review

Magnetic resonance imaging evaluation in neoadjuvant therapy of locally advanced rectal cancer: a systematic review

Roberta Fusco[1], Mario Petrillo[1], Vincenza Granata[1], Salvatore Filice[1], Mario Sansone[2], Orlando Catalano[1], Antonella Petrillo[1]

[1] Radiology Unit, Dipartimento di Supporto ai Percorsi Oncologici Area Diagnostica, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Via Mariano Semmola, Naples, Italy

[2] Department of Electrical Engineering and Information Technologies, Università degli Studi di Napoli Federico II, Via Claudio, Naples, Italy

Radiol Oncol 2017; 51(3): 252-262.

Received 29 December 2016
Accepted 21 June 2017

Correspondence to: Dr. Roberta Fusco, Radiology Unit, Dipartimento di Supporto ai Percorsi Oncologici Area Diagnostica, Istituto Nazionale Tumori - IRCCS - Fondazione G. Pascale, Via Mariano Semmola, Naples, Italy. Phone: +39 8159 0322; Fax: +39 8159 03825; E-mail: r.fusco@istitutotumori.na.it

Disclosure: No potential conflicts of interest were disclosed.

Background. The aim of the study was to present an update concerning several imaging modalities in diagnosis, staging and pre-surgery treatment response assessment in locally advanced rectal cancer (LARC). Modalities include: traditional morphological magnetic resonance imaging (MRI), functional MRI such as dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted imaging (DWI). A systematic review about the diagnostic accuracy in neoadjuvant therapy response assessment of MRI, DCE-MRI, DWI and Positron Emission Tomography/Computed Tomography (PET/CT) has been also reported.

Methods. Several electronic databases were searched including PubMed, Scopus, Web of Science, and Google Scholar. All the studies included in this review reported findings about therapy response assessment in LARC by means of MRI, DCE-MRI, DWI and PET/CT with details about diagnostic accuracy, true and false negatives, true and false positives. Forest plot and receiver operating characteristic (ROC) curves analysis were performed. Risk of bias and the applicability at study level were calculated.

Results. Twenty-five papers were identified. ROC curves analysis demonstrated that multimodal imaging integrating morphological and functional MRI features had the best accuracy both in term of sensitivity and specificity to evaluate preoperative therapy response in LARC. DCE-MRI following to PET/CT showed high diagnostic accuracy and their results are also more reliable than conventional MRI and DWI alone.

Conclusions. Morphological MRI is the modality of choice for rectal cancer staging permitting a correct assessment of the disease extent, of the lymph node involvement, of the mesorectal fascia and of the sphincter complex for surgical planning. Multimodal imaging and functional DCE-MRI may also help in the assessment of treatment response allowing to guide the surgeon *versus* conservative strategies and/or tailored approach such as "wait and see" policy.

Key words: magnetic resonance imaging; neoadjuvant therapy; evaluation; locally advanced rectal cancer

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Introduction

In the USA 39,220 new cases of rectal cancer occurred in 2016.[1] Despite the introduction of the screening programs, several patients are diagnosed in a locally advanced stage. Mortality has decreased thanks to prevention and early diagnosis and to effective management of the disease[2-12], such as the standardization of operative procedures and the introduction of adjuvant and neoadjuvant therapy[13-23], which determines a reduction of recurrence risk and a decrease of tumour size.

doi:10.1515/raon-2017-0032

Preoperative chemo-radiotherapy (pCRT) combined with following total mesorectal excision is the standard procedure of care for locally advanced rectal cancer (LARC).[13-24] However, there is an increase of conservative treatment strategies application for patients with substantial tumour regression after pCRT and "wait and see" policy for patients with complete pathological response. The advantage of this strategy is the reduction of morbidity and the possibility to provide a "true" organ-sparing approach. In this scenario, it is necessary to individualize the selection criteria for these strategies that accurately can assess neoadjuvant treatment response. Functional approaches have been exploited by several authors because of their capability to assess the residual tissue "vitality".[25-35] FDG positron emission tomography coupled with computed tomography (PET/CT) is widely used and it is considered the best technique for early response monitoring after pCRT in LARC.[13-14] However, other functional approaches including dynamic contrast enhanced-MRI (DCE-MRI) and diffusion weighted imaging (DWI) have been adopted to discriminate responder by non-responder patients and complete *vs*. non complete pathological response after pCRT.[13-14]

The objective of this manuscript is to present an update about the imaging modalities used in LARC staging with a specific focus on morphological MRI. Furthermore, a systematic review about the performance of imaging in the tumour response assessment after neoadjuvant therapy has been performed. We report diagnostic accuracy findings in terms of false and true positives, false and true negatives number for morphological MRI, DCE-MRI, DWI and PET/CT.

Overview about staging and restaging in LARC

The role of imaging is to provide a loco-regional staging as accurate as possible with the aim to assess the degree of tumour infiltration and extension. Moreover, the features detected by radiological imaging allow to evaluate pCRT response for guiding surgeon towards patient tailored strategies.[36-74]

In LARC, CT scan roughly show tumour size and its possible infiltration to internal organs: in fact, it can provide excellent contrast between tissues with large difference in X-ray absorption (bone *vs.* soft tissues); however, it can poorly discriminate between tissues with similar absorption such as different soft tissues, including tumours.[47]

PET/CT provides functional tissue information concerning metabolic activity fused with the morphological details of CT. The integration of tissue metabolic activity with anatomic information can improve its accuracy more that PET or CT when considered alone.[48-49]

Morphological MRI (T2 weighted images) has shown superior potential because it can provide an accurate evaluation not only of the tumour extent, but also of the adjacent soft tissues. Morphological MRI allows for comprehensive evaluation of disease stage including tumour infiltration degree, a precise assessment of the neoplasia distance by mesorectal fascia (circumferential margin) and an effective assessment of lymph nodes involvement and mesorectal infiltration.[26]

Traditionally, tumour response assessments have been achieved measuring the percentage reduction of the tumour size according to the response evaluation criteria in solid tumours (RECIST), as the change in tumour size is generally thought to be correlated with treatment efficacy.[17,50-53] However, this assessment approach is insensitive to early treatment changes, and it makes difficult to distinguish between active tumour and post-treatment fibrosis.

In fact, morphological MRI has been considered not to be conclusive in pCRT tumour response assessment since pathological down-staging is not always accompanied with tumour size effective reduction.[17,23-26,50-53] However, the high temporal resolution obtainable using more powerful sequences has allowed to perform perfusion and dynamic studies after paramagnetic contrast agent administration. The latter MRI techniques permit to obtain functional tissue information concerning the vitality of the tissue essential to differentiate fibrosis from residual tumour after anti-angiogenetic treatments.

Dynamic contrast MRI

In scientific literature the potential of DCE-MRI has been reported as a promising evaluation tool to monitor and predict therapy response thanks to the relationship between tumour growth and angiogenesis.[5-7,19,24-25] It is well known that angiogenesis is a key factor in the growth and dissemination of cancer. The characterization of the tumour angiogenic status on an individual patient basis could allow patient tailored treatments.[24]

Many clinical trials in rectal cancer have demonstrated that angiogenesis inhibition can increase treatment effectiveness. Consequently, imaging

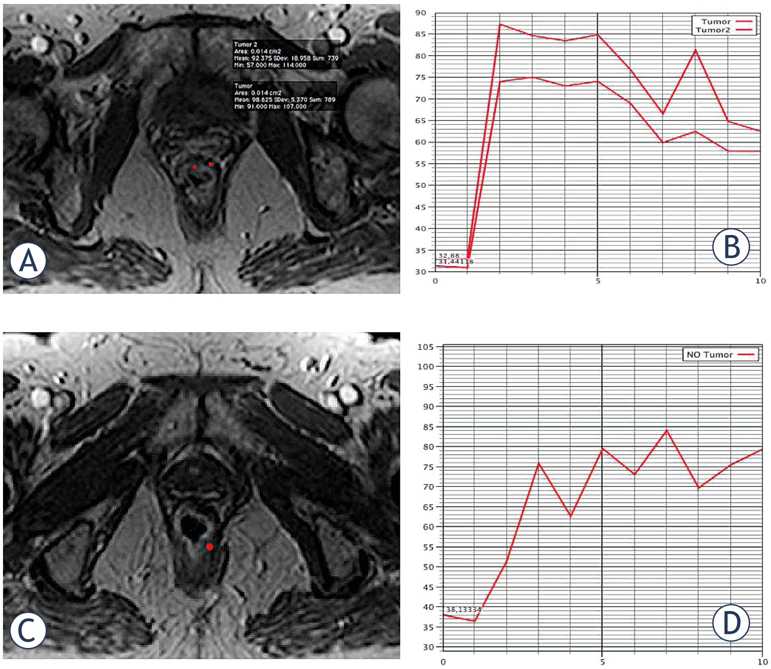


FIGURE 1. T1 weighted post contrast scan obtained before **(A)-(B)** and after **(C)-(D)** chemo-radiotherapy (CRT). The analysis of time intensity curve (TIC) show areas with rapid contrast uptake and fast discharge (B). After CRT, on the same areas no pathological contrast uptake is present confirming that hypo-intense tissue are tumour nests but only residual inflammation due to CRT.

modalities able to assess tumour vascularization might improve the treatment management in patients affected by LARC.[6-7,24-25]

To assess tissue perfusion by means of DCE-MRI several approaches to analyse time intensity curve (TIC) have been proposed. The most commonly used in the clinical radiological practice is the TIC visual inspection approach.[54] The main drawback of this qualitative approach is its dependence upon the experience of the operator and the absence of reproducibility. Petrillo *et al.*[52] utilized TIC visual inspection to assess pCRT response in LARC (Figure 1). According to[52], when patients with a partial or complete response to pCRT were included, a sensitivity, specificity and an accuracy of 79%, 76% and 78% respectively have been obtained. Instead, considering the performance of qualitative MRI evaluation in complete responders a sensitivity, a specificity and an accuracy of 94%, 76% and 84% respectively could be reached.

To overcome the limitations related to visual inspection alone, the quantitative or semi-quantitative approach for DCE-MRI data analysis have been proposed and investigated.

Quantitative model-based analysis involves compartmental tracer kinetic modelling[20-21] and pixel-by-pixel or region of interest based estimation of kinetic features, by means of a non-linear regression. The latter has been introduced to better correlate quantitative model-based features with physiological tissue properties. Kim *et al.*[55] showed that average Ktrans (a parameter associated to contrast agent transfer constant between plasma to extracellular extravascular space) had a large decrease after pCRT; this decrease was linked with a good therapeutic response in LARC. However, being influenced by many variables and since many different models are present in the literature, the quantitative approach still suffers from high output variability, poor clinical consistency and reproducibility.[20] Quantitative analysis findings in the therapy response assessment using 3T scanners are more encouraging as Intven *et al.* and Lim *et al.* have reported in their studies.[56-57]

To overcome previous problems several authors[58-61] performed semi-quantitative analysis. Lavini *et al.*[59], in order to discriminate benign and malignant pixels, used the following features: maximum signal difference, time to peak, maximum slope of increase, relative final slope and initial signal. Tuncbilek *et al.*[60] demonstrated that time to peak, wash-in intercept and maximum enhancement were strongly correlated to micro vessel density. Petrillo *et al.*[53] investigated a semi-quantitative analysis with a piecewise linear fitting and they individuated a combination of two TIC descriptors named Standardized Index of Shape (SIS). This latter is a linear weighted combination of relative change of maximum signal difference (ΔMSD) and relative change of wash-out slope (ΔWOS).[53] This index reached a sensitivity of 93.5% and a specificity of 82.1% with relevant gains respect to ΔMSD (+20.1% in sensitivity and +11.7% in specificity) and ΔWOS (+13.1% in sensitivity and + 4.3% in specificity) alone. Moreover, the standardized index of shape improved negative predictive value to 88.5% and positive predictive value to 89.6%.

Because many of the conducted studies are relatively small and study design is very heterogeneous, the evidence on DCE-MRI is rather inconsistent. Therefore, future research should aim at increasing sample sizes and standardization of imaging techniques and analyses.[61]

Diffusion weighted imaging

The use of DWI into a standard MR protocol is progressively increasing thanks to its capability in the tumour detection, characterization as well as its potentiality in the monitoring and in the prediction of treatment response.[8-12,62-65] By means of DWI data analysis is possible to estimate water molecules mobility that is related to cell density, vascularity, viscosity of extracellular fluid and cell membrane integrity.[12] By measuring these properties with apparent diffusion coefficient (ADC) and other diffusion coefficients characteristics of intravoxel incoherent motion, the DWI could be used as an imaging biomarker to better select patients with reduced prognosis who will benefit from a more aggressive neoadjuvant treatment.[8-12] It was demonstrated that ADC values in LARC correlate with prognostic factors including the mesorectal fascia status, the nodal stage and the histological differentiation grade.[8,40,62] There are several ways to analyse DWI data including visual evaluation, volumetric assessment, and ADC measurements. Visual DWI evaluation has been shown to improve the MRI performance to differentiate between patients with and without residual tumour after pCRT. Another approach is to measure the volume before and after therapy. Ha *et al.* reported that DWI tumour volumetry offered the best results to predict the complete response to chemoradiation treatment.[11] Furthermore, Sathyakumar *et al.*[19] demonstrated that DWI visual assessment post therapy and DWI tumour volume reduction were the best predictors of complete pathological response. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of DWI visual assessment to predict complete response were 81.8%, 94.3%, 75%, 96.1% and 76% respectively. Sensitivity, specificity and accuracy of tumour volume reduction (cut off value 95%) were 80%, 84.1% and 64.1%, respectively.

ADC measure (before, during, and after therapy) is the most widely studied approach to assess therapy response. Increases in ADC values after treatment are linked to decreases in tissue cellularity and thus it provides indirect evaluation of chemotherapy induced cell death. Kim *et al.*[62] demonstrated that the addition of DWI to standard MRI protocol yields better diagnostic accuracy than use of conventional MRI alone in the evaluation of pathological complete response. Marouf *et al.*[63] reported for conventional MRI a sensitivity of 60% and specificity of 33% with overall diagnostic accuracy of 46.5% in the assessment of T stage. Overall diagnostic accuracy increased adding DWI to 83.5% with the 87% of sensitivity and 80% of specificity. N stage prediction by conventional MRI had 74% of sensitivity and 80% of specificity with an overall accuracy of 78%. Overall accuracy to predict N stage increased adding DWI to 83%.

However, the evidence regarding the use of pre, during and post treatment ADC measurements to assess tumour response has so far been inconsistent, which is also related to the fact that ADC measurement are influenced by variations in MR scanner hardware, field strength, acquisition protocols and measurement methods. Lack of standardization hampers the implementation of ADC in clinical practice and should be the focus of future studies.[61]

PET/CT

PET/CT is constantly increasing in rectal cancer management for its ability to predict treatment response.[50] Avallone *et al.*[50] reported that early changes (12 days after the pCRT beginning) of the standardized uptake maximum value (ΔSUVmax) were predictive of pathological response with an optimal threshold value of -42.0% and an accuracy of 93.0%. In this study, the authors also observed that the findings obtained from late pre surgical PET/CT scans showed lower accuracy in predicting of pathologic response. Leccisotti *et al.*[70] analysed the metabolic activity modifications by PET/CT during and after pCRT in 124 patients with LARC demonstrating that the areas under ROC curve of the early response index to detect non-complete pathological response was 0.74 (optimal cut-off of ΔSUVmax was 61.2%). On the contrary, the optimal cut-off for the late response index was not being found. Niccoli-Asabella *et al.*[71] reported similar findings, with an area under ROC curve for ΔSUVmax of 0.67. Therefore, the literature data were discordant detecting in general the poor accuracy of late metabolic response to predict pathological response in LARC.

Systematic review

The review is the result of autonomous studies without protocol and registration number.

Search criterion

Several electronic database were searched: PubMed (US National Library of Medicine, http://www.ncbi.nlm.nih.gov/pubmed), Scopus (Elsevier, http://www.scopus.com/), Web of Science (Thomson Reuters, http://apps.webofknowledge.com/) and Google Scholar (https://scholar.google.it/). The following search criteria have been used: ''rectal cancer'' AND ''diffusion magnetic resonance imaging'' AND ''response'', ''rectal cancer'' AND ''dynamic

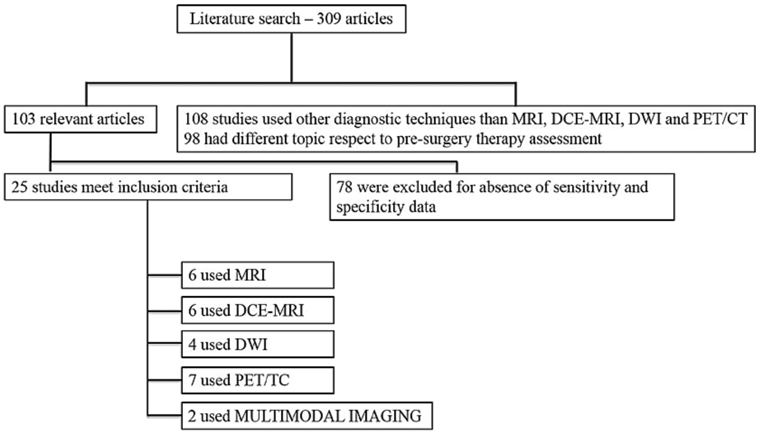


FIGURE 2. Included and excluded studies in systematic review.

DCE-MRI = dynamic contrast enhanced MRI; DWI = diffusion weighted imaging

TABLE 1. Number of studies and participants for each diagnostic modality

Diagnostic modality	Studies	Participants
MRI	6	329
DCE-MRI	6	340
DWI	4	133
PET/CT	7	366
MULTIMODAL IMAGING	2	70

DCE-MRI = dynamic contrast enhanced MRI; DWI = diffusion weighted imaging

contrast enhanced magnetic resonance imaging'' AND ''response'', ''rectal cancer'' AND ''positron emission tomography'' AND ''response'', ''rectal cancer'' AND ''multimodal imaging'' AND ''response''. In order to cover the last twelve years of the recent oncologic research literature, the research covered the years from 2005 through 2016. Moreover, the reference lists of the found papers were analysed for papers not indexed in the electronic databases.

All titles and abstracts were analysed and exclusively the studies reporting morphological MRI, DCE-MRI, DWI or PET/CT results in the preoperative therapy response assessment for LARC were retained.

If not otherwise stated, all the studies reviewed herein fulfil the following criteria: English language; thorough clinical characterization of the patients with rectal cancer studied by means morphological MRI, DCE-MRI, DWI and PET/CT to discriminate responders versus non responders to pCRT and exclusion of studies using other diagnostic techniques; articles, reviews and studies that did not present data about specificity, sensibility, positive and negative predictive value of tests treated were excluded; articles, reviews and studies that did not present data about specificity, sensibility, positive and negative predictive value of tests treated were excluded; reviews, general overview articles and congress abstracts were excluded. There was not defining a minimum number of patients as inclusion criteria due to the small number of studies for each imaging modality. Information extracted from each study included title, authors, year of publication, sample size, diagnostic modality and approach, reference standard, true and false positives number, true and false negatives number.

Data analysis

Review Manager (version 5.2) was used to perform data analysis for systematic review. The PRISMA statement for reporting systematic review was used.[75]

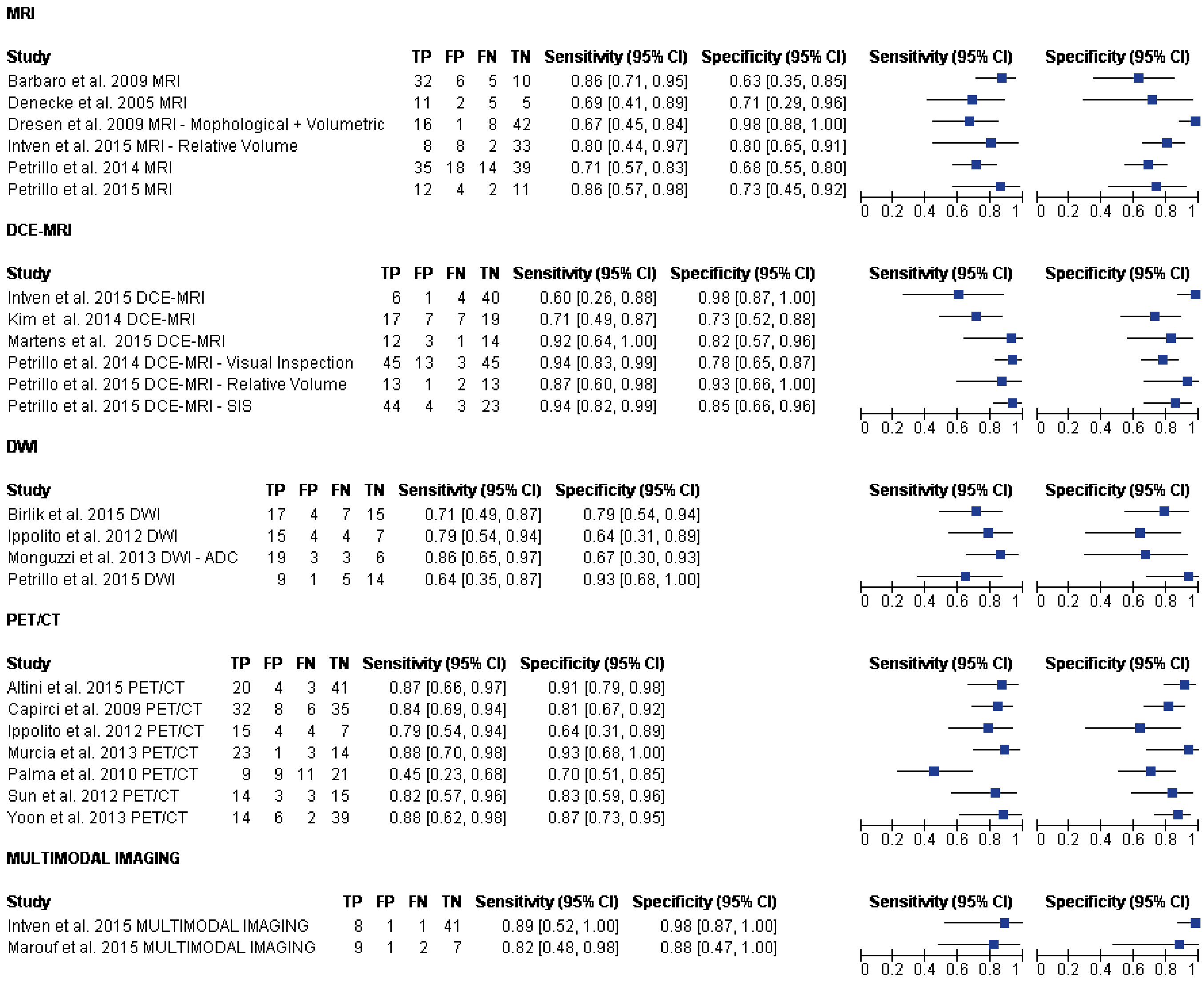
True and false positives number, true and false negatives number for each paper were collected and used to obtain the forest plots reporting the sensitivity, specificity values and relative 95% confidence intervals. ROC curves were also constructed. Moreover, to assess the quality and bias risk of diagnostic accuracy studies included in the review was used QUADAS-2 tool.[76]

Results

By using the search terms described earlier, we identified 309 studies from 2005 through 2016. One hundred eight studies used other diagnostic techniques than morphological MRI, DCE-MRI, DWI and PET/CT; 98 had different topic respect to presurgery therapy assessment; 78 were excluded for insufficient data (absence of sensibility and specificity value). Twenty-five studies remained for inclusion in our systematic review (Figure 2).

Table 1 shows the number of included studies and the overall number of participants grouped by diagnostic modality.

Details regarding the number of patients, imaging modality, the accuracy values and examined parameters were recorded. Table 2 summarizes the main characteristics of the examined methodologies in LARC studies.



MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Barbaro et al. 2009 MRI	32	6	5	10	0.86 [0.71, 0.95]	0.63 [0.35, 0.85]
Denecke et al. 2005 MRI	11	2	5	5	0.69 [0.41, 0.89]	0.71 [0.29, 0.96]
Dresen et al. 2009 MRI - Mophological + Volumetric	16	1	8	42	0.67 [0.45, 0.84]	0.98 [0.88, 1.00]
Intven et al. 2015 MRI - Relative Volume	8	8	2	33	0.80 [0.44, 0.97]	0.80 [0.65, 0.91]
Petrillo et al. 2014 MRI	35	18	14	39	0.71 [0.57, 0.83]	0.68 [0.55, 0.80]
Petrillo et al. 2015 MRI	12	4	2	11	0.86 [0.57, 0.98]	0.73 [0.45, 0.92]

DCE-MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Intven et al. 2015 DCE-MRI	6	1	4	40	0.60 [0.26, 0.88]	0.98 [0.87, 1.00]
Kim et al. 2014 DCE-MRI	17	7	7	19	0.71 [0.49, 0.87]	0.73 [0.52, 0.88]
Martens et al. 2015 DCE-MRI	12	3	1	14	0.92 [0.64, 1.00]	0.82 [0.57, 0.96]
Petrillo et al. 2014 DCE-MRI - Visual Inspection	45	13	3	45	0.94 [0.83, 0.99]	0.78 [0.65, 0.87]
Petrillo et al. 2015 DCE-MRI - Relative Volume	13	1	2	13	0.87 [0.60, 0.98]	0.93 [0.66, 1.00]
Petrillo et al. 2015 DCE-MRI - SIS	44	4	3	23	0.94 [0.82, 0.99]	0.85 [0.66, 0.96]

DWI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Birlik et al. 2015 DWI	17	4	7	15	0.71 [0.49, 0.87]	0.79 [0.54, 0.94]
Ippolito et al. 2012 DWI	15	4	4	7	0.79 [0.54, 0.94]	0.64 [0.31, 0.89]
Monguzzi et al. 2013 DWI - ADC	19	3	3	6	0.86 [0.65, 0.97]	0.67 [0.30, 0.93]
Petrillo et al. 2015 DWI	9	1	5	14	0.64 [0.35, 0.87]	0.93 [0.68, 1.00]

PET/CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Altini et al. 2015 PET/CT	20	4	3	41	0.87 [0.66, 0.97]	0.91 [0.79, 0.98]
Capirci et al. 2009 PET/CT	32	8	6	35	0.84 [0.69, 0.94]	0.81 [0.67, 0.92]
Ippolito et al. 2012 PET/CT	15	4	4	7	0.79 [0.54, 0.94]	0.64 [0.31, 0.89]
Murcia et al. 2013 PET/CT	23	1	3	14	0.88 [0.70, 0.98]	0.93 [0.68, 1.00]
Palma et al. 2010 PET/CT	9	9	11	21	0.45 [0.23, 0.68]	0.70 [0.51, 0.85]
Sun et al. 2012 PET/CT	14	3	3	15	0.82 [0.57, 0.96]	0.83 [0.59, 0.96]
Yoon et al. 2013 PET/CT	14	6	2	39	0.88 [0.62, 0.98]	0.87 [0.73, 0.95]

MULTIMODAL IMAGING

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Intven et al. 2015 MULTIMODAL IMAGING	8	1	1	41	0.89 [0.52, 1.00]	0.98 [0.87, 1.00]
Marouf et al. 2015 MULTIMODAL IMAGING	9	1	2	7	0.82 [0.48, 0.98]	0.88 [0.47, 1.00]

FIGURE 3. Forest plot subdivide for imaging modality including sensitivity and specificity estimates and their confidence intervals (95%).

CI = confidence interval; FN = false negative; FP = false positive; SIS = standardized index of shape; TN = true negative; TP = true positive

Figure 3 reports the values of true positive (TP), false positive (FP), false negative (FN), true negative (TN), sensitivity and specificity estimates and their confidence intervals (95%) for each study, subdivided according to the diagnostic modality used for therapy response assessment in LARC. Figure 4 shows ROC for each diagnostic modality.

Table 3 reports the diagnostic performance for each imaging modality in terms of sensitivity, specificity, positive predictive value and negative predictive value.

Figure 5 shows the bias risk and applicability analysis results. A very low risk of bias was present for the studies included in this systematic review.

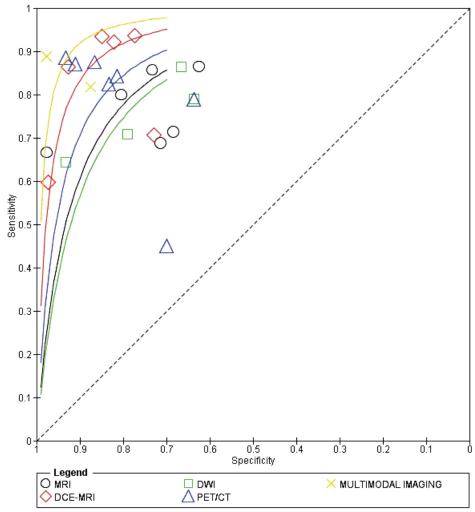


FIGURE 4. Estimated summary ROC curves and original data points for imaging techniques.

DCE-MRI = dynamic contrast enhanced MRI; DWI = diffusion weighted imaging

TABLE 2. Main characteristics summary of included studies in the systematic review: for each study the table reports imaging modality used; number of patients examined; parameters examined

Imaging modality	Authors	Approach	N. patients	Gold standard
MRI	Barbaro *et al.*[69]	Score system	53	TNM
	Denecke *et al.*[46]	Morphologic criteria	23	TNM
	Dresen *et al.*[45]	Morphologic + volumetric criteria	67	TNM
	Intven *et al.*[56]	Relative volume	51	TRG
	Petrillo *et al.*[52]	Score system	106	TRG
	Petrillo *et al.*[64]	Relative volume	29	TRG
DCE-MRI	Intven *et al.*[56]	Relative Ktrans	51	TRG
	Kim *et al.*[55]	Relative Ktrans	50	TNM
	Martens *et al.*[67]	TIC slope	30	TRG
	Petrillo *et al.*[52]	TIC visual inspection	106	TRG
	Petrillo *et al.*[64]	Relative volume	29	TRG
	Petrillo *et al.*[53]	Standardized index of shape	74	TRG
DWI	Birlik *et al.*[65]	ADC	43	TRG
	Ippolito *et al.*[40]	ADC	30	TRG
	Monguzzi *et al.*[68]	ADC	31	TRG
	Petrillo *et al.*[64]	Relative volume	29	TRG
MULTIMODAL IMAGING	Intven *et al.*[56]	Relative volume + relative Ktrans	51	TRG
	Marouf *et al.*[63]	MRI + DWI Score system	19	TNM
PET/CT	Altini *et al.*[36]	SUV	68	TRG
	Capirci *et al.*[42]	SUV	81	TRG
	Ippolito *et al.*[40]	SUV	30	TRG
	Murcia *et al.*[43]	SUV	41	TRG
	Sun *et al.*[41]	Total lesion glycolysis	35	TRG
	Yoon *et al.*[66]	Dual-point index	61	TRG
	Palma *et al.*[73]	SUV	50	TRG

ADC = apparent diffusion coefficient; DWI = diffusion weighted imaging; SUV = standardized uptake value; TIC = time intensity curve; TRG = tumour regression grade

Discussions

The objective of this systematic review was to evaluate the different imaging modalities (morphological MRI, DWI, DCE-MRI, PET/CT and multimodal imaging) in LARC management after pCRT. We collected the current evidence of the role of functional MRI and PET/CT in the assessment of pathological response after pCRT in LARC. The objective was linked to the potentiality of imaging to guide surgeon choice. In fact, patients with substantial (partial response) tumour regression after pCRT could be candidate to conservative strategy while patients reporting a complete response could be subjected to a "wait and see" policy. The advantage is the reduction of morbidity and the possibility to provide a "true" organ-sparing approach.

Our results, using a systematic review of literature and the ROC curves analysis, showed that multimodal imaging combining morphological and functional might achieve better results having the best accuracy in term of sensitivity and specificity (85% and 96%, respectively). However, it should be noted that only two studies have been retrieved from the literature for a total number of only 70 participants subjected to multimodal MRI examination.[56,63] Intven *et al.*[56] demonstrated on 51 patients with LARC that both the post therapy tumour volume and post therapy Ktrans values and their relative changes were predictive for patho-

TABLE 3. Performance pooled analysis for MRI, diffusion weighted imaging (DWI), dynamic contrast enhanced MRI (DCE-MRI), PET/CT and multimodal imaging

Performance Pooled Analysis	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
MRI	75,84	78,21	74,34	79,55	77,13
DCE-MRI	87,18	84,15	82,42	88,51	85,55
DWI	75,95	79,25	84,51	68,85	77,27
PET/CT	80,25	83,08	79,27	83,92	81,82
MULTIMODAL IMAGING	85,00	96,08	89,47	94,23	92,96

DCE-MRI = dynamic contrast enhanced MRI; DWI = diffusion weighted imaging

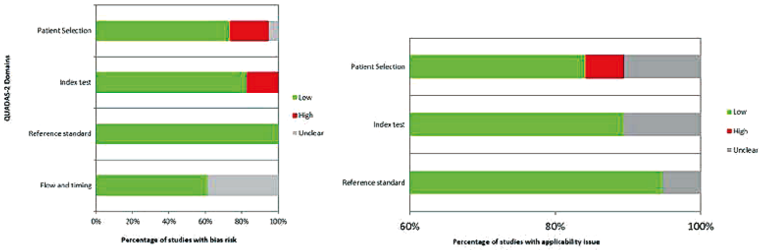


FIGURE 5. Assessment of bias risk and applicability analysis.

logical response. For the relative Ktrans, Intven *et al.*[56] reported a positive predictive value of 100% (with a Ktrans cut-off of 32%) to discriminate good responders. However, for pathological complete response, the best positive predictive value was 80% obtained with a multiparameter model of relative volume and relative Ktrans. Marouf *et al.*[63] reported an increase of diagnostic accuracy for the combination of morphological MRI and DWI from 84.2% to 94.7%. Although the number of patients is relatively small multimodal imaging seems to give promising results whose reliability is to be confirmed in future studies.

Moreover, DCE-MRI following to PET/CT showed a high diagnostic accuracy (sensitivity 87% and 80% respectively, specificity 84% and 83% respectively) and their results are also more reliable than conventional MRI and DWI alone (Figure 3 and 4). Instead, for morphological MRI alone, the sensitivity was of 76% and specificity of 78%. For DWI, the sensitivity was of 76% and specificity was of 79%. Our findings are comparable with recent meta-analysis that indicated that addition of DWI to standard MRI in a multimodal approach improves the sensitivity for T-staging after pCRT from 50% to 84%.[12]

Instead, Ippolito *et al.*[40] reported that the best predictors cut-off values for tumour regression grade (TRG) response were for PET/CT SUVmax of 4.4 and for ADC of 1.28×10^3 mm^{2}s^{-1}. ADC obtained sensitivity, specificity, accuracy, negative and positive predictive values of 77.3%, 88.9%, 80.7%, 61.5%, and 94.4%, respectively.

However, PET/CT showed an inferior diagnostic accuracy in comparison of DCE-MRI in pre-surgical assessment of therapy response in LARC but it had a high predict value in the early evaluation of therapy response. The early response assessment by PET/CT was a predictor of non-complete pathological therapy response allowing practical modification of treatment.

Kim *et al.*[72] revealed that SUVmax post threapy had a sensitivity of 60.4%, a specificity of 65.0%, and an accuracy of 55.9% to discriminate pathological complete response. Palma *et al.*[73] reported that maximum ΔSUVmax had a sensitivity of 45.0%, a specificity of 67.0%, and an accuracy of 89.0% while Altini *et al.*[36] shown a sensitivity of 87.0%, a specificity of 70.0% and an accuracy of 60.0%. Similar results were also observed in others advanced cancers such as esophageal cancer.[74] On the contrary, late response index was not sufficiently precise to guide the surgeon choice versus radical or local excision or versus a "wait and see" strategy.[50,70-73]

As well as PET/CT, DWI technology can be efficient for predicting pathological complete response in LARC[77-80] but inefficient to assess late response in pre-surgical phase. Chen *et al.*[79] reported DWI sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 60%, 64%, 60%, 60%, and 60%, respectively, in pathological complete response discrimination using a cut-off value of 0.866×10^{-3} mm^2/s for pre-treatment ADC value. Using a cut-off value for ADC percentage change of 58% the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 80%, 76%, 77%, 79% and 78%, respectively.[79] Moreover, the mean pre-treatment tumour ADC correlates with the degree of tumour response after therapy and patients who respond to treatment seem to have a lower ADC at presentation than do those who do not respond.[5] The association between high tumour ADC and poor response is consistent with the known relationship between necrosis and poor response to cancer treatment. However, both PET/CT and DWI had an important role in therapy prediction and in early therapy response assessment but showed a low accuracy in pre-surgical therapy evaluation.

Therefore, multimodal assessment combining different imaging modalities might be the best option for local restaging of locally advanced rectal cancer after CRT in pre-surgical phase.[81] According to this theory, recently Ippolito *et al.*[82] reported that the functional imaging combining ADC and SUVmax in a single analysis permits to detect changes in cellular tissue structures useful for the assessment of tumour response after the neoadjuvant therapy in rectal cancer, increasing the sensitivity in correct depiction of treatment response than either method alone.

A number of limitations of this analysis must be recognized. Most papers report on a limited number of patients and heterogeneity within the included studies with respect to patient selection, neoadjuvant treatment and imaging protocols and analyses. This pooled analysis should be regarded as an indicator of the general performance of functional MRI and PET/CT in the therapy response assessment. Validation and implementation in a multicenter setting are still awaited. Standardization of MRI acquisition protocols and data post processing approaches is mandatory to guarantee results reproducibility. Multicenter studies using large patient populations are needed to validate the role of functional imaging in order to identify those patients who may benefit from a less aggressive therapeutic approach after CRT.

We can conclude that in local staging, morphological MRI is superior respect to CT and PET/CT permitting a correct assessment of the disease extent, of the lymph node involvement, of the mesorectal fascia and of the sphincter complex for surgical planning. On the other side, in restaging for therapy response assessment, Multimodal MRI followed by DCE-MRI seem to give more promising results respect to PET/CT, DWI and conventional MRI. Multimodal Imaging including morphological and functional MRI and DCE-MRI alone could allow to better discriminate responder by non responders patients after neoadjuvant therapy with a high diagnostic accuracy.

In the future, the scientific research should be focused on the integration and combination of functional imaging modalities including also clinical data and molecular biomarkers. A greater number of studies should be performed in the future for each modality to improve the reliability of any conclusion.

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