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Lymph Node Ratio and Liver Metachronous Metastases in Colorectal Cancer

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The authors seek to assess whether the lymph node ratio (LNR) could predict the risk of metachronous liver metastases. Using the goal of sampling 12 lymph nodes for a proper staging of colorectal cancer is often "uncommon," and the LNR is what allows for a better prognosis selection of patients. A homogeneous group of 280 patients, followed up for at least 5 years, was evaluated. To highlight the groups with the highest risk of metachronous liver metastases, patients were divided into 4 quartiles groups in relation to the LNR. The number of lymph nodes sampled in group "Stage I" was significantly lower. Even if statistical significance between the global LNR and the development of liver metastases has not been reached, the subdivision into quartiles has made it possible to highlight that in the more advanced ratio groups, a higher incidence of metachronous liver metastases ($P < 0.028$) was registered and was a different distribution of patients with or without liver metastasis in function of quartiles ($P = 0.01$). The LNR has enabled us to prognosticate patients who are at greater risk of developing metachronous liver metastases. The lower lymph node sampling in the patients with less advanced staging (I) and in patients with node-negative cancer (I + II) who developed liver metastases, leads us to believe that some patients have been understaged. We believe that the LNR, especially in cases of adequate lymph node sampling, is a useful gauge to better substratify "node-positive" patients.

Key words: Colorectal cancer – Lymph node sampling – Lymph node ratio – Liver metastases

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During the 1990 World Congress of Gastroenterology in Sydney, Australia, it was agreed upon that in a patient treated radically for colorectal cancer the minimum number of nodes to be sampled in order to avoid understaging was 12. Indeed this number in recent years has been the subject of numerous controversies.[1,2] These controversies have led many authors to conclude that for a correct prognostic assessment of a patient, what should be considered is not the absolute number of lymph nodes sampled, but rather the lymph node ratio (LNR), *i.e.*, the ratio of positive nodes divided by the total number of retrieved nodes. The LNR would allow for a better selection of patients who are likely to develop recurrent disease.

In this study, in light of this premise we wanted to determine whether for patients radically treated for colorectal cancer the LNR could have a value in predicting the risk of developing recurrent disease and, more specifically, a metachronous liver metastasis. To our knowledge, we have not found similar studies in international literature.

Materials and Methods

This is a retrospective analysis of prospectively collected data from a single institution.

Among all patients treated for colorectal cancer in our department, we selected 280 who underwent surgery between January 2004 and December 2009 so that each patient had the opportunity to be followed up for at least 5 years by December 2014.

Patients who met the criteria had:

- undergone radical surgical resection (complete resection of the primary tumor and regional lymphadenectomy) of colorectal cancer; and
- initially adhered to the follow-up protocol.

The criteria to exclude the patients were:

- liver synchronous metastases or synchronous metastases of other types;
- invasion into nearby tissues or organs;
- preoperative radiotherapy (could interfere with lymph nodal sampling);[3]
- symptomatic hepatitis B virus (HBV) or hepatitis C virus (HCV) related liver disease (could interfere with the development of liver metastases);[4]
- patients with positive lymph nodes who had not underwent adjuvant chemotherapy for comorbidity or denial;
- neoplasia arising out of colorectal inflammatory disease; and
- patients who had incomplete follow-up.

The average age was 69.8 years (range: 26–92). Colorectal cancer was localized in the right colon in 98 cases, the transverse colon in 18 cases, the left colon in 38 cases, and the sigmoid colon and rectum in 126 cases.

All patients were staged according to the classification of American Joint Committee on Cancer (AJCC) 2010,[5] which allowed us to group patients in just 7 stages: stage I (T1–T2, N0, M0), stage IIA (T3, N0, M0), stage IIB (T4a, N0, M0), stage IIC (T4b, N0, M0), stage IIIA (T1–T2, N1, M0 or T1, N2a, M0), stage IIIB (T3–T4a, N1, M0 or T2–T3, N2a, M0 or T1–T2, N2b, M0), stage IIIC (T4a, N2a, M0 or T3–T4a, N2b, M0 or T4b, N1–N2, M0).

We recorded the lymph node sampling (LNS) determined by the pathologist for each of the 280 patients and the average LNS within each stage of the classification according to AJCC 2010. We then assessed whether there were differences between groups I, II, and III regarding the LNS and then compared the LNS of the 172 patients with stages I+II (nodes negative) with the LNS of the 108 patients with stage III (nodes positive).

The protocol employed for adjuvant chemotherapy is marked as "FOLFOX 4" (oxaliplatin and 5FU with the biochemical modulation of folinic acid) for an average of 12 cycles every 14 days.

The follow-up schedule included checks performed quarterly for the first 3 years and every 6 months for the fourth and fifth years. The strategy for diagnosing liver metastases was always the same: determining the blood carcinoembryonic antigen and performing both a liver ultrasound, as well as a contrast-enhanced abdominal computed tomography (CT) according to our scheduled follow-up.[6] We always attempted to confirm a liver metastasis diagnosis with a histologic exam.

In the patients belonging to the stage I and II (nodes negative) according to AJCC 2010 we recorded the incidence of hepatic metastases.

Within the group of 108 patients in stage III according to AJCC 2010 classification, we recorded the average LNR.

In order to avoid stratification according to arbitrary classification, the 108 in stage III patients were divided, as has been reported by other authors[7–10] in more recent literature, in 4 equally-populated quartiles, in relation to the LNR.

The 4 quartiles were formed accordingly:

LNR1: 0.01–0.09 (from the minimum up to the 25th percentile);
LNR2: 0.1–0.231 (up to the 50th percentile);
LNR3: 0.235–0.35 (up to the 75th percentile);
LNR4: 0.37–1 (up to the maximum value).

Within each quartile we recorded the incidence of patients without or with hepatic metastases.

We also determined whether the N-category according to AJCC 2010, which is based only on the number of metastatic lymph nodes, could be comparable to the LNR in selecting patients at risk of liver metastases. The N1a category provides only 1 metastatic lymph node, N1b up to 3, N2a up to 6, and finally N2b from 7 lymph nodes up.

Statistical methods

To evaluate differences between groups, we operated a 1-way ANOVA; the homogeneity of variance was confirmed by Levene's test. As the difference was significant, a post hoc test was performed to find the individual differences between groups. To evaluate the difference inside the stage III between nonmetastases patients and patients with hepatic metastases, we utilized the Student's *t* test for paired samples, applying $P < 0.05$ as the minimum level of significance. Pearson's chi square was used to identify significant association between the value of the quartile and the metastatic stage of the patient, as well as to verify any differences among patients with metastases based on the quartile they belonged to.

Statistical analyses was implemented using SPSS for Windows (PASW Statistics for Windows, version 18.0, SPSS Inc, Chicago, Illinois).

Results

The distribution of patients according to AJCC 2010 staging was as follows:

- Stage I: 17.9% (50/280);
- Stage IIA: 42.5% (119/280);
- Stage IIB: 0.4% (1/280);
- Stage IIC: 0.7% (2/280);
- Stage IIIA: 3.9% (11/280);
- Stage IIIB: 27.5% (77/280);
- Stage IIIC: 7.1% (20/280)

The average LNS of the 280 patients was 14.8 (range: 3–74); for 60.4% of the patients the LNS was $\geq$12, for the remaining 39.6%, it was $<$12.

The LNS was thus distributed according to the AJCC 2010 stage:

- 10.9 (3–27) in stage I;
- 15.2 (3–69) in stage IIA;
- 32 (32) in stage IIB;
- 16 (13–19) in stage IIC;
- 13.1 (5–29) in stage IIIA;
- 15.7 (3–74) in stage IIIB;
- 17.7 (9–33) in stage IIIC.

Then, globally, the LNS was 10.9 in stage I, 15.5 in stage II, and 15.8 in stage III.

The analysis of variance of the LNS between groups I, II, and III staged according to AJCC 2010 allowed us to highlight statistically significant differences between the groups ($P = 0.006$) and more specifically between group I and group II ($P = 0.011$) and between group I and group III ($P = 0.007$); instead there was no statistically significant difference between the group II and group III ($P = 0.954$).

During the 5 years of follow-up, 39 patients (9 in stage IIA and 30 in stage IIIA + IIIB + IIIC) were diagnosed with metastases in the liver. The histologic diagnosis of a liver metastasis was obtained either during the reoperation (14 patients) or through a transcutaneous biopsy either ultrasound or CT guided. The histologic diagnosis was not obtained in 6 cases either because the patient refused to undergo this procedure ($n = 2$) or because we encountered some technical difficulties during the biopsy ($n = 4$). However, in these cases the diagnosis of colorectal liver metastasis was supported by both blood chemistry (carcinoembryonic antigen) and well-documented instrumental (ultrasonography and CT) data.

The average onset of liver metastases was 13 months (6–42 months).

In the 108 patients belonging to the IIIA, IIIB, and IIIC groups according to AJCC 2010, the average LNS was 15.8 (range: 3–74) and the average LNR was 0.20 (range: 0.01–1); 30 of the 108 patients (27.8%) developed liver metastases of which 1 (9.1%; 1/11) were in stage IIIA, 21 (27.3%; 21/77) were in stage IIIB and 8 (40%; 8/20) in stage IIIC. In the 30 patients with liver metastases the average LNS was 13.4 (range: 4–39), and the average LNR was 0.31 (range 0.03–0.66).

The overall LNR difference between the 78 patients at stage III without liver metastases (LNR: 0.27) and the 30 patients at stage III (LNR: 0.31) with liver metastases was not statistically significant ($P = 0.273$).

Table 1 Distribution in quartiles of the 108 node-positive patients

	108 P. Stage III	78 P. Stage III no liver mts	30 P. Stage III with liver mts
LNR 1 (0.01–0.09)	27	24 (30.8%)	3 (10%)
LNR2 (0.1–0.231)	27	21 (26.9%)	6 (20%)
LNR3 (0.235–0.35)	27	16 (20.5%)	11 (36.7%)
LNR4 (0.37–1)	27	17 (21.8%)	10 (33.3%)

LNR, lymph node ratio; mts, metastases; stage III, stage III according to AJCC 2010.

Table 1 shows the distribution of 108 node-positive patients in quartiles (78 without liver metastases and 30 with metachronous liver metastases). We can notice in the first 2 quartiles (LNR1 + LNR2) an incidence of patients without or with liver metastases respectively of 57.7% and 30%. Meanwhile in the second 2 quartiles (LNR3 + LNR4) the percentages were 42.3% and 70%, respectively. There is a statistically significant correlation ($\chi 2 = 6.646$; $P = 0.01$) between the value of the quartile and the stage (metastatic or not) of the patient. Moreover, looking only at the 30 patients with liver metastases we notice that the difference between the first 2 quartiles (LNR1 + LNR2) and the second 2 quartiles (LNR3 + LNR4) was also statistically significant ($P < 0.028$). Furthermore, in order to compare the N-category according to AJCC 2010 with LNR, we recorded that among patients who developed liver metastases, 13/30 (43.3%) belonged to the N1a + N1b class according to AJCC 2010 whereas 17/30 (56.7%) to N2a + N2b according to AJCC 2010; the corresponding values of LNR were respectively 9/30 (30%) in LNR1 + 2 and 21/30 (70%) in LNR3 + 4. The difference between classes was statistically significant ($P < 0.001$).

In the 172 patients belonging to the stage I and II (nodes negative) according to AJCC 2010, 9 liver metastases (5.2%) were recorded. The LNS of the 172 patients was 13.6 (range: 2–69) and specifically 10.94 in stage I (range: 3–27) and 14.7 in stage II (range: 3–69). LNS of the 9 patients with liver metastases was 9.8 (range: 3–21).

Table 2 shows a comparison of the LNS between node-negative (stage I + II) and node-positive (stage III) patients and its statistical correlation.

Discussion

A prognostic classification of the patient is the main goal of a correct staging of a radically treated colorectal neoplasia. This classification does in fact make it possible to select categories with poor prognoses for which checks-up and targeted therapies can be provided.[11] Several prognostic factors have so far been considered in the clinical domain and, among them, both the number of lymph nodes sampled and the number of metastatic lymph nodes,[9,10,12–15] the latter already used by Jass in the '80s,[16] are today increasingly highlighted.[5]

In this regard, for over 20 years the "magic number"[17] 12 has always been considered the minimum number of lymph nodes to be sampled, which would allow for a correct diagnosis of "N0" in 90% of cases of colorectal cancer. However, this range is currently considered "uncommon" or "not adequate" or achievable only in specialized centers. This is due to both "changeable variables," such as the surgeon and the pathologist, and "unchangeable variables" related to the patient and to the cancer itself.[2]

In the United States, in reports published between 2005 and 2010, despite the "dense forest of articles,"[18] the lymphadenectomy was considered inadequate in percentages varying between 63% and 48% of cases,[18,19] and similar results were reported in Germany and England.[20–22]

In this study, we would like to point out that while on the one hand the overall average value of the lymph nodes sampled was 14.8, on the other, it was less than 12 in 39.6% of cases.

In 2005, the first who suggested overcoming this numerical issue by applying the LNR, (*i.e.*, the ratio of positive nodes divided by the total number of retrieved nodes) was Berger.[23] Applying the LNR would probably allow us to break free from a reduced

Table 2 Relationship of the LNS between nodes-negative (stage I + II) and nodes-positive (stage III) patients

	172 pts. Stage I + II[a]	108 pts. Stage III[a]	9 mts Stage I + II[b]	30 mts Stage III[b]
LNS (avg)	13.6 (2–69)	15.8 (3–74)	9.8 (3–21)	15.5 (4–39)

[a]172 stage I + II versus 108 stage III: P = ns (0.15).

[b]9 mts stage I + II versus 30 mts stage III: $P < 0.04$.

LNS, lymph nodes sampling; avg, average; pts, patients; mts, metastases; stage I + II, stage I + II according to AJCC 2010; stage III, stage III according to AJCC 2010.

lymph node sampling[8,10,14,24–29] and to substratify the node-positive patients so as to reduce the excessive prognostic heterogeneity.[7,8,12,13,26,27,29–31]

The idea of a correlation that we are suggesting in our research between the LNR and a selection of patients at risk of metachronous liver metastases came from the fact that the study of positive lymph nodes is the only primary colorectal tumor feature already considered in a multivariate analysis, as an independent predictor of outcome in patients undergoing liver resection for metastases from colorectal cancer.[32] It is also used in some nomograms such as that of the Memorial Sloan-Kettering Cancer Center (www.nomograms.org) that are instrumental in predicting disease-free interval (DFI) and overall survival of these patients undergoing liver resection.[33]

We have also conducted a thorough research in literature on MEDLINE, Scopus, and Web of Science to analyze other studies concerning the relation between the primary tumor LNR and the occurrences of metachronous liver metastases. We went about this by cross-searching in the title and in the abstract for words such as "colorectal cancer," "hepatic or liver metastases," "lymph node ratio or LNR." Although no studies related to this topic were found, our search seemed justified by the fact that this idea, which puts the LNR in relation to local recurrence in rectal cancer, has appeared in other recent publications.[8,34,35]

Objections to the LNR are that there is no universally known cut-off value and that the methods used to select the prognostic categories are various.[10,13,36,37] The method of using the quartiles (the one we used) is, instead, as already mentioned, more widespread.

The statistically significant figure that emerges when analyzing our records (Table 1), is that while the categories with more favorable LNR (LNR1 e LNR2) include 57.7% of the patients with no liver metastases and 30% of the ones with metachronous liver metastases, the categories with less favorable LNR (LNR3 e LNR4) include 42.3% and 70% of patients, respectively. Statistical evaluation of these data allowed us to determine that the different distribution of the patients with or without liver metastasis into quartiles proved highly significant ($\chi^2 = 6.646; P = 0.010$).

Moreover 70% of patients who developed liver metastases (Table 1) falls in the 2 quartiles whose ratio shows a higher rate of lymph node metastases ($P < 0.028$). Moreover the LNR compared with N category according to AJCC 2010, in our experience, seems better for identifying patients with liver metastases; in fact in the 2 quartiles (LNR3–LNR4) with a higher rate of lymph node metastases, 70% of patients developed hepatic relapses; this percentage drops to 56.7% in N2a–N2b ($P < 0.001$), which are the 2 most advanced classes of the AJCC 2010.

Therefore, in light of these data, we can safely say that the patients with higher LNR are at a greater risk of metachronous liver metastases and need to receive more attention during the follow-up and with adjuvant therapies.

Though not closely related to LNR, another piece of data worthy of attention is that a lower lymph node sampling in the "node-negative" (stage I + II) patients with liver metastases was statistically significant (Table 2) compared with the "node-positive" (stage III) patients (9.8 versus 15.5; $P < 0.04$).

This data along with what the LNS of patients at stage I is statistically lower compared with the LNS of patients with stage II ($P = 0.011$) or III ($P = 0.007$), allow us to recognize that we are most probably dealing with a case of understaging (Will Rogers phenomenon)[38] for some patients at stage I or II according to AJCC 2010. This is due to an insufficient sampling that can lead to an erroneously judged more favorable staging and therefore not subject to the adjuvant therapies that in the more advanced stage can guarantee an improvement in results.[39,40]

The main limitations of this research mainly stem from the fact that it is retrospective in nature, even though it was carried out within a prospective follow-up period standardized for several years. It should, however, be considered that this group of patients is homogeneous since all patients were surgically treated at the same center and had the opportunity to undergo a 5-year follow-up, and all stage III patients were subjected to the same postoperative adjuvant treatment.

To our knowledge, ours is the first research done that specifically investigates the relationship between LNR of colorectal cancer and the development of metachronous liver metastases.

We believe that the LNR, especially in cases of adequate lymph node sampling, is a useful gauge to better substratify "node-positive" patients. This is because it would allow us to prognosticate those who, with higher probability, are carriers of occult liver metastases that will manifest in follow-up and who therefore have to receive customized diagnostic and therapeutic strategies. In our opinion, however, further evaluation is still necessary particularly in order to calculate an absolute cut-off value that allows us, beyond complex statistical evaluations, to

determine when a node-positive patient is at greater risk of recurrent disease.

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