

Large variation between hospitals and pathology laboratories in lymph node evaluation in colon cancer and its impact on survival, a nationwide population-based study in The Netherlands

M. A. G. Elferink^{1*}, S. Siesling^{1,2}, O. Visser³, H. J. Rutten⁴, J. H. J. M. van Krieken⁵, R. A. E. M. Tollenaar⁶ & V. E. P. P. Lemmens^{7,8}

¹Department of Research, Comprehensive Cancer Centre North East, Enschede/Groningen; ²Department of Health Technology and Services Research, University of Twente, Enschede; ³Comprehensive Cancer Centre Amsterdam, Amsterdam; ⁴Department of Surgery, Catharina Hospital, Eindhoven; ⁵Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen; ⁶Department of Surgery, Leiden University Medical Centre, Leiden; ⁷Department of Research, Comprehensive Cancer Centre South, Eindhoven and ⁸Department of Public Health, Erasmus MC University, Rotterdam, The Netherlands

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Background: Adequate lymph node (LN) evaluation is important for planning treatment in patients with colon cancer. Aims of this study were to identify factors associated with adequate nodal examination and to determine its relationship with stage distribution and survival.

Patients and methods: Data from patients with colon carcinoma stages I–III who underwent surgical treatment and diagnosed in the period 2000–2006 were retrieved from the Netherlands Cancer Registry. Multilevel logistic analysis was carried out to examine the influence of relevant factors on the number of evaluated LNs. The relationship with survival was analysed using Cox regression analysis.

Results: The number of examined LN was determined for 30 682 of 33 206 tumours. Median number of evaluated LN was 8, ranging from 4 to 15 between pathology laboratories. Females, younger patients, right-sided pN+ tumours with higher pT stage and patients diagnosed in an academic centre were less likely to have nine or less LN evaluated. Unexplained variation between hospitals and pathology laboratories remained, leading to differences in stage distribution. With increasing number of evaluated LN, the risk of death decreased.

Conclusion: There was large diversity in nodal examination among patients with colon cancer, leading to differences in stage distribution and being associated with survival.

Key words: colon cancer, lymph node evaluation, survival, variation

introduction

Similar to other Western countries, colon cancer is frequently diagnosed in The Netherlands. Approximately 7500 new cases of colon cancer were diagnosed in 2006 [1]. Adequate lymph node (LN) analysis is important for planning treatment in patients with colon cancer as the result of randomised controlled trials showed that addition of chemotherapy significantly improves survival among patients with positive LNs [2, 3].

Large variations in the number of evaluated LNs have been described [4–6]. These variations can be attributed to three factors: (i) patient factors (e.g. differences in the immune response of patients, anatomic or individual variability in nodal

harvest), (ii) surgical factors (e.g. surgeon volume, the extent of the surgical lymphadenectomy) and (iii) pathological factors (e.g. the intensity of the examination of the pathologist, the technique used by the pathologist, examination by a pathologist versus pathology assistants) [5, 7–12].

A widely accepted standard of the number of LNs that should be evaluated is currently lacking. In literature, recommendations vary from 6 to 17 to as many as possible [13–15]. According to the guidelines of the International Union Against Cancer, usually ≥ 12 LNs are to be evaluated [16]. The Dutch colon cancer guidelines, revised in 2008, recommend a minimum of 10 negative LNs for accepting N0 status [17]. Still, adequate LN evaluation is lacking in a relatively large proportion of patients [4, 18]. This may result in under-staging of tumours and subsequent under-treatment of patients. Improvement of LN examination could improve quality of care and likely increase survival. Therefore, the proportion of patients with a minimum number of LNs investigated

*Correspondence to: M. A. G. Elferink MSc, Comprehensive Cancer Centre North East, Department of Research, PO Box 330, 9700 AH Groningen, The Netherlands.
Tel: +31-(0)-88-2345500; Fax: +31-(0)-88-2345599;
E-mail: m.elferink@ikno.nl

is often suggested as a quality indicator for colon cancer [19, 20].

The present study is a nationwide population-based study that describes the variation in LN examination, identifies factors associated with adequate LN evaluation and determines its relationship with stage distribution and survival.

methods

Netherlands Cancer Registry

In The Netherlands, all newly diagnosed *in situ* and invasive tumours are registered in the nationwide population-based Netherlands Cancer Registry (NCR). Main sources of notification are the automated pathological archive (PALGA) and the Haematology Departments. Furthermore, the National Registry of Hospital Discharge Diagnoses is an important source, which accounts for up to 8% of new cases [21].

Data are collected from the patient files in the hospital by specially trained registration clerks and are coded according to a national manual. Information on patient characteristics, tumour characteristics, pathology laboratory, treatment, hospital of diagnosis, hospital of treatment and follow-up is recorded. The International Classification of Diseases for Oncology is used for coding topography and morphology [22]. Cancers are staged according to the TNM (tumour–node–metastasis) classification [16]. Quality of the data is high [23]. The completeness is estimated to be at least 95% [24]. Follow-up for all patients is complete up to January 2008 by linking the NCR to the municipality registry. Because of privacy regulations, death certificates are not available in an identifiable form to the cancer registry.

patients

In this study, all patients who underwent surgical resection for stage I–III colon carcinoma (pT1–4NanyM0) and diagnosed in the period 2000–2006 were selected from the NCR ($N = 33\,206$ tumours). Patients who only underwent polypectomy or another local resection were excluded. Tumour site was divided into right sided (C18.0–C18.5), left sided (C18.6–C18.7) and unknown (C18.8–C18.9). Similar to the fifth edition of the TNM Atlas, patients in whom all the evaluated LNs were negative were considered as pN0, irrespective of the number of evaluated LNs [16].

hospitals, pathology laboratories and regions

Type of hospital was based on the hospital where the surgery was carried out. A teaching hospital was defined as a hospital that provides medical training to surgical residents. There is one specialised oncology centre in The Netherlands. This centre was classified as an academic hospital.

A teaching pathology laboratory was a laboratory that provides medical training to pathology residents. Type of hospital and type of pathology laboratory were combined into one variable, resulting in six different groups. Surgery was carried out in 97 different hospitals and LN evaluation was done by 58 different pathology laboratories. Most pathology laboratories serve more than one hospital. Volume of the pathology laboratory was based on the average number per year according to our study population.

statistical analyses

Patients with no examined LNs ($N = 1131$) were excluded from all analyses because certain factors (older age of the patient, acute resection, T1 tumour) might have led to a resection without lymphadenectomy. Correlation between number of evaluated LNs and nodal involvement and volume of the pathology laboratory was calculated by the Spearman's rank correlation test. LN ratio, determined by dividing the number of positive

LN by the total number of examined LNs, was split into quartiles with cut-off points at 0.140, 0.273 and 0.500.

Multilevel logistic analysis was carried out to examine the influence of gender, age at diagnosis, year of diagnosis, tumour site, depth of invasion, LN involvement, grade, type of hospital and type of pathology laboratory on the number of evaluated LNs. Multilevel analysis takes into account a hierarchical structure. Our data had a three-level data structure: tumours were clustered within hospitals of surgery, and hospitals of surgery were clustered within pathology laboratories. The magnitude of the variance of a level in combination with its standard error (SE) can be used as a rough test for judging significance of the variance. The dependency of observations within a certain level was estimated by the intraclass correlation coefficient (ICC). In a logistic multilevel analysis, the ICC can be estimated by the following: between-group variance/between-group variance + $(\pi^2/3)$ [25]. First, a null model without any variables was estimated. Second, patient and tumour characteristics were added stepwise to the model.

Cox proportional hazards modelling was used to investigate the relation between the number of evaluated LNs, the LN ratio and survival corrected for gender, age at diagnosis, tumour site, depth of invasion, tumour grade, number of positive LNs and adjuvant chemotherapy. Follow-up time was calculated as the time from diagnosis to death or to 1 January 2008. Second colon tumours and patients with another tumour before the colon tumour were excluded from the survival analyses. Pathology laboratories were split into quartiles based on their mean number of evaluated LNs to analyse differences in survival between pathology laboratories.

P values were considered significant at 0.05. For all analyses, STATA, version 10.0, was used.

results

In Table 1, the numbers of evaluated LNs by nodal involvement are listed. In total, the number of LNs examined could be determined for 30 682 (92%) patients. In 3% of all patients, no LNs were examined (pNX); these patients were excluded from further analysis. There were no large differences between hospitals in proportion of patients without evaluated LNs, with proportions ranging from 8.3% to 12.0% in five hospitals with the highest proportions.

Table 1. Number of evaluated lymph nodes (LN) by LN involvement

	pN0 ($N = 21\,886$) N (%)	pN+ ($N = 11\,320$) N (%)
0	1131 (5)	0 (0)
1–3	2974 (14)	923 (8)
4–6	4460 (20)	2136 (19)
7–9	3972 (18)	2378 (21)
10–12	3159 (14)	1917 (17)
13–15	1885 (9)	1303 (12)
16–18	1085 (5)	733 (6)
19–21	654 (3)	464 (4)
≥22	886 (4)	622 (5)
Number of examined LN	1383 (6)	790 (7)
unknown		
Unknown whether LN were examined/not registered in the Netherlands Cancer Registry	297 (1)	54 (1)

Ten or more LNs were examined in 35% of the patients with pN0 and in 44% of the patients with pN+ (in 38% of all patients). This proportion increased over time from 24% in 2000 to 52% in 2006 in patients with pN0 and from 31% to 62% in patients with pN+.

The median number of evaluated LNs was eight for the total study population, eight for patients with pN0 and nine for patients with pN+ (Table 2). The median number of evaluated LNs was the highest for patients operated in an academic hospital and of whom, the resection specimen was subsequently analysed in an academic pathology laboratory. Figure 1 shows the median number of evaluated LNs by volume and type of

pathology laboratory. The highest median number of examined LNs was found in low-volume departments of pathology ($\rho = -0.08$, $P < 0.001$). All academic pathology laboratories had low case volumes.

In Figure 2, the median number of evaluated LNs by pathology laboratory and the proportion of node-positive patients per pathology laboratory are depicted. The median number of evaluated LNs by pathology laboratory ranged from 4 to 15 LNs. The proportion of patients with positive LNs increased with rising median number of LNs examined ($\rho = 0.10$, $P < 0.001$). The trend line shows a proportion of 32% of patients with positive LNs at the pathology laboratory with

Table 2. Characteristics of study population (with surgical treatment, pT1-4NanyM0, 2000–2006) by lymph node (LN) involvement

	pN0		pN+	
	N (%)	Median examined LN	N (%)	Median examined LN
Total patients with exact number of examined LNs (≥ 1 LNs)	19 075 (100)	8	10 476 (100)	9
Gender				
Male	9456 (50)	8	5073 (48)	9
Female	9619 (50)	8	5403 (52)	9
Age at diagnosis (years)				
<50	816 (4)	11	625 (6)	12
50–69	6715 (35)	8	4149 (40)	10
≥ 70	11 544 (61)	8	5702 (54)	9
Year of diagnosis				
2000	2372 (12)	7	1294 (12)	8
2001	2395 (13)	6	1322 (13)	8
2002	2472 (13)	7	1342 (13)	8
2003	2685 (14)	7	1432 (14)	8
2004	2847 (15)	8	1615 (15)	9
2005	3067 (16)	10	1663 (16)	11
2006	3237 (17)	10	1808 (17)	11
Tumour site				
Right sided	10 997 (58)	9	6027 (58)	10
Left sided	7759 (41)	7	4241 (40)	8
Unknown	319 (2)	8	208 (2)	10
Depth of invasion				
pT1	1384 (7)	5	121 (1)	5
pT2	3652 (19)	7	762 (7)	8
pT3	12 292 (64)	9	7724 (74)	9
pT4	1747 (9)	8	1869 (18)	10
Tumour grade				
Well differentiated	1773 (9)	8	562 (5)	9
Moderately differentiated	13 107 (69)	8	6654 (64)	9
Poorly differentiated/undifferentiated	2456 (13)	9	2518 (24)	10
Unknown	1739 (9)	7	752 (7)	9
Adjuvant chemotherapy				
No	18 332 (96)	8	4738 (45)	8
Yes	743 (4)	8	5738 (55)	10
Type of hospital and type of pathology laboratory				
Non-teaching hospital and laboratory	4436 (23)	8	2472 (24)	9
Teaching hospital and non-teaching laboratory	4654 (24)	7	2567 (25)	8
Non-teaching hospital and teaching laboratory	3506 (18)	8	1908 (18)	9
Teaching hospital and laboratory	4911 (26)	8	2633 (25)	10
Non-teaching hospital and academic laboratory	339 (2)	10	184 (2)	10
Academic hospital and laboratory	1229 (6)	11	712 (7)	13

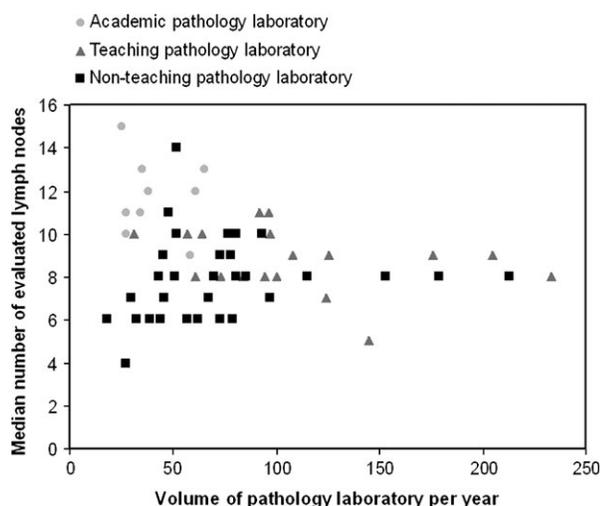


Figure 1. Median number of evaluated lymph nodes by type and volume of pathology laboratory.

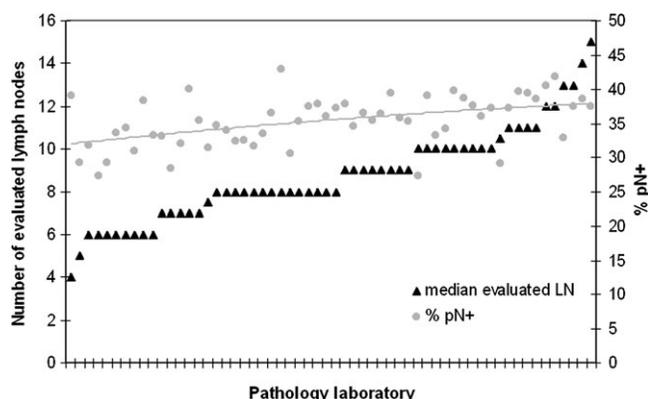


Figure 2. Median number of evaluated lymph nodes (LNs) and percent of patients with positive LNs (pN+) by pathology laboratory.

the lowest median and a proportion of 38% at the pathology laboratory with the highest median.

The proportion of patients who had any LNs examined but of whom the exact number was not stated in the pathology report also differed between the pathology laboratories. In the whole study population, the proportion of patients with an unknown number of evaluated LNs was 6% in patients with pN0 and 7% in patients with pN+ (7% in all patients, range 0% to 41%). In 12 pathology laboratories, the proportion of patients with an unknown number of examined LNs was >10%. The proportion of patients with an unknown number of evaluated LNs decreased by year of diagnosis from 11% in 2000 to 2% in 2006.

Comparing the variances of the levels in the null model of the multilevel analysis with its own SE, both the variance of the hospital level and the variance of the pathology laboratory level were significant. This indicates that the variation between these levels cannot be ignored. The ICC of the hospital level was 0.031 and of the pathology laboratory level was 0.064, meaning that 3.1% of the total variance could be

attributed to the hospital level and 6.4% to the pathology laboratory level.

After adding patient and tumour characteristics, females, younger patients, right-sided tumours, tumours with larger depth of invasion and with LN involvement were less likely to have nine or less LNs evaluated (Table 3). The odds ratio decreased by year of diagnosis, down to 0.27 in 2006. Patients operated on in an academic hospital whose LNs were evaluated in an academic pathology laboratory had the lowest odds of having nine or less LNs evaluated compared with those operated on in a non-teaching hospital whose LNs were evaluated in a non-teaching pathology laboratory. The variances of both levels remained significant after inclusion of these variables to the model, indicating that after correction for patient and tumour characteristics, unexplained variation between the pathology laboratories and hospitals remained. In the final model, the ICC of the hospital level was 0.032 and of the pathology laboratory level was 0.049.

After adjustment for relevant factors, both among patients with positive LNs and among patients with negative LNs, the risk of death increased by decreasing number of evaluated LNs (Figure 3). In both groups, patients with <10 evaluated LNs had a significant higher risk of death compared with those with 10–12 examined LNs. In patients with negative LNs, the lowest risk of death was found in patients with ≥22 evaluated LNs [hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.57–0.88] compared with those with 10–12 examined LNs.

The lowest risk of death in patients with positive LNs was found in patients with 19–21 examined LNs (HR 0.82, 95% CI 0.68–0.99) compared with those with 10–12 examined LNs. Both among patients with positive LNs and among patients with negative LNs, patients with an unknown number of evaluated LNs had a higher risk of death compared with those with 10–12 examined LNs (Table 4).

In Table 5, the results of the survival analyses of patients with positive LNs are shown, including LN ratio. The risk of death increased by rising LN ratio to 2.28 (95% CI 1.92–2.70) in patients with the highest LN ratio (0.501–1.000) after adjustment for number of evaluated LNs, gender, age at diagnosis, tumour site, depth of invasion, tumour grade, number of positive LNs and adjuvant chemotherapy.

Overall, pathology laboratories with the lowest mean number of evaluated LNs had a higher risk of death compared with pathology laboratories with the highest mean number of evaluated LNs after adjustment for relevant factors (HR 1.11, 95% CI 1.05–1.19).

discussion

The results of this nationwide study show an increasing proportion of patients with positive nodes with increasing median number of evaluated LNs. A Dutch regional population-based study already described a large variation in LN examination between the pathology laboratories in the south of The Netherlands [5]. Our study confirmed this variation for the entire Netherlands. Furthermore, we determined the influence of type of hospitals and type and

volume of pathology laboratories. It seems that there are important differences between pathology laboratories in techniques or degree of diligence in examining specimens for LNs. Our results, however, also showed variation in adequate LN evaluation between hospitals, suggesting that adequate LN evaluation depends on the efforts of the surgical teams as well

Table 3. Multilevel logistic regression with odds ratios of having had nine or less lymph nodes (LNs) evaluated

	OR (95% CI)
Gender	
Male	1.00 (reference)
Female	0.92* (0.87–0.96)
Age at diagnosis (years)	
<50	1.00 (reference)
50–69	1.83* (1.62–2.07)
≥70	2.76* (2.44–3.11)
Year of diagnosis	
2000	1.00 (reference)
2001	0.97 (0.88–1.08)
2002	0.81* (0.73–0.90)
2003	0.73* (0.66–0.80)
2004	0.58* (0.53–0.64)
2005	0.36* (0.33–0.40)
2006	0.27* (0.24–0.30)
Tumour site	
Right sided	1.00 (reference)
Left sided	1.84* (1.75–1.95)
Unknown	1.21* (1.00–1.47)
Depth of invasion	
pT1	1.00 (reference)
pT2	0.41* (0.35–0.47)
pT3	0.27* (0.23–0.31)
pT4	0.31* (0.26–0.36)
LN involvement	
pN0	1.00 (reference)
pN+	0.84* (0.79–0.89)
Tumour grade	
Well differentiated	1.00 (reference)
Moderately differentiated	0.86* (0.78–0.95)
Poorly differentiated/undifferentiated	0.80* (0.71–0.90)
Unknown	1.01 (0.88–1.15)
Type of hospital and type of pathology laboratory	
Non-teaching hospital and non-teaching department	1.00 (reference)
Teaching hospital and non-teaching department	1.02 (0.88–1.17)
Non-teaching hospital and teaching department	0.79* (0.65–0.98)
Teaching hospital and teaching department	0.73* (0.62–0.85)
Non-teaching hospital and academic department	0.49* (0.37–0.66)
Academic hospital and academic department	0.39* (0.32–0.47)

* $P < 0.05$.

CI, confidence interval; OR, odds ratio.

as the pathology team. If an excision is not wide enough, it is not possible for the pathologist to sample a sufficient number of LNs. Therefore, surgeons and pathologists have to collaborate and work as a team. Another study, using data from the population-based registry SEER (Surveillance, Epidemiology and End Results) showed variation in LN retrieval by patient geographic location as well, confirming the effect of local surgery and pathology practice patterns on LN evaluation [4].

As in the present study, two Canadian studies showed that surgery in a teaching hospital predicted a higher LN count [26, 27]. They suggested that this could be a reflection of increased resources available in both teaching hospitals and pathology laboratories and academic hospitals and pathology laboratories to provide quality multidisciplinary cancer care. The lower chance of inadequate LN examination in an academic department of pathology might relate to the supervision on the work of the pathology residents in these departments. Another explanation could be the workload. The detection of LNs is a labour-intensive and time-consuming process. Low-volume departments of pathology, which are among others all academic departments, have the highest median number of evaluated LNs. In line with this, a study in Ontario found that lack of time was a barrier to adequate LN assessment. More than 40% of the pathologists thought that it would be an increase in workload to identify five extra LNs per specimen [28]. A single-institution study found no association between LN harvest and the volume of the pathologists [9]. Other studies suggested differences in surgeon volume and extent of the dissection by different surgeons as explanation for the variation in examined LNs [9, 12, 29]. Unfortunately, no detailed information on surgeon or pathologist level was available on a national basis.

The association between LN retrieval and survival found in our study confirms the results of previous studies [10, 30–32]. This phenomenon could partly be explained by under-staging: patients with a small number of evaluated LNs may be incorrectly seen as node negative.

However, the also decreasing risk of death by number of evaluated LN in patients with node-positive disease shows that there has to be another explanation as well. The number of LNs examined may also reflect the differences in the biological behaviour of the tumour and host. Patients with fewer LNs evaluated may be those who have a reduced local immune response to their tumour leading to smaller LNs, which are difficult to detect [33]. This reduced immune response itself might be related to an inferior prognosis [34]. Others suggested that the relation between higher LN counts and better survival reflects the quality of surgical resection [30]. Surgeons may have carried out a more extended lymphadenectomy, with resection of any (micro-)metastases in the LNs or in the surrounding mesocolic tissue. This could partly explain the differences in survival between pathology laboratories.

Comparable to our study, several studies showed that LN ratio is an important prognostic factor for patients with stage III colon carcinoma [30, 32, 35–37]. When grouped according to N stage, a patient with 2 positive LNs out of 40 examined LNs is in the same prognostic group as a patient with 2 positive LNs out of 2 examined LNs. LN ratio makes a distinction between the prognosis for these patients [36].

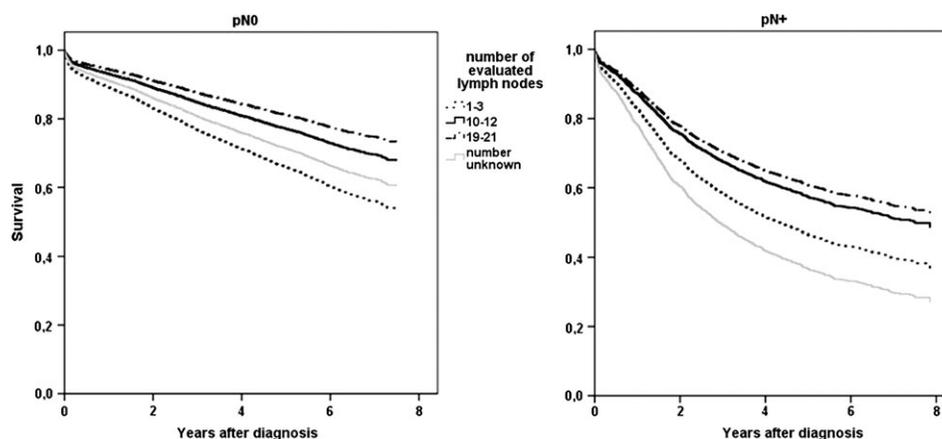


Figure 3. Survival (Cox regression) of patients with pN0 and pN+ by number of evaluated lymph nodes. For reasons of clarity, not all categories are shown.

Table 4. Risk of death by number of lymph nodes (LN) evaluated and LN involvement (multivariable survival analyses)

	pN0 HR (95% CI)	pN+ HR (95% CI)
No. of LNs evaluated ^a		
1–3	1.59* (1.43–1.76)	1.84* (1.61–2.09)
4–9	1.18* (1.08–1.30)	1.44* (1.31–1.58)
10–12	1.00 (reference)	1.00 (reference)
13–15	0.93 (0.81–1.06)	1.00 (0.88–1.13)
16–18	0.86 (0.73–1.03)	0.98 (0.84–1.14)
19–21	0.80 (0.65–1.00)	0.82* (0.68–0.99)
≥22	0.71* (0.57–0.88)	0.88 (0.74–1.04)
Number of examined LN unknown	1.29* (1.13–1.47)	1.80* (1.55–2.08)

^aAdjusted for gender, age at diagnosis, tumour site, depth of invasion, tumour grade, number of positive nodes and adjuvant chemotherapy.

**P* < 0.05.

CI, confidence interval; HR, hazard ratio.

A randomised control trial demonstrated that a formal lecture by an expert opinion leader was associated with an increase in the number of evaluated LNs [38]. Feedback about performance can also be effective in improving professional practice. Medical specialists would probably change their practice when their performance is worse than their colleagues or when it is inconsistent with the guidelines [39]. The increase in number of examined LNs by year of diagnosis in our data might be an effect of feedback to the medical specialists in multidisciplinary working groups [40]. In 2002, a lot of attention was paid to LN evaluation with feedback to all the departments of pathology as a result of the Dutch Total Mesorectal Excision trial.

Patients with stage II and <10 examined LNs are, according to the Dutch guidelines, defined as patients with high risk. Adjuvant chemotherapy should be considered for this group [17]. Apart from avoiding the burden of chemotherapy for the patient, a decreased proportion of patients with an inadequate LN evaluation could also lead to a reduction in expenses for chemotherapy [40].

Table 5. Risk of death by number of evaluated lymph nodes (LNs), number of positive LNs and LN ratio in patients with pN+ (multivariable survival analyses)

	HR (95% CI)
No. of LNs evaluated ^a	
1–3	1.16 (0.98–1.37)
4–9	1.22* (1.10–1.35)
10–12	1.00 (reference)
13–15	1.04 (0.92–1.18)
16–18	1.11 (0.95–1.30)
19–21	0.94 (0.77–1.15)
≥22	1.08 (0.90–1.29)
No. of positive nodes	
1–3	1.00 (reference)
4–6	1.11 (0.99–1.25)
>6	1.60* (1.36–1.87)
LN ratio ^b	
First quartile (0–0.140)	1.00 (reference)
Second quartile (0.141–0.273)	1.39* (1.24–1.56)
Third quartile (0.274–0.500)	1.63* (1.42–1.87)
Fourth quartile (0.501–1.000)	2.28* (1.92–2.70)

^aAdjusted for gender, age at diagnosis, tumour site, depth of invasion, tumour grade and adjuvant chemotherapy.

^bLN ratio was the number of positive LNs divided by the number of examined LNs.

**P* < 0.05.

CI, confidence interval; HR, hazard ratio.

Not only the number of evaluated LNs could be improved by the pathology laboratories, some pathology laboratories need to improve the quality of the pathology report as well. According to the Dutch guidelines for colon cancer, the number of excised LNs is a compulsory item in a pathology report [17]. In our study, the proportion of patients with an unknown number of examined LNs (*N* = 2173, 7% of the study population) ranged from 0% to 41%, although we found an improvement over time. Similar to our results, a study of Jestin et al. [41] found the same survival rates of the patients for whom the number of examined LNs was not stated in the pathology report as that of

patients with <12 LNs examined, suggesting that the quality of the pathology reports is an important factor for adequate staging.

In conclusion, we found a large diversity in LN evaluation with unexplained variation between hospitals and pathology laboratories, leading to differences in stage distribution and being associated with survival. To improve LN examination, surgeons and pathologists should work as a team. This will improve staging, leading to better treatment. Furthermore, it increases the detection of patients with positive nodes who should receive adjuvant chemotherapy and reduces the number of patients with stage II who receive unnecessary adjuvant chemotherapy. Advances in LN evaluation might lead to an increase in survival of patients with colon cancer.

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disclosure

The authors have declared no conflicts of interest.

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