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RESEARCH ARTICLE

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T-stage downstaging of locally advanced rectal cancer after neoadjuvant chemoradiotherapy is not associated with reduced recurrence after adjusting for tumour characteristics

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Abstract

Background and Objectives: Prior studies examining prognostic outcomes of locally advanced rectal adenocarcinomas achieving a complete pathological response following neoadjuvant chemoradiotherapy (nCRT) did not adjust for adverse prognostic factors in multivariate analyses and account for magnetic resonance imaging tumour staging inaccuracy pre-nCRT. We aimed to clarify prognostic outcomes in mT3 rectal adenocarcinomas with ypT-downstaging post-nCRT in robust adjusted analyses.

Methods: Retrospective analysis of prospectively-collected clinical data from 528 mT3 rectal adenocarcinomas ≤12 cm from the anal verge, any N-stage, no metastases, post-nCRT following total mesorectal excision (TME). Recurrence outcomes (local and distant combined) of tumours with complete ypT-downstaging (ypT0) post-nCRT before TME compared with no ypT-downstaging (≥ypT3) were examined using multivariate Cox regression, adjusting for confounders and accounting for pre-nCRT mT3-staging inaccuracy using bootstrapping.

Results: Complete ypT-downstaging was achieved in of 17.6% tumours and correlated strongly with complete pathological response. Complete ypT-downstaging was not associated with reduced recurrence hazards compared with no ypT-downstaging (hazard ratio = 0.60; 95% confidence interval [CI]: 0.23–1.56; $p = 0.30$). Lymphovascular invasion (LVI) and ypN+ve increased recurrence hazards by 1.8-fold (95% CI: 1.10–2.79; $p = 0.02$) and 2.3-fold (95% CI: 1.48–3.54; $p = 0.0002$), respectively.

Conclusion: Complete ypT-downstaging was not associated with reduced recurrence after adjusting for confounders and accounting for mT3-staging inaccuracy, even in the absence of adverse prognostic factors (ypN+, LVI).

KEYWORDS

neoadjuvant chemoradiotherapy, rectal cancer, recurrence, ypT-downstaging

1 | INTRODUCTION

Standard treatment for locally advanced rectal cancer (LARC) in the lower two thirds of the rectum comprises neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision (TME), with or without postoperative adjuvant chemotherapy.[1] Preoperative nCRT potentially reduces tumour size to facilitate tumour resectability.[2] Associations between tumours achieving a complete pathological response (pCR) following nCRT and favourable prognostic outcomes,[3–6] have prompted a potential shift in the management of select tumours achieving pCR to alternate treatment options, including organ-preserving surgery or a watch-and-wait regimen rather than major resection surgery.[7] More recently, randomised trials have demonstrated the potential of total neoadjuvant therapy (TNT), upfront preoperative neoadjuvant chemotherapy followed by chemoradiotherapy, as new standard-of-care treatment for certain LARCs.[8,9]

Two meta-analyses form the basis for evidence supporting superior prognostic outcomes in tumours achieving pCR.[3,4] In 2012, analysis of data from 12 of 16 included studies in the Martin et al.[3] meta-analysis found LARCs achieving pCR had 4.3-fold higher 5-year disease-free survival (DFS) ($p < 0.001$) and 3.3-fold higher survival ($p = 0.001$) compared with no pCR. However, eight included studies examined <30 tumours with pCR, four studies had no postoperative adjuvant chemotherapy data and five studies had <44 months follow-up.[3] In an earlier meta-analysis by Maas et al.[4] multivariate analysis of pooled data from 8 of 12 included studies, found LARCs achieving pCR ($n = 484$) reduced the hazard of recurrence by 46% (95% CI: 0.40–0.73) compared with tumours not achieving pCR, after adjusting for select baseline prognostic factors and postoperative adjuvant chemotherapy. More recently, Park et al.[10] found poor responses following nCRT in tumours staged as T3-4 or N+ by magnetic resonance imaging (MRI), computed tomography or endorectal ultrasonography was associated with higher risks of recurrence compared with complete responders (hazard ratio [HR] = 3.01; 95% CI: 1.75–5.16) in multivariate analysis.

In the context of examining prognostic outcomes following nCRT, recent studies have highlighted the importance of certain biological tumour characteristics in the ability to achieve pCR and/or prognostic outcomes. Lymphovascular invasion (LVI), poor tumour differentiation, extramural venous invasion (EMVI) and clinical (and histopathological) N2 stage are associated with adverse prognostic outcomes,[11–15] whereas lymphocyte infiltration (specifically high CD8+ and FOXP3+ cells) is related to improved outcomes.[16] Importantly, of the prior studies examining prognostic outcomes in tumours achieving pCR, only Park et al.[10] adjusted for lymphovascular and perineural invasion in multivariate analyses whereas Martin et al.[3] performed univariate analyses and Maas et al.[4] adjusted for some confounders (age, sex, surgical procedure, distance from anal verge, clinical N-stage and adjuvant chemotherapy) but not tumour characteristics.

A further consideration when examining tumour responses following nCRT and prognostic outcomes involves study design problems associated with T- and N-staging and inconsistency between the methods used to measure pathological responses to nCRT. In particular, (1) the initial staging method pre-nCRT by MRI is notably inaccurate compared with the final staging method, with histopathological examination of the resected rectum remaining the gold standard for ypT-staging and ypN-staging post-nCRT). While MRI accuracy for mT3-staging compared with final histopathology is estimated to be 60%–80%,[17–19] accuracy for staging N-negative tumours is only 38%–54% and 48%–71% for N-positive tumours[17,19] (notably, this inaccuracy is particularly relevant in watch-and-wait studies where a definitive histopathology result may be unavailable) and (2) methods to assess tumour regression grade (TRG) are not consistent across studies and are scored subjectively.[2,20–22] Further, assessment of nodal regression and downstaging is notoriously difficult, with nodal categorisation often simplified to ypN+ve or ypN-ve.

In the present study, we examined the association between mT3 rectal tumours with complete (ypT0) or partial (ypT1 or ypT2) ypT-downstaging and recurrence-free survival (RFS) following long-course nCRT compared with tumours with no ypT-downstaging (≥ypT3). To overcome study design problems, we used ypT-downstaging post-nCRT as an objective measure of pathological tumour responses and performed multivariate analysis adjusted for potential confounders, including ypN stage and LVI, and accounted for pre-nCRT mT-staging by MRI using a bootstrapping procedure.

2 | MATERIALS AND METHODS

2.1 | Data

Retrospective analysis of prospectively-collected data from BioGrid ACCORD Australia clinical colorectal cancer database collected between 2004 and 2017.[20] Biogrid comprises data from all colorectal cancer patients from 7 tertiary-referral hospitals (4 public, 3 private) with specialist colorectal surgery services in Melbourne, Australia via clinical notes, supported by radiology and histopathology reports. Biogrid was demonstrated to perform well in a validation study.[23]

2.2 | Extent of ypt-downstaging on recurrence outcomes post-nCRT

To examine the effect of ypT-downstaging post-nCRT on RFS, data were extracted from 534 rectal adenocarcinomas, ≤12 cm from the anal verge, staged mT3 by MRI that received long-course nCRT (1.8–2 Gy per fraction over 5–6 weeks with fluorouracil-based chemotherapy),[24] followed by major resection surgery (TME-associated resections; ultra-low anterior resection [ULAR, anastomosis <6 cm from anal verge] or abdominoperineal resection [APR]).

2.2.1 | Primary outcome

The primary outcome was RFS, defined as the time to first recurrence (distant or local [locoregional] combined) occurring from primary rectal adenocarcinoma, from the date of major surgery. Patients without tumour recurrence were censored on the date of death from any cause or the last recorded visit. RFS was selected as a proxy for examining prognostic outcomes, consistent with other studies examining DFS.[4,25,26] Moreover, DFS has been used as a primary endpoint in phase III trials.[27]

2.2.2 | Exposure and potential confounders

The main exposure was pathological response post-nCRT defined by ypT-downstaging in mT3 rectal tumours. Patients with no residual mural tumour in the resected specimen (ypT0) had 'complete ypT-downstaging', ≥ypT3 tumours had 'no ypT-downstaging' and all remaining cases (ypT1 and ypT2) had 'partial ypT-downstaging'.

We examined the correlation between ypT-level downstaging and tumour pathological response (a variable collected in Biogrid) post-nCRT and found close correlation for tumours with complete or no ypT-downstaging with 97% and 76% agreement, respectively (Table 1).

Potential confounding variables examined included gender, diagnosis age, distance from the anal verge (≤8 vs. >8 cm), time between nCRT and surgery, surgical method (laparoscopic vs. open), surgical procedure (ULAR vs. APR), type of hospital (public vs. private), ypN status (positive vs. negative), diabetes (yes vs. no), LVI (yes vs. no), differentiation (undifferentiated to well), mucinous histology (yes vs. no), inflammatory infiltrate (present vs. absent), postoperative chemotherapy (yes vs. no) and comorbidity marker/ASA[28] grade (<3 vs. ≥3). The most common postoperative adjuvant chemotherapy regimen was 5-fluorouracil with (33.1%) or without folinic acid (40.9%; Supporting Information: Table 1).

2.3 | Accuracy of MRI for staging rectal tumours

To determine the accuracy of mT-staging by MRI compared with final histopathology, we examined a separate cohort of mT3 rectal tumours who fulfilled all study inclusion criteria but did not undergo nCRT and had TME within 4 weeks of MRI ($n = 51$). We found 6%, 22%, 64% and 8% of tumours classified as mT3 by MRI were pT1, pT2, pT3 and pT4, respectively, on final histopathology (Supporting Information: Table 2).

2.4 | Statistical methods

2.4.1 | Summary statistics

Frequency tables were used to summarise study population characteristics. A survival analysis approach was used to examine

TABLE 1 Correlation between tumour response grade and ypT-downstaging in 501 individuals with locally advanced rectal cancer receiving long-term neoadjuvant chemoradiotherapy

Pathological response		Extent of ypT-downstaging[a]			
		No ypT-downstaging[b]	Partial ypT-downstaging[c]	Complete ypT-downstaging[d]	Total
Complete[e]	No of tumours	3	0	88	91
	Percentage	3.3%	0.0%	96.7%	100%
Partial[f]	No of tumours	221	130	5	356
	Percentage	62.1%	36.5%	1.4%	100%
None[g]	No of tumours	41	13	0	54
	Percentage	75.9%	24.1%	0%	100%
Total	No of tumours	265	143	93	501
	Percentage	52.9%	28.5%	18.6%	100%

[a]Assessed by comparing histopathology of ypT-stage in final resected specimen with T-stage assessed by MRI before nCRT (mT3). Only data from tumours where both pathological response and downstaging data was available is presented.

[b]Defined as ≥ypT3 rectal tumours.

[c]Defined as rectal tumours staged between >ypT0 and <ypT3.

[d]Defined as ypT0.

[e]Complete pathological responses were defined as having no visible tumour tissue in the final resected tumour (yN0p0).

[f]Partial pathological responses were defined as having some pathological response in the final resected tumour following nCRT (progressive, major or partial responses. That is,all responses that were not reported as having 'no' pathological response or a 'complete' pathological response following nCRT.

[g]No pathological response was defined as having no pathological response post-nCRT, as assessed by histopathology of the resected tumour.

the association between ypT-downstaging post-nCRT and the time to first tumour recurrence. Kaplan–Maier (KM) plots were used to plot estimates of survival curves.[29]

2.4.2 | Statistical model

Univariate and multivariate Cox proportional hazards (PH) models[30] were used to examine the association between the main exposure (ypT-downstaging of mT3 rectal tumours) and the hazard of tumour recurrence (local/distant combined). Potential confounders with $p \leq 0.15$ in univariate modelling were included in multivariate models.

2.4.3 | Accounting for MRI inaccuracy

In the separate cohort of patients not receiving nCRT only 64% of tumours classified as mT3 by MRI were pT3 on final histopathology (Supporting Information: Table 2). To account for potential misclassification of the remaining 36% of tumours, a bootstrap sampling procedure by Efron and Tibshirani was used.[31] Briefly, both univariate and multivariate Cox models were fitted 10 000 times. Each time, 6%, 22%, 64% and 8% of mT3 tumours (according to MRI) were randomly assigned an initial pT-stage of pT1, pT2, pT3 and pT4, respectively. Average HRs, 95% confidence intervals (CIs) and p values from all 10 000 models were presented as the final results (Supporting Information: Table 3). The PH assumption of the Cox model was checked using Schoenfeld residuals test.[32] Analyses were performed using STATA 15.0.[33]

3 | RESULTS

3.1 | Study population

Characteristics of 534 participants with mT3 rectal tumours receiving long-course nCRT before TME and tumour recurrence data are summarised (Table 2). The male:female ratio was 3:2 and ~73% of individuals were ≥55 years. The majority of tumours (70%) occurred ≤8 cm from the anal verge and 29% were ypN+ve. Seventy-two percent of individuals had ULAR.

Post-nCRT, 18%, 29% and 53% of tumours achieved complete (yT0), partial/incomplete (ypT1/ypT2) and no (≥ypT3) ypT-downstaging (Table 2), respectively, and corresponding recurrence rates were 8%, 18% and 33%, respectively. Individuals with complete, partial and no ypT-downstaging had 99%, 90% and 81% 1-year unadjusted RFS and 89%, 78% and 62% 5-year unadjusted RFS, respectively. Median follow-up time after TME for tumours with complete, partial and no ypT-downstaging was 51.7, 46.5 and 28.6 months, respectively (Supporting Information: Table 4).

Median time between cancer diagnosis and commencing nCRT was ~4 weeks and median time between nCRT and surgery was 8 weeks (Supporting Information: Table 5).

3.2 | Univariate Cox modelling

KM curves (unadjusted analyses) indicated tumours with complete ypT-downstaging post-nCRT had the highest RFS and no ypT-downstaging had the worse RFS (Figure 1). Similarly, univariate Cox modelling without adjusting for confounders, found complete and partial ypT-downstaging reduced the hazard of recurrence by 79% (95% CI: 0.10–0.44; $p = 0.0004$) and 54% (95% CI: 0.30–0.71; $p = 0.00003$), respectively, compared with no ypT-downstaging (Table 3). After accounting for MRI inaccuracy with bootstrapping in univariate analyses, complete and partial ypT-downstaging reduced recurrence hazards by 76% (95% CI: 0.12–0.49; $p < 0.0001$) and 40% (95% CI: 0.39–0.91; $p = 0.04$), respectively, compared with no ypT-downstaging (Supporting Information: Table 6).

Covariates associated with the hazard of tumour recurrence in univariate analysis included surgical procedure, ypN status (on final resection), LVI and distance from anal verge increased the hazard of recurrence but tumour characteristics [lymphocyte infiltration, mucinous histology and differentiation] did not increase recurrence hazards (Table 3, Supporting Information: -Figure 1 and Table 7). ypN+ve increased recurrence hazards threefold (95% CI: 2.13–4.23) compared with ypN-ve and LVI increased recurrence hazards 2.2-fold (95% CI: 1.47–3.24) compared with no LVI.

Covariates with a $p \leq 0.15$ in univariate analyses were included as potential confounders in multivariate Cox models.

Six patients had 'involved' radial margins but no local recurrences were found in these patients (Supporting Information: Table 8). No patients had 'involved' distal margins. Due to insufficient cases with 'involved' margins, examining the effect of margins (R0) on RFS by univariate analysis was not feasible.

3.3 | Multivariate Cox PH model accounting for MRI inaccuracy

Age, surgical procedure, distance from anal verge, diabetes, LVI and ypN status were included in the multivariate Cox model. After adjusting for these covariates and accounting for MRI inaccuracy staging mT3 tumours, complete ypT-downstaging reduced the hazard of recurrence by 40% compared with no ypT-downstaging but with no evidence of a difference (Table 3; 95% CI: 0.23–1.56, $p = 0.30$). Similarly, partial ypT-downstaging reduced the hazard of recurrence by 34% but with no evidence of a difference (95% CI: 0.39–1.10; $p = 0.17$).

ypN+ve versus ypN-ve status and LVI versus no LVI were associated with 2.3-fold (95% CI: 1.48–3.54; $p = 0.0002$) and 1.8-fold

TABLE 2 Characteristics and descriptive statistics of the study population

Baseline characteristics		Participants		Tumour recurrence[h]				Percentage (%) of patients with no tumour recurrence	
				Yes		No			
Covariate	Measure	No	%	No	%	No	%	1-year	5-year
Pathological response after nCRT[a] (extent of ypT-downstaging)[b] (*n* = 528)	No downstaging[e]	282	53.4	94	33.3	188	66.7	81.4	61.9
	Partial downstaging[f]	153	29.0	28	18.3	125	81.7	90.32	77.49
	Complete downstaging[g]	93	17.6	8	8.6	85	91.4	98.80	89.34
Patient characteristics									
Gender	Female	177	33.0	40	22.6	137	77.4	86.91	74.88%
(*n* = 537)	Male	360	67.0	91	25.3	269	74.7	87.15	70.17
Age at diagnosis (years)	<35	18	3.40	7	38.9	11	61.1	83.33	56.82
(*n* = 537)	≥35–<45	39	7.30	11	28.2	28	71.8	84.25	68.39
	≥45–<55	86	16.0	24	27.9	62	72.1	87.91	70.49
	≥55–<65	154	28.7	32	20.8	122	79.2	84.87	76.77
	≥65	240	44.7	57	23.8	183	76.3	89.11	71.04
ASA[c]	<3	384	71.5	96	25.0	288	75.0	87.31	72.0
(*n* = 537)	≥3	153	28.5	35	22.9	118	77.1	86.43	70.77
Diabetes	No	453	85.3	117	25.8	336	74.2	86.22	70.12
(*n* = 531)	Yes	78	14.7	13	16.7	65	83.3	92.08	80.41
Hospital type	Private	178	33.1	43	24.2	135	75.8	88.32	73.60
(*n* = 537)	Public	359	66.9	88	24.5	271	75.5	86.43	70.71
Surgical method	Laparoscopic	281	55.8	68	24.2	213	75.8	86.50	71.04
(*n* = 504)	Open	223	44.2	56	25.1	167	74.9	88.69	72.52%
Surgical procedure	APR	150	27.9	47	31.3	103	68.7	80.38	62.89
(*n* = 537)	Ultra Low AR	387	72.1	84	21.7	303	78.3	89.60	75.05
Tumour characteristics									
Distance from anal verge (cm)	≤8 cm	332	70.2	91	27.4	241	72.6	84.49	67.97
(*n* = 473)	>8 cm	141	29.8	21	14.9	120	85.1	94.05	84.28
Tumour differentiation[d]	Poor	23	5.4	8	34.8	15	65.2	77.8	61.4
(*n* = 427)	Poor-moderate	34	8.0	12	35.3	22	64.7	72.2	61.8
	Moderate	359	84.1	87	24.2	272	75.8	87.68	71.3
	Moderate-well	5	1.2	2	40.0	3	60.0	100.0	66.7
	Well	6	1.4	2	33.3	4	66.7	66.7	66.7
lymphovascular Invasion[d]	No	364	81.8	85	23.4	279	76.6	88.28	73.21
(*n* = 445)	Yes	81	18.2	35	43.2	46	56.8	77.51	46.27
Lymph node status (ypN)[d]	Negative	377	71.3	66	17.5	311	82.5	93.16	79.42
(*n* = 529)	Positive	152	28.7	64	42.1	88	57.9	72.00	51.50

TABLE 2 (Continued)

Baseline characteristics		Participants		Tumour recurrence[h]				Percentage (%) of patients with no tumour recurrence	
				Yes		No			
Covariate	Measure	No	%	No	%	No	%	1-year	5-year
Postoperative treatment									
Adjuvant chemotherapy	No	140	26.5	37	26.4	103	73.6	81.16	63.94
(*n* = 529)	Yes	389	73.5	92	23.7	297	76.3	89.49	74.22

Abbreviations: ASA, American Society of Anesthesiologists; nCRT, neoadjuvant chemoradiotherapy.

[a]Preoperative neoadjuvant chemoradiotherapy.

[b]ypT downstaging was determined by comparing histopathology of ypT-stage in final resected specimen with mT-stage (mT3) as assessed by MRI before nCRT.

[c]American Society of Anesthesiologists (ASA) physical status classification system used to assess patient's pre-anaesthesia medical comorbidities.[28] Patients with ASA 3 have severe systemic disease that is not incapacitating and patients with ASA 4 have severe systematic disease that is a constant threat to the life of the patient.

[d]Assessed by histopathology examination of final resected specimen.

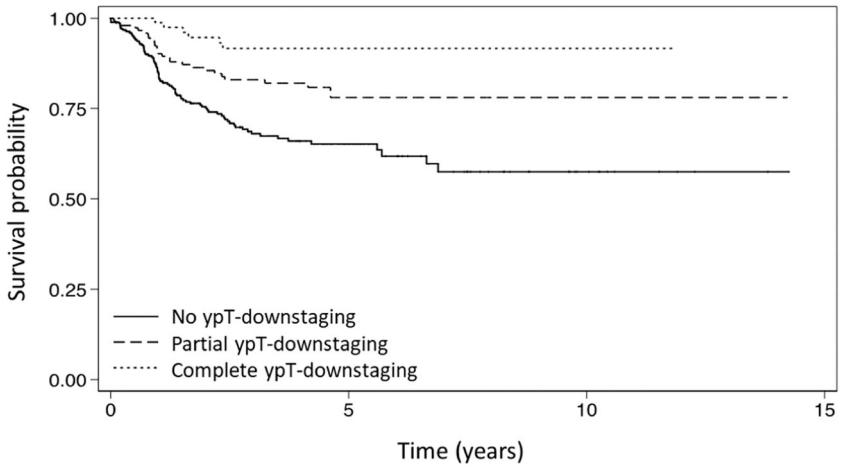
[e]Defined as ≥ypT3.

[f]Defined as ypT1 or ypT2.

[g]Defined as ypT0.

[h]Total recurrences (local and distal combined).

FIGURE 1 Recurrence-free survival by extent of ypT-stage downstaging of mT3 rectal tumours after neoadjuvant chemoradiotherapy



(95% CI: 1.10–2.79; $p = 0.02$) increased recurrence hazards, respectively, with evidence of a difference.

3.3.1 | Local versus distant recurrence

Recurrence location data were available for 111 individuals with tumour recurrences. Fifteen (13.5%) recurrences were locoregional and 96 (86.5%) were distant (Figure 2A). 100%, 91.3% and 84.3% of recurrences were distant in tumours with complete partial and no ypT-downstaging, respectively. Due to insufficient numbers of local and distant recurrences, subgroup analyses were not feasible.

KM curves examining local and distant recurrences separately indicated tumours with complete ypT-downstaging had superior RFS (Figure 2B,C).

4 | DISCUSSION

Following nCRT, 17.6%, 29.0% and 53.4% of mT3 rectal tumours had complete, partial and no ypT-downstaging, respectively, similar to previous estimates of pathological tumour responses post-nCRT.[4,26,34,35] Complete ypT-downstaging was not related to decreased risks of recurrence compared with no ypT-downstaging in multivariate analysis, adjusting for significant confounders and accounting for MRI inaccuracy (HR = 0.60; 95% CI: 0.23–1.56). However, ypN+ve and LVI were associated with a 2.3-fold and 1.8-fold increase in the risk of recurrence compared with ypN-ve and no LVI, respectively. Collectively, these results indicate that even patients with complete downstaging (ypT0 and ypN0) post-nCRT (i.e., complete pathological responders) do not have superior prognostic outcomes to patients with no ypT downstaging/pathological responses following nCRT. Further, patients achieving ypT0

TABLE 3 Univariate PH analyses and multivariate Cox PH analyses (accounting for MRI mT3 staging inaccuracy) examining the effect of covariates on recurrence-free survival (local and distance recurrence combined) in mT3 rectal cancer tumours after neoadjuvant chemoradiotherapy and major resection surgery

		Univariate analysis[h]			Multivariate analysis witha senstivity analysis[j]		
Covariate	**Measure**	**Hazard ratio**	**95% CI**	***p* value**	**Adjusted hazard ratio**	**95% CI**	***p* value**
Pathological response after nCRT[a] (extent of ypT-downstaging)[b] (*n* = 528)	No downstaging[e]	Reference			Reference		
	Partial downstaging[f]	**0.46**	**0.30-0.71**	**0.0004**	0.66	0.39–1.10	0.17
	Complete downstaging[g]	**0.21**	**0.10–0.44**	**0.00003**	0.60	0.23–1.56	0.3
Patient characteristics							
Gender	Female	Reference					
(*n* = 537)	Male	1.16	0.80–1.68	0.44	N/D[k]		
Age at diagnosis (years)	<35	Reference			Reference		
(*n* = 537)	≥35–<45	0.63	0.24–1.62	0.34	0.55	0.16–1.91	0.35
	≥45–<55	0.58	0.2–1.35	0.21	0.47	0.15–1.48	0.20
	≥55–<65	**0.45**[i]	**0.20–1.02**	**0.06**	**0.32**[l]	**0.11–0.98**	**0.05**
	≥65	**0.52**	**0.24–1.15**	**0.11**	**0.33**	**0.11–0.97**	**0.05**
ASA[c]	<3	Reference					
(*n* = 537)	≥3	0.98	0.66–1.44	0.898	N/D		
Diabetes	No	Reference			Reference		
(*n* = 531)	Yes	**0.59**	**0.33–1.04**	**0.07**	0.72	0.36–1.47	0.37
Hospital type	Private	Reference					
(*n* = 537)	Public	1.11	0.77–1.60	0.57	N/D		
Surgical method	Laparoscopic	Reference					
(*n* = 504)	Open	0.91	0.64–1.29	0.58	N/D		
Surgical procedure	APR	Reference			Reference		
(*n* = 537)	Ultra Low AR	**0.62**	**0.43–0.89**	**0.009**	**0.62**	**0.39–0.98**	**0.04**
Tumour characteristics							
Distance from anal verge (cm)	≤8 cm	Reference			Reference		
(*n* = 473)	>8 cm	**0.48**	**0.30–0.78**	**0.003**	**0.53**	**0.30–0.94**	**0.03**
lymphovascular Invasion[d]	No	Reference			Reference		
(*n* = 445)	Yes	**2.19**	**1.47–3.24**	**<0.001**	**1.75**	**1.10–2.79**	**0.02**
Lymph node status (ypN)[d]	Negative	Reference			Reference		
(*n* = 529)	Positive	**3.00**	**2.13–4.23**	**<0.0001**	**2.29**	**1.48–3.54**	**0.0002**
Tumour differentiation[d]	Poor	Reference					
(*n* = 427)	Poor-Moderate	1.01	0.41–2.48	0.98	N/D		
	Moderate	0.61	0.29–1.25	0.18	N/D		
	Moderate-Well	0.93	0.20–4.40	0.93	N/D		
	Well	0.82	0.18–3.88	0.81	N/D		

TABLE 3 (Continued)

Covariate	Measure	Univariate analysis[h]			Multivariate analysis witha senstivity analysis[j]		
		Hazard ratio	95% CI	*p* value	Adjusted hazard ratio	95% CI	*p* value
Postoperative treatment							
Adjuvant chemotherapy	No	Reference					
(*n* = 529)	Yes	0.88	0.58–1.34	0.56	N/D		
Time interval							
Period of time between completion of nCRT and surgery (*n* = 537)		1.00	0.97–1.03	0.89	N/D		

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; nCRT, neoadjuvant chemoradiotherapy; PH, proportional hazards.

[a]Preoperative neoadjuvant chemoradiotherapy.

[b]ypT downstaging was determined by comparing histopathology of ypT-stage in final resected specimen with mT-stage (mT3) as assessed by MRI before nCRT.

[c]American Society of Anesthesiologists physical status classification system used to assess patient's pre-anaesthesia medical comorbidities.[28] Patients with ASA 3 have severe systemic disease that is not incapacitating and patients with ASA 4 have severe systematic disease that is a constant threat to the life of the patient.

[d]Assessed by histopathology examination of final resected specimen.

[e]Defined as ≥ypT3.

[f]Defined as ypT1 or ypT2.

[g]Defined as ypT0.

[h]Univariate analysis to examine the effect of ypT downstaging after nCRT and all other covariates on RFS that did not include a sensitivity analysis to account for MRI inaccuracy in staging mT3 tumours.

[i]Boldface univariate results for covariates with $p < 0.15$ adjusted for in multivariate analysis with a sensitivity analysis.

[j]Multivariate Cox PH model with a sensitivity analysis to account for the inaccuracy of MRI to stage mT3 tumours, after adjusting for covariates with $p < 0.15$ in univariate analysis.

[k]Not done. Multivariate analysis did not include these covariates as covariates were not significant in univariate analysis ($p \geq 0.15$).

[l]Boldface are results with $p < 0.05$ in multivariate analysis with sensitivity analysis.

post-nCRT with ypN+ or LVI have a worse prognosis and while ypN+ and LVI may reflect difficulty in achieving pCR/ypT-downstaging, we adjusted for ypT-downstaging in these multivariate analyses.

While our findings conflict with previous studies reporting favourable prognostic outcomes associated with pCR, several prior studies did not adjust for relevant adverse prognostic factors in multivariate analysis.[3,4,36] In our analysis, we highlighted the importance of adjusting for LVI in multivariate analysis when we found complete ypT-downstaging significantly reduced the hazard of recurrence by 76% compared with no ypT-downstaging when we adjusted for all relevant covariates except LVI and accounted for MRI inaccuracy (HR = 0.34, 95% CI: 0.09–0.61, data not shown). Notably, while one study found the risk of recurrence was higher in poor responders post-nCRT compared with complete responders after adjusting for lymphovascular and perineural invasion in multivariate analysis,[10] this study did not account for pre-nCRT MRI-staging inaccuracy.

While we examined ypT-downstaging post-nCRT whereas most prior studies examined pCR, we demonstrated high correlation between ypT-downstaging and pathological responses. The use of ypT-downstaging post-nCRT as a proxy for pathological responses also avoided inconsistencies associated with employing different TRG systems to stratify responses (6-point grade,[20,21,25,26] Mandard 5-point[22,35] or the Rodel et al.[2] system)[2,37,38] and subjectivity associated with assessing TRG. Moreover, predictors of prognostic outcomes are not well-established. Bujko et al.[25] found ypT-category, not TRG, was an independent predictor of nodal disease, in support of our approach using ypT-downstaging to examine prognostic outcomes. Conversely, Huebner et al.[37] found both TRG and ypN status were independent prognostic markers of DFS, whereas other studies found ypN status alone[2,35] or TRG alone were significant prognostic markers.[38] Further, Dhadda et al.[35] found perineural invasion, circumference resection margin and Mandard TRG,[22] were significant predictors of DFS. Wheeler et al. found the correlation between tumour regression and downstaging was often inconsistent and R0 resection was a significant predictor of local recurrence.[20,39] However, we were unable to examine the effect of R0 resection on RFS due to an insufficient number of involved margins.

In the present study, bootstrapping minimised the effect of MRI mT-staging inaccuracy in analyses, thereby providing greater confidence that cases started as mT3 and any ypT-downstaging found on histopathology was genuine. MRI N-staging inaccuracies were circumvented by adjusting for ypN status in multivariate analyses, as mentioned. Subsequently, the finding of no association between ypT-downstaging and RFS is applicable for either ypN+ve or ypN-ve.

(A)

Recurrence		Extent of downstaging after nCRT			
		None	Partial	Complete	Total
Local	No. tumors	13	2	0	15
	Percentage	86.7%	13.5%	0.0%	100%
Distant	No. tumors	74	21	5	100
	Percentage	74.0%	21.0%	5.0%	100%
Total	No. tumors	87	23	5	115
	Percentage	75.7%	20.0%	4.3%	100%

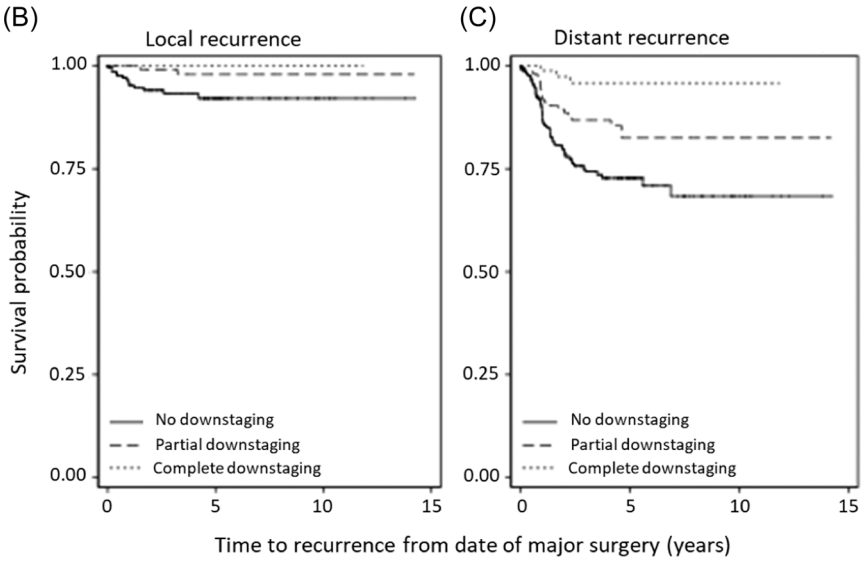


FIGURE 2 Local and distant recurrence by extent of ypT-stage downstaging of mT3 rectal tumours after neoadjuvant chemoradiotherapy. nCRT, neoadjuvant chemoradiotherapy. (A) Number and rates of local and distant recurrences of mT3 rectal tumors that with complete, partial and no ypT-downstaging following chemoradiotherapy (nCRT). (B) and (C) Kaplan-Maier plots representing an unadjusted univariate analysis of recurrence-free survival for local and distant recurrence (examined separately) by extent of ypT-stage downstaging of mT3 rectal tumors after nCRT

The effect of different tumour characteristics on the ability to achieve pCR and prognostic outcomes raises interesting issues concerning the biology of rectal tumours. Consistent with our findings, a Swedish study of 2649 stage II rectal cancers found LVI increased the hazard of recurrence 1.44-fold (95% CI: 1.09–1.90) in multivariate analysis, adjusting for known confounders, perineural invasion and mucinous histology, however, results were not stratified by nCRT use.[14] Further, a study of 4170 ypT0 rectal tumours post-nCRT by Baucom et al.[40] found LVI was also a predictive factor for ypT0N+ on final histopathology (adjusted odds ratio = 7.25; 95% CI: 3.93–13.37).

Consistent with our findings, Bujko et al.[25] found ypN+ post-nCRT was associated with tumour recurrence. In another study of 6555 LARCs, both clinical and histopathological N-stage post-nCRT were found to be independent risk factors for poorer survival in multivariate analyses.[15] Notably, nodal stage is considered an important factor for advising organ preserving treatment for tumours with pCR. Baucom et al. found ~10% of ypT0 rectal tumours were ypN+ on final histopathology, with 5-year survival differing significantly between ypN0, ypN1 and ypN2 ($p = 0.002$).[40] However, Habrgama et al.[41] found patients with pCR with positive nodal status that did not undergo major surgery were not at increased risk of tumour recurrence or more advanced metastatic disease compared with negative nodal status (39.7% vs. 46.8% 5-year surgery-free survival). However, only 62 positive and 135 negative nodal patients were examined and the authors acknowledged the potential nodal staging inaccuracy.

Distant recurrences represented the main cause of treatment failure for tumours with complete, partial or no ypT-downstaging post-nCRT, consistent with previous reports of improved local control and predominantly distant recurrences, especially for pCR.[42–44]

Whilst prognostic outcomes in complete pathological responders with and without adjuvant chemotherapy is the focus of recent studies,[45–49] our univariate analysis found no association between adjuvant chemotherapy and RFS. It is also pertinent to consider our findings in the context of potentially improved outcomes (longer DFS and metastasis-free survival) for LARCs following TNT, compared with standard long-course nCRT.[8] However, our study design could be equally applied to measure prognostic outcomes associated with ypT-downstaging following TNT.

Strengths of the present study include our robust survival methodology and comprehensive list of clinical variables, including tumour characteristics and precise nCRT and postoperative adjuvant chemotherapy regimens (type, dose and timing) and outcomes (recurrence and mortality). Subsequently, only data from individuals completing long-course nCRT ($n = 528$) were included in analyses. With 93 patients achieving complete ypT-downstaging, our study represents one of the largest studies examining prognostic outcomes post-nCRT.

Potential limitations include the failure to adjust for prognostic factors not collected in Biogrid, including MRI-measured depth of neoplastic infiltration within perirectal fat, perineural invasion, EMVI and proximity to circumferential resection margin (CRM).[10,35,50] While UK practice focusses on tumour proximity to CRM,[35] MRI mT-stage ≥3 is the primary determinant for nCRT in Australia and MRI restaging post-nCRT to assess downstaging and measure CRM is not routinely performed. While MRI-measured EMVI has been associated with adverse prognosis in LARC,[12] we indirectly addressed EMVI by measuring LVI on final histopathology.

5 | CONCLUSION

The present study is the first to examine prognostic outcomes following nCRT that accounted for pre-nCRT MRI-staging inaccuracy in multivariate analysis and adjusted for several significant confounders. These comprehensive analyses found complete or partial ypT-downstaging following nCRT in mT3 rectal cancer was not associated with improved RFS compared with no ypT-downstaging. Subsequently, ypT-downstaging (correlating to pathological response) post-nCRT should not be regarded as a favourable prognostic factor and adverse prognostic factors including ypN+ status and LVI need to be considered in future treatment regimens. Extrapolating from these results, following nCRT, evidence of regression of mural tumour found on repeat imaging or endoscopy (consistent with ypT-downstaging) before surgery may not translate to reduced metastatic potential. This has possible implications in decision making for cases considered for a nonoperative approach especially when nodal status appears negative.

AUTHOR CONTRIBUTIONS

Ian P. Hayes, Elasma Milanzi and Jeanette C. Reece were responsible for the study concept and design and data acquisition. Ian P. Hayes, Elasma Milanzi, Rachel M. Pelly, Peter Gibbs and Jeanette C. Reece were responsible for interpretation of the results. Ian P. Hayes, Elasma Milanzi and Jeanette C. Reece were responsible for writing the report. Elasma Milanzi was responsible for the analysis. Ian P. Hayes, Elasma Milanzi, Rachel M. Pelly, Peter Gibbs and Jeanette C. Reece were responsible for approving the final draft of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict interest.

DATA AVAILABILITY STATEMENT

The reidentifiable data used in the study are derived from Biogrid Australia https://www.biogrid.org.au/. Biogrid have not verified and are not responsible for the statistical methodology employed, or the conclusions drawn by the investigators using this data.

ETHICS STATEMENT

Biogrid data was collected from patients' clinical notes, supported by radiology and histopathology reports. Study ethics approval was obtained from Melbourne Health/Biogrid HREC, no. BG-201905/8. This study was performed in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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