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ORIGINAL ARTICLE – COLORECTAL CANCER

Prognostic Value of the Lymph Node Ratio in Stage III Colorectal Cancer: A Systematic Review

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ABSTRACT

Background. Although nodal invasion represents one of the most powerful prognostic indicators in colorectal cancer, marked heterogeneity exists within stage III patients. Recently, the lymph node ratio (LNR), defined as the ratio of the number of positive nodes over the total number of examined nodes, was proposed to stratify outcome in stage III patients.

Methods. A systematic search was performed for studies examining the prognostic significance of the LNR in colon or rectal cancer. Individual studies were assessed for methodological quality and summary data extracted. Hazard ratios from multivariate analyses were entered in a fixed-effects meta-analysis model.

Results. In total, 16 studies were identified including 33,984 patients with stage III colon or rectal cancer. In all identified studies, the LNR was identified as an independent prognostic factor in patients with stage III cancer of the colon or rectum. The prognostic separation obtained by the LNR was superior to that of the number of positive nodes (N stage). The pooled hazard ratios for overall and disease-free survival were 2.36 (95% confidence interval, 2.14–2.61) and 3.71 (95% confidence interval, 2.56–5.38), respectively.

Conclusions. The LNR allows superior prognostic stratification in stage III colorectal cancer and should be validated in prospective studies.

Colorectal cancer (CRC) kills more than half a million people worldwide per year, mainly in the developed world.[1] Among the known prognostic factors, the number of invaded locoregional lymph nodes has been established as the single most important prognosticator in both colon and rectal cancer, and this variable forms the basis of the current tumor, node, metastasis system (TNM) staging system of node positive disease.[2,3] Marked prognostic heterogeneity may exist, however, within the stage III population. One way to address this apparent heterogeneity has been to include the tumor (pT) stage as well as the number of positive nodes, resulting in the stage IIIA, IIIB, and IIIC subsets of the TNM staging system.[4]

Although the exact underlying mechanisms are unclear, it has become apparent over the last decade that the number of normal lymph nodes retrieved from the resection specimen conveys important prognostic information in both stage II and stage III CRC.[5–7] Possible explanations include stage migration, statistical effects, and, although less likely, a therapeutic benefit of removing more regional lymph nodes.

Intuitively, therefore, a prognosticator encompassing the information contained in the number of positive nodes and in the number of examined (or negative) nodes would allow better stratification of stage III CRC patients, allowing to tailor adjuvant therapy or the intensity of follow up. The lymph node ratio (LNR), i.e., the ratio of positive divided by the total number of examined nodes, combines both parameters and has been shown to represent a powerful independent prognosticator in several solid cancer types.[8–10] The aim of this work was to systematically review the available evidence on the additional prognostic value, if any, of the LNR as opposed to the number of positive nodes in stage III CRC.

METHODS

A systematic review of the literature was performed for the following electronic databases: Cochrane Central Register of Controlled Trials, ISI Web of Knowledge version 4.6 (Science Citation Index, Current Contents)

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from 1975 until June 2009, Embase, and Medline (PubMed). Electronic database searches were performed with the Boolean combination [(LNR or fraction or proportion or percentage or ratio) and nod* and (colo* or rectal)]. Additional information was retrieved from published reviews, reference lists from relevant papers, and ISI Scientific Web Plus. Search criteria were as follows: human studies including node positive (stage III) colon and/or rectal cancer; peer-reviewed full papers; and inclusion of the ratio of positive over total number of lymph nodes as a prognosticator of cancer outcome. No language restrictions were applied. The following data were extracted from the selected papers: author, publication year, total number of patients, number of patients with node-positive disease, median or mean number of nodes examined, type of study, definition of the LNR strata, type of survival analysis, and results from multivariate regression analysis. Whenever available, hazard ratios and associated 95% confidence intervals (95% CIs) from Cox proportional hazard regression were extracted and used to calculate the log rank observed minus expected events (O − E) and the log rank variance (*V*). A fixed-effects meta-analysis of individual trial data was performed by Peto's method (RevMan 5.0 software, Cochrane Collaboration). Heterogeneity across studies was assessed by the *Q* test.

All papers were assessed for study type, methodological quality, and the level of evidence. The level of evidence was scored according to the classification proposed by the Oxford Centre for Evidence-Based Medicine.[11] Data extraction and methodological evaluation were performed in duplicate; conflicting results were resolved by consensus.

RESULTS

Identification of Relevant Studies

No formal meta-analyses or systematic reviews were identified in the Cochrane Central Register of Controlled Trials on the prognostic value of the LNR in colon and/or rectal cancer. The primary electronic database search resulted in 1,317 potential full-text papers. After review of the title and/or abstract, 19 relevant publications were identified. Four papers were excluded from further analysis. The 2009 paper from Wang et al. reported additional results from analysis of the Surveillance, Epidemiology, and End Results (SEER) registry that was reported in a previous publication included in the analysis.[12] Similarly, the work of De Ridder et al., published as a letter, was also based on analysis of the SEER registry, and the information provided was therefore thought to be redundant to the work of Wang et al.[13] The report by Trufelli et al., describing a group of 106 colon cancer patients, was excluded because 58% of patients had stage IV disease and multivariate analysis of factors influencing survival in stage III patients was not available.[14] Along the same lines, the paper by Derwinger and Gustavsson was excluded because their study population consisted of stage IV patients only.[15] One additional paper was identified through a reference listing. Therefore, a total of 16 relevant papers were included in the analysis encompassing a total of 33,984 stage III CRC patients.

Methodological Quality

No prospective randomized trials were identified evaluating the prognostic significance of the LNR in stage III CRC. Four trials were retrospective nested cohort studies of patients enrolled in prospective randomized trials of either chemotherapy or chemoradiation in CRC (Table 1). Two trials reported on population-based cancer registry data (SEER and the New Zealand Cancer Registry). The remaining 10 trials were retrospective case series from one ($n = 9$) or several ($n = 1$) institutions.

Of the 16 identified trials, 8 (50%) included colon cancer patients only, 4 (25%) included rectal cancer only, and 4 (25%) included both colon and rectal cancer. Of the eight papers reporting on rectal cancer patients, only the work of Stocchi et al. specifically defined rectal cancer in anatomical terms.[16] Seven trials (44%) included only stage III cancers, while the other nine trials (56%) included both stage II and stage III disease. All identified trials used the TNM classification system.

In all but one trial, the prognostic value of the LNR was assessed in the presence of possible confounding covariates by Cox multivariate regression. Schumacher et al. reported univariate survival analysis only by the log rank test.[17]

Thirteen trials reported the median or mean numbers of lymph nodes collected; in only three of these was this value below 12. No summary statistic was calculated because four papers reported the mean instead of the median, and three trials reported node yield for stage II and III patients combined (Table 1). Demographic data are listed in Table 2.

Definition of LNR Categories

All 16 papers studied the prognostic value of the LNR as a categorical variable rather than as a continuous one. The number of categories varied between 2 and 10 (Table 2). In five papers (31%), the choice of the LNR categories is not motivated, while one study refers to published literature data and one study uses the mean LNR as a cutoff to create two categories. In eight studies (50%), LNR quartiles were constructed on the basis of the frequency distribution found in the individual studies; five of these papers used reclassification of the obtained categories based on

TABLE 1 Methodological quality of the identified studies

Study	Year of evidence	Location examined	N total/N stage III	Design	Level of evidence	Median # of examined nodes Stage III
Stocchi[16]	2001	Rectal	673/463	Nested multicenter cohort study (chemotherapy trials)	IIB	–
Berger[19]	2005	Colon	3,557/2,763	Nested multicenter cohort study (INT-0089 trial)	IIB	13
Edler[41]	2007	Colon + rectum	1025/527	Nested multicenter cohort study (chemotherapy trials)	IIB	5
Schumacher[17]	2007	Colon	232/74	Retrospective single-center study	IV	17[a]
Lee[42]	2007	Colon	201	Retrospective single-center study	IV	17
Derwinger[43]	2008	Colon	265	Retrospective single-center study	IV	11
Peng[44]	2008	Rectum	318	Retrospective single-center study	IV	12[b]
Peschaud[20]	2008	Rectum	352/127	Retrospective single-center study	IV	23[b]
Rosenberg[18]	2008	Colon + rectum	3,026/1,328	Retrospective single-center study	IV	16[a]
Wang[45]	2008	Colon	24,477	Population registry (SEER)	IIIB	–
Kim[46]	2009	Rectum	232	Nested single-center cohort study (CRT trials)	IIC	17
Moug[47]	2009	Colon + rectum	295/115	Retrospective multicenter study	IV	–
Priolli[48]	2009	Colon + rectum	113/50	Retrospective single-center study	IV	23[a,b]
Park[40]	2009	Colon	318	Retrospective single-center study	IV	24[b]
Vather[49]	2009	Colon	4,309/2,364	Population registry (New Zealand Cancer Registry)	IIIB	11
Vaccaro[50]	2009	Colon	362	Retrospective single-center study	IV	20
Total stage III			33,984			

CRT chemoradiotherapy, *SEER* surveillance, epidemiology, and end results cancer registry

[a] In the total group of patients (stage II and stage III)

[b] Mean value

maximal separation of the survival curves by univariate log rank analysis. Only the work by Rosenberg et al. mentions the use of an adapted statistical methodology (classification and regression trees) to define the cutoff points that result in optimal categorization of the LNR.[18]

The reported cutoff values defining the LNR category with the best outcome vary widely between 5 and 25% (mean 13.2%; median 11.5%).

Prognostic Value of the LNR Versus the Number of Positive Nodes

All identified studies showed the LNR to represent an independent predictor of overall survival (OS), disease-free survival (DFS), or cancer-specific survival by multivariate analysis (15 studies) or univariate analysis (1 study). Importantly, in seven papers (44%), the total number of positive nodes (N stage) no longer represented an independent prognosticator when the LNR was included in the regression model. In four studies (25%), the prognostic significance of the number of positive nodes was not available. Four papers (25%) reported that the number of positive nodes was found to be a statistically significant predictor of outcome but with a lower statistical significance compared to the LNR. Stocchi et al. found both LNR and number of positive nodes to predict OS in rectal cancer; no *P* values or other detailed measures of statistical significance are available in this report.[16] Of note, Berger et al. found that when less than 10 nodes were examined, the total number of positive nodes but not the LNR was statistically significantly associated with OS, i.e., the opposite of what was found when 10 or more nodes were examined.[19] Taken together, the 16 identified papers provide consistent and convincing evidence of the independent prognostic value of the LNR in colon and rectal cancer (Table 3).

Meta-Analysis

The hazard ratio and associated confidence interval associated with either DFS or OS was available in only a few studies. The hazard ratios for DFS (1.016) and OS (1.019) reported in the study by Peschaud et al. were considered not to be clinically important and were excluded from the meta-analysis.[20] The pooled hazard ratio for OS was 2.36 (95% CI, 2.14–2.61); heterogeneity was statistically significant (I^2 79%, Fig. 1a). The pooled hazard ratio for DFS was 3.71 (95% CI, 2.56–5.38); no heterogeneity was associated with this outcome parameter (Fig. 1b).

DISCUSSION

The presence of metastatic spread to locoregional lymph nodes has since long been established as an important

TABLE 2 Demographic and methodological details of studies of colorectal cancer

Study	Patient age	Inclusion period	Follow-up time	Outcome parameters	Treatment
Stocchi[16]	–	1979–1992	Median 6.7 years	LR, OS	Surgery, postoperative RT (NCCTG trials 79-47-51, 86-47-51, 90-47-51/INT 0114)
Berger[19]	Median 63.7 years	1988–1992	Median 6.6 years	OS, CSS, DFS	Surgery, postop CT (INT 0089 trial)
Edler[41]	313 < 60 years	1991–1997	Median 5 years	OS	Randomized trials of surgery alone vs. surgery and 5-FU based
	712 ≥ 60 years				5-FU based chemotherapy
Schumacher[17]	Median 71 years	1998–2004	–	OS, DFS	Surgery; adjuvant therapy according to stage and physician preference
Lee[42]	Median 59 years	1995–2001	Median 5.3 years	DFS	Surgery with adjuvant 5-FU based CT
Derwinger[43]	Mean 72 years	1999–2003	–	DFS	Surgery with (60%) or without adjuvant CT
Peng[44]	Mean 55.4 years	1990–2004	Mean 3.4 years	LR, DFS, OS	Surgery with (62%) or without adjuvant therapy
Peschaud[20]	Mean 64.5	1998–2004	Mean 3.2 years	OS, DFS	Preoperative RT or CRT (43%), surgery, adjuvant CT (33%)
Rosenberg[18]	Median 65 years	1982–2006	Median 6.6 years	CSS	Preoperative CRT (11%), surgery, adjuvant therapy (not specified)
Wang[45]	Mean 69.2 years	1988–2003	–	OS	Surgery, adjuvant therapy (not specified)
Kim[46]	Median 54 years	1996–2006	–	OS, DFS	Trials of postoperative CT and RT sequence (58%) and pre- vs. postoperative CRT (42%)
Moug[47]	Mean 70 years	2001–2004	Median 4 years	OS	Surgery and (neo)adjuvant therapy (28.5%)
Priolli[48]	Mean 58 years	–	–	OS	Surgery; no preoperative therapy; adjuvant therapy not specified
Park[40]	Median 61.3 years	1996–2006	Median 3 years	DFS	Surgery; no data on adjuvant therapy
Vather[49]	Mean 70 years	1995–2003	–	OS	Surgery; no data on adjuvant therapy
Vaccaro[50]	Mean 67.4 years	1980–2005	Median 3.5 years	OS, DFS, CSS	Surgery; >90% adjuvant CT

OS overall survival, *DFS* disease-free survival, *CSS* cancer-specific survival, *LR* local recurrence, *CT* chemotherapy, *5-FU* 5-fluorouracil, *RT* radiotherapy, *CRT* chemoradiation

prognosticator in most solid cancers. Uncertainty persists, however, regarding the biological significance of lymph node metastasis in the course of the disease. The classical Halstedian paradigm views the lymphatic barrier as the first line of defense against stepwise systemic spread. Assuming this model reflects the reality, timely and adequate lymphadenectomy would prevent systemic spread and improve outcome. The early systemic spread paradigm, on the contrary, contends that systemic spread starts early in the course of the tumor-host relationship, is independent from lymph node metastasis, and therefore the natural history of the disease will hardly be influenced by extensive locoregional surgery.[21]

A similar debate surrounds the role of lymphadenectomy in CRC. This debate has been fueled by the following paradox: on the one hand, clinical trials examining extensive (extramesenteric) lymphadenectomy in CRC failed to identify any survival benefit.[22,23] On the other hand, data from large retrospective studies have consistently shown a positive association between survival and the number of lymph nodes examined in the surgical specimen.[6] It is commonly assumed that this observation is not explained by a therapeutic effect of removing more lymph nodes, but rather reflects stage migration. Moreover, the association between node counts and survival is confounded by variables related to the tumor (location, microsatellite instability), the individual patient (age, obesity, immune response), and the health care setting (surgeon experience, hospital volume).[24–26] Several professional organizations have proposed a minimum node yield of 12 to allow accurate staging of stage II CRC.[27,28] The number 12 does not hold any particular biological significance; rather, it likely results from a statistical probability distribution indicating that once more than 12 nodes have been assessed, the likelihood of missing a remaining positive mesenteric node becomes very small (Fig. 2).[29] Others have argued that no minimal node yield should be specified, but that as many nodes as possible should be examined.[30] Recently, analysis of pathological staging of 131,953 patients from the SEER database by a beta-binomial model suggested that the minimum number of nodes required for adequate N staging depends on the T stage: to achieve a probability of correct staging of 90%, a single node needs to be examined for T1, four nodes for T2, 13 nodes for T3, and 21 nodes for T4 disease.[31]

TABLE 3 Summary of prognostic outcome data

Study	LNR categories (%)	LNR stratification basis	Data analysis	Prognostic significance		
				LNR	No. of positive nodes	Other
Stocchi[16]	<25, 25–50, 51–75, > 75	–	MV (Cox)	Significant predictor of LR and OS	Significant predictor of OS	–
Berger[19]	<5, 5–19, 20–39, 40–100	Literature data	MV (Cox)	Significant predictor of OS, DFS, and CSS when ≥ 10 nodes examined	NS when ≥ 10 nodes examined	pT, no. of examined nodes
Edler[41]	<20, 20–49, 50–69, 70–100	–	MV (Cox)	Significant predictor	–	No. of examined nodes of OS in colon and rectal cancer adjuvant CT when ≥12 nodes analyzed
Schumacher[17]	<18, ≥18	Mean LNR	UV (log rank)	Significantly associated with DFS but not OS	–	–
Lee[42]	1–11, 12–24, 25–92	Quartiles reclassified on the basis of Kaplan–Meier plots	MV (Cox)	Significant predictor of DFS	NS	Lymphovascular Invasion
Derwinger[43]	<12, 12–27, 27–45, 45–100	Ratio quartiles	MV (Cox)	Significant predictor of DFS ($P < .0002$)	$P < 0.04$	Differentiation adjuvant therapy
Peng[44]	<14, 14–49, 50–100	Quartiles reclassified on the basis of Kaplan–Meier plots	MV (Cox)	Significant predictor of LR, DFS, and OS	NS	pT stage
Peschaud[20]	1–7, 7–20, >20	Quartiles reclassified on the basis of Kaplan–Meier plots	MV (Cox)	Significant predictor of OS and DFS	NS	CRM positivity, neural invasion, differentiation
Rosenberg[18]	1–17, 18–41, 42–69, >70	Classification and regression trees	MV (Cox)	Significant predictor of CSS in colon and rectum	–	Age, differentiation, pT stage, time period, pM
Wang[45]	<7, 7–25, 25–50, 50–100	–	MV (Cox)	Significant predictor of OS RR 3.5*	RR 1.07*	Race, tumor size, differentiation, no. of examined nodes
Kim[46]	≤10, 11–20, 21–40, 41–100	Ratio quartiles	MV (Cox)	Significant predictor of OS and DFS	NS	Differentiation
Moug[47]	<5, 5–19, 20–39, 40–100	–	MV (Cox)	Significant predictor of OS in colon and rectal cancer	NS	–
Priolli[48]	<20, ≥ 21	Ratio quartiles	MV (Cox)	Significant predictor of OS ($P = 0.003$)	–	–
Park[40]	<6, 6–23, 24–100	Quartiles reclassified on the basis of Kaplan–Meier plots	MV (Cox)	Significant predictor of DFS ($P < 0.001$)	0.048	No. of examined nodes, preop CA19-9
Vather[49]	10 strata of 10	–	MV (Cox)	Significant predictor of OS χ^2 statistic 390*	χ^2 statistic 238*	No. of examined nodes
Vaccaro[50]	<25, ≥25	Quartiles reclassified on the basis of Kaplan–Meier plots	MV (Cox)	Significant predictor of OS, DFS, and CSS	NS	Sex, age, obstruction or perforation

LNR lymph node ratio, *OS* overall survival, *DFS* disease-free survival, *CSS* cancer-specific survival, *LR* local recurrence, *MV* multivariate, *UV* univariate, *NS* not significant, *CRT* chemo-radiation, *CRM* circumferential resection margin, *RR* relative risk

* $P < 0.0001$

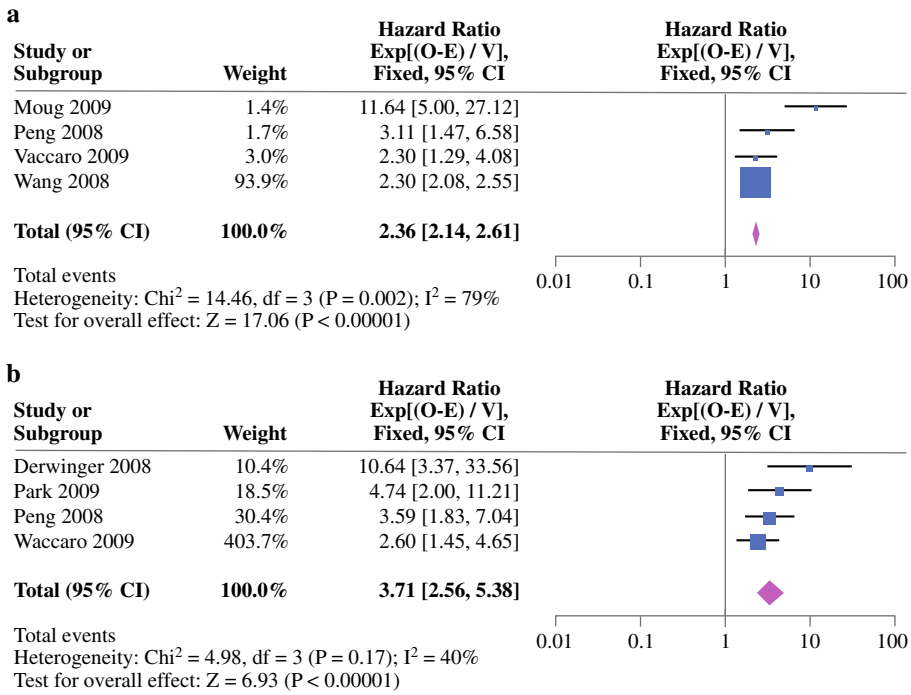

FIG. 1 **a** Fixed-effects meta-analysis of overall survival. **b** Fixed-effects meta-analysis of disease-free survival

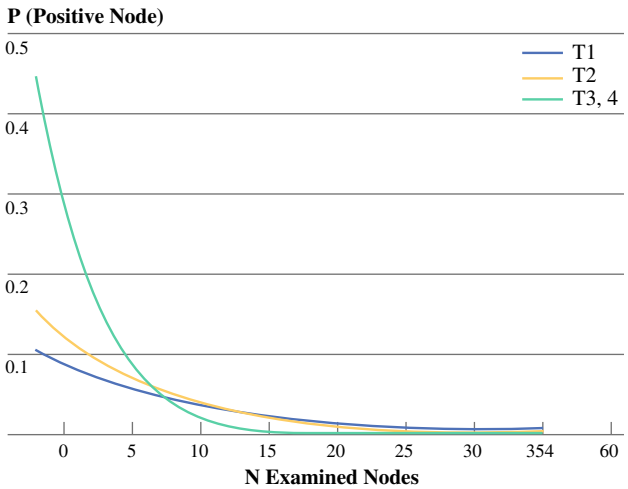

FIG. 2 Probabilistic explanation of the threshold of 12 to 15 examined nodes to minimize stage migration in colorectal cancer. The probability of finding a positive node in the resection specimen becomes very small once more than 12 negative nodes have been retrieved. Data were plotted by a Poisson probability function as described by Turner and Vollmer [29]

Although stage migration is undoubtedly the most important factor on a population-level scale, recent data indicate that in a subset of CRC patients, a survival benefit is reaped from surgically removing more lymph nodes. First, analysis of the INT-0089 adjuvant chemotherapy trial confirmed the prognostic significance of the number of nodes analyzed in stage II and III disease. However, because all patients received adjuvant chemotherapy and survival was similar in all treatment arms, stage migration did not play an important role.[32] Second, the prognostic significance of complete removal of the intact node bearing mesentery has been demonstrated in both colon and rectal cancer.[33,34] Whatever the underlying mechanisms, the total number of examined nodes is an established prognosticator in both stage II and III CRC. The 6th and upcoming 7th edition of the TNM classification, however, classify stage III patients on the basis of the number of positive nodes (Table 4). Intuitively, it seems evident that the prognostic significance of 4 positive nodes on a total of 4 examined is completely different when a total of 35 nodes were retrieved. Therefore, the ratio of positive to total number of examined nodes is expected to improve prognostication and therapy guidance in stage III CRC. The results of this systematic review confirm the superior prognostic significance of the LNR because in all papers that presented a multivariate proportionate hazard model, the number of positive nodes either lost its significance or was associated with a less significant statistical parameter (Table 3).

In patients with rectal cancer, neoadjuvant long-course radiotherapy or chemoradiation is known to negatively affect lymph node retrieval.[35,36] Contrary to the colon cancer, a reduced node count is not associated with a worse outcome in rectal cancer patients treated with neoadjuvant chemoradiation.[37,38] In patients treated with neoadjuvant chemoradiation, proximal (along major vessels) location of metastatic nodes was shown to predict metastatic disease.[39] Therefore, the LNR concept may not be valid in rectal cancer treated preoperatively with long-course (chemo)radiation. In

TABLE 4 TNM classification of colorectal cancer

TNM 6th edition				TNM 7th edition			
N Stage							
NX				NX			
N0				N0			
N1	1–3 positive nodes			N1a	1 positive node		
N2	4 or more positive nodes			N1b	2–3 positive nodes		
				N2a	4–6 positive nodes		
				N2b	7 or more positive nodes		
Stage grouping							
IIIA	T1,T2	N1	M0	IIIA	T1,T2	N1	M0
IIIB	T3,T4	N1	M0		T1	N2a	M0
IIIC	Any T	N2	M0	IIIB	T2	N2a,b	M0
					T3	N1a,b	M0
					T4a	N1a,b	M0
					T4a	N2a	M0
					T1	N2b	M0
					T3	N2a	M0
				IIIC	T3	N2b	M0
					T4a	N2b	M0
					T4b	N1a,b	M0
					T4b	N2a,b	M0

TNM tumor, node, metastasis system

the present review, only the study of Peschaud et al. included rectal cancer patients treated with neoadjuvant long-course (chemo)radiation.[20] This study found that approximately half of the 59 patients with a node count of <12 had received long-course (chemo)radiation. Interestingly, however, the LNR remained an independent prognosticator in the patient group with fewer than 12 nodes examined. Only 30 of these patients received long-course (chemo)radiation, however, and this precludes our drawing any firm conclusions.

Is a minimal node yield required that allows the LNR to represent a reliable prognosticator? Given the demonstrated prognostic significance of the denominator, i.e., the total number of nodes examined, one would expect that a sufficiently high number of nodes needs to be examined. The findings in the present review are somewhat contradictory. Although Berger et al. and Park et al. found that the LNR did not predict outcome when less than 10 or 12 nodes are examined, the study by Rosenberg et al. showed that the LNR remained an independent predictor of outcome in multivariate analysis even when less than 12 nodes are examined.[18,19,40] Because the relationship between the total number of nodes examined and the probability of finding a positive node has been repeatedly demonstrated, examination of a minimal number of nodes seems required not only to correctly identify node-negative disease, but also to reliably calculate the LNR in stage III disease.

Several limitations apply to the interpretation of this review. First, because all data were extracted from observational or retrospective studies, the strength of the association between the LNR and outcome remains uncertain because many potential confounders, such as adjuvant chemotherapy, are unaccounted for. Second, not only is there marked heterogeneity in the choice of different LNR categories, but these are also arbitrarily chosen. Only the study of Rosenberg et al. used statistical calculation to define an optimal LNR cutoff defining a subgroup of patients with a better prognosis.[18] The median LNR of approximately 10% identified across the 16 included studies could be used as a basis for prospective studies.

In summary, the results of this review demonstrate that in patients with stage III colon and rectal cancer treated without neoadjuvant long-course radiotherapy, the LNR provides superior prognostic stratification compared to the number of positive nodes. Future prospective studies are needed to define the LNR cutoff that allows optimal separation of subgroups of stage III patients, and to verify whether the LNR could be used to direct adjuvant therapy.

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REFERENCES

1. World Health Organization. Global burden of cancer. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/index.html. Accessed September 29, 2009.
2. Greene FL, Stewart AK, Norton HJ. New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: an analysis. *J Clin Oncol*. 2004;22:1778–84.
3. Greene FL, Stewart AK, Norton HJ. A new TNM staging strategy for node-positive (stage III) colon cancer—an analysis of 50,042 patients. *Ann Surg*. 2002;236:416–21.
4. Merkel S, Mansmann U, Papadopoulos T, et al. The prognostic inhomogeneity of colorectal carcinomas stage III—a proposal for subdivision of stage III. *Cancer*. 2001;92:2754–9.
5. Johnson PM, Porter GA, Ricciardi R, Baxter NN. Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer. *J Clin Oncol*. 2006;24:3570–5.
6. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst*. 2007;99:433–41.
7. Swanson RS, Compton CC, Stewart AK, Bland KI. The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined. *Ann Surg Oncol*. 2003;10:65–71.
8. Xing Y, Badgwell BD, Ross MI, et al. Lymph node ratio predicts disease-specific survival in melanoma patients. *Cancer*. 2009;115:2505–13.
9. Woodward WA, Vinh-Hung V, Ueno NT, et al. Prognostic value of nodal ratios in node-positive breast cancer. *J Clin Oncol*. 2006;24:2910–6.
10. Inoue K, Nakane Y, Iiyama H, et al. The superiority of ratio-based lymph node staging in gastric carcinoma. *Ann Surg Oncol*. 2002;9:27–34.
11. Oxford Centre for Evidence-Based Medicine. Levels of evidence. March 2009. Available at: http://www.cebm.net/index.aspx?o=1025. Accessed October 2, 2009.
12. Wang JP, Kulaylat M, Rockette H, et al. Should total number of lymph nodes be used as a quality of care measure for stage III colon cancer? *Ann Surg*. 2009;249:559–63.
13. De Ridder M, Vinh-Hung V, Van Nieuwenhove Y, et al. Prognostic value of the lymph node ratio in node positive colon cancer (letter). *Gut*. 2006;55:1681.
14. Trufelli DC, Miranda VDC, Palos CC, et al. Positive total dissected lymph nodes ratio as a prognostic factor in colon cancer. *Rev Assoc Med Bras*. 2007;53:539–42.
15. Derwinger K, Gustavsson B. A study of lymph node ratio in stage IV colorectal cancer. *World J Surg Oncol*. 2008;6:127.
16. Stocchi L, Nelson H, Sargent DJ, et al. Impact of surgical and pathologic variables in rectal cancer: a United States Community and Cooperative Group report. *J Clin Oncol*. 2001;19:3895–902.
17. Schumacher P, Dineen S, Barnett C, Fleming J, Anthony T. The metastatic lymph node ratio predicts survival in colon cancer. *Am J Surg*. 2007;194:827–32.
18. Rosenberg R, Friederichs J, Schuster T, et al. Prognosis of patients with colorectal cancer is associated with lymph node ratio a single-center analysis of 3026 patients over a 25-year time period. *Ann Surg*. 2008;248:968–78.
19. Berger AC, Sigurdson ER, LeVoyer T, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol*. 2005;23:8706–12.
20. Peschaud F, Benoist S, Julie C, et al. The ratio of metastatic to examined lymph nodes is a powerful independent prognostic factor in rectal cancer. *Ann Surg*. 2008;248:1067–73.
21. Punglia RS, Morrow M, Winer EP, Harris JR. Current concepts: local therapy and survival in breast cancer. *N Engl J Med*. 2007;356:2399–405.
22. Curti G, Maurer CA, Buchler MW. Colorectal carcinoma: is lymphadenectomy useful? *Dig Surg*. 1998;15:193–208.
23. Nagawa H, Muto T, Sunouchi K, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. *Dis Colon Rectum*. 2001;44:1274–80.
24. Soreide K, Nedrebo B, Soreide JA, Slewa A, Korner H. Lymph node evaluation in colon cancer is influenced by proximal location and microsatellite instability with lymph node ratio as independent prognostic factor. *Scand J Gastroenterol*. 2009;44:23.
25. Gilbert SM. Separating surgical quality from causality—gaining perspective in the debate on lymph node count and extent of lymphadenectomy. *Cancer*. 2008;112:2331–3.
26. Wong SL, Ji H, Hollenbeck BK, et al. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA*. 2007;298:2149–54.
27. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001;93:583–96.
28. Schofield JB, Mounter NA, Mallett R, Haboubi NY. The importance of accurate pathological assessment of lymph node involvement in colorectal cancer. *Colorectal Dis*. 2006;8:460–70.
29. Turner J, Vollmer RT. Lymph nodes in colorectal carcinoma—the Poisson probability paradigm. *Am J Clin Pathol*. 2006;125: 866–72.
30. Goldstein NS. Lymph node recoveries from 2427 pT3 colorectal resection specimens spanning 45 years—recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol*. 2002;26:179–89.
31. Gonen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. *J Clin Oncol*. 2009;27:6166–71.
32. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. *J Clin Oncol*. 2003;21:2912–9.
33. West NP, Morris EJA, Rotimi O, et al. Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study. *Lancet Oncol*. 2008;9:857–65.
34. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009;373(9666):821–8.
35. Beresford M, Glynne-Jones R, Richman P, et al. The reliability of lymph-node staging in rectal cancer after preoperative chemoradiotherapy. *Clin Oncol*. 2005;17:448–55.
36. Wichmann MW, Muller C, Meyer G, et al. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. *Arch Surg*. 2002;137:206–10.
37. Habr-Gama A, Perez RO, Proscurshim I, et al. Absence of lymph nodes in the resected specimen after radical surgery for distal rectal cancer and neoadjuvant chemoradiation therapy: what does it mean? *Dis Colon Rectum*. 2008;51:277–83.
38. Doll D, Gertler R, Maak M, et al. Reduced lymph node yield in rectal carcinoma specimen after neoadjuvant radiochemotherapy has no prognostic relevance. *World J Surg*. 2009;33:340–7.
39. Leibold T, Shia J, Ruo L, et al. Prognostic implications of the distribution of lymph node metastases in rectal cancer after neoadjuvant chemoradiotherapy. *J Clin Oncol*. 2008;26:2106–11.
40. Park IJ, Choi GS, Jun SH. Nodal stage of stage III colon cancer: the impact of metastatic lymph node ratio. *J Surg Oncol*. 2009;100:240–3.

41. Edler D, Ohrling K, Hallstrom M, Karlberg M, Ragnhammar P. The number of analyzed lymph nodes—a prognostic factor in colorectal cancer. *Acta Oncol*. 2007;46:975–81.
42. Lee HY, Choi HJ, Park KJ, et al. Prognostic significance of metastatic lymph node ratio in node-positive colon carcinoma. *Ann Surg Oncol*. 2007;14:1712–7.
43. Derwinger K, Carlsson G, Gustavsson B. A study of lymph node ratio as a prognostic marker in colon cancer. *Eur J Surg Oncol*. 2008;34:771–5.
44. Peng JJ, Xu Y, Guan ZQ, et al. Prognostic significance of the metastatic lymph node ratio in node-positive rectal cancer. *Ann Surg Oncol*. 2008;15:3118–23.
45. Wang JP, Hassett JM, Dayton MT, Kulaylat MN. Lymph node ratio: role in the staging of node-positive colon cancer. *Ann Surg Oncol*. 2008;15:1600–8.
46. Kim YS, Kim JH, Yoon SM, et al. Lymph node ratio as a prognostic factor in patients with stage III rectal cancer treated with total mesorectal excision followed by chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2009;74:796–802.
47. Moug SJ, Saldanha JD, McGregor JR, Balsitis M, Diament RH. Positive lymph node retrieval ratio optimises patient staging in colorectal cancer. *Br J Cancer*. 2009;100:1530–3.
48. Priolli DG, Cardinalli IA, Pereira JA, et al. Metastatic lymph node ratio as an independent prognostic variable in colorectal cancer: study of 113 patients. *Techn Coloproctol*. 2009;13:113–21.
49. Vather R, Sammour T, Kahokehr A, Connolly AB, Hill AG. Lymph node evaluation and long-term survival in stage II and stage III colon cancer: a national study. *Ann Surg Oncol*. 2009;16:585–93.
50. Vaccaro CA, Im V, Rossi GL, et al. Lymph node ratio as prognosis factor for colon cancer treated by colorectal surgeons. *Dis Colon Rectum* 2009;52:1244–50.