Histopathology

Histopathology 2024 DOI: 10.1111/his.15134

Lymph node regression after neoadjuvant chemoradiotherapy in rectal cancer

Sonay K Ozturk,[1] Cristina G Martinez,[1] David Mens,[2] Cornelis Verhoef,[2] Miriam Tosetto,[3] Kieran Sheahan,[3] Johannes H W de Wilt,[4] Geke A P Hospers,[5] Cornelis J H van de Velde,[6] Corrie A M Marijnen,[7] Rachel S van der Post[1] & Iris D Nagtegaal[1]

[1]*Department of Pathology, Radboud University Medical Centre, Nijmegen,* [2]*Department of Surgical Oncology, Erasmus Medical Centre, Rotterdam, the Netherlands,* [3]*Department of Pathology, St Vincent's University Hospital, Dublin, Ireland,* [4]*Department of Surgical Oncology, Radboud University Medical Centre, Nijmegen,* [5]*Department of Oncology, University Medical Centre Groningen, Groningen,* [6]*Department of Surgery and* [7]*Department of Radiotherapy, Leiden University Medical Centre, Leiden, the Netherlands*

Date of submission 17 September 2023
Accepted for publication 18 December 2023

Ozturk S K, Martinez C G, Mens D, Verhoef C, Tosetto M, Sheahan K, de Wilt J H W, Hospers G A P, van de Velde C J H, Marijnen C A M, van der Post R S & Nagtegaal I D (2024) *Histopathology*. https://doi.org/10.1111/his.15134

Lymph node regression after neoadjuvant chemoradiotherapy in rectal cancer

Aims: Lymph node metastases (LNM) are one of the most important prognostic indicators in solid tumours and a major component of cancer staging. Neoadjuvant therapy might influence nodal status by induction of regression. Our aim is to determine the prevalence and role of regression of LNM on outcomes in patients with rectal cancer.

Methods and results: Four independent study populations of rectal cancer patients treated with similar regimens of chemoradiotherapy were pooled together to obtain a total cohort of 469 patients. Post-treatment nodal status (ypN) and signs of tumour regression (Reg) were incorporated to form three-tiered (ypN− Reg+, ypN− Reg− and ypN+) and four-tiered (ypN− Reg+, ypN− Reg−, ypN+ Reg+ and ypN+ Reg−) classifications. In our cohort, 31% of patients presented with ypN+ rectal cancer. As expected, we found significantly worse overall survival (OS) in ypN+ patients compared to ypN− patients ($P = 0.002$). The percentage of ypN− patients with lymph nodes with complete regression was 20% in our cohort. While node-negative patients with and without regression had similar OS ($P = 0.09$), disease-free survival (DFS) was significantly better in node-negative patients with regression ($P = 0.009$).

Conclusions: Regression in lymph nodes is frequent, and node-negative patients with evidence of lymph node regression have better DFS compared to node-negative patients without such evidence.

Keywords: lymph node metastases, lymph node regression, neoadjuvant chemoradiotherapy, patterns of response, rectal cancer

Introduction

Lymph node metastases (LNM) are one of the oldest and most important prognostic indicators of tumour recurrence and patient survival in rectal cancer.[1] After neoadjuvant therapy, treatment effects can be observed in both primary tumours as well as LNM.[2] Traditional tumour regression grading (TRG) systems categorise the amounts of regressive changes after therapy in the primary tumour, mainly based on the principle of the ratio of therapy-induced fibrosis in relation to residual tumour. Response is often also

Address for correspondence: I D Nagtegaal, Department of Pathology, Radboud University Medical Centre, the Netherlands. e-mail: iris.nagtegaal@radboudumc.nl

observed in LNM, but due to the lack of reliable larger studies, clinical implications are unclear.

In 2007 Caricato *et al.*[3] first described lymph node regression grade (LRG) but did not establish its clinical relevance. Since then, a wide variety of methods has been applied to determine the impact of LRG on patient prognosis.[2,4–23] Some methods are based on Mandard's fibrosis–tumour ratio classification,[24] with diverse scales of this ratio (ranging from three to six tiers), using cumulative[7,20,21] or maximum scores.[16] Simplification into major and minor histological response have also shown interesting results in patients with oesophageal cancer,[11,18] but do not allow for clear-cut identification of complete regression patients.

A second issue is the variability in reporting LRG in the literature. Various terms are used, such as 'sterilised lymph nodes', 'downstaged N0 versus natural N0', 'pretreatment nodal stage' and 'regressive lymph nodes', all of which indicate regressed LNM with a complete pathological response. Upon histological review, these LNs present without tumour cells but tumour remnants are present, including fibrosis, mucin pools (for adenocarcinomas) and keratin pearls (for squamous cell carcinomas). These lymph nodes are classified as tumour-negative in the current TNM staging system.[25]

The reported incidence of patients with negative lymph nodes with signs of regression in rectal cancer ranges between 9 and 51%.[2–4,14,16] This wide range and the lack of clarity in the definition of lymph node regression suggest that this phenomenon is underreported. In this study, we aimed to determine the prevalence of regression of lymph node metastases in rectal cancer and the impact of its presence on outcome.

Materials and Methods

STUDY POPULATIONS

A retrospective cohort study was carried out by pooling four cohorts. Patients with locally advanced rectal adenocarcinoma receiving neoadjuvant chemoradiotherapy (CRT) were selected and included if all retrieved lymph nodes were available for review. Before surgery, patients from the Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) clinical trial received 25 × 1.8 Gy or 25 × 2 Gy + capecitabine; patients from Radboud University Medical Centre, the Netherlands and Erasmus Medical Center, the Netherlands received 50–50.4 Gy + capecitabine. Patients from St Vincent's University Hospital, Dublin, Ireland received 25 × 1.8 Gy + capecitabine and oxaliplatin (CAPOX) followed by surgery. The ethical standards of the research ethics committee and the Helsinki Declaration were thoroughly met.

LN REGRESSION GROUP DEFINITIONS

We scored tumour presence (ypN) and regression (Reg) in lymph nodes separately to create four different groups: ypN− Reg− (patients with negative lymph nodes without signs of regression), ypN− Reg+ (patients with negative lymph nodes with signs of regression), ypN+ Reg+ (patients with at least one positive lymph node and in other lymph nodes complete regression) and ypN+ Reg− (patients with at least one positive lymph node without signs of regression in other nodes) (Table 1).

PATHOLOGICAL EXAMINATION

Complete slide sets of surgical rectal resection specimens of all patients were collected and scanned. Two independent researchers (trained researcher C.G.M. and pathologist S.K.O.) reviewed all cases for signs of histological regression in lymph nodes, such as mucin pools and fibrosis (examples in Figure 1). Clinical and follow-up information, including clinical tumour necrosis metastasis (TNM) staging (8th edition), vital

Table 1. Definitions regarding patient groups according to LNM and regression status

Group	Definition	LNM Y/N	Regression Y/N
ypN−Reg− 'never positive'	Patients with negative lymph nodes and showing no signs of regression in any node	No	No
ypN−Reg+ 'formerly positive'	Patients with negative lymph nodes with signs of regression in at least one node	No	Yes
ypN+Reg− 'currently positive'	Patients with at least one positive lymph node showing no signs of regression in any node	Yes	No
ypN+Reg+ 'currently positive'	Patients with at least one positive lymph node and showing signs of regression in at least one node.	Yes	Yes

LNM, lymph node metastases; Y/N, yes/no.

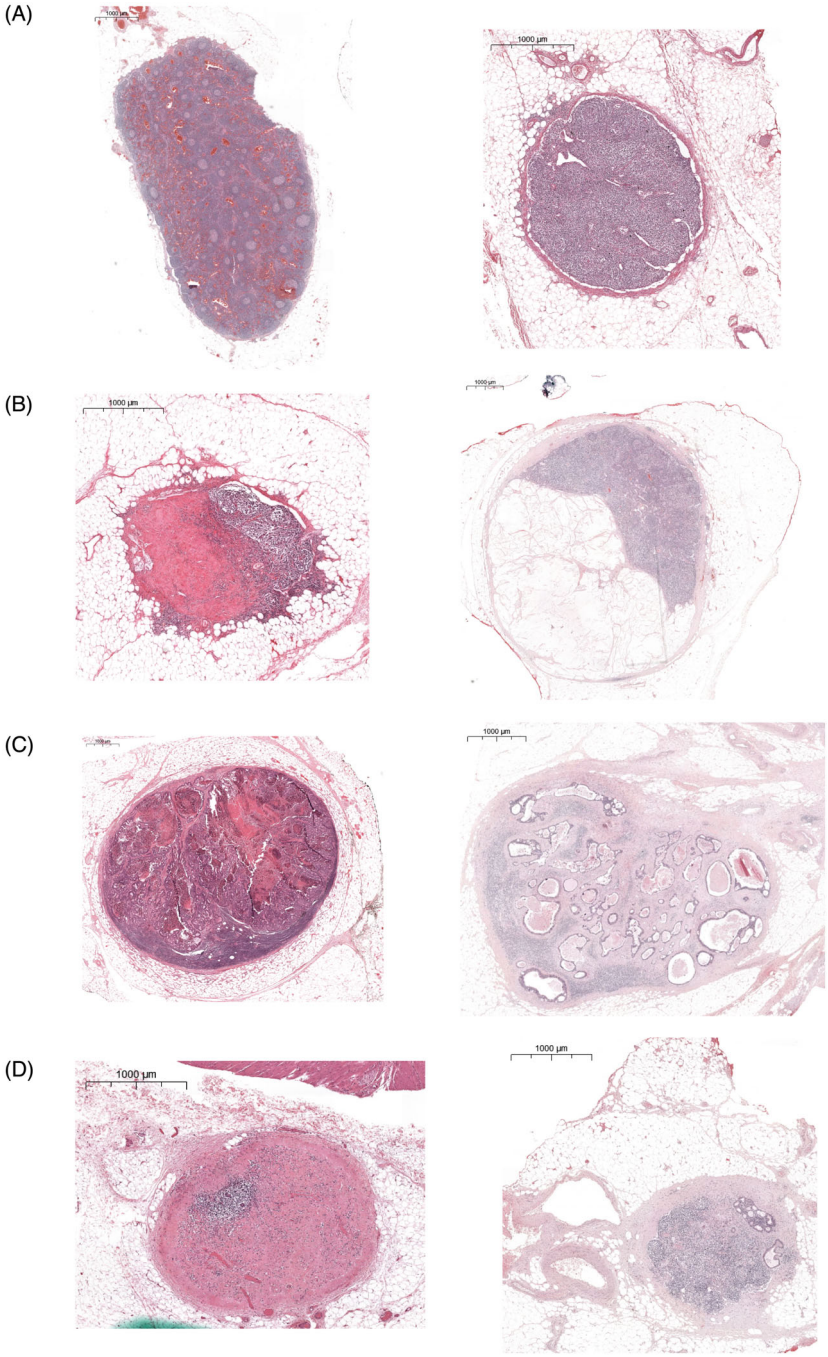

Figure 1. Histological examples of regression: **A**, ypN−Reg− lymph node. **B**, ypN−Reg+ lymph node (with parenchymal fibrosis in the left case and obvious mucin on the right case). **C**, ypN+Reg− lymph node. **D**, ypN+Reg+ lymph node.

status and date of loco-regional or distant disease recurrence were collected from individual medical records when available. Additional macroscopy and microscopy data relevant for assessment, such as pathological stage, were retrieved from institutional pathology databases. TRG (tumour regression grading) was scored according to Dworak[26] and College of American Pathologists[27]/Ryan[28] classifications on the primary tumour site. The histological pattern of tumour response on the primary tumour was scored as either shrinkage or fragmentation according to our recently published method[29] for all cases.

STATISTICAL ANALYSIS

RStudio (2020) was used for all analyses, and a second researcher confirmed results using SPSS Statistics version 25.0 (IBM Corporation, Armonk, NY, USA). Student's t-test and the χ^2 test were used for evaluation of the association between LN regression groups and clinical–pathological parameters. Overall survival (OS) was defined as time from surgery to death or end of follow-up. Disease-free survival (DFS) was defined as time to distant and/or loco-regional recurrence and/or death or end of follow-up (censored). The Kaplan–Meier method was used for survival probabilities, and the log-rank test was used for comparison of survival curves. Univariate and multivariate Cox regression analyses were performed to evaluate the differences in OS. Both three-tiered (ypN− Reg+, ypN− Reg− and ypN+) and four-tiered (ypN− Reg+, ypN− Reg−, ypN+ Reg+ and ypN+ Reg−) classifications were employed in the comparisons. In the multivariate analyses we included all variables that were significant in the univariate analysis. As TRG and pattern of response are strongly correlated, we included only patterns of response to the analysis. To avoid overestimation of dependent variables, we conducted several combinations of these variables (e.g. including the three-tier classification in one analysis and the four-tier in another). For all tests, a $P < 0.05$ was considered statistically significant.

Results

STUDY POPULATION

The pooled cohort consisted of 469 patients. Of these, 124 patients were from the standard arm of the RAPIDO clinical trial, 77 patients from St Vincent's University Hospital, Dublin, 238 from the Erasmus University Medical Center in Rotterdam and 30 patients from the Radboud University Medical Centre (Nijmegen). Survival data were available for 327 patients, and recurrence data were available for 301 patients. The clinicopathological characteristics per lymph node regression group are summarised in Table 2. By definition, nodal status was different between the four groups, both clinical (cN) and pathological (ypN) categories ($P < 0.001$ in both cases). The majority of ypN−Reg− patients were initially scored as cN+ according to their radiological findings (125 of 199 cases with known cN status, 63%). One-third of the patients showed regression in at least one lymph node (164 of 469 Reg+, 35%), while 20% of the patients presented with complete response in their lymph nodes without signs of remaining metastasis (95 of 469, ypN−reg+).

CLINICOPATHOLOGICAL DIFFERENCES ASSOCIATED WITH REGRESSION AND NODE POSITIVITY

Node-positive groups with and without regression (ypN+Reg+ versus ypN+Reg−) presented similar clinicopathological characteristics. cN category was the only significantly different feature among node-negative groups, with more cN0 patients in ypN−Reg− (37%) than in ypNReg+ patients (21%, $P = 0.01$) (Table 2).

Differences were observed when comparing the ypN−Reg+ group to node-positive groups (ypN+Reg+ and ypN+Reg−). The patients who remained node-positive after treatment (ypN+Reg+ and ypN+Reg−) presented with more advanced cN, ypT stages and less tumour regression compared to the group with complete response in their lymph nodes (ypN−Reg+). Moreover, the incidence of patterns of response was significantly different between these groups, with more cases of fragmentation in the ypN+ groups (fragmentation, 77% in ypN+ versus 50% in ypN−Reg+; shrinkage, 6% in ypN+ versus 32% in ypN−Reg+, $P < 0.001$) (Table 2).

OUTCOME IN RELATION TO REGRESSION STATUS

The three-tiered stratification showed a better 5-year OS (overall survival) in patients with ypN−Reg+ (85%) compared to ypN−Reg− (72%) and ypN+ patients (60%) (Figure 2A, $P < 0.005$). Similar results were obtained for DFS (5-year DFS 75% in ypN−Reg+, 58% in ypN−Reg− and 54% in ypN+, $P = 0.0044$, Figure 2B). In the node-negative group, the presence of regression was significantly associated with better DFS ($P = 0.009$, Figure 3B), although it did not reach significance in OS ($P = 0.09$, Figure 3A).

Using the four-tiered classification, we again observed significant differences in both OS ($P = 0.005$, Figure 4A) and DFS ($P = 0.013$, Figure 4B). There were no significant differences between the groups with positive nodes according to the presence of regression.

UNIVARIATE AND MULTIVARIATE ANALYSIS

Univariate Cox regression analysis showed that well-established clinical and histological markers of poor survival were also prognostic in our cohort (Table 3):

Table 2. Clinicopathological characteristics of the included patients stratified by lymph node regression and lymph node metastatic status

Clinicopathological characteristics	Total n = 469 (100%)	ypN+ Reg+ n = 69 (15%)	ypN+ Reg− n = 76 (16%)	ypN− Reg+ n = 95 (20%)	ypN− Reg− n = 229 (49%)	P-values
Gender	340 (100%)					*0.44
Male	212 (62%)	62%	72%	54%	63%	#0.24
Female	128 (38%)	38%	28%	46%	37%	†0.10
Age, median	62 (18–88)	59 (25–88)	62 (23–81)	62 (18–83)	62 (35–86)	*0.64, #0.29, †0.79
cT category	327 (100%)					*0.68
T2	7 (2%)	4%	4%	1%	1%	#0.94
T3	194 (59%)	63%	71%	58%	56%	†0.21
T4	126 (39%)	33%	25%	41%	43%	
cN category	406 (100%)					*0.18
N0	102 (25%)	5%	12%	21%	37%	#0.01
N1	130 (32%)	32%	41%	30%	30%	†0.05
N2	174 (43%)	63%	47%	49%	33%	
yp T category	405 (100%)					*0.55
T0	44 (11%)	7%	6%	16%	11%	#0.83
T1	27 (7%)	4%	0%	9%	9%	†0.003
T2	81 (20%)	16%	16%	23%	21%	
T3	195 (48%)	55%	63%	38%	45%	
T4	58 (14%)	18%	15%	14%	14%	
yp N category	413 (100%)					*0.14
N0	286 (69%)	5%	0%	100%	100%	#1
N1	93 (23%)	67%	75%	0%	0%	†< 0.001
N2	34 (8%)	28%	25%	0%	0%	
yp M category	272 (100%)					*0.85
M0	236 (87%)	82%	86%	92%	87%	#0.47
M1	36 (13%)	18%	14%	8%	13%	†0.32
Response pattern	386 (100%)					*0.99
pCR	28 (7%)	4%	5%	11%	7%	#0.37
Shrinkage	83 (22%)	6%	7%	32%	25%	†< 0.001
Fragmented	243 (63%)	77%	76%	50%	61%	
No response	32 (8%)	13%	12%	7%	7%	
TRG CAP/Ryan	396 (100%)					*0.60

Table 2. (*Continued*)

Clinicopathological characteristics	Total *n* = 469 (100%)	ypN+ Reg+ *n* = 69 (15%)	ypN+ Reg− *n* = 76 (16%)	ypN− Reg+ *n* = 95 (20%)	ypN− Reg− *n* = 229 (49%)	*P*-values
0	28 (7%)	4%	5%	11%	7%	#0.35
1	47 (12%)	12%	6%	17%	11%	†0.006
2	236 (60%)	55%	52%	57%	64%	
3	85 (21%)	29%	37%	15%	18%	
Dworak TRG	386 (100%)					*0.53
0	32 (8%)	12.5%	12%	7%	6%	#0.53
1	49 (13%)	15%	27%	9%	10%	†0.03
2	230 (60%)	56%	49%	56%	65%	
3	47 (12%)	12.5%	7%	17%	12%	
4	28 (7%)	4%	5%	11%	7%	

*, #, †, Indicated *P*-values of ypN+ Reg+ versus ypN+ Reg−, ypN− Reg+ versus ypN− Reg− and ypN+ versus ypN− Reg+ groups, respectively.

lack of response in the primary tumour [hazard ratio (HR) = 4.82, 95% confidence interval (CI) = 2.19–10.60], a fragmented pattern of response (HR = 2.00, 95% CI = 1.14–3.50), a Dworak score of TRG0 (HR = 12.10, 95% CI = 1.55–94.11), presence of distant metastases (HR = 2.47, 95% CI = 1.46–4.18) and remaining LNM (ypN1, HR = 1.72, 95% CI = 1.11–2.66 and ypN2, HR = 2.09, 95% CI = 1.21–3.61) were found to be indicators of poor survival.

Multivariate analysis showed that the presence of distant metastases (HR = 2.48, 95% CI = 1.39–4.44) and tumour pattern of response (fragmented, HR = 2.23, 95% CI = 1.08–4.58 compared to shrinkage pattern) were the only independent prognostic markers of survival (Table 3).

Discussion

Our results show that 35% of patients show regression in at least one lymph node, while 20% of patients present with complete response in their lymph nodes. We analysed the relation of response with outcome in two ways with a three- and four-tiered classification, and found better disease-free survival (DFS) rates in patients with regression in the node-negative setting.

The three-tier system is the most investigated classification in both upper[6,8–10,12,13,15,17,30] and lower gastrointestinal tumours,[2,4,7,16] where node-negative patients with (ypN−Reg+) and without response (ypN−Reg−) are compared with ypN+ patients. In our cohorts, we observed that patients with ypN−Reg+ have at least similar OS to and even better DFS than those with never positive nodes (ypN−Reg−). Their relatively good outcome is in line with the findings of Tominaga *et al.* and Vychnevskaia *et al.*,[2,14] who reported improved survival in patients with lymph node (LN) regression compared to those without regression in ypN0.

Apparently, the higher aggressiveness of tumours, that is assumed by the presence of lymph node metastases (LNM), can be neutralised in a significant proportion of cases by neoadjuvant treatment. However, the lack of association with response in the primary tumour suggests that regression in LNM is an independent phenomenon. Moreover, complete response is more frequent in LNM compared to primary tumour [20% ypN-Reg + versus 7% pathological complete response (pCR)]. This might be directly related to the lower tumour burden in LNM compared to primary tumour.

Indeed, a mouse model study indicated the uniqueness of the immune microenvironment in lymph nodes compared to the primary tumour.[31] Researchers proved an increase or decrease in cytotoxic T cells in the case of primary tumour or tumour-draining lymph node irradiation, respectively. They suggested that tumour-draining LNs are

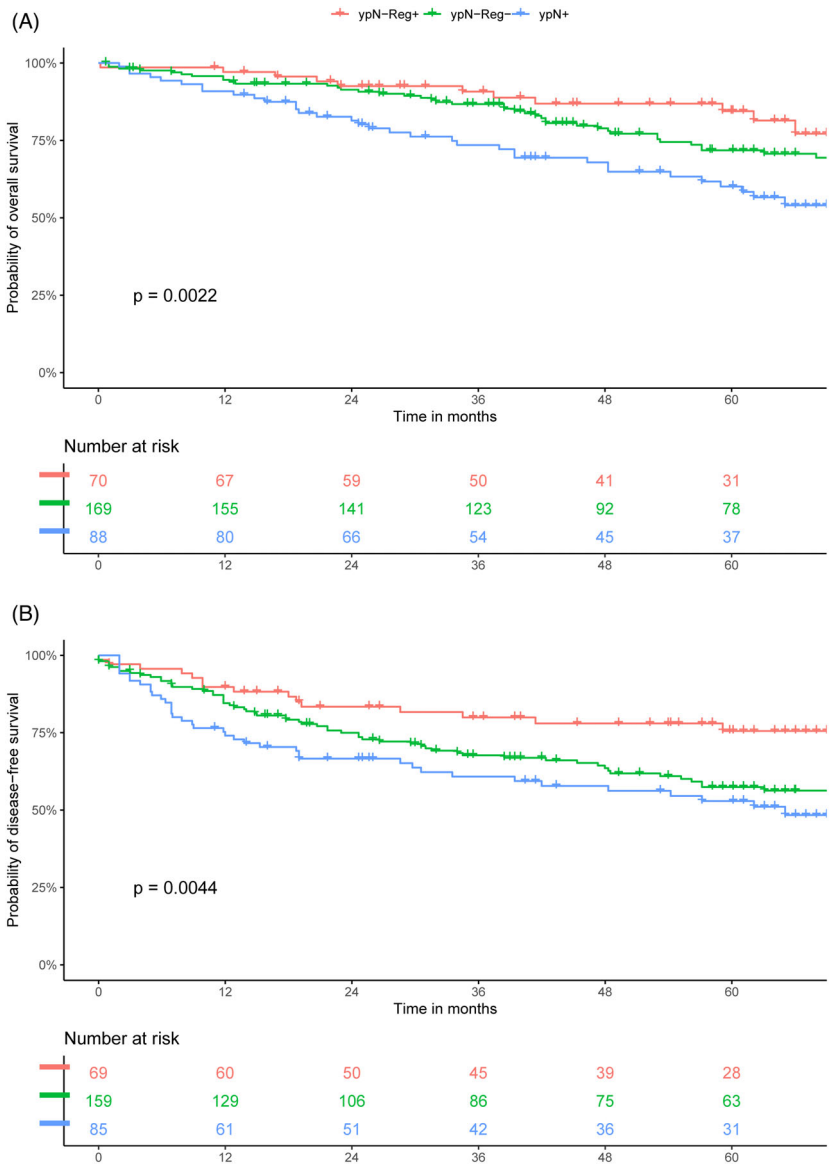

Figure 2. Overall survival (**A**) and disease-free survival (**B**) according to lymph node regression group (three-tier).

resources for cytotoxic T cells, which can promote the abscopal effect[31] – a systemic response resulting in the reduction of distant tumours in response to local treatment. The abscopal effect in LNM was also reported in clinical studies in various organ tumours, including rectal cancer following local treatment of the primary tumour.[32–34] This suggests that the abscopal effect might be more pronounced in LNM compared to the primary tumour due to their distinctive immune microenvironment.

Another potential reason why LNM respond to neoadjuvant therapy independent from primary tumour might be their molecular divergence. Several CRC studies indicated the heterogeneity in mutations and copy number changes in primary tumour and LNM,[35–38] probably due to the late-onset molecular alterations occurring in LNM.

Our careful examination of all lymph nodes supports the large gap observed between clinical node staging and pathological staging, with clinical node positivity suspected in 63% of the cases where nodes were negative without any indication of regression (ypN−Reg−).[39] There are several explanations for this large gap. First, and most importantly, the clinical nodal staging is inaccurate in recognising LNM.[39] Secondly, it has been suggested that, based on the

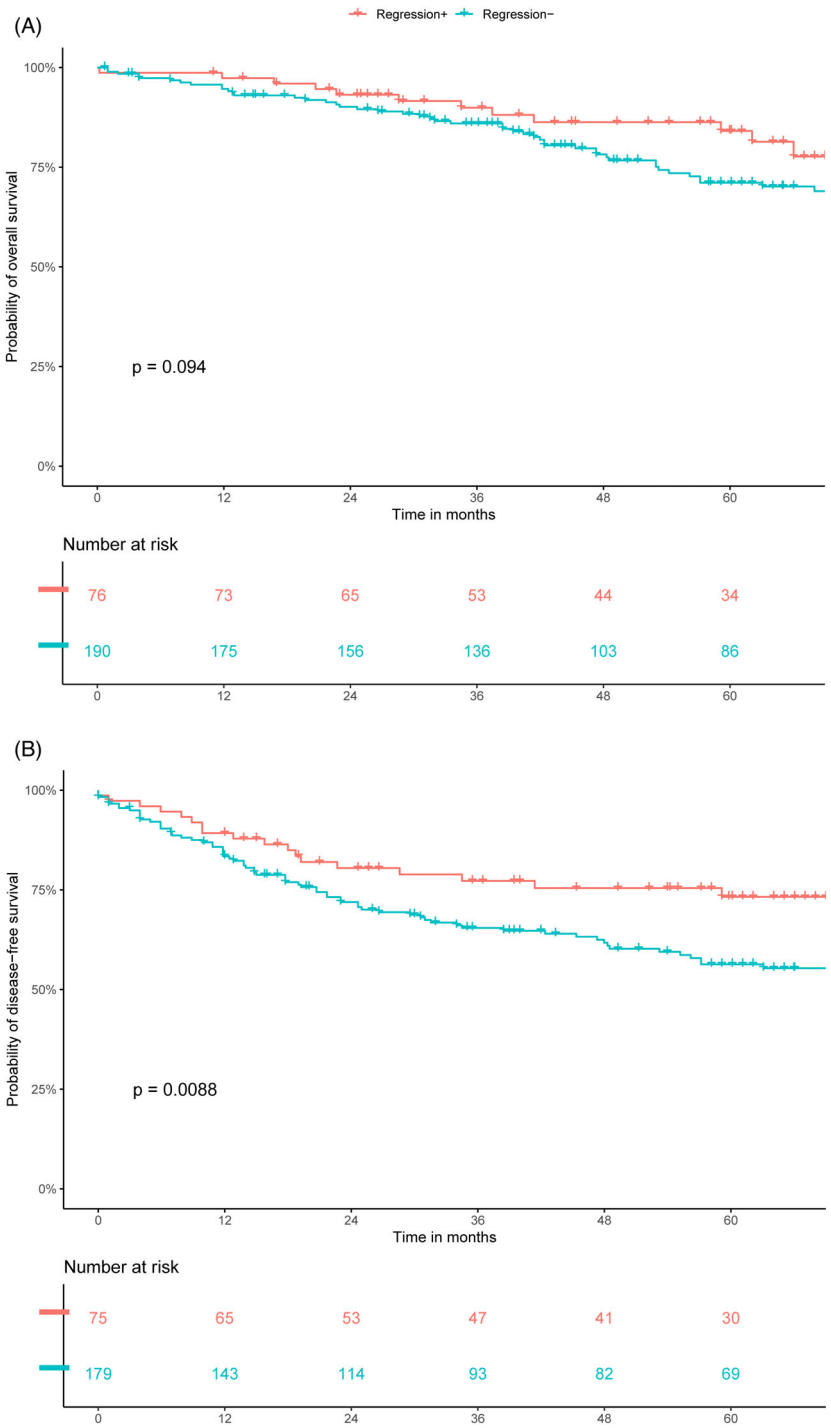

Figure 3. Overall survival (**A**) and disease-free survival (**B**) according to lymph node regression in node-negative patients.

lower numbers of lymph nodes detected after neoadjuvant therapy, several nodes can disappear.[40] In a study with short-term radiotherapy, we have shown that metastatic lymph nodes are indeed smaller after treatment.[41] Therefore, in theory, some of the positive nodes might be eliminated, leaving only the original negative nodes intact. Lastly, as lymph nodes are three-dimensional objects, there might be a possibility

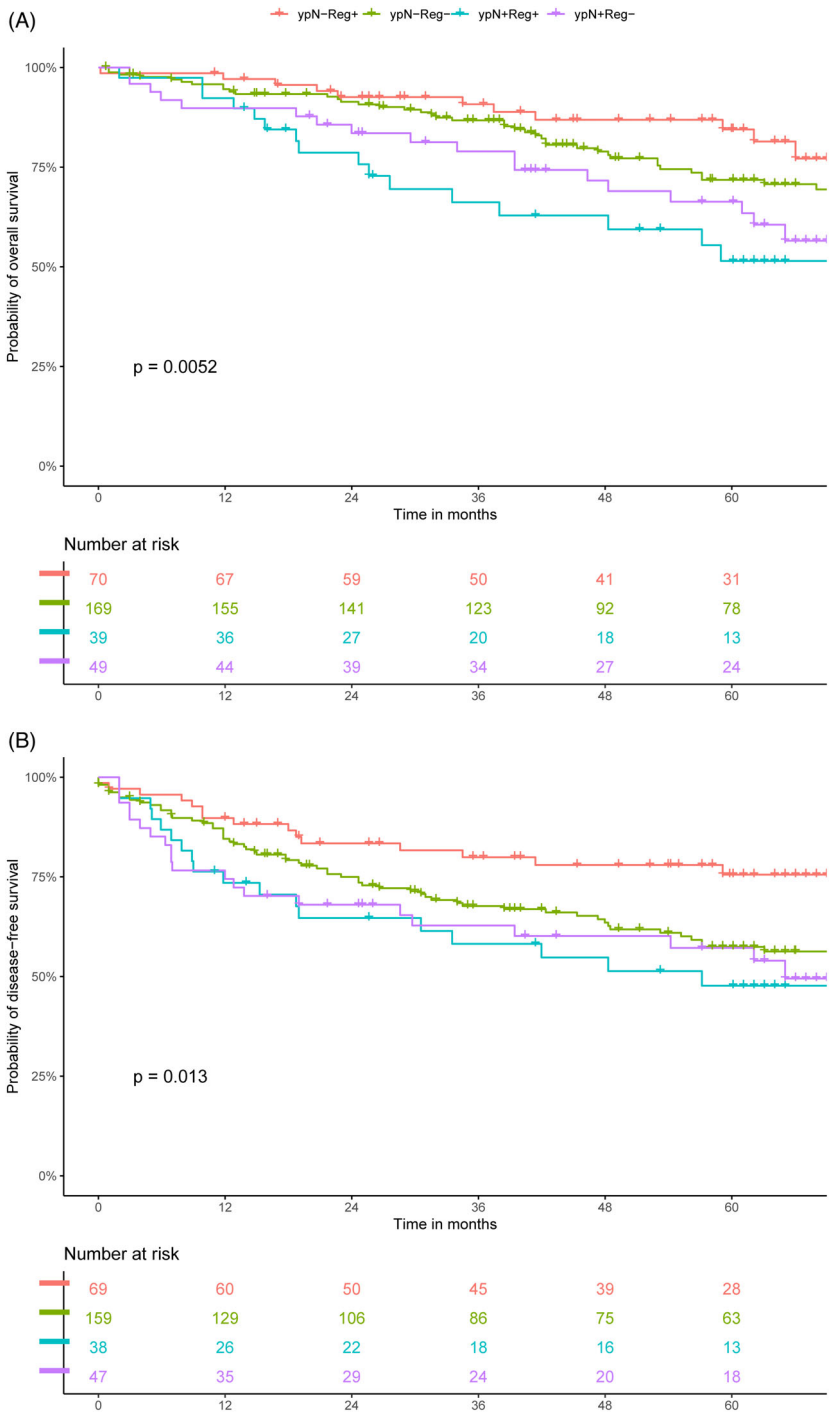

Figure 4. Overall survival (**A**) and disease-free survival (**B**) according to lymph node regression group (four-tier).

of missing focal regression changes during two-dimensional pathological examination.

Node-negative patients after neoadjuvant therapy constitute a heterogeneous group, including both patients with low-stage cancers that did not spread to the lymph nodes and those with clinical stage 3 disease, where LNM have responded very well to treatment. It is intriguing to observe better DFS in patients who were initially diagnosed with more advanced-stage disease in our study. The response in

Table 3. Univariate and multivariate survival analysis for overall survival

	Total (*n*)	Univariate HR (95% CI)	Multivariate (4-tiered) HR (95% CI)	Multivariate (3-tiered)
Pattern of response	327			
pCR	14	0.39 (0.05–3.00)	0.34 (0.04–2.74)	0.35 (0.04–2.78)
Shrinkage	78	1.00	1.00	1.00
Fragmented	212	2 (1.14–3.50)	2.24 (1.09–4.62)	2.23 (1.08–4.58)
No response	23	4.82 (2.19–10.60)	2.79 (0.93–8.38)	2.71 (0.90–8.17)
TRG Dworak	327			
0	23	12.10 (1.55–94.11)		
1	39	5.32 (0.69–40.98)		
2	207	3.96 (0.54–28.68)		
3	44	4.85 (0.64–36.60)		
4	14	1.00		
LN 4-tier	469			
ypN+				
Reg+	69	2.04 (1.23–3.38)	0.63 (0.16–2.46)	
Reg−	76	1.25 (0.76–2.05)	0.45 (0.11–1.80)	
ypN−				
Reg+	95	0.59 (0.34–1.09)	0.69 (0.31–1.55)	
Reg−	229	1.00	1.00	
yp M category	272			
M0	236	1.00	1.00	1.00
M1	36	2.47 (1.46–4.18)	2.49 (1.40–4.45)	2.48 (1.39–4.44)
yp N category	375			
N0	263	1.00	1.00	1.00
N1	80	1.72 (1.11–2.66)	2.34 (0.65–8.33)	2.28 (0.63–8.28)
N2	32	2.09 (1.21–3.61)	4.06 (0.93–17.74)	3.98 (0.89–17.79)
LN 3-tier	469			
ypN+	145	1.54 (1.03–2.30)		0.53 (0.14–2.05)
ypN− Reg+	95	0.59 (0.32–1.09)		0.69 (0.30–1.55)
ypN− Reg−	229	1.00		1.00

pCR, pathological complete response; TRG, tumour regression grade; LN, lymph node; HR, hazard ratio; CI, confidence interval.

LNM after immunotherapy can guide treatment decisions in melanoma,[42] and further studies in rectal cancer are necessary to evaluate whether this is also true in this setting.

In conclusion, we have shown that node-negative patients with evidence of lymph node regression after neoadjuvant therapy in rectal cancer are present in 20% of cases, associated with a good outcome.

Acknowledgements

This study was supported by a KWF programme grant (KWF 2016-2-10602).

Conflicts of interest

All authors declare that they have no conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Bacon HE, McElwain JW, Trimpi HD. Surgical management of large bowel lesions. *Bull. N. Y. Acad. Med.* 1953; **29**; 34–46.
2. Tominaga T, Akiyoshi T, Tominaga NY *et al*. Prognostic value of metastatic lymph node regression grade after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer. *Surgery* 2019; **166**; 1061–1067.
3. Caricato M, Ausania F, Caricato ED *et al*. Tumor regression in mesorectal lymph nodes after neoadjuvant chemoradiation for rectal cancer. *Eur. J. Surg. Oncol.* 2007; **33**; 724–728.
4. Manceau G, Margot N, Manceau JA *et al*. YpN0 rectal cancer patients with sterilized lymph nodes after neoadjuvant chemoradiotherapy are of greater risk of recurrence. *Dig. Liver Dis.* 2020; **52**; 214–220.
5. Pereira MA, Ramos MFKP, Pereira ARD *et al*. Lymph node regression after neoadjuvant chemotherapy: a predictor of survival in gastric cancer. *J. Surg. Oncol.* 2020; **121**; 795–803.
6. Zhong J, Wang K, Fang S, Fu J. Prognostic impact of sterilized lymph nodes in esophageal squamous cell carcinomas after neoadjuvant chemoradiotherapy. *Eur. J. Surg. Oncol.* 2021; **47**; 3074–3080.
7. Cui J, Zhang L, Yang L *et al*. The prognostic significance of the treatment response of regional lymph nodes and the refinement of the current TNM staging system in locally advanced rectal cancer after neoadjuvant chemoradiotherapy. *Cancer Med.* 2020; **9**; 9373–9384.
8. Brinkmann S, Noordman BJ, Hölscher AH *et al*. External validation of pretreatment pathological tumor extent in patients with neoadjuvant chemoradiotherapy plus surgery for esophageal cancer. *Ann. Surg. Oncol.* 2020; **27**; 1250–1258.
9. Nieman DR, Peyre CG, Watson TJ *et al*. Neoadjuvant treatment response in negative nodes is an important prognosticator after esophagectomy. *Ann. Thorac. Surg.* 2015; **99**; 277–283.
10. Shapiro J, Biermann K, van Klaveren D *et al*. Prognostic value of pretreatment pathological tumor extent in patients treated with neoadjuvant chemoradiotherapy plus surgery for esophageal or junctional cancer. *Ann. Surg.* 2017; **265**; 356–362.
11. Schneider PM, Baldus SE, Metzger R *et al*. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. *Ann. Surg.* 2005; **242**; 684–692.
12. Zanoni A, Verlato G, Giacopuzzi S *et al*. ypN0: does it matter how you get there? Nodal downstaging in esophageal cancer. *Ann. Surg. Oncol.* 2016; **23**; 998–1004.
13. Donohoe CL, O'Farrell NJ, Grant T *et al*. Classification of pathologic response to neoadjuvant therapy in esophageal and junctional cancer: assessment of existing measures and proposal of a novel 3-point standard. *Ann. Surg.* 2013; **258**; 784–792.
14. Vychnevskaia K, Dumont F, Agostini J *et al*. Prognostic value of sterilized lymph nodes after preoperative chemoradiotherapy for patients with ypN0 rectal cancer. *Ann. Surg. Oncol.* 2017; **24**; 1304–1311.
15. Hsu PK, Yeh YC, Chien L, Huang CS, Hsu HS. Clinicopathological significance of pathologic complete lymph node regression after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. *Ann. Surg. Oncol.* 2021; **28**; 2048–2058.
16. Mirbagheri N, Kumar B, Deb S *et al*. Lymph node status as a prognostic indicator after preoperative neoadjuvant chemoradiotherapy of rectal cancer. *Colorectal Dis.* 2014; **16**; O339–O346.
17. Zhu YL, Sun YK, Xue XM, Yue JY, Yang L, Xue LY. Unnecessity of lymph node regression evaluation for predicting gastric adenocarcinoma outcome after neoadjuvant chemotherapy. *World J. Gastrointest. Oncol.* 2019; **11**; 48–58.
18. Bollschweiler E, Hölscher AH, Metzger R *et al*. Prognostic significance of a new grading system of lymph node morphology after neoadjuvant radiochemotherapy for esophageal cancer. *Ann. Thorac. Surg.* 2011; **92**; 2020–2027.
19. Davies AR, Myoteri D, Zylstra J *et al*. Lymph node regression and survival following neoadjuvant chemotherapy in oesophageal adenocarcinoma. *Br. J. Surg.* 2018; **105**; 1639–1649.
20. Choi JP, Kim SJ, Park IJ *et al*. Is the pathological regression level of metastatic lymph nodes associated with oncologic outcomes following preoperative chemoradiotherapy in rectal cancer? *Oncotarget* 2017; **8**; 10375–10384.
21. Sun Y, Wu X, Lin H, Lu X, Huang Y, Chi P. Lymph node regression to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer: prognostic implication and a predictive model. *J. Gastrointest. Surg.* 2021; **25**; 1019–1028.
22. Hagens E, Tukanova K, Jamel S *et al*. Prognostic relevance of lymph node regression on survival in esophageal cancer: a systematic review and meta-analysis. *Dis. Esophagus* 2022; **35**; doab021.
23. He L, Xiao J, Zheng P, Zhong L, Peng Q. Lymph node regression grading of locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy. *World J. Gastrointest. Oncol.* 2022; **14**; 1429–1445.
24. Mandard AM, Dalibard F, Mandard JC *et al*. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer* 1994; **73**; 2680–2686.
25. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours*. 8th ed. Oxford, UK: Wiley-Blackwell, 2017; 55–105.
26. Dworak O, Keilholz L, Hoffmann A. Pathological features of rectal cancer after preoperative radiochemotherapy. *Int. J. Colorectal Dis.* 1997; **12**; 19–23.
27. Mace AG, Pai RK, Stocchi L, Kalady MF. American Joint Committee on Cancer and College of American Pathologists regression grade: a new prognostic factor in rectal cancer. *Dis. Colon Rectum* 2015; **58**; 32–44.
28. Ryan R, Gibbons D, Hyland JMP *et al*. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005; **47**; 141–146.

29. Kus Ozturk S, Graham Martinez C, Sheahan K *et al*. Relevance of shrinkage versus fragmented response patterns in rectal cancer. *Histopathology* 2023; **83**; 870–879.
30. Bausys A, Senina V, Luksta M *et al*. Histologic lymph nodes regression after preoperative chemotherapy as prognostic factor in non-metastatic advanced gastric adenocarcinoma. *J. Cancer* 2021; **12**; 1669–1677.
31. Buchwald ZS, Nasti TH, Lee J *et al*. Tumor-draining lymph node is important for a robust abscopal effect stimulated by radiotherapy. *J. Immunother. Cancer* 2020; **8**; e000867.
32. Shao C, Yang M, Pan Y *et al*. Case report: abscopal effect of microwave ablation in a patient with advanced squamous NSCLC and resistance to immunotherapy. *Front. Immunol.* 2021; **12**; 696749.
33. Ebner DK, Kamada T, Yamada S. Abscopal effect in recurrent colorectal cancer treated with carbon-ion radiation therapy: 2 case reports. *Adv. Radiat. Oncol.* 2017; **2**; 333–338.
34. Vilinovszki O, Andratschke N, Huellner M, Curioni-Fontecedro A, Kroeze SGC. True abscopal efect in a patient with metastatic non-small cell lung cancer. *Radiat. Oncol.* 2021; **16**; 194.
35. Ulintz PJ, Greenson JK, Wu R, Fearon ER, Hardiman KM. Lymph node metastases in colon cancer are polyclonal. *Clin. Cancer Res.* 2018; **24**; 2214–2224.
36. Puccini A, Seeber A, Xiu J *et al*. Molecular differences between lymph nodes and distant metastases compared with primaries in colorectal cancer patients. *NPJ Precis. Oncol.* 2021; **5**; 95.
37. Baldus SE, Schaefer KL, Engers R, Hartleb D, Stoecklein NH, Gabbert HE. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. *Clin. Cancer Res.* 2010; **16**; 790–799.
38. Del Carmen S, Sayagués JM, Bengoechea O *et al*. Spatiotemporal tumor heterogeneity in metastatic CRC tumors: a mutational-based approach. *Oncotarget* 2018; **9**; 34279–34288.
39. Brouwer NPM, Stijns RCH, Lemmens VEPP *et al*. Clinical lymph node staging in colorectal cancer; a flip of the coin? *Eur. J. Surg. Oncol.* 2018; **44**; 1241–1246.
40. Heijnen LA, Maas M, Beets-Tan RG *et al*. Nodal staging in rectal cancer: why is restaging after chemoradiation more accurate than primary nodal staging? *Int. J. Colorectal Dis.* 2016; **31**; 1157–1162.
41. Mekenkamp LJM, van Krieken JHJM, Marijnen CAM, van de Velde C, Nagtegaal ID, Pathology Review Committee and the Co-operative Clinical Investigators. Lymph node retrieval in rectal cancer is dependent on many factors—The role of the tumor, the patient, the surgeon, the radiotherapist, and the pathologist. *Am. J. Surg. Pathol.* 2009; **33**; 1547–1553.
42. Reijers ILM, Menzies AM, van Akkooi ACJ *et al*. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. *Nat. Med.* 2022; **28**; 1178–1188.