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Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination

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Abstract

Correct staging of colon cancer is decisive regarding further oncological treatment, surveillance and prediction of long-term survival. This study investigated the variability in accuracy of pathology reports with focus on differences between pathology departments and their compliance to regional guidelines. Data from the colon cancer register (1997–2002) of the Uppsala/Örebro, Sweden, health care region were analysed and the seven pathology departments in this region were compared. Included were 3735 patients who had undergone resection of a colon cancer. Cumulative 5-year survival was the main end-point.

For 64% ($n = 2390$) of the cases, the number of lymph nodes examined was given (median 8). Survival in stage II was lower when fewer than 12 nodes were examined or when the number of nodes sampled was not given ($P = 0.001$, log-rank test). In stage III, those with at the most 3 nodes positive (N1) had a better survival than those with 4 or more nodes positive (N2) ($P < 0.001$, log-rank test). An index of metastases (IM), derived from the number of nodes with metastases divided by the number of nodes examined, was calculated for stage III tumours. Examination of 12 nodes is necessary to assure stage III cases with the median IM (0.32), whereas 20 nodes are necessary to assure 90% of cases with the lower quartile of IM (0.16). Irrespective of the number of nodes investigated, overall survival was better among patients with IM < 0.33 *vs.* IM $\geqslant 0.33$ ($P < 0.001$, log-rank test). The prognostic information of the IM was higher than that of the N-stage. Quality of a pathology department, measured by the median number of lymph nodes investigated and by the proportion of reports where the number is given, was determined to indicate correct staging and management of the patient. An index of metastases (IM) is a possible basis for guidance in the choice of adjuvant treatments that appears superior to that of N-stage.

Keywords: Colon cancer; Epidemiology; Quality control; Lymph nodes; Tumour staging; Survival

1. Introduction

The staging of patients operated for colon cancer is a determining factor for further oncological treatment and for prediction of long-term survival. Different staging systems for classification have been used since Dukes introduced his classification system for rectal cancer in 1932 [1], and most commonly used today is the TNM classification [2]. As several studies have shown that postoperative chemotherapy in patients with a stage III colon cancer has a beneficial effect on survival [3–5], it is even more important to improve not only the surgical technique, but also sampling of nodes and staging. There appears to be a breakpoint in the number of lymph nodes examined that will properly determine the proportions of tumour stages II and III [6].

During the past decade, the surgeon and the surgical technique have been in focus in research concerning quality and survival in colorectal cancer [7–11]. An important recent step in attempts to further improve

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the surgical quality in rectal cancer has been the provision for immediate feedback from the pathologist to the surgeon [12]. Important advances have also been made in pre- and post-operative oncological treatment [3,13]. However, a prerequisite for a proper decision by the oncologists about postoperative treatment is a valid report from the pathologist after examination of the resected specimen. Several attempts have been made to estimate the number of nodes necessary to examine for correct staging. Between 6 and 18 nodes have been recommended [14–16]. According to the World Congress of Gastroenterology (Sydney, Australia, 1990) [6], a minimum of 12 lymph nodes should be examined for correct classification of tumours as stage II.

In population-based studies, the proportions of colon cancer in stages II and III are approximately 40% and 30% [17–19], with survival rates varying between 50–80% and 30–60%, respectively. However, there are reasons to believe that the proportion of stage III tumours is in fact higher than has been reported, on account of inadequate examination of lymph node metastases. During the past decade it has been considered a gold standard to offer adjuvant chemotherapy to patients operated on for a colon cancer stage III, as several studies have shown that this increases survival by approximately 10%, whereas this is not yet the case in stage II where uncertainties about the value of adjuvant chemotherapy still exist [3,5,20,21]. It is therefore of immediate importance to identify all patients with lymph node metastasis.

The aim of this study was to investigate the variability in the accuracy of pathology reports, with special attention to differences between pathology departments and to their compliance to regional guidelines. Since the number of nodes is influenced by preoperative radiotherapy, frequently used for rectal cancer [13], and a clear survival benefit of postoperative chemotherapy has been found for colon, but not for rectal cancer, our investigation was focused solely on colon cancer. Our primary hypothesis was that the differences in quality between pathology departments influence the classification of tumours into stages and that stage dependent outcome was influenced by the quality.

2. Materials and methods

Since 1997 all colon cancers (adenocarcinoma) in the Swedish health care region of Uppsala/Örebro (population 1.9 million in 2001) have been reported to a population-based register run by the Regional Oncologic Centre (ROC). During this period, common regional guidelines for diagnosis, staging and treatment of colorectal cancer have been settled and agreed upon in consensus, by surgeons, oncologists and pathologists. The guidelines include, among others, recommendations concerning the pathologists' examination of the specimen. Registration of the number of mesenteric lymph nodes examined and the number of lymph nodes with metastases is mandatory, and these data are reported prospectively to the registry. No guidelines for lymph node-clearing techniques are given. These techniques therefore might differ between pathology departments, as well as over time, and the specific methods used are not documented.

Data from the ROC registry was analysed with respect to compliance to the guidelines, and the seven departments of pathology in the region were compared. Each department serves one county including one university or general district hospital and up to four district hospitals. During the period studied (1997–2002), 4205 patients were reported to the colon cancer registry, 3748 of them underwent surgical resection. Thirteen patients were excluded as they were operated on at a hospital outside the Uppsala/Örebro region. Thus, a total number of 3735 patients were eligible for further analyses.

2.1. Statistical methods

Statistica® software (StatSoft, Tulsa, USA) was used for statistical analyses. Distribution fitting of data were checked with the Kolmogorov–Smirnow test. Most parameters appeared to be normally distributed, with many patients in each group, whereas for others there were groups of variable size that did not fit in that distribution model. Thus, the non-parametric Mann–Whitney U test was generally used to calculate the significance of differences in continuous variables, whereas the χ^2 test was applied in cases of dichotomous response parameters and to test differences in proportions between groups. Correlation was calculated by the Spearman rank correlation test. The Kaplan–Meier method was used to calculate cumulative survival. Differences in survival between groups were tested for significance by the log-rank method. Factors considered to be possible determinants of survival were first checked in univariate Cox proportional hazard regressions. The influence of the possible determinants was also tested in multivariate Cox proportional hazard regressions with 95% confidence intervals [22].

An index of metastases (IM) was derived from the number of nodes with metastases divided by the number of nodes examined. The term IM+ was used for patients classified as stage III but the IM could not be calculated due to insufficient information about number of nodes examined and/or number of nodes with metastases. The likelihood to identify a stage III tumour in our material was calculated and plotted against the number of nodes examined according to the IM.

3. Results

Characteristics of the included patients are listed in Table 1. In 64% ($n = 2390$) of the cases, the number of lymph nodes examined was given in the pathology report. In these, the median overall number of lymph nodes examined was 8 (mean 9.4), with a variation in medians between pathology departments from 6 to 12 lymph nodes (Table 2). During the study period, an improvement was seen regarding the proportion of reports where the number of nodes examined was given (20% in 1997 and 90% in 2002) as well as regarding the number of nodes examined (median 6 in 1997 and 9 in 2002). However, overall there was a variation in the relative proportions of tumour stages II and III between different pathology departments, with less stage II the more lymph nodes examined (Fig. 1). These differences were not related to specific hospitals within the catchment area of the pathology department or to hospital category, but to the pathology departments themselves. Three of the departments examined significantly fewer nodes compared to the other four departments (median 6 compared to $\geqslant 9$; $P < 0.001$) (Table 2). For tumour stages I–III there was a correlation between stage and number of lymph nodes examined ($r^2 = 0.01$; $P < 0.001$), with an increase stage by stage in the median number (stages I–III: 7, 8 and 9 lymph nodes, respectively; $P < 0.001$) (Fig. 2).

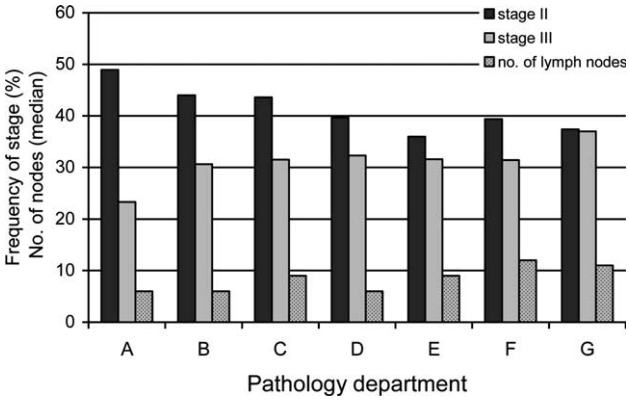

Fig. 1. Frequency of tumour stages II and III compared to the median number of lymph nodes examined per pathology department.

In 1049 (68%) of 1554 patients with tumour stage II the number of lymph nodes examined was given. The survival rate was lower among patients in whom fewer than 12 mesenteric lymph nodes (as stated in the recommendations) were examined than among those with 12 or more nodes examined ($P = 0.001$, log-rank; median follow-up in survivors 40 months). Survival in the group where the number of nodes examined was not stated was identical to that in the group where less than 12 nodes were examined (Fig. 3). The same difference in survival rate was seen when the cut-off was set to 8 nodes examined (median in our material, data not illustrated). In patients with tumour stage I, we found no such difference.

There was a difference in survival rate in patients with tumour stage III, comparing N1 and N2-tumours with a better survival rate for N1-tumours ($P < 0.001$, log-rank). For patients classified as tumour stage III but

Table 1
Characteristics of the included patients ($n = 3735$)

		P
Gender ratio (M:F)	1817/1918 (0.95)	
Mean age (ranges); year		
Male	71 (19–98)	<0.001*
Female	73 (12–98)	
Tumour stage (TNM)		
Stage I	434 (12)	
Stage II	1554 (42)	
Stage III	1151 (31)	
N1	502	
N2	246	
N+	403	
Stage IV	577 (15)	
Stage unknown	19	

Values in parentheses are percentages unless otherwise indicated; N+ means that the number of positive nodes was not stated.
* Mann–Whitney U test.

Table 2
Basic data regarding pathology departments included

Pathology department	Number of resections	Cases where number of lymph nodes examined is given	Number of lymph nodes examined
	n	n (%)	Median (range)
A	593	323 (54)	6 (0–30)
B	621	339 (55)	6 (0–57)
C	550	403 (73)	9 (1–38)
D	496	277 (56)	6 (0–23)
E	528	431 (82)	9 (0–43)
F	487	346 (71)	12 (1–49)
G	460	271 (59)	11 (0–39)
All	3735	2390 (64)	8 (0–57)

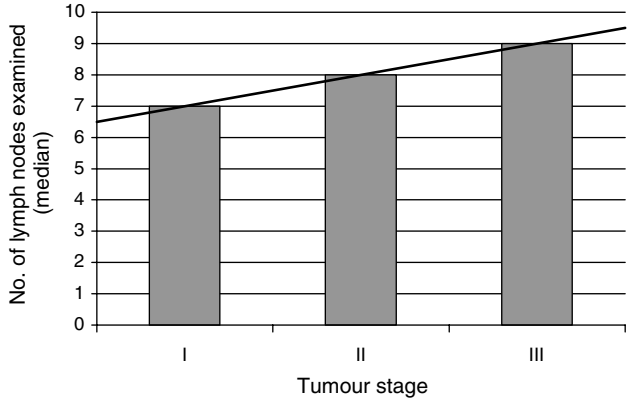

Fig. 2. Median number of lymph nodes examined, by tumour stage.

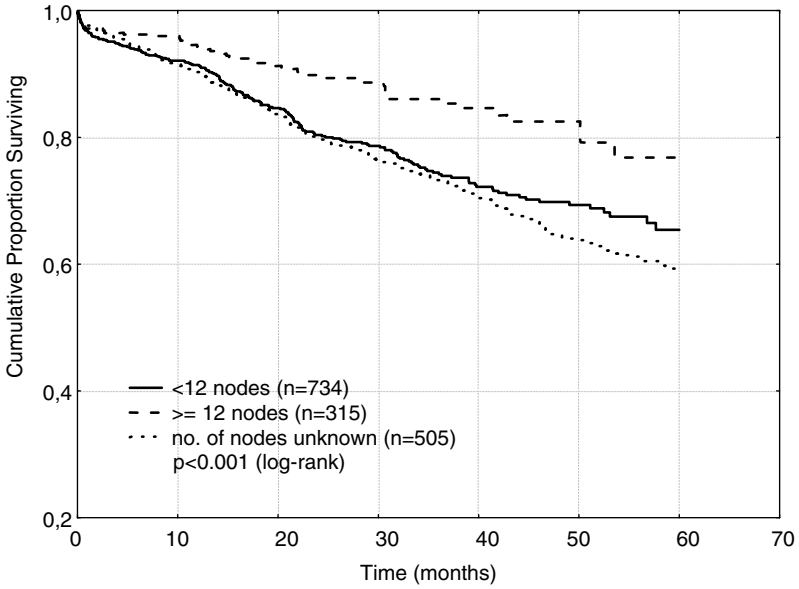

Fig. 3. Survival rates in patients with tumour stage II. Comparison between patients where 12 or more lymph nodes were examined, fewer than 12 nodes were examined, and the number of nodes examined was unknown.

for whom the number of metastases was not given, N+, the survival rate was in between that of N1 and N2, respectively (Fig. 4).

An index of metastases (IM) could be calculated in 733 (64%) of the 1151 patients with stage III tumours. The median IM was 0.32. The overall survival rate was better among patients with IM < 0.33 than in those with IM $\geqslant 0.33$ ($P < 0.001$, log-rank) (Fig. 5). To evaluate the number of lymph nodes necessary to examine for proper staging, the proportion of cases correctly classified as stage III are plotted in Fig. 6. The number of nodes necessary to examine is dependent of IM. Thus, in this material, examination of 12 nodes is necessary to correctly classify cases with the median IM (0.32), whereas 20 nodes are necessary to assure 90% of the cases with the lower quartile of IM (0.16).

There was a larger difference in survival rate when patients were grouped by IM than by N-stage (χ^2 log-rank 39.1 *vs.* 27.0, both $P < 0.001$) (Fig. 7). In a Cox proportional hazard model, including N-stage (N1 *vs.* N2) and IM (<0.33 yes or no), IM had the strongest prognostic information (HR = 3.18 (95% C.I. 2.18–4.64)) with no significant additional information of N-stage (HR = 1.03 (95% C.I. 0.99–1.07)). N1 patients with 12

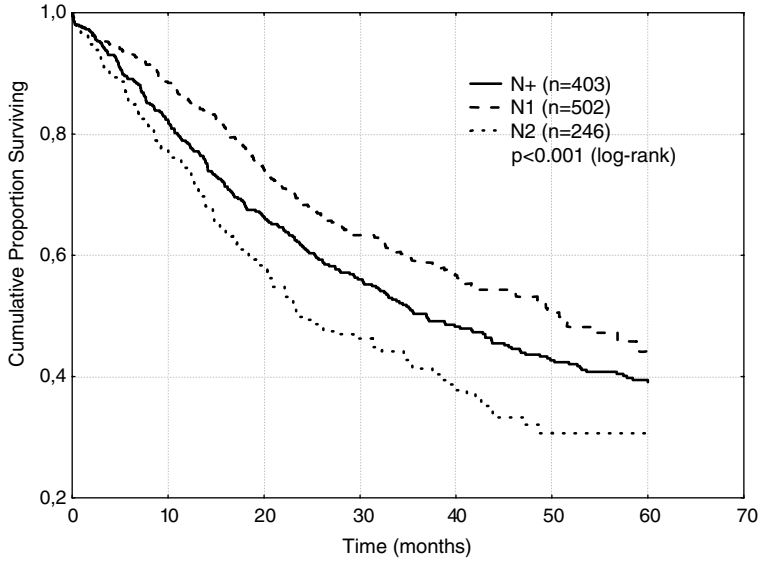

Fig. 4. Survival rates in patients classified as stage III. Comparison between patients with N-stages N1, N2 and N+. N+ means that the number of positive nodes was unknown.

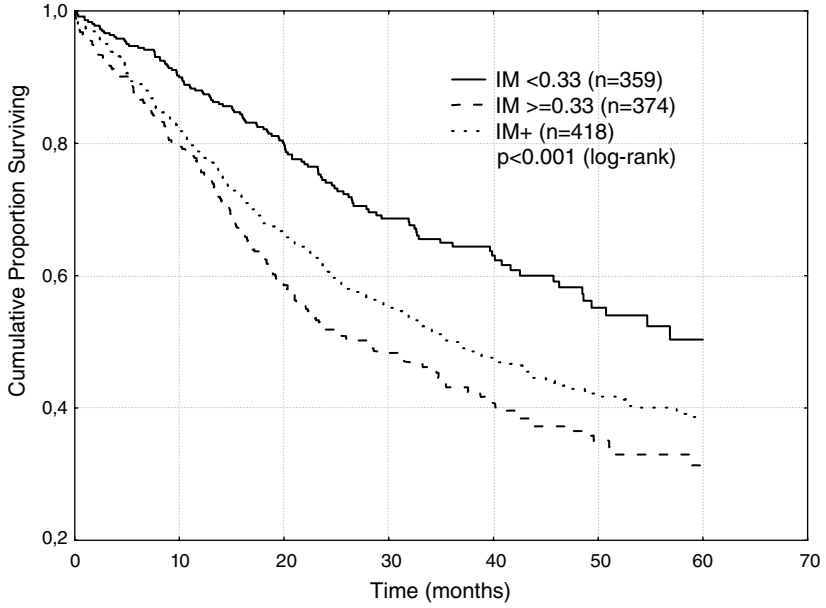

Fig. 5. Survival rates in patients classified as stage III. Comparison between patients with an index of metastasis, IM < 0.33, IM $\geqslant 0.33$ and IM+. IM+ means that the IM was unknown.

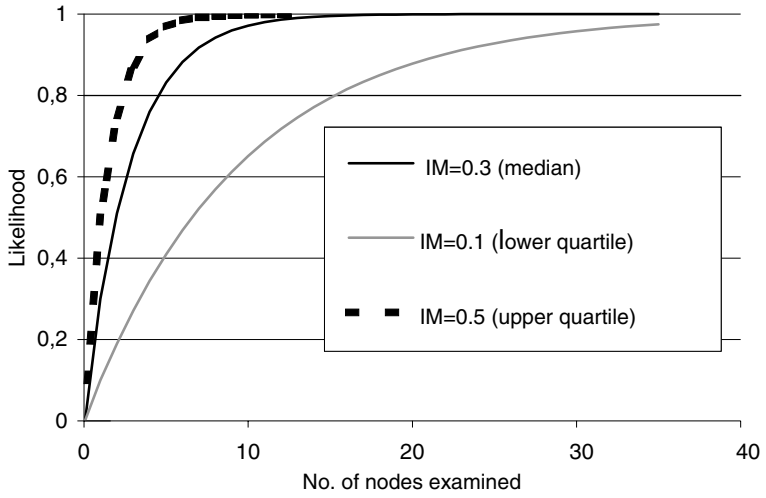

Fig. 6. Likelihood to identify tumour stage III depending on number of nodes examined and proportion of nodes with metastases, IM (index of metastases).

or more nodes investigated or with an IM < 0.33 had a better prognosis than those with fever nodes or with IM $\geqslant 0.33$ (5-year survival rate 50–60% *vs.* 30–40%, $P < 0.005$ for both comparisons). Also patients in stage N2 had a poorer prognosis when fewer nodes were investigated or when the IM was $\geqslant 0.33$, but the differences were then not statistically significant (25–30% 5-year survival *vs.* 40–50%, $P =$ n.s. for both).

Among patients younger than 75 in stage III, approximately 80% were offered adjuvant chemotherapy, whereas this proportion was 15% in stage II (Table 3). In stage II, the proportion did not differ according to number of nodes investigated, whereas in stage III, fever individuals got chemotherapy if the number of nodes investigated was not stated or <12. In stage III, N-stage or IM did not influence whether adjuvant chemotherapy was offered or not.

4. Discussion

In the present population-based study, the number of nodes examined was recorded in 64% of the cases and only 19% of the examinations fulfilled the recommendations regarding a minimum of 12 examined nodes and that the number examined should be stated.

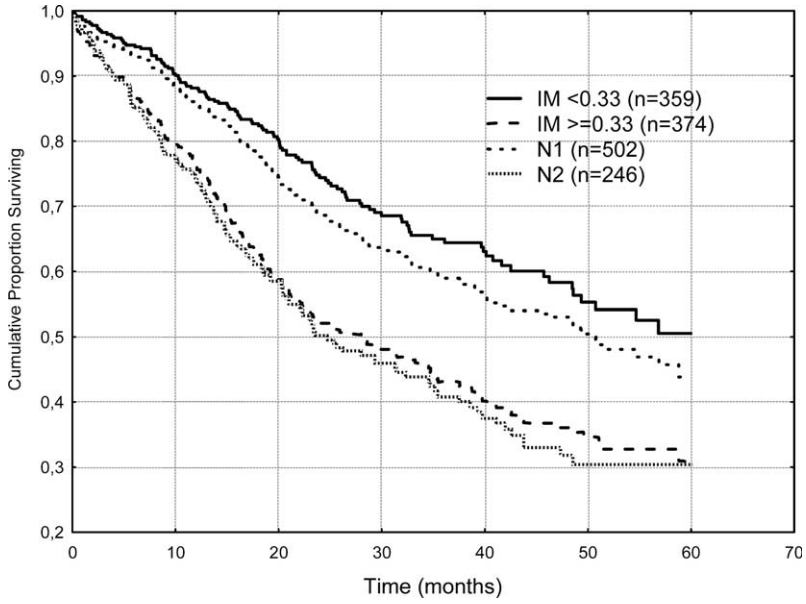

Fig. 7. Survival rates in patients classified as tumour stage III, comparing IM (index of metastases) <0.33 *vs.* ⩾0.33 and N1 *vs.* N2.

Table 3
Number of patients <75 years of age who were offered adjuvant chemotherapy according to the number of lymph nodes examined after resection of tumours classified as stages I–III

Tumour stage	Number of patients (%) offered adjuvant chemotherapy/total number of patients				P^*
	Number of examined nodes				
	All	Unknown	<12	⩾12	
I	0/213	0/63	0/119	0/31	
II	118/783 (15)	30/235 (13)	52/356 (15)	36/192 (19)	0.208
III	470/592 (79)	131/192 (68)	201/246 (82)	138/154 (90)	0.032
I–III	588/1588 (37)	161/490 (33)	253/721 (35)	174/377 (46)	<0.001

Values in parentheses are percentages.
* χ^2 test (<12 nodes *vs.* ⩾12 nodes examined).

Our data were taken from the colon cancer registry, and not directly from the pathology report. However, a previous validation of the registry [23] showed that missing data (regarding number of lymph nodes examined) is not due to improper reports to the registry, but to a lack of a statement in the pathology report and of sampling. With good clinical practice, patients with tumour stage II should have a 5-year survival rate of almost 80%, as seen in this study when 12 or more nodes were examined. The fact that the survival rate among patients for whom the pathologist did not report the number of nodes examined was the same as that among patients with fewer than 12 nodes examined, strengthens our hypothesis that the quality of the specimen examination is a determining factor for correct staging. The differences in survival rate between patients with stage II tumours in whom more or fewer than 12 nodes were examined must be interpreted meaning that a proportion of stage III tumours were improperly classified as stage II due to too few examined nodes. This has been described in several studies where "breakpoints" have been calculated as, for example, to 13 or 20 nodes [24,25], and to more than 18 nodes in a mathematical model [16].

In contrast to Prandi *et al.* [26], we found that the number of nodes examined was also relevant for stage III. This was particularly evident in N1-stage, which is logical since the fewer nodes sampled the less likelihood to detect 4 or more positive nodes. Thus, some patients with N2-stage are classified as N1 due to improper sampling. The distinction between N1 and N2 is prognostically important (Fig. 4), and has recently been reported also by others for colon cancer [27] as well as for rectal cancer [28,29]. However, since the sampling of nodes was far from ideal, we introduced a calculation of an index of metastases (IM, number of positive nodes divided by number of sampled nodes) in order to reduce the error in the N-classification. Actually, this IM had prognostic information that was superior to that of the N-stage (Fig. 7), which would be expected if some

N1-tumours were in fact N2, if the sampling had been properly done.

Every effort should be made to adequately sample sufficient number of nodes, not only for the distinction between stages II and III, which has immediate practical implications for the postoperative care, but also for sub-staging of stage III. The latter sub-staging is prognostically important, having an impact on the information given to the patients, but may also be of immediate practical value in the choice of adjuvant therapy or in follow-up routines. If the sampling is not perfect, the data show that the IM is superior to the N1/N2-classification and that it therefore in this situation could be used clinically whenever a subdivision of stage III is relevant. In order to evaluate the IM with reasonable accuracy, at least 7 nodes ought to be investigated. But to accurately assure the median IM, at least 12 nodes should be sampled (Fig. 6), *i.e.* the same number as recommended by the World Congress of Gastroenterology [6] for correct classification of tumour stage II. Thus, the use of IM may partly compensate for poor pathology reports with few nodes examined when predicting survival for stage III patients.

A meta-analysis of the randomised adjuvant colon cancer trials have indicated that the relative reduction in recurrence rate from adjuvant chemotherapy is independent of N-stage [5]. Thus, the greater the risk of recurrence, the more patients have benefit from the treatment. This absolute reduction in recurrences should be decisive for whether treatment should be given or not, or for whether a more intensive therapy can be motivated. There are also studies that indicate that it is easier to understand absolute reductions than relative reductions [30]. The division into stage II and III gives some information in the guidance of the appropriate use of adjuvant therapy, the addition of N1 and N2 within stage III gives further information but the consideration of the number of nodes sampled, or the IM in stage III, gives even better guidance. This may be of advantage in the choice of whether adjuvant therapy should be given at all, or if a chemotherapy combination, having greater risks of acute and late effects, such as the addition of oxaliplatin to 5FU/leucovorin [31], will be accepted. It must be borne in mind that other risk factors also provide information, although they may not always be as easily available.

From this population-based colon cancer registry, we know that 80–85% of patients with tumours of stage III, younger than 75, are offered adjuvant chemotherapy [17]. Even if, as discussed above, the number of nodes investigated and the index of metastases (IM), as calculated in our present study, might be used for the purpose of selecting the appropriate adjuvant therapy, these factors had, of course, no influence in the decision making of whether adjuvant therapy was given or not during the period studied. During the time period studied, the surgeons reading the pathology reports were basically unaware of the prognostic importance of the number of nodes examined for survival in stage II. Unless a patient participated in an ongoing randomised trial, virtually only patients in stage III had adjuvant therapy. The recommended treatment was 5FU/leucovorin for 6 months.

One can of course discuss whether an insufficient number of nodes depend on sub-optimal surgery, indicating that the surgeon has not harvested sufficient number of lymph nodes. This seems more unlikely as in colon cancer surgery, the colon resection is standardised according to site of the tumour and to oncological principals. The fact that one department of pathology serves several hospitals and the catchement area is population-based and similar for all pathology departments, strengthen our hypothesis that it is not the surgeon but merely the pathologist who fail in the lymph node harvesting process or documentation of the investigation result.

The quality of the examination of a colon cancer specimen, as measured by the number of lymph nodes examined, has an impact on the tumour staging and thus the management of the patient. Cases classified as tumour stage II where fewer than 12 lymph nodes were examined and where the number of nodes examined is not given, are at higher risk of death than those with more than 12 nodes examined. Furthermore, the number of nodes examined is also of relevance in tumour stage III. The index of metastases (IM) can aid in decision-making regarding the use of more potent adjuvant drugs, and is superior to N-stage when lymph node sampling is insufficient.

Conflict of interest statement

None declared.

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