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ORIGINAL ARTICLE

A high lymph node yield in colon cancer is associated with age, tumour stage, tumour sub-site and priority of surgery. Results from a prospective national cohort study

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Abstract
Aim To determine the relation between patient-related and histopathological factors, as well as the influence of national programs for diagnosing and treatment of colon cancer and a lymph node yield (LNY) ≥ 12.
Method An analysis was carried out of the LNY in a nationwide Danish cohort treated by curative resection of stage I–III colon cancer in the period 2003–2011. The association between a LNY ≥ 12 and age, sex, body mass index, open vs. laparoscopic surgery, acute vs. elective surgery, pT stage, tumour sub-site and year of diagnosis was analysed.
Results A total of 13,766 patients were eligible for the analysis. In total, 71.4 % of the patients had a LNY ≥ 12. In multivariate analysis, age, pT stage, tumour sub-site and priority of surgery were independently associated with the probability of a LNY ≥ 12. Odds ratios (ORs) were as follows: age <65 1, 65–75 0.685 (confidence interval (CI) 0.586–0.800), >75 0.517 (CI 0.439–0.609); T1 1, T2 2.750 (CI 2.168–3.487), T3 6.016 (CI 4.879–7.418), T4 6.317 (CI 4.950–8.063); right colon 1, left colon 0.568 (0.511–0.633); elective surgery 1, acute surgery 0.748 (CI 0.625–0.894). Moreover, year of diagnosis was associated with the probability of a LNY ≥ 12: OR 1.480 (CI 1.445–1.516) for each increasing year in the study period.
Conclusion A LNY ≥ 12 is significantly associated with age, pT stage, tumour sub-site and priority of surgery. A significant increase in the LNY over the period of the study was observed, probably reflecting the effect of national programmes initiated by the Danish Colorectal Cancer Group.

Keywords Colon cancer · Lymph nodes · Lymph node yield · National guidelines

Introduction

The identification of metastatic infiltrated lymph nodes (LNs) is essential in predicting long-term survival for colon cancer patients as well as in the identification of those who might benefit from postoperative adjuvant chemotherapy. The TNM system proposed by the American Joint Committee on Cancer (AJCC) [1] is the most widely used staging system. According to the AJCC guidelines, a minimum of 12 LNs should be presented in the surgical specimen in patients with lymph node-negative (N-negative) disease to ensure correct staging [2, 3].

These guidelines are founded on more than 20 years of recommendations based on level III–IV evidence drown from fat clearance studies that included both colon and rectal cancer [2, 4–8]. In these recommendations, it was concluded that to achieve an accuracy of >90 %, a minimum LN yield (LNY) of 12 negative LNs is needed to guarantee N-negative disease [2].

Despite these guidelines, debate still exists regarding the optimal LNY to guarantee proper staging [9, 10], and subsequent studies have demonstrated that patient-related and histopathological factors including sex, age, tumour location, BMI, pT category as well as acute surgery seem to influence the LNY [11–15].

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Although there is this ongoing debate, most countries, including Denmark [16], have accepted the 12 LN guidelines. Despite the recommendations from AJCC, recent national cohorts fulfil the 12 LN recommendations in only a limited number of patients [13, 17, 18].

The Danish Colorectal Cancer Group (DCCG) [19] was established in 2001. In addition to improved treatment of colon and rectal cancer patients, one of its main purposes has been to promote uniform diagnostics including a sufficient LNY in the surgical specimens from colorectal cancer patients. Since 2001, there has been an increasing focus on the diagnosis and treatment of colorectal cancer in Denmark including centralization of its treatment [20].

Aims

The aims of the present study were, based on prospective data from a national cohort of patients with non-metastatic (stage I–III) radical resected colon cancer, to examine whether

- There is an association between age, sex, BMI, open vs. laparoscopic surgery, acute vs. elective surgery, T-stage, tumour sub-site and a LNY ≥ 12.
- Standardization and centralization of diagnosing and treating colon cancer is associated with the probability of achieving a LNY ≥ 12.

Material and methods

On 1 May 2001, the DCCG established a nationwide database, and since then, all patients aged 18 years or older with a first-time diagnosis of colorectal adenocarcinoma treated in all Danish colorectal surgical departments have been prospectively recorded. Surgery for colorectal cancer is performed at public hospitals in Denmark. Patients are identified by the unique civil registry number, which has been allocated to all Danish citizens since 1968 by the Central Population Registry. The data are provided from the surgical departments and includes demographics, tumour location and stage, diagnostic and therapeutic procedures and postoperative complications. The completeness of the data collection is estimated annually and has improved from 86.4 to 96.7 % in the study period 2001–2011 [21]. The high completeness is achieved through linkage to the Danish National Patient Register and Danish Cancer Register. Histopathology of the primary tumour was extracted from the Danish Pathology Registry. The DCCG database and the Danish Pathology Registry were used for data extraction and evaluation. Variables including age, sex, tumour location, pT stage, BMI, open vs. laparoscopic surgery, acute vs. elective surgery and LNY were extracted for use in the present study (Table 1). The Dukes classification was standard for staging CRC patients in Denmark in the first 2 years of the database (2001–2002) [19], but since it is not specific about the T-stage, we decided to exclude patients from that period. All patients with a first-time diagnosis of colon cancer and a subsequent curative colon resection, defined as an R0 resection of a stage I–III adenocarcinoma located beyond 15 cm of the anal verge (1 January 2003 to 31 December 2011), were included.

Definitions

Right-sided tumours were located proximal to splenic flexure of the colon, and left-sided tumours were located from the splenic flexure to the rectosigmoid junction (i.e. 15 cm from the anal verge).

Table 1 Patient and tumour characteristics

n = 13,766	*n* (%)
Sex	
Male	6694 (48.6)
Female	7072 (51.4)
Age (years)	
<65	2011 (14.6)
65–75	6528 (47.4)
>75	5227 (38.0)
BMI (kg/m^2)	
<25	4952 (30.0)
25–29	3386 (24.6)
≥30	1481 (10.8)
Missing value	3947 (28.7)
Location	
Right	7265 (52.8)
Left	6501 (47.2)
T-stage	
pT1	728 (5.3)
pT2	1566 (11.4)
pT3	9078 (65.9)
pT4	2303 (16.7)
Missing value	91 (0.7)
Priority of surgery	
Elective	11918 (86.6)
Acute	1845 (13.4)
Type of surgery	
Open	9683 (70.3)
Laparoscopic	4080 (29.6)
LNY total median (quartiles)	15 (11–22)
Lymph node yield (LNY)	
<12	3939 (28.6 %)
≥12	9827 (71.4 %)

Statistics

Data were analysed statistically using the IBM SPSS version 22 (IBM Corp., Armonk, NY, USA). The patient characteristics and histopathological data were analysed by non-parametric statistics.

The association between year of diagnosis, pT stage, age, sex, BMI, open vs. laparoscopic surgery, acute vs. elective surgery, tumour sub-site and an LNY ≥ 12 was explored using multiple logistic regressions with an LNY ≥ 12 as outcome measure and reported as odds ratios (OR) with 95 % confidence intervals (95 % CI).

A p value of <0.05 was used as the level of significance in all analyses.

Ethics

The Danish National Committee on Biomedical Research Ethics and the Danish Data Protection Agency approved the use of the database for the present study.

Results

Patient characteristics

Data from 13,766 patients (males 48.7 %) were available for the analysis (Fig. 1). In total, 71.4 % of the patients had an LNY of larger than or equal to 12 (Table 1). There was a steady increase in the median LNY, from 11 [interquartile range (IQR) 7–15] to 23 (IQR 16–33) over in the study period ($p < 0.0001$).

The median age was 70 (IQR 62–78), and the median LNY was 15 (IQR 11–22). No difference in the median LNY was observed in relation to sex and BMI (Table 2). The LNY decreased with increasing age with a median LNY of 17 (IQR 12–25) for the group of patients <65 years of age and a median LNY of 15 (IQR 11–21) for those >75 years of age. The median LNY in right-sided tumours was significantly higher than that in left-sided tumours [17 (IQR 12–24) vs. 15 (IQR 10–21), respectively] (Table 2). A significant association between increasing pT stage and increasing LNY was observed with a median LNY ranging from 10 (IQR 5–15) in pT1 tumours to 18 (IQR 13–26) in pT4 tumours, $p < 0.0001$ (Table 2).

In the univariate analysis, we found a significant association between pT stage and the proportion of patients having an LNY ≥ 12, 41.1 % (pT1) vs. 77.8 % (pT4) ($p < 0.0001$). A decreasing proportion of patients having an LNY ≥ 12 were observed with increasing age: 76.1 % in the group of patients <65 years vs. 68.3 % in the group >75 years ($p < 0.0001$). Tumour location had a significant association with the proportion of an LNY ≥ 12: In right-sided tumours, 77.1 % of the patients had an LNY ≥ 12 vs. 65.0 % in left-sided tumours ($p < 0.0001$). A minor but significant difference in the proportion of patients with an LNY ≥ 12 according to sex was observed with a percentage of 72.6 vs. 70.1 % in favour of women ($p < 0.001$). A proportion of patients with an LNY ≥ 12 of 71.4 vs. 67.7 % ($p < 0.0001$) was observed in laparoscopic surgery vs. open surgery. Finally, a significant difference in the proportion of patients having an LNY ≥ 12 was observed in the group of patients having an acute operation (64.7 %) vs. those having an elective operation (72.4 %), $p < 0.0001$ (Table 3).

A substantial increase throughout the study period in the proportion of patients having an LNY ≥ 12 was observed: 44.8 % at the beginning of the period vs. 93.4 % at its end, ($p < 0.0001$) (Fig. 2).

Logistic regression

In the logistic regression analysis, age, tumour location, pT stage, priority of surgery and year of diagnosis were independently associated with the probability of an LNY ≥ 12. No association was observed with sex, BMI and laparoscopic vs. open surgery. Odds ratios for achieving an LNY ≥ 12 are seen in Table 4.

Discussion

In our study, we have demonstrated a significant association between pT stage and the proportion of patients having an LNY greater than or equal to 12: 41.1 % (pT1) vs. 77.8 % (pT4). This relation remained significant in the multivariate analysis with an OR of 6.317 for pT4 tumours compared to T1 tumours. The reason for the association between T-stage and LNY is unknown, but it has been proposed by others that tumour necrosis results in an increased exposure of the host immune system to tumour antigens which could explain why high T-stage tumours are associated with a higher LNY compared to low T-stage ones [22]. Others have argued that larger tumours are more likely to compromise the gut mucosal barrier and cause an inflammatory response in regional lymph nodes [23].

A reduced LNY with increasing age was also demonstrated in our study. This has been reported by others [14, 23–25], and it has been suggested that a reduced LNY in elderly patients may be due to a decreasing immune function [17, 26], while others have argued that a reduced LNY in elderly patients is due to less extensive resection in these patients [24]. Unfortunately, no relevant data were available in our material.

Patients with right-sided colon cancers have consistently been shown to have a higher LNY than patients with left-sided colon cancers [17, 23, 27, 28], which is consistent with our findings with an OR of achieving a sufficient LNY in left-

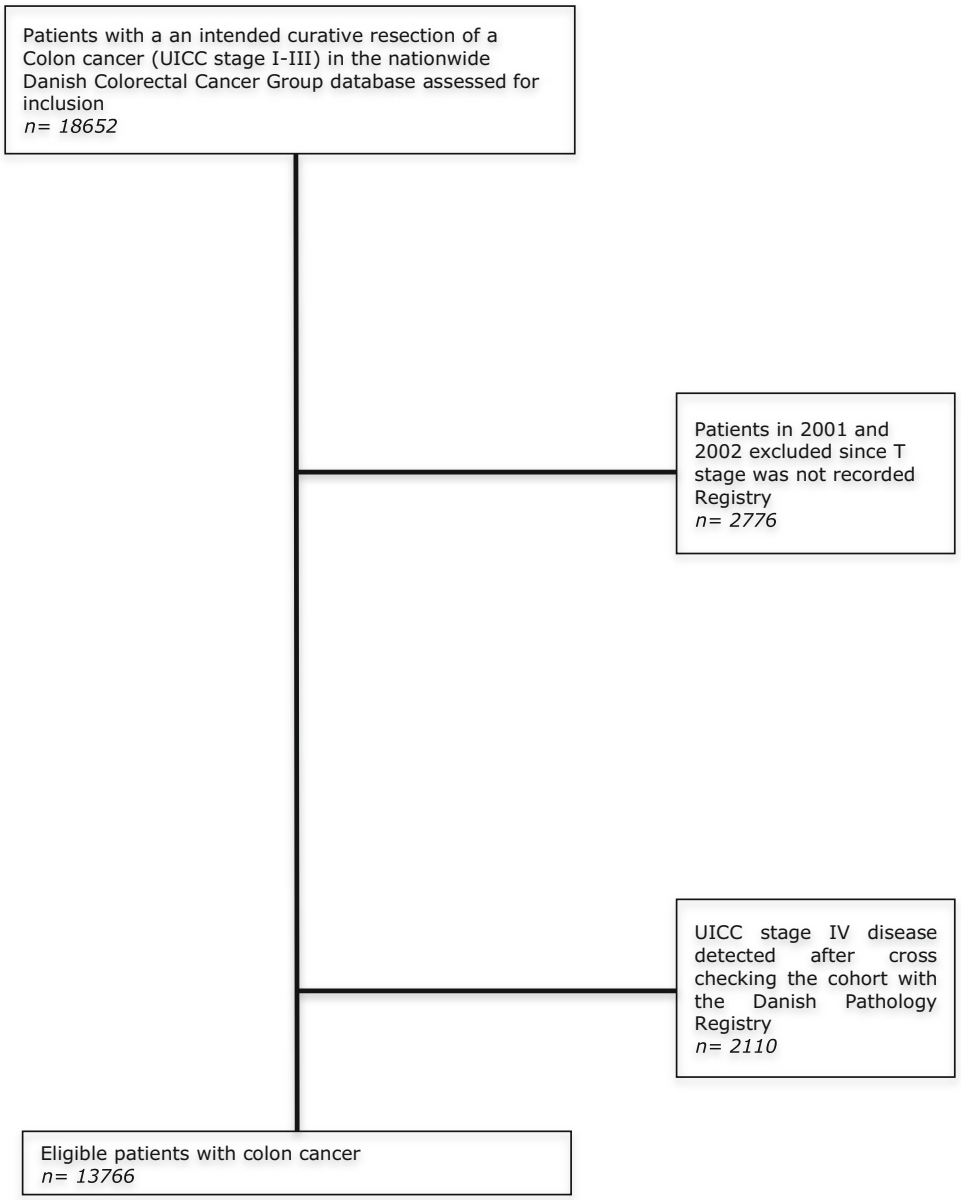

Fig. 1 The complete patient cohort indicating those groups excluded during the process to isolate the final group of patients included in the analysis. *UICC* Union for International Cancer Control

sided colon cancers of 0.568 compared to right-sided colon cancers. A part of the explanation for this could be related to a potentially greater length in the surgical specimen after a resection of a tumour in the right colon including both the ileocolic and middle colic artery that allows a greater LNY compared to the inferior mesenteric artery in most tumours in the left colon. Others have argued that chromosomal instability is the most common pathway for the development of tumours in the left colon whereas microsatellite instability, which is associated with more immunogenic tumours giving a higher LNY, is more frequently located in the right colon [29–32].

The proportion of an LNY larger than or equal to 12 according to sex was 72.6 vs. 70.1 % in favour of women. These findings are almost identical to a study by Nedrebø et al. analysing data from the Norwegian Colorectal Cancer Registry reporting an LNY ≥ 12 of 71.5 vs. 68.1 % in favour of women [15], but this finding could not be verified in our multivariate analysis.

No difference in the proportion of patients with a LNY larger than or equal to 12 in the multivariate analysis was observed when laparoscopic surgery was compared to open surgery.

We found a significant difference in the proportion of an LNY larger than or equal to 12 when acute surgery was compared to elective surgery: 64.7 vs. 72.4 % ($p < 0.0001$) in favour of elective surgery. This difference remained significant in the multivariate analysis (OR 0.748 for acute surgery). The

Table 2 LNY according to patient and tumour characteristics

$n = 13,766$	LNY: median (interquartile range)	p value
Gender		
Female	15 (11–22)	<0.002[a]
Male	15 (10–22)	
Age (years)		
<65	17 (12–24)	<0.0001[b]
65–75	16 (11–22)	
>75	14 (10–22)	
BMI (kg/m^2)		
<25	16 (12–24)	<0.003[b]
25–29	16 (11–22)	
≥30	16 (11–23)	
Tumour location		
Right	16 (12–23)	<0.0001[a]
Left	14 (9–20)	
pT stage		
pT1	10 (5–15)	<0.0001[b]
pT2	13 (8–18)	
pT3	16 (11–22)	
pT4	17 (12–24)	
Priority		
Elective	15 (11–22)	<0.0001[a]
Acute	14 (9.5–19.5)	
Surgical approach		
Laparotomy	14 (10–20)	<0.0001[a]
Laparoscopic	17 (12–24)	

[a] Mann-Whitney U test

[b] Kruskal-Wallis test

Table 3 The distribution of an LNY </≥12 according to patient and tumour characteristics

$n = 13,766$	LNY < 12	LNY ≥ 12	p value
Gender			
Female	27.4 %	72.6 %	<0.001[a]
Male	29.9 %	70.1 %	
Age (years)			
<65	23.9 %	76.1 %	<0.0001[b]
65–75	27.6 %	72.4 %	
>75	31.7 %	68.3 %	
BMI (kg/m^2)			
<25	24.8 %	75.2 %	<0.031[b]
25–29	27.4 %	72.6 %	
≥30	25.5 %	74.2 %	
Tumour location			
Right	22.9 %	77.1 %	<0.0001[a]
Left	35.0 %	65.0 %	
pT stage			
pT1	58.9 %	41.1 %	<0.0001[b]
pT2	41.0 %	59.0 %	
pT3	25.4 %	74.6 %	
pT4	22.2 %	77.8 %	
Priority			
Elective	27.6 %	72.4 %	<0.0001[a]
Acute	35.3 %	64.7 %	
Surgical approach			
Laparotomy	32.3 %	67.7 %	<0.0001[a]
Laparoscopic	28.6 %	71.4 %	

[a] Fisher's exact test

[b] Pearson's chi-squared test

reason for this is unknown, but it seems obvious that the surgical field per se is more complicated in an acute setting than in an elective setting, and it emphasizes that acute surgery for colon cancer is a complicated procedure that requires a skilled surgical team.

A consistent increase in the LNY during the period of data collection was observed with an increase in the proportion of an LNY ≥ 12 from 44.0 % (2003) to 93.4 % (2011), and in the multivariate analysis, the year of diagnosis turned out to be an substantial independent prognostic factor with an OR of 1.48 for achieving an LNY ≥ 12 for every year in the study period. The finding of a proportion of more than 90 % of the patients meeting the recommendations of an LNY ≥ 12 at the end of the study period was better than the findings in several recent national cohort studies [13, 15, 17, 18]. In other studies, it has been shown that surgeons specialized in colorectal surgery and histopathologists with a special interest in gastrointestinal pathology achieve a significantly higher LNY compared with non-specialized surgeons and histopathologists [26, 33]. Unfortunately, it was not possible to examine the impact of the skill of the surgeons and histopathologists on LNY, as such data were not available in the database. However, in Denmark, there has been an increased focus over the last 15 years on the diagnostic, staging and treatment of colorectal cancer, including introduction of multidisciplinary teams, certification of surgeons performing CRC surgery, centralization of the surgical departments treating it [20] as well as development of national guidelines by the DCCG [16]. It is very likely that improvements in surgical and histopathological practice as well as centralization of surgical departments treating colorectal cancer have contributed to the observed increasing proportion of an LNY larger than or equal to 12. This is in accordance with results from a German [34] and a Norwegian [15] study concluding that a high case load in a department has a positive impact on the LNY.

The current analysis has several positive attributes in addition to the fundamental strength of its population-based design. The study included patients from all Danish departments conducting colon surgery during the study period and was further strengthened by an almost complete and unselected

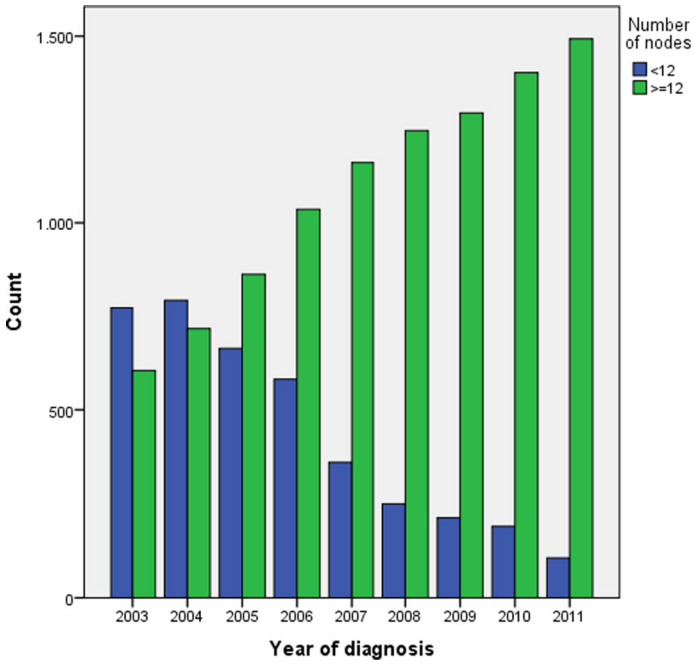

Fig. 2 The proportion of patients (%) with an LNY of ≥12 between 2003 and 2011

Year of diagnosis	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
n	1382	1513	1530	1621	1520	1499	1509	1593	1599	13766
>=12 (%)	44.0	47.5	56.4	63.9	76.3	83.3	85.9	88.1	93.4	71.4

p<0.0001, Pearson Chi-Square

Table 4 Logistic regression analysis, dependent variable is lymph node yield </≥12

Variable	Odds ratio (confidence Interval)	*p* value
Male	1	
Female	1.088 (0.980–1.208)	0.113
Age <65 years	1	
Age 65–75 years	0.685 (0.586–0.800)	<0.0001
Age > 75 years	0.517 (0.439–0.609)	<0.0001
Elective surgery	1	
Acute surgery	0.748 (0.625–0.894)	0.001
BMI < 25	1	0.116
BMI 25–29	0.886 (0.791–0.993)	0.038
BMI ≥ 30	0.958 (0.821–1.118)	0586
Open surgery	1	
Laparoscopic surgery	0.956 (0.837–1.092)	0.506
Tumour location right	1	
Tumour location left	0.568 (0.511–0.633)	<0.0001
pT1	1	
pT2	2.750 (2.168–3.487)	<0.0001
pT3	6.016 (4.879–7.418)	<0.0001
pT4	6.317 (4.950–8.063)	<0.0001
Year of diagnosis	1.480 (1.445–1.516)	<0.0001

compilation of data merged from two different population-based national registers. Moreover, the patients, a priori, have had a uniform treatment since the treatment of colon cancer in Denmark was standardized following the recommendation by the DCCG.

There were some limitations to the study. First, it is not possible in an observational study to tell whether the findings are associations rather than causal relationships. Secondly, we found missing data on BMI in 28 % of the patients.

In spite of these limitations, our study has demonstrated that the probability for achieving an LNY ≥ 12 as recommended by the AJCC is significantly associated with lower age, high pT stage, right-sided tumours and elective surgery.

Further research should consider whether age, pT stage and tumour location should be taken into account when the recommended LNY of the surgical specimen in colon cancer is decided.

Moreover, we found that an increased awareness of the disease brought about by a national institution like DCCG, including introduction of multidisciplinary teams, centralization of surgical departments treating colon cancer and the development of national guidelines, is associated with the quality of the surgical specimen with regard to a sufficient LNY.

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