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Magnetic Resonance Imaging in Rectal Cancer: Ability to Predict Response to Neo-adjuvant Treatment

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Abstract

Magnetic Resonance Imaging (MRI) is recommended in recent guidelines for the initial staging done at the primary diagnosis of a cancer of the lower two thirds of the rectum, selecting patients requiring a neoadjuvant treatment in order to reduce local recurrence.

Radiotherapy with concurrent chemotherapy has shown its effectiveness in improving the patient outcome and adjusting the surgeon approach by downsizing and downstaging tumors as well as increasing R0 resection. However this response has shown to be variable.

Whereas, minimizing the operative approaches without compromising the oncological control re- quires a very effective and accurate selection of good responder patients to chemo radiotherapy on the one hand and an accurate assessment of their response once the preoperative treatment is achieved on the other hand.

Keywords: Neo-adjuvant treatment; Chemo radiotherapy; Tumour; SIAD Radiological; MRI

Introduction

To better discern why some patients show excellent response while others do not, we proposed to analyze the ability of initial MRI to select patients with a predicted good response or a predicted absence of response to neoadjuvant treatment and conclude to an imaging prediction model.

We carried a ten year retrospective study of 30 patients with a cancer of the lower two thirds of the rectum who had undergone MRI assessment at the time of primary diagnosis and needed a neoadjuvant chemo radiotherapy before radical surgery in order to analyze the strengths and weaknesses of the ability of MRI to improve prediction of tumor response to neoadjuvant chemo radiotherapy in rectal cancer [1].

Materials and Methods

Data was analyzed retrospectively from patients' medical records from the archives of both general surgery and medical imaging departments of Habib Thameur Hospital. We included patients who had a histological confirmed diagnosis of rectal adenocarcinoma in a T3, T4 and/or N+ tumor of the lower two thirds of the rectum benefitting from a treatment based on neoadjuvant chemo radiotherapy associating Capecitabine to classic radiotherapy procedure (45 GY divided into 25 sessions) followed by a radical surgical tumoral resection after neo-adjuvant treatment. We excluded patients with inflammatory chronic bowel disease and a synchronous colic or other organ primary cancer.

We analyzed all clinical and biological features including main symptoms, digital rectal exam, endoscopy results, CT scan and tumor blood markers. MRI was

All MRI exams were done with the same protocol (Table I) and reread. Features of loco regional assessment were detailed. We used the SIAD radiological report template (Figure 1) to build our assessment canvas We did not consider only overall TNM stage ; we also analyzed all details of tumoral invasion and nodal invasion as reported in this template [2-4].

MRI Protocol		
Pelvic phased	Array Coil	1.5 T GE Healthcare MRI
Endorectal coil	Rectal Contrast Media	Intravenous or Intramuscular Antispasmodic
Three-dimensional fat-suppressed T1	Weighted Gradient	Echo images before and after Intravenous Gadolinium
High resolution oblique axial and coronal T2	Weighted Sequences	

Table 1: MRI protocol used.

We used YPTNM staging system for final histological response assessment done on the radical surgery resection specimen. 2 grades were used based on comparison of YPTNM and initial MRI TNM staging as following: first non-responsive tumors including the ones presenting with ypT and/or ypN stages unchanged or more advanced than T and/or N stage and second responsive tumors including the ones presenting with YPTNM less advanced than initial TNM including tumors with complete response, defined as absence of viable tumor cells (meaning ypT0N0M0).

Statistical analysis was performed using SPSS. Results were expressed in descriptive study in percentages and in averages. Regarding the analytic study, Chi-square and Fisher analysis were selected for the univariate logistic regression analysis of the data to determine predictive factors of response to neoadjuvant treatment and concordance between post chemo radiotherapy MRI and final histological findings. Every time we had a more than one statistical outcome variable in the univariate analysis, a multivariate analysis according to Forward LR method was performed [5,6].

Results

The studied group of patients included 22 men (73%) and 8 women (27%) with a mean age of 57 years old. Tumor occurred in the lower third of the rectum in 10 patients (33%) and in the middle third in 20 patients (67%).

Initial MRI, based as recommended in literature on two-dimensional FSE T2-weighted oblique sequences showed: a mesorectal invasion in 23 patients (77%), an involvement of the mesorectal fascia in 11 patients (37%) and a nodal invasion in 25 patients (83%).

Mean tumoral distance to the anal verge assessed by initial MRI was 53mm. It ranged from zero to 90mm. Internal anal sphincter was reached by the tumor in 6 patients (20%) (Figure 2, 3 and Table 2) [7-9].

Eighteen patients (60%) had MRI between 9 and 12 weeks after the neoadjuvant treatment to assess tumoral response before surgery. Tumoral response to neoadjuvant treatment was considered as subtle in 3 patients (17%), almost complete in 3 patients (17%) and partial in 12 patients (66%) with necrosis in 9 patients (50%) and fibrotic changes in 7 patients (40%) (Tables 3-5) [10].

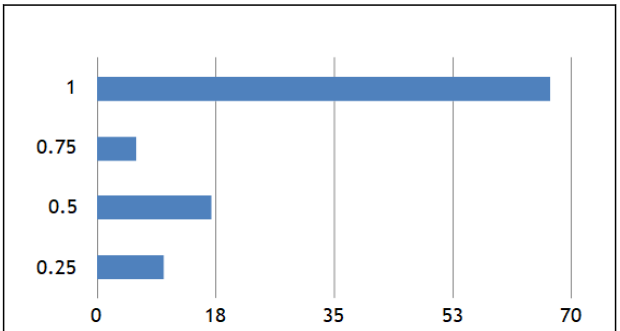

Figure 1: Distribution of percentage of the rectal circumference invaded by the tumor distribution in our population.

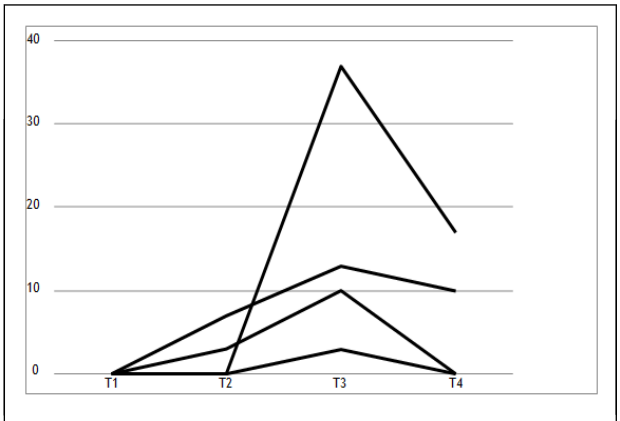

Figure 2: Distribution of the nodal invasion stage depending on tumor loco regional invasion stage of TNM staging system in percentage.

Organ directly invaded by the Tumour	Number and percentage of patients
Visceral peritoneum	4(50%)
Bladder	3(37%)
Prostate	2(25%)
Seminal vesicle	2(25%)

Table 2: Organs invaded in the T4 tumors of our population and their distribution in this sub-group.

Assessment	Positive results	Negative results
Tumoral location	(Increased distance to anal verge)	(Decreased or unchanged distance to anal verge)
	8 patients (44%)	10 patients (56%)
Tumoral measurements	(Decreased length)	(Increased or unchanged length)
	11 patients (61%)	7 patients (39%)
Tumoral circumferential invasion	(Decreased percentage of circumferential invasion)	(Increased or unchanged per- centage of circumferential in- vasion)
	9 patients (50%)	9 patients (50%)
Mesorectal invasion	(Decreased invasion)	(Increased or unchanged in- vasion)
	4 patients (22%)	14 patients (78%)
Overall response	(Partial or important re- sponse)	(Subtle response)
	15 patients (83%)	3 patients (17%)

Table 3: Organs invaded in the T4 tumors of our population and their distribution in this sub-group.

Assessment	Result
Tumoral location	Unchanged distance to anal verge
Tumoral measurement	10 mm decrease (33%)
Tumoral circumferential invasion	25% decrease
Mesorectal tumoral invasion	Unchanged
Tumoral signal	Predominant fibrosis
Overall response	Important

Table 4: MRI preoperative assessment after neo-adjuvant chemo radiotherapy for the one patient who appeared to have a complete histological postoperative response.

Assessment	Patient 4	Patient 5
Tumoral location	(Distance to anal verge)	(Distance to anal verge)
	10 mm increase	Unchanged
Tumoral measurements	24 mm (24%) de- crease	20 mm (50%) increase
Tumoral circumferential invasion	Unchanged	Unchanged
Mesorectal tumoral invasion	Unchanged	Progression
Tumoral signal	Unchanged	Unchanged
Overall response	Subtle	Subtle

Table 5: MRI preoperative assessment after neo adjuvant chemo radiotherapy for the two patients who appeared not to have any histological postoperative response.

Anterior resection of the rectum was performed in 18 patients (60%) while abdominoperineal resection was performed in the other 12 patients (40%). All of the patients were operated by laparotomy 9 to 12 weeks after the end of neoadjuvant treatment (Figure 4) [11].

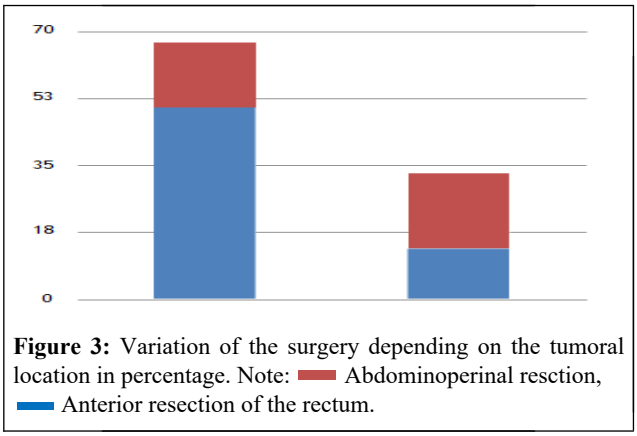

Figure 3: Variation of the surgery depending on the tumoral location in percentage. Note: Abdominoperinal resction, Anterior resection of the rectum.

Assessment of final histological response done only on the radical surgery specimen showed non responsive tumors in 6 patients (20%) and responsive tumors in 24 patients (80%) including 2 patients (7%) with a complete response.

One of the patients with complete response had an abdominoperineal resection.We analyzed all clinical, biological and initial MRI features to highlight predictive factors of responsive and non-responsive locally advanced rectal cancer to neo adjuvant chemo radiotherapy (Tables 6-8).

We could not study predictive factors of complete response apart because of the small sample size [12].

		Complete or Partial response	No response	p
		N=24 (80%)	**N=6 (20%)**	
Stenotic tumor	Yes	6 (75%)	2 (25%)	0.68
	No	18 (82%)	4 (18%)	
Complication	None	11 (79%)	3 (21%)	0.91
	Intestinal obstruction	1 (100%)	0 (0%)	
	Rectal hemorrhage	11 (79%)	3 (21%)	
	Infected and obstructive tumor	1 (100%)	0 (0%)	
Ascites	Yes	1 (100%)	1 (100%)	0.27
	No	23 (82%)	5. (18%)	

Table 6: Clinical tumour presentation in prediction of absence of histological tumoral response.

		Complete or Partial response	No response	P
	N=24 (80%)		**N=6 (20%)**	
Invasion of higher third of the rectum	Yes	16 (80%)	4 (20%)	1
	No	8 (80%)	2 (20%)	
Percentage of circumferential tumoral invasion	0.25	2 (67%)	1 (33%)	0.439
	0.5	5 (100%)	0 (0%)	
	0.75	1 (50%)	1 (50%)	
	1	16 (80%)	4 (20%)	
Mesorectal invasion	Yes	19 (83%)	4 (17%)	0.391
	No	4 (67%)	2 (33%)	
Internal sphincter invasion	Yes	5 (83%)	1 (17%)	0.891
	No	19 (79%)	5 (21%)	

Tumoral loco regional inva-sion staging (T)	T2	2 (67%)	1 (33%)	0.731
	T3	15 (79%)	4 (21%)	
	T4	7 (87%)	1 (13%)	
Loco regional lymph nodes invasion (N)	Nx	1 (100%)	0 (0%)	0.16
	N0	4 (100%)	0 (0%)	
	N1	5 (56%)	4 (44%)	
	N2	14 (87%)	2 (13%)	
Distant metastatic invasion (M)	Mx	1 (50%)	1 (50%)	0.426
	M0	21 (84%)	4 (16%)	
	M1b	2 (67%)	1 (33%)	

Table 7: Initial radiological tumoral features that were not significantly associated with absence of tumoral response to neoadjuvant treatment.

Radiological assessment	P value in uni variate analysis	P value in multi variate analysis
Overall number of loco regional lymph nodes (including suspicious and non-suspicious ones)	0.0001	0.998
Measurement of the biggest suspicious loco regional lymph node	0.0001	0.386
Presence of suspicious iliac lymph nodes	0.0001	0.998

Table 8: Multivariate analysis of the radiological tumoral features showing a significant effect on the tumoral response to neo-adjuvant treatment in the univariate analysis.

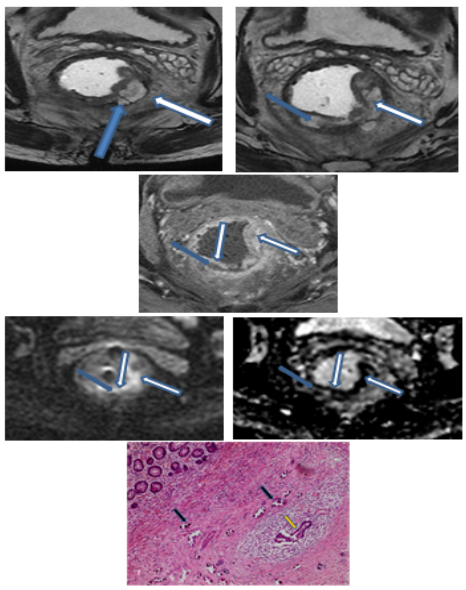

Figure 4: Patient presenting with a partially responsive low rectum cancer.

Advanced initial TNM stage, tumoral invasion of the mesorectum, high percentage of circumferential extension, longitudinal extension including sphincter and with the complex involvement were not significantly associated with non-responsive tumors.

Univariate analysis observed that having more than five loco regional lymph nodes (including suspicious and non suspicious ones), a more than 10 mm and with the suspicious loco regional lymph node and suspicious iliac lymph nodes on the initial MRI significantly increased (p=0.0001) the risk of absence of histological response by respectively 60%, 60% and 66%.

However the multivariate analysis proved interdependence between these three lymph node MRI features and did not come out with any independent significant predictive factor [13].

A : Initial MRI showing the tumor initially staged as T3N2 invading the mesorectum with a mucinous component.

B, C, D, E : Post neoadjuvant treatment showing on one hand a posterior internal necrosis (blue arrow) with respectively a high T2 signal, no enhancement, low diffusion signal and high ADC

values and on the other hand residual tumor (white arrow) with respectively a high T2 signal, enhancement, high diffusion signal and low ADC values.

F : the predominant histologic changes seen included fibrosis, inflammation and calcifications (black arrow) with a minimal residual neoplastic gland (yellow arrow) (x100).

While studying agreement between post chemo radiotherapy MRI and final histological assessment of response to neoadjuvant treatment, we found that important tumoral decline in preoperative MRI was not significantly associated with complete histological response (p=0.167). However, partial response and subtle response in post chemo radiotherapy MRI were significantly concordant to respectively partial histological response and absence of final histological response (p respectively 0.025 and 0.02).

With regards to MRI assessment detailed features after chemo radio- therapy, there was a significant agreement with final histological assessment only on invaded loco regional lymph nodes (p=0.025).

Discussion

Even if MRI has been introduced in practice in the systematic initial tests at the diagnosis of an adenocarcinoma of the lower two thirds of the rectum in our institutions since 2005, to our knowledge, our study is the first one in Tunisia highlighting the ability of imaging features in the initial MRI, done at the diagnosis of this disease, in predicting histological final response to neo-adjuvant chemo radiotherapy.

It is true that a previous thesis was carried in Tunis trying to highlight predictive factors of complete histological response of rectal adenocarcinoma to neo-adjuvant treatment. However this study dating from 2011 focused mainly on biological and clinical factors than precise imaging findings and it included all neo-adjuvant treatment regimens even those without concomitant chemotherapy.

Our results seemed to be quite acceptable and valid regarding that response to chemo radiotherapy was only studied on histological exam of the resected specimen. As a matter of fact, we did not include assessment of response based on post chemo radiotherapy MRI or assessment on post neo-adjuvant treatment biopsy for more accuracy. This has been reproduced in all past reports and studies about this subject. We excluded rectal tumors occurring on inflammatory chronic bowel disease and those synchronous to colic or other organ primary cancer in order to avoid susceptibility bias. As the presence of these two factors might change the effects of the studied factors on the response to a systemic or a loco regional treatment. We chose not to include only information reported by the previous radiologists and reread all MRI in order not to under estimate results regarding the missed features or overestimate results regarding the reported ones.

Our results as the latter can be definitely used for only patients receiving Capecitabine, the most used molecule in our practice. In support of this idea, in their very recent study dating from 2019, created separate monograms depending on the chemotherapy regimen when studying predicting factors of pathological response to neoadjuvant treatment.

In summary, despite its high precision, we propose to generalize the results regarding initial MRI imaging features for predict histological response (responsive and mainly non responsive tumors) to chemo radiotherapy based on a classic 45 Gy radiotherapy and capecitabine for an adenocarcinoma of the lower two thirds of the rectum not developed on inflammatory chronic bowel disease nor developed with synchronous colic or other organ primary cancer.

With regards to predictive factors of response, found that gender, age, American Society of Anesthesiologists score and Body Mass Index were not significant factors for predicting tumoral response. Our study comes to support the latter study by finding that gender and age did not show any statistically significant effect on histological response to neoadjuvant treatment [14,15].

CEA initial levels were available in only 43% of our patients making it difficult to study its effect on predicting response. As for radiological predictive factors, we chose the mediane lymph node number of all patients as a cut off in our study. As for the size, we chose a 10 mm threshold larger than the reported one for suspicious lymph nodes (9 mm) in order not to confuse thresholds for tumoral invasion and tumoral response prediction. Multivariate study showed an interdependence between these nodal factors. Conventional MRI features appeared to have different contradictory effects on pathological response to neo adjuvant treatment in literature. This might be due to the different neoadjuvant treatment regimen and the sampling differences.

Diffusion and perfusion were not sufficiently used in our report for availability and time consumption reasons. So their features were not studied. The role of perfusion in predicting tumor response found a higher pretreatment K trans was predictive of responsive tumors while others found the contrary (Table 9).

Complete response	Good down staging	No response
Lower CEA	Lower CEA	
CEA<2.5 microgr/L	- -	-
CEA<=5 microgr/L	<=5 microgr/L	-
-	- High CEA	
CEA<=5 microgr/L	-	-

Table 9: CEA in predicting histological response in recent reports.

With regards to diffusion, ADC values on the initial pretreatment MRI were higher in some reports for patients who completely responded to neoadjuvant treatment than for those who did not. An ADC threshold was not found. However, these findings are still controversial and high ADC also were found in non-responsive tumors explained by resistance of necrotic tissue to radiotherapy.

While studying concordance between post neoadjuvant treatment MRI and final pathological as assessment, our report agreed with literature showing a non-significant agreement to pathological exam with regards to mesorectal invasion and T stage.

However, it was reported that distance to anal verge, tumoral circumference and size on post chemo radiotherapy MRI predicted complete response.

With regards to lymph nodal invasion, MRI is less accurate. There is usually a sterilization of most of the lymph nodes. Nodal short axis size is more reliable than its morphology. Our report showed a significant agreement of post chemo radiotherapy MRI to pathological exam for lymph node invasion with a sensibility of 70% and a specificity of 78%. This joins the results of a meta-analysis who have found MRI to be 77% sensitive and 71% specific for lymph node involvement. Infact conventional MRI sequences have difficulties to distinguish post radiotherapy fibrosis from tumoral residue as both can present with the signal characteristics and MRI are limited in the detection of small tumour remnants within fibrotic tissue after neo adjuvant chemoradio therapy of rectal cancer. Diffusion weighted images come to present additional information to highlight tumoral lesion presenting a diffusion restriction. Functional MRI including perfusion could provide a more comprehensive picture of tumour heterogeneity and its changes as a response to treatment [16].

Conclusion

Recent reports have tried to determine predictive factors of good down staging and bad down staging as well as complete response after neo adjuvant treatment. This could select predicted responsive patients for a less aggressive surgery and select predicted non responsive patients for a primary radical surgery leading to a personalized treatment roadmap and improving the patient out come.

We led a retrospective study between 2007 and 2017 of 30 patients with locally advanced adenocarcinoma of the two lower thirds of the rectum, who had been imaged by MRI at the time of diagnosis, had a neoadjuvant 45 to 50 Gyradio therapy with a concomitant chemotherapy based on Capecitabine and had a radical surgery. Our study aimed to analyze the ability of MRI to predict response of these tumors to neoadjuvant treatment.

Eighteen patients (60%) had MRI between 9 and 12 weeks after the neoadjuvant treatment to assess tumoral response before surgery. Tumor response to neoadjuvant treatment was considered as subtle in 3 patients (17%), almost complete in 3 patients (17%) and partial in 12 patients (66%) with necrosis in 9 patients (50%) and fibrotic changes in 7 patients (40%).

Assessment of final histological response done only on the radical surgery specimen showed non responsive tumors in 6 patients (20%) and responsive tumors in 24 patients (80%) including 2 patients (7%) with a complete response. One of the patients with complete response had an abdominoperineal resection.

We analyzed all clinical, biological and initial MRI features to highlight predictive factors of responsive and non responsive locally advanced rectal cancer to neo adjuvant chemo radiotherapy. We could not study predictive factors of complete response apart because of the small sample size.

Advanced initial TNM stage, tumoral invasion of the mesorectum, high percentage of circumferential extension, longitudinal extensions including sphincter complex involvement were not significantly associated with non responsive tumors. Our report did not consider only overall N stage like it was done in the previous reported studies; it also analyzed all details of this nodal invasion: uni-variate analysis observed that having more than five loco regional lymph nodes (including suspi- cious and non-suspicious ones), a more than 10mm suspicious loco regional lymph node and suspicious iliac lymph nodes on the initial MRI significantly increased (p=0.0001) the risk of absence of histological response by respectively 60%, 60% and 66%. However the multivariate analysis proved interdependence between these three lymph node MRI features and did not come out with any independent significant predictive factor.

While studying agreement between post chemo radiotherapy MRI and final histological assessment of response to neoadjuvant treatment, we found that important tumoral decline in preoperative MRI was not significantly associated with complete histological response (p=0.167).

However, partial response and subtle response in post chemo radiotherapy MRI were significantly concordant to respectively partial histological response and absence of final histological response (p respectively 0.025 and 0.02). With regards to MRI assessment detailed features after chemo radiotherapy there was a significant agreement with final histological assessment only on invaded loco regional lymph nodes (p=0.025).

Functional MRI including mainly diffusion-weighted sequence was not studied commonly in our study for availability reasons despites its reported effectiveness in predicting and assessing response to neoadjuvant treatment in some reports.

Both conventional and functional MRI features are still controversial in literature with regards to their role in predicting and assessing response of locally advanced rectal cancer to neoadjuvant treatment.

However, combining their findings seems to have promising results in the most recent reports helping the surgeon build a prediction model or nomogram at the initial diagnosis and replan the treatment after the neo-adjuvant chemo radiotherapy.

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