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Original Article

Prevalence of nodal involvement in rectal cancer after chemoradiotherapy

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Abstract

Background: The purpose of this study was to investigate the prevalence of ypN+ status according to ypT category in patients with locally advanced rectal cancer treated with chemoradiotherapy and total mesorectal excision, and to assess the impact of ypN+ on disease recurrence and survival by pooled analysis of individual-patient data.

Methods: Individual-patient data from 10 studies of chemoradiotherapy for rectal cancer were included. Pooled rates of ypN+ disease were calculated with 95 per cent confidence interval for each ypT category. Kaplan–Meier and Cox regression analyses were undertaken to assess influence of ypN status on 5-year disease-free survival (DFS) and overall survival (OS).

Results: Data on 1898 patients were included in the study. Median follow-up was 50 (range 0–219) months. The pooled rate of ypN+ disease was 7 per cent for ypT0, 12 per cent for ypT1, 17 per cent for ypT2, 40 per cent for ypT3, and 46 per cent for ypT4 tumours. Patients with ypN+ disease had lower 5-year DFS and OS (46.2 and 63.4 per cent respectively) than patients with ypN0 tumours (74.5 and 83.2 per cent) ($P < 0.001$). Cox regression analyses showed ypN+ status to be an independent predictor of recurrence and death.

Conclusion: Risk of nodal metastases (ypN+) after chemoradiotherapy increases with advancing ypT category and needs to be considered if an organ-preserving strategy is contemplated.

Lay summary

When patients are diagnosed with rectal cancer and the tumour grows beyond the rectal wall there is a high risk that the tumour has spread to nearby lymph nodes. This study showed that this relationship between tumour invasion depth and lymph node involvement is similar after treatment with (chemo)radiotherapy. Patients who have tumour cells remaining in the lymph nodes after (chemo) radiotherapy have a worse prognosis than patients who do not have cancer cells remaining in the lymph nodes. When an organ-preserving treatment is considered as an alternative therapy, this should be kept in mind during patient counselling.

Introduction

Total mesorectal excision (TME) and neoadjuvant (chemo) radiotherapy have improved rectal cancer treatment[1,2] by reducing local failure rates. Neoadjuvant therapy may also facilitate organ-preservation strategies, whereby adequate local control may be achieved without the morbidity and

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quality-of-life implications associated with surgery[3–5]. For patients with a good response but a small residual lesion, some believe that local excision of the residual disease is appropriate, provided that regional lymph nodes have been sterilized with chemoradiotherapy[6,7].

In primary early rectal cancer, the baseline tumour characteristics (T category) can be used to estimate the risk of lymph node metastases (N status). This helps both the selection of patients for primary treatment by local excision and in the decision whether or not to perform a completion TME after local excision[8–14]. The same strategy could be used for patients with a small residual tumour after chemoradiotherapy, but fewer data are available regarding the prevalence of ypN+ among small residual lesions in patients with a locally advanced tumour at baseline. Overall, ypN+ rates reported in the literature vary from 0 to 11 per cent for ypT1 disease, 8 to 29 per cent for ypT2 disease, and 37 to 40 per cent for ypT3 disease[15–17]. To gain more insight into the risk of ypN+ status in locally advanced rectal cancer, this study investigated the prevalence of ypN+ according to ypT category in patients with locally advanced rectal cancer treated with chemoradiotherapy and TME, by pooled analysis of individual-patient data.

Methods

Patient data were selected from a data set that was used for a pooled meta-analysis of individual-patient data examining the prognostic significance of a complete response after chemoradiotherapy for patients with locally advanced cancer[18]. As the study contained data from previously published studies, no ethics approval or patient consent was needed. In total, 14 studies were included in the original study by Maas and colleagues[18], of which 10[19–28] could be included in the present analysis. One study was excluded because only patients with ypN0 disease were included, two were excluded because of missing data on ypT categories (other than ypT0 *versus* ypT+) or missing information on receipt of adjuvant chemotherapy, and the author of another study declined participation for this analysis. The data from previous studies were combined into a single data set. The data comprised patient characteristics, baseline staging data, treatment details, histological data, and follow-up details.

Statistical analysis

The frequency of ypN+ status according to ypT category was calculated for each study, and pooled for all studies with 95 per cent confidence intervals by use of a random-effects model. To stabilize the variance of the proportions from individual studies, Freeman-Tukey arcsine square root transformation of the proportion with ypN+ status was used[29]. The transformed proportions were pooled using a DerSimonian and Laird random-effects model to account for heterogeneity among studies[30]. Heterogeneity was quantified by the I^2 index and Cochran's Q test[31]. For comparison of the 5-year cumulative probability of local and distant recurrence, as well as disease-free survival (DFS) and overall survival (OS) between patients with ypN+ and ypN0 status, Kaplan–Meier analysis and Cox proportional hazards models stratified by study were used. For these time-to-event analyses, follow-up started on the day of surgery and ended on the day of disease relapse or death or day of last follow-up. Patients were censored if, by the end of the follow-up period, they had not developed the outcome of interest or were lost to follow-up. The log rank test was used to compare Kaplan–Meier curves. The Cox proportional hazards assumption was tested on the basis of Schoenfeld residuals after fitting a model and by visual inspection of log minus log plots. The proportional hazards assumption is not violated if the proportionality test is not significant and the plots show that the survival curves for the groups being compared run parallel to each other. $P \leq 0.050$ was considered statistically significant. Analyses were performed using StatsDirect® software (StatsDirect, Altrincham, UK).

Results

Patient and treatment characteristics for each study are shown in *Table 1* and *Table S1*. The imaging technique used for clinical staging varied between studies; it mainly consisted of endorectal ultrasonography and CT, with additional MRI in some studies. A total of 2026 patients were included in the data sets of the original 10 selected studies, of whom 128 were excluded owing to unknown ypT or ypN category. Therefore, 1898 patients were included in the present analyses. Survival data were available for 1856 patients. All studies used external beam radiotherapy in doses ranging from 45 to 50.4 Gy in 25–28 fractions. The interval between chemoradiotherapy and surgery was most commonly 6–8 weeks. Chemotherapy using 5-fluorouracil was administered as a radiosensitizer in the majority of patients. Most patients also received adjuvant chemotherapy (5-FU-based); the type of adjuvant therapy was unknown for two studies.

Of all 1795 patients with available data on cT category, 1708 (95.1 per cent) were diagnosed with cT3–4 disease before neoadjuvant treatment. Data on cN status were available for 1802 patients, of whom 1080 (59.9 per cent) had cN+ disease, whereas only 26.2 per cent had ypN+ disease at histological examination of the resection specimen. Median follow-up was 50 (range 0–219) months.

The pooled rate of ypN+ disease was 7 (95 per cent c.i. 3 to 12) per cent for ypT0 ($I^2 = 56$ per cent; $P = 0.015$), 12 (4 to 24) per cent for ypT1 ($I^2 = 53$ per cent; $P = 0.025$), 17 (12 to 23) per cent for ypT2 ($I^2 = 62$ per cent; $P = 0.005$), 40 (36 to 44) per cent for ypT3 ($I^2 = 32$ per cent; $P = 0.154$), and 46 (34 to 57) per cent for ypT4 ($I^2 = 0$ per cent; $P = 0.586$) (*Fig. 1*). *Table 2* provides an overview of the proportion of patients with (y)pN+ disease according to (y)pT category after chemoradiotherapy in the present study, compared with rates reported in the literature for patients who did not receive neoadjuvant treatment.

Long-term outcome

Patients with ypN+ disease had a lower DFS and OS rates at 5 years than patients with ypN0 disease (*Fig. 2*). Patients with cN+ tumours before chemoradiotherapy who had ypN0 status after chemoradiotherapy had similar 5-year DFS to patients who had cN0 lesions at primary staging and ypN0 after chemoradiotherapy: 74.8 (95 per cent c.i. 72 to 78) and 73.7 (70 to 78) per cent respectively. cN status had limited accuracy, reflected by the large number of patients staged as cN0 who had ypN+ disease after TME (156 of 722, 21.6 per cent). In addition, cN had only moderate predictive value for long-term DFS (hazard ratio (HR) 1.03, 95 per cent c.i. 0.84 to 1.28) and OS (HR 1.20, 0.94 to 1.54).

In the subgroup of patients with ypT0–2 disease, there was a difference in 5-year DFS between ypN+ and ypN0 groups: 65.0 (57 to 74) and 81.3 (78 to 84) per cent respectively ($P < 0.001$). Five-year OS rates also differed: 81.1 (73 to 88) *versus* 87.5 (85 to 90) per cent ($P = 0.005$). Additional survival analyses according to ypN status separated by ypT category are shown in *Fig. S1*.

Table 1 Characteristics of included studies

Reference	Population	No. of patients	Type of neoadjuvant treatment	Interval between CRT and surgery (weeks)	Type of adjuvant chemotherapy	Type of study	Clinical staging modality
Valentini *et al.*[22]	LARC, extraperitoneal, T3–T4 or N+	474	External RT or IORT, 5-FU + mitomycin C/cisplatin	6–8	5-FU	Prospective	EUS + CT
Rödel *et al.*[28]	Stage II–III	348	External RT, 5-FU	6	5-FU	Prospective (arm of RCT)	EUS + CT
Kuo *et al.*[26]	T3–T4 N+M0	242	External RT, 5-FU, mitomycin C	6–8	n.r.	Retrospective	MRI
García-Aguilar *et al.*[19]	Stage II–III	154	External RT, 5-FU	6	5-FU and leucovorin	Retrospective	EUS + CT
Hughes *et al.*[20]	T3–T4	147	External RT, 5-FU	6–12	n.r.	Prospective	EUS + CT + MRI
Suárez *et al.*[27]	LARC	119	External RT, 5-FU	6	n.r.	Retrospective	CT
Díaz-González *et al.*[21]	T3–4 N+	117	External RT/IORT, 5-FU or tegafur	4–6	5-FU and leucovorin	Prospective	EUS + CT
Pucciarelli *et al.*[23]	T3–4 N+M0	106	External RT, 5-FU + leucovorin/ carboplatin/oxaliplatin	6–8	5-FU and leucovorin	Retrospective	EUS + CT
Biondo *et al.*[25]	T3–4 LARC	103	External RT, 5-FU	6–8	5-FU and leucovorin	Prospective	CT
Theodoropoulos *et al.*[24]	All	88	External RT, 5-FU +/– leucovorin	6	n.r.	Retrospective	EUS + CT

Adapted from Maas *et al.*[18]. CRT, chemoradiotherapy; LARC, locally advanced rectal cancer; N+, clinically node-positive; RT, radiotherapy; IORT, intraoperative radiotherapy; 5-FU, 5-fluorouracil; EUS, endorectal ultrasonography; n.r., not reported.

In a multivariable Cox regression model, stratified by centre (including sex, age, cT, cN, distance from anal verge, type of surgery, ypT, and chemotherapy as independent variables), ypN+ status was a predictor of recurrence and death, with HRs of 2.45 (1.70 to 3.54) and 2.05 (1.28 to 3.29) for DFS and OS respectively in the subgroup of patients with ypT0–2 (*Table 3*), but also in the total patient group (*Table 4*).

Discussion

This study has shown that the pooled prevalence of lymph node metastases after neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer increases with increasing depth of residual tumour, and is in the same range as that for non-irradiated tumours. With a tumour complete response (ypT0) there is still a 7 per cent risk of lymph node metastases. In this setting, the presence of lymph node metastases is a strong predictor of poor long-term outcome, as for non-irradiated tumours.

The findings of this study are in accordance with previous reports. Generally, rates of lymph node metastases in patients with ypT0 disease are below 10 per cent in most studies[15,32,33]. In ypT2 tumours, lymph node metastases have been reported in up to 29 per cent of patients[15,16], which is higher than the 17 per cent in the present study. However, the GRECCAR 2 trial[17] reported a much lower incidence of nodal involvement of 8 per cent, which may be explained by differences in the study population as the GRECCAR 2 trial included patients with smaller tumours (less than 4 cm) with cT2–3 N0–1 stage, with at most limited nodal disease at diagnosis. The present study included more locally advanced tumours at diagnosis.

A focus on the prevalence of lymph node metastases is particularly relevant when organ preservation is being contemplated. With all organ-preserving strategies (including local scar excision) the regional lymph nodes are left *in situ* and are a potential source of recurrence. Although it is often stated that the risk of leaving involved nodes behind is small for ypT0–1 tumours and too high for ypT2 tumours, the differences were not that marked in the present study (7, 12, and 17 per cent for ypT0, ypT1, and ypT2 respectively). The prevalence of 40 per cent for ypT3 tumours was substantially higher. Whether or not to consider organ preservation or to undertake TME is reliant on a risk–benefit assessment that should include information from baseline and post-treatment staging, histology if local excision was performed, and also patient preference and co-morbidity.

It is also interesting to note that in a pooled analysis of 880 patients with a clinical complete response managed according to a watch-and-wait strategy, only 11 patients had nodal regrowth[3]. This is much lower than would be expected from the present findings. There are a number of possible reasons for this. Not all lymph node metastases detected by the pathologist in the TME specimen 6–8 weeks after irradiation may represent viable tumour, and the longer interval between restaging and the decision to watch and wait may allow further regression[34]. Residual macrometastases in nodes are associated with a poor prognosis. However, small residual micrometastases found in the nodes at histopathology 6–8 weeks after chemoradiotherapy might regress if a longer interval is applied, and may not be of clinical significance (62 per cent ypN0 within 4–8 weeks *versus* 73 per cent ypN0 within 8–12 weeks)[35,36]. ypT category is also a crude measure of response to chemoradiotherapy that does not correlate directly with tumour volume. Patients who have an apparently (near) complete response at restaging (MRI and endoscopy) but actually have a small ypT2 remnant that becomes obvious with follow-up could have a lower proportion of lymph node metastases than patients with a moderate response and a large remaining ypT2 tumour. Finally, although still controversial in early disease[37], MRI has improved local staging, so patients with obvious lymph node metastases on imaging are not selected for organ preservation and undergo formal TME, which reduces the risk of nodal regrowth. In addition to ypT category, there are other histological

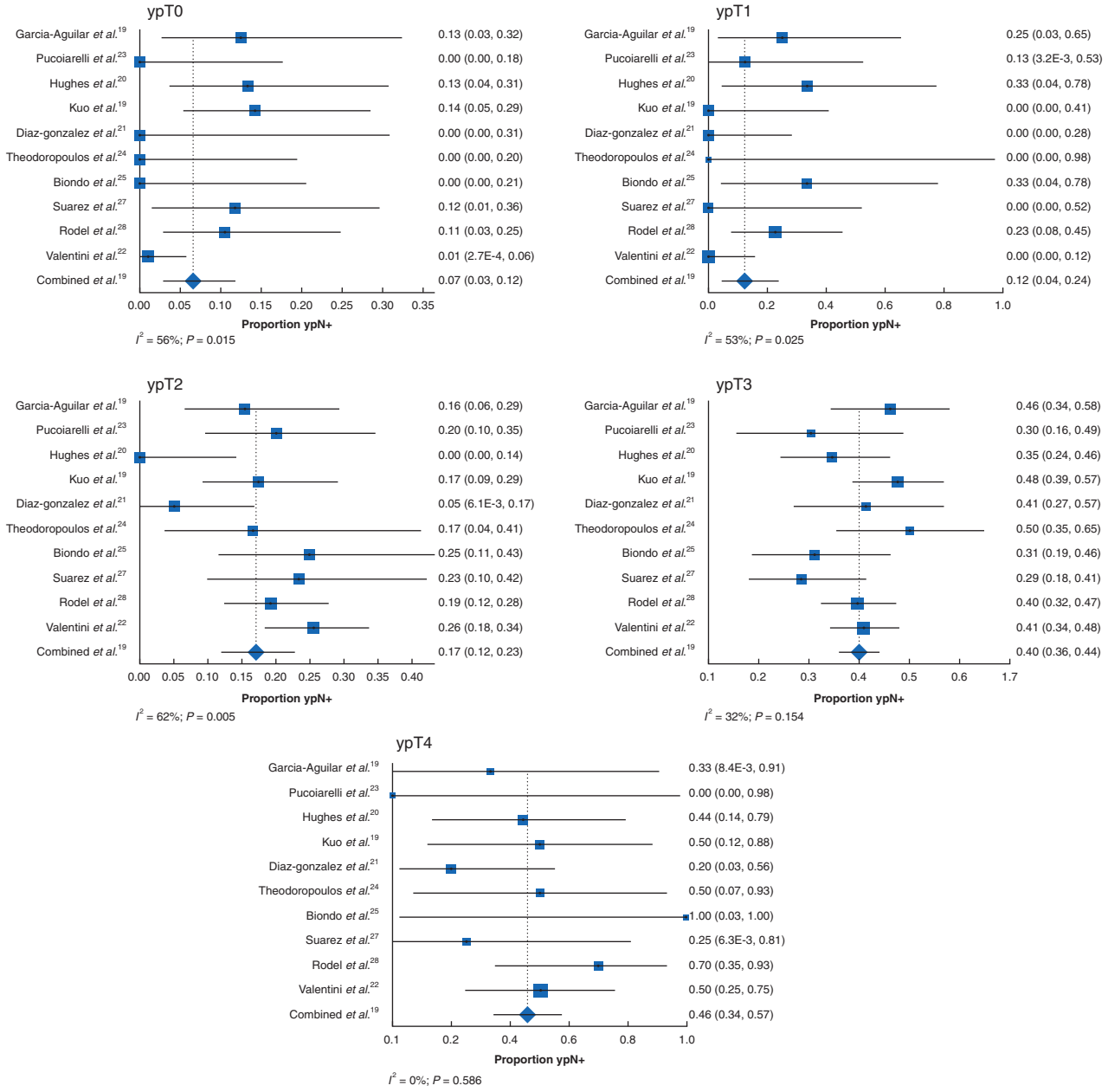

Fig. 1 Pooled proportions of ypN+ disease by ypT category

a ypT0, **b** ypT1, **c** ypT2, **d** ypT3, and **e** ypT0. A random-effects model was used for meta-analysis. Proportions are shown with 95 per cent intervals. Heterogeneity is indicated by the I^2 value.

Table 2 Proportion of patients with positive lymph nodes according to (y)pT category after chemoradiation in the present study compared with results reported in the literature for patients not treated with neoadjuvant chemoradiotherapy

	ypN+ rate (%)	
	After chemoradiotherapy (present study)	Without neoadjuvant treatment (published studies)
(y)pT0	7	
(y)pT1	12	6–14[8–14]
(y)pT2	17	17–23[8–14]
(y)pT3	40	49–66[8,13]
(y)pT4	46	50–79[8,13]

parameters by which to identify patients at a higher risk of lymph node metastases who are less suitable for organ-preserving treatment, such as lymphatic or vascular invasion and differentiation grade[38,39]. As differentiation grade and other histopathological factors of the tumour were poorly recorded in this pooled data set, these factors could not be included in the analyses.

It has been suggested that adjuvant therapy could improve oncological outcome in patients with lymph node metastases. However, a meta-analysis[40] found that patients with rectal cancer did not benefit from adjuvant chemotherapy with regard to DFS (HR 0.91, 95 per cent c.i. 0.77 to 1.07; $P = 0.230$) and distant recurrence (HR 0.94, 0.78 to 1.14; $P = 0.523$) compared with observation. In the present study, cN category lacked predictive value for survival outcomes. This was probably related to the low

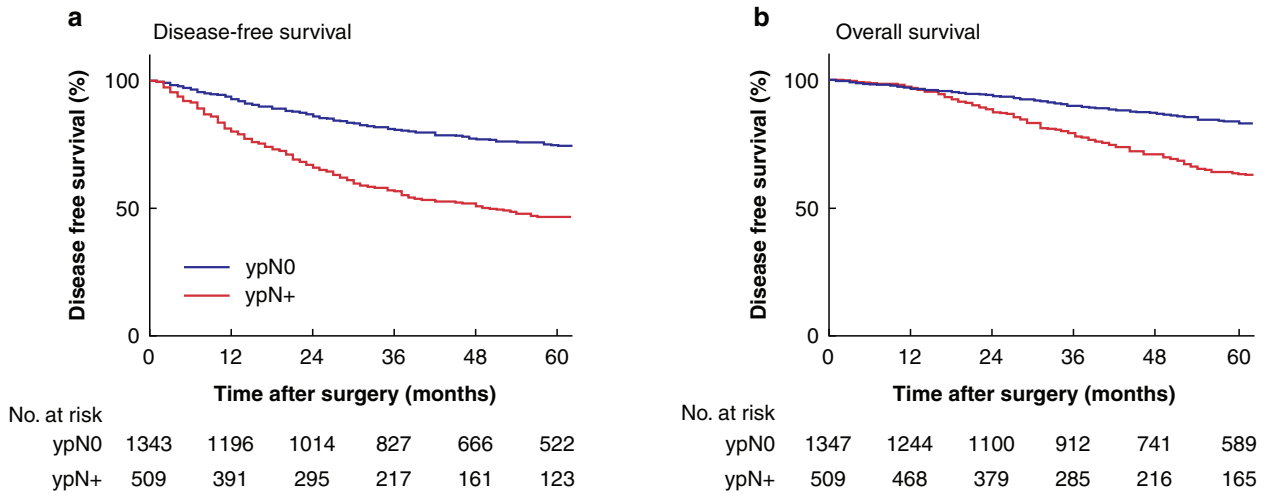

Fig. 2 Survival curves by ypN status for the total patient group

a Disease-free survival and **b** overall survival. **a,b** $P < 0.001$ (log rank test).

Table 3 Adjusted hazard ratios from multivariable Cox proportional hazards models for patients with ypT0–2 disease stratified by data set

	Hazard ratio	
	Disease-free survival	**Overall survival**
Sex		
M	1.00 (reference)	1.00 (reference)
F	0.84 (0.61, 1.17)	0.73 (0.49, 1.11)
Age (per year)	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)
Clinical tumour category at baseline		
cT1	0.54 (0.24, 1.24)	1.04 (0.34, 3.22)
cT2	0.98 (0.51, 1.86)	0.60 (0.23, 1.58)
cT3	1.00 (reference)	1.00 (reference)
cT4	1.88 (1.20, 2.97)	1.58 (0.92, 2.74)
Clinical node category at baseline		
cN0	1.00 (reference)	1.00 (reference)
cN+	0.94 (0.67, 1.35)	1.14 (0.76, 1.73)
Distance from anal verge (cm)		
≤5	1.00 (reference)	1.00 (reference)
>5	1.09 (0.78, 1.55)	1.40 (0.93, 2.13)
Type of surgery		
LAR	1.00 (reference)	1.00 (reference)
APR	1.48 (1.00, 2.20)	1.81 (1.15, 2.89)
Other	1.55 (0.73, 3.28)	2.21 (0.98, 5.04)
Pathological T category		
pT0	1.00 (reference)	1.00 (reference)
pT1	0.75 (0.42, 1.36)	0.77 (0.40, 1.48)
pT2	1.10 (0.77, 1.58)	0.84 (0.56, 1.28)
Pathological N category		
pN0	1.00 (reference)	1.00 (reference)
pN+	2.45 (1.70, 3.54)	2.05 (1.28, 3.29)
Adjuvant chemotherapy		
No	1.00 (reference)	1.00 (reference)
Yes	0.64 (0.44, 0.96)	0.49 (0.30, 0.81)

Values in parentheses are 95 per cent confidence intervals; LAR, low anterior resection; APR, abdominal perineal resection. A hazard ratio below 1 indicates a lower probability of an unfavourable event.

accuracy of clinical nodal staging, which was mainly performed with endorectal ultrasonography and CT. Currently, MRI is the recommended modality for assessment of node status; however, T2-weighted MRI also only yields a moderate sensitivity and specificity of 77 and 60 per cent respectively. The per-lesion sensitivity for nodal staging after chemoradiotherapy is 91 per cent, indicating a low rate of false-negative findings when staging individual mesorectal nodes[41]. Lahaye and colleagues[42] reported sensitivities of up to 85 per cent for nodal staging with T2-weighted MRI after chemoradiotherapy based on size criteria, further confirming the low risk of missing lymph node metastases. Nevertheless, given the 17 per cent prevalence of lymph node metastases in ypT2 disease, physicians should remain alert to the possible presence of lymph node metastases in patients with substantial downstaging of the primary rectal cancer.

This study has several limitations. Data were retrieved from a subset of individual studies with a heterogeneous patient population and differences between studies. Some of the studies were

Table 4 Adjusted hazard ratios from multivariable Cox proportional hazards models for the total cohort stratified by data set

	Hazard ratio	
	Disease-free survival	Overall survival
Sex		
M	1.00 (reference)	1.00 (reference)
F	0.84 (0.70, 1.01)	0.81 (0.65, 1.02)
Age (per year)	0.99 (0.98, 1.00)	0.99 (0.99, 1.01)
Clinical tumour category at baseline		
cT1	0.75 (0.43, 1.34)	1.27 (0.57, 2.84)
cT2	0.99 (0.60, 1.63)	0.63 (0.30, 1.31)
cT3	1.00 (reference)	1.00 (reference)
cT4	1.33 (1.04, 1.72)	1.23 (0.92, 1.67)
Clinical node category at baseline		
cN0	1.00 (reference)	1.00 (reference)
cN+	1.03 (0.84, 1.28)	1.20 (0.94, 1.54)
Distance from anal verge (cm)		
≤5	1.00 (reference)	1.00 (reference)
>5	1.03 (0.85, 1.27)	1.16 (0.92, 1.48)
Type of surgery		
LAR	1.00 (reference)	1.00 (reference)
APR	1.52 (1.23, 1.90)	1.65 (1.27, 2.15)
Other	1.23 (0.79, 1.94)	1.50 (0.89, 2.55)
Pathological T category		
pT0	1.00 (reference)	1.00 (reference)
pT1	0.85 (0.48, 1.51)	0.82 (0.44, 1.57)
pT2	1.15 (0.82, 1.63)	0.85 (0.57, 1.28)
pT3	2.01 (1.46, 2.77)	1.62 (1.13, 2.33)
pT4	2.89 (1.77, 4.74)	2.37 (1.37, 4.11)
Pathological N category		
pN0	1.00 (reference)	1.00 (reference)
pN+	2.26 (1.87, 2.74)	2.08 (1.66, 2.62)
Adjuvant chemotherapy		
No	1.00 (reference)	1.00 (reference)
Yes	0.61 (0.49, 0.76)	0.51 (0.40, 0.68)

Values in parentheses are 95 per cent confidence intervals; LAR, low anterior resection; APR, abdominal perineal resection. A hazard ratio below 1 indicates a lower probability of an unfavourable event.

retrospective. However, a random-effects model was used to take heterogeneity into account when pooling the proportions of lymph node metastases by ypT category, and Cox proportional hazards analyses with stratification by data set were used to evaluate long-term outcome. Because of missing data, not all patients could be included in all analyses. Additionally, some baseline and histopathological details were lacking, such as the presence of tumour deposits, extramural vascular invasion, completeness of resection, size and number of harvested and involved nodes, and size and exact location of residual tumour in the bowel wall; this information could be of help in interpreting the data[39,40,43]. Moreover, clinical staging was probably suboptimal (specifically for nodal status) as MRI was not used in most studies, which may have influenced the outcomes. Finally, this pooled analysis was based on historical studies published between 2002 and 2008. However, this provided a unique opportunity to evaluate lymph node metastases in patients with rectal cancer who receive chemoradiotherapy and all undergo surgery, in contrast to current cohorts in which organ preservation is increasingly being offered.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

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