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MRI-DIAGNOSED TUMOUR DEPOSITS AND EMVI STATUS HAVE SUPERIOR PROGNOSTIC ACCURACY TO CURRENT CLINICAL TNM STAGING IN RECTAL CANCER

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Running head: Improved MRI staging in Rectal Cancer

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MINI ABSTRACT

There is increasing recognition that TNM-based staging is an oversimplification of the true manifestations of rectal cancer spread, and has limited prognostic power. In this study, only tumour deposits and EMVI status were predictive of prognosis on MRI. Clinical staging needs radical modification to improve prognostic prediction and treatment planning.

ABSTRACT

Summary Background Data: MRI assessment of rectal cancer not only assesses tumour depth and surgical resectability but also extramural disease which affects prognosis. We have observed that non-nodal tumour nodules (tumour deposits; mrTDs) have a distinct MRI appearance compared to lymph node metastases (mrLNMs).

Objective: We aimed to assess whether mrTDs and mrLNMs have different prognostic implications and compare these to other known prognostic markers.

Methods: This was a retrospective cohort study of 233 patients undergoing resection for rectal cancer from January 2007-October 2015. Data were obtained from electronic records and MRIs blindly re-reported. Survival was determined using Kaplan-Meier method. Prognostic markers were evaluated using Cox regression and competing risks analysis. Inter-observer agreement for mrTD was measured using Cohen's Kappa.

Results: On multivariable analysis, baseline mrTD/mrEMVI (extramural venous invasion) status was the only significant MRI factor for adverse survival (HR 2.36(1.54-3.61) for OS, 2.37(1.47-3.80) for DFS (both p<0.001), superseding T and N categories. mrLNMs were associated with good prognosis (HR 0.50(0.31-0.80)p= 0.004 for OS, 0.60(0.40-0.90)p=0.014 for DFS). On multivariable analysis, mrTDs/mrEMVI were strongly associated with distant recurrence (HR 6.53(2.52-16.91)p=<0.001) whereas T and N category were not. In a subgroup analysis of post-treatment MRIs in post-chemoradiotherapy (CRT) patients, mrTD/mrEMVI status was again the only significant prognostic factor; furthermore those who showed a good treatment response had a prognosis similar to patients who were negative at baseline. Inter-observer agreement for detection of mrTDs was κ0.77 and κ0.83.

Conclusion: Current MRI staging predicting T and N status does not adequately predict prognosis. Positive mrTD/mrEMVI status has greater prognostic accuracy and would be superior in determining treatment and follow-up protocols. CRT may be a highly effective treatment strategy in mrTD/mrEMVI positive patients.

INTRODUCTION

Magnetic resonance imaging (MRI) plays a pivotal role in the assessment of rectal cancer. MRI can both predict prognosis and determine the optimal treatment strategy by detecting factors such as circumferential resection margin (CRM) involvement, extramural venous invasion (EMVI) status and depth of direct tumour invasion(1). MRI staging in its current form attempts to predict the pathological AJCC/UCC Tumour Node Metastasis (TNM) stage of the tumour because this is considered to be linked to prognosis. There have been noted limitations to using MRI in this way. Firstly, predicting the presence of lymph node metastases (LNMs) on MRI is only moderately accurate. In the past there has been a focus on the size of lymph nodes with the assumption that enlarged nodes will contain tumour. This has been largely disproved(2,3) in that size alone has low accuracy and other features must be taken into account. Additionally, predicted nodal status on MRI has not been shown to be as prognostically useful as MRI assessment of EMVI and CRM status(1,4–6).

It is now increasingly appreciated that not all "nodules" seen in the mesorectal fat represent lymph nodes. There remains considerable overlap in the pathological diagnosis of LNMs and extranodal tumour deposits (TDs), predominantly due to changing definitions in each TNM edition (7). However, there is increasing evidence that TDs indicate a worse prognosis compared with LNM status (8,9) suggesting that distinguishing between these two entities may be of great importance. It is only very recently that efforts have been made to distinguish TDs from LNMs on MRI. We have observed that TDs have a completely different appearance to lymph nodes on MRI. TDs are seen as irregular nodules within the mesorectum and appear to directly interrupt the course of veins but are discontinuous from the primary tumour (figure 1). TDs can be distinguished from LNMs as they cannot be separated from the vein when assessed on two orthogonal views and tend to taper into the vein (described as a comet-tail appearance) rather than being alongside the vein and forming an acute angle. This relationship with veins is not always evident on histopathology due to the nature of the discrete sections used and the fact that the vessel may have been completely destroyed by tumour/radiotherapy within the area being examined. With the benefit of three-dimensional MRI, the relationship of TDs to venous anatomy will still be visible in these cases.

The primary objective of this study was to determine whether tumour nodules that are not lymph nodes, as seen on MRI (mrTDs), have a different prognostic effect to that of mrLNMs on both pre- and post-treatment imaging. We also aimed to document the prevalence of TDs both pre- and post chemoradiotherapy and determine how reliably TDs were identified by radiologists. Secondary objectives were to compare mrTDs against other known MRI and pathological prognostic features to determine their individual contribution to prognosis.

METHODS

Local ethics approval was obtained from the hospital's research and development committee. Patients were identified from a prospectively maintained institutional database, which included patient data from a referral network of 6 hospitals, in additional to national and international tertiary referrals. All patients had been discussed in a central colorectal cancer multi-disciplinary team (MDT) meeting where individual treatment plans were determined. MRI scans were carried out and reported as per previously published guidelines(10). Standard management included consideration of CRT for all locally advanced tumours threatening the CRM as well as those with mrEMVI. All patients who had received CRT were given adjuvant chemotherapy (unless there were other contraindications) regardless of histopathology results. Those who had positive LN on histopathology but had not undergone CRT were also given adjuvant chemotherapy (again unless there were contraindications).

Consecutive patients undergoing resectional surgery for rectal cancer within the South West London Cancer Network between January 2007 and October 2015 were eligible for inclusion in the study. The end of the follow up period was October 2018 to ensure that at least 3 years follow up was available for all patients. Patients were eligible for inclusion if they had a primary rectal or rectosigmoid tumour (as defined on MRI) and underwent surgery with curative intent. Patients in the deferral of surgery trial were excluded. Other exclusion criteria included inability to undergo MRI, synchronous tumours, distant metastatic disease at presentation, early tumours removed with endoscopic treatment or local excision only, patients undergoing total pelvic exenteration, or disease which subsequently was proved not to be colorectal adenocarcinoma. Patients treated with palliative intent for any other reason (e.g. patient wishes, frailty) were also excluded. If no follow up data was available for international or national patients who had returned to their referral hospital after surgery they were excluded.

Demographic data, MRI and pathology results and follow up data were obtained from electronic hospital records. MRI scans from before 2012 (when mrTD status started to be routinely included in reports) were blindly re-reported for mrTD status on both pre- and post-treatment scans if applicable, by an experienced consultant radiologist who was blinded to the patient's outcome. Some of the MRIs had previously been reported by the same radiologist but, as only MRIs from before 2012 were re-reported, at least 6 years had elapsed by the time of re-review. To test whether these results would be reproducible, a sample size of 35 MRI studies were reviewed by two further consultant radiologists from separate institutions to test inter-rater agreement for the detection of mrTDs.

To test the primary endpoint, we determined the effect of having mrTDs compared with mrLNMs on overall survival (OS), disease-free survival (DFS), overall, local and distant recurrence. For secondary endpoints we also determined the above outcomes according to mrT stage, mrEMVI, mrCRM, pT/ypTstage, pLNM/ypLNM, pTD, pEMVI/ypEMVI, pCRM/ypCRM and tumour differentiation. In those patients undergoing long course chemoradiotherapy (CRT), the post-treatment scans were also assessed as a subgroup analysis, taking into account ymrT stage, ymrEMVI, ymrLNM, ymrCRM and ymrTRG (MRI tumour regression grade).

Statistical analysis

Overall survival was defined as the number of patients alive at the date of censor. Disease free survival was defined as the number of patients alive and free from local or distant cancer recurrence at date of censor. Recurrence was defined as local if it was confined to the pelvis or distant if it was outside the pelvis. The follow up period was calculated from the date of surgery to last censor.

Statistical analysis was carried out in SPSS and Stata software. Survival was determined using the Kaplan-Meier method. The difference between survival curves was assessed for statistical significance with Log Rank (Mantel-Cox) analysis. Univariable and multivariable Cox Proportional Hazards models were used to evaluate individual prognostic markers in relation to overall and disease-free survival. Competing risks analysis was carried out to evaluate prognostic markers in relation to local recurrence and distant recurrence. MRI and pathology based prognostic factors were assessed in separate multivariable regression models. In multivariable analysis, mrTDs and mrEMVI were combined due to multicollinearity, however both factors were also evaluated individually using a model where the other factor was excluded to assess their individual effect. Inter-rater reliability was assessed using Cohen's Kappa coefficient.

Sample Size

In order to estimate the appropriate sample size for regression analysis, a 10 events per variable calculation was used. With an expected DFS of approximately 70% at 3 years, and evaluation of 5 main prognostic variables, a sample size of at least 167 patients was required with a minimum follow up of 3 years.

Ethics Approval

This study was peer reviewed and approved by the Royal Marsden NHS Foundation Trust's Research and Development Team.

RESULTS

Overall 233 patients were included in the analysis. Figure 2 shows the reasons for exclusion from the final analysis. The median age was 66 (range 26-88) and 62% of patients were male. Median follow up was 61 months (range 0-132 months). 117 patients (52%) underwent neoadjuvant therapy; of these 103 had long course chemoradiotherapy and 7 had short course radiotherapy. In terms of the surgical procedure carried out, 173 patients (74%) underwent an anterior resection, 47 (20%) had an abdominoperineal excision of rectum, 9 (4%) had a Hartmann's Procedure, and 4 (2%) had a proctocolectomy. 126 (54%) went on to have adjuvant chemotherapy. For the whole cohort, 5 year OS was 76% and DFS was 61%. The local recurrence rate was 12% and distant recurrence rate was 25%.

Relationship Between MRI and Pathology Findings

Table 1 shows the relationship between mrTDs, mrEMVI, mrLNMs and other MRI and pathological prognostic factors. mrTDs were strongly associated with mrEMVI, increased mrT stage, threatened mrCRM and were positively associated with pTDs and pEMVI/ypEMVI but not tumour differentiation. Of note only one of the patients found to have TDs on pathology did not have TDs on MRI, and this patient was mrEMVI positive. There was a strong association between having pTDs and mrTDs (OR 24.85 (3.17-194.85 p=<0.001) although they were reported far more commonly on MRI (36% vs 6%). There was no significant association between having mrLNMs and pLNM/ypLNMs or mrEMVI and pEMVI/ypEMVI but there was a significant association between mrTDs and pLNM/ypLNMs (OR 2.66 (1.50-4.74) P=0.001)

Effect of Baseline MRI Characteristics on Prognosis

mrTDs were strongly associated with poor overall and disease free survival (figure 3). 5 year OS for those with mrTDs was 64% vs 81% if mrTD negative, similarly 5 year DFS was 45% vs 68% respectively (both p<0.001). If mrEMVI was present (sup fig 1) 5 year OS was 65% vs 85% if negative, for DFS this was 48% vs 72% respectively (both p<0.001). OS and DFS in patients with mrLNMs was not statistically different to those without (figure 3). Although there was a significant overlap between mrTDs and mrEMVI, the presence of mrTDs did confer an incrementally worse prognosis compared to mrEMVI alone (figure 3). In patients with neither mrEMVI nor mrTDs vs those with only mrEMVI vs those with both mrEMVI and mrTDs, 5 year OS was 85% vs 70% vs 64% (p=0.001) and 5 year DFS was 73% vs 54% vs 45% (p<0.001)

We wanted to test the hypothesis that MRI assessment focussing only on proven high-risk features MRI (and no longer reporting MRI nodal status) could result in missing patients with pathological lymph nodes which might lead to poor prognosis patients being undertreated. In order to assess the prognostic impact of this we compared the outcomes of patients who would have been predicted to have low risk using these MRI criteria (<5mm extramural spread, mrTD-ve, mrEMVI –ve, safe CRM) with pLNM/ypLNMs with both those without

pLNM/ypLNMs and also with the MRI-predicted high-risk group (defined as patients with at least one of these features). The low-risk MRI group with pLNM/ypLNMs (i.e. the patients who could be missed if mrLN status were ignored) was found to have no statistical difference in either 5 year OS (84% vs 89% p=0.619) or DFS (68% vs 77% p=0.833) compared to the group who were negative for both. The high-risk MRI group did significantly worse with 5-year OS of 59%and DFS of 46%% (both p<0.001). In terms of actual numbers, there were 25/233 patients who were found to have pLNM/ypLNMs but were low-risk on MRI, 8 of these (32%) developed a recurrence during follow up compared to 43/117 of the MRI low-risk patients who were pathological node negative and developed a recurrence (37%).

Table 2 shows univariable and multivariable hazard ratios for each prognostic factor on MRI and pathology. In multivariable regression analyses, mrEMVI and mrTDs were evaluated as a combined prognostic factor due to the degree of multicollinearity but also evaluated separately by excluding the other factor from the model on competing risks analysis. On multivariable assessment of known preoperative prognostic factors, only combined mrTD/mrEMVI status remained significant as a poor prognostic marker with a hazard ratio of 2.07 (1.20-3.56) p=0.008 for OS and 2.20 (1.39-3.59) p=0.002 for DFS. mrTD status also remained significant when mrEMVI was excluded with HR 1.95 (1.22-3.14) p=<0.001 for OS and 1.88 (1.23-2.86) p=0.003 for DFS. Likewise, mrEMVI was significant when mrTDs were excluded with HR 2.14 (1.38-3.32) p=0.001 for OS and 2.15 (1.33-3.47) p=0.002 for DFS. mrLNMs were a marker of improved survival on multivariable analysis, with HR 0.50 (0.31-0.80) p=0.004 for OS and 0.60 (0.40-0.90) p=0.014 for DFS. In terms of pathological prognostic markers, only pTD/ypTD retained significance on multivariable analysis for with HR 3.37 (1.73-7.99) p=0.001 for OS and 2.60 (1.29-5.21) p=0.007 for DFS.

Table 3 shows univariable and multivariable hazard ratios for overall, local and distant recurrence. For MRI, only combined mrTD/mrEMVI status retained prognostic significance on multivariable analysis for overall recurrence and distant recurrence. There was a particularly strong association with distant recurrence with HR 6.53 (2.52-16.91) p=<0.001. No MRI or pathological features were predictive of local recurrence on multivariable analysis.

Post-Treatment MRI Findings: Subgroup Analysis of Patients Undergoing Chemoradiotherapy

Of the 110 patients undergoing long course CRT, all had a post-treatment MRI. The effect of treatment on each MRI prognostic factor is outlined in supplementary table 1 , http://links.lww.com/SLA/C656. Although all prognostic features showed a significant change in status, mrEMVI status showed the greatest improvement with almost half of patients who were initially positive becoming negative on their post-treatment scan. ymrTDs remained a poor prognostic factor when seen on post-treatment imaging, and this was the only factor which retained prognostic significance on multivariable analysis, both alone (2.70 (1.46-4.98) p=0.002 for OS and 3.91 (2.18-7.03) p=<0.001 for DFS) and when evaluated as a combined factor with ymrEMVI (2.10 (1.07-4.15) p=0.032 for OS and 3.12 (1.65-5.92)

p=<0.001 for DFS) (supplementary table 2 , http://links.lww.com/SLA/C657). Those who had a good response to CRT and changed from positive to negative mrTD status had a far better prognosis, similar to those who were mrTD negative throughout, whereas those who had persistent mrTDs had very poor survival outcomes. (figure 4). The effect of ymrEMVI and ymrLNM on DFS and OS is also shown in figure 4.

The Effect of Adjuvant Therapy on Survival

Adjuvant therapy was deliberately excluded from the multivariable analyses presented in table 2 and 3 as the aim was to assess the contribution of each MRI and pathological marker in determining prognosis. As the use of adjuvant therapy would have been decided on the basis of these markers it was not logical to include it in the model. To ensure it was not a significant predictor of prognosis however, the analysis was run separately with adjuvant therapy included as a factor. This confirmed that it was not a significant predictor of prognosis either on univariable or multivariable analysis (on univariable analysis p=0.474 for OS and 0.120 for DFS) and would therefore not have influenced our results.

Interobserver Variation in Reporting of mrTDs

Kappa scores for the two additional radiologists re-assessing MRIs compared to the lead radiologist were κ0.77 and κ0.83 (p<0.001) indicating substantial and almost perfect agreement respectively.

DISCUSSION

In this study of 233 patients, treated during an 8-year period, we have demonstrated that it is possible to separately distinguish tumour deposits from lymph node metastases on MRI, with excellent inter-rater agreement, and that these two phenomena have entirely different effects on prognosis. mrTDs, along with mrEMVI, (which together affect 54% of patients) result in a greater than 7-fold increased risk of distant failure. The groups with mrEMVI/mrTDs had poorer outcomes than those without and this was irrespective of pathology nodal status. On multivariable analysis of MRI-based prognostic factors, only mrTDs and mrEMVI remained a significant adverse prognostic marker for both overall and disease-free survival as well as for overall recurrence and distant recurrence. 56% of patients with mrTDs and 66% of patients with mrEMVI had negative pLNMs (table 1) which would suggest we are not reporting a surrogate marker of pathological nodal involvement. No prognostic factors predicted local recurrence which may be due to the low numbers of patients who developed local recurrence in this group and our treatment strategy of using long course chemoradiotherapy for all patients with locally advanced tumours and other high-risk features, leading to a low pCRM rate of 4%. This successful treatment of known prognostic markers allows us to uncover new prognostic markers among this already high-risk group.

In those patients undergoing CRT, the finding of persistent mrTDs was a marker of particularly poor prognosis. Those who had a good response to treatment and became mrTD negative had outcomes similar to those who had been negative throughout. This suggests that CRT may be a highly effective treatment for this group of patients.

This study has a number of potential limitations. As well as it's retrospective design, there were likely inconsistencies in pathology reporting. During the time period of the study, pathologists were using TNM 5, which did not recognise TDs as a separate entity and instead recommended that any TDs of >3mm in size were recorded as LNMs. This means that many "LNMs" reported on pathology were likely to have been TDs. The fact that there was a strong association between mrTDs and pLNM/ypLNMs but no association between mrLNMs and pLNM/ypLNMs in this study supports this. In 6% of patients, TDs were specifically mentioned in the report (which is very different to the 22.5% median prevalence reported in a recent meta-analysis(8)) and these patients had a particularly dismal prognosis with only two alive and none disease free at 5 years. Perhaps these TDs were especially large or numerous which prompted the pathologist to mention them separately rather than calling them LNMs. Studies are needed to assess the ability of pathologists to separate LNM from TD in more detail. When reported, their effect on prognosis was far worse than that of LNMs, confirming the importance of differentiating between the two phenomena and reassessing their current position within the TNM system. When survival was analysed in patients with "LNMs" on pathology but no other high risk MRI features, this group had a similar outcome to those who were negative for pLNM/ypLNMs suggesting that pLNM/ypLNMs, in the absence of mrTDs or mrEMVI, have little prognostic importance. This study is not able to directly compare the diagnosis of TDs on MRI and pathology due to the pathology limitations already discussed. Therefore we are unable to definitely prove that what we are categorizing as mrTDs are, in fact, pTDs. This is being addressed in the COMET trial(11) which aims to directly map

deposits seen on MRI and match them with pathology findings. The trial is currently mid-way to recruitment target. The problem of MRI and pathology correlation in the diagnosis of TDs is difficult until a clearer histopathological definition of TDs is developed and proven to be consistent and reproducible. This is currently being addressed in an international Delphi consensus project.

The case-mix of this study was perhaps not standard as a significant proportion of patient showing a good response entered the Deferral of Surgery trial and were therefore excluded. This may have skewed our results and lead to an underestimate of treatment effect. The majority of patients also had locally advanced tumours with high risk features. This is a reflection of our practice as a tertiary referral centre dealing with complex rectal cancer patients. We do not believe that this limits the generalisability of our results however, as this high risk group of patients will be present in all institutions (albeit in a smaller proportion) and present the greatest dilemma in treatment planning.

It may seem surprising that T stage was not shown to be significant predictors of prognosis on multivariable analysis in this study, in contrast to other published data. This is likely to be related to the fact that the T3 category, for example (which comprised 80% of our patients), is known to have a heterogeneous survival. When mrEMVI and mrTDs are present they generally co-exist with the T3 category and less advanced tumours are almost always EMVI and TD negative. The prognostic disadvantage of either mrEMVI or mrTDs is so great that on multivariable analysis it knocks out the T category. mrTDs and mrEMVI therefore allow us to identify the subgroup of T3 and T4 tumours which have poor outcomes.

There is an increasing recognition that lymph node assessment alone (whether this is on imaging or pathology) is an oversimplification of the true manifestations of cancer spread within and beyond the mesorectum. Our findings in this study are entirely in line with recent pathological studies showing that extranodal disease is associated with a worse prognosis than nodal metastases(9). This means that even if nodal staging on MRI had 100% accuracy, it would still be suboptimal in predicting prognosis. The definition of a node is *"a small mass of tissue in the form of a swelling, knot or protuberance, either normal or pathological"*. We recognize that in the past the word "node" has been assumed to mean "lymph" node – we suggest that the results of this paper indicate that regarding every "nodule" as a lymph node is an over-simplification that does not enable the distinction between two pathological processes. In this paper, the radiologists have identified two patterns of spread – one that is characterised by an absence of the usual lymph node architecture, following the course of vessels and forming discrete nodules and the other as characterised by the familiar shape and capsule typical of lymph nodes. This is the first time mrLNMs and mrTDs have ever been separately classified and related to outcome in rectal cancer – previously they would have been conglomerated into a single category of "nodes" thereby losing important prognostic information. The lymphatic pathway, as a means of spread to distant metastasis, is increasingly being questioned (12–14), with a vascular pathway seeming more likely as this represents a more direct anatomical pathway to the liver, the most common site of metastasis in colorectal cancer(15). This study lends support to this hypothesis. By using the current form of the TNM system in MRI staging, with its emphasis on nodal stage, we are not

accurately separating patients into good and poor prognostic groups in a way which can properly inform treatment decisions. Once TDs are considered separately, predicted lymph node metastases on MRI cease to be prognostically important and may indeed be a marker for improved survival if mrEMVI and mrTDs are absent. The lack of correlation between MRI nodal status and pathology nodal status suggests that these nodes may be part of an appropriate immune response and are being overcalled as malignant (16–18), this contrasts with our finding that mrTDs are strongly linked to pLNM/ypLNMs.

Our results suggest that once LNMs are separated from TDs on MRI, they neither predict pathological nodal status, nor predict poor survival. We are not yet in a position where we can completely abandon giving chemotherapy to patients with "lymph nodes" but we should take an opportunity to consider that the small margins of gain that have been observed in rectal cancer from adjuvant therapy may be due to the fact that the TME operation removes the lymph nodes which lie contained and limited to the mesorectal envelope. The operation largely eliminates the possibility of recurrence from "lymph nodal" disease but does not always remove the pathways of recurrence and relapse mediated by the vascular pathways which, on the contrary, have the capacity to permeate beyond the mesorectal boundary. In this paper, we observe on MRI that these pervasive channels of spread within the pelvis notably result in local and distant failure

The longstanding controversy surrounding which patients should undergo neoadjuvant treatment in rectal cancer may have resulted from inaccurate selection of the true high risk groups of patients who are likely to see the most benefit with the use of chemoradiotherapy, perhaps contributing to disappointing trial results. There is widespread agreement that patients with locally advanced tumours, which threaten the CRM, require chemoradiotherapy to downstage the tumour, however those with safe surgical margins but other high risk features pose a greater difficulty and there is great variation in how they are treated from one institution to another. We hypothesise that if patients are selected on the basis of true high risk MRI characteristics (i.e. EMVI and TDs); they are likely to see a greater benefit with treatment than previously shown in trials which have not adequately risk-stratified patients. This needs to be taken into account in the design of future clinical trials.

This study has shown that MRI staging needs to move away from simply reporting features in line with the TNM system as prediction of prognosis using this system is weak. Identification of the true high risk group of patients using MRI assessment of EMVI/TD status allows a more accurate preoperative discussion about prognosis with patients, informed decision making about the risks and benefits of neoadjuvant treatment and will aid the development of future clinical trials.

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Figure Legends

Figure 1. MRI images illustrating the appearance of tumour deposits (arrows)

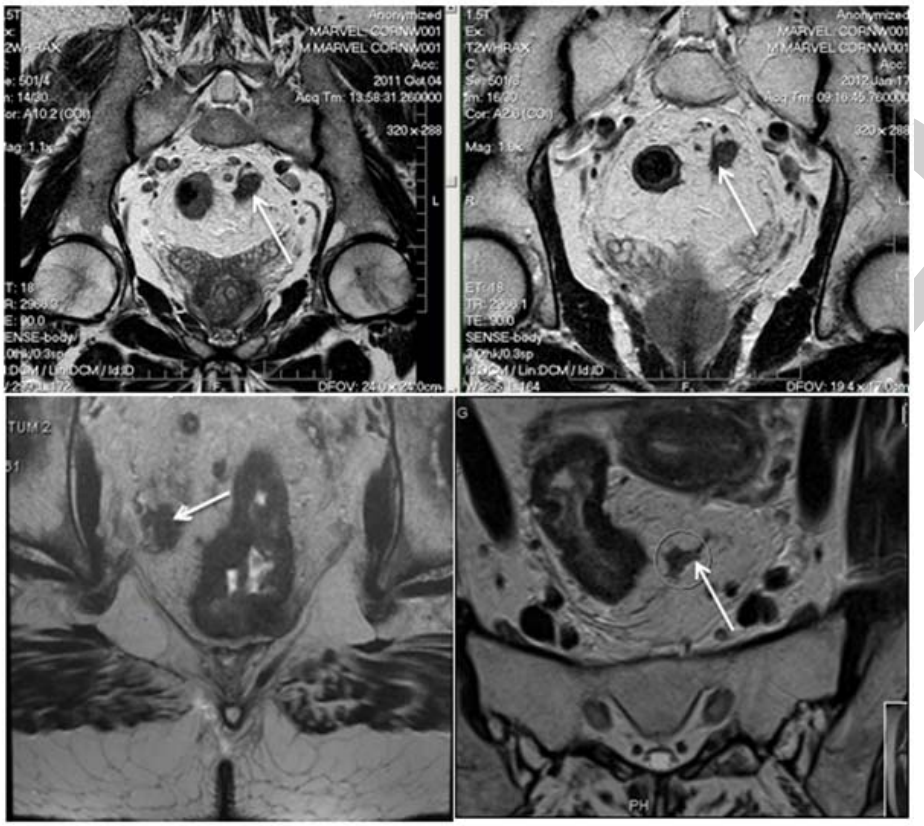

Figure 2. Flowchart showing exclusions from final analysis

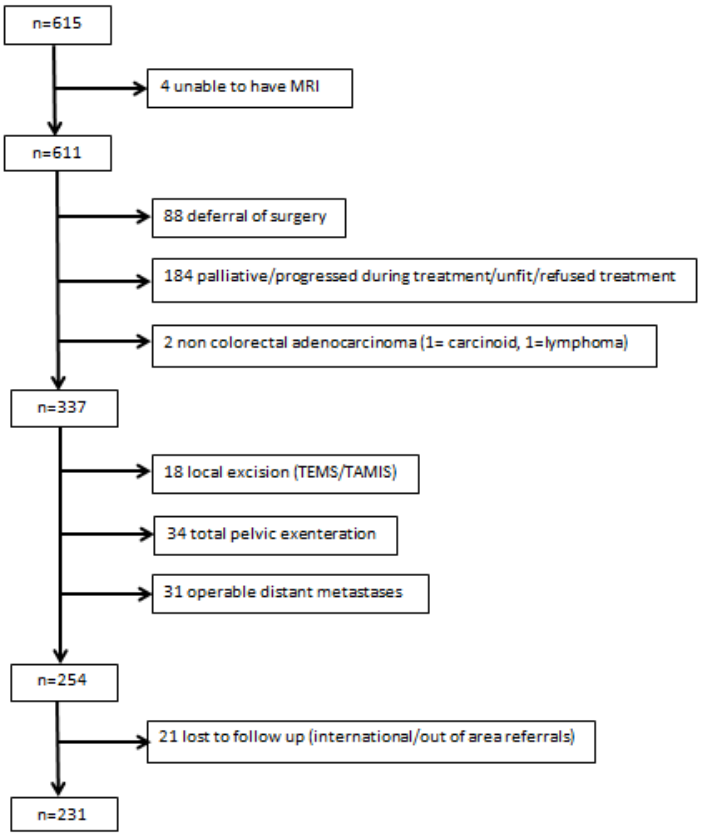

Figure 3. Kaplan-Meier charts showing overall and disease-free survival according to mrTD status (top), mrLN status (middle) and separated mrTD and mrEMVI status (bottom). The prefix "mr" denotes MRI-detected features. TD: tumour deposits, LNM: lymph node metastases, EMVI: extramural venous invasion

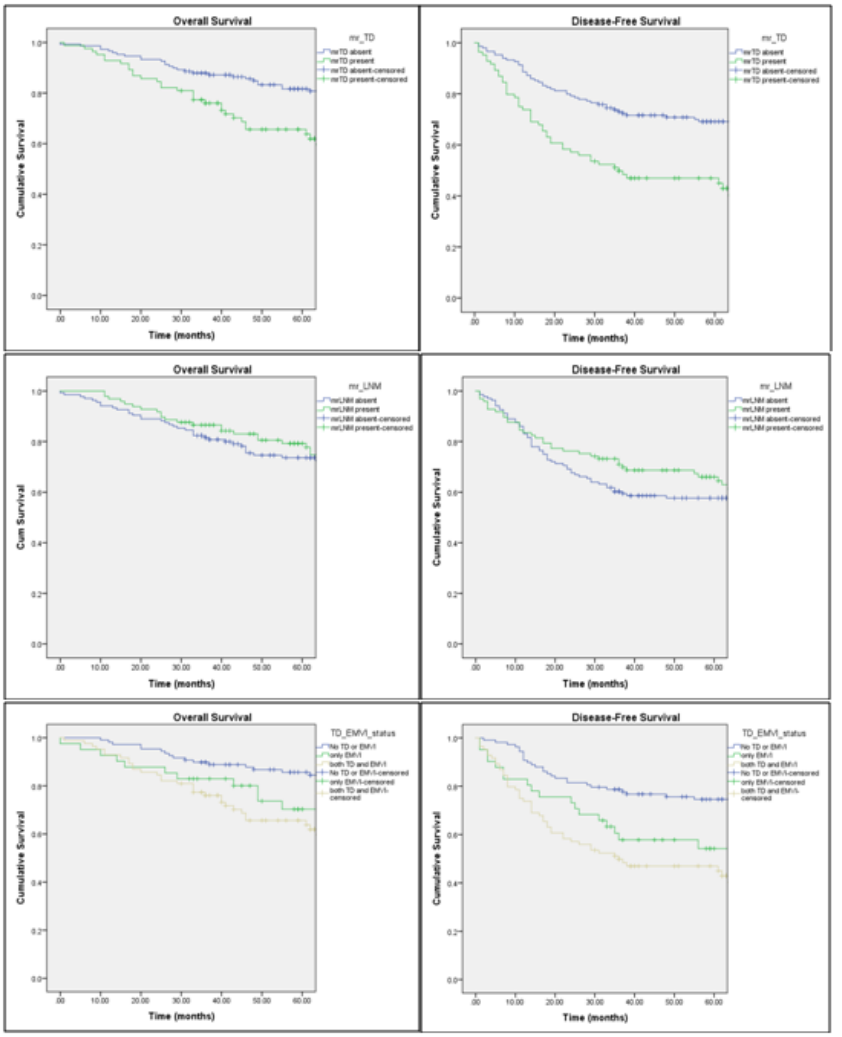

Figure 4. Kaplan-Meier charts showing overall and disease-free survival according to ymrTD status (top), ymrEMVI status (middle) and ymrLNM status (bottom). The prefix "mr" denotes MRI-detected features and "y" denotes post-treatment status. TD: tumour deposits, LNM: lymph node metastases, EMVI: extramural venous invasion

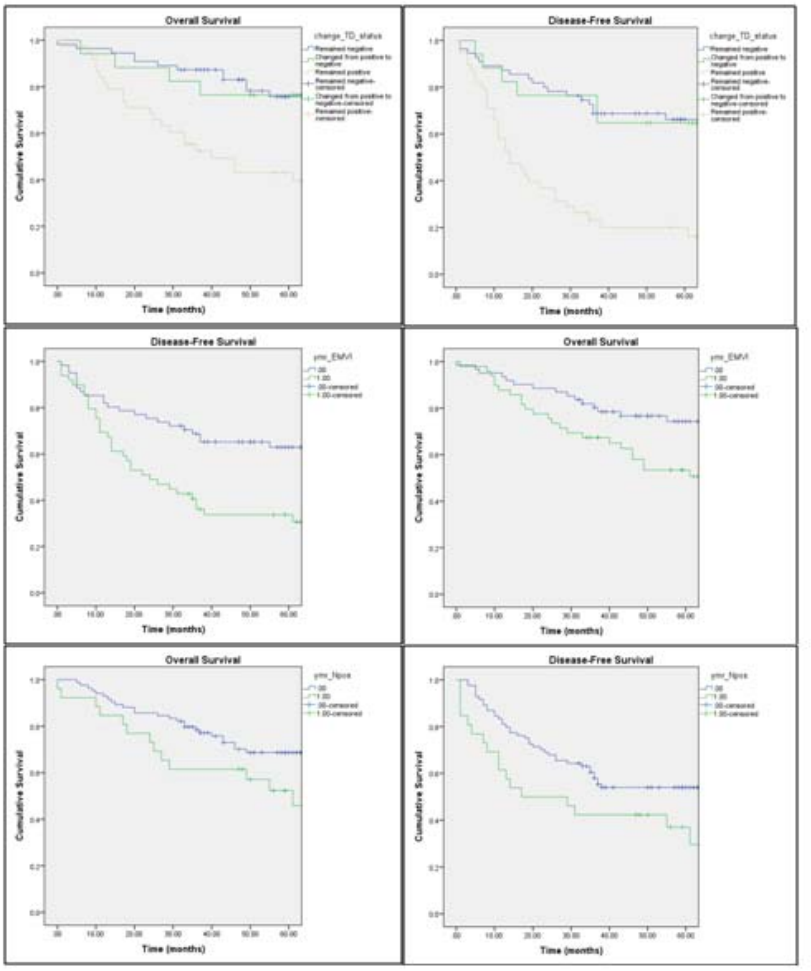

Table 1. Relationship between mrTD, mrEMVI, mrLNM and other prognostic features seen on both MRI and pathology. Prevalence and odds ratios of the association between each prognostic feature are presented. (The prefix "mr" denotes MRI-detected features and the prefix "p" denotes pathology-detected features. "y" denotes post-treatment status. TD: tumour deposits, EMVI: extramural venous invasion, CRM: circumferential resection margin, LNM: lymph node metastases, OR: odds ratio).

Prognostic Factor	**Category and Prevalence**	**Number (%), OR with 95% confidence interval and p value**		
		mrTD positive	**mrEMVI positive**	**mrLNM positive**
		n=84 (36%)	**n=119 (51%)**	**n=98 (44%)**
mrT stage	T1-T2 n=47 (20%)	1 (1%)	1 (1%)	9 (10%)
	T3-T4 n=186 (80%)	83 (99%)	118 (99%)	89 (90%)
		OR 37.07 (5.00-274.48) P=<0.001	**OR 79.82 (10.77-591.89) P=<0.001**	**OR 3.87 (1.77-8.46) p=<0.001**
mrLNM	Positive n=98(42%)	39 (46%)	60 (50%)	-
	Negative n=135 (58%)	45 (54%)	59 (50%)	-
		OR 1.32 (0.77-2.27) p=0.335	**2.03 (1.19-3.46) p= 0.011**	
mrEMVI	Positive n=119 (51%)	80 (95%)	-	-
	Negative n=114 (49%)	4 (5%)	-	-
		OR 56.41 (19.38-164.22) p=<0.001		
mrCRM	Involved/Threatened n=76 (33%)	42 (50%)	61 (51%)	38 (39%)
	Safe n=157 (67%)	42 (50%)	58 (49%)	60 (61%)
		OR 3.38 (1.91-6.00) p=<0.001	**OR 6.94 (3.62-13.31) p= <0.001**	OR 1.62 (0.93-2.81) p=0.88
pLNM/ypLNM	Positive n=71 (30%)	37 (44%)	41 (34%)	34 (35%)

	Negative n=162 (70%)	47 (56%) **OR 2.66 (1.50-4.74) P=0.001**	78 (66%) **OR 1.47 (0.84-2.58) p=0.201**	64 (65%) OR 1.41 (0.80-2.47) p= 0.234
pTD/ypTD	Positive n=13 (6%)	12 (19%)	13 (11%)	7 (7%)
	Negative n=218 (94%)	71 (81%) **OR 24.85 (3.17-194.85 p=<0.001**	105 (89%) **OR 1.12 (1.06-1.20) p=<0.001**	90 (93%) OR 1.66 (0.54-5.10) p=0.399
pEMVI/ypEMVI	Positive n= 41 (17%)	20 (24%)	25 (21%)	18 (18%)
	Negative n=192 (83%)	64 (76%) **OR 1.91 (0.96-3.77) P=0.074**	94 (79%) **1.63 (0.82-3.24) P=0.173**	80 (82%) OR 1.10 (0.55-2.16) p=0.862
Tumour different-iation	Well/mod n=206 (88%)	71 (85%)	99 (83%)	85 (87%)
	Poor/mucinous n=27 (12%)	13 (15%) OR 1.77 (0.79-3.96) p=0.201	20 (17%) **OR 3.09 (1.25-7.62) p=0.013**	13 (13%) OR 1.32 (0.59-2.95) p=0.538

Table 2. Univariable and Multivariable Hazard ratios for each potential prognostic factor. (The prefix "mr" denotes MRI-detected features and the prefix "p" denotes pathology-detected features. TD: tumour deposits, EMVI: extramural venous invasion, CRM: circumferential resection margin, LNM: lymph node metastases, OR: odds ratio).*TD and EMVI status combined for multivariable analysis due to degree of overlap. Age and gender were also entered into the multivariable analysis but were not significant.

Prognostic factor		**No. Patients**	**Overall Survival**		**Disease Free Survival**	
			Univariable Hazard Ratio	**Multivariable Hazard Ratio**	**Univariable Hazard Ratio**	**Multivariable Hazard Ratio**
Demographics						
Age	Median (range)	66 (26-88)	1.01 (0.99-1.03) p=0.145	**1.02 (1.00-1.03) p=0.023**	1.01 (.099-1.02) p=0.387	1.01 (0.99-1.03) p=0.205
Gender	Female					
	Male		1.08 (0.70-1.68) p=0.726	1.13 (0.76-1.69) p=0.554	0.92 (0.62-1.35) p=0.65	0.90 (0.61-1.32) p=0.596
MRI findings						
mrTD	Absent	149 (64%)				
	Present	84 (36%)	**2.19 (1.43-3.36) p=<0.001**	**1.95 (1.22-3.14) p=<0.006 (mrEMVI excluded)**	**2.14 (1.46-3.13) p=<0.001**	**1.88 (1.23-2.86) p=0.003 (mrEMVI excluded)**
mrEMVI	Absent	112 (48%)				
	Present	121 (52%)	**2.14 (1.38-3.32) p=0.001**	**2.14 (1.26-3.65) p=0.005 (mrTD excluded)**	**2.18 (1.47-3.22) p=<0.001**	**2.15 (1.33-3.47) p=0.002 (mrTD excluded)**
Combined mrEMVI and/or mrTD	Absent	108 (46%)				
	Present	125 (54%)	**2.47 (1.63-3.75) p=<0.001**	**2.07 (1.20-3.56) p=0.008**	**2.22 (1.49-2.30) p=<0.001**	**2.20 (1.39-3.59) p=0.002**
mrCRM	Safe	157 (67%)				
	Threatened	76 (33%)	**1.60 (1.03-2.40) p=0.035**	1.30 (0.81-2.09) p=0.275	1.44 (0.97-2.14) p=0.070	1.10 (0.72-1.69) p=0.653)

mrT stage	T1-T2 T3-T4	46 (20%) 187 (80%)	**1.81 (1.02-3.23) p=0.044**	1.24 (0.62-2.47) p=0.546	**1.79 (1.06-3.03) p=0.029**	1.22 (0.64-2.32) p=0.551
Distance from anal verge	>6cm <6cm	152 (65%) 81 (35%)	1.11 (0.72-1.71) P=0.652	1.28 (0.64-2.59) p=0.486	1.02 (0.69-1.51) p=0.920	1.09 (0.73-1.64) p=0.656
mrLNM	Absent Present	136 (58%) 97 (42%)	**0.59 (0.38-0.94) p=0.027**	**0.50 (0.31-0.80) p= 0.004**	0.70 (0.48-1.04) p=0.080	**0.60 (0.40-0.90) p=0.014**
Pathology Findings						
pT/ypT stage	T0-T2 T3-T4	96 (41%) 137 (59%)	**2.03 (1.29-3.21) p=0.002**	1.57 (0.96-2.65) p=0.071	**1.78 (1.97-2.66) P=0.005**	1.45 (0.95-2.23) p=0.088
pLNM/ypLNM	Absent Present	163 (70%) 70 (30%)	**1.82 (1.17-2.85) p=0.008**	1.48 (0.93-2.34) p=0.097	**1.99 (1.34-2.97) p=0.001**	**1.80 (1.93-2.72) p=0.005**
pEMVI/ypEMVI	Absent Present	190 (82%) 42 (18%)	**2.40 (1.45-3.96) p=0.001**	1.36 (0.76-2.43) p=0.299	**2.08 (1.32-3.28) p=0.002**	1.23 (0.74-2.08) p=0.424
pTD/ypTD	Absent Present	216 (94%) 14 (6%)	**5.38 (2.69-10.76) p=<0.001**	**3.72 (1.73-7.99) p=0.001**	**3.66 (1.94-6.92) p=<0.001**	**2.60 (1.29-5.21) p=0.007**
pCRM/ypCRM	Not involved Involved	224 (96%) 9 (4%)	**3.87 (1.78-8.44) p=0.001**	2.20 (0.98-4.93) p=0.056	**3.17 (1.46-6.85) p=0.003**	1.99 (0.90-4.40) p=0.091

Table 3. Number of patients with overall, local and distant recurrence according to baseline MRI and pathological prognostic factors. Hazard ratios.are presented for each prognostic.factor. Results of multivariable competing risks regression for all prognostic factors which remained statistically significant are included at the end of each section. TD and EMVI status were combined in the multivariable analysis due to multicollinearity. (The prefix "mr" denotes MRI-detected features and the prefix "p" denotes pathology-detected features. TD: tumour deposits, EMVI: extramural venous invasion, CRM: circumferential resection margin, LNM: lymph node metastases, OR: odds ratio).

Prognostic Factor and prevalence			**Number, Hazard ratio (HR), 95% confidence interval and p value**			
			Local recurrence		**Distant recurrence**	
			Present	Absent	Present	Absent
			27	206	59	174
			(12%)	(88%)	(25%)	(75%)
MRI findings						
mrT stage	T1-T2	46 (20%)	5	41	9	37
	T3-T4	187 (80%)	22	165	50	137
			HR 1.14 (0.42-3.11) p=0.791		HR 1.49 (0.73-3.03) p=0.267	
mrTD and/or EMVI	Pos	125 (54%)	15	110	46	79
	Neg	108 (46%)	12	96	13	95
			HR 1.09 (0.49-2.45) p=0.833		**HR 4.26 (2.15-8.43) p=<0.001**	
mrLNM	Pos	97 (42%)	11	86	21	76
	Neg	136 (58%)	16	120	38	98
			HR 0.90 (0.42-1.95) p=0.797		HR 0.67 (0.39-1.15) p=0.153	
mrCRM	<1mm	76 (33%)	10	65	25	51
	Safe	157 (67%)	17	140	34	123
			HR 1.23 (0.56-2.69) P=0.600		**HR 1.68 (1.00-2.83) p=0.048**	
Factors retaining significance on multivariable logistic regression			**None**		**mrTD/mrEMVI** **HR 6.53 (2.52-16.91) p=<0.001**	

Pathology findings						
pT/ypT stage	T1-T2	96 (41%)	7	89	16	80
	T3-T4	137 (59%)	20	117	43	94
			HR 2.10 (0.89-4.94) p=0.089		**HR 2.25 (1.26-4.01) p=0.006**	
pTD	Pos	14 (6%)	5	9	8	6
	Neg	219 (94%)	22	197	51	168
			HR 4.88 (1.79-13.31) p=0.002		**HR 3.83 (1.75-8.37) P=0.001**	
pEMVI/ypEMVI	Pos	42 (18%)	10	32	15	27
	Neg	190 (82%)	17	173	43	147
			HR 3.28 (1.49-7.20) p=0.003		**HR 1.92 (1.06-3.49) P=0.030**	
pLNM/ypLNM	Pos	70 (30%)	13	57	27	43
	Neg	163 (70%)	14	149	32	131
			HR 2.24 (1.06-4.75) p=0.035		**HR 2.23 (1.33-3.72) p=0.002**	
pCRM/ypCRM	Pos	9 (4%)	3	6	5	4
	Neg	224 (96%)	24	200	54	170
			HR 4.01 (1.05-15.30) p=0.042		**HR 3.08 (1.18-7.97) p=0.021**	
Factors retaining significance on multivariable logistic regression			**None**		**pTD/ypTD HR 3.12 (1.42-6.83) p=0.004** **pLNM/ypLNM HR 2.42 (1.13-3.20) p=0.016**	