



Magnetic Resonance Imaging Value to Predict Pathologic Staging in Locally Advanced Rectal Cancer After Neoadjuvant Chemoradiation

Lokal İleri Rektum Tümöründe Neoadjuvan Kemoradyasyon Sonrası Patolojik Evrelemeyi Tahmin Etmek İçin Manyetik Rezonans Görüntülemenin Değeri

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ABSTRACT

Aim: This study was designed to evaluate the role of magnetic resonance imaging (MRI) on preoperative restaging of locally advanced rectal cancer after neoadjuvant chemoradiotherapy (CRT), in order to facilitate individualization of surgical management.

Method: We analyzed 117 patients who had received neoadjuvant CRT, underwent a MRI before and after CRT. All patients underwent restaging MRI followed by surgery after the end of CRT. The primary end point of this study was to estimate the accuracy of post-CRT MRI as compared with pathologic staging.

Results: Pathologic T classification matched the post-CRT MRI findings in 44 (37.6%) of 117 patients. Sensitivity in T0, T1, T2, T3 and T4 was 23.8%, 16.7%, 25.6%, 48.9% and 83.3% respectively. Specificity in T0, T1, T2, T3 and T4 were 87.5%, 93.7%, 79.5%, and 64% and 88.3% respectively. Sensitivity in N0 and N1 were 82% and 20% respectively. Specificity was 88% in N0 and 87% in N1. Fifty two (44.4%) of 117 patients were downstaged in T classification. Pathologic N classification matched the post-CRT MRI findings in 73 (62.4%) of 117 patients. Twenty one (17.9%) were overstaged in N classification. Twenty seven (23%) of 117 patients who had been down staged on MRI after CRT were confirmed on the pathological staging with same stage (T and N). 17p with ypT0 were correlated with MRI after CRT in 5 patients (4.3%).

Conclusion: MRI has low accuracy for restaging locally advanced rectal cancer after preoperative CRT so it is currently not consistent enough for clinical application.

Keywords: MRI, neoadjuvant chemoradiotherapy, prediction

ÖZ

Amaç: Bu çalışma, neoadjuvan kemoradyoterapi (CRT) sonrası lokal ileri rektum kanserinin preoperatif olarak yeniden düzenlenmesinde, cerrahi tedavinin bireyselleştirilmesini kolaylaştırmak için manyetik rezonans görüntülemenin (MRG) rolünü değerlendirmek için tasarlanmıştır.

Yöntem: MRG öncesi ve sonrasında neoadjuvan CRT alan 117 hastayı inceledik. Tüm hastalara yeniden evreleme için MRG ve takiben CRT bittikten sonra operasyon yapıldı. Bu çalışmanın birincil bitiş noktası, CRT sonrası MRG evrelemesinin patolojik evrelemeye göre doğruluğunu tahmin etmektir.

Bulgular: Patolojik T sınıflaması, CRT sonrası MRG bulgularını 117 hastanın 44'ünde (%37,6) eşleştirdi. T0, T1, T2, T3 ve T4'te sensitivite sırasıyla %23,8, %16,7, %25,6, %48,9 ve %83,3 idi. T0, T1, T2, T3 ve T4'te spesifite sırasıyla %87,5, %93,7, %79,5 ve %64 ve %88,3 idi. N0 ve N1'de sensitivite sırasıyla %82 ve %20 idi. Spesifite N0'da %88 ve N1'de %87 idi. Yüz onyediyen hastadan 52 tanesi (%44,4) T sınıflamasına alındı. Patolojik N sınıflaması, 117 hastanın 73'ünde (%62,4) CRT sonrası MRG bulgularına uyuyordu. Yirmi bir hasta (%17,9) N sınıflamasına alındı. CRT sonrası MRG'de evrelenen 117 hastanın 27'sinde (%23) patolojik evrelemede aynı aşamada bulunduğu doğrulandı (T ve N). T0 ile 17 hasta, 5 hastada (%4,3) CRT sonrası MRG ile korele idi.

Sonuç: MRG preoperatif CRT sonrası lokal ileri rektum kanserinin yeniden evrelemesinde düşük bir hassasiyete sahiptir, bu nedenle klinik uygulama için yeterince tutarlı bir tetkik değildir.

Anahtar Kelimeler: MRG, neoadjuvan kemoradyoterapi, tahmin edilebilirlik



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Introduction

Colorectal cancer is the third most common malignancy worldwide. GLOBOCAN data base estimated over 37.229 new cases in 2020 and 16.838 rectal cancer associated deaths in Spain.¹ Neoadjuvant chemoradiotherapy (CRT) has become the standard of care for patients with locally advanced rectal cancer (LARC). The primary objective of CRT improves local control and resectability. It has been demonstrated that the final pathologic features at resection time remain the most important prognostic factors in the rectal cancer treatment. Other possibilities are the 'wait and see strategy' after CRT treatment in pathologic complete response (pCR) patients with high surgical risk or surgery refuse.

High-resolution pelvic magnetic resonance imaging (MRI) has assumed an important role in staging and in treatment decisions of rectal cancer. This is very important in the diagnostic accuracy of preoperative MRI in predicting circumferential resection margin (CRM) of rectal cancer.² The reported overall accuracy of MRI in predicting the pathologic stage of no irradiated rectal cancer is 71-91% (mean, 85%) for T classification, 43-85% (mean, 75%) for N classification, and 92-95% for CRM involvement.³ Due to the therapeutic effect of preoperative CRT, 30-50% of the patients who had received preoperative CRT experienced down staging of the rectal tumor.⁴ MRI is repeatedly performed for restaging and reassessment of CRM after preoperative CRT in LARC. The interpretation of post-CRT MRI in rectal cancer is not easy due to the post-radiation effect, the role of MRI in restaging rectal tumors after neoadjuvant CRT is not clear.³ The efficacy of restaging MRI for predicting the pathologic stage in rectal cancer is controversial.^{5,6}

Our purpose was evaluating MRI in post-neoadjuvant CRT treatment to predict pathologic stage for rectal cancer patients.

Materials And Methods

Patient Eligibility

Retrospectively we analyzed 117 patients with primary rectal cancer who had received preoperative CRT with 50,4 Gy in 28 fractions and concomitant fluoropyrimidine (capecitabine, 825 mg/m² twice daily or 5FU continuous infusion). All patients underwent total mesorectal excision, which was scheduled to take place 6-8 weeks after the CRT. The Ramón y Cajal University Hospital Institutional Review Board approved this study (protocol 228-16).

The eligibility criteria were: (i) histologically confirmed adenocarcinoma; (ii) lower, middle and higher tumor; (iii) IIA-IIIC stage determined by MRI and/or

endorectal ultrasonography; (iv) no evidence of distant metastasis; and (v) complete radiotherapy treatment. The schedule of treatment included chemoradiotherapy with fluoropyrimidine concomitant with 50,4 Gy in 28 fractions. The patients with recurrent tumors, short course radiotherapy, and other chemotherapy schedule or radiotherapy incomplete treatment were excluded.

Evaluation

Clinical staging work-up included digital rectal examination, complete blood count, liver and renal function test, level of carcinoembryonic antigen and colonoscopy, chest and abdomen computed tomography (CT) and pelvic MRI before preoperative CRT.

The clinical target volume included the gross tumor volume and the presacral area, mesorectal area and internal iliac lymphnodes. Invaginaoranus involvement of external iliac and inguinal lymph nodes were included. The planning target volume was symmetrically generated with 2 cm around the macroscopic tumor.

Three-dimensionally planned conformal radiotherapy (3D-CRT) was planned for each patient. The radiation fields included one posterior field, and two lateral fields.

Small bowel, bladder, and both femur heads were organs at risk. The constrains was in small bowel: V45<195 cc and V45<25%; bladder V50<60% and femur heads: V50<5%.

Pre-CRT MRI was performed for local tumor and nodal staging. The conventional rectal MRI protocol was done. Initially, precontrast T2-weighted sagittal, coronal, and axial images perpendicular to the long axis of the rectum were obtained. Each patient received an intravenous bolus injection of gadopentetate dimeglumine. Finally, postcontrast T1-weighted axial and sagittal images were obtained after 60s.

The depth of tumor infiltration on MRI was evaluated and staged as follows: 1) mrT1, tumor confined to the mucosa and submucosa; 2) mrT2, tumor invading the muscularis propia but confined to the rectal wall; 3) mrT3, tumor penetrating into the perirectal tissues without involvement of the surrounding organs; and 4) mrT4, tumor penetrating into surrounding organs. The short-axis diameter of lymph node of >5 mm observed on MRI was considered to be clinically positive.

In our analysis, using the same protocol for pre-CRT MRI performed post-CRT MRI before curative surgery 6 weeks after radiotherapy treatment. Images of post-CRT MRI were compared to those of pre-CRT MRI by a radiologist who had specialized in gastrointestinal radiology. Circumferential radial margin (CRM) on MRI was defined as an involvement when the tumor was 61 mm of the margin and radiologic regression grade.

Surgery and Pathology Review

All patients underwent surgery, which was scheduled 8 to 12 weeks after the completion of radiotherapy. After curative surgery, post-CRT tumor stage was determined according to the TNM classification system recommended by the 7th edition of the American Joint Committee on Cancer criteria. Experienced colorectal pathologists, using the standardized method, evaluated pathologic specimens. Histologic grade, presence of lymph node metastasis, response to CRT, and circumferential and distal rectal margin were all evaluated. Downstaging rate was evaluated by comparing clinical and post-CRT pathological stages, and was defined as yp Stage 0-I (ypT0-2N0M0). Pathologically complete response (ypT0N0) was defined as the complete absence of viable tumor, and only fibrotic mass in the pathologic specimen. The pathologist used Ryan score to grade response to chemoradiotherapy.⁷

Statistical Analysis

The primary endpoint of the present study was to estimate the accuracy of MRI post-CRT as a predictor of pathologic stage. The secondary end-point was to assess the agreement between post-CRT MRI and pathologic staging in clinically down staged patients.

The grade of agreement of post-CRT MRI and pathologic staging was calculated with Cohen kappa concordance index. Concordance was considered poor for values between 0 and 0.20, fair for values between 0.21 and 0.40, moderate for values between 0.41 and 0.60, substantial or good for values between 0.61 and 0.80, and almost perfect or excellent for values more than 0.81. This study was designed to determine whether restaging MRI after CRT could predict the pathologic stage.

Results

One hundred seventeen patients with primary rectal cancer who had received chemoradiotherapy in Ramón y Cajal Hospital were evaluated.

We included patients who underwent restaging MRI at a median 5.9 (range, 2-12) weeks after the end of radiotherapy before surgery. One hundred eleven patients (95%) were restaged with MRI between 5-9 weeks, only 6 patients (5%) were restaged between 2-4 weeks (3p) or 10-12 weeks (3p). We did not find statistical differences between groups (p=0.91). They also received curative surgery at a median 83.5 days (range, 45-230) after the end of radiotherapy. The median age of the patients was 67.9 years (range, 41-85 years). There were 74 men and 43 women. Pre-CRT MRI showed that 10 (8.55%) patients had cT2 lesions, 87 (74.3%) patients had cT3 lesions and 20 (17.15%) patients had cT4 lesions. At the time of diagnosis, 43 (36.75%) of the 117 patients had clinically node-positive disease. Ten patients could not receive complete prescribed doses of chemotherapy because of gastrointestinal toxicity (8p), dermal toxicity (1p) and hematological toxicity (1p). These patients received total doses of radiotherapy. We analyzed correlation between T and N stages in MRI and pathologic specimen and no significant difference (p=0.26) was found.

Accuracy of Restaging MRI After Preoperative CRT

Of the 117 patients, 52 (44.4%) achieved downstaging of T classification and 21 (17.9%) had down staging of N classification. Table 1 shows the comparison between post-CRT MRI and postoperative pathologic T and N classifications. The findings in 44 (37.6%) of 117 patients agreed in post-CRT MRI and pathologic T classification, and the concordance degree was low (k=0.1).

Table 1. Summarizes the sensitivity, specificity, positive predictive value, and negative predictive value of restaging MRI according to the ycT and ycN classifications

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ycT0	5/21 (23.8%)	84/96 (87.5%)	5/17 (29.4%)	84/100 (84%)
ycT1	1/6 (16.67%)	104/111 (93.7%)	1/8 (12.5%)	104/109 (95.4%)
ycT2	10/39 (25.64%)	62/78 (79.5%)	10/26 (38.46%)	62/91 (68.1%)
ycT3	22/45 (48.89%)	46/72 (63.9%)	22/48 (45.8%)	46/69 (66.7%)
ycT4	5/6 (83.34%)	98/111 (88.3%)	5/18 (27.78%)	98/99 (99%)
ycN0	68/83 (81.9%)	15/34 (44.11%)	68/87 (78.16%)	15/30 (50%)
ycN1	5/25 (20%)	81/92 (88%)	5/16 (31.25%)	81/101 (80.2%)
ycN2	0/9 (0%)	94/108 (87%)	0/14 (0%)	94/103 (91.3%)

MRI: Magnetic resonance imaging, PPV: Positive predictive value, NPV: Negative predictive value

Compared with the pathologic T classification, 21 (18%) of 117 patients were over staged and 52 (44.4%) of 117 patients were under staged in post-CRT MRI. Findings from post-CRT MRI and pathologic N classification agreed in 73 (62.4%) of 117 cases, and the concordance degree was moderate ($k=0.3$). Compared with pathological N classification, 21 (16.9%) and 23 (19.65%) of 117 patients were over staged and under staged in post-CRT MRI, respectively. Over staging of T and N classifications was more common than under staging. Of the 117 patients, 27 patients (23%) achieved correlation between MRI and pathologic classification, 60 patients (51.3%) was over staged with MRI and 30 patients (25.7%) were under staged with MRI.

Prediction of Pathologic Downstaging Using MRI After CRT

Time to MRI and surgical resection was in 2 to 6 weeks in 92p (78.6%), only in 25p was between 7-42 weeks (11p in seven week). We analyzed correlation between T and N stage in MRI and pathologic specimen and time between MRI and surgery and no significant difference ($p=0.89$) was found.

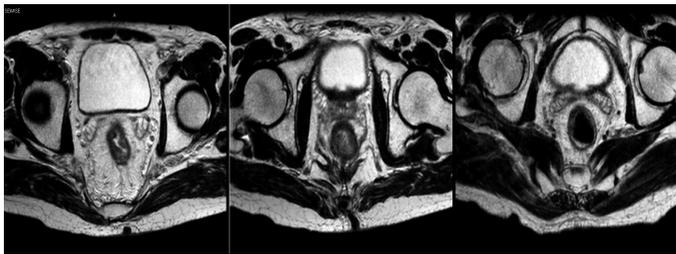


Figure 1. The images shows patient with rmT2N0 and after 2 weeks ypT0N0 in pathologic specimen

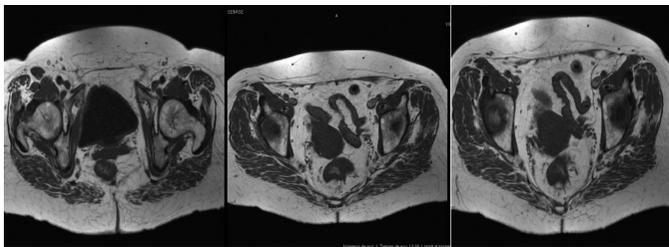


Figure 2. The images shows patient with rmT4N0 and after 2 weeks ypT4N0 in pathologic specimen

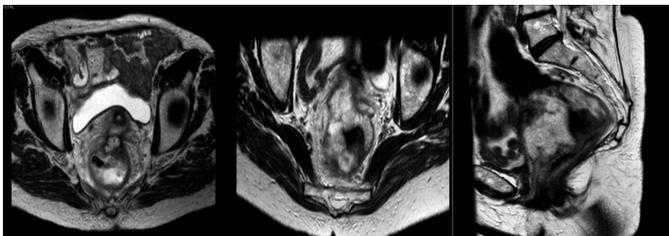


Figure 3. The images shows patient with rmT0N0 and after 2 weeks ypT3N1 in pathologic specimen

Of the 117 patients, 74 (63.24%) achieved down staging of a rectal tumor and 17 (14.5%) had a pathologically complete response (ypT0N0). Of 47 patients who achieved downstaging on MRI after CRT, 27 (23%) actually were down staged on the pathologic specimen. Twenty seven (23%) of 117 patients displayed the same findings in post CRT MRI and pathologic staging, and the concordance degree was low. Twenty (17.1%) of 117 patients were under staged on post-CRT MRI as compared with pathologic staging. In Figures 1, 2 and 3 we showed MRI imaging examples.

Sensitivity in T0, T1, T2, T3 and T4 was 23.8%, 16.7%, 25.6%, 48.9% and 83.3% respectively. Specificity in T0, T1, T2, T3 and T4 were 87.5%, 93.7%, 79.5%, and 64% and 88.3% respectively. Sensitivity in N0 and N1 were 82% and 20% respectively. Specificity was 88% in N0 and 87% in N1.

Discussion

Neoadjuvant CRT improves resectability of LARC.^{5,6} The macroscopic evaluation of disease becomes difficult to differentiate fibrosis or tumor. These items combined with the limited ability of preoperative imaging to stage both the T and N categories, render conventional tumor-node and metastasis (TNM) staging of limited value as a method to evaluate a tumor response. Pateletal⁸ assessed the importance of MRI detected tumor response to neoadjuvant CRT on survival outcomes in LARC. Patients deemed to have a poor response (mriT3b-T4), had a 5 year overall survival of 27% versus 72% for good responders. Preoperative residual tumor evaluation is important for performing minimally invasive surgery such as sphincter preservation; an accurate non-invasive diagnostic image-based approach has been sought.

Guidelines recommend that patients with LARC and neoadjuvant treatment should undergo surgery in 6-8 weeks (ESMO)⁹ or 5-12 weeks (NCCN)¹⁰ after completion of long-course chemoradiotherapy or within 7-10 days of completion of short-course radiotherapy. However, the better interval between chemoradiotherapy and surgery has long been a subject of investigation. In our study timing after chemoradiotherapy to surgery was 8-12 weeks.

Timing to MRI after chemoradiotherapy is uncertain. A prospective clinical trial is currently ongoing that investigates the feasibility of adopting a nonoperative management strategy for patients with LARC who are selected based on the degree of mrTRG between 8 and 12 weeks after completion of neoadjuvant chemoradiotherapy.¹¹ In our study median evaluation with MRI was in 5.9 weeks. This timing may affect the results of this study.

MRI accuracy is poor after rectal CRT. Because it is difficult to differentiate tumor cells in fibrosis tissue.^{12,13,14,15} Post

CRT MRI is a poor predictor of final histology and should not be relied upon to guide the extent of surgical resection. Larsen et al.¹⁵ felt that to achieve R0 resection, optimal surgery should be based on pre-treatment MRI. The study has initiated a new approach to pathological classification of the removed specimen where they introduce a MRI assisted technique for investigating the areas at risk outside the mesorectal fascia in the specimen.¹⁵ Kang et al.¹⁶ concluded that the tumor volume reduction ratio was not significantly associated with T and N downstaging. Our study demonstrates that MRI is unable to detect the majority of patients who have a complete pathological response. Similar to our study, other studies demonstrate that there are low agreement on the use of MRI after long-course radiotherapy.¹⁷ Martellucci et al.¹⁸ suggested against restaging with MRI and recommended transrectal ultrasound (TRUS). They found that regarding the depth of invasion after treatment, TRUS agreed with pathology in 67.5%, CT agreed 59.5 %, and MRI in 60%. They therefore suggest limiting the use of MRI for restaging to selected cases similar to our study. A systematic search was performed by Saklani et al.¹⁹ evaluated the role of MRI in rectal cancer surgery with 72 articles analyzed. They concluded that MRI post chemoradiotherapy for rectal cancer remains controversial, but it is necessary to planning radical surgery improves R0 resection rates and decreases local recurrences. Lee et al.²⁰ analyzed 150 patients, restaging MRI has low accuracy for the prediction of the pathologic T and N classifications in rectal cancer patients similar to our study. Maretto et al.²¹ analyzed 46 patients classified with proctoscopy, TRUS, and CT scan and MRI. Findings were compared with the pathologic TNM stage. They concluded that all rectal cancer staging modalities after CRT allows good prediction of node-negative cases, although none of them is able to predict the pCR on the rectal wall.

However, using high-resolution MRI, standardizing image acquisition techniques and interpretation of images, comparative evaluation of pre and post CRT MRI images, adding diffusion-weighted imaging (DWI) to the standard approach, and importantly, experience and awareness of the limitations can improve diagnostic accuracy of MRI for re-staging. Functional MRI techniques allow for the quantification of tumor biological processes, such as microcirculation, vascular permeability, and tissue cellularity. This new technology has begun to show potential advantages over standard morphologic imaging in the restaging of rectal cancer, allowing for more accurate prognostication of response and potentially introducing an earlier treatment alteration and more accurate non-invasive surveillance, which could improve patient outcomes.²² Our study included DWI but there was not increased concordance between pathologic and post treatment MRI

staging lymph nodes (LN) evaluation is not clear. Ryu et al.²³ evaluated the added value of DWI in the evaluation of LN eradication after CRT in patients with LARC. Pathological reports served as the reference standards for LN eradication. They concluded that adding DWI to T2W imaging provided no additional diagnostic benefit for the evaluation of LN eradication following CRT in patients with LARC.²³ Results of a meta-analysis showed that none of the three commonly used imaging modalities used in rectal cancer can provide reliable evaluation on regional LN metastasis. Perhaps we should conduct further research on specific contrast agents or functional imaging to try and improve the accuracy. The data available, however, indicate that MRI is more accurate than endoscopic ultrasound particularly for evaluating LN metastasis after neoadjuvant therapy. MRI at a high field-strength improves the diagnostic accuracy for LN evaluation.²⁴ In our serie MRI in LN had more concordance than tumor invasion probably because of using all sequences of MRI including DWI.

Recent studies have reported that changes in 18F-FDG uptake before and after CRT could differentiate responders from non-responders and predict the patient's outcome.^{25,26} However, 18F-FDG uptakes have been reported to be nonspecific for malignant tumors, particularly in post-CRT rectal cancers, because of radiation-induced inflammation and physiological bowel uptake,^{27,28,29} for this problem in our center don't use routinely PET (positron emission tomography)/CT to restaging patients with rectal tumor after chemoradiotherapy. Choi et al.³⁰ analyzed PET/CT exhibited better accuracy in diagnosing tumor response. Fischer et al.³¹ in a prospective study showed an excellent diagnostic accuracy for prediction of pathological response. Leccisotti et al.³² showed the ability of early metabolic response assessment using PET/CT to predict non-cPR in patients with LARC. But in a systematic review, a total of 14 publications on DWI and 25 on PET/CT demonstrate that both imaging modalities have a low positive predictive value in the prediction of pCR. A study with 17 patients confirmed the predictive power of tumor segmentation based on PET/CT imaging for response evaluation in patients with rectal cancer after neoadjuvant CRT therapy.³³ The major strength of DWI and PET/CT lies in the identification of non-responders who are not candidates for organ preservation. Up to now, DWI and PET/CT are not accurate enough to safely select patients for organ-sparing strategies. Although few data are available, early changes in FDG-uptake seem promising in the prediction of pCR and the role of PET/CT during CRT should be further investigated. Future research must focus on the integration of functional imaging with clinical data and molecular biomarkers.³⁴ Future advances

in the radiological imaging and biological detection might help in accurately correlating the presence of pCR but, nowadays, no optimal selection criteria for pCR are available. Furthermore, as recently highlighted in a systematic review, the rationale of a *wait and see* policy after complete response relies mainly on retrospective observations from only one centre in Brazil.³⁵ Maggiori et al.³⁶ showed that the overall morbidity rate was similar between pCR and non-pCR groups of patients. However, both the severe morbidity and infection related morbidity rates were less in pCR group. The results proposed that the greater postoperative complication rates for patients with major pathologic response group significantly contribute to a poor prognosis and may cut the oncological benefits of the neoadjuvant CRT. Other studies described no difference in the frequency of overall operative complications between pCR and non-pCR groups.

It is not easy to predict pathologic stage solely with simple MRI. There are some reports that PET/CT and functional MRI or imaging biomarkers may be helpful in the prediction and assessment of tumor response to CRT. Awareness of tumor volume and metabolic change helps physicians to achieve appropriate restaging of irradiated rectal cancer with MRI and can lead to a reduction in under staging or over staging.

Study Limitations

Limitations of study included the inclusion of 10 patients with reduce doses of chemotherapy; this item could be a confusion factor. Difference between timing to MRI after chemoradiotherapy treatment could be confusion factor and could be pretty long for evaluation and explain or results. We need more prospective studies to evaluate utility of MRI in re-evaluation after neoadjuvant treatment of LARC.

Conclusion

In conclusion, for rectal cancer patients who have received preoperative CRT, restaging MRI has low accuracy in the prediction of the pathologic T and moderate in the prediction of pathologic N classifications mainly due to under staging. For patients who achieved clinical downstaging on MRI after CRT, the diagnostic accuracy was relatively low in our analysis. In this topic, future well-designed prospective trials will be needed to verify our results with better MRI techniques or imaging biomarkers.

Ethics

Ethics Committee Approval: The Ramón y Cajal University Hospital Institutional Review Board approved this study (protocol 228-16).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Concept: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Design: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Data Collection or Processing: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Analysis or Interpretation: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Literature Search: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S., Writing: C.d.l.P., M.M., C.S., A.H., E.F.I., F.L., S.S.

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