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Prognostic importance of Mandard tumour regression grade following pre-operative chemo/radiotherapy for locally advanced rectal cancer

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ABSTRACT

Purpose: To assess the prognostic value of the Mandard tumour regression score (TRG) following pre-operative chemo/radiotherapy in patients with locally advanced rectal cancer.
Methods and materials: The study involved 158 patients with locally advanced rectal cancer treated with pre-operative long course chemo/radiotherapy at Nottingham University Hospital between April 2001 and December 2008. Patients were treated with radiotherapy to a dose of 50 Gy in 25 fractions over 5 weeks with or without concurrent capecitabine chemotherapy at a dose of 1650 mg/m^2/day. Surgery was normally performed after an interval of 6–10 weeks. The response to pre-operative treatment was carefully graded by a single pathologist using the five point Mandard score. The median follow-up was 40 months (range 3–90 months).
Results: Of the 158 patients 14% were TRG1, 41% were TRG2, 31% were TRG3, 13% were TRG4 and 1% were TRG5. The groups were combined into TRG1, TRG2 and TRG3–5 to simplify further analysis. The Mandard score was clearly related to both disease-free ($p < 0.001$) and overall survival ($p = 0.012$). On multivariate analysis perineural invasion, nodal status, TRG and circumferential resection margin status were the most powerful predictors of disease-free survival.
Conclusions: The Mandard tumour regression score is an independent prognostic factor and predicts for long-term outcome following pre-operative chemo/radiotherapy in rectal cancer.

1. Introduction

Rectal cancer is the third commonest malignancy worldwide. There are 13,000 new cases and 5000 deaths within the UK every year.[1] Pre-operative chemo/radiotherapy is now considered standard treatment for patients with a locally advanced rectal cancer and a threatened circumferential resection margin.[2] The primary purpose of chemo/radiotherapy is to improve local control and resectability. However, response to pre-operative therapy has been shown to be linked to long-term outcome in several studies.[3–6]

Various scoring systems have been developed to grade the response to pre-operative chemo/radiotherapy although none has gained universal acceptance. The Mandard scoring system has been shown to be prognostic for patients following pre-operative chemo/radiotherapy in oesophageal cancer.[7]

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Our prior work has revealed that it strongly predicts for response to pre-operative chemo/radiotherapy in rectal cancer.[8]

The purpose of the current study was to explore whether the Mandard scoring system was prognostic in rectal cancer. Currently the lack of a standard method to assess pathological tumour response following pre-operative chemo/radiotherapy in rectal cancer remains a major source of discrepancy in studies.

2. Methods and materials

All patients referred to Nottingham City Hospital, UK, between April 2001 and December 2008 for long-course pre-operative chemo/radiotherapy before surgery for rectal cancer were identified. All of these patients had locally advanced rectal cancer, cT3/4 and/or N+ and were considered inoperable or of borderline resectability due to potential circumferential resection margin (CRM) involvement. There was a policy change in the department in May 2004 with concurrent chemotherapy becoming the standard of care. Therefore there was a cohort of patients who had had radiotherapy alone and a cohort who had combined treatment. In total, 175 patients were identified. Three patients who had radiotherapy alone had to be excluded as they refused to have surgery upon the completion of radiotherapy. Two patients who had concomitant chemotherapy died of non-neutropenic bronchopneumonia before surgery. This left a cohort of 53 patients who had been treated with pre-operative radical radiotherapy alone and 117 patients treated with concurrent chemo/radiotherapy. Pretreatment work-up consisted of digital rectal examination, sigmoidoscopy and biopsy, barium enema, pelvic magnetic resonance imaging (MRI)/computed tomography and computed tomography of the chest and abdomen. All patients were discussed at a multidisciplinary team meeting consisting of specialist colorectal surgeons, oncologists and radiologists before being referred for neoadjuvant treatment. The study was approved by the Nottingham University Hospital ethics committee before commencement.

2.1. Radiotherapy technique

All rectal radiotherapy was computed tomography planned, with the patient in the prone position, with a marker at the anal margin. The radiotherapy technique used has been previously described.[8] Patients were treated with an Elekta linear accelerator using 10 MV photons to a prescribed dose of 50 Gy in 25 fractions to the International Commission on Radiation Units reference point. Fractionation was 2 Gy/day, 5 days/week with all fields being treated daily.

2.2. Chemotherapy

The standard of care at Nottingham City Hospital changed in May 2004, with locally advanced rectal cancer patients being treated with concurrent capecitabine and pre-operative radical radiotherapy. One cycle of capecitabine was given (1250 mg/m^2 twice a day for 14 of 21 days) whilst the radiotherapy planning was in progress. During the concurrent phase of the treatment, the dose was reduced to 825 mg/m^2 twice a day daily throughout the radiotherapy. There was no change in the radiotherapy dose fractionation, with all patients having 50 Gy in 25 fractions. Adjuvant chemotherapy was given to all patients postoperatively unless there was no evidence of tumour response to chemo/radiotherapy.

2.3. Surgery

All surgery was carried out by dedicated colorectal surgeons experienced in the management of rectal cancer, with surgery generally scheduled 6–8 weeks after the completion of radiotherapy (see acknowledgements). This was undertaken at the Nottingham University Hospital or Kings Mill Hospital, Sutton-in-Ashfield, Nottinghamshire. The choice of surgical procedure was left to the individual surgeon's discretion.

2.4. Pathology

The pathological specimen after resection was reviewed by a single pathologist (AMZ). The tumour volume in the resected specimen was assessed by macroscopic and microscopic examination. Large and small blocks were taken through the complete transverse section of the possible tumour mass. The response to radiotherapy was graded by a single pathologist (AMZ) using a rectal radiotherapy grading system adapted from Mandard et al.[7] This comprised the following:

TRG 1: complete response with absence of residual cancer and fibrosis extending through the wall.
TRG 2: presence of residual tumour cells scattered through the fibrosis.
TRG 3: increase in the number of residual cancer cells, with fibrosis predominant.
TRG 4: residual cancer outgrowing fibrosis.
TRG 5: absence of regressive changes.

The tumour specimens were subsequently reviewed independently by a separate pathologist (NG) to allow an assessment of inter-observer variability between two pathologists.

2.5. Follow up

Patients were followed up prospectively in the Colorectal Cancer clinic for at least 5 years. Frequency of follow-up was initially every 3 months with tumour marker assessment and clinical examination. Routine CT scans were carried out at 18 and 36 months to exclude distant metastases.

2.6. Statistical analysis

All statistical analysis was carried out using the SPSS 16.0 statistical program. Overall and disease-free survival analyses were undertaken using Kaplan Meier analysis. Chi-square was used to compare local recurrence and nodal status rates for Mandard score and T stage. Multivariate analysis using Cox Regression was performed on variables which were significant on univariate analysis. Differences of $p < 0.05$ were considered of statistical significance. The inter-observer variability between pathologists for the tumour regression

Table 1 – Demographical characteristics of patients in study.

Demographical characteristics	
Age (median)	65 years (range 29–86)
Sex	
Male	105 (66%)
Female	53 (34%)
Site of tumour	
Upper	21 (13%)
Mid	67 (42%)
Lower	70 (44%)
Pre-op treatment	
Radiotherapy alone	44 (28%)
Concurrent chemo/radiotherapy	114 (72%)
Interval to surgery (median)	65 days (range 15–328)
Type of resection	
Anterior resection	73 (46%)
Abdomino-perineal resection	62 (39%)
Hartmans	21 (13%)
Pelvic exenteration	2 (1%)
Resection margin	
R0	141 (89%)
R1	17 (11%)
Pathological response (Mandard)	
TRG 1	22 (14%)
TRG 2	65 (41%)
TRG 3	49 (31%)
TRG 4	20 (13%)
TRG 5	2 (1%)

grading systems was measured using the Cohen Kappa statistic. Kappa values of >0.75 were taken as showing excellent agreement.

3. Results

There was a cohort of 53 patients who had radiotherapy alone. Nine patients out of this series did not proceed to a surgical resection, either because of irresectable tumour or discovery of peritoneal/liver metastases at the time of laparotomy. This left a total of 44 patients who were evaluated. One hundred and seventeen patients were treated with concomitant chemotherapy. In this series, three patients were found to have irresectable tumour or peritoneal metastases at the time of surgery and, hence, no resection was carried out. There were thus 114 patients in this cohort who were evaluated and therefore a total of 158 patients included in this study (Table 1). Of the 158 patients 22 (14%) were TRG1, 65 (41%) were TRG2, 49 (31%) were TRG3, 20 (13%) were TRG4 and 2 (1%) were TRG5. There was a good agreement between the two pathologists with regards to the Mandard score (Kappa = 0.85, $p < 0.001$). Median follow-up was 40 months (range 3–90 months). One patient was lost to follow-up.

There were 66 recurrences and 49 deaths over the follow-up period in this series. The addition of chemotherapy to pre-operative radiotherapy was found to have no impact on either disease-free ($p = 0.81$) or overall survival ($p = 0.08$). There was no benefit found for analysing TRG3, 4 and 5 separately possibly due to the small numbers in TRG 4 and 5. As

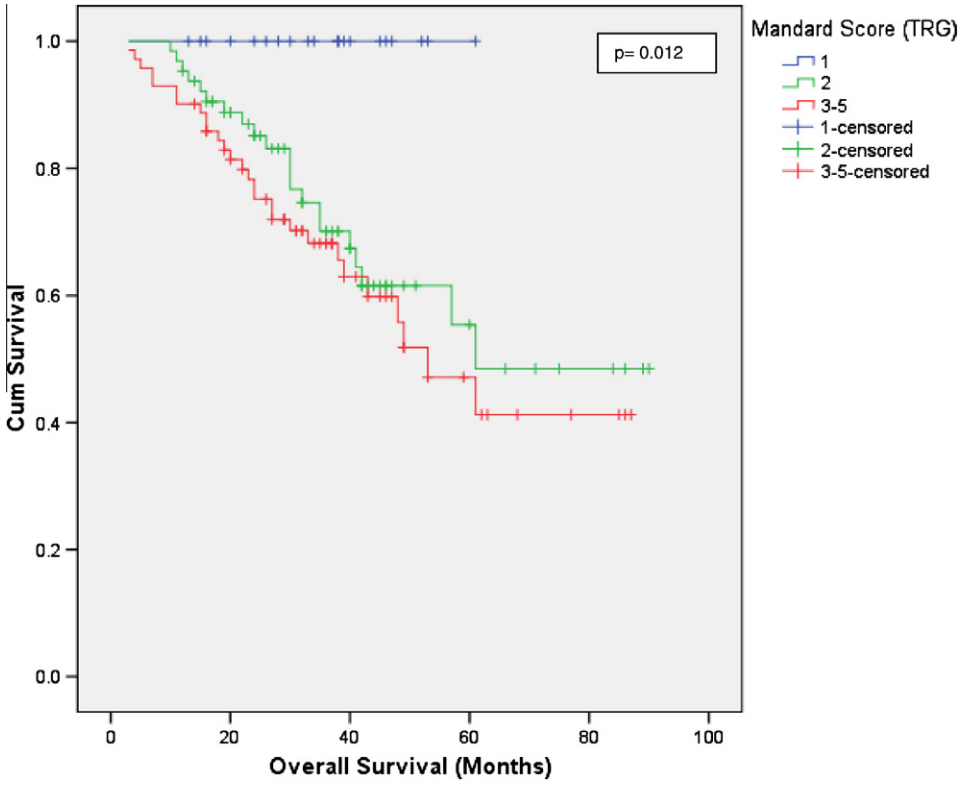

Fig. 1 – Overall survival (months) for patients with locally advanced rectal cancer following pre-operative chemo/radiotherapy according to Mandard score.

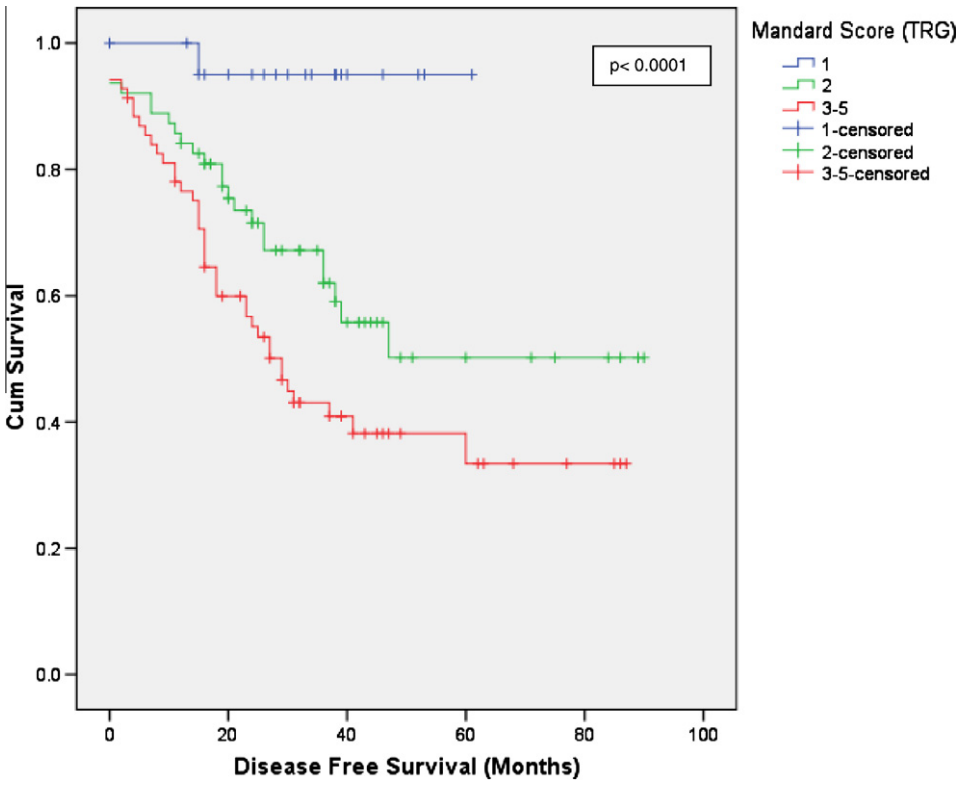

Fig. 2 – Disease-free survival (months) for patients with locally advanced rectal cancer following pre-operative chemo/radiotherapy according to Mandard score.

TRG3–5 represent tumours with poorer response to pre-operative treatment the groups were collated into TRG 1, TRG 2 and TRG 3–5 for further analysis. On Kaplan–Meier survival analysis the TRG score was clearly related to both disease-free ($p < 0.0001$) and overall survival ($p = 0.012$) as shown in Figs. 1 and 2 and Table 2. The disease-free survival and overall survival for patients who had a complete pathological response (TRG 1) was 95% and 100% at 5 years, respectively.

There were 12 local recurrences (16/158 = 10%) in this series. The local recurrence rate per Mandard score was: TRG1 5%, TRG2 6%, TRG3–5 15%. This was not statistically significant on Chi-square testing ($p = 0.24$). The nodal metastasis

Table 2 – Disease-free (DFS) and overall (OS) survival according to Mandard score.

	DFS		OS	
	Median	5 year	Median	5 year
TRG1	NR	95%	NR	100%
TRG2	NR	50%	61 months	55%
TRG3–5	25 months	33%	48 months	41%
		$p < 0.0001$		$p = 0.012$

Table 3 – Multivariate Cox Regression analysis of independent predictors of disease-free survival (CRM = circumferential margin status, PNI = perineural invasion, TRG = tumour regression grade).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Variables in the equation								
TRG	.480	.226	4.520	1	.034	1.617	1.038	2.517
Nodal_Status	.810	.172	22.302	1	.000	2.248	1.606	3.147
PNI	1.090	.280	15.121	1	.000	2.975	1.717	5.155
CRM	−1.040	.334	9.715	1	.002	.353	.184	.680

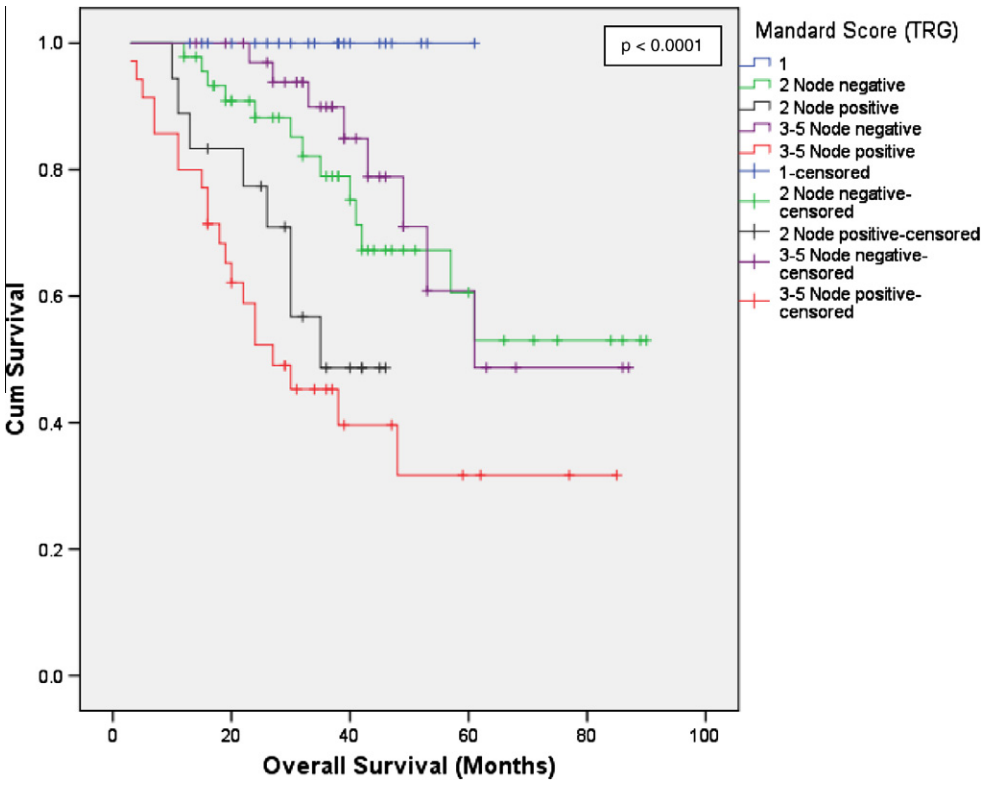

Fig. 3 – Overall survival according to Mandard score stratified by nodal status.

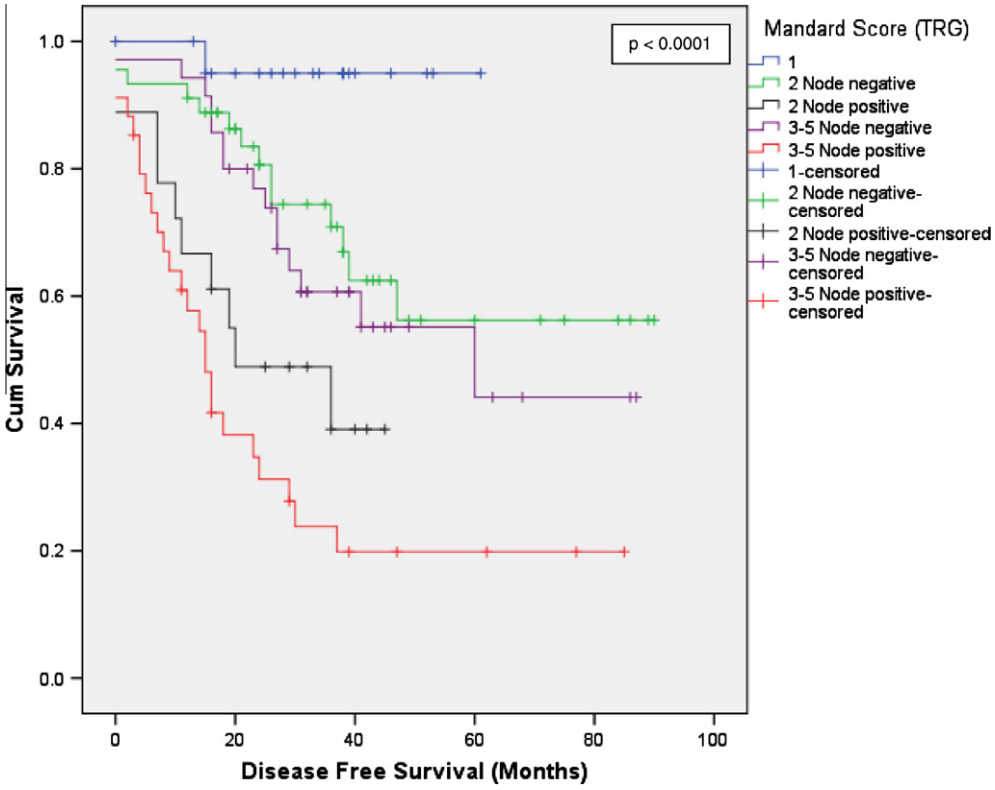

Fig. 4 – Disease-free survival (months) according to Mandard score stratified by nodal status.

rate per Mandard score was: TRG1 0%, TRG2 28%, TRG 3–5 50%, this was statistically significant on Chi-square testing ($p < 0.0001$). In comparison the nodal metastasis rate was 0% for ypT0, 0% for ypT1, 17% for ypT2, 49% for ypT3 and 50% for ypT4 ($p < 0.0001$).

On Cox Regression analysis Mandard score, perineural invasion, circumferential resection margin status and nodal status were found to significantly predict for disease-free and overall survival (Table 3). In contrast T stage and vascular invasion were not found to be independently prognostic on multivariate analysis.

When the data were analysed to take into account node positivity and Mandard score it became clear that in TRG groups 2, 3–5 nodal status plays an important part in future prognosis ($p < 0.0001$). This is shown in Figs. 3 and 4 and Table 4. Hence, it would seem logical that the presence of nodal metastases should be either incorporated into the TRG system or considered separately. The interval between relapse and death was short in patients with node positive disease with a median of 10 months for TRG 2 and 8 months for TRG 3–5.

If nodal status was to be incorporated into a tumour regression grade we would propose a simplified system as follows:

TRG 1: complete response with absence of residual cancer and fibrosis extending through the wall.
TRG 2: presence of residual tumour cells scattered through the fibrosis.
TRG 3: increase in the number of residual cancer cells, with fibrosis predominant.
TRG 4: macroscopic tumour; absence of regressive changes; any node positive within irradiated volume.

Using this new proposed system the inter-observer variability between our pathologists was measured using

Table 4 – Disease-free (DFS) and overall (OS) survival according to Mandard score stratified by nodal status.

	n	DFS		OS	
		Median	5 year	Median	5 year
TRG2 node negative	47	NR	57%	NR	60%
TRG2 node positive	18	20 months	39%	35 months	
TRG3–5 node negative	36	60 months	50%	61 months	49%
TRG3–5 node positive	35	15 months	20%	27 months	32%
			$p < 0.0001$		$p < 0.0001$

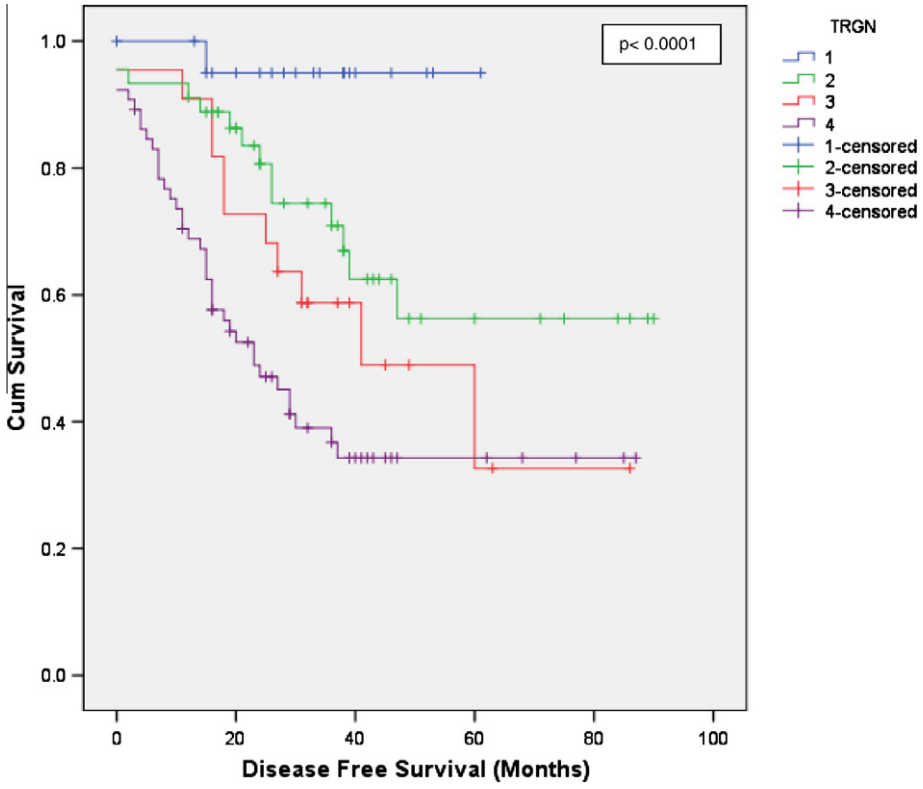

Fig. 5 – Disease-free survival (months) for patients with locally advanced rectal cancer according to new proposed tumour regression system (TRGN).

Table 5 – Multivariate Cox Regression analysis of independent predictors of disease-free survival (CRM = circumferential margin status, PNI = perineural invasion, TRGN = new proposed tumour regression grade).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Variables in the equation								
PNI	1.192	.279	18.270	1	.000	3.293	1.907	5.687
CRM	−1.101	.331	11.052	1	.001	.332	.174	.636
TRGN	.433	.144	9.035	1	.003	1.543	1.163	2.047

the Cohen Kappa statistic and found to have excellent agreement (Kappa = 0.89, $p < 0.0001$). The new system significantly predicted for long term disease-free survival on Kaplan–Meier analysis as shown in Fig. 5. On Cox multivariate analysis it independently and significantly predicted for disease-free survival along with circumferential margin status and presence of perineural invasion (Table 5).

4. Discussion

Downstaging of tumours is generally reported in studies and has been shown be predictive of outcome. However, using only downstaging alone may not necessarily be an accurate reflection of a tumours response to pre-operative therapy. The weakness of using simply downstaging on T stage to assess response is that a tumour may have regressed little but may have been downstaged from T3 to T2 whilst a tumour showing a good response with only microscopic foci of tumour cells in the subserosa may still be staged as T3. Hence, there appears to be a distinct need to adopt a response grading system to pre-operative therapy alongside the tradition ypTNM staging system to allow patients to be allocated into appropriate prognostic groups. Indeed a recent study has shown that pathologic response assessed by Mandard grade is a better prognostic factor than down staging for disease-free survival after pre-operative chemo/radiotherapy for advanced rectal cancer.[9]

The scoring system developed by Mandard to evaluate tumour regression in patients with oesophageal cancer treated with pre-operative chemo/radiotherapy was shown to be an independent predictor of disease-free survival. Several response grading systems have been proposed; all of which have their own inherent weaknesses and hence have not been widely adopted.

Lossi et al. used the five point Dworak system retrospectively in 106 patients with resected locally advanced rectal cancers following pre-operative chemo/radiotherapy.[10] Overall the grading system along with tumour downstaging and pathological stage were found to be prognostic factors. However, there was overlap and little difference between grades 2 and 3 (GR3: very few tumour, difficult to find, in fibrotic tissue; GR 2: predominantly fibrotic tissue with few tumour cells which are easy to find) with the definitions allowing for a degree of subjectivity. The grade of regression on multivariate analysis was statistically significant although the groups were divided into two, GR3–4 and GR0–2, for this purpose. The analysis also did not include pathological T and N stage. Similarly Vecchio et al. used the Mandard system and showed that it was prognostic but again only if grouped into TRG1–2 and TRG 3–5.[11] This retrospective study of 144 patients also had six different pre-operative chemo/radiotherapy schedules as well as 34 patients having intraoperative radiotherapy.

Wheeler et al. retrospectively reviewed surgical specimens of 42 patients with T3/4 rectal cancer treated with pre-operative chemo/radiotherapy.[12] The tumour specimens were analysed by a single pathologist into three grades of regression: RCRG 1: either pCR or microscopic foci of adenocarcinoma, RCRG 2: marked fibrosis with macroscopic tumour, RCRG 3: poor response with little or absent fibrosis in presence of abundant macroscopic tumour. Certainly several studies suggest that patients with a pCR consistently have an excellent prognosis and hence this probably should be considered separately from patients with residual microscopic foci of disease.[13,14] Whether residual tumour cell density is an important factor remains unknown with Berger et al.[15] suggesting this is not prognostic but Kaminsky-Forrett et al.[16] suggesting patients having rare foci of residual tumour have a better survival rate.

Our study shows that one of the most important prognostic factors on multivariate analysis is the presence of positive nodes. The presence of positive nodes within the irradiated volume may indicate resistance of tumour cells to pre-operative therapy. Nodal metastases are normally of smaller volume and hence should be better oxygenated and more radiosensitive than primary tumours. From radiobiological principles we should see regression of tumour at an earlier stage in smaller volume nodal metastases. Residual nodal metastases post chemo/radiotherapy could signal both chemotherapy and radiotherapy resistance and hence it is not surprising that these patients have a poorer prognosis. This seems to be confirmed by the short interval between relapse and death in these patients with prognosis being in the order of 8–10 months despite further palliative chemotherapy. The new grading system proposed would allow integration of nodal status into a tumour regression system. We would like to stress that this does require validation before its use can be advocated routinely but does warrant further investigation.

Adjuvant chemotherapy following pre-operative chemo/radiotherapy in rectal cancer remains controversial. Data from the EORTC 22921 trial suggested a trend towards benefit of adjuvant therapy with 5FU but was not adequately powered to answer this question. The subgroup analysis by Collette suggested a benefit of adjuvant chemotherapy for patients downstaged to T0–2 with no apparent benefit for patients T3–4.[17] Patients who have a pCR may actually have very little to gain from further chemotherapy.[18]

As the TRG score does appear to be a strong independent prognostic factor, following pre-operative chemo/radiotherapy, it may be logical to consider its use when considering

patients for further adjuvant treatment. Patients with TRG1/2 are more likely to have fluoropyrimidine sensitive tumours and hence may benefit from further adjuvant fluoropyrimidine chemotherapy. TRG3–5 or node positives have a poorer prognosis as shown in our study and may require more intensive combination chemotherapy. This again would need to be validated in future studies of adjuvant chemotherapy following pre-operative chemo/radiotherapy for rectal cancer.

We have shown that the Mandard TRG score is a prognostic factor and its utilisation would allow us to refine the prognostic groups we allocate patients into following pre-operative chemo/radiotherapy on top of the ypTNM staging system. We are currently lacking prospective studies where tumour regression grading systems have been employed. There are data to suggest that the consistency between pathologists and reproducibility of tumour regression grade scoring systems is good enough for clinical use.[19] The agreement of a reliable consistent method to evaluate tumour regression remains a priority. This would allow further individualisation of any proposed adjuvant therapy as well as consistency of reporting between studies.

Conflict of interest statement

None declared.

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