https://doi.org/10.31925/farmacia.2026.1.7 **ORIGINAL ARTICLE**

LYMPH NODE YIELD IN COLORECTAL CANCER: BEYOND THE "RULE OF 12"

MARIUS ZAMFIR [1,2], ANDREI-BOGDAN VĂCĂRAȘU [1,2*], MARA MARDARE [1,2], NICOLETA-IRINA BONDOC [1,2], ALINA-IOANA PUȘCAȘU [2,3], THEODOR ANTONIU [2], FLAVIA ULTIMESCU [1,2], FLORIN GRAMA [1,4], LUIZA ȘERBĂNESCU [1,2], GEANINA PAPUC [2], NICULAE IORDACHE [1,5], MIRCEA-BOGDAN MĂCIUCEANU-ZĂRNESCU [6], TUDOR-ION NĂSTĂSESCU [7], DIANA IULIANA STANCIU [8], ARIANA HUDIȚĂ [8], BIANCA GĂLĂȚEANU [8], OCTAV GINGHINĂ [1,2]

[1]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[2]Department 3 Surgery, "Prof. dr. Al. Trestioreanu" Oncologic Institute of Bucharest, Bucharest, Romania
[3]University of Medicine and Pharmacy "Grigore T. Popa", Iași, Romania
[4]Department of Surgery, "Colțea" Clinical Hospital, Bucharest, Romania
[5]Department of Surgery, "Sf. Ioan" Emergency Clinical Hospital, Bucharest, Romania
[6]Plastic and Reconstructive Surgery Discipline - Bucharest Emergency Clinical Hospital, Department 11, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[7]Department of Surgery, Tulcea County Emergency Hospital, Tulcea, Romania
[8]Faculty of Biology, University of Bucharest, Bucharest, Romania

**corresponding author: vacarasu.andrei@gmail.com*

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Abstract

Colorectal cancer (CRC) staging depends heavily on lymph node evaluation, especially because the threshold of 12 examined nodes is used as a standard across all treatment guidelines. The yield of lymph node excision varies depending on tumour position, extent of dissection, histopathological examination, and neoadjuvant treatment. We performed a retrospective study of 86 patients who underwent CRC surgery, analysing the total number of lymph nodes, the number of positive nodes (N+), the lymph node ratio (LNR), and the relationship between tumour location and surgical approach. The median yield value was 12 nodes with compliance ≥ 12 in 52.3% and extended harvest ≥ 18 in 31.4%. The number of nodes differed significantly between locations, with the highest values in the right colon (mean 24) and the lowest in the rectum (mean 9). Compliance ≥ 12 was 28.6%. The LNR (mean 0.086) can help to complete the staging when the harvest is suboptimal. In conclusion, we consider that the threshold of 12 nodes remains a useful minimum in clinical practice, but new values tailored to tumour location may improve patient prognosis.

Rezumat

Stadializarea cancerului colorectal (CRC) depinde foarte mult de evaluarea ganglionilor limfatici, mai ales deoarece pragul de 12 ganglioni examinați este folosit ca standard în toate ghidurile terapeutice. Randamentul exciziei ganglionilor variază în funcție de localizarea tumorii, amploarea disecției, examinarea histopatologică și tratamentul neoadjuvant. Am efectuat un studiu retrospectiv pe 86 de pacienți operați pentru CRC, analizând numărul total de ganglioni, ganglionii pozitivi (N+), raportul ganglionar (LNR) și relația cu localizarea și abordul chirurgical. Randamentul median a fost 12 ganglioni (media 14,5), cu conformitate ≥ 12 în 52,3% și recoltare extinsă ≥ 18 în 31,4%. Numărul de ganglioni a diferit semnificativ între localizări cu valori maxime în cazurile de colon drept (media 24) și minime în rect (media 9), unde conformitatea ≥ 12 a fost 28,6%. LNR (medie 0,086) poate ajuta la completarea stadializării atunci când recoltarea este suboptimală. În concluzie considerăm că pragul de 12 ganglioni rămâne un minim util în practica clinică, însă noi valori adaptate în funcție de localizarea tumorii, precum și integrarea coeficientului LNR pot îmbunătăți prognosticul pacientului.

Keywords: lymph node, colorectal cancer, laparoscopic surgery, oncology

Introduction

Staging of colorectal cancer (CRC) is based on how far the disease has spread locally and whether it has reached the lymph nodes. This is done because N status is one of the most important factors in determining prognosis and survival (1). Evaluating lymph nodes (LN) is very important for determining cancer stage, associated oncologic risk, and adjuvant treatment options. Recent studies in modern registries and population-based settings have shown that examining more lymph nodes improves oncologic outcomes by reducing the risk of understaging and increasing the number of lymph nodes examined. This might also indicate the quality of surgical resection and histopathological examination (2-5).

Lymph nodes not only serve as simple filters along the path of tumour dissemination; they are also highly

specialized immune organs that integrate several crucial processes, such as antigen presentation, lymphocyte activation, and regulation of antitumor immune responses. In CRC, regional lymph nodes are the primary sites where tumour-derived antigens are presented by dendritic cells to naive T and B lymphocytes, thereby initiating adaptive immune responses that may limit tumour progression (6).

In clinical practice, a minimum of 12 lymph nodes has been widely accepted as the standard, reflecting the quality of surgical and histopathologic processing (7-10). Although lymph node yield is influenced by many factors, including tumour location, surgical procedure type, quality of mesocolic or mesorectal dissection, degree of immune response, patient age, and neoadjuvant treatment, it is particularly affected in rectal cancer (11-16). Considering this, recent studies support the setting of thresholds tailored to stage and tumour site, with higher target values in some locations, such as the right colon (17-19). In parallel, other parameters, particularly the ratio of positive lymph nodes to the total number of lymph nodes assessed (lymph node ratio, LNR), have been suggested as potential prognostic markers to better define risk and to minimize understaging in situations where the node count is low (20-30).

From an oncologic perspective, lymph nodes serve both as (i) markers of metastatic spread and (ii) functional components of the antitumor immune microenvironment (Figure 1). The number of the harvested lymph nodes may therefore indicate not only the extent and quality of surgical resection and pathological examination, but also the biological interaction between the tumour and the host immune system. Tumours that are typically associated with a strong immune response, such as those with high microsatellite instability, are often accompanied by lymphoid hyperplasia and increased detectability of lymph nodes. In contrast, neoadjuvant therapies and immunosuppressive tumour phenotypes may induce lymph node atrophy and reduced yields, particularly in rectal cancer. This immunobiological perspective provides a conceptual framework for understanding why lymph node count varies by tumour location and treatment context, and why quantitative thresholds should be interpreted alongside biological and clinical factors (31).

Therefore, available evidence suggests that the results in colorectal cancer are not only influenced by factors related to the tumour or the surgical intervention, but also in a larger context of the multimodal treatment, including administration of systemic therapy and radiotherapy. Types of practice and guidelines may differ across institutions and healthcare systems, which can influence short- and long-term outcomes. These aspects have been discussed in many studies and provide an important perspective on current data in real-life practice (32-38).

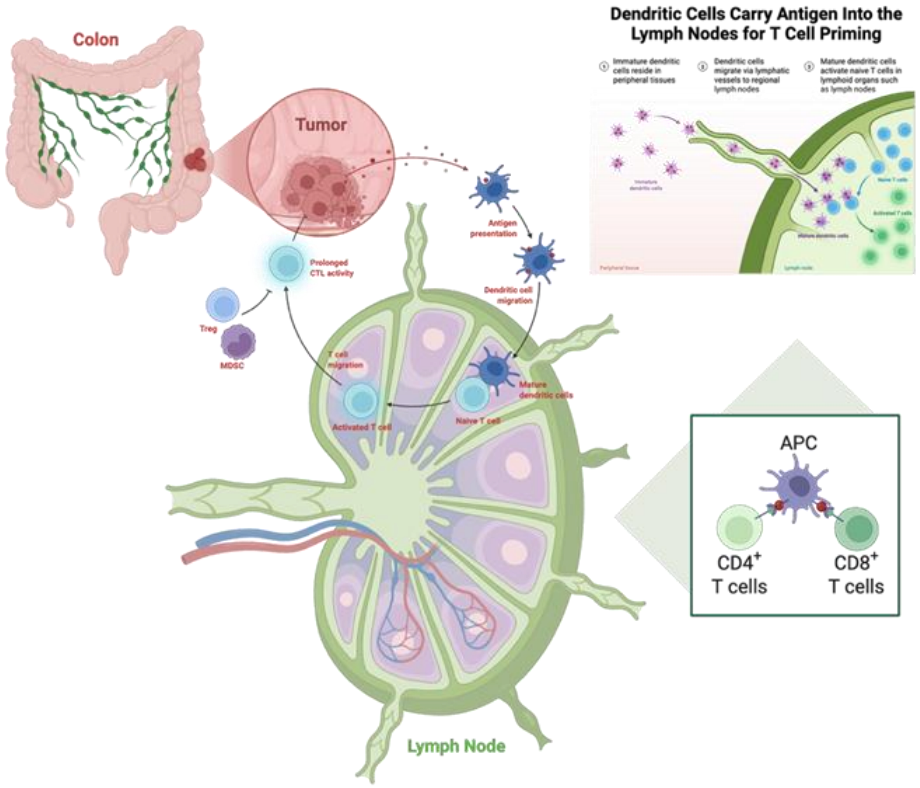

Figure 1.
Immunological role of lymph nodes in colorectal cancer (created with BioRender.com)

In this context, the aim of the current study was to determine the factors affecting lymph node yield in CRC, how often we achieve the 12-node target, and whether the lymph node ratio is helpful when node counts are low.

Materials and Methods

Study design and setting

This was a retrospective single-centre study based on an internal institutional registry. The cohort was formed from consecutive patients who underwent surgery for colorectal cancer in Oncological Institute of Bucharest "Prof. dr. Al. Trestioreanu", a tertiary academic and clinical hospital, during a study period of one year in 2025. The study was approved by the institutional Ethics Committee (approval No. 10/18.03.2025).

Patient selection

Inclusion criteria were age ≥ 18 years, histologically confirmed primary colorectal adenocarcinoma, elective and curative resection with oncologic lymphadenectomy, and availability of a final pathology report including lymph node harvest. Patients were excluded if they underwent only local excision (polypectomy, transanal local excision/TEM/TAMIS), palliative operations without oncologic lymphadenectomy, R1/R2 resections, surgery for recurrent colorectal cancer, or surgery for hereditary colorectal cancer syndromes (familial adenomatous polyposis, Lynch syndrome). Patients with synchronous distant metastases (stage IV) were excluded.

Clinical and tumour variables

From the institutional registry and pathology reports, we recorded age, sex, length of hospital stay, post-operative days, surgical procedure type, and surgical approach (open or laparoscopic). Tumour location was classified by the type of resection as right colon, transverse colon, left colon, rectosigmoid, and rectum. Tumour-related variables collected (when reported) included pathological T stage, pathological N stage, overall TNM stage, histologic subtype, differentiation grade, and lymphovascular invasion. Still, not all reports included perineural invasion or microsatellite instability/deficient mismatch repair (MSI/dMMR) status, so these variables were excluded from the study.

Neoadjuvant and adjuvant treatment

The patients who received neoadjuvant and adjuvant therapy were recorded. Neoadjuvant chemoradiotherapy (CRT) was administered to patients with locally advanced rectal cancer according to a multidisciplinary team decision. Long-course CRT typically consisted of pelvic radiotherapy 45 - 50.4 Gy delivered in 25 - 28 fractions with concurrent chemotherapy (capecitabine) (32, 33). Where indicated, short-course radiotherapy (25 Gy in 5 fractions) followed by systemic therapy and/or surgery could be used (32, 33). Adjuvant chemotherapy was considered in accordance with standard indications (stage III and high-risk stage II colon cancer and selected rectal cancer scenarios), most commonly with oxaliplatin-based schemes (FOLFOX or CAPOX) or fluoropyrimidine monotherapy when appropriate (32-34). Information on neoadjuvant/adjuvant systemic therapy and radiotherapy was incomplete because some members of the cohort received these treatments at external centres. Because we were missing this information, these variables were excluded from the analytic model.

Surgical procedures

Surgical procedures included right and left hemicolectomy, transverse colectomy, rectosigmoid resection and rectal resections. Surgical approach was recorded as open, laparoscopic, or hybrid. For colon cancer, oncologic resection aims to adhere to the principles of complete mesocolic excision (CME), defined as sharp dissection along the embryological mesocolic planes with an intact mesocolic fascia and central vascular ligation at the origin of the supplying vessels (38). For rectal cancer, total mesorectal excision (TME) was defined as the complete removal of the mesorectum within the visceral mesorectal fascia with an intact cylindrical specimen, preserving the mesorectal tissue (36).

Pathological examination of specimens

All resection specimens were processed in accordance with the institution's colorectal cancer pathology protocol. Specimens were fixed, and the mesenteric/mesorectal fat was carefully dissected and palpated to identify lymph nodes. When needed, additional fat dissection was performed to maximize nodal retrieval. Lymph nodes were submitted for the routine histopathological examination, and the total number of examined nodes and the number of metastatic (positive) nodes were extracted from the final pathology report.

Definition of study variables

The primary study variable was the total number of lymph nodes examined, as reported in the final pathology report. Secondary variables included the number of positive lymph nodes and the lymph node ratio (LNR), calculated as the number of positive lymph nodes divided by the total number of examined nodes. Adequate lymph node harvest was defined as ≥ 12 examined lymph nodes. An extended harvest was defined as ≥ 18 examined lymph nodes, a threshold previously associated with improved prognostic stratification and survival in lymph node-negative colon cancer (14). For LNR, we used a pragmatic cut-off of 0.20, which has been widely applied in the literature and supported by population-based data and meta-analyses (29, 30).

Statistical analysis

The statistical analysis assessed data quality by identifying missing values and range plausibility, calculating the mean ± standard deviations (SD) for approximately normal distributions and the median IQR for asymmetric distributions, and reporting

proportions for categorical variables. The distribution tests used were the Shapiro-Wilk test for normality and qualitative inspection of histograms and Q-Q plots with Levene's test for homogeneity of variances within ANOVA. For group comparisons, we used the Student's t-test for two groups with normal distributions and the Mann–Whitney U test for two groups with non-normal distributions. For more than two groups with normal distributions, we used ANOVA/Welch ANOVA; for more than two groups with nonparametric distributions, we used the Kruskal-Wallis test; and for both, we conducted post hoc Mann-Whitney tests with the Bonferroni correction. To evaluate correlation, we used Pearson (for normally distributed data) and Spearman (for ordinal or non-normally distributed data) correlation coefficients. To evaluate the probability of adequate lymph node harvest (≥ 12 nodes), we applied a logistic regression. When some data structures were inadequate for the model, the interpretation relied on exact comparisons and robust estimation. A $p < 0.05$ level was used for statistical significance. Statistical analyses were performed using IBM SPSS version 30 and Microsoft Excel.

Results and Discussion

Patient characteristics and overall lymph node yield

The results we obtained in the analysed study group are consistent with the international specialty literature on the importance of efficient lymph node harvesting for the prognosis of colorectal cancer. In our study group, the mean number of lymph nodes examined and the rate of conformity to the 12 thresholds fall within the ranges reported in other large population-based series and multicentre studies, confirming the validity of our observations (1-6).

During the study period, a total of 102 consecutive patients were registered, but only 86 met the eligibility criteria; these patients were included in the final analysis. The mean age was 66.4 ± 13 years (median 68, IQR 56 - 75), and 60.5% were male. Baseline demographic and perioperative characteristics are summarized in Table I.

The median number of lymph nodes examined was 12 (IQR 7 - 20), with a mean of 14.5 (Figure 2). Node-positive disease was identified in 22/86 patients (25.6%). Adequate harvesting (≥ 12 lymph nodes) was achieved in 45/86 cases (52.32%), and an extended harvest (≥ 18 lymph nodes) in 27/86 cases (31.4%) (Figure 3).

Table I

Demographic characteristics of the group

Indicator	Value
No. patients (n)	86
Age (years), mean ± SD	66.38 ± 11.31
Male, n (%)	52 (60.5%)
Duration of hospitalization (days), mean ± SD	11.30 ± 3.13
Postoperative days (days), mean ± SD	8.49 ± 3.00
Excised lymph nodes (total), mean ± SD	14.55 ± 9.76
Positive nodes, mean ± SD	1.26 ± 3.31
LNR, mean ± SD	0.086 ± 0.198
Compliance ≥ 12 nodes *, n/N (%) [CI5%]	45/86 (52.32%) [0.424-0.632]
N+, n (%) [CI5%]	22 (25.6%) [0.175-0.357]
LNR ≥ 0,20, n (%) [CI5%]	12 (14.0%) [0.082-0.228]

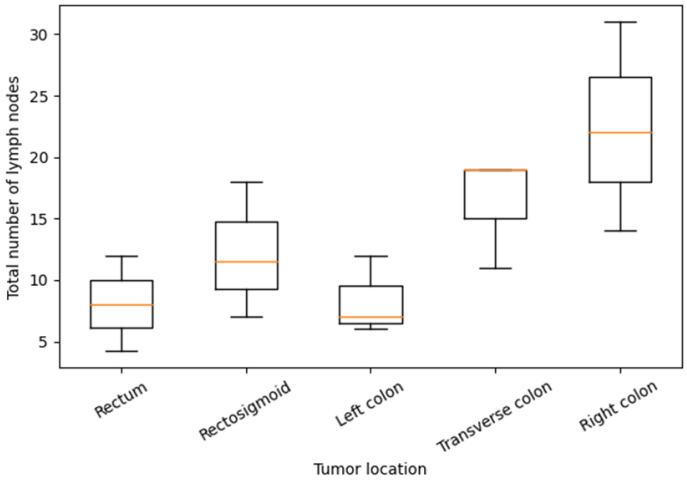

Figure 2.

Total number of harvested lymph nodes by tumour location

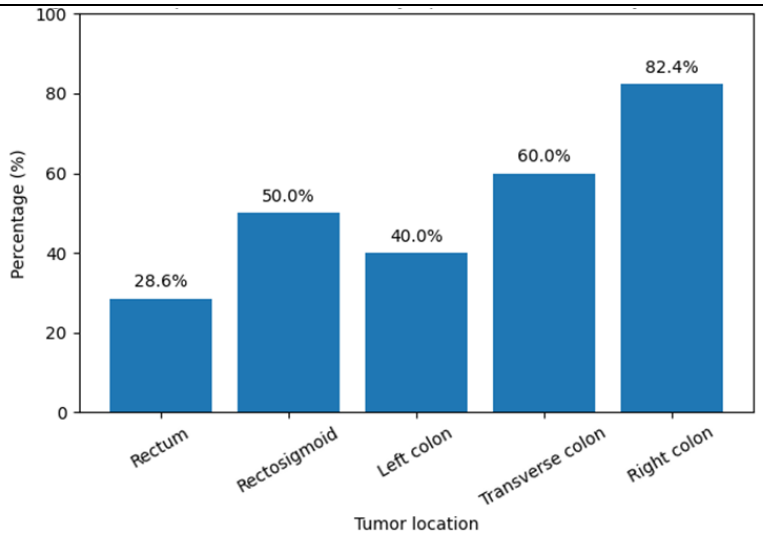

Figure 3.
Compliance with the ≥ 12 lymph node threshold by tumour location

Lymph node yield according to tumour location
The differences in anatomic and oncologic locations are presented in Table II.
The total number of lymph nodes differed significantly across locations (Kruskal-Wallis H = 21.45, p = 0.0003). The right colon represented the best yield of lymph nodes (mean 24 ± 11.7), compared to the rectum (mean 9.1 ± 6.8). The conformity of ≥ 12 also varied between locations (χ^2 p = 0.043), achieving 82.4% in the right colon, but only 28.6% in the rectum.

Table II
Lymph node indicators by tumour location

Location	n	Total LN (mean ± SD)	Total LN (median [Q1–Q3])	≥ 12LN, %	N+, %	LNR mean
Rectum	14	9.1 ± 6.8	8.0 [4.2–12.0]	28.6	21.4	0.129
Rectosigmoid	44	12.6 ± 7.3	11.5 [7.0–18.0]	50.0	22.7	0.061
Left colon	5	10.6 ± 7.4	7.0 [6.0–12.0]	40.0	20.0	0.133
Transverse colon	5	19.0 ± 10.4	19.0 [11.0–19.0]	60.0	40.0	0.147
Right colon	17	24.0 ± 11.7	22.0 [14.0–31.0]	82.4	35.3	0.081

This profile is connected with the clinical reality that in rectal cancer, the neoadjuvant treatment and the particularities of the mesorectum can significantly reduce the number of identified lymph nodes, even in the conditions of a correct total mesorectum excision. The low harvesting efficiency is often attributed to the effects of neoadjuvant treatment and to tissue alterations induced by chemoradiotherapy.
Referral centres with extensive experience suggest that even inverse relationships between the number of lymph nodes and outcome may exist, depending on post-neoadjuvant nodal status, underscoring that thresholds must be interpreted differently from those in the colon.
Lymph node positivity and lymph node ratio
Lymph node involvement was present in 22 patients (N+, 25.6%, CI95% 0.175 - 0.357). Although the N+ rates varied numerically across locations, the differences were not statistically significant in this cohort (χ^2, p = 0.753), likely due to the small sizes of some subgroups. From the perspective of staging quality, a critical aspect is that a low harvest can mask lymph node metastases; in intermediate stages, it influences the indication for adjuvant therapy.
The mean LNR was 0.086 ± 0.198, with a strongly asymmetric distribution. A widely used clinical cut-off is LNR ≥ 0.20. In our study group, 12 patients (14%, CI95% 0.082 - 0.228) have met this criterion.
In the event of a low harvest, LNR becomes unstable and may under- or overestimate the risk, depending on the absolute number of lymph nodes. This statistical finding supports the recommendation that LNR should be interpreted together with the total harvest and in a clinical context.
Influence of surgical approach on lymph node harvest
Regarding the surgical approach, in the unadjusted analysis, there was no significant difference in the total number of lymph nodes among the laparoscopic, open, and mixed approaches (Kruskal-Wallis, p = 0.151). In the adjusted model, the laparoscopic approach was not independently associated with achieving the threshold of ≥ 12 (OR 1.19, p = 0.752).
This result is compatible with the hypothesis that differences in lymph node harvest are due to the

anatomy, the quality of mesocolon or mesorectum resection, and the intensity of histopathological examination, rather than the surgical approach.

Interpretation of lymph node yield and alternative prognostic indicators

The variability in lymph node harvest yield between patients and across tumour locations can be explained by factors related to the specimen, surgical technique, and histopathological examination. Studies that analysed these determinants, including tumour characteristics, resection quality, and histological examination, suggest that lymph node yield is a composite indicator reflecting both the quality of the resection and the rigor of the histological examination (16, 17).

In a recent analysis, Ye Tian et al. identified N-stage-specific inflection points and suggested that overall survival improves when the number of examined lymph nodes exceeds 18 for N0 and N1a disease and 19 for N1b and N2a disease (1).

In stages II - III, Hyunwook Kim *et al*. (two large observational cohorts) reported that examining < 20 nodes was more strongly associated with worse prognosis than the traditional < 12 threshold and that higher yields increased detection of pN2 disease (4).

In a Japanese nationwide cohort, Kazuma Ito et al. reported a median harvest of 18 nodes (stage II IQR 12 - 25; stage III IQR 13 - 25), with higher counts in right-sided versus left-sided cancers (median 21 *vs* 17) (5).

In stage III, Ran Wei *et al*. demonstrated better long-term outcomes for patients with ≥ 17 examined nodes and showed that the benefit from adjuvant chemotherapy was most evident when ≥ 12 nodes were examined (9).

Paweł Mroczkowski *et al*., in 7012 stage II - III colon cancer patients, reported a mean yield of 22 nodes (median 20) with improved 5-year overall survival when ≥ 12 nodes were examined (68% *vs* 63%); they also showed stepwise survival stratification by lymph node ratio (LNR), from 75.5% for LNR < 0.05 to 33.1% for LNR ≥ 0.4 in the ≥ 12 group (12).

For N0 situations, Fei-Long Ning *et al*. analysed 6269 pN0 colon cancer cases and identified an 18-node threshold as independently associated with better overall survival (13).

Together, these data support a refined interpretation: the 12-node threshold remains minimal but targets can be more ambitious in some subgroups, especially in right colon cancer, with the mention that thresholds should be adjusted in the clinical context for rectal cancer.

Clinical implications and limitations of the "Rule of 12"

The debate over the fixed rule of 12 lymph nodes highlights the utility of the threshold as an indicator, but also the risk of turning it into a rigid target that is unrelated to context (19). In special scenarios (*e.g.*, synchronous metastasis), the yield may remain prognostically relevant, as Jiao *et al*. suggested (22).

From the perspective of systemic therapy, lymph node evaluation determines the indication for adjuvant chemotherapy. In colorectal cancer, stage III is defined by the presence of metastatic lymph nodes and represents a definite indication for adjuvant chemotherapy. In stage II, a low number of harvested nodes (< 12) is often considered a risk factor and warrants closer monitoring (32). Therefore, these situations can lead to understaging (false pN0) with possible undertreatment if no chemotherapy is administered because of an incomplete nodal evaluation.

For rectal cancer, the interpretation of lymph node yield is further complicated by neoadjuvant therapy, which can reduce node size and detectability. Guidelines increasingly emphasize integrating pre-treatment staging, response to neoadjuvant therapy, circumferential resection margin risk and postoperative pathological findings (including ypN status) when deciding on adjuvant systemic therapy or total neo-adjuvant therapy strategies (33, 34). Accordingly, low lymph node counts after neoadjuvant treatment should not be treated as a stand-alone marker of "poor quality" without considering the therapeutic context.

For N+ cases, including LNR in reports can improve internal stratification and comparability (3, 28). In metastatic disease (stage IV), LNR can predict overall survival (24). In biological subgroups such as CCR MSI-high, the number of negative nodes was investigated as a supplementary prognostic marker (25). In stage III, modified LNR-based systems can improve risk stratification compared with classic N staging (26). A meta-analysis supports LNR as a survival predictor, further consolidating its inclusion in prognostic discussions (29).

Revaluations of the extent of lymph node dissection in primary resection have shown that a higher number of lymph nodes is not always better across all sub-groups, and that a low node yield remains a major risk for substaging (18). When lymph node harvest is suboptimal, alternative methods for evaluating the nodal status can aid risk prediction and are recommended (27).

Conclusions

Lymph node evaluation is essential for accurate staging of colorectal cancer and for assessing the quality of the surgical procedure. In our study group, data on node yield and conformity with the 12 threshold are comparable to those reported in the current literature, with significant differences in tumour location, particularly between the right colon and rectum, reflecting known anatomical and therapeutic particularities.

The data obtained support the use of a 12-node threshold as a minimum standard but highlight the need for an interpretation adapted to the clinical context. Integrating new indicators, such as LNR, can provide supplementary prognostic information, especially in cases with suboptimal node yield, thereby improving staging and treatment guidance.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Ethics approval and consent to participate

All experimental procedures were approved by the Ethics Committee (approval No. 10/18.03.2025). Informed consent was obtained from all patients included in the study.

AI use disclosure

During the preparation of this manuscript, the author(s) used Grammarly AI for editing assistance and language improvement, specifically to improve spelling, grammar, word choice, readability and clarity. The author(s) reviewed and revised all outputs from these tools and take(s) full responsibility for the final content of the work.

Conflict of interest

The authors declare no conflict of interest.

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