

# Original Article

## Number of Disected Lymph Nodes In Colorectal Cancer Patients Submitted To Radical Surgery: The Quality of Oncology Treatment

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### Abstract

**Introduction:** the correct evaluation of lymph node disease influences the therapeutical decisions of colon and rectal cancer (CRC) patients. The number of dissected lymph nodes is a variable that have prognostic value and serves as an indicator of the quality of oncology treatment. For a correct evaluation of N stage to be accepted, the minimum number of dissected lymph nodes considered must be 12. In rectal cancer patients submitted to neoadjuvant radiochemotherapy, the interpretation of the number of dissected lymph nodes remains inconclusive. **Objective:** is to evaluate the number of dissected lymph nodes in CRC patients submitted to curative surgery and determine this latter impact in oncologic treatment results. In cases of rectal cancer, to study the effect of neoadjuvant radiochemotherapy in dissected lymph nodes count. **Method:** in the period 1991-2004, 852 CRC patients were treated in Hospital A. C. Camargo . Patients with metastases at the time of diagnosis, synchronous and metachronic tumors, total colectomy or total proctocolectomy and hereditary colorectal cancer were excluded. The sample was constituted by 423 patients with sporadic colorectal adenocarcinoma who undergone curative radical surgery (168 colon primary tumors and 255 rectal tumors). Colon cancer patients, treated primarily by surgery, had also received adjuvant chemotherapy (5-FU) according to risk criteria. Rectal cancer patients with fixed or half-fixed injuries or clinically compromised lymph nodes (T3, T4 or N+) had received neoadjuvant radiochemotherapy, followed by surgery and chemotherapy (5-FU). **Results:** the median of the number of dissected lymph nodes in colon cancer patients was 17. In the case of rectal cancer patients, the median of dissected lymph nodes in the groups with and without neoadjuvant radiochemotherapy had been respectively 9 and 15 ( $p < 0.001$ ). 5-year specific survival rates for colon and rectal cancer patients were respectively EC I 100%, EC II 89%, EC III 79,5% e EC I 97,8%, EC II 79%, EC III 64,9%. In colon cancer patients, despite the differences observed in survival rates, there was no statistical difference among dissected lymph nodes categories  $< 12$  and  $\geq 12$  (NO patients:  $< 12$  76% and  $\geq 12$  95%,  $p = 0.106$ ; N(+):  $< 12$  patients = 89% and  $\geq 12$  77%,  $p = 0.318$ ), as well as among rectal cancer patients NO ( $< 12$  78% and  $\geq 12$  90%,  $p = 0.576$ ). However, among rectal cancer patients N(+), the division according to the number of dissected lymph nodes distinguished patient groups of different prognostics ( $< 12 = 51.9\%$  and  $\geq 12 = 76\%$ ,  $p = 0.018$ ). **Conclusions:** the medians of the number of dissected lymph nodes in colon and rectal cancer patients and survival rates found demonstrate the good quality of oncologic treatment; neoadjuvant radiochemotherapy reduces dissected lymph nodes findings; rectal cancer patients N(+) with less than 12 dissected lymph nodes constitute a group of worse prognostic.

**Key words:** Lymph node/anatomy and histology. Colorectal neoplasms. Prognosis. Efficacy, Treatment.

### Introduction

The detection of lymphonodal metastases is of vital importance for the judgment of the prognostic and complementary therapeutical institution of in colorectal cancer (CRC) patients. It has been

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suggested that patient that present a small number of dissected lymph nodes in surgical specimens have worse prognostics, probably due to incomplete lymphadenectomies and in consequence sub-stadiation.<sup>1</sup> Besides the standardization technique for anatomopathological analysis, the obedience to oncology principles in resection is vital for obtaining the expected minimum number of lymph nodes. Therefore, surgeons and pathologists are responsible for the correct evaluation of lymphonodal condition and it can be used for measuring the quality of oncologic treatment.

LeVoyer et al.<sup>1</sup> demonstrated that the median number of lymph nodes removed at colectomy was 11 (range: one to 87). Of the 3411 assessable patients, 648 had no evidence of lymph node metastasis. Multivariate analyses were performed on the node-positive and node-negative groups separately to ascertain the effect of lymph node removal. Survival decreased with increasing number of lymph node involvement. After controlling for the number of nodes involved, survival increased as more nodes were analyzed. Even when no nodes were involved, overall survival and cause specific survival improved as more lymph nodes were analyzed. The authors consider that the number of dissected lymph nodes in colon cancer patients is directly related to prognostic, both in pN(+) and pN0 patients, and 12 to be the minimum number of dissected lymph nodes for the correct evaluation of lymphonodal condition.

Among rectal cancer patients, the minimum number of necessary lymph nodes and the impact of neoadjuvant treatment with radiochemotherapy on the lymphadenectomy field and lymphonodal evaluation are not well defined. In Baxter et al.<sup>2</sup> evaluation, if one considers 12 to be the expected minimum number, only 20% of patients will be able to present it. Thus, lymph node staging in patients who undergo preoperative RT must be interpreted with caution and studies are needed to evaluate the clinical relevance of node number and pathologic staging after preoperative RT for rectal cancer.

The objective of this study is to evaluate the number of dissected lymph nodes in CRC patients submitted to curative surgery and de-

termine this latter impact in oncologic treatment results, as well as the effect of neoadjuvant radiochemotherapy in dissected lymph nodes count in surgical specimens coming from rectal cancer patients.

## Method

In the period 1991-2004, 852 CRC patients were treated in Hospital A. C. Camargo. With the exclusion of patients with metastases at the time of diagnostic, synchronous and metachronic tumors, total colectomy or total proctocolectomy and hereditary colorectal cancer, the sample was constituted by 423 patients with sporadic colorectal adenocarcinoma who undergone curative radical surgery (168 colon primary tumors and 255 rectal tumors). Colon cancer patients were treated primarily by surgery. The then current protocols indicated adjuvant chemotherapy (5-Fluorouracil) for high risk Stage II and Stage III. 264 patients did not receive adjuvant chemotherapy (83 Stage I, 130 Stage II and 51 Stage III). For medium and low rectal cancer patients in T3, T4 or N(+) clinical stages adjuvant chemotherapy (external radiotherapy – 45Gy in pelvis and 50.4Gy in primary tumor, concomitantly to chemotherapy with 5-Fluorouracil 425mg/m<sup>2</sup>/day and leucovorin 20mg/m<sup>2</sup>/day each 7 days during radiotherapy) was indicated. Adjuvant chemotherapy was indicated for patients that had received neoadjuvant treatment. Among rectal cancer patients who did not receive neoadjuvant treatment, the ones presenting high risk (preoperative CEA >5; T3 and T4 tumors; compromised lymph nodes; presence of sanguineous or lymphatic embolization; little differentiated and undifferentiated tumors) had undergone radiochemotherapy and adjuvant chemotherapy. Patients presenting rectal tumors above the peritoneal reflection were treated primarily by surgery and undergone adjuvant chemotherapy following an indication for colon cancer.

For colon adenocarcinoma patients, the number of dissected lymph nodes was evaluated according to primary tumor localization: right colon (n=54), transverse colon (n=20), descending colon (n=17) and sigmoid colon (n=77). For rectal adenocarcinoma patients, the number of dissected

lymph nodes in the groups with and without neoadjuvant radiochemotherapy was evaluated. For examining the prognostic value of the number of dissected lymph nodes, 2 categories were adopted: up to 12 lymph nodes and 12 or more lymph nodes, following the number the literature considers necessary for the correct evaluation of lymphonodal stadiation. For calculating actuarial estimators of cancer-specific survival (SCE) we used Kaplan-Meier technique and survival curves were compared using Log Rank tests. Statistical significance was defined for the values of  $p < 0.05$ .

## Results

Mean and median values for the number of dissected lymph nodes according to colon primary tumor localization and according to the use of neoadjuvant radiochemotherapy for rectal tumor patients are in Table 1.

The median of the number of dissected lymph nodes was above 12 in all interventions for tumors located in colon. For rectum tumor patients, the median one of the number of dissected lymph nodes was bigger in the group without neoadjuvant radiochemotherapy (15 versus 9,  $p < 0.001$ ).

Cancer-specific survival rates in 5 years for colon cancer patients according to stage grouping (pTNM), N Stage and number of dissected lymph nodes are in Table 2. The respective cancer-specific survival curves are represented in Figure 1.

**Table 1** - Number of dissected lymph nodes in patients who undergone radical surgery for colon and rectal cancer

| Location            | N   | Mean dissected lymph nodes | Median dissected lymph nodes |
|---------------------|-----|----------------------------|------------------------------|
| Colon               |     |                            |                              |
| Right               | 54  | 22.48                      | 21.5                         |
| Transverse          | 20  | 23.50                      | 26.0                         |
| Descending          | 17  | 19.24                      | 14.0                         |
| Sigmoid             | 77  | 17.13                      | 13.0                         |
| Total colon         | 168 | 19.82                      | 17.00                        |
| Rectum              |     |                            |                              |
| Without neoad.RT/CT | 165 | 16.64                      | 15.00                        |
| With neoad.RT/CT    | 90  | 10.03                      | 9.00                         |
| Total rectum        | 255 | 14.31                      | 12.00                        |

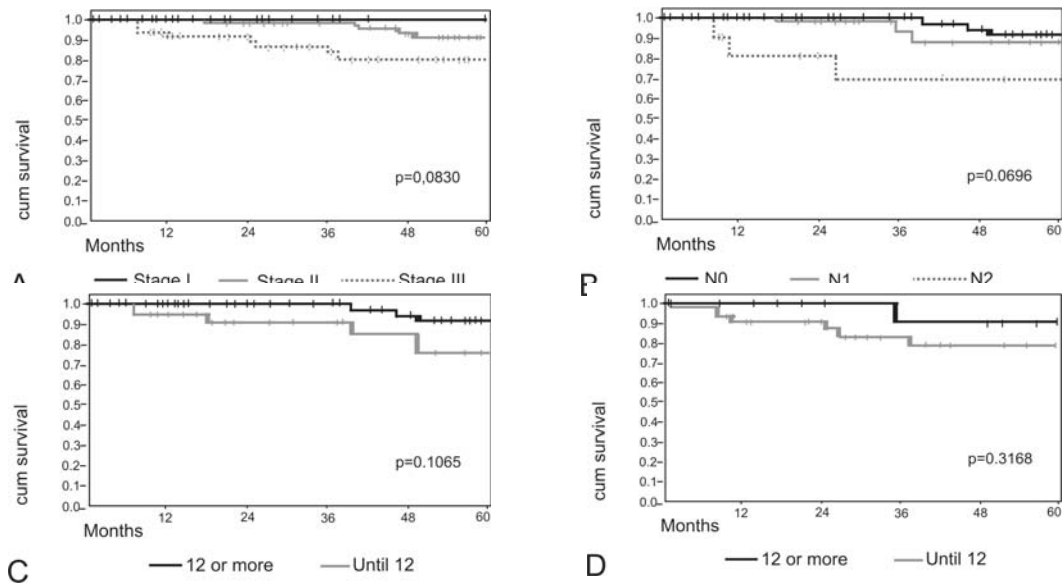
**Table 2** - Cancer-specific survival rates (CSS) in 5 years in 168 colon cancer patients submitted to treatment with curative intention

| Variable                         | CSS 5 years (%) | p (Log-Rank) |
|----------------------------------|-----------------|--------------|
| Staging                          |                 |              |
| I                                | 100.0           | 0.0830       |
| II                               | 89.0            |              |
| III                              | 79.5            |              |
| N                                |                 |              |
| N0                               | 88.0            | 0.0696       |
| N1                               | 84.0            |              |
| N2                               | 66.0            |              |
| Patients N0                      |                 |              |
| Up to 12 lymph nodes dissected   | 76.0            | 0.1068       |
| 12 or more lymph nodes dissected | 95.0            |              |
| Patients N1/N2                   |                 |              |
| Up to 12 lymph nodes dissected   | 89.0            | 0.3188       |
| 12 or more lymph nodes dissected | 77.00           |              |

Cancer-specific survival rates in 5 years for rectal cancer patients according to stage grouping (pTNM), N Stage and number of dissected lymph nodes are in Table 3. The respective cancer-specific survival curves are represented in Figure 2.

**Table 3** - Cancer-specific survival rates (CSS) in 5 years in 255 rectal cancer patients submitted to treatment with curative intention

| Variable                         | CSS 5 years (%) | p (Log-Rank) |
|----------------------------------|-----------------|--------------|
| Staging                          |                 |              |
| I                                | 97.8            | 0.0248       |
| II                               | 79.0            |              |
| III                              | 64.9            |              |
| N                                |                 |              |
| N0                               | 82.8            | 0.0010       |
| N1                               | 76.8            |              |
| N2                               | 66.00           |              |
| Patients N0                      |                 |              |
| Up to 12 lymph nodes dissected   | 78.0            | 0.5765       |
| 12 or more lymph nodes dissected | 90.0            |              |
| Patients N1/N2                   |                 |              |
| Up to 12 lymph nodes dissected   | 51.9            | 0.0180       |
| 12 or more lymph nodes dissected | 76.0            |              |
| Patients N1                      |                 |              |
| Up to 12 lymph nodes dissected   | 69.0            | 0.1320       |
| 12 or more lymph nodes dissected | 85.9            |              |
| Patients N2                      |                 |              |
| Up to 12 lymph nodes dissected   | 0               | 0.0003       |
| 12 or more lymph nodes dissected | 64.0            |              |



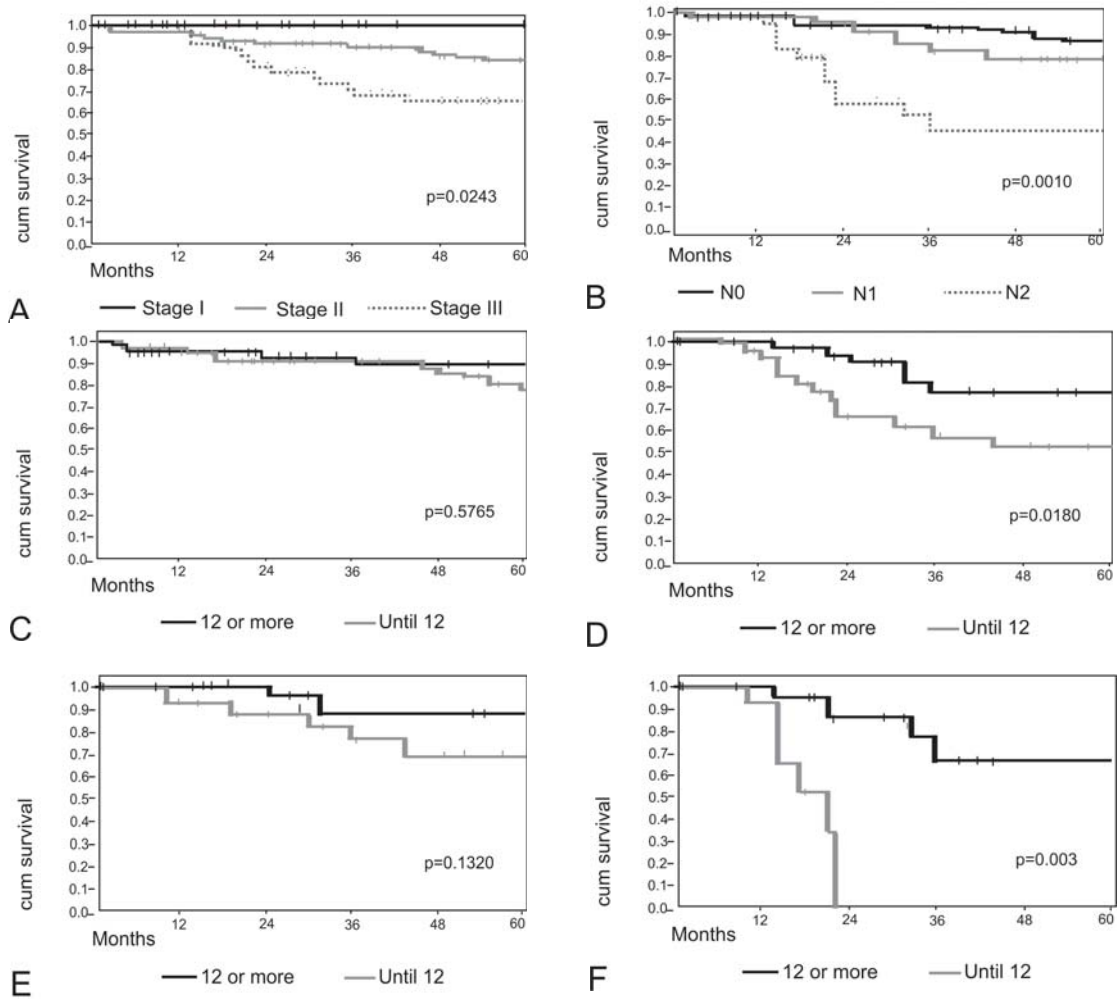
**Figure 1** – Colon cancer: Cancer-specific survival (n=168): A – staging; B – lymphonodal condition (N); C – number of dissected lymph nodes in N0; D – number of dissected lymph nodes in N(+)

## Discussion

Several studies have demonstrated the importance of the number of dissected lymph nodes in colorectal cancer surgery. LeVoyer et al.<sup>1</sup> had demonstrated that the number of dissected lymph nodes is related directly to prognostic, both in pN(+) and in pN0 patients, and propose 12 to be the minimum number of dissected lymph nodes for the correct judgment of lymphonodal condition. Considering this, an analysis of the median number of dissected lymph nodes and the rates of cancer-specific survival rates dividing patients in categories according to the number of dissected lymph nodes (up to 12 and 12 or more) allowed to evaluate the quality of oncologic treatment in the Hospital A. C. Camargo. Moreover, we also evaluated the impact of radiochemotherapy in the pathological evaluation of the lymphonodal condition. Our results had found a median of 17 dissected lymph nodes in the interventions for treatment of colon cancer patients and 12 for rectal cancer patients. Differences between the number of dissected lymph nodes in patients submitted to the same surgical procedure can be justified from some considerations: quality of surgery as regards

principles of oncologic resection, the quality of anatomopathological evaluation and individual variability.<sup>3,4</sup> Considering the first two, both are characteristics that allow to evaluate the quality of a service. As concerns the impact in the treatment, we all know that when the number of lymph nodes is inferior to 12, the patient must be individually evaluated as to the necessity of adjuvant treatment, since the lymphonodal condition cannot be evaluated with precision. The correct judgment of the lymphonodal condition can allow a group of patients to be exempted from adjuvant treatment without additional risks. In contrast, when the determination is not trustworthy (up to 12 dissected lymph nodes), part of the patients will receive complementary chemotherapy due to the lack of an adequate lymphonodal stadiation, sometimes unnecessarily. Besides individual consequences, this procedure burdens significantly oncologic treatment, particularly when schemes include oxaliplatin.<sup>5-6</sup>

Considering the current proposal of a preferential use of neoadjuvant radiochemotherapy for T3, T4 or N(+) rectal cancer patients<sup>8</sup> and the orientation that even when there are complete responses to treatment



**Figure 2** – Rectal cancer: Cancer-specific survival (n=255): A – staging; B – lymph node condition (N); C – number of dissected lymph nodes in N0; D – number of dissected lymph nodes in N(+); E – number of dissected lymph nodes in N1; F – number of dissected lymph nodes in N2

surgery remains indicated,<sup>9</sup> a parallel consideration of the number of dissected lymph nodes in rectal cancer patients must be made. It is known that preoperative radiochemotherapy affects anatomopathological evaluation.<sup>10</sup> Intramural spread and tumor deposit, budding, and micrometastasis were significantly decreased in the radiation group, compared with the non-radiation group;<sup>11</sup> however, the ideal number of dissected lymph nodes in this condition was not established until now.<sup>12</sup> In Baxter et al.<sup>2</sup> evaluation, if we consider 12 to be the expected minimum number, only 20% of the patients will present this number, with a median of 7 in the preoperative radiotherapy group and of 10 in the group without previous treatment. The same authors presented

16% of rectal tumor patients who undergone preoperative radiotherapy whose anatomopathological examinations had not identified lymph nodes. In our series, we observe medium of 15 lymph nodes in the group without radiochemotherapy and 9 in the group of preoperative radiochemotherapy (p<0.001). As patients in the two groups had been operated by the same surgical team, according to well-established standardization, we can consider that the observed difference must be due to effect of neoadjuvant treatment. In this group, the finding of number of lymph nodes inferior to 12 does not mean impossibility of an adequate judgment of the lymphonodal condition in the sense of non-observance of oncologic principles, where the rules

of mesorectum total excision spread out by Heald et al. must be respected.<sup>13-15</sup> In rectal cancer, it can be said that preoperative radiochemotherapy determines a regression in pathological stadiation, besides causing the reduction of the number of evaluated lymph nodes.<sup>16</sup> A recent study demonstrated that the pathological classification of the T variable continues to be an important predictive factor of lymphonodal metastasis risk in rectal cancer patients submitted to neoadjuvant radiochemotherapy. In this study, the risk of lymphonodal metastasis was 3.4% in patients who regressed to ypT0 or ypT1 stages.

Thorn et al.<sup>17</sup> consider that the number of lymph nodes identified in the surgical specimen has a positive correlation to tumor size and that in N(+)patients the number of dissected lymph nodes increases in function of the extension of the lymphadenectomy field. An analogous reasoning allows to suppose that this justifies the worse prognostic of N+ colon cancer patients with more than 12 dissected lymph nodes observed in our series, that is, when the surgeon detected in the intra-operative the macroscopic involvement of lymph nodes, the lymphadenectomy field was extended and therefore the number of dissected lymph nodes was bigger, but the impact of lymphonodal compromising in the prognostic is more relevant. In Wong et al.<sup>18</sup> series, the number of examined lymph nodes varied from 0 to 78 (median: 17 lymph nodes); N0 patients had a lesser number of examined lymph nodes than N+ ones (median: 14 versus 20,  $p=0.003$ ).

In colon cancer patients, we do not observe a significant difference in survival rates when the groups had been divided in categories according to the number of dissected lymph nodes. Our interpretation is that perhaps the number of patients is so small for this to be observed, being associated with the relatively small number of events, that is, in all stages cancer-specific survival rates were high, with a low index of death because of the disease. Among rectal cancer patients, the differences were apparent, particularly those that presented lymphonodal disease. In this group are patients who undergone and did not undergone preoperative radiochemotherapy. As demonstrated, radiochemotherapy have an effect on the number of dissected lymph nodes, and this leads us to believe that the number of patients

with a higher number of dissected lymph nodes comes from the group without previous treatment and that therefore they would present a better prognostic (cN0). However, N(+)patients that had not received preoperative radiochemotherapy due to sub-stadiation undergone this therapeutical modality in the postoperative, as determined by the protocol then followed. Thus, we believe that the benefit observed in patients with more than 12 dissected lymph nodes is a consequence of the adequate surgical procedure, for despite the current evidences of the highest rates of local control with preoperative radiochemotherapy, overall survival rates had no change.<sup>8</sup> This analysis makes us believe that even in the group of preoperative radiochemotherapy, the number of dissected lymph nodes is important and patients with 12 or more dissected lymph nodes have a better prognostic. In the analysis of sub-groups, the N2 patients with 12 or more dissected lymph nodes had significantly superior cancer-specific survival rates (no N2 patient with less than 12 dissected lymph nodes survived more than 24 months). Despite these considerations, it is not possible to establish an ideal minimum number for the necessary judgment of lymphonodal condition in rectal cancer patients treated with neoadjuvant radiochemotherapy. Tumor regression as well as residual tumor cell density were found to be predictive factors of survival in rectal carcinoma patients after preoperative radiotherapy.<sup>19</sup> Even after preoperative radiotherapy, the pathologic stage of the surgical specimen remained a prognostic factor. The use of a standardized approach for pathologic evaluation must be implemented to allow comparison between the results of various treatment approaches.

## Conclusion

For this sample of 423 colorectal adenocarcinoma patients, the median of dissected lymph nodes was of 17 in cases of colon cancer and 12 in cases of rectal cancer. In rectal cancer patients, neoadjuvant radiochemotherapy affected the evaluation of the number of dissected lymph nodes (9 versus 15;  $p<0.001$ ). In N(+) rectal cancer patients, the division according to dissected lymph nodes number (up to 12; 12 or more)

divided patients in different prognostic groups, with worse survival rates for N(+) patients with up to 12 dissected lymph nodes. The high cancer-specific survival rates prove the good quality of the oncologic surgical treatment.

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