unknown treatment (4 cases); palliative surgery (e.g. colostomy only) (151 cases); treatment outside of Umbria (102 patients). Throughout the study period lymph node resection was not performed in about 20% of all 5,885 registered cases (Cuzick's test $p = 0.5$), 1.8% of whom (mostly T1NxM0) underwent surgery (trend $p = 0.4$).

From the total sample of 4,724 cases, lymph nodes were examined in 4,634 (98.1%) and data on both NLN and surgical specimen length were available for 4,481 (94.9%).

Study variables included age and gender, diagnosis at screening or at testing because of symptoms, neo-adjuvant treatment for rectal cancers, TNM stage, grading, number of positive nodes, hospital where surgery was performed and its pathology unit, cancer site and sub-site which were coded according to ICDO3T classification.[13] Table 1 reports the few missing data for study variables. Cancer site was re-coded in right colon (C18.0–C18.5), left colon (C18.6–C18.7, C19), and rectum (C20).

### *Statistical analysis*

Unadjusted regression models were fitted to investigate the influence of date of diagnosis on study variables. Linear regression analysed surgical specimen length. Negative binomial regression analysed the NLN. Since the likelihood ratio test for over-dispersion was significant ($p < 0.001$), negative binomial regression, rather than the Poisson model, was chosen to explore the influence of study variables on the NLN. Surgical specimen length was first included in the models by variable quintiles. The shape of the relationship between surgical specimen length and lymph nodes was further explored using fractional polynomials, adjusted for the other significant independent variables. Fractional polynomials are study variable transformations based on selected powers as proposed by Royston and Altman.[14] Nested models corresponding to the null model, the linear model and the best fitting first- and second-degree powers were compared, using the partial likelihood ratio test to perform linearity and non-linearity significance tests.

A logit model investigated the influence of study variables on compliance with the recommended ≥12 lymph node cut-off (model not shown). Statistical analyses were performed using Stata software (version 13).

## Results

Mean age at diagnosis was 70.8 in males and 71.7 years in females. Nearly 75% of all cases were elderly (≥65 years). Over 70% of cases had pT3–T4 disease at diagnosis, which dropped from 74% in 2002 to 66% in 2008, two years after the screening program had started. Stage III or IV at diagnosis accounted for 45% of cases. Table 1 reports the distribution of study variables.

Neo-adjuvant treatment was administered in 155 cases (3.3% of all study cases; 17% of rectal cancers).

No lymph node was examined or retrieved during surgery in 87 cases and data on examined lymph nodes was

Table 1
Distribution of cases according to selected study variables.

| Variables | | n. | % | P |
|---|---|---|---|---|
| Total cases | | 4724 | 100 | |
| Gender | Males | 2666 | 56.4 | |
| | Females | 2057 | 43.6 | |
| Age class | <50 | 178 | 3.8 | |
| | 50–64 | 1079 | 22.9 | |
| | 65–74 | 1571 | 33.3 | |
| | 75–84 | 1537 | 32.5 | |
| | ≥85+ | 358 | 7.6 | |
| Laterality | Right colon | 1715 | 36.3 | <0.001 |
| | Left colon | 1930 | 40.9 | |
| | Rectum | 1076 | 22.8 | |
| | X | 2 | 0.04 | |
| Grading | 1 | 821 | 17.4 | 0.001 |
| | 2 | 2644 | 56.0 | |
| | 3 | 1173 | 24.8 | |
| | X | 85 | 1.8 | |
| pT | 0[a] | 28 | 0.6 | 0.002 |
| | 1 | 548 | 11.6 | |
| | 2 | 777 | 16.5 | |
| | 3 | 2947 | 62.4 | |
| | 4 | 397 | 8.4 | |
| | X | 26 | 0.6 | |
| Stage | 0[a] | 27 | 0.6 | 0.05 |
| | I | 1069 | 22.6 | |
| | II | 1441 | 30.5 | |
| | III | 1256 | 26.6 | |
| | IV | 861 | 18.2 | |
| | X | 32 | 0.7 | |
| | T1NxM0 | 37 | 0.8 | |
| Screening | NSD | 4273 | 90.5 | 0.001 |
| | SD | 450 | 9.5 | |

Abbreviations: SD, screening detected; NSD, non-screening detected.
[a] After neo-adjuvant chemo-radiotherapy.

missing for 3 cases. From 2002 to 2008 the median NLN per intervention was 12, increasing linearly from 10 in 2002 to 13 in 2008 ($p < 0.001$) while cases with ≥12 examined lymph nodes increased from 43% to 64% ($p < 0.001$). The unadjusted odds ratio (OR) of compliance with the recommended ≥12 NLN for year of diagnosis was 1.16 (95% CI from 1.13 to 1.19). Throughout the study an average of about 40% lymph nodes were positive but node positivity decreased significantly over time ($p = 0.001$, unadjusted OR 0.94, 95% CI from 0.91 to 0.96). Table 2 reports independent predictors of NLN according to the negative binomial regression model. More NLN were associated with young age, right colon cancer, pT3–T4 disease, stages II and III and higher grading. Fewer NLN and poorer compliance with the recommended ≥12 NLN cut-off were associated with neo-adjuvant treatment in rectal cancer patients and short surgical specimen length.

Information about surgical specimen length was missing for 161 cases. Median surgical specimen length measured after formalin fixation was 24 cm shortening from 25 cm in 2002 to 22 cm in 2008 ($p < 0.001$). The test for non-linearity was non-significant ($p = 0.2$). A total of 1,021 patients (21.6%) underwent laparoscopy, increasing from 4%

Table 2
Negative binomial regression model for the number of examined lymph nodes.[a]

| Variables | n. of examined nodes | | | |
|---|---|---|---|---|
| | RR | L | U | P |
| Year | 1.05 | 1.03 | 1.08 | <0.001 |
| Age | | | | |
| <50 | Ref. | | | |
| 50–64 | 0.83 | 0.77 | 0.90 | <0.001 |
| 65–74 | 0.77 | 0.73 | 0.82 | <0.001 |
| 75–84 | 0.74 | 0.68 | 0.80 | <0.001 |
| ≥85 | 0.63 | 0.57 | 0.70 | <0.001 |
| Surgery[b] | | | | |
| Open | Ref. | | | |
| Laparoscopy | 0.97 | 0.91 | 1.02 | 0.25 |
| Laterality | | | | |
| Right colon | Ref. | | | |
| Left colon | 0.86 | 0.82 | 0.91 | <0.001 |
| Rectum | 0.93 | 0.90 | 0.96 | <0.001 |
| Rectum NT[c] | 0.76 | 0.72 | 0.80 | <0.001 |
| Specimens[d] | | | | |
| Qt1 <160 | Ref. | | | |
| Qt2 160–199 | 1.20 | 1.16 | 1.25 | <0.001 |
| Qt3 200–259 | 1.24 | 1.15 | 1.34 | <0.001 |
| Qt4 260–349 | 1.32 | 1.19 | 1.46 | <0.001 |
| Qt5 350+ | 1.41 | 1.30 | 1.53 | <0.001 |
| pT | | | | |
| 1 | 0.77 | 0.67 | 0.88 | <0.001 |
| 2 | 0.94 | 0.88 | 1.01 | 0.12 |
| 3 | Ref. | | | |
| 4 | 1.02 | 0.99 | 1.05 | 0.14 |
| X | 0.52 | 0.31 | 0.87 | 0.01 |
| Stage | | | | |
| I | 0.90 | 0.84 | 0.98 | 0.01 |
| II | 1.01 | 0.98 | 1.04 | 0.4 |
| III | Ref. | | | |
| IV | 0.92 | 0.83 | 1.00 | 0.06 |
| X | 0.10 | 0.04 | 0.26 | <0.001 |
| Grade | | | | |
| 1 | Ref. | | | |
| 2 | 1.07 | 1.00 | 1.14 | 0.05 |
| 3 | 1.07 | 1.01 | 1.14 | 0.02 |
| X | 1.09 | 0.85 | 1.39 | 0.5 |

Abbreviations: CI, confidence interval; RR, relative risk; L, lower bound; U, upper bound; OR, odds ratio.
[a] Also adjusted for hospital of surgical treatment [T1NXM0 and ypT0 excluded].
[b] Laparoscopy was forced in the model even if not significant.
[c] Rectum treated with neo-adjuvant therapy.
[d] Length of surgical specimens (mm).

in 2002 to nearly 40% in 2008 ($p < 0.001$). Median surgical specimen length was 25 cm with open surgery and 20 cm with laparoscopy. Laparoscopy was preferred for short resections (<21 cm in 70% of operations) and open surgery for total colectomies (>35 cm in 90% of operations).

In a regression model longer surgical specimen length was associated with male gender, younger age, higher pathological tumour stage (pT), laparotomy, non-screening detected tumours and right-sided tumours (Table 3). Surgical specimens were on average about 2 cm longer in males than in females and 2.5 cm shorter in the elderly

and when diagnosis was by screening. Laparoscopy was associated with a 2.8 cm shorter surgical specimen than open surgery. When laparoscopy and diagnosis at screening were included in the model, year of diagnosis was not significant. In the negative binomial model surgical specimen length was a significant predictor of NLN (Table 2). When length was 10–19 cm under 50% of cases had ≥12 NLN. Length <16 cm was associated with few NLN (median 10) so a low percentage of cases (about 38%) had ≥12 NLN. When length was <10 cm, 19.5% of cases had ≥12 NLN (Table 4). There was a high risk of having <7 NLN and a nearly 10% probability of no lymph node removal. Figure 1 illustrates the relationship between surgical specimens and NLN.

Results were adjusted for hospital where surgery was performed. The hospital pathology laboratory did not impact on the other study variables when it was included in the model with the hospital. Therefore, the pathology laboratory was not retained in the final model.

## Discussion

As expected, given the guideline recommendations, NLN increased over time in the present study, reaching a median of 13 nodes in 2008, when 64% of cases had at least 12 examined lymph nodes, concurring with other studies.[15] As reported, a better focus on guidelines and communication between surgeons and pathologists[16,17] was the main determinant of this rise in NLN which was achieved in Umbria, Italy without any incentive, unlike what was reported in other countries.[18] In our study a rise in NLN was associated with a drop in node positive patients, probably because more early stage cancers were diagnosed through the organized screening program.

Despite this progress, many patients were still not receiving the optimal standard of care even at the end of the study period. Factors impacting upon a harvest of <12 NLN included neo-adjuvant treatment in 17% rectal cancer patients which significantly reduced the NLN.[19] Thus the median NLN was somewhat lower than for colon cancer sites but still similar to SEER reports in the same period.[15] Furthermore, <12 NLN was linked to older age. One might speculate that older patients, many with co-morbidities, are less suitable candidates for extensive surgery and that their dampened immunological reaction to cancer and inflammation might not make lymph nodes visible to the surgeon, who will not then remove them.[20] Early-stage, low grade and left-sided tumours were also associated with <12 NLN.

On the contrary, in the present study the highest number of NLN and the most cases with at least 12 NLN were observed in patients with advanced stage disease and the right colon as disease site even after adjustment for stage and specimen length. Advanced stage disease is associated

Table 3
Regression model for the length of surgical specimens (cm).[a]

| Variables | | B | L | U |
|---|---|---|---|---|
| Gender (p < 0.0001) | Female | Ref. | | |
| | Male | 2.1 | 1.2 | 3.0 |
| Age (p = 0.004) | <50 | −1.1 | −3.6 | 1.5 |
| | 50–64 | Ref. | | |
| | 65–74 | −0.4 | −1.6 | 8.0 |
| | 75–84 | −1.5 | −2.8 | −0.3 |
| | ≥85 | −3.4 | −5.3 | −1.5 |
| Laterality (p < 0.0001) | Right colon | Ref. | | |
| | Left colon | −3.3 | −4.3 | −2.2 |
| | Rectum | −4.3 | −5.5 | −3.1 |
| pT (p < 0.0001) | 0[b] | −1.2 | −7.0 | 4.7 |
| | 1 | −3.4 | −4.9 | −1.9 |
| | 2 | −2.1 | −3.4 | −8.6 |
| | 3 | Ref. | | |
| | 4 | 3.5 | 1.8 | 5.2 |
| Surgery (p < 0.0001) | Laparoscopy | −2.8 | −4.0 | −1.6 |
| | Open | Ref. | | |
| Screening (p = 0.01) | SD | −2.1 | −3.8 | −0.5 |
| | NSD | Ref. | | |

Abbreviations: SD, screening detected; NSD, non-screening detected; CI, Confidence Interval; L, lower bound; U, upper bound; B, beta coefficient.
[a] Also adjusted for hospital of surgery.
[b] After neo-adjuvant chemio-radiotherapy.

Table 4
Median number of examined lymph nodes and proportion of cases with ≥12, ≥7, and 0 examined lymph nodes by length of surgical specimen class.[a]

| Specimen length (mm) | n. | Median NLN | % of cases with NLN | | |
|---|---|---|---|---|---|
| | | | ≥12 | ≥7 | 0 |
| 29–99 | 149 | 7 | 19.5 | 54.4 | 9.4 |
| 100–199 | 1016 | 11 | 47.0 | 77.2 | 2.4 |
| 200–299 | 1383 | 13 | 58.7 | 86.3 | 0.9 |
| 300–399 | 666 | 13 | 63.7 | 87.8 | 1.2 |
| 400–499 | 266 | 13 | 60.5 | 87.6 | 0.4 |
| 500–599 | 101 | 13 | 62.4 | 85.1 | 1.0 |
| 600+ | 153 | 14 | 64.7 | 90.2 | 0.7 |

Abbreviations: NLN, number of examined lymph nodes.
[a] Stage IV cases were excluded.

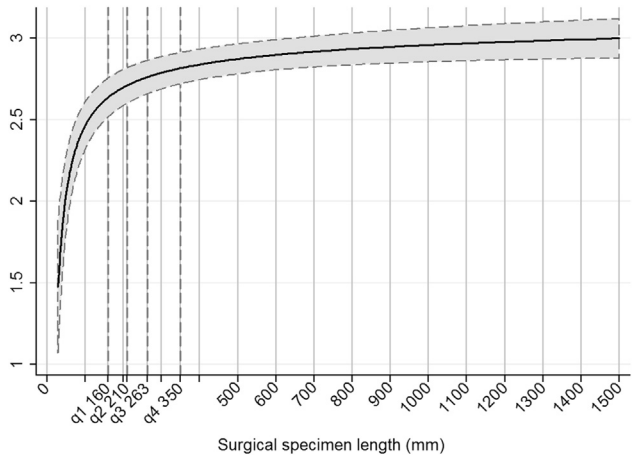


Figure 1. Relationship between surgical specimen length and number of examined lymph nodes.

with a stronger immune response which renders lymph nodes visible for removal[22,23] while right colon tumours are associated with micro-satellite instability[18,23] and other variations in tumour biology, which might account for the greater lymph node counts.

The present study confirmed surgical specimen length was an independent predictor of NLN[9–11,20,21,24,25] as, in all tumour localizations, longer specimens have significantly more lymph nodes in their surrounding tissues. Very short surgical specimens (<10 cm) correlated with a low NLN, as only 19% of cases had 12 or more, and 46% of cases had under 7 NLN. When surgical specimens were 10–19 cm in length compliance with the 12 NLN recommendation was still <50%. Longer surgical specimens were found in males, younger patients, non-screening detected tumours, tumours with a high pathological stage and localized in the right colon. On the other hand, short surgical specimens were associated with laparoscopy, which was increasingly used due to early stage diagnosis. Laparoscopy offers several advantages over open surgery in the immediate post-operative period. When performed by an expert surgeon it is as safe and as effective as open surgery.[6] Compared with open surgery, laparoscopy was not associated with significantly different lymph node harvests[26–28] but was associated with specimen length which, in turn, impacted on NLN. Thus, the lower NLN which was associated with laparoscopy in the present study did not reflect a lower lymph node yield for specimens of similar length, but surgeon preference for an open surgery when large resections were required (e.g. total colectomies).

NLN correlated with overall survival in stages II and III colon cancer[1] and may determine therapeutic choices. In node positive patients, adjuvant chemotherapy is standard treatment. A large NLN harvest may counteract the metastatic spread through the lymphatic drainage system. In node negative patients a large NLN harvest will define those for whom surgery alone should be curative while poor node harvesting might mask stage III disease, thus denying them the benefit of adjuvant chemotherapy and therefore lowering survival rates.[29] In fact, chemotherapy is always recommended for patients with under 10 harvested negative lymph nodes.[6] In the present study specimens <20 cm were associated with a high risk of inadequate NLN and, among node negative patients, 47% of cases had less than 10 examined nodes *vs* 30% when specimens where ≥20 cm. Furthermore, we could hypothesize a certain degree of over-treatment for those true node negative patients which, due to less than 10 NLN, received adjuvant chemotherapy.

Could a more accurate node evaluation reduce the number of patients who are referred to chemotherapy by better identification of positive nodes? The relevance of micrometastases in stage II CRC survival has been appreciated for many years.[29,30] Sentinel node mapping may identify more nodal metastases than standard pathological techniques, and meticulous detection of occult micrometastatic disease may upstage the disease, and impact positively on survival. However, due to the relatively high rate of false negative cases, sentinel node biopsy is now suggested not as an alternative to standard lymphadenectomy, but as an additional approach that improves staging.[31]

The main limitations of the present study are common to cancer registry-based analyses: retrospective nature, delay in data reporting and lack of uniformity in diagnostic and treatment protocols. For example, in the present study, there was no shared protocol for node examination, even though all centres made at least 3 slices. On the other hand, our large unselected patient cohort constituted the main study advantage as it provided data on differences in routine clinical practice which could be extrapolated to the general population.

In conclusion, present findings indicate a 6-year trend towards more conservative surgical approaches like laparoscopy for CRC, a larger lymph node harvest and better compliance with ≥12 NLN for all sites, particularly the right colon and rectum when not treated with neo-adjuvant chemo-radiotherapy. Surgical specimen length emerged as a major determinant of NLN and compliance with international guidelines. Since specimens <20 cm were associated with a low NLN, they should be avoided so as to reduce the risk of over-treatment as adjuvant chemotherapy is recommended for node negative patients with under 10 NLN. Otherwise, strategies to increase NLN should be used when short resections are performed.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

FS conceived the study, and participated in its design and coordination; performed the statistical analysis and wrote the manuscript. FB coordinated the data collecting and reviewed the data quality; performed the statistical analysis. SL, FLR and VL were involved in data collecting. AL, FLR, CJHvdV and CA have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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