Int Surg 2014;**99:**344–353
DOI: 10.9738/INTSURG-D-13-00052.1

A Lymph Node Ratio of 10% Is Predictive of Survival in Stage III Colon Cancer: A French Regional Study

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Lymph node ratio (LNR) (positive lymph nodes/sampled lymph nodes) is predictive of survival in colon cancer. The aim of the present study was to validate the LNR as a prognostic factor and to determine the optimum LNR cutoff for distinguishing between "good prognosis" and "poor prognosis" colon cancer patients.

From January 2003 to December 2007, patients with TNM stage III colon cancer operated on with at least of 3 years of follow-up and not lost to follow-up were included in this retrospective study.

The two primary endpoints were 3-year overall survival (OS) and disease-free survival (DFS) as a function of the LNR groups and the cutoff. One hundred seventy-eight patients were included. There was no correlation between the LNR group and 3-year OS ($P = 0.06$) and a significant correlation between the LNR group and 3-year DFS ($P = 0.03$). The optimal LNR cutoff of 10% was significantly correlated with 3-year OS ($P = 0.02$) and DFS ($P = 0.02$). The LNR was not an accurate prognostic factor when fewer than 12 lymph nodes were sampled. Clarification and simplification of the LNR classification are prerequisites for use of this system in randomized control trials. An LNR of 10% appears to be the optimal cutoff.

Key words: Colon cancer – Lymph node ratio – Surgery – Survival

Colon cancer is the third most frequent cancer in France, with approximately 36,000 new cases per year. Of the several prognostic factors identified to date,[1] lymph node status is crucial for determining postoperative care for colon cancer patients.[2,3] Indeed, lymph node evaluation is a crucial aspect of the TNM system introduced by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) and now applied worldwide.[4] Although, TNM stage III colon cancer (Tx N+ M0) is heterogeneous, the same chemotherapy regimen is prescribed for all stage III patients.[2] Based on analysis of the lymph nodes, a range of prognostic parameters has been highlighted. These include node location, node size, the number of sampled lymph nodes (SLNs), the number of positive nodes sampled[5–9] and, most recently, the lymph node ratio (LNR: the number of positive lymph nodes divided by the total number of lymph nodes sampled). The LNR has been studied several times in the field of colon and rectal cancer and is associated with overall survival (OS) and disease-free survival (DFS).[6,10–13] Nevertheless, in most of studies, lymph node distribution is unclear thus the LNR cannot be used as a prognostic factor in routine clinical practice. The aim of the present regional study was to validate the LNR as an easy-to-use, prognostic factor in colon cancer and to determine the optimum cutoff for distinguishing between "good prognosis" and "poor prognosis" stage III colon cancer patients.

Patients and Methods

Study design, inclusion criteria and ethical approval

This was a retrospective, multicenter study. From January 2003 to December 2007, all physicians dealing with colon cancer in the Picardie region of northern France (digestive surgeons, gastroenterologists, oncologists, and pathologists in 12 public hospitals and 7 private clinics) were invited to participate in the study. All patients with TNM stage III colon adenocarcinoma (Tx N + M0) operated on in the participating centers, with a minimum of three years of follow-up and not lost to follow-up were included in the study (Fig. 1).

The study objectives and design were presented at the annual congress of the regional digestive oncology association (*Association Picarde de Cancérologie Digestive*, APCD). Institutional authorizations and ethical approval were then sought. Invitations to participate in the study were sent to the centers first by mail and then a second and third time by e-mail. Patients eligible for inclusion in the study were identified in hospital databases. Surgical records were reviewed in order to include all colectomies performed in participating centers during the study period. Pathology lab reports on patients having undergone colectomy during the study period were reviewed and stage III colon cancers were selected for the study. Follow-up data were collected from surgeons', gastroenterologists', and oncologists' notes. The data were collected from all centers by three investigators (CS, LR, and FLR) and reviewed by a single investigator. The

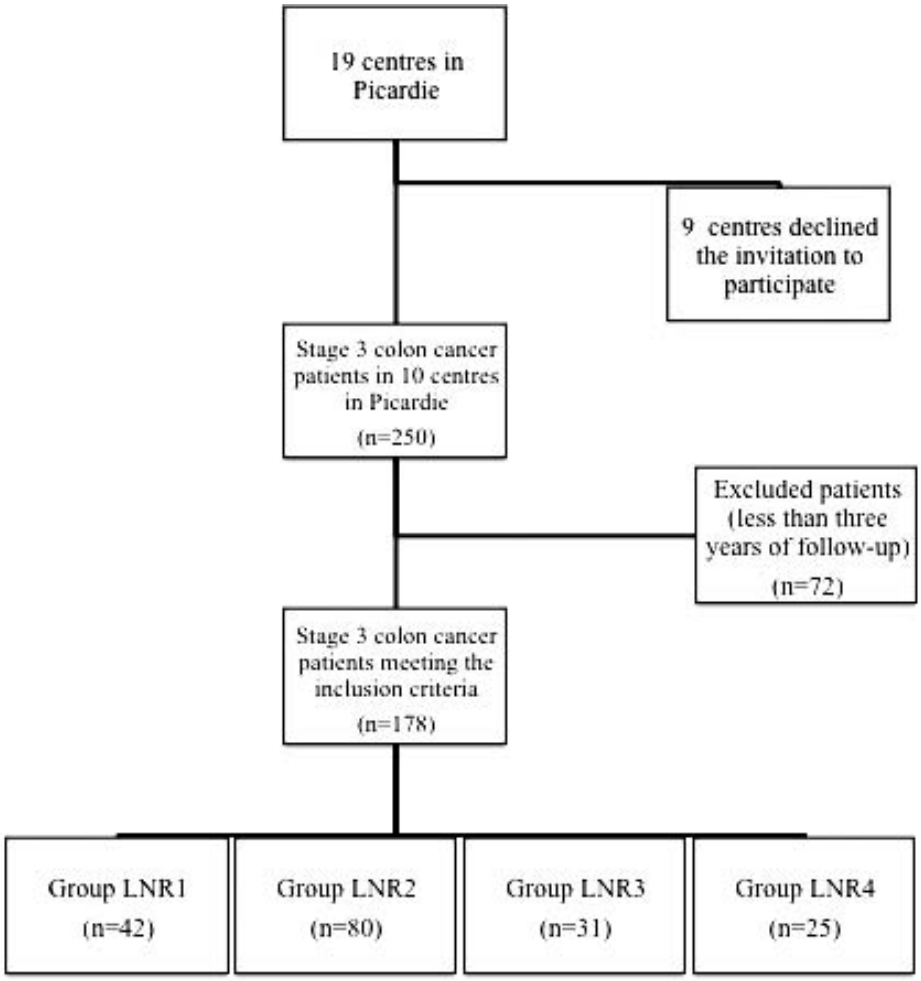

Fig. 1 Study patient disposition.

inclusion period was chosen so that sufficient data on 3-year OS and DFS would be available. The great majority of the included patients had received oxaliplatin-based chemotherapy after surgery.[2] This study was funded by grants from the University Hospital of Amiens (AOL 2009) and by the APCD. The study protocol was submitted to and approved by the French Advisory Committee on Information Processing in Healthcare Research (*Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé*, authorization #40170 bis) and the French National Commission for Data Protection (*Commission Nationale Information et Liberté*, authorization 911244).

Study endpoints

Primary endpoints

The primary endpoint was the evaluation of survival data (3-year OS, 3-year DFS). Survival data were evaluated as a function of (1) the LNR group (see below), (2) a cutoff determined by a receiver operating characteristic (ROC) curve based on survival data and (3) the number of SLNs (<12 or ≥ 12). The analysis of at least 12 nodes is required to define a specimen as oncologically safe. The correlation between LNR groups and the site of recurrence was studied.

There is no standard definition of LNR groups. We used Wang et al's classification,[14] in which LNR1 corresponds to an LNR below 0.07, LNR 2 ranges from 0.07 to 0.25, LNR 3 ranges from 0.25 to 0.5, and LNR4 corresponds to an LNR greater than 0.5.

Secondary endpoints

The secondary endpoints related to the evaluation of operative, postoperative outcomes, such as the anastomosis leak rate. Pathological data (T stage, N stage, mean number of positive lymph nodes, mean

number of SLNs, tumor size and tumor differentiation) were also analyzed as potential prognostic factors for colon cancer. The postoperative chemotherapy rate and reason for nonprescription of postoperative chemotherapy were also studied. Control quality parameters and compliance with guidelines were monitored in order to ensure the validity of the survival-related outcomes and provide feedback on the regional management of colon cancer patients.

Study population

Confirmed colon cancer was defined as the explicit mention of an adenocarcinoma of colonic origin in the pathology lab report. Colon cancers were classified according to the UICC TNM staging method.[4] Stage III colon cancer was defined as any T lesion with positive lymph nodes and no distant metastases. T and N status were assessed on the basis of the pathology lab report. We checked that the absence of distant metastases had been confirmed both preoperatively (on chest and abdominal CT scans) and peri-operatively. All patients operated on for stages III colon cancer in the participating study centers during the study period were included in the study. Only those patients not lost to follow-up and for whom a full dataset was available were included in the final analysis. Patients with negative lymph nodes and distant metastases, synchronous colon cancer, previous malignancies, rectal cancer, and familial colonic cancer were excluded from the study. Cancer was considered to be of colonic origin when the tumor was located between the caecum and the rectosigmoid junction.

Treatment

Surgery

Both open and laparoscopic procedures were considered for the study. Procedures were considered as being guideline-compliant when free margins of at least 5 cm were present and a large section of the regional lymph-node-bearing mesentery had been resected.[15]

Pathology lab results

Pathological analyses were performed in each center. Specimens were not reviewed and so the study was limited to assessment of the original pathology lab report forms. The French guidelines on colon cancer management require the analysis of at least 12 nodes.[15] The LNR was defined as the number of positive lymph nodes divided by the total number of SLNs.

Adjuvant treatment

In all centers, each case was discussed in multidisciplinary care team meetings. The use and choice of chemotherapy was considered for all stage III colon cancer patients, in accordance with French national guidelines and the patient's general health status. Since 2004, all participating centers have used oxaliplatin-based postoperative chemotherapy regimens.[2]

Follow-up

All patients were monitored every 3 months for 2 years, every 6 months for the following 3 years, and then every year. Patients lost to follow-up were not included in the study.

Statistical analyses

Chi-square or Fisher's exact tests were used to compare frequencies. Mann-Whitney or Student's *t* tests were used to compare quantitative variables. Overall survival was defined as the time between surgery and the date of death or the date of last follow-up. Disease-free survival was defined as the time between surgery and any recurrence of cancer (whether local or general) or the date of last follow-up. Survival distributions were estimated using the adjusted Kaplan-Meier method (inverse probability of treatment weighting). Multivariate analyses were performed using Cox regression models for survival and logistic regression for the recurrence risk. All variables that differed significantly ($P < 0.05$) were included in the logistic model. The LNR was studied as a continuous variable using a ROC curve for survival. Depending on these results, DFS and OS were studied according to a single LNR cutoff. The threshold for statistical significance was set to $P < 0.05$. All variables with $P < 0.05$ were included in the multivariate analysis. All tests were performed using SPSS statistical software (version 15.0 for Windows, SPSS Inc., Chicago, Illinois).

Results

Study population

Of the 19 eligible digestive oncology centers in the Picardie region, 10 (53%) agreed to participate in the

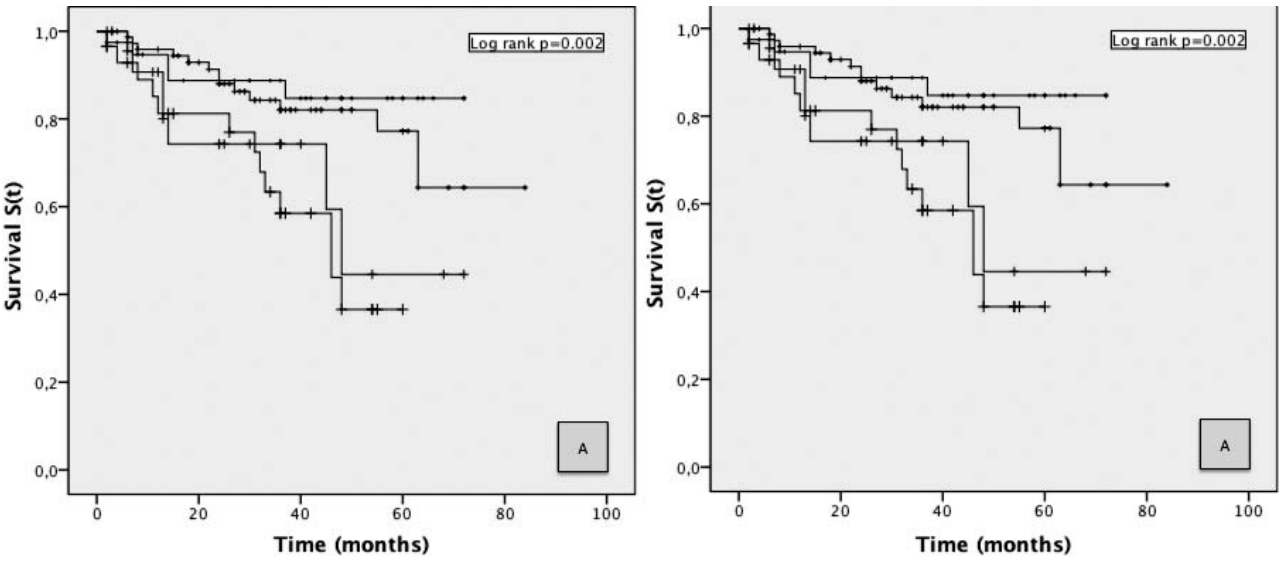

Fig. 2 (A) Disease-free survival (DFS) as a function of the LNR group. The 1-point cross curve is LNR1 DFS curve, the 2-point cross curve is LNR2 DFS curve, the 3-point cross curve is LNR3 DFS curve, and the 4-point cross curve is LNR4 DFS curve. (B) Overall survival (OS) as a function of the LNR group. The 1-point cross curve is the LNR1 OS curve, the 2-point cross curve is the LNR2 OS curve, the 3-point cross curve is LNR3 OS curve, and the 4-point cross curve is the LNR4 OS curve.

study (7 public-sector hospitals and 3 private-sector clinics). In total, 178 patients treated in participating centers during the study period met the inclusion criteria (92 women (52%) and 86 men (48%); mean age: 70.3±13.3 years (range: 30–97); mean body mass index: 25.6 ± 4.8 kg/m^2 (range: 16–36). There were 79 right-side colon tumors (44.5%) and 99 left-side colon tumors (55.5%).

Endpoints

In the study population, 24% (n = 42) of the patients were in the LNR1 group, with 45% (n = 80) in the LNR2 group, 17% (n = 31) in the LNR3 group and 14% (n = 25) in the LNR4 group. The patients' distribution across the LNR groups was essentially the same in the public- and private-sector institutions ($P = 0.9$).

Primary endpoint

Survival as a function of the LNR group. There was no correlation between the LNR group and 3-year OS [88% (n = 37) versus 82.5% (n = 66) versus 64.5% (n = 20) versus 72% (n = 18) for LNR groups 1, 2, 3, and 4, respectively; $P = 0.06$] but a highly significant correlation between the LNR group and mean OS (log rank $P = 0.002$) (Fig. 2A). The 3-year DFS differed significantly as a function of the LNR group [88% (n = 37) versus 67.5% (n = 54) versus 61% (n = 19) versus 64% (n = 16) for LNR groups 1, 2, 3, and 4, respectively; $P = 0.03$] (Fig. 2B).

ROC curve analysis and determination of an LNR cutoff. An LNR of 10% is associated with the greater sensitivity and specificity for predicting DFS (sensitivity: 80%; specificity: 53%; positive predictive value: 21%; negative predictive value: 89%, area under the curve: 0.71) (Fig. 3).

Survival data as a function of the LNR cutoff of 10%. Mean OS (log rank $P = 0.01$), 1-year OS (97% versus 87% in the LNR<10% and LNR≥10% groups, respectively; $P = 0.009$) and 3-year OS (82% versus 63%, respectively; $P = 0.02$) were significantly improved in the LNR<10% group (Table 1) (Fig. 4A). Mean DFS (log rank $P = 0.01$) the 1-year DFS (92% versus 77% in the LNR<10% and LNR≥10% groups, respectively; $P = 0.009$) and the 3-year DFS (82% versus 63%, respectively; $P = 0.02$) were also improved in the LNR<10% group ($P = 0.02$) (Table 1) (Fig. 4B).

Survival data as a function of the LNR and the number of SLNs. In the subgroup of patients who were compliant with the guidelines on SLNs (*i.e.*, SLN≥12), LNR groups were significantly correlated with the mean OS (log rank $P = 0.04$) and 3-year OS [88% (n = 37) versus 66% (n = 39) versus 59% (n = 10) versus 55.5% (n = 5) for LNR groups 1, 2, 3, and 4,

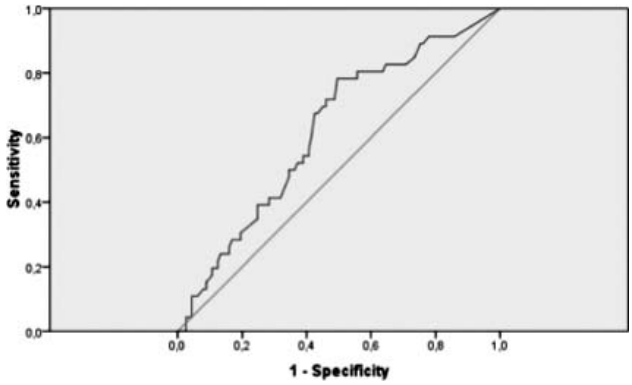

Fig. 3 A ROC curve analysis for determining the optimum LNR cutoff. The area under the curve is 0.65.

respectively; $P = 0.01$]. The LNR group was also associated with the mean DFS (log rank $P = 0.03$) and 3-year DFS [88% (n = 37) versus 66% (n = 39) versus 59% versus 55.5% (n = 5) for LNR groups 1, 2, 3, and 4, respectively; $P = 0.01$).

In the SLN≥12 group, the mean OS (log rank $P = 0.006$), the 3-year OS was [85% (n = 55) versus 58% (n = 36) in the LNR<10% and LNR≥10% groups, respectively; $P = 0.04$], the mean DFS (log rank $P = 0.007$) and the 3-year DFS [85% (n = 55) versus 58% (n = 36) in the LNR<10% and LNR≥10% groups, respectively; $P = 0.04$] were better in the LNR<10% group.

In the subgroup of patients who were not compliant with the SLN guidelines (*i.e.*, SLN<12), none were in the LNR1 group because the lowest possible LNR was 0.09 (1 out of 11), *i.e.*, above the upper limit of the LNR1 group (0.07).

In this SLN<12 group, there were no differences between the LNR groups in terms of 3-year OS [80% (n = 16) versus 69% (n = 9) versus 71% (n = 10) for classes 2, 3, and 4, respectively; $P = 0.8$] and DFS [75% (n = 15) versus 69% (n = 9) versus 71% (n = 10), respectively; P = 0.9].

Table 1 Overall survival, disease-free survival, and the liver metastasis rate with an LNR cutoff of 10%

	LNR<10% % (n)	LNR≥10% % (n)	*P*
Overall survival			
At 1 year	97 (71)	87 (91)	0.009
At 3 years	82 (60)	63 (66)	0.02
At 5 years	71 (52)	55 (58)	0.06
Disease-free survival			
At 1 year	92 (67)	77 (81)	0.009
At 3 years	82 (60)	63 (66)	0.02
At 5 years	71 (52)	55 (58)	0.09
Liver metastases			
At 1 year	3 (2)	10 (11)	0.07
At 3 years	8 (6)	16 (17)	0.1
At 5 years	11 (8)	21 (22)	0.1

Predictive factors for metastasis. In a univariate analysis, LNR group ($P = 0.04$), N-stage ($P = 0.009$), the number of positive lymph nodes ($P = 0.01$) and LNR>10% ($P = 0.05$) were associated with metachronous liver metastases recurrence. In multivariate analysis, not one of these factors was a predictive factor for metastases (Table 2).

Secondary endpoints

Operative and postoperative data. Surgery was elective in 71% of cases (n = 127). The laparoscopy rate was 6% (n = 11). The anastomosis rate was 60% (n = 107), the rate of iatrogenic tumor perforation was 1% (n = 2) and the rate of iatrogenic colon perforation was 0.6% (n = 1).

There were no complications in 57% of the cases (n = 101). The anastomosis leakage rate was 4.5% (n = 8) and re-operation was necessary in 6% of cases (n = 10). Public- and private-sector institutions did not differ significantly in terms of these outcomes ($P = 0.8$).

Pathological analyses. In the study population, the median number of SLNs was 15 ± 6.9 (range: 3–36). This number did not differ when comparing public- and private-sector institutions ($P = 0.7$). The mean number of positive lymph nodes was 2 ± 3 (range: 1–22). More than 12 lymph nodes were sampled in 76% of cases (n = 135). There were 3% (n = 5) of T1 cases, with 4.5% (n = 8) for T2, 59.5% (n = 106) for T3, and 33% (n = 59) for T4. There were 69% (n = 124) of N1 cases and 31% (n = 54) of N2 cases. The tumor was well differentiated in 45% of cases (n = 80), moderately differentiated in 46% (n = 82) and poorly differentiated in 9% (n = 16). There was vascular invasion in 25% of cases (n = 44) and perineural invasion in 20% of cases (n = 36).

The LNR groups did not differ significantly in terms of T stage distribution ($P = 0.07$), the parietal invasion rate or the perineural invasion rate ($P = 0.7$). Rate of vascular invasion ($P = 0.01$) and N stage ($P = 0.0001$) were significantly different between groups with a higher rate of vascular invasion and N2 patients in the LNR4 group (Table 3). In a univariate analysis, T-stage ($P = 0.002$), N-stage ($P = 0.0001$), and LNR<10% ($P = 0.003$) were correlated with DFS. In a multivariate analysis, T-stage and LNR>10% were correlated to DFS (Table 4).

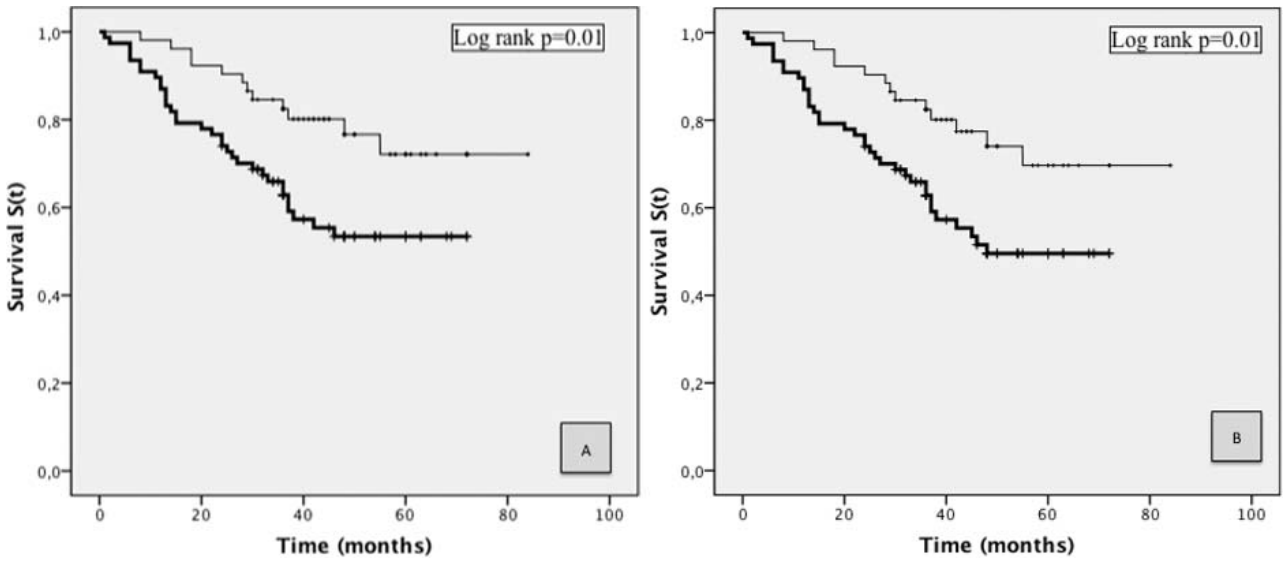

Fig. 4 (A) Disease-free survival (DFS) in the LNR<10% and LNR≥10% groups. The thin and 1-point cross curve is LNR<10% group DFS curve. The large and 2-point cross curve is LNR>10% group DFS curve. (B) Overall survival in the LNR<10% and LNR≥10% groups. The thin and 1-point cross curve is LNR<10% group overall survival curve. The large and 2-point cross curve is LNR>10% group overall survival curve.

Chemotherapy and guideline-compliant management. Less than 12 lymph nodes were sampled in 24% (n = 43) of the patients. Postoperative chemotherapy was performed in 68% of cases (n = 121). The contraindications for postoperative chemotherapy in the remaining patients were known coronary artery disease or heart failure in 61% of these cases (n = 35) and poor overall physical status in 39% (n = 22).

Discussion

The LNR is an established prognostic factor in colon cancer.[13,14] Although the value of chemotherapy in stage III colon cancer has been well established, this patient group is heterogeneous and varies in terms of the presence or absence of prognostic factors.[5–9] In the present study, there was no correlation between the LNR group and 3-year OS (ranging from 88% to 64.5%, $P = 0.06$) and a significant correlation between the LNR group and the 3-year DFS (ranging from 88% to 61%, $P = 0.03$). Our results confirm that LNR is a prognostic factor for colon cancer. Nevertheless this classification is imperfect as we found only a difference for the 3-year disease-free survival and not for the 3-year overall survival, even if we had chosen the 3-year survival as it was,

Table 2 Predictive factors for metachronous liver metastases recurrence

	Predicting factors for metachronous liver metastases recurrence			
	Univariate analysis	Multivariate analysis		
	P	*P*	HR	95%
LNR group	0.04	0.6	0.83	0.42–1.6
LNR≥10%	0.05	0.3	1.78	0.54–5.5
T-stage	0.06			
N-stage	0.009	0.7	2.78	0.92–8.4
Number of positive lymph nodes	0.01	0.8	1.02	0.85–1.2
Number of sampled lymph nodes	0.2			
Vascular invasion	0.18			
Perineural invasion	0.3			
Postoperative chemotherapy	0.2			
Anastomosis leakage	0.6			
Emergency procedure	0.8			

Table 3 Comparison of pathological data as a function of the LNR group

	LNR1 n (%) n = 42	LNR2 n (%) n = 80	LNR3 n (%) n = 31	LNR4 n (%) n = 25	*P*
T-stage					
T1	0 (0)	4 (5)	1 (3)	0 (0)	0.07
T2	4 (9.5)	1 (1)	3 (10)	0 (0)	
T3	25 (59.5)	52 (65)	18 (58)	11 (44)	
T4	13 (31)	23 (29)	9 (29)	14 (56)	
N-stage					
N1	41 (98)	65 (81)	14 (45)	4 (16)	0.0001
N2	1 (2)	15 (19)	17 (55)	21 (84)	
Parietal invasion	7 (28)	13 (22)	2 (12)	6 (27)	0.6
Vascular invasion	8 (22)	17 (24)	7 (27)	12 (60)	0.01
Perineural invasion	6 (17)	17 (24)	7 (27)	6 (30)	0.7

this was the best cutoff to find a difference between groups.

The present study data were representative of regional practice. Over the study period, approximately 600 stage III colon cancer patients were treated in Picardie. With a lost-to-follow-up rate of 30% (the rate seen in the present study), a total of 420 patients could have been included. Hence, the study population (n = 178) represents 42% of all stage III colon cancer patients treated in Picardie.[16]

The prognostic value of the LNR has been established in several studies. Nevertheless, this parameter has not been included in the latest version of the TNM classification[4] or in trials designed to evaluate the optimum duration of adjuvant chemotherapy in colon cancer.[17] This lack of inclusion may be due to heterogeneity in the definition of LNR groups. In the present study, we chose to use Wang et al' s definition (which is based on the mean LNR in the latter's study population),[14] The definitions of LNR groups vary from one system to another in terms of the number of groups (from 2 to 10) and the range, making it hard to compare study outcomes,[13] Use of LNR as a predictive factor could modify the management of stage III colon cancer patients or be used as a validation criterion for modulating the duration of adjuvant chemotherapy,[17] A randomized, controlled trial in which four groups each have a different treatment is unlikely to be clinically relevant and would be difficult to run. In the literature, only 3 studies have studied the LNR in 2 groups. These groups were based on the quartiles[18,19] or the mean LNR[20] and not on the correlation between LNR and survival.

In the present study, an LNR of 10% was the optimum cutoff; in a univariate analysis, we observed a significant difference in 3-year DFS and OS between the LNR<10% and LNR≥10% groups.

The prognostic value of the LNR when fewer than 12 lymph nodes are analyzed is subject to debate. In the present study, LNR was a prognostic

Table 4 Factors associated with disease-free survival

	Univariate analysis	Factors associated with disease-free survival		
		Multivariate analysis		
	P	*P*	HR	95% CI
LNR group	0.08			
LNR≥10%	0.01	0.03	2.74	1.1–6.8
T-stage	0.002	0.01	2.19	1.21–3.9
N-stage	0.0001	0.4	1.41	0.58–3.4
Number of positive lymph nodes	0.2			
Number of sampled lymph nodes	0.06			
Vascular invasion	0.3			
Perineural invasion	0.6			
Postoperative chemotherapy	0.3			
Anastomosis leakage	0.06			
Emergency procedure	0.9			

HR: Hazard ratio, 95% CI: 95% confidence interval

factor when more than 12 lymph nodes were analyzed but had no prognostic value (according to the LNR groups or LNR<10%) for OS and DFS when less than 12 lymph nodes were analyzed. In the analysis of the intertrial group 0089, Berger et al did not find the LNR to be a prognostic factor when less than 10 lymph nodes were analyzed.[21] In contrast, Rosenberg et al found that the LNR was indeed a prognostic factor, regardless of the number of SLNs (12 or more versus less than 12).[22]

We evaluated the correlation between the LNR and recurrence (both local and general). To the best of our knowledge, our study is the first to have studied this correlation. The LNR2 and LNR3 groups had a significantly greater rate of metachronous liver metastasis recurrence than the LNR1 group did. These results may lead to a change in liver monitoring in these groups of patients—especially if serum levels of carcinoembryonic antigen (CEA) increase in the absence of any evidence of metastases on a routine follow-up CT scan,[23] In turn, elevated CEA levels may prompt the use of other imaging methods to screen for recurrence. Liver metastasis recurrence was also associated with the LNR>10% group, the N2 group and the number of positive lymph nodes. These results must be moderated, as not one of these factors was associated with the risk of liver recurrence in multivariate analysis.

These outcomes confirm the crucial importance of lymph node evaluation in colon cancer patients and emphasize the need for systemic, postoperative chemotherapy. Knowledge of the difference in DFS and OS when comparing LNR<10% and LNR≥10% groups and the potential difference in the liver recurrence risk as a function of the LNR group may prompt the physician to modulate chemotherapy. The fact that clinical studies are examining the modulation of chemotherapy in stage III colon cancer shows that practice is likely to change. Surprisingly, LNR is not used for the patient selection in these trials—perhaps because LNR classifications are overly complex,[17]

In conclusion, the number of SLNs per patient remains an important parameter. The LNR is predictive of survival in colon cancer but is not still used routinely in patient management; in particular, the LNR has not been included in the 7th edition of the TNM classification system[4] or in trials designed to evaluate the duration of adjuvant chemotherapy in colon cancer,[17] Clarification and simplification of the LNR group classification (based on survival) are prerequisites for use of this parameter in randomized control trials. An LNR of 10% appears to be the optimum cutoff for distinguishing between "good prognosis" and "poor prognosis" stage III colon cancer patients.

Acknowledgments

The authors received grants from the University hospital of Amiens (AOL 2009) and by the APCD. None of the authors have a conflict of interest. The role of the funding source was for data collection management and statistics.

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