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Improved Lymph Node Harvest from Resected Colon Cancer Specimens Did Not Cause Upstaging from TNM Stage II to III

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Abstract
Background The number of lymph nodes retrieved and examined from a resected colon cancer specimen may be crucial for correct staging. We examined if efforts to increase the lymph node harvest to more than 12 lymph nodes per specimen would upstage some patients from TNM stage II to III.
Methods Three hospitals compared results from 2000 with those of 2007 in 421 resected patients with stage II and III colon cancer. Hospital A endeavored to improve the surgical procedure while the pathologists enhanced the quality of lymph node sampling. Hospital B did not make any marked changes, while hospital C introduced the GEWF lymph node solvent (glacial acetic acid, ethanol, distilled water, and formaldehyde) in their pathology method.
Results In 2000, 12 or more lymph nodes were harvested in 39.6, 45.0, and 21.1% of the specimens from the three hospitals, while the figures for 2007 were 85.7, 42.0, and 90.3%, respectively. The significant increase in lymph node harvest in two of the hospitals in 2007 compared to 2000 ($p < 0.001$) did not affect the share of patients with stage III in 2007 (38.7%) compared to 2000 (44.1%) ($p = 0.260$). The number of positive lymph nodes and the lymph node ratio (LNR) decreased from 2000 to 2007. A lymph node yield of 12 or more was not associated with an increased probability of positive lymph nodes in a multivariable logistic regression analysis.
Conclusion More radical surgery and dedicated pathologists and the use of the GEWF solvent significantly increased the lymph node yield but did not upstage patients from TNM stage II to III.

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Introduction

There are clear indications that more extensive surgery for colon cancer will improve the prognosis of the patient [1]. In this context, lymph nodes may act as a surrogate marker for sufficient surgery with the removal of metastatic lymph nodes in TNM (tumor-node-metastases) stage III. However, there are also reports that increased lymph node sampling may improve prognosis even for stage II tumors, indicating that mere removal per se of as many nodes as possible may do something to improve outcome [2, 3]. A lower limit of 12 lymph nodes harvested in colon cancer has been recommended [4]. The hypothesis of this strategy has been that a minimum number of lymph nodes are needed to correctly stage tumors, meaning that the more lymph nodes the more likely the pathologist is to detect metastases, even though 12 is a rather arbitrary level [1, 5, 6].

It is confounding that many variables influence the lymph node harvest, such as patient and tumor characteristics and the surgical and pathological methods used [7]. However, even if many centers have endorsed the concept of detecting a minimum number of lymph nodes, this strategy has been condoned by some [8]. The importance of lymph node detection has even been contradicted through interpretation of American data [9, 10].

In Norway, patients younger than 75 years of age with TNM stage III colon cancer are routinely offered chemotherapy and this has raised overall survival figures [11]. Consequently, it is important to stage patients correctly. Many consider that an increase in the number of harvested lymph nodes will also increase the share of stage III patients, the so-called Will Rogers phenomenon [12]. However, this is largely an assumption that has not really been convincingly shown [9, 13]. In our multicenter study of three Norwegian hospitals, we wanted primarily to examine if an increased lymph node harvest would also cause migration from TNM stage II to III. A secondary aim was to examine if an increase in lymph node yield would also affect the number of N+ nodes and the lymph node ratio (LNR) of positive vs. total number of lymph nodes in each specimen.

Material and methods

Three teaching community hospitals (A, B, C) with stable catchment areas compared results for segmental R0 and TNM stage II to III segmental colon resections from 2000 with those of 2007 in 421 patients, while 144 patients with stage I ($n = 90$) and IV ($n = 54$) were excluded from analysis. Patients who had double resections or subtotal colectomy ($n = 4$) were also excluded. According to the TNM classification, 247 patients (58.7%) were stage II and 174 patients (41.3%) stage III.

The importance of the lymph node (Ln) harvest was examined overall for more than 12 nodes and divided into these four groups: Ln group 1, 0–6 lymph nodes; Ln group 2, 7–11 nodes; Ln group 3, 12–17 nodes; and Ln group 4, >18 nodes. Patient age, gender, and tumor locations are given in Table 1.

Specimen examination and preparation

Hospital A endeavored to improve the surgical procedure in 2007 and recorded data as part of a prospective study. At the same time, the Department of Pathology at hospital A had improved the dissection of colon cancer specimens, including an optimal lymph node sampling. Hospital B did not make any changes for the time being, while hospital C changed their pathology method to include the lymph node-detecting solvent GEWF (glacial acetic acid, ethanol, distilled water, and formaldehyde) to detect a maximum number of lymph nodes [14]. Hospital A fixed the specimens in formalin for a minimum of 2 days and thereafter examined the specimen and retrieved lymph nodes mainly by palpation. The sections were processed embedded in paraffin using standard techniques. Sections were cut at 4 μm and stained with hematoxylin and eosin (HE) for routine histology. Collaboration with pathologists ensured

Table 1 Clinical and pathologic characteristics of 421 patients with TNM stage II and III in 2000 and 2007 from three Norwegian hospitals

Variables	2000 ($n = 204$)	2007 ($n = 217$)	p
Age (years) [mean (range)]	71.36 (20–93)	72.32 (29–93)	0.261*
Gender [n (%)]			0.026**
Female	118 (57.5)	102 (47.0)	
Male	86 (42.2)	115 (53.0)	
Location [n (%)]			0.101**
Right colon	90 (44.1)	82 (37.8)	
Transverse colon	38 (18.6)	49 (22.6)	
Left colon	7 (3.4)	9 (4.1)	
Sigmoid colon	49 (24.0)	67 (30.9)	
Rectosigmoid	20 (9.8)	10 (4.6)	
T category [n (%)]			0.198**
T1 + 2	9 (4.4)	5 (2.3)	
T3	165 (80.9)	185 (85.3)	
T4	30 (14.7)	27 (12.4)	
No. of lymph nodes [mean (range)]	10.52 (1–26)	15.72 (1–60)	<0.001*

TNM tumor-node-metastases

* Mann–Whitney U test; ** Pearson's χ^2 test

a heightened state of alert regarding lymph node dissection. Moreover, resection specimens with fewer than 12 lymph nodes after the first dissection were evaluated a second time. Hospital B followed a similar procedure except that the pathologist received specimens removed during daytime directly from the operating room and performed a macroexamination before fixation in formalin. Hospital C also followed a similar routine to the first hospital in 2000 but used the lymph node solvent GEWF in 2007. The specimens from this hospital were opened, pinned, and allowed to fix in GEWF for about 48 h. Each specimen was cut in parallel sections about 5 mm thin, and standard sections were taken from different parts of the tumor. All lymph nodes in the mesenteric fat were easily identified as white nodules that were different from the yellow fat. The sections were then processed similar to the other two hospitals.

Surgery

All three hospitals did ordinary colon resections in 2000. This can best be described as intermediate mesocolic resections in the majority of cases. In 2007, hospital A changed to a more standardized radical approach with removal of apical lymph nodes [1]. Surgeons at hospital B did not change their surgical strategy or routine handling of specimens but may have increased their effort inadvertently to raise the number of lymph nodes in the specimens. Hospital C followed a similar open surgical procedure.

Ethics

The Regional Committee for Medical and Health Research Ethics of Western Norway and the Data Inspectorate for National Registries approved this study. The study is part of a prospective project registered with clinicaltrials.gov (NCT00963352).

Statistical analysis

The distribution of lymph nodes was analyzed using three-way and two-way analyses of variance. The TNM stages were compared using Pearson's χ^2 test. The level of significance was set at 0.05 for all statistical tests. All analyses were done using SPSS 17, Syntax04.sps, Output04j, and k.spv.

Results

Demographics, tumor characteristics, and overall lymph node harvest for 421 patients with colon cancer are given in Table 1. There were significantly more female patients operated on in 2000 compared to 2007, but more male patients were operated on in 2007 than in 2000 ($p = 0.026$), and 64.4% of the patients were 70 years or older. Tumors were most common in the right colon (40.9%) and sigmoid (27.6%). The two cohorts did not differ in mean age, tumor location, or distribution of T categories.

Lymph node harvest overall

The total number of lymph nodes was significantly higher ($p < 0.001$) in 2007 ($n = 15.7$) than in 2000 ($n = 10.5$) (Table 1). The share of patients with a lymph node harvest of 12 or more was significantly higher for hospitals A ($p < 0.001$) and C ($p < 0.001$) in 2007. Hospital B had an unchanged harvest ($p = 0.887$) (Fig. 1).

Table 2 shows that in a multivariable (Poisson regression) analysis, age younger than 70 years ($p < 0.001$), year 2007 ($p < 0.001$), hospital A and C vs. B ($p = 0.028$), location of tumor in the right colon ($p < 0.001$), and T category ($p = 0.027$) were significant variables for an increased lymph node count.

Detection of positive lymph nodes and lymph node ratio (LNR)

The number of positive lymph nodes did not increase overall from 2000 to 2007 ($p = 0.563$) (Table 3). When all three hospitals combined were compared for year 2000 vs. 2007, there was a significant decrease in 2007 ($p = 0.004$).

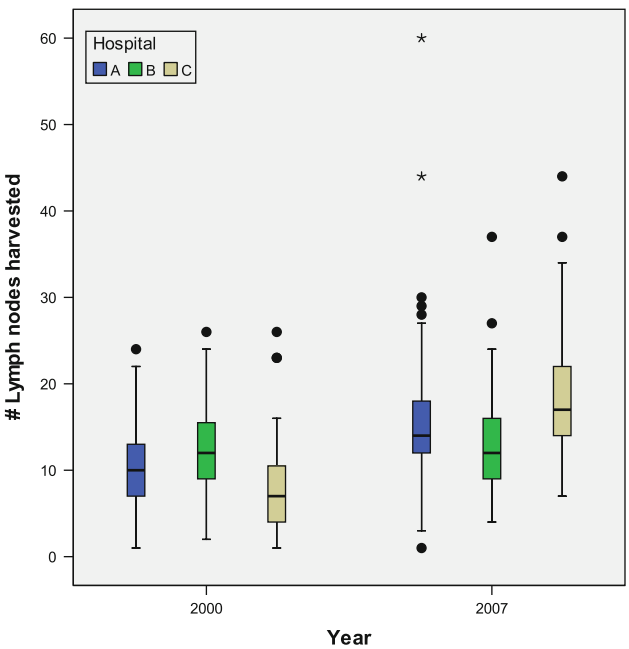

Fig. 1 The number of lymph nodes were significantly different for hospitals A and C from the year 2000 to 2007, but not for hospital B

Table 2 Poisson regression model of total number of lymph nodes harvested with respect to clinical variables[a] for 421 patients with TNM stage II or III from three Norwegian hospitals

Variable	*n*	Coef.	RF	95% Wald CI	*p**
Intercept	421	1.911	6.760	(5.646, 8.092)	<0.001
Year					<0.001
2007	217	0.829	2.291	(2.073, 2.532)	
2000	204	0	1	Ref	
Age					<0.001
<70 years	150	0.118	1.126	(1.066, 1.189)	
≥70 years	271	0	1	Ref	
Sex					0.171
Male	201	0.037	1.038	(0.984, 1.095)	
Female	220	0	1	Ref	
Hospital					0.028
A	125	0.298	1.347	(1.197, 1.516)	
B	158	0.465	1.592	(1.437, 1.763)	
C	138	0	1	Ref	
Location					<0.001
Right colon	172	0	1	Ref	
Transverse colon	87	−0.061	0.941	(0.875, 1.011)	
Left colon	16	−0.098	0.906	(0.789, 1.042)	
Sigmoid colon	116	−0.156	0.856	(0.800, 0.915)	
Rectosigmoid colon	30	−0.070	0.932	(0.832, 1.045)	
T category					0.027
T1 + 2	14	0	1	Ref	
T3	350	0.181	1.198	(1.018, 1.409)	
T4	57	0.113	1.120	(0.941, 1.334)	
Year × Hospital					<0.001
2007 × A		−0.425	0.654	(0.566, 0.756)	
2007 × B		−0.775	0.460	(0.402, 0.528)	
Otherwise		0	1	Ref	

TNM tumor node metastasis, *RF* relative frequency = exp(coef.); *CI* confidence interval

* Likelihood ratio test

[a] None of these variables was significantly different in 2000 compared to 2007

Hospitals A and B found a mean of 2.6 positive nodes in 2000 and a mean of 1.0 positive nodes in 2007, but hospital C increased the number from 1.2 to 2.1 positive nodes.

The presence of N+ was found in a simple logistic regression analysis to have age <70 years, location in the right colon, and T category as significant variables (Table 4). Similarly, in multiple regression analysis, age <70 years ($p = 0.016$), location in the right colon vs. left colon ($p = 0.023$), and T category ($p > 0.001$) increased N+ significantly. When Ln groups were compared per year, we did not find that patients with a high lymph node count in 2000 and 2007 (Ln groups 3 and 4: ≥12 lymph nodes) had more N+ (stage III) than patients with Ln groups 1 and 2 ($p = 0.441$).

Overall, there was a significant decrease in LNR at stage III from 2000 to 2007 ($p < 0.001$). LNR decreased despite an increasing number of lymph nodes in stage III patients (Fig. 2). However, when the hospitals were compared separately, only hospital A had a significant decrease in LNR from 2000 to 2007 ($p = 0.023$) (Table 3).

TNM stage II and III numbers

No stage migration occurred even though the lymph node harvest was significantly better in 2007 ($p < 0.001$). The TNM stage distribution did not significantly change when divided into hospitals A ($p = 0.154$), B ($p = 0.614$), and C ($p = 0.838$). The result was similar overall ($p = 0.402$). Table 4 shows that the detection of the total number of lymph nodes had no influence on the occurrence of a TNM stage III tumor. Stage III was more likely to be diagnosed in younger patients, in right colon cancers compared to the sigmoid colon, and in category T4.

A rather spurious effect is that the likelihood of having a TNM III cancer was much higher for stage T1 + 2 than for stage T3 or T4. This was probably a selection effect as most T1 + 2 patients were excluded from the analysis because they had mostly TNM 1.

Discussion

The lymph node yield from colon cancer specimens may be a surrogate measure for radical colon cancer surgery. It has been suggested by some that the detection of a minimum number of lymph nodes in the specimen is necessary for a proper staging of the tumor [5]. A lower limit of 12 lymph nodes has been endorsed by international organizations [4], although 18 has also been suggested [6] or even as many as possible [1]. Thus, as a consequence, tumors would be upstaged and a worse prognosis could be expected unless adjuvant treatment would compensate for this, according to the authors of a recent Dutch report [5]. They found a rate of 36.3% N+ in patients with only 6–11 lymph nodes in the specimen while 12 or more yielded a rate of 41% N+. In patients with 12 or more lymph nodes this effect seemed to level of. A recent large Canadian survey found that the effect of the number of lymph nodes on stage composition applied only when there were fewer than 7 lymph nodes [15]. Overall, our study population had stage III tumors in 41.3% of the patients. This is only slightly less than the 46–48% that others have found when stage I and IV are excluded [1, 16, 17]. However, if studies on lymph node harvest and its effect on staging are based on less-than-optimal surgery and pathology methods, there is the

Table 3 TNM stage and total lymph node harvest of 421 patients with stage II and III in 2000 and 2007 according to three Norwegian hospitals

Variables	2000	2007	*p*
Stage III	$n = 90$	$n = 84$	
Lymph nodes [mean (range)]	10.98 (1–26)	15.61 (4–37)	<0.001*
No. of N+ [mean (max)]	3.76 (22)	3.33 (22)	0.563*
LNR [mean (SEM)]	0.37 (0.02)	0.22 (0.02)	<0.001*
All specimens	$n = 204$	$n = 217$	
No. of N+ [mean (max)]	1.66 (22)	1.29 (22)	0.205*
LNR [mean (SEM)]	0.16 (0.02)	0.09 (0.01)	0.024*
Lymph node harvest ≥12 nodes [*n*/*N* (%)]			<0.001*
Hospital A	19/48 (39.6)	66/77 (85.7)	<0.001**
Hospital B	36/80 (45.0)	32/78 (42.0)	0.887**
Hospital C	6/76 (21.1)	56/62 (90.3)	<0.001**
No. of positive lymph nodes	1.667 (0.229)	1.290 (0.194)	0.004***
Hospital A [mean (SEM)]	2.562 (0.437)	0.948 (0.345)	
Hospital B [mean (SEM)]	1.525 (0.339)	0.962 (0.343)	
Hospital C [mean (SEM)]	1.224 (0.347)	2.129 (0.385)	
LNR	0.161 (0.018)	0.158 (0.011)	0.024†
Hospital A [mean (SEM)]	0.215 (0.047)	0.057 (0.014)	0.023†
Hospital B [mean (SEM)]	0.131 (0.022)	0.093 (0.018)	0.360†
Hospital C [mean (SEM)]	0.159 (0.029)	0.112 (0.023)	0.684†
TNM stage overall [*n* (%)]			0.260**
Stage II	114 (55.9)	133 (61.3)	
Stage III	90 (44.1)	84 (38.7)	
TNM stage per hospital [*n*/*N* (%)]			0.402*
Hospital A			0.154**
Stage II	27/48 (56.3)	53/77 (68.8)	
Stage III	21/48 (43.8)	24/77 (31.2)	
Hospital B			0.614**
Stage II	44/80 (55.0)	46/78 (59.0)	
Stage III	36/80 (45.0)	32/78 (42.0)	
Hospital C			0.838**
Stage II	43/76 (56.6)	34/62 (54.8)	
Stage III	33/76 (43.4)	28/62 (45.2)	

TNM tumor-node-metastasis, *SEM* standard error of the mean, *LNR* lymph node ratio, i.e., positive number ÷ total number of lymph nodes harvested

* Mantel-Haenszel's test and Breslow-Day's test for homogeneity gave $p = 0.489$ for TNM and $p < 0.001$ for lymph node harvest

** Pearson's χ^2 test

*** p for interaction in two-way analysis of variance

† Mann–Whitney U test

potential for several confounding factors [7]. A large national Norwegian study found a 5% increase to 35% in N+ patients during two recent time periods but did not offer further explanation for this [11].

A concept of upstaging may rest in part on the hypothesis that skip lesions abound. Merrie et al. [18] found an 18% incidence of skip lesions using PCR, but it is questionable if these were skip lesions in the true meaning of the word as only 5% had lesions detected in apical nodes in Dukes B patients. Only about 1% had positive apical nodes without histological proof of metastases in nodes closer to the colonic wall. The importance of finding skip lesions with respect to the prognosis of the patient remains to be proven. A recent study of nodal ultrastaging found only 30% N+ in colorectal cancer specimens examined with conventional histology, even with a mean number of 20 lymph nodes, but increased this share to 44.3% after ultrastaging [19]. In their resections, more than 80% had 12 or more nodes detected. Ultrastaging with detection of cancer cell clusters of <0.2 mm did not significantly change 4-year disease-free survival. Detection of micrometastases (MM) (cell clusters >0.2–2 mm) was recognized as true upstaging and these received adjuvant chemotherapy. They found that a patient with >12 nodes harvested and N0, without micrometastases (N0i-), were cured with surgery alone, while harvesting 12 lymph nodes was significant for the 4-year disease-free survival figures.

Stage 1 may perhaps have fewer detectable lymph nodes [7]. TNM stages were not a significant variable for the overall lymph node count in our study. It follows that the picture is somewhat confusing as to what is really achieved with more extensive surgery and a higher lymph node yield. Our results showed, first of all, that it is possible to increase the lymph node yield by various independent methods. A conjoint effort by surgeons and pathologists in one hospital resulted in a significant increase in the number of patients with a harvest of 12 or more lymph nodes using

Table 4 Simple and multiple logistic regression analysis of the presence of stage III in 421 patients with colon cancer stage II or III in three Norwegian hospitals in 2000 and 2007

Variable	Simple		*p*	Multiple		*p**
	OR	95% CI		OR	95% CI	
Year			0.260			0.843
2000	1	Ref		1	Ref	
2007	0.800	(0.542, 1.180)		1.048	(0.660, 1.664)	
Age (years)			0.039			0.016
<70	1.529	(1.021, 2.290)		1.713	(1.105, 2.653)	
≥70	1	Ref		1	Ref	
Gender			0.072			0.103
Male	1.430	(0.968, 2.114)		1.418	(0.931, 2.162)	
Female	1	Ref		1	Ref	
No. of nodes			0.624			0.467
≤6	1.071	(0.559, 2.054)		1.027	(0.475, 2.217)	
7–11	1.405	(0.803, 2.460)		1.479	(0.793, 2.757)	
12–17	1.276	(0.753, 2.162)		1.410	(0.803, 2.476)	
≥18	1	Ref		1	Ref	
Hospital			0.343			0.168
A	1	Ref		1	Ref	
B	1.343	(0.829, 2.176)		1.526	(0.897, 2.595)	
C	1.408	(0.857, 2.313)		1.633	(0.939, 2.838)	
Location			0.021			0.023
Right colon	1	Ref		1	Ref	
Transverse colon	0.756	(0.448, 1.275)		0.922	(0.527, 1.613)	
Left colon	0.674	(0.235, 1.937)		0.736	(0.246, 2.206)	
Sigmoid colon	0.485	(0.295, 0.798)		0.489	(0.287, 0.836)	
Rectosigmoid	1.469	(0.672, 3.210)		1.777	(0.763, 4.134)	
T category			<0.001			<0.001
T1 + 2	22.547	(2.916, 174.364)		28.801	(3.516, 235.896)	
T3	1	Ref		1	Ref	
T4	2.385	(1.350, 4.213)		2.433	(1.339, 4.421)	

OR odds ratio, *CI* confidence interval

* From likelihood ratio test. No interactions were significant

conventional methods for histology. The use of the lymph node detection solvent GEWF caused a highly significant increase of lymph nodes in hospital C. However, no increase in stage III over stage II was detected when all hospitals were analyzed together. In fact, a slight and probably coincidental drop was found at hospital A. In 2000 the mean number of positive nodes in the three hospitals was 3.6 compared to 3.7 in 2007. This demonstrates that only the number of negative nodes rose appreciably in the two hospitals with an improved harvest and examination with routine staining methods. This is in concert with a recent Japanese study [20].

Some have also focused on lymph node ratio (LNR) as a prognostic factor, meaning that the higher the ratio the worse the prognosis [17, 21, 22]. However, LNR did not matter when fewer than 10 lymph nodes were detected [23]. The explanation for this is obscure but may perhaps be explained by inferior surgical quality [1]. In hospitals A and C with an increased yield, the ratio fell with an increasing number of nodes. In hospital B, with an unchanged number of nodes, the ratio was unchanged. Overall, the LNR decreased with an increasing number of lymph nodes. This suggests that inadequate resections with many positive nodes will have a higher ratio and thus indicate a poor prognosis because of less extensive surgery. Another explanation is that a high ratio suggests a worse biological behavior in itself if a large number of positive nodes are found. Rosenberg et al. [17] found a decreasing survival rate with increasing LNR. They used statistically identified cutoff values from an earlier work on a population cohort consisting of 17,134 patients from the Munich region. They showed better prognostic discrimination with LNR than with pN, and LNR was useful in patients with a lymph node harvest of both more and fewer than 12 nodes.

The prognostic value of a high lymph node yield in stage III patients has been debated. Some authors argue

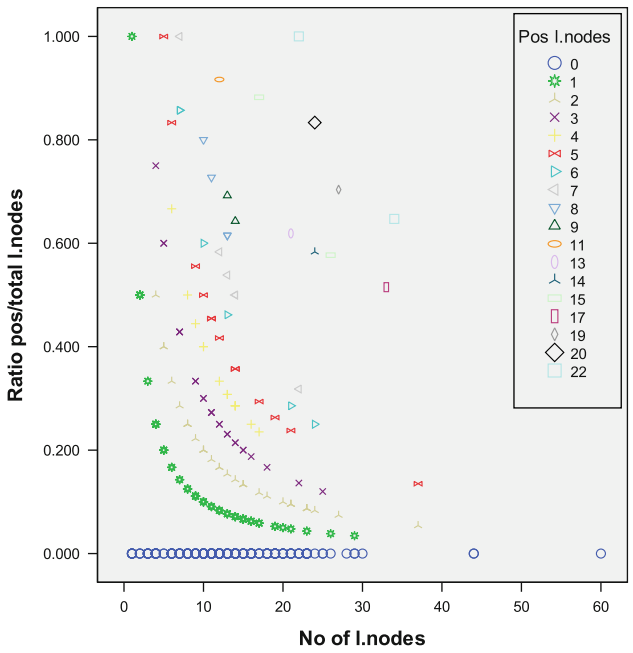

Fig. 2 Lymph node ratio (LNR) decreased significantly with increased lymph node harvest in stage III patients

that a high lymph node harvest does not improve prognosis for patients with a high LNR [5, 21] because the disease is no longer localized and adjuvant therapy is necessary. Although the prognosis is still worse with a high LNR than with a low LNR, patients with a low LNR, as well as stage II patients, may benefit from a high lymph node harvest [17]. The reason for this is obscure but biological factors may be important [10]. Radical lymph node removal, even if it does not increase survival, may potentially reduce local recurrences. This should be of importance to the patient.

With increased scrutiny of the specimen and use of PCR techniques, one will more often find smaller nodes and so-called tumor deposits that make it increasingly difficult to agree on the meaning of such findings. A tumor collection of more than 3 mm or with a round contour has been suggested to represent a lymph node [7, 22]. Further subdivisions have emerged in the shape of micrometastases, sub-micrometastases, and isolated tumor cells categories, but opinions have been divided over their importance [7, 19, 24]. Despite this, the UJCC 7th edition has taken this issue into account, to much criticism [25]. A recent review found no significance attached to tumor deposits in the mesentery [24]. Therefore, it seems that even though refined and meticulous techniques are able to increase the number of metastases or tumor deposits in the specimen, the importance of such findings has not as yet been ascertained. Even though the discovery of micrometastases may upstage some patients, this upstaging does not relate to an increased survival and consequently it is still uncertain what oncological importance it may carry [19].

So far, only the number of lymph nodes in the specimen seems to have a bearing on the prognosis, but opinions differ as to what influences this parameter, i.e., patient, tumor, surgeon, or pathologist [10], even though the pathologist seems to hold the key [7]. It is also debatable what should be the minimum number, but we had agreed with our pathologists to look for at least 12 lymph nodes. Hohenberger et al. [1, 26] found improved prognosis when more than 28 nodes were detected. In contrast, Wong et al. [9] did not show that lymph node numbers in US hospitals were associated with staging or survival. Nevertheless, the metastatic pattern to regional lymph nodes would support extensive surgery in most cases [26–29]. However, it was not within the scope of the present study to examine the effect of an increased lymph node yield on outcome. This will be studied in forthcoming reports.

We conclude that the lymph node harvest in our patients could be increased significantly by different surgical and pathological methods without increasing the share of stage III patients compared with stage II patients. In concert, the overall number of N+ fell and so did the LNR. In effect, the Will Rogers phenomenon did not occur. Thus, the whole concept that more lymph nodes are needed to stage patients correctly is contentious.

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