ORIGINAL CONTRIBUTION

Prognostic Impact of Lymph Node Harvest and Lymph Node Ratio in Patients With Colon Cancer

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BACKGROUND: The prognostic impact of the number of lymph nodes and ratio in colon cancer is still debated.

OBJECTIVES: The aim of this study was to evaluate lymph node harvest in patients with colon cancer over time, and to test the hypotheses that investigation of more lymph nodes, and low lymph node ratio in stage III patients, has positive prognostic impact.

DESIGN: This is a prospective, observational study.

SETTINGS: This study was conducted in a single institution treating all patients with colon cancer in a defined catchment area.

PATIENTS: All patients admitted in the period 1993 to 2009 (n = 1481) were included.

MAIN OUTCOME MEASURES: The primary outcomes measured were the number of examined regional lymph nodes according to treatment period, 5-year overall survival and time to recurrence, and univariate (Kaplan-Meier) and multivariate (Cox regression) analyses of prognostic factors.

RESULTS: Nine hundred fifty (65%) patients underwent curative resection. Median number of examined lymph nodes increased from 7 to 15 (p < 0.001), and the proportion of patients with stage III disease increased from 25% to 33% (p = 0.02) during the study period. In patients with stage I to III disease, time to recurrence (proportion of patients without recurrence or death of colon cancer) improved from 65% to 82% during the period (p < 0.001). An association between lymph node count (<8 compared with ≥12) and overall survival was found for patients with stage II disease (57% vs 71%, p = 0.004). Hazard ratio for death within 5 years was 0.7 (p = 0.043) when 8 to 11 nodes were examined and 0.6 (p = 0.001) when ≥12 nodes were examined (<8 reference). In patients with stage III disease, increasing lymph node ratio was associated with reduced overall survival and time to recurrence in uni- and multivariate analyses.

LIMITATIONS: This study was limited by the small number of patients in each stage.

CONCLUSIONS: The number of examined lymph nodes increased in the study period. A stage migration was observed, and time to recurrence improved in patients with stage I to III disease. In patients with stage III disease, lymph node ratio was a stronger prognostic factor than the total number of lymph nodes examined.

KEY WORDS: Colon cancer; Prognostic factor; Lymph node metastasis; Lymph node ratio.

In Norway the incidence of colorectal cancer has almost tripled over the past 50 years, and is now among the highest in the world. The life-time risk of developing colorectal cancer is approximately 6%, and in 2004 to 2008, it was the second most common cancer in females, and third most common in males. 1

In recent years, several studies have documented an improved survival for patients with colon cancer in whom a larger number of lymph nodes were examined in the pathological specimen after colectomy. This advantage is
convincing for stage I/II disease, but results are conflicting for patients stage III disease. Survival differences are generally explained by the understaging of the disease because of suboptimal cancer surgery or inadequate pathological examination of the specimen.

Currently, no general consensus on the threshold value for defining an adequate lymph node number after surgery exists, although several studies have proposed sampling cutoffs. The adequacy of the surgical resection and the completeness of the pathological examination vary, and lymph node retrieval is used as an important measure of the quality of cancer care by many medical organizations.

Several recent studies have reported that in patients with stage III disease, the lymph node ratio (LNR), ie, the ratio between the number of positive nodes to the total number of nodes analyzed, has prognostic significance. LNR seems to have a stronger impact on survival than either the total number of examined nodes or the pN stage as graded according to the TNM system. However, one of the problems with LNR is to find the optimal cutoff point for distinguishing between a good and a poor prognosis, and different threshold values have been proposed.

The objective of this study was to evaluate the quality of lymph node retrieval in colon cancer specimens over time. We hypothesized that the examination of more lymph nodes in patients with stage I to III disease, and low LNR in patients with stage III disease, would have positive prognostic impact.

MATERIALS AND METHODS

Study Population

All patients with adenocarcinoma of the colon, including the rectosigmoid flexure (down to 16 cm above the anal verge), admitted to Oslo University Hospital, Aker, Norway, in the period 1993 to 2009 were registered prospectively and included in the study. A total of 1481 patients were registered. The hospital has a catchment area of approximately 210,000 inhabitants. The database of the Cancer Registry of Norway was consulted to ensure that all new patients diagnosed with colon cancer during the period had been identified.

Clinical Management

Major resection was defined as resection of the tumor-bearing segment of the colon. The routine procedure of the department was to perform “high tie”, ie, central ligation of the vessels (corresponding to D3 dissection in Japanese terminology). However, the patients were operated on by many different surgeons during the study period, and the technique may have varied between intermediate (D2) and central ligation of the vessels (D3). The quality of the registration of lymph node dissection type was not sufficient to evaluate the treatment results on the basis of this parameter.

Operations performed in patients admitted as emergencies because of obstruction, perforation, or profuse bleeding were defined as emergency operations. These patients did usually not receive bowel emptying before operation. In elective patients, preoperative bowel emptying was routinely performed until 2007, but has since been abandoned.

Follow-up

Patients up to 75 years of age who had undergone curative resection were routinely included in a standard follow-up program, and patients older than 75 years were included at the surgeon’s discretion. The program included outpatient visits every 6 months for 2 years, followed by visits 3 and 5 years after the operation. The outpatient visits included clinical examination, x-ray of the chest, and ultrasound of the liver in the period 1993 to 2006, which was changed to CT scan of the chest and abdomen in the period 2006 to 2009. Colonoscopy was performed preoperatively and repeated within a few months of the operation if it had been incomplete preoperatively. A final colonoscopy was performed after 5 years. CEA was measured every third month for 2 years, then at the outpatient visits for a total of 5 years. Patients who did not attend the follow-up program were usually evaluated and treated in our hospital if they developed symptomatic recurrence. Time and causes of death were collected from hospital records for those who died in hospital. For others, data were obtained from the Norwegian Cause of Death Registry.

In the period 1993 to 1997, adjuvant chemotherapy was not routinely used. Since 1997, the Norwegian guidelines for colon cancer treatment have recommended adjuvant chemotherapy for patients with stage III disease who are under 75 years, and, since 2007, also to fit patients aged 75 to 80 years on an individual basis.

Classification

The Union for International Cancer Control/American Joint Committee on Cancer classification version 6 was used for TNM staging, based on preoperative examination, intraoperative findings, and pathology reports. The latter also described tumor differentiation, the number of lymph nodes with and without metastases, and the resection margins in all specimens. The histopathological examinations were made by 8 different pathologists during the period. R0 refers to resection without macroscopic or microscopic evidence of residual tumor after operation and no radiological signs of distant metastases. R1 refers to resection with microscopic tumor at the resection margin, and R2 to resection with macroscopic (or radiological) local and/or distant residual tumor after operation.
**Evaluation of Lymph Nodes**

The specimens were fixed in formalin for 3 to 5 days, and slices were obtained from tumor and macroscopically identified lymph nodes (LNs) in the mesocolic fat. Then 3- to 4-μm-thick paraffin-embedded sections were routinely stained with hematoxylin-eosin before microscopic examinations. Since 2005, the pathologists have been asked to reexamine the specimen if less than 8 LNs were examined primarily. The specimens were not regularly pinned out on a cork plate.

Examination of 12 or more nodes is widely recommended for optimal staging, but different recommendations exist. We analyzed the effect on stage distribution and the effect on survival when the number of examined LNs was <8, 8 to 11, and ≥12.

The LNR was defined as the number of positive nodes divided by the total number of all examined nodes in the specimens. The patients were stratified into 4 subgroups based on quartiles of LNR, and each group comprised the following LNRs: first quartile, LNR <0.11; second quartile, LNR 0.11 to 0.18; third quartile, LNR 0.19 to 0.40, and fourth quartile, LNR >0.40.

**Study Period**

To study development over time, the cohort was divided into 3 groups of similar size according to date of operation (date of admission for those not operated on), 1993 to 1998, 1999 to 2004, and 2005 to 2009.

**Study Ethics**

The study was performed according to the Helsinki declaration, and approved by the regional ethics committee for medical research and the Norwegian Data Inspectorate (607-05194 1.2005.162).

**Statistical and Survival Analyses**

All data were registered on special forms and then recorded in a Microsoft Access database, and the statistical analyses were performed with SPSS 17.0 (Statistical Package for Social Sciences, Chicago, IL). Most sets of continuous data had nonnormal distribution. Measures of central tendency were given as median (range), and nonparametric tests (Mann-Whitney or Kruskal-Wallis as appropriate) were used for comparisons. Differences between proportions were analyzed with the χ² test.

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### FIGURE 1.

Treatment of the patients admitted in the study period.
The Kaplan-Meier method was used to estimate 5-year overall survival (OS) and 5-year time to recurrence (TTR) with the log-rank test to compare factors. In the analysis of OS, death from any cause was defined as event. TTR was defined as time to any event related to the primary colon cancer: Recurrence, locoregional or distant, and death from the same cancer were defined as events. Patients were censored at loss to follow-up (date of the last consultation for colon cancer), and at the time of death from any other cancer, noncancer disease, or postoperative complications (treatment-related death). These definitions are in accord with the conclusions from a consensus conference in 2007. Cox regression analyses were used to identify independent prognostic factors.

A p value of <0.05 was considered statistically significant.

**RESULTS**

A total of 1481 patients, 668 (45%) men and 813 (55%) women, median 75 (range, 27–97) years of age, were admitted in the study period. Nine hundred fifty patients with stage I to III disease who underwent curative (R0) resection (Fig. 1) are included in the analyses of LN numbers and LNR related to survival. Age and sex distribution of those who underwent R0 resection was similar to that of the whole series. Clinical and histopathological characteristics are shown in Table 1.

### Table 1. Clinical and histopathological characteristics of stage I–III patients with R0 resection (n = 950)

| Characteristic                  | n  | %  |
|--------------------------------|----|----|
| **Tumor location**             |    |    |
| Cecum/ascending colon          | 385| 41 |
| Right flexure                  | 60 | 6  |
| Transverse colon               | 74 | 8  |
| Left flexure                   | 40 | 4  |
| Descending colon               | 40 | 4  |
| Sigmoid                        | 256| 27 |
| Rectosigmoid flexure           | 63 | 7  |
| Multiple tumors                | 32 | 3  |
| **Operation**                  |    |    |
| Elective                       | 805| 85 |
| Emergency                      | 145| 15 |
| **T stage**                    |    |    |
| pT1                            | 53 | 6  |
| pT2                            | 144| 15 |
| pT3                            | 691| 73 |
| pT4                            | 62 | 6  |
| **N stage**                    |    |    |
| pN0                            | 663| 70 |
| pN1                            | 200| 21 |
| N2                             | 87 | 9  |
| **UICC/AJCC stage**            |    |    |
| Stage I                        | 174| 18 |
| Stage II                       | 489| 52 |
| Stage III                      | 287| 30 |
| **Tumor differentiation grade:** |    |    |
| High                           | 66 | 7  |
| Middle                         | 737| 78 |
| Low                            | 118| 12 |
| Mucinous                       | 10 | 1  |
| Unknown                        | 19 | 2  |

Figures within each separate section are percentages of the total number in the section, n = 950.

**Number of Examined LNs and Stage Migration**

The median number of examined LNs was 12 (range, 0–73), but the number increased from 7 to 15 during the period, as did the proportion of patients in whom more than 8 and more than 12 nodes were examined (Table 2). In the last 2 periods (1999–2009), 33% of the patients with R0 resection had stage III disease, in comparison with 25% in the first period (p = 0.02). The proportion of patients with stage III disease increased when ≥8 nodes were examined (p = 0.001) (Tables 3 and 4).

During the study period, the proportion of patients with stage III disease with LNR in the lowest quartile increased and the proportion of patients with LNR in the highest quartile decreased (Table 5).

**Survival According to Time Period**

Overall survival in the whole study population was 43% for women and 45% for men (p = 0.51), and improved during the study period (Fig. 2). The proportion of patients with stage IV disease did not change during the study period. In patients with stage I to III disease who underwent R0 resection (n = 950), OS was 61%, 66%, and 61% in the 3 periods (p = 0.6), whereas TTR improved during the
whole period, from 65% to 82% ($p < 0.001$). TTR improved significantly in stages I and II, and there was a trend toward improvement in stage III (Fig. 3).

Multivariate analysis also confirmed the independent prognostic impact of time period on TTR with HR 0.6 ($p = 0.02$) for patients operated on later than the first period, ie, after 1998.

**Survival in Relation to Number of Examined LNs**

Univariate analyses showed that in patients with stage II disease, a higher number of examined LNs was associated with improved OS after R0 resection, and there was a trend in patients with stage I and III disease (Table 6). There was a significant association between LN count and TTR in stages II and III, and a trend in patients with stage I disease (Table 6). Multivariate analyses confirmed the independent prognostic impact of LN number on OS and TTR (Table 7).

**Survival According to LNR in Patients With Stage III Disease**

In patients with stage III disease, a higher LNR was significantly associated with reduced OS; 70% in patients with LNR $<0.11$ (lowest quartile) compared with 46% in patients with LNR $\geq 0.11$ ($p = 0.002$). LNR also had a great impact on TTR. These findings were confirmed in multivariate analyses, showing increased hazard ratio for both OS (data not shown) and TTR in patients with LNR in the second (HR 2.5, CI 1.2–5.3), third (HR 2.7, CI 1.3–5.7), and fourth quartile (HR 3.4, CI 1.6–7.2), when adjusted for sex, age, emergency operation, tumor differentiation grade, total number of examined LNs, and treatment with chemotherapy.

**DISCUSSION**

The first main finding in this study was that OS for all admitted patients with colon cancer improved during the study period from 1993 to 2009. In patients who underwent curative resection, the results with regard to cancer-related events apparently improved; TTR improved significantly in patients with stage I and stage II disease, and there was a trend toward improvement in patients with stage III disease. TTR is a sensitive and a strictly cancer-related end point, defining only recurrence and colon cancer death as events.

In the same period, the LN count increased from a median of 7 nodes analyzed in the first period to a median of 15 in the last period. The proportions of samples with less than 8 nodes, and with less than 12 nodes, were greatly reduced. Improved LN retrieval was accompanied by stage migration, and the proportion of patients with stage III disease increased from 25% to 33%.

A minimum of 12 examined LNs is usually recommended to obtain correct staging.21,22 In this study, we observed stage migration when 8 or more nodes were examined, but no further migration when the group with 8 to 11 nodes was compared with the group with at least 12 nodes. This finding is comparable to the report from Baxter et al,23 showing stage migration with increasing number of LNs up to 5 to 7 in pT3 tumors.
The present single-center study is prospective and population based. Selection bias is unlikely because the hospital is responsible for all patients in a defined catchment area. In addition, we consider that the data on treatment and follow-up are of high quality, and that the results are reliable. OS is a robust end point that is always correct, but with the disadvantage that it is not very sensitive. TTR is a very sensitive end point, taking into account all deaths and recurrences of the same cancer, censoring deaths of other causes and loss to follow up. In analyses of TTR, however, false cause of death and missed recurrences might introduce bias. In some of the patients who did not undergo curative resection, and those who did not attend follow-up, the cause of death was uncertain. Some cases of recurrence in older patients, who did not attend follow-up, might have been missed or at least discovered later than if they had been followed. However, we believe that biases for these reasons are minimal when it comes to evaluation of the prognostic impact of LN number and LNR. Another limitation of the study is the relatively small number of patients in each stage and the possibility of type II errors.

The study shows that patients with stage II and stage III disease with a larger number of LNs examined had a survival advantage, in terms of both OS and TTR. Multivariate analyses demonstrated that OS improved when ≥8 nodes were examined, and TTR improved when ≥12 nodes were examined. Several other studies in recent years have demonstrated that analyzing a larger number of nodes confers a survival advantage in patients with stage II disease, but there are conflicting results for patients with stage III disease.

The association between improved LN retrieval and apparently improved survival is usually considered to be the result of stage migration and Will-Rogers phenomenon. In specimens where a small number of nodes are analyzed, metastases may be overlooked and the stage falsely classified as I/II disease. Analyzing a larger number of nodes decreases the risk of missing a positive node. When patients with false-negative stage I/II are correctly rediagnosed as stage III (stage migration), the prognosis improves in both groups.

This phenomenon is named after the famous US comedian Will Rogers. Generally speaking, the phenomenon is obtained when moving an element from I set to another set raises the average values of both sets. The effect will occur when both of these conditions are met. First, the

### Table 6

| Stage | No of lymph nodes | 5-y overall survival | 5-y time to recurrence |
|-------|-------------------|----------------------|------------------------|
|       | All patients      | 0–7                  | 8–11                   | ≥12 | p  | All patients | 0–7 | 8–11 | ≥12 | p  |
| I     | 78                | 70                   | 83                     | 83 | 0.08 | 90            | 83  | 94   | 96  | 0.09 |
| II    | 65                | 57                   | 61                     | 71 | 0.004 | 75            | 68  | 71   | 81  | 0.03 |
| III   | 52                | 38                   | 60                     | 54 | 0.06  | 62            | 46  | 61   | 69  | 0.02 |

**FIGURE 3.** Time to recurrence in patients with stage I to III disease who underwent R0 resection; comparison of time periods. Cum = cumulative.

**TABLE 6.** Overall survival (%) and time to recurrence (%) according to number of examined lymph nodes and stage (R0 resection)
The routine procedure in the department during the whole study period was to perform central lymphovascular dissection and ligation (D3 dissection). However, the operations were performed by many surgeons, both consultants and residents, and about 15% of the curative resections were performed as emergencies, which means that the surgical technique may have varied. Still, we believe it is unlikely that more radical surgery is the cause of the observed stage migration.

The completeness of the pathological examination of the specimen depends on the skill and dedication of the pathologist, the examination methods, and the use of standardized protocols for the report. The methods used for LN examination in the Department of Pathology did not change during the study period. However, despite the lack of a protocol, there was increasing awareness of the importance of examining a large number of LNs, especially because the TNM guidelines from 2002 recommended a minimum of 12 nodes to be examined. Although the relative influence of the surgeon and the pathologist in stage migration is debated, we believe that improved quality of the pathology examination is the main factor explaining the improved LN harvest in the present study.

Another important finding in this study was the significant prognostic impact of LNR in patients with stage III disease, which is in line with several recent reports. In multivariate models, the number of retrieved LNs was not a prognostic factor when analyzed together with LNR. Divergent results are reported when these factors are analyzed together, but most studies conclude that LNR has a stronger prognostic impact than LN count.

Interestingly, as the number of retrieved LNs increased during the study period, resulting in the detection of more patients with stage III disease, we observed a corresponding decrease in LNR. The explanation may be that those patients who had previously been falsely classified as stage II had few metastatic nodes. The median number of metastatic LNs in stage III was equal in the 3 periods, although the total number increased.

There is no consensus on where to set the threshold value of LNR to obtain optimal prognostication of patients with stage III disease. Fit patients with stage III disease usually receive adjuvant chemotherapy, whereas old/frail patients usually do not. There is an intermediate group of patients who are treated on an individual basis, and in this group adjuvant treatment could be omitted for patients with relatively good prognosis. In this study, TTR of patients with LNR in the lowest quartile (LNR <0.11) was 83%. This may indicate that, for optimal prognostication, the cutoff value could be set between the lowest and the 3 highest quartiles. The corresponding figures for quartiles based on the number of involved nodes will obviously differ between series, mainly because of large differences in the median number of evaluated nodes.

### TABLE 7. Overall survival and time to recurrence according to number of examined lymph nodes (R0 resection, stages I–III); hazard ratio for death within 5 years

| Factors                  | Overall survival | Time to recurrence |
|--------------------------|------------------|--------------------|
|                          | HR (95% CI)      | p                  |
| No of lymph nodes        |                  |                    |
| ≤ 7                      | Reference        | Reference          |
| 8–11                     | 0.7 (0.5–0.9)    | 0.04               |
| ≥ 12                     | 0.6 (0.5–0.8)    | 0.001              |
| Sex                      |                  |                    |
| Females                  | Reference        | Reference          |
| Males                    | 1.1 (0.9–1.4)    | 0.3                |
| Age                      |                  |                    |
| < 65 y                   | Reference        | Reference          |
| 65–74 y                  | 1.8 (1.2–2.6)    | 0.006              |
| 75–81 y                  | 2.4 (1.6–3.5)    | <0.001             |
| > 81 y                   | 3.3 (2.2–4.8)    | <0.001             |
| Type of operation        |                  |                    |
| Elective operation       | Reference        | Reference          |
| Emergency                | 2.2 (1.7–2.9)    | <0.001             |
| TNM stage                |                  |                    |
| Stage I                  | Reference        | Reference          |
| Stage II                 | 2.8 (1.6–4.9)    | <0.001             |
| Stage III                | 5.3 (3.0–9.5)    | <0.001             |
| Differentiation grade    |                  |                    |
| High                     | Reference        | Reference          |
| Middle                   | 1.3 (0.8–2.1)    | 0.3                |
| Low                      | 1.7 (1.0–3.0)    | 0.05               |
| Mucinous                 | 1.3 (0.5–4.0)    | 0.6                |
| Unknown                  | 2.0 (0.9–5.9)    | 0.1                |

The reasons for the heterogeneity in LN sampling across studies may include surgeon-, pathologist-, patient-, and/or tumor-related variables. The surgeons’ method of lymphovascular dissection varies, and agreement is still not reached on whether removal of the central LNs improves survival, but this is recommended to ensure correct staging. LN retrieval also depends on surgical competence and skill, which is generally considered to be associated with surgeon volume and surgical completeness of resection.

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CONCLUSIONS

Overall survival improved in patients with colon cancer during the 16-year study period. An increasing number of regional LNs was examined, which may be caused by better quality of the pathological examination. Examination of more LNs was associated with stage migration, which most likely contributed to improved survival (TTR) in patients with stage I to III disease. Examination of at least 12 nodes should be the aim to obtain correct staging and optimal prognostication. LNR is a stronger prognostic factor than the number of examined LNs in patients with stage III disease, but the definition of optimal threshold values for clinical use needs further study.

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