



The prognostic value of lymph node ratio in a national cohort of rectal cancer patients

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Abstract

Objective: To analyze the prognostic implications of the lymph node ratio (LNR) in curative resected rectal cancer.

Summary Background Data: It has been proposed that the LNR has a high prognostic impact in colorectal cancer, but the lymph node ratio has not been evaluated exclusively for rectal cancer in a large national cohort study.

Methods: All 6793 patients in Denmark diagnosed with stage I to III adenocarcinoma of the rectum, and so treated in the period from 2003 to 2011, were included in the analysis. The cohort was divided into two groups according to whether or not neo-adjuvant treatment had been given.

Results: In a multivariate analysis the pN status, ypN status and lymph node yield were found to be independent prognostic factors for overall survival, irrespective of neo-adjuvant therapy. The LNR was also found to be a significant prognostic factor with a Hazard Ratio ranging from 1.154 (95% CI: 0.930–1.432) (LNR: 0.01–0.08) to 2.974 (95% CI: 2.452–3.606) (LNR > 0.5) in the group of patients who had surgery to begin with and from 1.381 (95% CI: 0.891–2.139) (LNR: 0.01–0.08) to 2.915 (95% CI: 2.244–3.787) (LNR > 0.5) in the group of patients who had neo-adjuvant treatment.

Conclusions: The LNR reflects the influence on survival from N-status and the lymph node yield and since LNR was shown to be a significant prognostic predictor for overall survival in patients with curatively resected stage III rectal cancer irrespective of neo-adjuvant therapy we recommend that the introduction of LNR should be considered for rectal cancer in a revised TNM classification.

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Keywords: Rectal cancer; Lymph node ratio; Survival; Neo adjuvant therapy; Lymph node yield

Introduction

In rectal cancer the occurrence of metastatic lymph nodes (MLN) is a strong prognostic factor and the current, 7th AJCC, nodal staging system is primarily based on the number of MLN.¹ Moreover the appearance of MLN in the surgical specimen of rectal cancer is a major determinant of the need for adjuvant therapy.²

According to the 7th AJCC staging system, examination of a sufficient number of lymph nodes (LNs), a minimum of 12 in both colon and rectal cancer, is essential for

avoiding nodal under-staging (UICC Stage I–II disease vs. UICC Stage III disease). Moreover it has been demonstrated that the lymph node yield (LNY) achieved during rectal cancer resection is associated with survival,^{3,4} but so far its impact as a prognostic factor in rectal cancer has been debated.^{5–7} Nevertheless, in a recently published study we have demonstrated that a high LNY is associated with improved survival in UICC stage I–III rectal cancer.⁸ The LNY has not been incorporated in the current staging system; a way of achieving this is by using the lymph node ratio (LNR), defined as the ratio of MLN to the total LNY in the surgical specimen. In recent years, the LNR has gained increasing attention in colorectal cancer research. In colon cancer the LNR has demonstrated a promising prognostic value,^{9–13} but so far only a limited number of studies

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concerning the relevance of LNR exclusively for rectal cancer have been published, together with mixed studies for both colon and rectal cancer.^{14–18}

The assessment of LNR in rectal cancer is more complex than in colon cancer since a number of the patients have had neo-adjuvant therapy and it has been demonstrated that the proportion of patients with an LNY larger than or equal to the recommended 12 LNs is smaller in rectal cancer patients who have received neo-adjuvant therapy compared to those who have had surgery to begin with.¹⁹ Moreover, it has been demonstrated that a reduced number of MLNs are identified in the surgical specimens from rectal cancer patients who have received neo-

adjuvant therapy, indicating that neo-adjuvant therapy somehow sterilizes the MLNs in some of the patients with rectal cancer²⁰ which may weaken the accuracy of the N-staging in those patients.

To our knowledge, the relevance of LNR as a prognostic factor exclusively for rectal cancer has not yet been established in a large-scale national study.

Aim

The study aimed to examine the association between the LNR and survival in a national cohort of radically resected rectal cancer patients with UICC Stage III disease.

Table 1
Patient (n = 6793) and tumor characteristics.

	Surgery initially n(%) = 4670 (68.8)	NAT n(%) = 2123 (31.2)	Total n= 6793
Gender n(%)			
Male	2782 (59.6)	1355 (63.8)	4237 (60.9)
Female	1888 (40.4)	768 (36.2)	2656 (39.1)
Age years median (IQR)	69 (61–77)	66 (58–72)	68 (60–75)
<60	949 (20.3)	614 (28.9)	1563 (23.0)
61–75	2202 (47.2)	1135 (53.5)	3337 (49.1)
>75	1519 (32.5)	374 (17.6)	1893 (27.9)
ASA: n(%)			
1	1163 (25.2)	548 (26.3)	1711 (25.5)
2	2609 (56.5)	1223 (31.9)	3832 (57.2)
3	793 (17.2)	298 (14.3)	1091 (16.3)
4	54 (1.2)	11 (0.5)	65 (1.0)
N-Status n(%)			
N0	2953 (63.2)	1450 (68.3)	4403 (64.8)
N1	1016 (21.8)	432 (20.3)	1448 (21.3)
N2	701 (15.0)	241 (11.4)	942 (13.9)
UICC Stage III disease n(%)	1717 (36.8)	673 (31.7) (p < 0.0001)*	2390 (35.2)
T-stage n(%)			
ypT0		84 (4.0)	84 (1.2)
pT1/ypT1	367 (7.9)	131 (6.2)	498 (7.3)
pT2/ypT2	1161 (24.9)	535 (25.2)	1696 (25.0)
pT3/ypT3	2807 (60.1)	1170 (55.1)	3977 (58.5)
pT4/ypT4	315 (6.7)	173 (8.1)	488 (7.2)
Missing value	20 (0.4)	30 (1.4)	50 (0.7)
LNY UICC Stage I–III median (IQR)	15 (10–22)	10 (6–15) (p < 0.0001)**	13 (9–20)
LNY UICC Stage III median (IQR)	16 (12–24)	12 (8–16) (p < 0.0001)**	15 (10–21)
LNY UICC Stage I–III </>=12 n(%)			
<12	1440 (30.8)	1225 (57.7) (p < 0.0001)*	2665 (39.2)
>=12	3230 (69.2)	898 (42.3)	4128 (60.8)
LNY UICC Stage III </>=12 n(%)			
<12	404 (23.5)	329 (44.9) (p < 0.0001)*	733 (30.7)
>=12	1313 (76.5)	344 (51.1)	1657 (69.3)
Lymphnode ratio n(%)			
LNR0 (UICC Stage I–II)	2944 (63.2)	1444 (68.3)	4388 (64.8)
LNR1 (0.01–0.08)	422 (9.1)	93 (4.4)	515 (7.6)
LNR2 (0.09–0.25)	668 (14.3)	246 (11.6)	914 (13.5)
LNR3 (0.26–0.50)	394 (8.5)	201 (9.5)	595 (8.8)
LNR4 (>0.50)	233 (5.0)	131 (6.2)	364 (5.4)
Types of surgery n(%)			
Open	3360 (71.9)	1688 (79.5)	5048 (74.3)
Laparoscopy	1310 (28.1)	435 (20.5)	1745 (25.7)
Blood transfusion: n(%)	989 (21.3)	582 (27.5)	1571 (23.2)

ASA, American Society of Anesthesiologists; LNY, lymph node yield; -NAT, Neo-adjuvant therapy not received; +NAT, Neo-adjuvant therapy received.

* Fisher's exact test.

** Mann–Whitney's test.

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