Lymph node staging in colon cancer

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Chapter 2

Impact of the number of histologically examined lymph nodes on prognosis in colon cancer: a population-based study in the Netherlands.

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Abstract

Purpose: To study the impact on survival of the reported number of lymph nodes at pathological examination of colon specimens.

Methods: This is a retrospective review on the data of 2,281 patients with localized colon cancer. The effect of tumor characteristics and surgical and pathological factors on the number of lymph nodes and examined lymph node numbers on nodal status and survival were analyzed.

Results: The number of examined nodes increased with T-stage, left sided tumors and mucinous morphology, but decreased with age. The proportion of node-positive patients (N_+) increased with a larger number of nodes. A high number of examined nodes and high T-stage affected nodal status. The 5-year overall survival was 51.3% for N_+ versus 68.2% for node-negative (N_0) patients. N_0 patients had a significantly higher 5-year crude and relative survival when more lymph nodes were examined. This was not found for the N_+ group and for all patients combined.

Conclusions: T-stage, localization and patient age were predictive for the number of nodes examined. A higher number of examined nodes was associated with an increase in node-positivity. The survival benefit can be explained by stage migration. Eventually this may lead to an overall survival benefit, as more patients are classified as node positive, and therefore will receive adjuvant therapy.

Introduction

Colorectal carcinoma (CRC) is the most common gastro-intestinal malignancy and the second leading cause of cancer related deaths in the world. Each year, worldwide, nearly one million cases are newly diagnosed and 500.000 patients die of this disease.[1] Adequate surgical lymphadenectomy and pathological evaluation of resected lymph nodes are prerequisites for accurate tumor staging. The primary treatment for colon cancer is a radical surgical resection including en-bloc removal of the involved colon segment and associated mesenteric lymph nodes. Staging of patients based on the pathological tumor, node, metastasis (pTNM) classification system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC), is important for selecting patients for adjuvant treatment and for prediction of long-term survival.[2] The single most important determinant of prognosis in patients with localized colon cancer is the presence of nodal metastases at the time of surgical treatment. The 5-year survival rate is 70-80% for patients with node negative disease (stage I/II), but only 45-50 % for those with node positive tumors (stage III).[3] In patients with stage III colon cancer adjuvant chemotherapy improves survival considerably.[4-6] In addition, a recent meta-analysis showed that there might be a benefit of adjuvant treatment in high-risk stage II colon cancer patients.[7] Therefore, it is highly important to accurately reflect the status of the regional lymph nodes. The number of removed nodes in a surgical specimen may depend on the extent and diligence in identifying nodes at the pathological examination.[8-17] In this population based survey of nodal staging in colon cancer we emphasize the influence of the number of histologically examined lymph nodes on nodal stage, and it's impact on survival.

Patients and Methods

Patients

All patients were treated for colon cancer in the Northern Netherlands between January 1998 and December 2002. Exclusion criteria were exploratory surgery only and an incomplete pathological report not mentioning the number of examined lymph nodes. Since the number of nodes is influenced by pre-operative radiotherapy which is routinely used for rectal cancer in The Netherlands, patients with rectal cancer, defined as a tumor situated within 15 cm distance from the anus, were also excluded.[18] Furthermore, patients with distant metastatic (M1) disease, patients with in-situ carcinomas and patients treated with a polypectomy were excluded as the surgical and pathological approach for these patients may have differed from standard recommendations. Also excluded were patients who underwent a (sub)total colectomy, patients with non-adenocarcinomas as well as

patients with a previous diagnosis of invasive cancer, other than non-melanoma skin cancer.

Data collection by the cancer registry

The data was retrospectively collected. Patients were selected from the regional cancer registry of the Comprehensive Cancer Centre North-Netherlands. This registry covers the Northern part of the Netherlands, a main rural area with a population of about 2.1 million, served by 16 community hospitals, one university medical centre and seven pathology laboratories. PALGA, the nationwide Dutch network and registry of histo- and cytopathology, regularly submits reports of newly diagnosed malignancies to the registry. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. After notification, trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports. Vital status was established through linkage of cancer registry data with population registries of all municipalities in the Netherlands, last in 2005. In the Netherlands the municipal population registries contain information on the vital status of their inhabitants. Patients were staged according to the TNM system of the UICC.[2]

Guidelines

The Dutch Cancer guidelines (www.oncoline.nl) with respect to the standard surgical resection and pathological examination have not been changed during the study period. This implies that an en-bloc resection of the involved colon segment with wide margins and its mesocolon with draining lymph nodes should have been performed in all patients. Pathological examination of the resected specimens was performed according to these guidelines, which are followed by all Dutch pathologists. In brief, the lymph nodes were recovered with manual dissection after overnight fixation in 10% neutral buffered formalin and treated with conventional H&E staining at 5 mm intervals. According to the above mentioned guidelines at least 12 nodes have to be recovered to accurately predict nodal status. In the pathological report the histological type of tumour, the differentiation grade, the total number of lymph nodes as well as the number of positive nodes and their location have to be described. Adjuvant chemotherapy was indicated for node positive patients.

Statistical analysis

SPSS 12.0 (SPSS, Inc, Chicago, IL) and Stata 8.0 (Stata Corporation, College Station, Texas) for Windows were used for analyses. Differences in proportions between groups were assessed with the χ^2 test, the Mann-Whitney U test was used to compare continuous variables. The association of the number of examined nodes with patient and tumor characteristics was assessed in a log-linear regression analysis, binary logistic regression analysis was used to asses associations of these factors with the presence of nodal metastasis. Survival was calculated from the date of diagnosis until the date of death, the date of most recent linkage with the municipal population registries or the date of last contact (date of last hospital visit or last contact with the general practitioner), whichever came first. Follow-up was terminated at 31-12-2005. The Expected Survival (ES) probability was calculated using age and period matched mortality rates based on life expectancy tables for the Northern Netherlands.[19] The ES was estimated using the Ederer II method.[20] As we have no acces to cause of death data, we used relative survival and excess mortality ratio to estimate the mortality due to tumor. The relative survival, the ratio of the crude survival and the ES was analyzed using Stata and a relative survival function written by Dickman (www.pauldickman.com/teaching/tampere2004). The relative survival can be considered as an estimator of the excess risk of death or of the excess mortality ratio. The excess mortality rate was calculated by subtracting the expected number of deaths, as estimated from the expected survival probability, from the observed number of deaths and dividing this figure by the accumulated person-years. The excess mortality ratio (EMR) is derived from the ratio of the excess mortality rates. Excess mortality ratios were estimated in a generalized linear model with a Poisson error structure based on collapsed relative survival data, using exact survival times.[21] It estimates the excess hazard of death for a given covariate once the hazard for death of the general population has been taken into account. In this model the effect of the number of examined nodes was studied, while adjusting for the effect of various co-variables on the excess mortality. Follow-up time was stratified in annual intervals. Variables included in the model were the age at diagnosis, the tumor invasion depth, the number of positive lymph nodes and chemotherapy given. Model fit was evaluated with the model based Pearson Chi-square goodness-of-fit test statistic. Differences in 5-year overall survival were calculated using the Wilcoxon test. Differences in relative survival were calculated using the Wald test derived from Poisson regression analysis for relative survival. All reported p-values are two sided; the statistical significance level was set at a p-value of <0.05.

Results

Patients

A total of 2.751 patients fulfilled the selection criteria en were entered in this study. In 443 patients the exact number of examined nodes was not mentioned in the pathology report, in 18 patients the T-status was not mentioned in the pathology report and in 15 patients the tumor location was not described. Some of these missing data were in the same patients. The number of patients with an unknown number of examined nodes did not differ between age groups (p=0.76). The operative records were complete for all patients. Patients with missing data were excluded from the analysis. The remaining 2.281 patients were eligible for the final analysis. Patients and tumor characteristics are described in table 1.The mean age of the patients at the time of surgery was 69.9 (median 71, range 21-99) years.

Nodal status and adjuvant therapy

The proportion of node-positive patients increased with a larger number of examined nodes. In multivariate logistic regression analysis the odds ratio of having positive nodes was 25% higher for right-sided tumors and increased with invasion depth of the tumor (T-stage) and with a higher number of identified nodes. Patient age and tumor morphology were not associated with the nodal status (table 1). The effect of an increase in the number of examined nodes appeared to level off at 12-15 nodes. Adjuvant chemotherapy was given to 381 node-positive patients (51.6%). Younger patients more often received chemotherapy. While 82% of the node-positive patients younger than 60 years received adjuvant chemotherapy, this rate decreased to 71%, 42% and 3% for patients aged 60-69 years, 70-79 years and patients older than 80 years, respectively.

Number of examined nodes

The median number of examined nodes in the study period was 7 with an interquartile range of 4-11 (table 2). The number of examined nodes was significantly higher in 1998 compared to the other years. It increased with higher T-stage ($p<0.001$) and with a mucinous morphology ($p=0.002$), but decreased with older age with significantly more nodes being examined in the group aged younger than 60 years ($p<0.001$). The proportions of patients with <12 examined nodes were 75%, 83%, 85% and 85% for patients aged <60, 60-69, 70-79, and ≥80 years, respectively ($p<0.001$). In a multivariate log linear regression analysis, tumor location, T-stage and age were associated with the number of examined nodes (table 2).

Table 1. Patient and tumor characteristics and lymph node status

	N_0 (%)	N_1 (%)	N_2 (%)	Univariate (p)	Multivariate N_0 vs N_+		
				(N0 vs N+)*	p	OR	95% CI
Total	1543 (67,6)	556 (24,4)	182 (8,0)				
Tumor location				0.504	0.019		
Right	828 (68,3)	296 (24,4)	90 (7,3)	0.94		1.25	1.03-1.51
Left	715 (66,9)	260 (24,3)	92 (8,7)	1.00		1.00	
T-stage				<0.001	<0.001		
T1	146 (96,1)	5 (3,3)	1 (0,7)	1.00		1.00	
T2	262 (79,2)	63 (19,0)	6 (1,8)	6.41		5.77	2.43-13.65
T3	973 (63,6)	413 (27,0)	143 (9,4)	13.90		12.25	5.35-28.04
T4	162 (60,2)	75 (27,9)	32 (11,9)	16.07		14.35	6.08-33.85
Tumor type				0.892	0.337		
Mucinous	206 (68,0)	71 (23,4)	26 (8,6)	1.02			
Non-mucinous	1337 (67,6)	485 (24,5)	156 (7,9)	1.00			
Age (years)				0.127	0.285		
<60	299 (65,3)	109 (23,8)	50 (10,9)	1.00			
60-69	368 (64,9)	157 (27,7)	42 (7,4)	1.02			
70-79	560 (69,4)	191 (23,7)	55 (6,8)	0.83			
>80	316 (70,2)	99 (22,0)	35 (7,8)	0.80			
Age centered to mean (age-69.9)				0.045	0.313		
Nr lymph nodes				<0.001	<0.001		
0-5	713 (75,6)	207 (22,0)	23 (2,4)	1.00		1.00	
6-11	545 (63,7)	230 (26,9)	80 (9,4)	1.76		1.60	1.29-1.98
12-15	161 (58,8)	69 (25,2)	44 (16,1)	2.18		1.90	1.41-2.54
>16	124 (59,3)	50 (23,9)	35 (16,7)	2.13		1.85	1.34-2.56
Adjuvant chemotherapy	32 (2,1)	283 (50,9)	98 (53,8)	n.a.	n.a.		

*N_0 = node negative, N_1=1-3 positive nodes, N_2= 4 or more positive nodes, N_+=N_1or N_2

** The odds ratios for T-stadium are calculated compared to T1 as a reference.

Table 2. Log-linear model for number of examined nodes (>=1 nodes examined)

	Number	Median nr of nodes (interquartile range)	Univariate (p)	Multivariate P	RR	95% CI
Total	2180	7 (4-11)				
Tumor location			<0.001	<0.001		
Right	1137	6 (3-10)	0.72		0.74	0.69-0.79
Left	1043	8 (5-12)	1.00		1.00	
T-stage			<0.001	<0.001		
T1	114	4 (2-7)	1.00		1.00	
T2	317	6 (3-9)	1.42		1.40	1.20-1.64
T3	1492	8 (4-11)	1.83		1.69	1.47-1.94
T4	257	8 (4-12)	1.90		1.73	1.47-2.02
Tumor type			0.002	0.28		
Mucinous	293	9 (4-12)	1.00			
Non-mucinous	1887	6 (4-11)	0.88			
Age (years)			<0.001			
<60	446	9 (5-12)	1.00			
60-69	547	6 (4-11)	0.85			
70-79	764	6 (4-10)	0.80			
>80	423	6 (4-10)	0.79			
Age (continuous)			<0.001	<0.001*		
Age-69.9			0.99		0.991	0.988-0.994
Intercept**				<0.001	4.70	4.32-5.12

* For the multivariate analysis age centered to the mean was used

** the estimated median number of examined nodes for patients aged 69,9 years (mean age) with a T1 tumor located in the left colon

Model fit: Pearson X^2: 1075 (df=2174); p=1.00

Survival

The median follow up was 4.3 years with a range of 3.5 to 6,9 years. During follow up 872 patients died (32.5%). The 5-year overall survival rate was 51.3% (95% CI 47.4% -55.1%) for node positive patients and 68.2% (95% CI 65.6% -70.6%) for node negative patients, respectively. Table 3 shows the 5-year crude and relative survival proportions according to the number of examined nodes, stratified for the presence of positive nodes. The overall survival in node-negative patients was better in the group with more examined lymph nodes. In node positive patients there was a trend towards a better overall survival, although not statistically significant. Relative survival also improved among node-negative patients when more nodes were examined. However, for the node-positive group as well as for node-negative and node-positive patients combined, the relative survival was not associated with the number of examined nodes. In the latter group relative survival was only associated with the number of examined nodes after adjustment for the presence of positive nodes. In table 4 the observed and expected number of deaths and the EMR are groups shown according to age, invasion depth, number of lymph nodes examined, number of positive lymph nodes, chemotherapy received and year of diagnosis. In multivariate analysis, the EMR increased significantly with increasing depth of invasion and a higher number of positive lymph nodes. It decreased with a higher number of examined nodes and if treated with adjuvant chemotherapy. Age was also associated with excess mortality in this analysis. This implies that patients with tumors in higher T-stages and more positive lymph nodes experience higher excess mortality due to colon cancer, whereas patients with more examined lymph nodes or patients treated with adjuvant chemotherapy show lower excess mortality due to colon cancer.

Table 3 Five year overall survival (OS) and relative survival (RS) according to the number of nodes examined, stratified for the presence of positive nodes

	Pts	Deaths observed	5-yr OS	95% CI	P ¥	5-yr RS	95% CI	P #
Node-negative					0.0013			0.0323
<6 nodes	713	255	63.5%	59.5-67.2		82.1%	77.0-86.9	
6-11 nodes	545	177	70.2%	65.9-74.1		88.6%	83.2-93.4	
≥12 nodes	285	76	75.9%	70.0-80.8		91.6%	84.5-97.5	
Node-positive					0.0756			0.2927
<6 nodes	230	125	46.3%	39.4-52.9		59.6%	50.8-68.0	
6-11 nodes	310	145	53.9%	47.9-59.6		66.7%	59.2-73.7	
≥12 nodes	198	94	53.1%	45.5-60.1		62.1%	53.2-70.3	
All patients					0.0208$			0.3109$
					0.0002*			0.0288*
<6 nodes	943	380	59.3%	55.8-62.6		76.6%	72.2-80.8	
6-11 nodes	855	322	64.3%	60.8-67.6		80.6%	76.3-84.8	
≥12 nodes	483	170	66.5%	61.8-70.8		79.4%	73.7-84.5	

$ Overall test, unadjusted ; * Overall test, adjusted for the presence of positive lymph nodes (categorical); ¥ wilcoxon test ; # based on Wald test derived from Poisson regression analysis for relative survival. OS: Observed Survival; RS: Relative Survival; 95% CI: 95% confidence interval

Table 4 Estimated Excess Mortality Ratios (EMR) and 95% confidence intervals (95%CI)#

	Univariate statistics				Multivariate regression model		
	Patients	Deaths observed	Deaths expected	Person years	p-value	EMR	95%CI
Age					0.0353		
< 60 yrs*	458	101	11.9	2220.8		1.00	
60-69 yrs	567	161	45.1	2585.7		1.12	0.82-1.54
70-79 yrs	806	342	153.9	3163.6		1.35	0.99-1.83
80+ yrs	450	268	227.8	1541.2		0.78	0.48-1.26
Invasion depth					<0.0001		
T1/T2*	483	115	100.1	2289.3		1.00	
T3/T4	1798	757	338.7	7224.2		4.34	2.41-7.80
Positive nodes					<0.0001		
None*	1543	508	322.2	6750.3		1.00	
1-3	556	248	97.5	2186.4		3.20	2.39-4.29
4+	182	116	19.1	576.7		8.40	5.94-11.87
Nodes examined					<0.0001		
< 6*	943	380	194.9	3741.0		1.00	
6-11	855	322	167.7	3674.1		0.61	0.47-0.80
12-15	274	100	39.7	1190.4		0.50	0.34-0.74
16+	209	70	36.4	907.9		0.46	0.30-0.72
Chemotherapy					<0.0001		
No*	1868	720	404.6	7716.2		1.00	
Yes	413	152	34.1	1797.3		0.45	0.33-0.62

#Adjusted for time since follow-up

*Reference

Discussion

Radical surgical resection remains the most effective treatment for adenocarcinomas of the colon. It is known that the number of detected lymph nodes in a colectomy specimen varies widely. The difference in numbers of identified nodes may depend on variations in the pathological and/or surgical technique.

Because this study is retrospective there are several limitations. It was impossible to retrieve adequate information on the quality of the surgical resection other than the description of the surgical procedure in the operative record. This is also the case for the pathological reports. In The Netherlands, all pathologists are well organized and the specimens are usually examined according to the guidelines as provided by the Dutch Cancer Centers (www.oncoline.nl), which are based on the AJCC guidelines. [2] We assumed that the guidelines were followed properly.

This population-based study with a relatively large number of patients with a nearly complete follow up for vital status shows that tumor location, T-stage and patient age are associated with the number of nodes examined by the pathologist. It is well known that in sigmoidectomy and transversectomy specimens generally fewer lymph nodes are found than in a right or left hemicolectomy specimen. A clear-cut explanation for the association of age and T-stage with the number of retrieved nodes is difficult. It is possible that surgical resections are more limited in older patients or that the pathologists are less diligent in retrieving nodes in older patients. On the other hand fewer examined lymph nodes may reflect differences in the biological behavior of the tumor and/or host. The immune response against aggressive tumors may be different, or older patients and patients with more co-morbidity may have a diminished immune response leading to smaller lymph nodes in the draining lymphatic basin and thus fewer identified nodes.[22] It is known that mucinous tumors are of a different biological entity with a more aggressive behavior than other colorectal tumors.[23,24] In the univariate analysis in our study more lymph nodes were found for mucinous tumors, although this could not be confirmed in the multivariate analysis. A higher number of examined lymph nodes in T3 and T4 tumors might be explained by the fact that large tumors evoke a more intense inflammatory reaction than small tumors, leading to distension of lymphatic sinusoids with lymph node enlargement, and consequently to a higher number of nodes being identified by the pathologist.

T-stage and the retrieved number of nodes were associated with the nodal status in univariate as well as multivariate analysis. An increase in node-positivity with higher T-stages was expected, as these tumors usually represent more advanced disease. A higher number of examined nodes was associated with an increase in node-positivity, improving

the accuracy of the pathological status. This might be explained by the detection of small metastatic regional nodes with more diligent pathological sampling. Goldstein stated that there is no minimal number that reliably or accurately stages all patients and that as much lymph nodes as possible should be recovered, including those of 1 or 2 mm in diameter.[8] Furthermore, the studies of Haboubi et al. and Hida et al. showed that more than 70% of the metastatic lymph nodes are smaller than 5 mm in diameter.[9,10]

Numerous attempts have been made to estimate the minimum number of nodes necessary for correct staging, varying from 6 to 18 to an unlimited number of nodes.[8,12,17,25,26] There is currently consensus that at least 12 lymph nodes should be examined before considering a patient node-negative.[2] A review of over 100,000 patients from a National Cancer Institute registry showed that less than half of pathologic evaluations met these criteria during the period 1988 and 2001.[27] Joseph et al have estimated that more than 30 lymph nodes are needed to achieve a 85% probability of true N0 status at standard histology.[12] In our study we found a cut off point between 12 and 15 lymph nodes, which corresponds to the recommended amount of nodes to be examined by the AJCC [2] and the Dutch Oncological Society (www.oncoline.nl). However, compared to the study of Baxter et al, in the majority of patients in our study (79%) fewer than 12 nodes were examined, which reflects a rather poor pathological sampling in the study period. It is well possible that with more thorough pathological sampling more lymph nodes will be found and that the cut off point changes to a higher number of nodes.

There is substantial evidence in the literature that the number of lymph nodes examined has an important impact on survival in patients with colon cancer.[8,11,13,28] There are three potential explaining factors. Firstly, a more extensive lymphadenectomy may in itself convey a decreased risk of local and regional recurrence. Secondly, a surgeon who performs a more extensive lymphadenectomy may provide better cancer care in other respects. Thirdly, a pathologist who performs a more precise examination of the specimen will assure a more accurate staging, resulting in stage migration within patient populations. Until now, it has not been possible to identify a single mechanism for improved outcome with increasing nodal yield. In our study, node-negative patients showed a significantly higher 5-year crude and relative survival when more lymph nodes were examined. However, the relative survival in the node-positive group and the total group was not different when less than 6 or more than 12 nodes were examined. Only after adjustment for the presence of positive lymph nodes, the number of examined nodes was associated with a decreased survival in these groups. This implies stage migration to some extent in our study population: the improved staging accuracy leads to a better prognosis in all patient

strata, but will not affect the prognosis of the patient population as a whole.[29] There is probably a fourth reason why it is important to harvest more lymph nodes in a colectomy specimen. An increase in the number of nodes leads to more node positive patients with stage III colon cancer. These patients with stage III colon cancer are routinely offered adjuvant chemotherapy, as opposed to those with stage II colon cancer.[30,31] In our study only 51.6% of the patients were treated with adjuvant chemotherapy. This was mostly influenced by age, as >80 % of the younger stage III patients were treated with adjuvant therapy. It may be explained by the presence of more co-morbidity in older patients compared to younger patients.

This lack of treatment leads to insufficient power to calculate the exact survival benefit in our study. Looking at our study group in which the node-positive rate increased up to 12-15 examined nodes, the vast majority of patients had a less than optimum number of examined lymph nodes. This means that there is certainly potential for understaging and possibly, undertreatment with respect to adjuvant therapy. Following the recent ASCO guidelines for the use of adjuvant chemotherapy in high-risk stage II patients, about 80% of our N_0 patients are possible candidates for adjuvant therapy, because less than 12 nodes were detected at the pathological examination.[7] In summary, in our northern Dutch population with curable colon carcinoma there has been substantial pathological understaging from 1998 to 2002. At least 12 lymph nodes have to be examined to accurately predict nodal status. A higher number of examined nodes leads to stage migration. Through stage migration, more patients will be treated with adjuvant therapy. This may lead to a survival benefit for the entire group.

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