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ROLE OF MRI IN LOCAL STAGING OF RECTAL CANCER AND FOLLOW UP AFTER ADJUVANT AND NEOADJUVANT THERAPY

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Abstract

This study evaluated the MRI as a diagnostic tool for diagnosis and staging of colorectal carcinoma as well as evaluation of the response to adjuvant and neo adjuvant chemotherapy. Thirty patients were included in this study, 18 males and 12 females with their ages ranged between 32 and 75 years, and the mean age was 52.5 years. All patients were presented with rectal cancer proved by histology. Patients were referred from the outpatient clinics and department of Surgery in Al-Hussein University Hospital during the period from 2009 to 2012.

The results showed that all patients were subjected to Pre and Post chemotherapy MRI examinations. At initial MRI examination, the locations of the tumours were as the follow. The lesion located in the lower third in 5 cases, in the middle third in 15 cases, in the upper third of the rectum in 10 cases.

Key words: Colorectal carcinoma, MR imaging of colorectal carcinoma, Staging of colorectal carcinoma, follow up of colorectal carcinoma after neoadjuvant chemotherapy.

Introduction

Colorectal carcinoma is the second most common cancer in Western society with 148,620 new cases and 55,170 deaths in the United States each year (Jemal *et al,* 2005) and the worldwide incidence is rapidly increasing as diet and lifestyles change. Accurate preoperative diagnosis and staging of rectal carcinoma, which are essential for treatment planning and prognosis, can be achieved with endorectal sonography and CT (Kim *et al,* 2006). Because of its superior soft-tissue contrast and multiplanar capability, MRI is becoming increasingly accepted by radiologists, surgeons, and patients for imaging of the rectum. Use of MRI also eliminates the risks of ionizing radiation and nephrotoxicity from iodinated contrast material (Sinha *et al,* 2006). About 30% of all colorectal cancers were diagnosed in the rectum, and rectal cancer has a worse prognosis for both metastases and local recurrence than does colon cancer (Brown *et al,* 2005). Preoperative imaging for staging of rectal cancer becomes an important aspect of current approach to rectal cancer management, because it helps to select suitable patients for neo-adjuvant chemoradiotherapy and determined the appropriate surgical technique (Tapan *et al,* 2014). Imaging modalities as endoscopic ultrasonography, computed tomography, and magnetic resonance imaging (MRI) play an important role in assessing the depth of tumor penetration, lymph node involvement, mesorectal fascia and anal sphincter invasion, and presence of distant metastatic diseases (Mizukami *et al,* 2011).

Over the past few years, significant progress has been made in the management of rectal cancer (Michael *et al,* 2003). Preoperative therapy became standard procedure for locally advanced rectal cancer. Tumor shrinkage due to preoperative chemotherapy-radiation therapy (CRT) is now a reality, and pathologically complete responses are not uncommon (Valentini *et al,* 2009). Advances in surgical technique, neoadjuvant and adjuvant therapies led to significant improved outcome for some patients (Jederán *et al*, 2012). MRI is the most promising technique for the local staging of rectal cancer and follows up after adjuvant and neoadjuvant therapy (Vliegen *et al,* 2005). Glynne-Jones *et al*. (2006) reported that the CRM status predicts outcome after surgery alone, preoperative radiotherapy and preoperative

chemoradiation. Yet, CRM status and its measurement was poorly documented in the literature, and rarely as a prospective measure of outcome. The CRM should be measured and documented in all cases, using the definition of <or= 1 mm to denote an involved CRM. This definition should also be incorporated into future rectal cancer studies with use of a standardized proforma. Rectal Cancer European Equivalence (MERCURY, 2007) showed that high-resolution MRI can accurately predict involvement of the surgical resection margin (≤ 1 mm) and extramural tumor invasion (Glimelius and Oliveira, 2008).

Patients, Materials and Methods

Thirty patients were included in this study, 18 males and 12 females with their ages range between 32 and 75 years, and the mean age was 52.5 years. All patients were presented with rectal cancer proved by histology. They were referred from department of Surgery, the outpatient clinics, Al-Hussein University Hospitals from 2009 to 2012. Diagnosis of rectal cancer was based on patients' proctoscopy and biopsy.

Magnetic Resonance Imaging: All patients were examined using 1.5 Tesla superconductive scanner (Philips Achiva 1.5 T) equipped with received phased array 8 channels coil anterior to pelvis and fixed with straps. All metallic parts like watches, hair pins, magnetic credit cards or mobiles were kept outside examination room. Cardiac pacemaker, coronary stents, past aneurismal clipping, and metallic bony prosthesis of contra-indicated for MRI examination were reported.

Results

Thirty patients were included; 18 males and 12 females with ages ranged between 32 & 75 years. All patients were subjected to Pre & Post CRT (neoadjuvant therapy) MRI examinations. Rectal tumor location was in the initial pre-operative MRI (Tab. 1)

Table 1: Distribution of tumors by anatomical location in MRI examination:

Tumor location	No. of cases	Percentage
Upper third (12-16 cm from anal verge)	10	33
Middle third (8-11 cm from anal verge)	15	50
Lower third (4-7 cm from anal verge)	5	17
Total	30	100

Characterization of lesions by using T2 weighted MRI: At initial MRI staging 27 (90.0%) patients had high signal, 2 (6.6%) patients had very high signal and one (3.3%) patient has intermediate signal. At post CRT restaging MRI examinations; 19 patients (63.3%) had high signal, 5 patients (16.6%) had intermediate signal, 3 patients (10%) had isointense signal and 3 patients (10%) without signal. At histopathology, 2 cases were mucinous adenocarcinoma (their tumor showed very high T2 signal in the initial MRI examinations). The 3 cases whose lesions showed no signal were those with complete response to CRT. One of 5 cases with intermediate signal was completely responsive to CRT, while others showed partial response to CRT and radiation therapy.

Tumor staging: In initial MRI staging, 5 patients were diagnosed tumour stage 2, 21 patients tumour stage 3 &4 patients tumour stage 4. After neoadjuvant chemoradiotherapy (CRT), restaging MRI scanning showed, 3 patients were diagnosed tumour stage 0, 1 patient tumour stage1, 4 patients tumour stage 2, 21 tumour stage 3, while tumour stage 4 were 1 patient. Post-operative pathology showed tumour stage T0 were 4 patients, T1 were 2 patients, T2 were 5 patients and T3 were 19 patients. No T4 was found at pathology. Responses to CRT were complete response in 4 cases (13.3%), disease progression in 4 cases (13.3%), partial response in 21 cases (70.0%) and stable disease in 1 case (3.3%); agreed was 80% (accuracy). In initial MRI examinations 2 cases No, 9 was diagnosed N1 & 19 was N2.

In post CRT MRI examinations, 9 cases were diagnosed N0, 18 cases were diagnosed N1 and 3 cases were N2 (Fig.1).

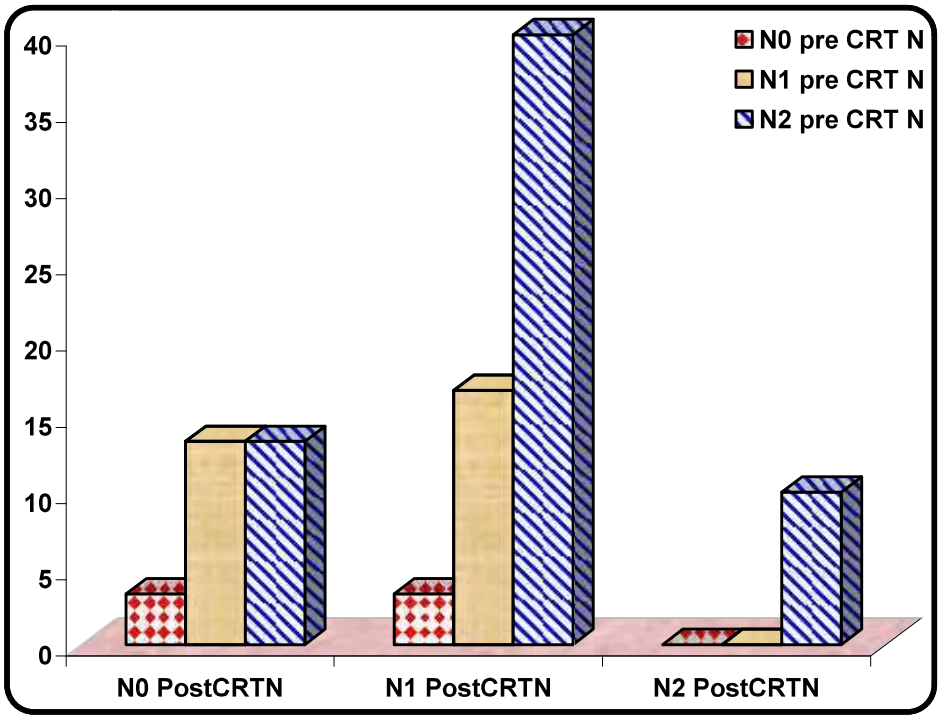

Fig. 1: Compared to post CRT LN staging; 9 cases stage N0, 18 cases stage N1 and 3 cases stage N2, agreements (accuracy) was 83.3% and P < 0.001 (Tab.2).

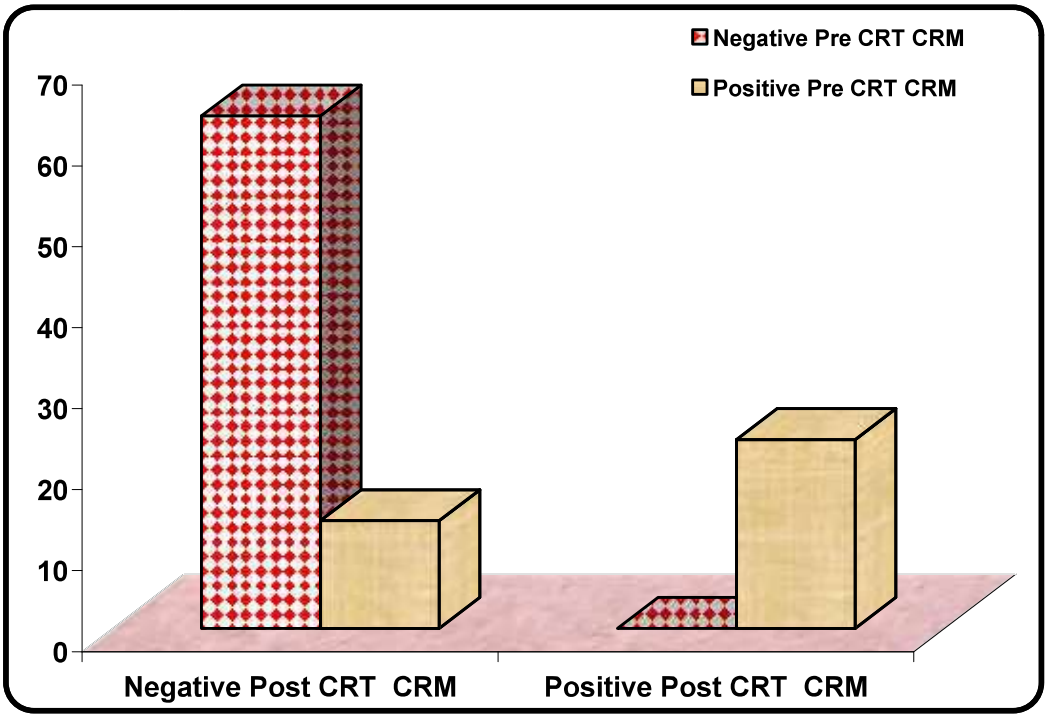

Fig. 2: relation between Pre and post CRM

At diffusion weighted images in the Pre CRT MRI examinations 28 patients (93.3%) showed bright signal at long b value (1000) and 2 patients (6.6%) showed very bright signal (they were represents mucinous type of adenocarcinoma at pathology).

Table 2: Pathology

		Pathology N								Chi-Square	
		N0		N1		N2		Total			
		N	%	N	%	N	%	N	%	X^2	P-value
Pre CRT LN	N0	1	3.33	1	3.33	0	0.00	2	6.67	3.005	0.557
	N1	5	16.67	4	13.33	0	0.00	9	30.00		
	N2	8	26.67	8	26.67	3	10.00	19	63.33		
Post CRT LN	N0	9	30.00	0	0.00	0	0.00	9	30.00	35.628	<0.001*
	N1	5	16.67	13	43.33	0	0.00	18	60.00		
	N2	0	0.00	0	0.00	3	10.00	3	10.00		
Agreement %		83.33%									

At initial MRI, 11 cases were positive CRM & 19 cases were negative CRM, at post CRT MRI examinations 7 cases showed positive CRM involvement and 23 cases showed negative CRM (Fig. 1), comparing with the post-operative pathology results, 10 cases showed positive CRM and 20 cases showed negative CRM. Sensitivity was 60 %, specificity was 95%, PPV was 85.71 %, NPV was 82.61% and accuracy was 83%.

Table 3: Pre and Post CRT MRI examinations

Pre CRT 1000B		Post CRT 1000 B			
		No signal	Bright	Very bright	Total
Bright	N	4	24	0	28
	%	13.33	80.00	0.00	93.33
Very bright	N	0	1	1	2
	%	0.00	3.33	3.33	6.67
Total	N	4	25	1	30
	%	13.33	83.33	3.33	100.00
Chi-Square	X^2	6.299			
	P-value	0.043*			

In post CRT MRI examination, 4 patients (13.3%) showed no signal at long b value represented complete response to treatments at pathology, 35 patients (83.3%) showed bright signal (response to treatments and one patient showed very bright signal at long b value and one of mucinous type of adenocarcinoma at histopathology. Mean ADC value of complete responses were not detected (negative) except one case showed mean ADC 1.4x10-3 (above 1x10-3), cut off value (Tab. 4). Others showed partial response to CRT showed increased ADC value in post CRT examinations compared to pre CRT examinations, generally the mean ADC value for tumour in pre CRT stage was 7.485±1.161SD but mean ADC for tumour in post CRT stage was 10.900±3.975SD.

Table 4: Statistics

	Post CRT mean ADC				ANOVA	
	Range			Mean ± SD	F	P-value
CR	14.000	-	14.000	14.000	3.132	0.046*
PR	1.300	-	15.000	11.600±3.701		
stable	1.800	-	1.800	1.800		
DP	6.000	-	11.000	8.900±2.347		

Due to CRT there were changes in the tumour size, the cases that showed complete response showed mean size of 1.100±00SD, the cases that showed PR had mean post CRT tumour size 2.124, the cases that had stable disease showed mean tumour size 2.500 while the cases that had DP showed mean tumour size 5.100.

Table 5: Post chemotherapy-radiation therapy

	Post CRT T size			ANOVA	
	Range			Mean ± SD	F	P-value
CR	1.100	-	1.100	1.100±0.000	19.672	<0.001*
PR	1.100	-	4.300	2.124±0.802		
Stable	2.500	-	2.500	2.500±0.		
DP	4.600	-	5.900	5.100±0.560		

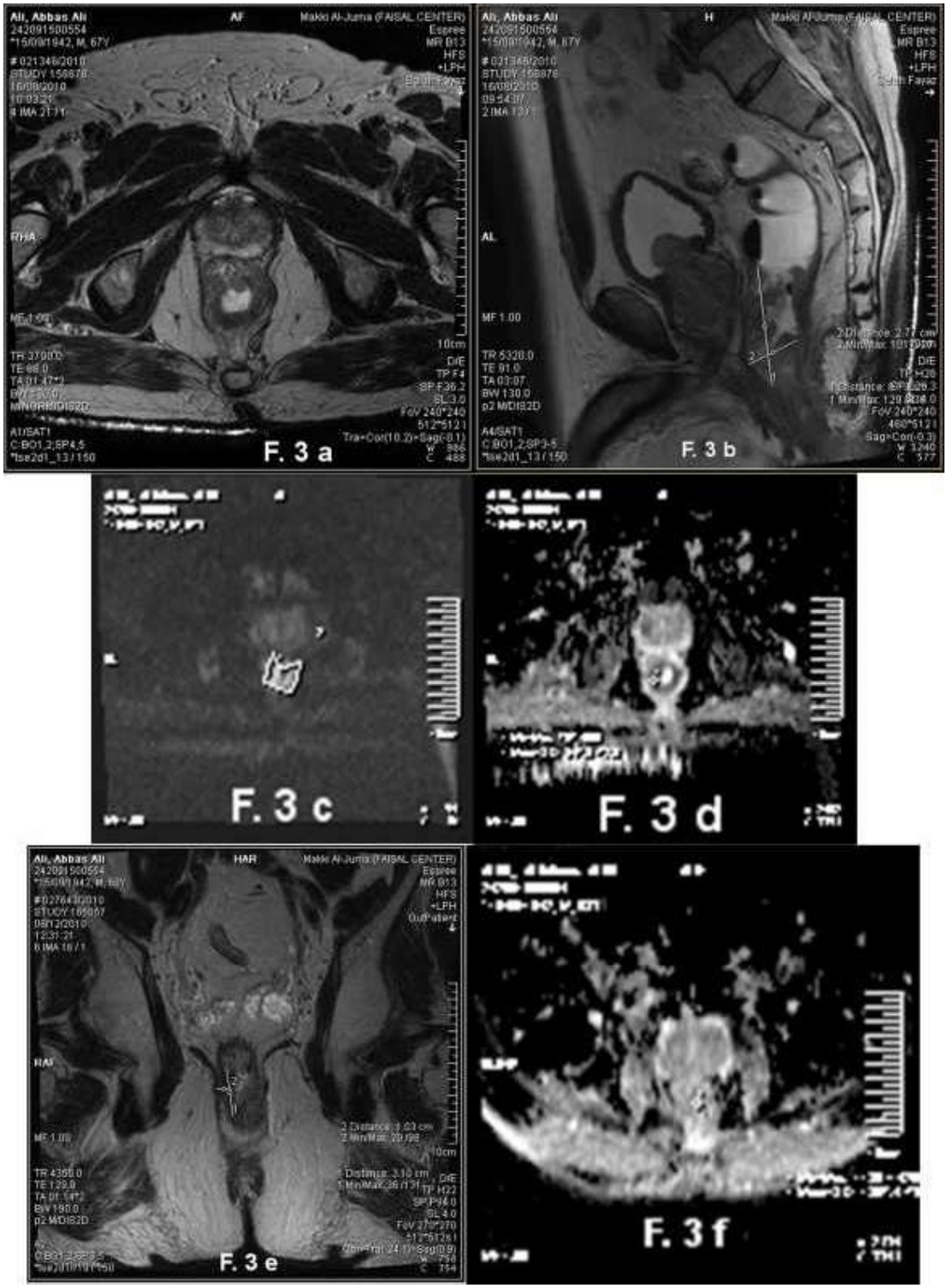

Fig. 3: A 46 –year old male patient presented by bleeding per-rectum. (A) Axial T2WI HR Pre CRT showed circumferential mural mass.(B) SagittalT2WIpreCRT showed intermediate signal of a mass measures 6.5x27cm.(C) DWI(1000 b value) shows bright signal at tumour site.(D) ADC shows black signal at tumour site.(E) Coronal HRT2WI post CRT showed decrease in tumour size.(F) ADC=1.4x10 mm/sec, showed decrease in black signal

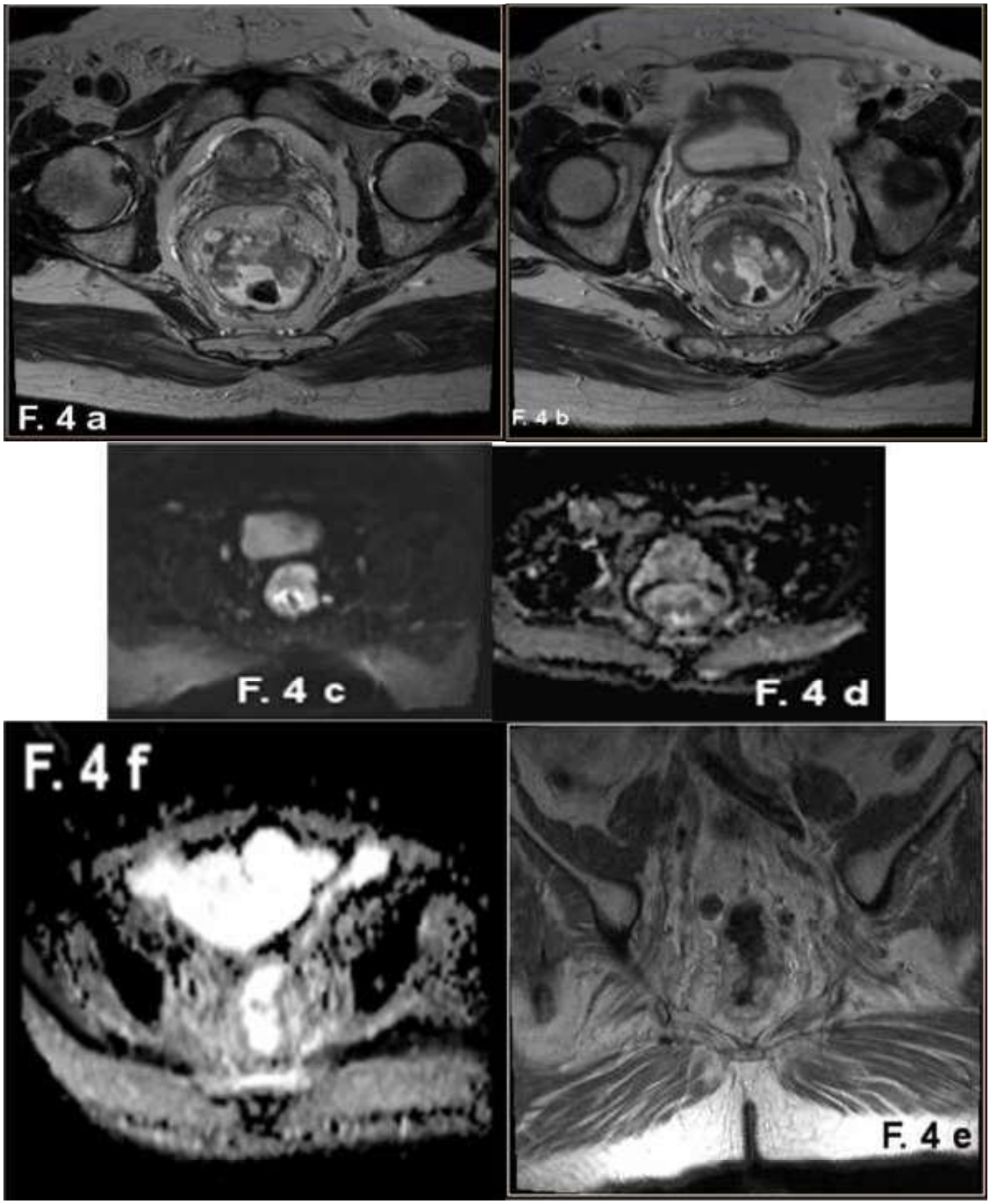

Fig. 4: A 69 –year old male patient presented by bloody stained stool with pelvic pain. (A) Axial T2WI HR Pre CRT showed rectal tumour of intermediate signal and LNs. (B) AxialT2WIP showed bright signal within the tumour denoting its mucinous type. (C) DWI(1000 b value) showed bright signal of tumour and LNs.(D) ADC showed black signal at tumour site.(E) Axial HRT2WI post CRT showed decrease in tumour size.(F) ADC=1.1x10 mm/sec showed decrease in black signal of tumour.

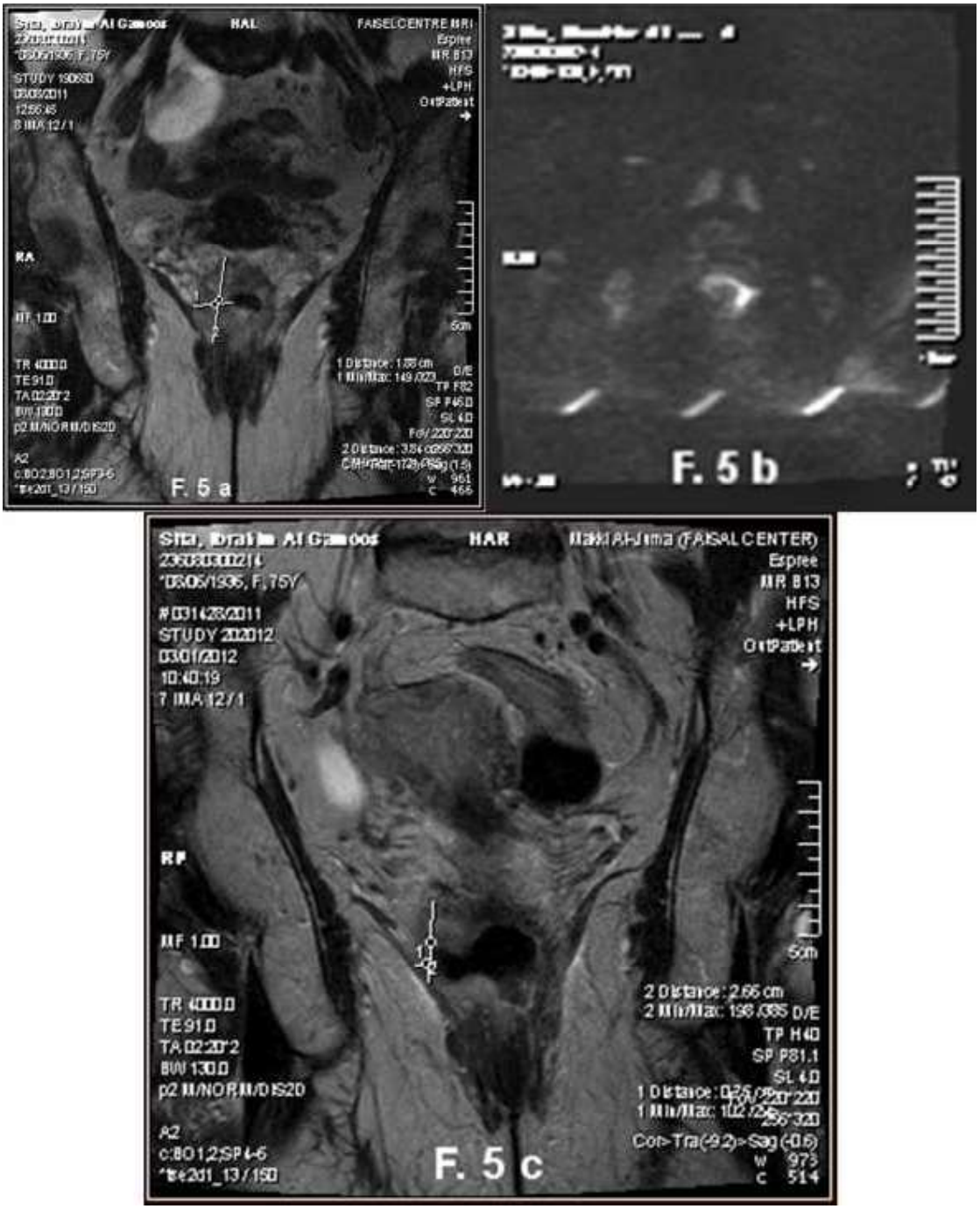

Fig. 5: A 74 –year old female patient presented by bleeding per rectum and fever. (A) Coronal T2WI HR Pre CRT showed rectal mass infiltrating the levator ani muscles. (B) Coronal T2WI showed regression of tumour size.(C) Post CRT DWI(1000 b value) shows minimal bright signal at tumour site.

Discussion

The advances in preoperative assessment through accurate staging and the recognition of the importance of the relationship of the tumour to the mesorectal fascia allowed the selection of patients for a preoperative strategy to down-size/down-stage the tumour if fascial layer was involved or threatened. Improvements in the quality of surgical resection through the acceptance of the principle of total mesorectal excision have ensured that optimal surgery remained cornerstone to

successful treatment. They added that more refinements of the MDT process strive to improve outcome. Accurate radiological staging, optimal surgery and detailed histopathologic assessment together with consideration of a preoperative neoadjuvant strategy should now form the basis for current treatment and future research in rectal cancer.

The prognosis for patients with rectal cancer is closely related to the stage of the disease at the time of diagnosis and the choice of treatment. The risk of postoperative tumor recurrence is 5% for stage T1, 10% for stage T2, and 25% for stage T3, using the TNM staging system. In case of lymph node involvement, the risk of tumor recurrence increases to 33% for a stage T2 tumor and 66% for stage T3 (Michael *et al*, 2003). Tumor shrinkage due to preoperative chemotherapy–radiation therapy (CRT) was a reality and pathologically complete responses common (Valentini *et al,* 2009). Magnetic resonance (MR) imaging is the most promising technique for the local staging of rectal cancer and follows up after adjuvant and neoadjuvant therapy (Vliegen *et al*, 2005). Invention of DWI improved utility of MRI in patients with rectal cancer. Rao *et al.* (2008) showed that the addition of DWI to T2-weighted imaging improved accuracy of rectal cancer detection. Ichikawa *et al*. (2006) studied high-b-value DWI in 33 col orectal cancer patients (14 with rectal cancer) and reported 91% sensitivity and 100% specificity. DWI was utilized for detection of metastatic lymph nodes in rectal cancer. Thirty patients were included, 18 males & 12 females with ages between 32 & 75 years, with mean of 55.4 years. All patients had rectal cancer proved by histology. In disagreement with Michael *et al*. (2003), in the present study male patients were more than female ones. The diagnoses of rectal cancer in these patients were established based on their proctoscopy and biopsy. The present study showed the role of pelvic MRI in local staging of rectal cancer and followed them after neoadjuvant therapy to restage the diseases and hence to assess response to treatment and compare with the operative pathological results, and to follow patients who needed adjuvant therapy

Imaging Criteria for irradiated rectal cancer after neoadjuvant therapy: On standard MRI, a normalized rectal wall without any detectable wall thickening was considered a definite criterion for a complete response. A solid residual mass with intermediate signal intensity on T2-weighted MRI was considered a definite criterion for residual tumor. Hypointense signal intensity changes indicated fibrosis, in which case undetermined scores were assigned. On the diffusion images, residual high-signal intensity on the location of the primary tumor was considered a criterion for residual tumor, whereas the absence of increased signal on DWI agreed with Barbaro *et al*. (2009). In the present study, 20 patients underwent low anterior resection, 10 had abdominoperineal resection, and 2 had more extended surgery due to metastatic LNs outside the mesorectum. One patient showed extraluminal vascular invasion of the rectal veins, at histology, 4 patients had ypT0, 2 had ypT1, 5 had ypT2 and 19 had ypT3. Two patients had mucinous type adenocarcinoma. The mean time interval between the restaging MRI and surgery was 7 (range 1–14) days. Chun *et al*. (2006) reported that viable tumour was predefined as an area of signal intensity on the T2WI higher than that of the surrounding muscle layer, also viable tumour was predefined as the presence of residual high signal intensity on DWI (b-value, 1000 sec mm–2) and reduced ADC on the ADC map in the corresponding tissue. The reference standard was the signal intensity of the unaffected rectal wall (b-value, 1000 sec mm–2). In the initial MRI staging, 5 patients were diagnosed tumour stage 2, 21 patients tumour stage 3 and 4 patients tumour stage 4, after neoadjuvant chemoradiotherapy (CRT), restaging MRI scanning showed, 3 patients were diagnosed tumour stage 0, 1 patient tumour stage1, 4 patients tumour stage 2, 21

tumour stage 3, while tumour stage 4 were 1 patient, the post-operative pathology results showed tumour stage T0 were 4 patients, T1 were 2 patients, T2 were 5 patients and T3 were 19 patients. No T4 was found at pathology results.

The responses to CRT were complete response in 4 cases (13.3%), disease progression in 4 cases (13.3%), partial response in 21 cases (70.0%) and stable disease in 1 case (3.3%); the agreements was 80% (accuracy), the results approximately agreed with Valentini *et al.* (2009) who report the results of CCRT in 81 patients with stage T3 rectal cancer. At least partial tumor response was seen in 62 patients (77%), with complete tumor response in seven patients (9%); no tumor response was in 19 patients (23%), minor difference could be due to the small sample of patients and some cases were stages 2 & 4. Agreements degree (accuracy) in or prediction of pathological stage for irradiated rectal cancer for T staging was 80% with P was < 0.001 which better than Chen *et al.* (2005) who proved that overall accuracy of MR imaging in predicting the pathologic stage of irradiated rectal cancer is 47%–54% (50%) for T staging, also agreed with Burton *et al*. (2006) who proved that CCRT resulted in a 60-70% tumor response rate, in particular a 10-20% complete tumor response rate, leading to improved resectability and local control 20% of patients even show complete tumour regression (sterilization).According to the operative results of our study 14 patients were LN stage 0, 13 patients were LN stage N1 & 3 patients were LN stage 2, in comparison to post CRT LN staging, 9 cases were stage N0, 18 stage N1 and 3 cases stage N2 with of agreements evidence of 83.3% and P < 0.001 the present study showed increased accuracy of MRI in predicting the pathological stage for irradiated LN compared to Chen *et al*. (2005) who proved overall accuracy 64%–68% (65%) for N staging, as any detectable LN with suspicious morphological criteria to be metastatic LN and also due to large number of the cases(18) were stage N1. In the present study at post CRT MRI examinations 7 cases showed positive CRM involvement and 23 cases showed negative CRM, comparing these results with the post-operative pathology results where there were10 cases showed positive CRM and 20 cases showed negative CRM, sensitivity of the CRM involvement was 60 %, specificity was 95%, PPV was 85.71 %, NPV was 82.61% and accuracy was 83% that were in garments with Kim *et al.* (2009) who found sensitivity, 75%; specificity, 88-98%; accuracy, 85-92%; PPV, 66.7-92.3%; NPV, 91.5-92.3% for prediction of CRM involvement during restaging of irradiated rectal cancers by using T2-weighted imaging along with gadolinium-enhanced T1-weighted imaging with minor difference could be explained by differences in the study population and the cut-off level. In the present study, increased accuracy for prediction of CRM involvement agreed with Vliegen *et al*. (2008) who found MR imaging accuracy of 66% in predicting CRM involvement during restaging of irradiated rectal cancers (sensitivity, 100%; specificity, 35%; positive predictive value, 58%; negative predictive value, 100%).

Conclusion

Our results showed that magnetic resonance (MR) imaging is the most promising technique for the local staging of rectal cancer and follow up after adjuvant and neoadjuvant therapy. The study showed that MRI is reproducible and allows patients to be selected on this basis for preoperative treatment. As a result, this form of preoperative staging is more widespread and is becoming mandatory in certain countries. The outcome results showed increased accuracy of MRI in predicting the pathological stage for irradiated rectal tumour and LNs.

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