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ORIGINAL ARTICLE

Magnetic resonance imaging in restaging rectal cancer after neoadjuvant chemoradiotherapy

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Summary

Purpose: *To evaluate the accuracy of magnetic resonance imaging (MRI) for restaging locally advanced nonmucinous rectal cancer after neoadjuvant chemoradiotherapy (CRT).*

Methods: *A total of 94 consecutive patients with histologically proven locally advanced middle or low located nonmucinous rectal adenocarcinoma, who were treated with preoperative CRT, followed by radical surgery 6-8 weeks later, were analyzed in this retrospective study. Preoperative MR images were reinterpreted by one observer and the results were compared with the histologic findings. The overall MRI tumor (T) and nodal (N) restaging accuracy were calculated. The agreement between post-CRT MRI examination and histological assessment was evaluated by using kappa statistics.*

Results: *The overall accuracy of MRI for T restaging was 49%, with overstaging and understaging occurring in 40.4% and 10.6% of the patients, respectively. Only 18% of the patients with pathological complete response (pCR) were staged correctly by MRI, nevertheless an excellent 100% specificity in predicting pCR was detected. For N restaging with MRI, the overall accuracy was 63.8%, whereas 26.6% of the patients were overstaged and 9.6% were understaged. Kappa statistics revealed poor concordance of MRI restaging after preoperative CRT and pathological results in both T (k=0.156) and N staging (k=0.289).*

Conclusions: *Restaging rectal cancer still remains a challenge and better methods are urgently required. The surgical plan before treatment should not be changed except in those cases who had pCR, intolerance or refusing radical operation, for whom an observation strategy could be taken into consideration after the excellent specificity in predicting pCR.*

Key words: *magnetic resonance imaging, preoperative chemoradiotherapy, rectal cancer, restaging*

Introduction

Neoadjuvant CRT is routinely performed nowadays for locally advanced rectal cancer, which has been proven to achieve downsizing and downstaging of the tumor, thus increasing the chance to perform either radical resection or a sphincter preservantion procedure [1,2], improving local control [3,4] and long-term survival [2,5]. Therefore, preoperative accurate staging of rectal cancer, including depth of tumor invasion into the rectal wall, nodal status and distant metastasis, is extremely important to assess the efficiency of preoperative CRT and to develop an optimal individual therapy that involves a multidisciplinary approach. It has been reported that downstaging, including partial and/or complete response to CRT, is accompanied with better clinical outcome [2,6] and a more conservative approach with either observation or local excision has been recommended by some clinical investigators, with high survival and low recurrence rates [7-10]. Considering all these, optimal treatment could be performed if tumor response to CRT could be accurately assessed. Preoperative MRI has been widely applied and displayed a significant role in restaging locally advanced rectal cancer after preoperative CRT [11,12]. However, controversy still exists on the

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utility of MRI after CRT, and its predictive role in the postoperative pathologic staging has not been well studied yet.

The purpose of this study was to further evaluate the diagnostic performance of MRI after neoadjuvant CRT, with pathological results as reference standard.

Methods

Patient characteristics

Between January 2007 and December 2013, 102 consecutive patients with histologically proven mid to low rectal adenocarcinoma (within 10 cm from the anal verge), clinically T3-4 Nx tumors, or Tx N+ tumors staged by pelvic MRI, without distant metastasis (clinical stage II–III according to TNM classification), without history of previous pelvic chemotherapy or radiation therapy, who underwent preoperative concurrent CRT and subsequently underwent radical surgery were studied restrospectively. Eight patients with mucinous tumors histologically confirmed before treatment were excluded. We came to this decision because of the tendency of such tumors to retain high signal intensity after CRT, resulting in difficulty in differentiating true tumor mass from mucin remained. Pelvic MR images to stage the tumors before and post CRT and detailed surgical and histologic findings were available in all patients. Consequently, 94 patients were included in this study (68 males and 26 females; mean age 56.97 years).

Neoadjuvant therapy

In brief, patients received a total dose of 50.4-55Gy to the true pelvis in fractions of 2Gy/day in 5 weeks, with a boost to the tumor bed of 5.4-10.0 Gy. Concurrent chemotherapy regimens were as follows: continuous capecitabine (850-1250mg/m^2) during radiation, with or without oxaliplatin (85-130mg/m^2) on days 1 and 22.

Surgery

Radical resection was performed, including total mesorectal excision 6-8 weeks after the completion of CRT. Thirty-three patients were subjected to standard abdominoperineal resection, 61 patients were prepared for radical resection with sphincter preservation, 54 cases underwent low anterior resection and 7 cases underwent Hartmann's operation.

Imaging technique

MR imaging was performed using a 1.5T or 3.0T unit with a pelvic phased array surface coil (Intera Achieva, Philips Medical Systems, Best, The Netherlands). Patients did not have bowel preparation, air insufflation, or intravenous spasmolytic medication. The standard MR protocol consisted of two-dimensional (2D) T2-weighted fast spin echo sequences (TR/TE 8456/130 ms, 90° flip angle, 25 echotrain length, 6 number of signal averages [NSA], 0.78×1.14×3.00-mm acquisition voxel size, 30 slices, 6.03-min acquisition time) in sagittal, axial and coronal planes.

Image evaluation

One to two weeks before surgery, restaging was performed using MRI. All images were interpreted by a radiologist with 10 years of specific expertise in reading pelvic MRI who was blinded to whether the image was pre-CRT or post-CRT and to the histologic results. The tumor stage for depth of tumor invasion and lymph node involvement was categorized according to AJCC (American Joint Committee on Cancer) TMN system (7th edition) [13]. Identification of metastatic lymph nodes (LN) was by size. The presence of a metastatic LN on MRI was defined as >0.5 cm in diameter. Nodal staging was defined as y(c)N0(Nodal negative) or y(c) N+(Nodal positive). A clinical complete response (cCR) was defined as absence of adenocarcinoma in MRI after CRT.

Histopathologic examination

The pathologic classification was assessed according to AJCC TNM stage (7th edition). Restaging of post-CRT MRI was correlated with that of the pathologic staging. Good response was defined as 0–I pathological stages. A pathological complete response (pCR) was defined as absence of adenocarcinoma cells in the surgical specimen (ypT0 N0 M0). The pathologic stage of residual tumor (ypT) was based on the deepest location of residual cells in the surgical specimen. Nodal status was classified as either positive(ypN+) or negative(ypN-).

Statistics

Data were analyzed using the SPSS version 15.0 statistical software package (SPSS Inc, Chicago, Ill, USA). The agreements between post-CRT MRI and final histopathological results were measured by kappa statistics, in which a kappa value < 0.5 was deemed poor agreement. The sensitivity, specificity, and overall accuracy were calculated for each T and N stage.

Results

The tumor was localized in the lower third of rectum (within 5 cm from anal verge) in 67 cases (71.3%) and in the middle third (5-10 cm from the anal verge) in 27 cases (28.7%). According to the results of the pre-CRT MRI staging for T status, 75 out of 94 patients (79.8%) had advanced T3 tumors, 8 (8.5%) patients had T4 tumors with adjacent

organ invasion, and 11 (11.7%) patients had T2 tumors. For initial N status, 77 (81.9%) patients had N+ and 17 (18.1%) patients had N0. Eighty-one percent (76/94) had TNM stage III disease, and the remainder had stage II disease.

Staging

Table 1 displays the staging correlation between the results from post-CRT MRI and pathology. The pathological results demonstrated that 23.4% (22/94) of the cases had pCR and 12.8% (12/94) had stage 0-I (pT1-2, pN0), respectively. Actually, no patient was found to be stage 0 (ypTisN0M0). However, the data from post-CRT MRI indicated that only 4.3% (4/94) of the patients had cCR who had finally been confirmed as pCR. In other words, only 18.2% (4/22) of pCR patients could be predicted by post-CRT MRI, suggesting the method had poor sensitivity (18%) for predicting the pCR patients despite its excellent specificity (100%). In addition, among those 12 patients with ypStage 0–I, who were named as good responders to CRT, up to 91.7% (11/12) were overestimated by post-CRT MRI, with a poor sensitivity (8%) and acceptable specificity (84%). Furthermore, 14 patients scored as stage 0-I by post-CRT MRI were found overstaged in 7 cases and understaged in 6 cases. Totally, only 43% (40/94) of the patients were correctly restaged by MRI.

The comparison between post-CRT MRI and histopathologic staging is shown in Tables 2 and 3, with the related statistical values. The overstaging, understaging, accuracy, sensitivity and specificity were also calculated for each T stage and N stage. The results revealed that the overall accuracy of T and N stage by MRI was 49% and 63.8%, respectively, whereas 40.4% of the patients were overstaged and 10.6 % understaged in T stage, and 26.6% were overstaged and 9.6% understaged in N stage. For each histopathologic T staging, namely pT0, pT1, pT2, pT3, or pT4, the corresponding accuracy rate of post-CRT MRI restaging was 16%, 0, 25%, 76%, and 50%, respectively. Obviously, the overstaging of T0–T2 contributed to most of the inaccuracy for T staging. For histopathologic nodal status, 34 patients with pN(+) and 60 patients with pN(-) were noticed, and the corresponding accuracy rate of MRI restaging was 73.5% and 58.3%, respectively. Its sensitivity and specificity were 74% (25/34) and 58% (35/60).

Kappa statistics revealed poor agreement between post-CRT MRI and pathology stages (T stage, k= 0.156; N stage, k= 0.289).

Table 1. Stages: Comparison of MRI after CRT and pathologic results by TNM classification

		ycStage				*Total (cases)*
		cCR	*0-I*	*II*	*III*	
ypStage	pCR	4	6	2	10	22
	0-I	0	1	5	6	12
	II	0	7	10	9	26
	III	0	0	9	25	34
Total (cases)		4	14	26	50	94
Accuracy (%)		18.2	8	38.5	73.5	43
Sensitivity (%)		18	8	39	74	-
Specificity (%)		100	84	76	58	-

yc(p)Stage: 0=Ttis, N0; I=T1-2, N0; II=T3-4, N0; III=Tx,N+
pCR: pathologic complete response
cCR: clinical complete response predicted by MRI after CRT

Discussion

Surgery alone in locally advanced rectal cancer may not be satisfactory with relatively high local recurrence rate [14,15]. Preoperative concomitant chemoradiotherapy has been proven to downsize and downstage the tumor, increase the opportunity of sphincter preservation, reduce the frequency of local recurrence or distant metastasis and improve survival [1-6,10,16]. Good responders or pCR patients have an advantage in outcome compared with poor responders [6,11]. On the basis of these results, either an observation approach for pCR or nonconventional surgery (ie, local excision) for excellent response has been suggested recently [7,11], although whether these approaches are safe to be performed after CRT is still a matter of debate. Therefore, valid preoperative restaging after CRT is essential to determine the individualized optimal treatment strategy for irradiated rectal cancer, especially in cases with good response to CRT, fear of surgical risk or refusing radical operation [7-9]. MRI has been commonly used for preoperative assessment of rectal cancer, proven to be highly accurate in the initial disease staging [12,17,18]. 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 non malignant 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 [11,19-21]. A recent systematic review and meta-analysis showed that MRI restaging after CRT showed poor mean sensitivity (50.4%) [21]. 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

Table 2. T stage: MRI after combined chemoradiotherapy vs pathologic examination

		ycT					*Total*
		0	*1*	*2*	*3*	4	
ypT	0	4	0	11	10	0	25
	1	0	0	1	4	0	5
	2	0	0	3	9	0	12
	3	0	1	8	38	3	50
	4	0	0	0	1	1	2
Total		4	1	23	62	4	94
Overstaged (%)		84.0	100.0	75.0	6.0	-	40.4
Understaged (%)		-	0.0	0.0	18.0	50.0	10.6
Accuracy (%)		16	0	25	76	50	49
Sensitivity (%)		16	0	25	76	50	-
Specificity (%)		100	99	76	45	97	-

ycT=T stage after combined chemoradiotherapy according to magnetic resonance imaging;
ycT vs ypT: p=0.008, k=0.156

Table 3. N stage after combined chemoradiotherapy magnetic resonance imaging vs pathologic examination

		ycN		*Total*
		0	*(+)*	
ypN	0	35	25	60
	(+)	9	25	34
Total		44	50	94
Overstaged (%)		41.7	-	26.6
Understaged (%)		-	26.5	9.6
Accuracy (%)		58.3	73.5	63.8
Sensitivity (%)		58	74	42
Specificity (%)		74	58	26

ypN = N stage according to pathologic examination;
ycN vs ypN: p=0.003, k=0.289

rectal cancer [11,19].

In our study, the overall diagnostic accuracy for T restaging was 49%, with overstaging and understaging in 40.4% and 10.6% of the patients, respectively. Overstaging of T0–T2 results in most of the inaccuracy. There were altogether 12.8% (12/94) cases with pathologically confirmed good response to CRT, namely yp 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 overstaging occurred in 11 cases as ycT2 and in 10 cases as ycT3. Morever, 20.5% (9/44) of the patients considered to be node-negative at post-CRT MRI, proved to have nodal metastases by histopathology. For N restaging with MRI, the overall accuracy was 63.8%, whereas 26.6% of the cases were overstaged and 9.6% were understaged. These results were similar with previous reports [11,19,22]. Yet, the much better accuracy rate was reported by Cho et al., with 67% for T stage and 75% for N stage [23]. On the one hand, when considering local excision in good responders or observation stategy for pCR, MRI provided limited value which should be taken into consideration on the basis of these findings. On the other hand, in view of the excellent 100% specificity in predicting pCR, observation strategy could be taken into account 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 as a result of high signal intensity after CRT which could result in difficulty in differentiating true tumor mass from mucin remained in place [20]. 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.

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 commonly used in similar studies [22]. Its overall accuracy was 63.8%, whereas 26.6% of the cases showed overstaging and 9.6% understaging. Kappa statistics revealed poor concordance in N staging (k=0.289) after preoperative CRT. Previous studies had reported similar results [24,25]. 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 [26]. Few studies had shown improved sensitivity with the use of irregular borders or signal homogeneity [24,27]. A new development of an utrasmall 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 [28]. 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 nonmetastasis, because of limited utility of this method to identify micrometastases 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 [11], 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 rate of 48% in T stage and 63.8% in N stage in restaging rectal tumors after CRT, in which overstaging results in most of the inaccuracy. The agreement between post-CRT MRI and the pathologic staging in both T and N stages was far less satisfactory. Restaging rectal cancer after neoadjuvant therapy still remains a challenge. Furthermore, MRI is insufficient in detecting pCR. Based on these conclusions, 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 cases who had pCR, intolerance or refusing radical operation, observation strategy could be considered owing to MRI's excellent specificity in predicting pCR.

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