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Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer

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Abstract

The diagnosis of a lymph node-negative colorectal carcinoma should imply a good prognosis; however, the outcomes for TNM stage II patients remain variable. Few studies have examined the relationship of the number of lymph nodes examined to the prognosis of this stage. The aim of this study was to determine whether the number of lymph nodes examined has an effect on prognosis of a relatively large sample of patients undergoing curative surgery for stage II colorectal cancer at a single institution. Data on patients who underwent surgery for colorectal cancer between January 1980 and April 2000 were prospectively collected in a database. Patients with TNM stage II or stage III tumours who were treated with curative intent were removed. Patients over 80 years of age were excluded from the survival analysis. Survival comparisons were made using Kaplan–Meier curves and the log-rank test. Multivariate analysis was performed using a Cox regression model. A total of 625 cases of TNM stage II cases and, for comparison purposes, 415 stage III cases, were analysed. Lymph node retrieval in stage II cases was affected by the patient's age ($P = 0.04$) and gender ($P = 0.02$), tumour grade ($P < 0.0001$), tumour site ($P < 0.0001$), and necessity to carry out extended resection ($P < 0.0001$). In stage III cases, lymph node retrieval was affected by patient age ($P < 0.0001$), tumour grade ($P = 0.02$), and tumour site ($P = 0.002$). Decreased lymph node detection was associated with increasing hazard ratios among the 480 TNM stage II patients under 80 years of age, but not among the 345 patients with TNM stage III tumours. Five year survival rate for patients with stage III tumours with only 1–3 positive lymph nodes (52.6%) was similar to that of patients with stage II tumour who had nine or fewer lymph nodes examined (51.3%). These results demonstrate that the prognosis of TNM stage II colorectal cancer is dependent on the number of lymph nodes examined. Patients with few nodes examined have a poorer prognosis. It is possible that a smaller number of lymph nodes examined reflects a diminished immune response. It can be presumed that those patients with stage II tumour with only a few nodes examined should be offered postoperative chemotherapy on a routine basis.

Keywords: Colorectal neoplasms; Survival; Prognosis; Lymph node assessment; Staging

1. Introduction

For patients undergoing curative surgery for colorectal cancer (CRC), it is critically important to accurately differentiate between the group with localised or node-negative disease (TNM stage II) and the group with regional or node-positive disease (TNM stage III), since this has a significant effect on prognosis and treatment. Five-year survival for stage II CRC is 70–75% [1]; survival for stage III CRC is 45% [1,2]. Patients with stage III CRC are routinely offered postoperative adjuvant chemotherapy, whereas those with stage II CRC are not [2–4].

Nevertheless, the outcome for TNM stage II patients remains highly variable, with a number of patients far-

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ing worse than those with apparently more advanced tumours. A proportion of these disappointing outcomes may be explained by understaging [5]. Adequate retrieval and assessment of colorectal mesenteric lymph nodes is critical to ensure that the lymph nodes do not contain metastatic disease. Failure to examine enough lymph nodes may result in a failure to identify patients in whom lymph nodes are affected by cancer and thus may result in understaging [6]. Several studies have examined the relationship of the number of lymph nodes examined to the prognosis of stage II CRC, [6–12] and some of these have attributed understaging to the worse prognosis of those cases in which few lymph nodes had been examined [5–7]. However, other authors have hypothesised that a smaller number of lymph nodes examined reflects differences in the biologic behaviour of the tumour and/or host, such as a diminished immune response [5]. The differing results of the studies carried out on this subject could be attributed to differences in the methods used. Studies based on large numbers of cases [6] yield results that are statistically reliable, but are multicentric; it would be reasonable to assume that different pathologists use different techniques and degrees of diligence in examining specimens for lymph nodes, and that there may be some variability in the extent of dissection by different surgeons. Monocentric studies reduce the variation in the pathologist's examination and in the surgical techniques, although those available in the literature refer to limited sample sizes [5,9–12]. Tepper and colleagues [8] reviewed data from a relatively large prospective rectal cancer trial (1664 patients), but the report did not address patients with colon cancer.

The aim of this study was to determine whether the number of lymph nodes examined has an effect on prognosis of a relatively large sample of patients who underwent curative surgery for stage II CRC at a single institution.

2. Patients and methods

The notes on all patients undergoing surgery for CRC in the General Surgical Clinics and Surgical Therapy Section of the Surgical Sciences Department at the University of Parma, Italy, between January 1980 and April 2000, were prospectively collected in a database. Patients with a known history of familial adenomatous polyposis or cancer, those with Crohn's disease or ulcerative colitis, and those with synchronous or recurrent tumours were excluded. All tumours were staged according to the TNM system [13]. Those with TNM stage II tumours who underwent surgery with curative intent and with histologically confirmed disease-free resection margins were included in the study. A similarly constituted group of stage III patients from the same time period was analysed for comparison purposes. Cases with known distant metastases or incomplete clearance of the tumour were excluded. The investigations used to rule out distant metastases at the time of resection were preoperative liver ultrasonography, chest X-ray and intraoperative exploration.

During the study period, a uniform surgical management protocol was in place. In all cases, curative resection had included the main lymphovascular supply to the bowel. For proximal colon tumours, lymphadenectomy was extended to the origin of the ileocolic, right colic and middle colic arteries. For distal colon tumours and rectal tumours, lymphadenectomy was extended to the origin of the lower mesenteric artery. Total mesorectal excision was performed in all patients with tumours of the middle and lower rectum; a distal clearance of at least 2 cm of healthy mucosa from the lower edge of the tumours was provided in all cases. Only patients who underwent surgery under 75 years of age and after 1990 for stage III colon cancer, received adjuvant chemotherapy [3]. The drug regimen for chemotherapy was mg/m^2/day 5-fluorouracil (5-FU) 375 and 20 mg/m^2/day levamisole, 5 days/week, every 4 weeks, for 6 months. Patients who underwent surgery after 1988 for rectal cancer received irradiation therapy administered in a dosage of 40 Gy, divided into 16 daily doses of 2.5 Gy each (4 doses/week for 4 weeks) before surgery [14].

The standard clinical variables documented were age, gender, tumour localisation (recorded as right, left, or rectal), histological type and differentiation (as described by Dukes and Bussey) [15]. The right colon was defined as the large bowel proximal to the right half of the transverse colon; the left colon was defined as the large bowel between the right colon and the recto-sigmoid junction; the rectum was defined as the recto-sigmoid junction and the rectum. In accordance with the classification of tumours by the World Health Organization [16], tumours were defined as mucinous if 50% or more of the tumour displayed the specific cell type, and as undifferentiated if features of tumour-cell differentiation were absent. Other tumours were classified as ''adenocarcinoma, not otherwise specified''. The number of lymph nodes assessed was retrieved from the tumour template in the pathology report. The same team of pathologists examined surgical specimens for lymph nodes, and the same technique for lymph node assessment was utilised during the entire period of the study. Lymph nodes were identified by palpation, and routine histological examination was performed using triple levelling techniques and staining with haematoxylin and eosin. No special clearance or staining techniques were employed.

Patients were followed-up every six months with clinical assessment and serum carcinoembryonic antigen measurement, annual chest X-ray and colonoscopy for five years, then colonoscopy every two years, with

further investigations performed as indicated. Follow-up was updated in April 2003 for the current study.

All data were recorded and analysed with a standard statistical software package (Stata: StataCorp. 2003. Stata Statistical Software: Release 8.0. College Station, TX: Stata Corp LP.). Patients over 80 years of age were excluded from the survival analyses, since the high percentage of deaths during the course of the study from causes other than the neoplastic disease rendered this group unsuitable for analysis. The Kaplan–Meier [17] probability of survival analysis was used to examine the prognostic effects of the different variables, including the number of lymph nodes examined. Differences among groups were assessed using the log-rank test [18]. The simultaneous effect of more than one prognostic factor was estimated by the Cox proportional hazards model. The age and nodes examined were first entered in the model as continuous variables; another model was then made including them as categorical variables. The cut-off points were chosen by means of tertiles. The significance level was set at $P = 0.05$ and Confidence Intervals (CIs) were at the 95% level.

3. Results

During the study period, 745 cases of T3-4N0 (stage II) and, for comparison purposes, 493 cases of T3-4N1-2 (stage III) colon cancer were reported. The exact number of lymph nodes examined was not clear for 65 stage II and 43 stage III patients, and 11% of all cases were reported as lost to follow-up; these cases were considered as being unsuitable for the study, leaving 625 stage II and 415 stage III patients for further statistical analysis. Clinical and pathological data, and details regarding the number of lymph nodes reported, are given in Table 1. The distribution of the number of lymph nodes examined is shown in Fig. 1.

For TNM stage II tumours, there was a significant association between the number of lymph nodes examined and patient age ($F = 4.24$ $P = 0.04$). As Fig. 2 shows, the number of lymph nodes examined decreases with the increase of age. An association between the number of nodes examined and age was also found for TNM stage III tumours ($F = 14.01$ $P < 0.0001$; regression coefficient [RC] = −0.156 nodes examined; 95% CI = −0.37–0.004; $P < 0.0001$). Table 2 shows that lymph node retrieval in stage II cases was affected by other factors: number of lymph nodes examined was higher in tumours of female patients, in moderately or poorly differentiated tumours, in mucoid tumours, in those situated in the right colon, and in those requiring extended resection. Depth of invasion (T3 vs. T4) did not affect the extent of lymph node assessment ($P = 0.385$). In stage III cases, lymph node retrieval was only affected by tumour grade and tumour site, and there was a significant correlation between the number of positive nodes and the number of lymph nodes examined (RC = 0.127 positive nodes, 95% CI = 0.08 0.16; $P < 0.001$).

Table 1
Clinical data of 1040 patients who underwent curative surgery for TNM stage II and stage III colorectal cancer

	Stage II	Stage III	*P* value
No. of patients	625	415	
Mean age (range)	70.2 ± 11.5	67.8 ± 12.4	0.002
Male/female (%)	53/47	52/48	0.696
Tumour site (no./%)[a]			0.737
Right colon	194/31	130/31	
Left colon	238/38	148/36	
Rectum	193/31	135/33	
Histology (no./%)			0.017
ADK	485/78	295/71	
Mucoid ADK	140/22	120/29	
Tumour grades (no./%)[a]			0.0001
G1	171/27	8/2	
G2	235/38	143/41	
G3	219/35	198/57	
TNM stage (no./%)			
T3	162/26	41/10	
T4	463/74	374/90	
N1		263/63	
N2		152/37	
Astler and coller stage (no./%)			
B1	162/26		
B2	463/74		
C1		41/10	
C2		374/90	
Widen surgery (no./%)	41/7	20/5	0.245
Mean no. of lymph nodes reported ± SEM	15.15 ± 10.8	16.7 ± 10.6	0.026
Kaplan–Meier 5-year survival estimates	61.1%,	42.9%	0.0001
Kaplan–Meier 10-year survival estimates	55.3%	37.4%	0.0001

SEM, standard error of the mean.
[a] Some data are missing.

The median follow-up times were 78 months for stage II cases and 56 months for stage III cases. The difference in the median follow-up times is a reflection of the survival experience of these two groups (Table 1). Ten-year survival rates for patients over 80 years of age were not affected by tumour stage: 14.2% for stage II, 11.4% for stage III. This result is a reflection of the numerous deaths in both groups from causes not attributable to the tumour. For this reason, we considered that patients over 80 years of age could not supply us with the necessary information for the analysis of the influence on survival of the number of lymph nodes examined, and thus for the subsequent survival analyses we considered only patients under 80 years of age.

TNM stage II and stage III patients under 80 years numbered 480 and 345, respectively. Among the 480

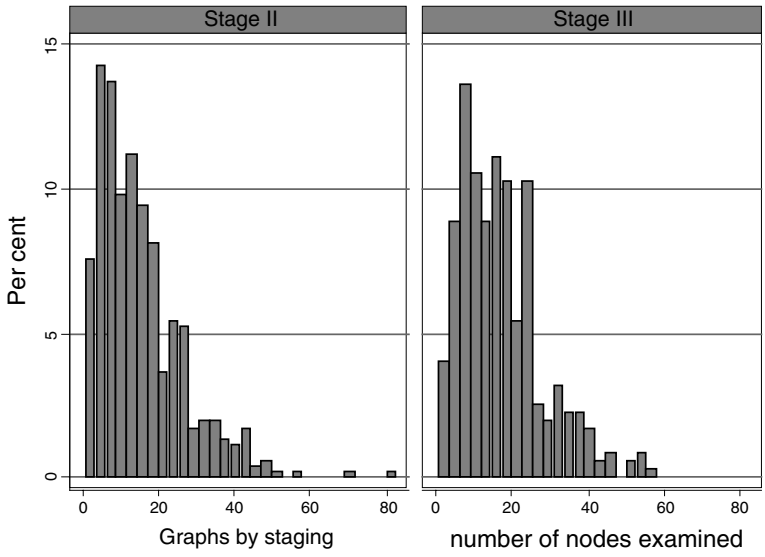

Fig. 1. Percentage distribution of the number of lymph nodes examined according to stage is shown.

TNM stage II patients, Kaplan–Meier survival curves demonstrated that the 10-year survival rates were clearly dependent on the number of lymph nodes examined (Table 3). Table 3 shows that survival rates were also significantly dependent on patient's gender and age, and on the depth of tumour invasion.

Only 78% of patients with stage II rectal cancer had radio-therapy after surgery. The survival rates for rectal tumour patients treated with and without postoperative radiotherapy were not significantly different (Table 3).

As reported in Fig. 3, the Cox regression analysis showed that in the stage II group, patient's age and gender, depth of tumour invasion and extent of nodal examination were significant contributors to the model. Decreased nodal detection was associated with increasing hazard ratios (HR), both when the variable was analysed as a continuous variable (HR = 0.981, CI = 0.968–0.995, $P < 0.008$) (Fig. 4), and when the number of lymph nodes was analysed as a categorised variable (Fig. 5): compared with cases with more than 19 nodes examined, the examination of less than 10 nodes increased a patient's hazard to 1.501 (95% CI = 1.009–2.233, $P < 0.045$), whereas taking 10 to 18 nodes did not increase it significantly ($P = 0.725$).

Among 345 patients with TNM stage III tumours, the survival curves according to whether nine or fewer or more than 10 lymph nodes were examined were not significantly different ($P = 0.434$). The Cox regression

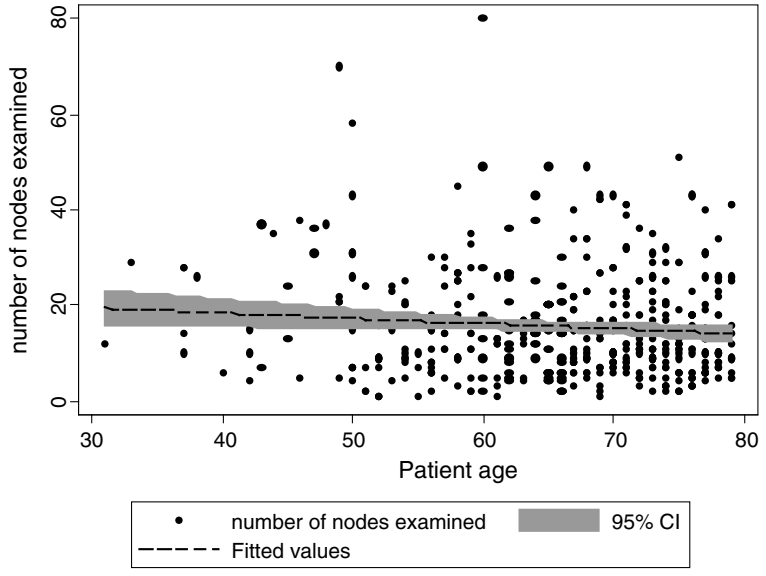

Fig. 2. Number of lymph nodes examined according to the age of 625 patients with TNM stage II colorectal cancer (regression coefficient = −0.109 nodes examined; 95%, Confidence Interval: −0.21–0.005; $P = 0.04$).

Table 2
Univariate analysis of factors affecting lymph node assessment in 625 TNM stage II (node-negative) and 415 stage III (node-positive) colorectal cancers

	Stage II		Stage III	
	Number of lymph nodes examined (mean ± standard deviation)	*P* value	Number of lymph nodes examined (mean ± standard deviation)	*P* value
Gender				
Male	14.60 ± 10.34	0.022	16.24 ± 19.81	0.409
Female	16.97 ± 12.11		17.10 ± 12.11	
Tumour grade				
G1	11.31 ± 8.25		7.50 ± 3.74	
G2	17.05 ± 11.80	0.0001	17.17 ± 10.92	0.025
G3	17.89 ± 11.78		17.42 ± 9.56	
Histology				
ADK	14.65 ± 10.99	0.0001	16.41 ± 10.96	0.204
Mucoid ADK	19.65 ± 11.31		17.27 ± 9.67	
Tumour site				
Right colon	19.12 ± 11.23	0.0001	19.27 ± 10.94	
Left colon	14.92 ± 11.57		16.26 ± 11.219	0.002
Rectum	13.40 ± 9.93		14.73 ± 9.08	
Widen surgery				
Yes	23.17 ± 12.98	0.0001	14.25 ± 8.10	0.298
No	15.17 ± 10.94		16.78 ± 10.71	

analysis showed that, in the stage III group, patient's gender (HR 1.817, $P = 0.001$), depth of tumour invasion (HR = 1.426, $P < 0.0001$), tumour histology (HR 1.562, $P < 0.018$), tumour grade (HR 0.638, $P < 0.003$) and number of positive nodes (1–3 vs. >3) (HR 1.042, $P < 0.010$) were significant contributors to the model.

Five-year survival rates for patients with TNM stage III tumours (42.9%, 95% CI = 36.9–48.8) were significantly worse than for those with stage II overall (61.1%, 95% CI = 56–65.8), stage II with more than 10 lymph nodes examined (69.9%, 95% CI = 61.4–77.2), and stage II with nine or fewer lymph nodes examined (51.3%, 95% CI = 43.2–58.9); however, survival for those with stage III tumours with only 1–3 positive lymph nodes (52.6%, 95% CI = 44.7–60.00) was similar to that of patients with stage II tumours who had nine or fewer lymph nodes examined.

4. Discussion

In our patient group, the age and gender distribution were comparable to other published studies, as were the survival figures.

The results of this study confirm the opinion that the number of lymph nodes examined is a prognostic variable for patients with TNM stage II CRC. Besides the number of lymph nodes, the depth of tumour invasion, age and gender were also prognostic variables for this group. The significance of age is not clear from this analysis, although it may be related to comorbid disease. The significance of gender is also unclear from this study, although previous studies have suggested that survival following surgery for CRC is better in women than in men [19].

Why does the prognosis of stage II CRC depend on the number of lymph nodes examined? The number of lymph nodes examined depends on the extent of the dissection by the surgeon and the extent of the examination of the tissue by the pathologist, but also on the number of lymph nodes present.

The differences in the extent of the dissection by surgeons directly affects survival. The surgeon must perform an adequate surgical resection, including the main lymphovascular supply to the bowel, to provide the pathologist with enough lymph nodes to dissect, but also, and above all, to guarantee a thorough clearance of the tumour and hence the best possible prognosis. It has been pointed out in the literature that it would be reasonable to assume that there may be some variability in the extent of the dissection by different surgeons [6,11], and that this difference may make the interpretation of multicentric studies difficult. However, in the analysis presented here, the extent of the dissection by the surgeon cannot have influenced the number of lymph nodes examined, since the study was conducted at a single centre using a standardised surgical technique which always involved the excision of the blood supply and lymphatics at the level of the origin of the primary feeding vessel. We can thus assert that the reason the number of lymph nodes examined relates to prognosis in this study has no connection with the extent of the dissection by the surgeon. The correlation between tumour location and the number of lymph nodes

Table 3
Kaplan–Meier 5–10 year survival estimates, by clinicopathological variables, in 480 TNM stage II patients in the study

Variables	5-Year survival (%) ± standard error of the mean	*P* value[a]	10-Year survival (%) ± standard error of the mean	*P* value[a]
Gender		0.001		0.0001
Male	75.43 ± 2.7		53.54 ± 3.4	
Female	87.23 ± 2.3		71.31 ± 3.5	
Age (years)		0.001		0.002
31–63	89.98 ± 2.4		68.05 ± 4.2	
64–72	81.92 ± 3.0		62.12 ± 4.1	
73–79	69.20 ± 3.8		52.42 ± 4.5	
Tumour site		0.033		0.234
Right colon	84.54 ± 3.7		63.20 ± 4.5	
Left colon	85.23 ± 2.6		60.92 ± 4.0	
Rectum	80.63 ± 3.3		60.19 ± 4.4	
Histology		0.194		0.523
ADK	81.96 ± 2.0		61.58 ± 2.8	
Mucoid ADK	75.07 ± 4.7		59.52 ± 6.0	
Tumour grade		0.011		0.234
G1	86.13 ± 3.0		60.14 ± 4.3	
G2	83.12 ± 2.9		65.53 ± 4.2	
G3	72.76 ± 3.7		58.37 ± 4.6	
Extended resection		0.193		0.883
Yes	72.41 ± 8.3		67.59 ± 9.0	
No	81.25 ± 1.9		60.91 ± 2.6	
Depth of tumour invasion		0.016		0.003
T3	87.44 ± 2.9		71.54 ± 4.4	
T4	78.00 ± 2.3		56.95 ± 3.0	
Number of lymph nodes examined		0.800		0.013
0–9	82.22 ± 3.2		51.38 ± 4.0	
10–18	78.02 ± 3.4		69.03 ± 4.0	
>18	81.50 ± 3.0		70.90 ± 4.2	
Therapy[b]		0.655		0.899
Surgery alone	81.17 ± 2.0		61.06 ± 2.7	
Surgery with radiotherapy	78.40 ± 4.5		61.57 ± 6.0	

[a] Log-rank test for equality of survivor functions.
[b] About 154 patients affected by rectal cancer.

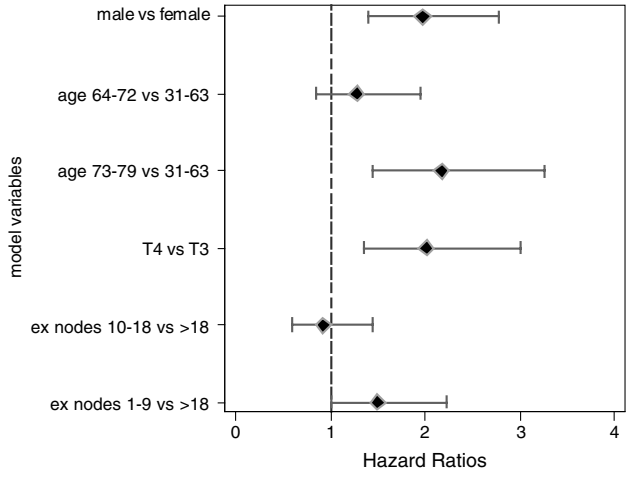

Fig. 3. Cox proportional hazard model for 480 TNM stage colorectal cancer. Hazard Ratios are expressed with 95% Confidence Intervals. (ex nodes = lymph nodes examined).

examined does not depend on the surgeon, but it confirms observations previously reported [5,20–22] and is not unexpected, given that the specimen may often contain a larger amount of mesentery in right-sided resections, and in subtotal colectomy.

A second factor that may influence the number of lymph nodes examined is the adequacy of assessment of lymph nodes by pathologists. If pathologists use inadequate techniques or an inadequate degree of diligence in examining specimens for lymph nodes, the assessment of lymph nodes will be inadequate. In this case, some patients with designated stage II disease may have a poor survival rate because they are likely to have understaged stage III disease. This is why a number of techniques, including fat clearance with xylene and alcohol, lymph node-revealing solution, an increased use of pathology assistants, and the use of pathology template, have all been suggested as improving lymph

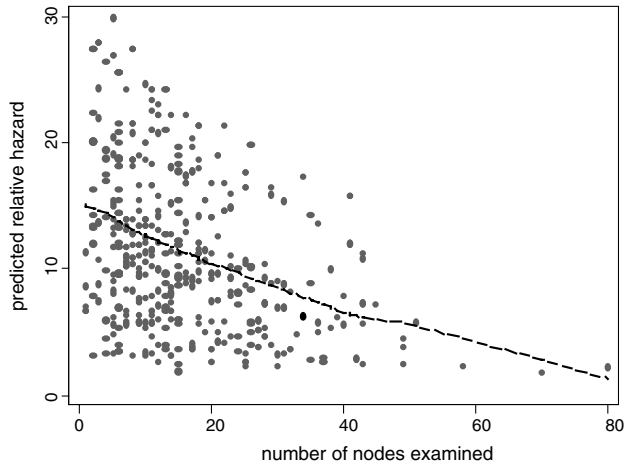

Fig. 4. Scattergram demonstrating that in a group of 480 patients undergoing curative resection of TNM stage II colorectal cancer, decreased node detection was associated with increasing hazard ratios, (Hazard Ratio = 0.981, 95%, Confidence Interval: 0.965–0.999, $P < 0.045$) also when the number of lymph nodes examined was analysed as a continuous variable adjusted for age, gender and depth of tumour invasion (the dotted line represents the lowess smooth of the model predicted Hazard ratio).

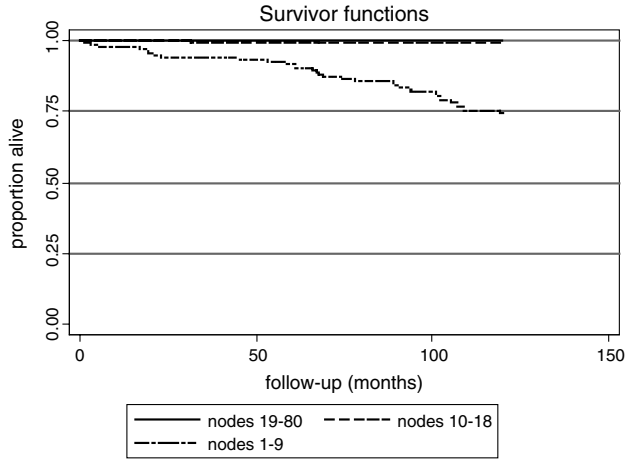

Fig. 5. Survivor functions of number of lymph nodes examined divided according to tertiles adjusted for age, gender and depth of tumour invasion, in a group of 480 patients undergoing curative resection of TNM stage II colorectal cancer.

node assessment [9,23–25]. However, in the present study, the same team of pathologists examined surgical specimens for lymph nodes, and the same technique for lymph node assessment was utilised during the entire study period. We therefore consider it unlikely that the number of lymph nodes examined, higher in some patients than in others, can have been influenced by differing techniques or degrees of diligence on the part of pathologists.

A third possibility should also be considered, that is, that the number of lymph nodes examined, and hence the prognosis for the patient, may be due to the differing numbers of lymph nodes present in the different specimens. It is possible that a smaller number of lymph nodes examined reflects differences in the biological behaviour of the tumour and/or host. There may be less immune response generated by aggressive tumours, or else the group of patients with fewer lymph nodes identified may be patients who have a diminished immune response [5]. The size and morphology of lymph nodes are modified by immune responses. Distension and prominence of the lymphatic sinusoids may represent a host immune response against neoplastic cell products. This is a common phenomenon seen in lymph node draining cancer, and leads to lymph node enlargement. Lower immune response may lead to smaller lymph nodes, with a lower number being identified. Patients with a small number of lymph nodes examined may have a poorer prognosis because of an insufficient immune response. This hypothesis seems to be borne out by the observation in a recent study that the pattern of failure in stage II CRC patients with low lymph node counts is mainly characterised by an increase in cases with distant disease, especially hepatic metastases [26]. The results of this study would also appear to support this hypothesis. The number of lymph nodes examined correlates with the age and gender of patients, and with the histology and grade of tumours. It is unthinkable that a surgeon would carry out a resection of a differing extent in male patients from that in women, or in tumours subsequently classified as being G1 instead of G2 or G3. In the same way, it is unthinkable that the pathologist would utilise different techniques with different degrees of diligence for mucinous tumours and non-mucinous adenocarcinomas, or for specimens of younger and older patients. It is much more likely that young and old patients, as well as males and females, have differing immune responses, and that well differentiated and poorly differentiated tumours, adenocarcinomas and mucinous adenocarcinomas have different biological behaviors [27,28].

In all of these different situations, varying numbers of lymph nodes may be present, and the situations in which few lymph nodes can be examined could be those that will subsequently have worse prognoses. Caplin and colleagues [5] reported that overall survival was diminished in patients with stage II disease with fewer than seven lymph nodes examined compared with patients with stage II disease and seven or more lymph nodes examined. Law and colleagues [26] also confirmed these results. In our study, the number of lymph nodes examined below, which the prognosis of stage II CRC patients had, a worse outcome was 10. Other studies have suggested that 12–17 lymph nodes should be examined to stage CRC adequately [8–10,20,29].

However, in our opinion, all of these cut-off points are to be considered useful, but artificial, that is, they are merely a mathematical exercise, at least to some ex-

tent. The association between the number of nodes examined and risk appears to be linear and not step-function. Thus, in the light of the above considerations, a more important prognostic factor than establishing a minimum number of lymph nodes to be examined would appear to be the number of lymph nodes that the pathologist is able to analyse. If the prognosis of stage II CRC varies as a function of the number of lymph nodes examined, then we maintain, in agreement with Swanson and colleagues [6], that studies for stage II CRC should be stratified according to the number of lymph nodes examined. This observation may also have several important implications for patients. Patients with TNM stage II colon cancer are routinely offered postoperative adjuvant chemotherapy, whereas those patients with stage III colon cancer are not [2,3]. In our study, 5-year survival for patients with stage II tumour who had nine or fewer lymph nodes examined was similar to that of patients with stage III tumours with only 1–3 positive lymph nodes. Perhaps patients with stage II tumour with nine or fewer nodes examined should also be offered postoperative chemotherapy on a routine basis. Further studies are required in order for this hypothesis to be verified.

Conflict of interest statement

None declared.

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