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ORIGINAL ARTICLES

MRI in Evaluation of Rectal Cancer pre- and post-Chemo-Radiation Treatment.

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Abstract

Rectal cancer is associated with a high risk of metastases and local recurrence; local recurrence rates after surgical treatment being up to 32%. An accurate local staging at the time of initial diagnosis is therefore very important. Magnetic Resonance Imaging (MRI) is already established as an accurate tool for the preoperative staging of rectal cancer and has resulted in marked improvements in staging accuracy.

Material and Methods: This study used MRI in comparing the morphologic features of rectal cancer before and after 8 weeks of chemo-radiation treatment (CRT) and to correlate the post treatment MRI appearances with the histological findings in resected tumors. 45 patients with histo-pathologically proven rectal adenocarcinoma received standardized 8 weeks chemo-radiation therapy and subjected to MRI before and after treatment for clinical staging. A correlation between pathological response and MRI findings was done.

Results: The MRI diagnostic accuracy to diagnose T2 is 74.2% with relatively low specificity (64.7%). The diagnostic accuracy of MRI in evaluation of stage T3 and T4, the MRI sensitivity was 96.2% however of low specificity 26.3%. The diagnostic accuracy was 66.7%. Additionally, in evaluation of T2 stage, the sensitivity of MRI was very low 27.3% and specificity relatively high 94.7%. Diagnostic accuracy was 70%.

Post RCT, based on downstaging after CRT, the sensitivity of MRI to show no tumor was very low 0% with diagnostic accuracy 88.9%. However, to evaluate stage T2, the sensitivity was 84.6% with low specificity 66.7% and the diagnostic accuracy was 74.2%.

Conclusion: MRI had an accuracy average of 81.6% in T stage and 68.9% in N stage in re-staging rectal tumors after CRT. Over-staging results of majority of the inaccuracy. The statistical agreement between post-CRT MRI and the pathologic staging involving T and N stages was not satisfactory. In view of the above, Post CRT, restaging rectal cancer remains a challenge.

Keywords: Rectal cancer, Pre and post chemo-radiotherapy. MRI.

Introduction

Colorectal cancer is remarkably common, representing the fourth leading cause of cancer mortality and the second most common malignancy worldwide, with nearly 1 million newly diagnosed cases each year [1, 2]. Of all the colorectal cancers, rectal cancer (RC) comprises over one third of the cases [1,3], and is associated with a high risk of local recurrence and metastases. Local recurrence rates after surgical treatment of RC could reach 32% [4], mostly due to the incomplete resection of the tumor [5,6], and the circumferential safety of resection [7,8]. Therefore, an accurate local staging of RC at the time of initial (preoperative) diagnosis is crucial.

High spatial resolution MRI is an established reliable tool for the preoperative staging of RC [4], that has markedly improved the staging reliability [5]. MRI also delineates the relationship between the tumor and the meso-rectal fascia, which represents the circumferential resection

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margin (CRM) in the surgical excision process [6]. An involved CRM is when the tumor extends to within 1 mm of the meso-rectal fascia [6]. Patients with stage T3 or T4 disease or disease involving the potential CRM on MRI are offered chemo-radio therapy [6]. CRT followed by resection has proved to reduce the postoperative recurrence rate [6].

The MRI and Rectal Cancer European Equivalence (MERCURY) Study evaluated the survival of patients who underwent initial surgery vs preoperative CRT and surgery [8]. The study found that post-CRT, MRI evaluation of the tumor regression grade (TRG) corresponded to the disease-free survival, overall survival and prognosis; and that post-CRT MRI assessment of potential CRM involvement provided prognostic information on the risk of local recurrence [8]. Furthermore, both post-CRT MRI T-staging and TRG assessments were significantly correlated with the pathologic T stage; and the pathologic T stage in turn was strongly correlated with the overall and disease-free survival and local recurrence [8]. MRI's power to forecast good and poor responses after pre-operative CRT enables the further modification of the treatment [9].

The literature reveals several knowledge gaps. First, not many studies assessed the accuracy of pre-surgery MRI findings with the final outcomes and survival. In addition, the ongoing development of the MRI technology in terms of increased resolution and better techniques mean that MRI findings could translate into better forecast of outcomes and survival, as recommended by Kevin et al 2019 [10]. These considerations were the motivations to undertake the current study.

Therefore, this retrospective study bridges this knowledge gap to compare pre-surgery MRI findings of RC with post-surgery histopathology findings of the resected tumors as a gold standard. The specific objectives were to compare, at two time points (before and after 8 weeks of CRT), the:

1. Morphologic characteristics of RC as outlined by MRI vs histopathology
2. Staging features of RC outlined by MRI vs histopathological findings

Material and methods

Forty-five patients with histo-pathologically proven rectal adenocarcinoma received standardized 8-week CRT and subjected to MRI before and after treatment for clinical staging. A correlation between pathological response and MRI findings was done.

This is a retrospective and prospective study that includes 45 patients, 39 of them with biopsy-proven stage III and IV rectal adenocarcinoma who received standardized 8 weeks CRT. Lower stages of rectal cancer were used to examine the MRI accuracy and not exposed to CRT treatment. The indications for CRT were biopsy-proven locally advanced rectal cancer. In this regard, a locally advanced rectal cancer patient will be selected on the basis of clinical staging MRI findings of a high likelihood of circumferential resection margin involvement and hence possibility of inadequate immediate resection.

Informed consent was obtained from all patients after full explanation of the technique of MRI which is noninvasive, without any risk approved till now. Privacy of all patients' data is guaranteed.

Exclusion criteria included patients without available histopathology results.

Radiological evaluation: Computed tomography (CT) to exclude pulmonary and abdominal metastasis of all patients. MRI: All cases underwent MRI examination in the Radio diagnosis Department (Hamad Hospital and Rumela hospital) using a machine (Siemens 1.5 Tesla) with abdominal surface coil. All patients were positioned in the supine position. The following sequences are used, axial, sagittal and coronal T2WI. Axial cuts with fat saturated fast spin-echo T2WI and TIWI were obtained. Also, axial, sagittal and coronal T1WI were taken immediately after a manual intravenous injection of 0.1 mg of Gd-DTPA/kg of body weight (Dotarem). Patients were asked to do breathe-holding techniques to the extent tolerable.

Results

The sample size comprised 45 (82.2%) males and 8 (17.8%) females. Mean age of the sample was (22.5 years) and the range was 29. In terms of location, the majority of lesions were in the upper and mid rectum.

General characteristics:

High rectal tumors comprised nearly half (48.9%) the sample, followed closely by mid rectal tumors (46.7%) while low rectal tumors were rare (4.4%). (High rectal tumor: > 15 cm from the anal verge; Mid rectal tumor: 10-15 cm from the anal verge; Low rectal tumor: within 5-10 cm from anal verge).

MRI show lower diagnostic accuracy to differentiate mucinous and non-mucinous rectal tumors, 47.7%. This value was in post-chemo-radiotherapy with low specificity 33.3%.

Also, pre chemotherapy diagnostic accuracy of MRI was low 46.5% and low specificity 29.6%.

Post CRT, MRI in evaluation of lymph nodes involvement, sensitivity was 84.6%, diagnostic accuracy 68.9% however low specificity 47.4%.

Morphology Features	**Pre CRT**			**Post CRT**		
	MRI	**HP**	**P**	**MRI**	**HP**	**P**
	N (**%**)	N (**%**)		N (**%**)	N (**%**)	
Tumor						
Histologic grade						
Well differentiated	—	9 (20)	—	—	9 (20)	*0.000*
Moderately differentiated	—	28 (62.2)	—	—	28 (62.2)	
Poor differentiated	—	8 (17.8)	—	—	8 (17.8)	
Type			*0.003*			*0.003*
Not Mucinous	12 (26.7)	27 (62.8)		14 (31.8)	27 (61.4)	
Mucinous	33 (73.3)	16 (37.2)		30 (68.2)	17 (38.6)	
MRI post contrast						
Washout			—			0.002[a]
No washout	16 (35.6)	—		32 (71.1)	—	
Washout	29 (64.4)	—		13 (28.9)	—	
Enhancement			—			*< 0.001[a]*
Enhancement	45 (100)	—		40 (88.9)	—	
No Enhancement	0 (0)	—		5 (11.1)	—	
Diffusion WI			—			*< 0.001[a]*
Not restricted	2 (4.4)	—		25 (55.6)	—	
Restricted	43 (95.6)	—		20 (44.4)	—	
Lymph nodes						
Intramesorectal lymph nodes						
Uniformity			—			*0.002[a]*
Uniform	13 (28.9)	—		30 (66.7)	—	
Heterogeneous	32 (71.1)	—		15 (33.3)	—	
Regularity			—			*0.008[a]*
Regular	16 (35.6)	—		31 (68.9)	—	
Irregular	29 (64.4)	—		14 (31.1)	—	
Extramesorectal lymph nodes						
Uniformity			—			0.45
Uniform	9 (20)	—		9 (20.0)	—	
Heterogeneous	10 (22.2)	—		36 (80.0)	—	
Regularity			—			—
Regular	11 (24.4)	—			—	
Irregular	8 (17.8)	—			—	
Non exist	26 (57.8)					

—: not applicable; [a] comparison of pre vs post CRT MRI values

Table 1. Comparison of morphologic features of MRI vs histopathology (HP) before and after CRT

Table 1: shows the comparison of morphologic features of MRI vs histopathology before and after CRT. Histologically, most cases of rectal cancer where the moderately differentiated (62.2%), with the well differentiate and poorly differentiated adenocarcinoma were a minority (20% and 17.8% respectively). 100% of cases showed enhancement in Pre CRT, however restricted diffusion was in 95.6% of Pre CRT cases.

Staging Features	**Pre CRT**			**Post CRT**		
	MRI	**HP**	**P**	**MRI**	**HP**	**P**
	N (%)	N (%)		N (%)	N (%)	
Tumor T staging			*0.000*			0.395[b]
Stage 0	0 (0)	4 (8.9)		1 (2.2)	4(8.9)	
Stage 1	0 (0)	3 (6.7)		1 (2.2)	3 (6.7)	
Stage 2	6 (13.3)	12 (26.7)		20 (44.4)	13 (28.9)	
Stage 3	31 (68.9)	21 (46.7)		17 (37.8)	19 (42.2)	
Stage 4	8 (17.8)	5 (11.1)		6 (13.3)	6 (13.3)	
CRM involvement by tumor			—			*0.012[a]*
Not involved	28 (62.2)	—		—	37 (82.2)	
Involved	17 (37.8)	—		—	8 (17.8)	
CRM involvement by lymph nodes			—			—
Not involved	12 (26.7)	—		—	—	
Involved	33 (73.3)	—		—	—	
Anal sphincter involvement			—			1.000[a]
Not involved	32 (71.1)	—		—	32 (71.1)	
Involved	13 (28.9)	—		—	13 (28.9)	
EMVI			—			*0.021 [a]*
Not involved	31 (68.9)	—		—	39 (86.7)	
Involved	14 (31.1)	—		—	6 (13.3)	
Peritoneal reflection involvement			—			*0.022[a]*
Not involved	30 (66.7)	—		—	33 (73.3)	
Involved	15 (33.3)	—		—	12 (26.7)	
Metastases			—			—
M1	3 (6.7)	—		—	—	
M0	42 (93.3)	—		—	—	
Involved Mesorectal LN			—			0.392[b]
N0	9 (20)	—		32 (71.1)	26 (57.8)	
N1	20 (44.4)	—		10 (22.2)	16 (35.6)	
N2	16 (35.6)	—		3 (6.7)	3 (6.7)	
Involved Extramesorectal LN			—			—
Yes	19 (42.2)	—		—	—	
No	26 (57.8)	—		—	—	

—: not applicable; [a] comparison of pre-CRT MRI vs post CRT HP values; [b] comparison of pre-CRT MRI vs post CRT MRI values; EMVI: extra mural venous invasion; LN: lymph node.

***Table 2**. Comparison of staging features of MRI vs histopathology before and after CRT*

Table 2 displays the staging correlation between the results from post-CRT MRI and pathology. According to the results of the pre-CRT MRI staging for T status, 31 patients (68.9%) had advanced T3 tumors, 8 (17.8%) patients had T4 tumors with adjacent organ invasion, and 6 (13.3%) patients had T2 tumors. For initial N status, 36 (80%) patients had positive lymph node and 9 (20%) patients had negative lymph node.

The pathological results demonstrated that 19 (42.2%) of the cases had T3, 13 (28.9%) T2, 6 (13.3%) T4 and 4 cases (8.9%) no tumor found. However, the data from post-CRT MRI indicated that 20 (44.4%) of the patients had T2 tumor.

T stage	Sen	Spec	PPV	NPV	LR+	LR-	Diagnostic Accuracy
T2	75%	29.6%	38.7%	66.7%	1.07	0.84	46.5%

Sen: sensitivity; Spec: specificity, PPV: positive predictive value; NPR: negative predictive value; LR+ likelihood ratio positive; LR-: likelihood ratio negative.

Table 3: Pre CRT MRI accuracy indices compared with pre-CRT biopsy for stage T2 Tumors

Variable	Sen	Spec	PPV	NPV	LR+	LR-	Diagnostic Accuracy
T3+T4	96.2%	26.3%	64.1%	83.3%	1.31	0.14	66.7%

Sen: sensitivity; Spec: specificity, PPV: positive predictive value; NPR: negative predictive value; LR+ likelihood ratio positive; LR-: likelihood ratio negative.

Table 4: Pre CRT MRI accuracy indices compared with pre-CRT biopsy for stage (T3+T4)

The diagnostic accuracy of MRI in evaluation of the T3 and T4, the MRI sensitivity was 96.2%, however low specificity 26.3%. The diagnostic accuracy was 66.7%.

Variable	Sen	Spec	PPV	NPV	LR+	LR-	Diagnostic Accuracy
T2	27.3%	94.7%	75%	69.2%	5.18	0.77	70%

Sen: sensitivity; Spec: specificity, PPV: positive predictive value; NPR: negative predictive value; LR+ likelihood ratio positive; LR-: likelihood ratio negative.

Table 5: Accuracy of MRI in diagnosing T2 in reference to biopsy findings.

In evaluation of T2 stage, the sensitivity of MRI was very low 27.3% and specificity relatively high 94.7%. Diagnostic accuracy was 70%.

T stage	Sen	Spec	PPV	NPV	LR+	LR-	Diagnostic Accuracy
T2	70.6%	33.3%	40%	64.3%	1.06	0.88	47.7%
T3	84.6%	66.7%	64.7%	85.7%	2.54	0.23	74.2%
Intra-mesorectal LNs (N1+N2)	84.6%	47.4%	68.8%	69.2%	1.61	0.32	68.9%

Sen: sensitivity; Spec: specificity, PPV: positive predictive value; NPR: negative predictive value; LR+ likelihood ratio positive; LR-: likelihood ratio negative.

Table 6: Post CRT MRI and Post CRT Biopsy accuracy indices.

Post RCT, stage T3 tumor, the sensitivity was 84.6% with low specificity 66.7% and the diagnostic accuracy was 74.2%. In other words, the MRI the diagnostic accuracy to diagnose T3 is 74.2% with relatively low specificity (66.7%).

Lymph Node staging	MRI pre-CRT	MRI post CRT	0.000
N0	9 (20.0)	32 (71.1)	
N1	20 (44.4	10 (22.2)	
N2	16 (35.6)	3 (6.7)	

Table 7. MRI and intra-mesorectal lymph nodes correlation

MRI in evaluation of intra-mesorectal lymph nodes pre- and post-CRT revealed significant statistical correlation.

Discussion:

In regional advanced rectal cancer, surgical treatment only may not be sufficient as relatively high local recurrence rate [11, 12]. Preoperative CRT has been proven to regress the size and regress the tumor stage, augmenting the chance of sphincter preservation, reduction of the local recurrence rate or distant metastasis and improve survival rate [13, 14]. Good responders or pathological complete response (pCR) patients have a better outcome in comparison with poor responders [14, 15].

On the background of these results, either an observation approach for pathological complete response or non-conventional surgery (i.e., local excision) for better response has been assumed [16], although safeness of the approaches after CRT is remains questionable. So, accurate preoperative restaging after CRT is crucial to determine the optimal treatment plan for irradiated cancer rectum, especially in cases with good response to CRT, fear of surgical risk or radical operation refusal [16, 17].

MRI has been commonly used for preoperative assessment of rectal cancer, proven to be highly accurate in the initial disease staging [18, 19, 20]. However, when used for restaging after CRT, MR imaging are far less accurate as a result of limited ability to differentiate visible residual tumors from nonmalignant tissue, such as fibrosis, rectal wall thickness, and inflammatory infiltration induced by neoadjuvant therapy, so that the extent of local rectal tumor may be either overestimated or underestimated [15, 21, 22, 23].

A recent systematic review and meta- analysis showed that MRI restaging after CRT showed poor mean sensitivity (50.4%) [23]. Unsatisfactory accuracy had also been reported by other investigators with 47-52% for T staging and 64- 68% for nodal staging, by using MRI in irradiated rectal cancer [15, 21].

In our study, the overall diagnostic accuracy for T restaging was 46.5% and low specificity 29.6%. This was comparable to the study of *Shufang Zhan et al,* 2015 [24].

Overstating of T0–T2 results in most of the inaccuracy. In our study, sensitivity of MRI in T2 was 27.3% only.

Cases with pathologically confirmed good response to CRT, namely Stage 0–I, and up to 91.7% (11/12) were overestimated, with a poor 8% sensitivity and an acceptable 84% specificity. Moreover, MRI barely discovered 18.2% (4/22) of the cases with pCR, with a poor 18% sensitivity and an excellent 100% specificity. When it comes to T stages after CRT, only 4 out of 25 (16%) patients with ypT0 were correctly identified, whereas over-staging occurred in 11 cases as ycT2 and in 10 cases as ycT3. Moreover, 20.5% (9/44) of the patients considered to be node-negative at post-CRT MRI, proved to have nodal metastases by histopathology.

For nodal restaging with MRI, the overall accuracy was 63.8%, whereas 26.6% of the cases were over-staged and 9.6% were under-staged. These results were similar with previous reports [15,21, 25]. Yet, the much better accuracy rate was reported by *Cho et al.,* with 67% for T stage and 75% for N stage [26].

On the one hand, when considering local excision in good responders or observation strategy for pCR, MRI provided limited value which should be taken into consideration based on these findings. On the other hand, in view of the excellent 100% specificity in predicting pCR, observation strategy could be considered in cases with pCR, anxiety for surgical risk or refusing the radical operation.

Our study excluded 8 patients with histologically proven rectal mucinous tumors, taking into consideration the tendency to increase the inaccuracy rate in staging because of high signal intensity after CRT which could result in difficulty in differentiating true tumor mass from mucin remained in place. However, this exclusion criterion seemed not to contribute to an increased diagnostic performance.

Kappa statistics revealed poor concordance in both T (k=0.156) and N staging (k=0.289) after preoperative CRT in this study. [23]

The presence of nodal involvement is an important prognostic indicator for oncologic outcomes. Up to now, there is no imaging modality that can precisely evaluate the lymph node status, and the optimal criteria to define nodal involvement have also not been established.

The criterion of a metastatic LN on MRI applied in this study was defined as axes >0.5 cm in diameter, which is the most used in similar studies [25]. Its overall accuracy was 63.8%, whereas 26.6% of the cases showed over-staging and 9.6% under-staging. Kappa statistics revealed poor concordance in N staging (k=0.289) after preoperative CRT.

Previous studies had reported similar results [27, 28]. However, the size criterion was not very reliable for accurate assessment; even lymph nodes smaller than 5 mm had also been reported to contain tumor [29]. Few studies had shown improved sensitivity with the use of irregular borders or signal homogeneity [27, 30]. A new development of an ultrasmall superparamagnetic iron oxide as a lymph node contrast material has been shown to increase the accuracy for detection of nodal metastases after CRT, but this agent has not been approved in Europe [31].

In the present study, considering nodal metastasis, a moderate 58% sensitivity and acceptable 74% specificity were observed. What should be kept in mind is that a negative MR imaging of nodes is not equivalent of no metastasis, because of limited utility of this method to identify micro metastases within the lymph nodes.

In summary, with the poor agreement in staging between MRI after CRT and histopathological findings, we suggest that radical surgical approach should be performed, regardless of the result of MR imaging after neoadjuvant therapy [15], unless a new imaging modality is developed to achieve considerably improved accuracy in clinical practice. However, for cases with pCR, fear of surgical risk or refusing radical operation, an observation strategy could be considered in view of the excellent 100% specificity of MRI in predicting pCR. Certainly, this study has some

limitations: firstly, its retrospective nature might result in inaccuracies, and secondly, the relatively limited number of patients could potentially lead to bias.

Conclusions

MRI had an accuracy average of 81.6% in T stage and 68.9% in N stage in re-staging rectal tumors after CRT. Over-staging results of majority of the inaccuracy.

The statistical agreement between post-CRT MRI and the pathologic staging involving T and N stages was not satisfactory. In view of the above, Post CRT, restaging rectal cancer remains a challenge. In addition, MRI is in satisfactory to diagnose pCR. Therefore, the surgical plan before treatment should not be changed unless a new modality is used to achieve high accuracy in clinical practice. However, for those patients with pCR, intolerance or refusing radical operation, observation plans should be recommended owing to MRI's high specificity to predict pCR.

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