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Prognostic significance of lymph node count in high-risk node-negative colon carcinoma

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ABSTRACT

Background: the prognostic value of the number of lymph nodes isolated (< 12 *versus* ≥ 12) in the surgical specimen continues to be controversial. In this study, the impact of isolating fewer or more than 12 lymph nodes in stage II colon cancer with a high-risk biologic phenotype was analyzed, such as the presence of perineural invasion.

Methods: all cases of stage II disease (T3-4N0M0) with perineural invasion (PNI+) were retrospectively identified from a prospective database of patients undergoing surgery for colon cancer. The cohort was divided into two groups depending on the number of

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lymph nodes isolated (< 12 *vs* ≥ 12). Apart from clinical and surgical data, the patterns of recurrence, overall (OS) and disease-free survival (DFS) at five and ten years were analyzed.

Results: sixty patients met the inclusion criteria, 31.7 % had < 12 lymph nodes isolated and 68.3 % had more than 12 isolated. There were no clinical or surgical differences between the two groups. OS at five and ten years was significantly lower in the patients with < 12 lymph nodes isolated (84.2 %, 62.7 % *vs* 94.6 % and 91.6 %, p = 0.01). DFS at five and ten years was 51 % *vs* 86.5 %, respectively (p = 0.005).

Conclusion: the number of lymph nodes isolated (with a cutoff of 12) in stage II colon cancer with PNI+ has prognostic value and should therefore be borne in mind when planning adjuvant chemotherapy.

Keywords: Colon cancer. Stage II. Perineural invasion. Lymph node count. Survival. Surgery.

INTRODUCTION

Colon cancer is the second leading cause of cancer mortality after lung cancer in males and females in Western Europe and the United States (1). Tumor stage (TNM) and the pathologic characteristics of the tumor are the most important prognostic factors in potentially curative stages (I-III). However, other prognostic markers have recently been reported (2-4).

Stage II (T3-4N0M0) accounts for 25 % of colon tumors and five-year survival is between 70 % and 80 %. However, 25 % of patients develop distant metastases and have a survival rate similar to that of stage III disease (5,6). As a result, there has been a lot of interest in the identification of the pathologic factors underlying the poor prognosis associated with this stage, in order to establish a firmer basis for the administration of adjuvant chemotherapy (2,7,8).

The number of lymph nodes isolated (< 12 *versus* ≥ 12) in the resected specimen is one of the prognostic factors referred to above, although there is controversy surrounding this issue (9,10). In this study, the influence of the number of lymph nodes isolated in the surgical specimen in a series of patients with stage II colon cancer who also

presented a high-risk morphologic phenotype such as perineural invasion was analyzed (11,12).

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the center and was performed according to STROBE norms. Patients with stage II colon cancer (T3-4N0M0) (13) with perineural invasion undergoing surgery with curative intent (RO) were retrospectively identified from a prospective database of 3,141 colorectal cancer patients, between 2000 and 2016. Colon cancer was defined as all tumors proximal to the rectosigmoid junction.

Adenocarcinoma was histologically confirmed in all patients and tumors were staged using computed tomography (CT) of the thorax, abdomen and pelvis. All patients previously underwent colonoscopy (with the exception of occluded patients) in order to rule out synchronous tumors.

Demographic data (age and gender), body mass index (BMI, which was calculated as weight in kilograms divided by height in meters squared), functional status (as defined by the classification of the American Society of Anesthesiologists [ASA]), preoperative carcinoembryogenic antigen levels (CEA) and type of surgery (open or laparoscopic) were recorded for each patient in the cohort. Right-sided tumors were defined as those located between the cecum and the splenic flexure and left-sided tumors are located between the flexure and the upper third of the rectum (> 15 cm of the anal margin). Splenic flexure tumors were considered as left-sided tumors.

Colectomies were performed following the criteria of the American Society of Colon and Rectal Surgeons, with an “en bloc” resection of the tumor and of the mesocolon from the root of the feeding vessels and the adjacent organs when necessary (14). Multivisceral resection was defined as the “en bloc” resection of the primary tumor plus the adjacent organs. From 2008, most surgeries were performed laparoscopically following the same oncologic principles.

Surgical specimens were analyzed following the norms of the American Society of Pathologists (15). Proximal, distal and radial margins were analyzed. The degree of differentiation and tumor stage (TNM) were assessed using the criteria of the World

Health Organization (WHO) (16) and the 7th edition of the American Joint Committee Cancer Staging Manual (13). Perineural and lymphovascular invasion were defined using the criteria of Batsakis and Sato, respectively (17,18).

Adjuvant chemotherapy based on 5-FU and oxaliplatin was administered 4-6 weeks after surgery, depending on the risk factors involved, according to the guidelines of the European Society of Medical Oncology (19). Patients were monitored following the National Comprehensive Cancer Network guidelines (NCCN) (20). Locoregional recurrence was defined as radiologic and/or pathologic evidence of a tumor with the same histology in the tumor bed. Distant recurrence was diagnosed based on two consecutive CT scans within 4-6 weeks. Histological confirmation was performed when feasible.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM, SPSS Statistics for Window, Armonk, NY, USA). Descriptive statistics with categorical variables were summarized as frequencies and percentages. Quantitative variables were summarized as means and standard deviation (SD). The statistical significance of distribution differences in dichotomous variables was assessed using the Chi-squared test (X2), whereas the Mann-Whitney test was used for ordinal values. All p-values were two sided and a p-value less than 0.05 was considered as statistically significant. The univariate relation between each variable and the number of nodes retrieved (12 *vs* > 12) was assessed using a single factor logistic model for continuous variables and categorical variables. Independent variables in the univariate analysis were entered into the multivariate logistic regression model, adjusted for age, sex, BMI, laparoscopic resection, localization of the tumor and lymphovascular invasion.

Overall survival (OS) was defined as the interval from surgery to death or end of follow-up. Disease-free survival (DFS) was defined as the time between surgery and the occurrence of loco-regional recurrence, distal metastases or death due to any cause. OS and DFS were evaluated by the Kaplan-Meier method and compared using the long-rank test and Cox regression analysis.

RESULTS

A total of 60 were identified with colon cancer stage II accompanied by perineural invasion from 3,141 patients that underwent surgery for colorectal cancer between 2000 and 2016. Thus, these 60 patients were included in the study. Table 1 summarizes the clinical and pathologic characteristics of the series, which was split into two groups regarding the number of isolated nodes.

There were 24 males and 36 females, with a mean age of 62.9 years (SD: 12.1) and a mean BMI of 26.4 kg/m^2 (SD: 4.5). Most of the patients had an ASA classification grade of II, n = 40 (66.7 %). Thirteen (21.7 %) right-sided hemicolectomies, five (8.3 %) resections of the transverse colon, 15 (25 %) left-sided hemicolectomies, 23 (38.3 %) sigmoidectomies, two (3.3 %) full colectomies, one (1.7 %) anterior resection and one Hartmann intervention were performed. The mean hospital stay was 7.9 days.

The mean number of lymph nodes isolated was 15.8 (SD 1.27) and more than 12 lymph nodes were isolated in 41 patients (68.3 %). Fifty-four patients (90 %) presented moderately differentiated tumors and lymphovascular invasion was observed in 25 (41.7 %). There were no significant differences between the two groups in terms of sex, age, ASA grade, tumor location, surgery, tumor phenotype characteristics and the administration of adjuvant chemotherapy (Table 1). No difference was found between the two groups according to the multivariate analyses adjusted by age, sex, BMI, type of surgery, location and lymphovascular invasion.

Fourteen (23.4 %) patients had distant recurrence during a mean follow-up of 104 months. There were nine (15 %) in the liver, six (10 %) in the lung, four (6.7 %) in the peritoneum and one locoregional recurrence. Overall five- and ten-year survival in the two groups (< 12 *vs* ≥ 12 lymph nodes isolated) was 84.2 %, 62.7 %, 94.6 % and 91.6 %, respectively (p = 0.01, OR 4.63, 95 % CI: 1.15-18.56) (Fig. 2). The mean overall survival (120 months) was 96 and 107 months, respectively (p = 0.005). Five and ten-year disease-free survival was 51 % and 86.4 % depending on the number of lymph nodes isolated (p = 0.017, HR 4.199, 95 % CI: 1.40-12.54) and the mean disease-free survival (120 months) was 77 and 107 months (p = 0.005). Figures 1 and 2 show the overall and disease-free survival curves depending on the number of lymph nodes isolated. Overall and disease-free survival were significantly higher when more than 12 lymph nodes

were isolated ($p < 0.01$ and $p < 0.005$). No difference in survival was observed between patients who had received adjuvant chemotherapy and those without adjuvant chemotherapy.

There were no significant differences between other prognostic factors such as right- or left-sided location ($p = 0.79$), CEA levels ≤ 5 ng/ml *vs* > 5 ng/ml ($p = 0.25$), local infiltration ($p = 0.49$) and lymphovenous infiltration ($p = 0.51$).

DISCUSSION

The standard surgical treatment of stage II colon cancer is resection of the tumor with lymphadenectomy, including at least 12 lymph nodes and resection of the adjacent organ (9,14). However, different studies disagree on the beneficial effect of isolating more than 12 lymph nodes, both in stage II and stage III disease. Thus establishing the minimum number of lymph nodes remains controversial (21). Therefore, this study was performed of the prognostic value of the number of lymph nodes isolated in stage II disease with a high-risk biologic phenotype, as represented by the presence of perineural invasion (22).

This study found that the isolation of at least 12 lymph nodes was associated with a significant increase in OS and DFS at five and ten years, which is consistent with other studies (9,23). This outcome has been linked to several mechanisms. Firstly, the isolation of a minimum of 12 lymph nodes allows a more complete staging and avoids any possible under-staging of more advanced tumors (stage III) with a poor prognosis and susceptible to adjuvant chemotherapy (ACT) (10,24).

In this study, even though a non-significant difference was observed in the chemotherapy administration between the two groups ($p = 0.24$), more patients (70.7 %) with ≥ 12 nodes received adjuvant chemotherapy. Besides the improvement in the lymphadenectomy (complete mesocolon excision) throughout the study period, the administration criteria of chemotherapy was clearly defined and implemented as well. However, other studies have not found this association. In fact, the isolation of more than 12 lymph nodes has been linked to the host immune response to the tumor, such that the isolation of a greater number of lymph nodes results in a more intense immune response. This confirms the seminal report by Jass et al. in 1987 (25) on the

prognostic value of tumor inflammatory infiltrate, which was recently highlighted (25-28).

Tumor aggressiveness is not solely a cancer-cell process but rather the interaction between the tumor and the innate and cell-mediated immune response. A standardized methodology was not amenable during the study period, despite the potential benefit of risk stratification based on tumor-infiltrating lymphocytes in colon cancer.

Although the degree of lymphocyte infiltration in the tumor was not quantified in this study, the prognostic value of the lymphocyte infiltrate (Immunoscore®) has been recently reported in the oncologic outcomes of 1,434 patients with stage II colon cancer (29). In line with these findings, Moore et al. (30) reported lower survival rates for patents in whom less than 12 lymph nodes were isolated in a study of 11,399 patients with stage I-III colon cancer. The authors linked this to an increased aggressiveness of the tumor and a suboptimum or inadequate immune response and not to a possible under-staging of the tumor. Recent studies have confirmed the direct passage of malignant cells from the lymph nodes to blood vessels, highlighting an inefficient immune response (31,32).

Limitations

This study suffers from the limitations inherent to a retrospective study, although we used a database which was assembled prospectively and the series in itself is very homogeneous. We are aware that the series is small, mainly due to the strict selection criteria applied (T3-4N0M0, PNI+). Furthermore, although a standard lymphadenectomy was performed and four surgeons who are experts in colorectal surgery participated, the number of lymph nodes isolated may vary according to the surgeon and the diligence of the pathologist (33).

In conclusion, the isolation of fewer than 12 lymph nodes in the pathologic analysis in stage II colon cancer with presence of perineural invasion is associated with a worse overall and disease-free survival compared with at least 12 isolated lymph nodes. This factor should be borne in mind when planning adjuvant treatment.

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Table 1. Clinical and pathological characteristics of 60 stage II colon cancer patients with perineural invasion by lymph node count grouped as < 12 and ≥ 12 nodes

Variable	*All participants (60)*	*< 12 nodes (n = 19)*	*≥ 12 nodes (n = 41)*	*p*
Male	24 (40 %)	8 (42.1 %)	16 (39 %)	0.520
Age, *years*, mean (SD)	62.9 (12.1)	65.5 (13.9)	61.6 (11.1)	0.243
BMI, *kg/m²*, mean (SD)	26.4 (4.5)	24.3 (4.1)	27.2 (4.5)	0.029
ASA class on admission (%)				
- I and II	40 (66.7 %)	14 (73.7 %)	26 (63.4 %)	0.232
- III and IV	15 (25.0 %)	3 (15.8 %)	12 (29.3 %)	
- Unknown	5 (8.3 %)	2 (10.5 %)	3 (7.3 %)	
Tumor location				
- Right colon	20 (33.3 %)	4 (21 %)	16 (39 %)	0.140
- Left colon	40 (66.7 %)	15 (78.9 %)	25 (61 %)	
Local invasion	12 (20 %)	5 (26.3 %)	7 (17.1 %)	0.307
Type of surgery				
- Laparoscopic	16 (26.7 %)	2 (26.3 %)	14 (34.1 %)	0.066
Tumor histology				
- Adenocarcinoma	56 (93.3 %)	18 (94.7 %)	38 (92.7 %)	0.623
- Mucinous	4 (6.7 %)	1 (5.3 %)	3 (7.3 %)	
Depth of tumor invasion T stage				
- T3	54 (90 %)	18 (94.7 %)	36 (87.8)	0.749
- T4	6 (10 %)	1 (5.3 %)	5 (12.2 %)	
Tumor differentiation				
- Well differentiated		0	0	0.666
- Moderately differentiated	54 (90 %)	16 (84.2 %)	38 (92.7 %)	
- Undifferentiated	4 (6.7 %)	1 (5.3 %)	3 (7.3 %)	
- Unknown	2 (3.3 %)	2 (10.5 %)	0	
Lymphovascular invasion				
- Yes	25 (41.7 %)	4 (21.1 %)	21 (51.2 %)	0.074

Adjuvant chemotherapy				
- Yes	40 (66.7 %)	11 (57.9 %)	29 (70.7 %)	0.244

SD: standard deviation; BMI: body mass index: weight in kilograms divide by the squared of the height in meters; ASA: American Society of Anesthesiologists classification.

Table 2. Pattern of recurrence in colon cancer stage II with perineural invasion following resection with regard to lymph node yield

	All participants	*< 12 nodes (n = 19)*	*≥ 12 nodes (n = 41)*	*p*
Total location of recurrence	14 (23.3 %)	9 (47.4 %)	5 (12.2 %)	0.005
- Liver metastases	9 (15.0 %)	6 (31.6 %)	3 (7.3 %)	0.023
- Lung metastases	6 (10 %)	4 (21.1 %)	2 (4.9 %)	0.074
- Peritoneal metastases	4 (6.7 %)	3 (15.8 %)	1 (2.4 %)	0.188
- Locoregional	1 (1.7 %)	1 (5.3 %)	0 (0.0 %)	0.317

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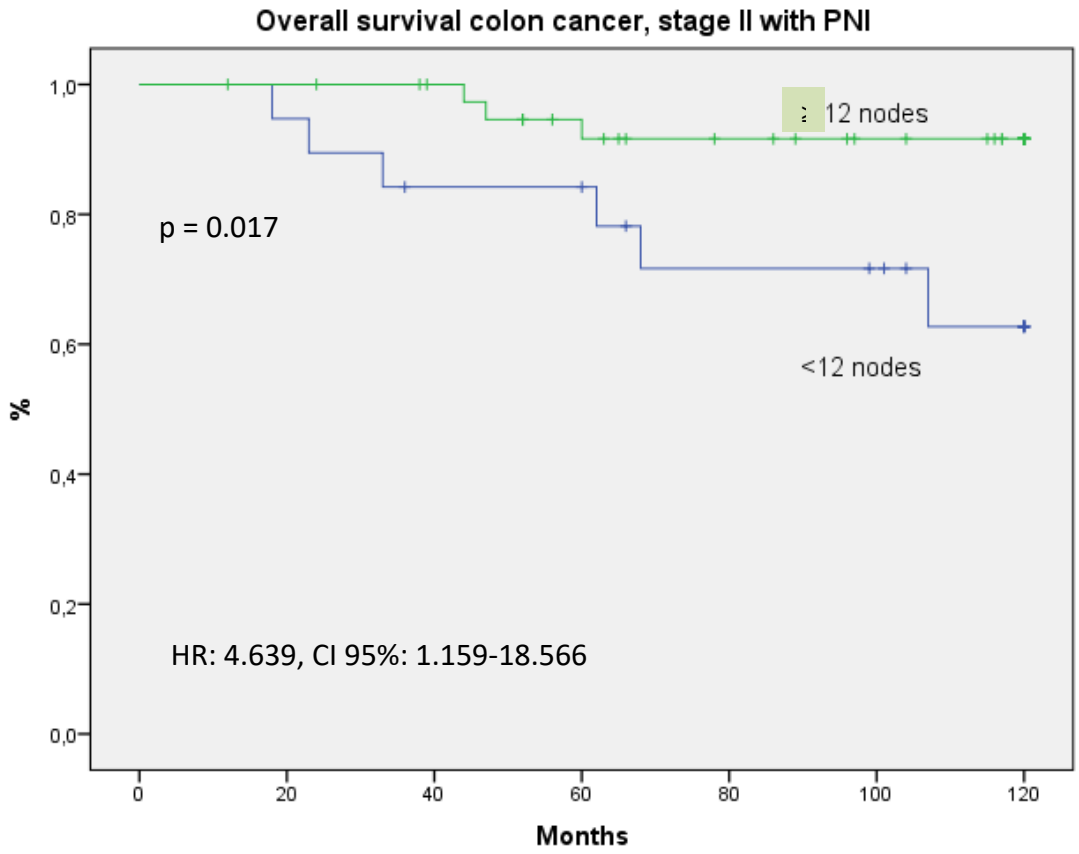


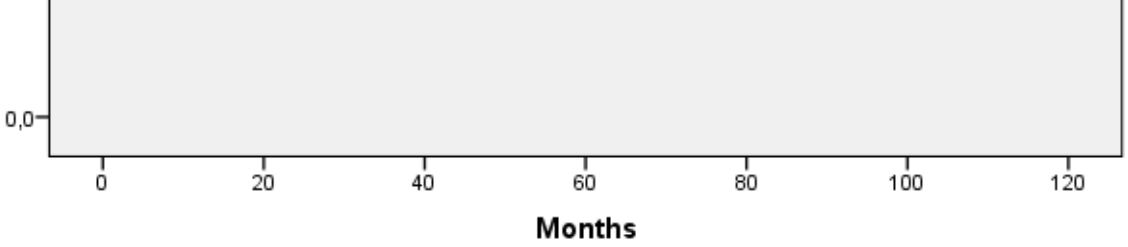
Overall survival ≥ 12 nodes

Months	0	12	24	36	48	60	72	84	96	108	120
No.	41	41	41	39	38	35	31	27	26	24	22
Surv.	100	100	100	100	94.6	94.6	91.6	91.6	91.6	91.6	91.6

Overall survival < 12 nodes

Months	0	12	24	36	48	60	72	84	96	108	120
No.	19	19	17	16	15	15	14	11	11	11	7
Surv.	100	100	94.7	84.2	84.2	84.2	71.7	71.7	71.7	62.7	62.7

Fig. 1. Overall survival in stage II colon cancer with PNI.



Disease-free survival ≥ 12 nodes

Months	0	12	24	36	48	60	72	84	96	108	120
No.	41	41	40	35	30	30	29	27	26	23	21
Surv.	100	100	94.7	89.3	86.4	86.4	86.4	86.4	86.4	86.4	86.4

p = 0.005

Disease-free survival < 12 nodes

Months	0	12	24	36	48	60	72	84	96	108	120
No.	19	19	18	16	13	11	9	8	8	6	6
Surv.	100	94.7	84.2	73.7	62.3	51.0	51.0	51.0	51.0	51.0	51.0

HR 4.199; CI 95% 1.406 - 12.541

Fig. 2. Disease-free survival. Stage II colon cancer with PNI.