Published in final edited form as:

Br J Surg. 2019 October ; 106(11): 1530–1541. doi:10.1002/bjs.11233.

Early MRI predictors of disease free survival in locally advanced rectal cancer from the GRECCAR 4 trial

Stéphanie Nougaret^{1,2}, Florence Castan³, Hélène de Forges⁴, Hebert Alberto Vargas⁵, Benoit Gallix⁶, Sophie Gourgou³, Philippe Rouanet⁷, the GRECCAR Study Group

¹Radiology Department, Institut du Cancer de Montpellier, Univ. Montpellier, Montpellier, France

²Institut de Recherche en Cancérologie de Montpellier (IRCM), INSERM, U1194, Montpellier, France.

³Biometrics Unit, Institut du Cancer de Montpellier, Univ. Montpellier, Montpellier, France

⁴Clinical Research unit, Institut du Cancer de Montpellier, Univ. Montpellier, Montpellier, France

⁵Department of Radiology, Memorial Sloan Kettering Cancer Center, New-York, USA.

⁶Department of Radiology, Royal Victoria Hospital, McGill University Health Center, Montreal, Canada

⁷Surgical oncology Department, Institut du Cancer de Montpellier, Univ. Montpellier, Montpellier, France

Abstract

Background: Tailored neo-adjuvant treatment of locally advanced rectal cancer (LARC) may improve outcomes. The aim of this study was to determine early MRI prognostic parameters to stratify neoadjuvant treatment in patient with LARC.

Methods: All patients from a prospective phase II, multicenter, randomized study (GRECCAR4-NCT01333709) were included in this study and underwent rectal MRIs before treatment, 4 weeks after induction chemotherapy and after completion of chemoradiation (CRT). Tumor volumetry, MRI Tumor Regression Grade (mrTRG), T staging, N staging, Circumferential resection margin (CRM) status, and MRI extramural vascular invasion (EMVI) presence were evaluated.

Results: 133 randomized patients were analyzed. Median follow-up was 41.4 months [95% CI: 36.6–45.2]. 31 patients (23%) recurred. At baseline, in univariate analysis, mrEMVI was the only prognostic factor associated with poorer outcome ($p=0.0152$). After induction chemotherapy, a higher tumor volume on MRI ($p=0.019$), a tumor volume regression $\geq 60\%$ ($p=0.002$), involvement of the CRM ($p=0.037$), mrEMVI ($p=0.026$) and a poor mrTRG ($p=0.023$) were associated with poor outcome. After completion of CRT, the absence of complete response on MRI ($p=0.004$), mrEMVI ($p=0.04$) and a poor mrTRG ($p=0.005$) were associated with shorter DFS. A final multivariate model including all significant variables (baseline, post-induction, post-CRT) found

Correspondance to: Dr Stephanie Nougaret, Institut du Cancer de Montpellier (ICM), 208 rue des Apothicaires, 34 298 Montpellier, France, Tel: +33 4 67 61 47 25, Fax: +33 4 67 61 23 15, stephanienougaret@free.fr.

Disclaimers: The authors claim no conflict of interest regarding this manuscript.

ECOG status ($p=0.011$), sphincter involvement ($p=0.009$), EMVI presence at baseline ($p=0.002$) and early tumor volume regression 60% after induction ($p=0.007$) were associated with relapse.

Conclusion: Baseline and early post-treatment MRI parameters are associated with prognosis in LARC. Future preoperative treatment should stratify treatment according to baseline EMVI status and early tumor volume regression.

Keywords

Rectal Cancer; Magnetic Resonance Imaging; disease-free survival

Introduction

The standard treatment for locally-advanced rectal cancer (LARC) is chemoradiotherapy (CRT) followed by surgical resection, irrespective of tumor response^{1,2}. However, personalized cancer therapy potentially changes this management. Patients can now be stratified by their response to treatment to minimally-invasive treatments for potentially good responders and more “aggressive” approach for patients likely to show a poor response^{3–5}. The CRT regimens used are also evolving. Several studies have demonstrated the feasibility of adding oxaliplatin to standard preoperative CRT with improved efficacy and acceptable toxicity and compliance^{6–8}. Others have evaluated different radiation regimens^{9–11}. In this context, finding reliable prognostic indicators for early monitoring of treatment response is critical in order to switch to alternative strategies if required¹².

Several approaches to assess tumor response using MRI have been described. These include morphological changes with MRI tumor regression (mrTRG)¹³ and volumetry^{12,14–19}, or functional changes using diffusion-weighted imaging (DWI)^{14,15,20–24} and dynamic contrast-enhanced MRI (DCE-MRI)^{25–29}. Tumor volumetry is a strong predictor of tumor response and outcome, especially when combined with DWI^{12,15–18,30–36}. The advantage of T2W-DWI volumetry is that it capitalizes on tumor biology rather than relying only on morphologic appearance. Thus better differentiating postradiation fibrosis from residual tumor^{14,16,17,37,38}. Other studies have evaluated the mrTRG derived from the pathologic tumor regression grade (pTRG)¹³. In the MERCURY study, a mrTRG of 1 to 3 (good response)⁷ was associated with higher disease-free (DFS) and overall survival compared with a mrTRG of 4 or 5 (poor response) ($p<0.001$)³³.

To validate the concept of a more individualized treatment strategy of LARC, a multicenter randomized phase II study was conducted from May 2011 to October 2014 (GRECCAR 4-[NCT01333709](#)). The trial objective was to determine whether induction chemotherapy with oxaliplatin could be used to identify subgroups of patients in whom treatments, especially the radiation doses and regimens, could be de-escalated or intensified. Primary results were reported in 2017⁷. The objective of the present study was to determine early MRI prognostic indicators that may help personalizing the treatment in this population.

Patients and Methods

Study design and patients

All patients initially enrolled in the original prospective phase II multicenter randomized study (GRECCAR4-[NCT01333709](#)) were eligible for the present analysis (n=206). The inclusion criteria were as follows: primary tumor evaluated using MRI (initial stage: mriT3 c or mriT4; or the predictive CRM was ≤ 1 mm), age ≥ 18 years, ECOG performance status ≤ 2 and adequate hematological, hepatic and renal functions. The exclusion criteria were indications for immediate surgery, no MRI evaluation of the primary tumor available, and previous pelvic radiotherapy or contraindication to radio- and/or chemotherapy.

GRECCAR 4 stratified patients according to the MRI tumor volume reduction after 4 weeks of induction chemotherapy. Patients were then divided into two strata based on the tumor response. A favorable response (stratum I) was defined as shrinkage $\geq 75\%$ from the initial tumor volume with a predictive CRM > 1 mm. These patients were randomly assigned (1:1 ratio) to receive immediate surgery (experimental arm, arm A) or classical CRT (Cap 50) followed by surgery (standard arm, arm B). An unfavorable response (stratum II) was defined as shrinkage $< 75\%$ from the initial tumor volume or a predictive CRM ≤ 1 mm. Patients were randomized to receive Cap 50 (standard arm, arm C) or intensified CRT (Cap 60; experimental arm, arm D). Randomization was centralized and stratified by center and initial tumor stage. The study was approved by the institutional review board and informed consent was obtained from all patients.

The GRECCAR 4 trial initially included 206 patients, among whom 194 underwent induction chemotherapy and initial MRI assessment. Finally, 133 patients were randomized. After the inclusion of the 51 planned patients in arm D (Cap60), randomization in stratum II was stopped and all patients with an unfavourable response were included in arm C (Cap50). Randomization kept going in stratum I to try to reach the number of patients required in arm A. Finally, after inclusion of 61 more patients in arm C, the study independent committee recommended stopping all inclusions because of the difficulty to recruit in stratum I. Analyses were performed on all patients included in stratum I and all randomized patients in stratum II to have a homogenous population with clean data⁷.

Treatments

Neoadjuvant Treatment—All patients received FOLFIRINOX as induction chemotherapy: four cycles of 180mg/m² irinotecan, 85mg/m² oxaliplatin, 200mg/m² elvovir and 5-FU (400mg/m² bolus followed by 2400mg/m² continuous infusion for 46 hours) delivered over 8 weeks.

Chemoradiotherapy—The standard Cap50 CRT regimen comprised a 50 Gy radiation dose administered as conventional 3D conformal or intensity-modulated radiation therapy (IMRT) (2Gy/fraction, 5 fractions/week for 5 weeks: 44Gy as mini-pelvic radiotherapy with a 6-Gy boost to a reduced target peritumoral volume) with concomitant oral capecitabine (1600mg/m² daily in two identical doses taken on the radiotherapy days). The experimental Cap60 regimen consisted of 60 Gy irradiation (2Gy/fraction, 5 fractions/week for six weeks:

44Gy as mini-pelvic radiotherapy with a 16-Gy boost to a reduced target peritumoral volume) with the same concomitant oral capecitabine intake as in the Cap50 regimen.

Surgery—Surgery was performed in each center by an expert colorectal surgeon. Total Mesorectal Excision (TME) was performed by laparoscopic, robotic surgery, or open surgery. Surgical quality was evaluated using the Quirke mesorectum grading system.

Magnetic Resonance Imaging (MRI)

Imaging—Rectal MRIs were performed in all patients prior to treatment and after 4 weeks of induction chemotherapy. A third MRI after completion of CRT prior to surgery was performed at the discretion of each center (n=94).

Imaging was performed using a phased array body coil at 1.5 or 3T (Supplementary Table 1). Briefly, the MRI protocol consisted of standard T2-weighted fast spin echo sequences in multiple acquisition planes. All exams included dedicated transverse planes angled along the long axis of the tumor, using the sagittal planes as reference³⁹. An additional diffusion-weighted echo planar imaging sequence was acquired with b0 as the lowest and b1500 s/mm² as the highest b-factor. The MRI parameters reported in the 16 participating centers are presented in Supplementary Table 1. All MRIs were performed in accordance with the European Society of Gastrointestinal and Abdominal Radiology guidelines^{40,41}.

Interpretation—All images were independently analyzed by a single highly experienced radiologist (centralized reading), blinded to all clinical information, other imaging results, and histopathology.

Tumor evaluation before treatment, after 4 weeks of induction chemotherapy and after completion of CRT was evaluated according to “DISTANCE” parameters⁴²: Dis: Distance from the inferior part of the tumor to the transitional skin, T:T staging, A: Anal complex, N: Nodal staging, C: Circumferential resection margin, and E: Extramural vascular invasion. Presence of mucin was also collected.

For each patient, tumor volumetry was performed manually, tracing the tumor boundaries on the axial oblique images on T2W-MR images in conjunction with the highest b value image as to exclude areas of T2 fibrosis and include only the residual tumor. The volume of the whole tumor was then calculated multiplying each cross-sectional area by section thickness (including the slice gap if present). For each patient, the reader determined (1) the “T2+DWI” pretreatment tumor volume, (2) the “T2+DWI” post induction treatment tumor volume, and (3) the “T2+DWI” post CRT tumor volume. The tumor volume reduction ratio after induction chemotherapy and after CRT was calculated as such: [DELTA]volume = (Pretreatment tumor volume - Posttreatment tumor volume) × 100/(Pretreatment tumor volume).

The mrTRG was also evaluated to determine the degree of tumor replacement by fibrotic or mucinous changes stroma¹³. Favorable mrTRG was defined as grades 1 and 2, and unfavorable mrTRG as stages 3, 4 and 5¹³.

Histopathologic Assessment

After TME, the specimen was axially sectioned into 3- to 5-mm slices, as described by Quirke *et al.*⁴³. A dedicated gastrointestinal pathologist specialized in rectal cancer in each center evaluated in a blinded manner specimens for the post-treatment yT and yN stages. Tumour regression was evaluated in pathology using the tumor regression grade (pTRG) described in the Dworak *et al.* study⁴⁴. A favorable pTRG was defined as Dworak 3 and 4, and an unfavorable pTRG as Dworak 0, 1 and 2.

Follow-up

Patients were followed-up according to the trial rules. This comprised outpatient assessment every 4 months for 2 years, followed by assessment every 6 months for the 5 following years. Clinical follow-up included physical examinations, routine blood tests, and 6 months computed tomography of the thorax, abdomen, and pelvis. Recurrence was confirmed pathologically with findings from surgical resections, biopsies, and/or radiologic examinations. The surgical data, date of operation, procedure performed, and quality of the specimen were recorded prospectively. Date of enrollment, last follow-up, date of disease progression, and date and cause of death were also collected. The presence of distant metastatic disease or local recurrence at the time of death was recorded as rectal cancer-specific death.

Statistical Analysis

Data are expressed with medians and ranges for continuous variables and numbers and percentages for categorical variables. Associations between clinical and pathologic characteristics were evaluated using the Chi-squared or Fisher's exact tests for categorical variables and the Kruskal-Wallis tests for continuous variables.

Disease-free survival (DFS) was defined as the time between enrollment and occurrence of the first event among local recurrence, metastasis or death whatever the cause. Patients without event at the time of the analysis were censored at the date of the last informative follow-up. DFS rates were estimated by the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazard's regression model to estimate the hazard ratio and included baseline characteristics and MRI features. Comparisons were performed using the log-rank test for univariate analysis. Independent effects were evaluated from the likelihood ratio statistics. The final multivariate model was defined using backward stepwise selection ($p < 0.20$) and a step-by-step method was used to include only the significant parameters ($p < 0.05$). $p < 0.05$ was considered statistically significant. All analyses were performed using the Stata software Version 13 (Texas, USA).

Results

Patients

Patients' demographics and baseline characteristics are detailed on Supplementary Table 2.

MRI predictors of tumor response assessed by Dworak score

The Dworak score was evaluated in 117 patients (88%). Fifty-six patients (48%) showed a poor response on pathology (Dworak score 0 to 2) and 61 patients (52%) showed a good pathologic tumor response (Dworak score 3 and 4). The median initial tumor volume on MRI was larger in poor responders (50.3cm^3 [range=3–387]) compared to good responders (28.3cm^3 [range= 3.3–115]) ($p<0.001$) (Table 1).

After induction chemotherapy, a larger tumor volume on MRI ($p<0.001$), MRI stages T3 and T4 ($p=0.008$), a high rectal tumor location ($p=0.009$), MRI-detected EMVI (mrEMVI) ($p<0.001$) and a poor mrTRG ($p<0.001$) were associated with a poor pathologic response (Table 2).

Prior to surgery, a larger MRI tumor volume ($p<0.001$), poorer T staging ($p<0.003$), T3 and 4 stages ($p=0.002$), a high rectal tumor location ($p=0.037$), mrEMVI ($p=0.048$) and a poor mrTRG ($p<0.001$) were associated with poor response on pathology (Table 3).

MRI predictors of patient outcomes

After a median follow-up of 41.4 months (95% CI: 36.6–45.2), 31 of the 133 patients (23%) developed recurrence. Distant metastases were the most frequent type of relapse, reported in 22/31 patients (71%). Among them, 11 patients presented with lung metastases. Four patients (13%) had local recurrence. Among all patients with recurrence, 29 were asymptomatic, with recurrence detected by routine imaging. Two recurrences were detected in association with abnormal CEA levels.

At baseline, in univariate analysis, mrEMVI was the only prognostic factor associated with shorter DFS (HR=2.6 [1.1–6.1], $p=0.0152$). In multivariate analysis, a poor ECOG status (HR=17.93 [3.65–88.17], $p=0.008$), sphincter involvement (HR=3.30 [1.44–7.55], $p=0.007$) and mrEMVI (HR=3.98 [1.65–9.62], $p<0.001$) were independently associated with a shorter DFS (Table 3).

After induction chemotherapy, a higher tumor volume on MRI (HR=1.01 [1.00–1.02], $p=0.019$), tumor volume regression 60% (HR=3.15 [1.51–6.59], $p=0.002$), involvement of the CRM (HR=2.16 [1.07–4.39], $p=0.037$), mrEMVI (HR=2.25 [1.11–4.55], $p=0.026$) and a poor mrTRG (HR=2.73 [1.05–7.11], $p=0.023$) were associated with shorter DFS (Table 3). In multivariate analysis, tumor volume regression 60% (HR=3.32 [1.50–7.32], $p=0.002$), and mrEMVI (HR=2.40 [1.01–5.71], $p=0.04$) were associated with a shorter DFS.

After completion of CRT, the absence of complete response on MRI (HR=8.5 [1.13–64.1], $p=0.004$), mrEMVI (HR=3.11 [1.15–8.43], $p=0.04$) and a poor mrTRG (HR=4.30 [1.40–13.21], $p=0.005$) were associated with shorter DFS, regardless of the patient arm (Table 4). In multivariate analysis, mrTRG was the only factor associated with DFS (HR=7.33 [1.49–36.03], $p=0.017$).

An overall multivariate analysis model was created, including all significant clinical and MRI variables, adjusted according to the patient arm. In this model, an ECOG status of 2 (HR=16.53 [3.28–83.31], $p=0.011$), sphincter involvement at baseline (HR=3.33 [1.38–

8.05], $p=0.009$), mrEMVI at baseline (HR=3.60 [1.49–8.72], $p=0.002$) and an early tumor volume regression < 60% after induction chemotherapy (HR=2.97 [1.28–6.92], $p=0.007$) were associated with progression (Figure 1). Patients without sphincter involvement and mrEMVI at baseline and with a tumor volume regression on T2+DWI > 60% after induction chemotherapy had only 11.5% risk of recurrence. On the contrary, patients with sphincter involvement and mrEMVI at baseline and with a tumor volume regression < 60% had 57.1% risk of recurrence (Figure 1).

The lack of pathologic complete response on MRI was the only pathologic prognostic factor for shorter DFS (HR=8.70 [1–18–64.0], $p=0.002$). The pTRG (Dworak) was not associated with patient survival (HR=1.77 [0.83–3.78]).

Discussion

In the present study sphincter involvement, mrEMVI at baseline, and a tumor volume regression < 60% after induction chemotherapy were associated with a higher risk of relapse. Stratifying patient treatment according to baseline EMVI status, tumor height and early tumor volume regression may thus improve patient survival.

Tumor volume reduction >60% after induction chemotherapy is an early surrogate marker for a favorable outcome. In the initial GRECCAR 4 trial, 75% tumor volume regression was chosen to define favorable response and stratify patients. This very high threshold was based on previous studies that reported that a threshold > 70% was associated with better patient outcomes after CRT^{12,16,18,36,45}. In GRECCAR 4, most patients had a tumor volume reduction ranging between 50% and 75%, possibly because posttreatment volumes were measured after only 4 cycles of chemotherapy instead of at the end of CRT, as reported in other studies. Furthermore, contrary to other previous studies^{12,32,36}, the “functional” residual tumor volume using the T2 and DWI combination instead of the T2 volume alone was evaluated. Volume measurements based on T2 alone often encompass fibrotic changes among the residual tumor¹⁹. The advantage of T2W-DWI volumetry is that it capitalizes on tumor biology rather than relying on only morphologic appearance that better differentiates post radiation fibrosis from residual tumor. As such, a lower threshold of 60% tumor volume reduction after induction chemotherapy was found to be an early predictor of patient outcome.

The present study found that mrEMVI at baseline is a strong predictor of DFS. This is concordant with previous studies that have found mrEMVI to be associated with poor prognosis^{46–53}. In a large meta-analysis including 1262 patients, patients with mrEMVI developed metastases more frequently than patients with mrEMVI-negative tumors (OR=5.68, $p<0.001$). These findings highlight the critical role of mrEMVI evaluation in patient stratification. Despite the strong prevalence of mrEMVI and its poor prognosis, the treatment of patients with mrEMVI lacks consensus. In a survey, only 55% of surgeons and 57% of oncologists considered mrEMVI when deciding on postoperative treatment^{54,55}. This may undertreat an MRI-identified group with higher risk of recurrence who should be considered for more aggressive therapy.

Sphincter involvement at baseline was associated with poor outcome. Low rectal tumors are associated with poorer prognosis than proximal tumors^{56,57}. In the present study, prior to treatment, about 25% of patients showed sphincter involvement, that was reduced to 1% after neoadjuvant treatment. As such, sphincter involvement after induction chemotherapy and CRT was not associated with patient outcome. The type of surgery, *i.e.* intersphincteric resection in previously involved sphincter *versus* extralevator resection based on initial presentation of the tumor, may also contribute to the correlation between sphincter involvement and prognosis.

This study has several limitations. Beside the small sample size, radiologic evaluation was performed by one reader and reproducibility is therefore not assured. However, the volumetry technique is widely performed and reproducibility has previously been evaluated^{45,58}. Automated methods for volumetry evaluation with artificial intelligence may eventually overcome this limitation. The study median follow-up was 41.4 months; therefore confirmation with longer follow-up will be required. Although a dedicated gastrointestinal pathologist specialized in rectal cancer evaluated all resection specimens in a blinded manner, central pathological assessment would have been preferable. The GRECCAR 4 clinical trial only included bulky locally-advanced tumors. The MRI prognostic parameters found in this study will therefore need to be tested on smaller tumors to demonstrate the reliability of this technique in smaller lesions.

In the era of personalized medicine, tailored treatment of LARC according to MRI parameters is essential. In this study, baseline sphincter involvement, mrEMVI presence, and early tumor volume reduction after induction chemotherapy were key predictors of shorter DFS. Further prospective studies may need to consider therapy intensification for mrEMVI-positive patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The GRECCAR Study Group was composed of the following, who participated in this work: Eric Rullier (Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France), Bernard Lelong (Institut Paoli-Calmettes, Marseille, France), Philippe Maingon (Centre Georges François Leclerc, Dijon, France), Jean-Jacques Tuech (Centre Hospitalier Universitaire de Rouen, Rouen, France), Denis Pezet (Centre Hospitalier Universitaire de Clermont-Ferrand, Clermont-Ferrand, France), Michel Rivoire (Centre Léon Bérard, Lyon, France), Bernard Meunier (Centre Hospitalier Universitaire de Rennes, Rennes, France), Jérôme Loriau (Hôpital Saint Joseph, AP-HP, Paris, France), Alain Valverde (Groupe Hospitalier Diaconesses, Paris, France), Jean-Michel Fabre (Centre Hospitalier Universitaire Montpellier, Saint Eloi, Montpellier, France), Michel Prudhomme (Centre Hospitalier Universitaire Carémeau de Nîmes, Nîmes, France), Eddy Cotte (Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Lyon, France), Guillaume Portier (Hôpital Purpan, Centre Hospitalier Universitaire de Toulouse, Toulouse, France), Laurent Quero (Hôpital Saint Louis, AP-HP, Paris, France), and Benoit Gallix (Centre Hospitalier Universitaire de Montpellier, Montpellier, France) and from the Institut régional du Cancer de Montpellier (ICM), Montpellier, France: Claire Lemanski, Marc Ychou, Frédéric Bibeau. Dr Stéphanie Nougaret is supported by the SIRIC Montpellier Cancer Grant INCa_Inserm_DGOS_12553.

Support/Funding: French National Cancer Institute (INCa).

Grant number INCa-DGOS_5506: PHRC-K 2012-112.

List of where the study was presented, if applicable: Not applicable

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Figure 1.

78 year-old patient with a low rectal adenocarcinoma and sphincter involvement; T2WI (a) and Fused T2WI+DWI (b) show tumor (white arrow) with adjacent extramural vascular invasion (black arrow). After induction chemotherapy (c, d), the tumor has decreased in volume, but less than 60%, and tumor deposit is still present (black arrow). The patient relapsed 14 months after surgery.

58 year-old patient with a mid-rectal adenocarcinoma. T2WI (e) and Fused T2WI+DWI (f) show a tumor (white arrow) without extramural vascular invasion. After induction chemotherapy (g, h), the tumor has largely decreased in volume, more than 60% (white arrow). Note the added value of DWI that better delineates residual tumor among therapy changes. No relapse was reported for this patient yet.

Table 1:

Association between baseline MRI features, the Dworak score and DFS in univariate analysis

N=133		values	DWORAK (n=117)			DFS (n=128)		
			0–1–2	3–4	P-value	HR	95% CI	P-value
Tumor Volume		36 [3–387]	50.3 [3–387]	28.3 [3.3–115]	<0.001	1	1.00–1.00	0.38
T	3A/B	13 (9.77%)	3 (25%)	9 (75%)		1		
	3C/D/4	120 (90.23%)	53 (50.5%)	52 (49.5%)	0.09	0.69	0.24–1.98	0.51
CRM	0	44 (33.08%)	23 (60.5%)	15 (39.5%)	0.06	1		
	1	89 (66.92%)	33 (42%)	46 (58%)		1.54	0.69–3.44	0.28
N	0	21 (15.79%)	7 (39%)	11 (61%)		1		
	1	112 (84.21%)	49 (49.5%)	50 (50.5%)	0.41	1.71	0.52–5.64	0.34
Sphincter involvement	0	100 (75.19%)	45 (52%)	42 (48%)		1		
	1	33 (24.81%)	11 (37%)	19 (63%)	0.16	1.80	0.86–3.77	0.13
Tumor Location	Low	50 (37.59%)	17 (37%)	29 (63%)		1		
	Mid	65 (48.87%)	30 (54%)	26 (46%)		0.80	0.37–1.72	
	High	18 (13.53%)	9 (60%)	6 (40)	0.15	0.98	0.34–2.79	0.82
EMVI	0	59 (44.36%)	22 (42%)	30 (58%)		1		
	1	74 (55.64%)	34 (52%)	31 (48%)	0.28	2.63	1.13–6.11	0.015
Mucinous Content	0	98 (73.68%)	40 (45.5%)	48 (54.5%)		1		
	1	35 (26.32%)	16 (55%)	13 (45%)	0.36	1.53	0.73–3.20	0.27

MRI: Magnetic Resonance Imaging; DFS: Disease-free Survival; 95% CI: 95% Confidence Interval; CRM: Circumferential Resection Margin; EMVI: Extramural venous invasion

Table 2:

Association between postinduction MRI features, the Dworak score and DFS in univariate analysis

N=128	Values		DWORAK (117)			DFS (n=128)		
			0–1–2	3–4	P-value	HR	95%CI	P-value
Tumor Volume		12 [0–217]	16.5 [0–217]	9.3 [0–47.6]	<0.001	1.01	1.00–1.02	0.019
Volume regression	60	51 (39.84%)	20 (47%)	23 (53%)		3.15	1.51–6.59	
	>60	77 (60.16%)	36 (51%)	35 (49%)	0.66	1		0.002
T	0/1/2	39 (29.32%)	11 (30%)	26 (70%)		1		
	3/4	94 (70.68%)	45 (56%)	35 (44%)	0.008	2.18	0.84–5.67	0.083
CRM	0	91 (70.0%)	37 (45%)	45 (55%)	0.17	1		0.037
	1	39 (30.0%)	19 (59%)	13 (41%)		2.16	1.07–4.39	
N	0	53 (39.85%)	19 (39%)	30 (61%)		1		
	1	80 (60.15%)	37 (54%)	31 (46%)	0.095	2.0	0.89–4.46	0.077
Sphincter involvement	0	126 (95.45%)	53 (48%)	58 (52%)		1		
	1	6 (4.55%)	3 (60%)	2 (40%)	0.67	1.65	0.39–6.93	0.522
Tumor Location	Low	44 (33.08%)	12 (30%)	28 (70%)		1		
	Mid	68 (51.13%)	32 (53%)	28 (47%)		0.85	0.38–1.89	
	High	21 (15.79%)	12 (71%)	5 (29%)	0.009	1.06	0.39–2.92	0.866
EMVI	0	89 (66.92%)	29 (37%)	50 (63%)		1		
	1	44 (33.08%)	27 (71%)	11 (29%)	<0.001	2.25	1.11–4.55	0.0255
Mucinous Content	0	95 (71.97%)	39 (46%)	46 (54%)		1		
	1	37 (28.03%)	17 (55%)	14 (45.2%)	0.39	1.92	0.94–3.94	0.080
TRG	1	1 (0.75%)	0	1 (100%)				
	2	41 (30.83%)	10 (26%)	29 (74%)				
	3	31 (23.31%)	7 (28%)	18 (72%)				
	4	51 (38.35%)	31 (70%)	13 (30%)				
	5	9 (6.77%)	8 (100%)	0	<0.001			
TRG 1–2/3–5	1–2	42 (31.58%)	10 (25%)	30 (75%)		1		
	3–4–5	91 (68.42%)	46 (60%)	31 (40%)	<0.001	2.73	1.05–7.11	0.0227

Table 3:

Association between presurgery MRI features, the Dworak score and DFS in univariate analysis.

N=94	Values		DWORAK (n=81)			DFS (n=94)		
			0–1–2	3–4	P-value	HR	95% CI	P-value
Tumor Volume		6 [0–111]	8.5 [0–111]	0 [0–37]	<0.001	1.01	0.99–1.03	0.29
Volume regression	60	20 (21.28%)	9 (60%)	6 (40%)		2.17	0.80–5.88	
	>60	74 (78.72%)	21 (32%)	45 (68%)	0.041	1		0.14
T	0/1/2	49 (52.13%)	10 (22%)	35 (78%)		1		
	3/4	45 (47.87%)	20 (56%)	16 (44%)	0.003	1.98	0.73–5.36	0.17
CRM	0	71 (82.56%)	24 (39%)	38 (61%)	0.618	1		0.21
	1	15 (17.44%)	6 (46%)	7 (54%)		2.04	0.70–5.91	
N	0	62 (65.96%)	18 (31%)	40 (69%)		1		
	1	32 (34.04%)	12 (52%)	11 (48%)	0.076	1.79	0.69–4.63	0.24
Sphincter involvement	0	93 (98.94%)	NA	NA	NA	NA	NA	NA
	1	1 (1.06%)						
Tumor Location	Low	35 (38.04%)	8 (25%)	24 (75%)		1		
	Mid	44 (47.83%)	15 (41%)	22 (59%)		0.59	0.20–1.75	
	High	13 (14.13%)	7 (70%)	3 (30%)	0.037	1.38	0.40–4.71	0.39
EMVI	0	78 (82.98%)	22 (32%)	47 (68%)		1		
	1	16 (17.02%)	8 (67%)	4 (33%)	0.048	3.11	1.15–8.43	0.0384
Mucinous Content	0	73 (78.49%)	21 (33%)	42 (67%)		1		
	1	20 (21.51%)	8 (47%)	9 (53%)	0.296	1.46	0.51–4.16	0.49
TRG	1	21 (22.34%)	1 (5%)	18 (95%)				
	2	28 (29.79%)	5 (19%)	21 (81%)				
	3	23 (24.47%)	9 (56%)	7 (44%)				
	4	19 (20.21%)	13 (72%)	5 (28%)				
	5	3 (3.19%)	2 (100%)	0	<0.001			
TRG 1–2/3–5	1–2	49 (52.13%)	6 (13%)	39 (87%)		1		

N=94	Values	DWORAK (n=81)			DFS (n=94)			
		0–1–2	3–4	<i>P</i> -value	HR	95% CI	<i>P</i> -value	
	3–4–5	45 (47.87%)	24 (67%)	12 (33%)	<0.001	4.30	1.40–13.21	0.005

Table 4:

Multivariate analysis including all significant variables (baseline, post induction, post CRT) regarding patient outcome.

N=128		HR	95% CI	P-value
ECOG	0	1		
	1	2.36	[0.94–5.91]	0.011
	2	16.53	[3.28–83.31]	
Arm	A surgery	1		
	B Cap 50 then surgery	0.21	[0.02–2.34]	0.44
	C Cap 50 then surgery	0.45	[0.09–2.36]	
	D Cap 60 then surgery	0.31	[0.06–1.59]	
Sphincter involvement (MRI 1- Baseline)	NO	1		
	YES	3.33	[1.38–8.05]	0.009
EMVI (MRI 1- Baseline)	NO	1		
	YES	3.60	[1.49–8.72]	0.002
Tumor volume regression (MRI2/MRI1)	60%	2.971	[1.28–6.92]	
	> 60%	1		0.007