

How reliable is current imaging in restaging rectal cancer after neoadjuvant therapy?

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Abstract

In patients with advanced rectal cancer, neoadjuvant chemo radiotherapy provides tumor downstaging and downsizing and complete pathological response in up to 30% of cases. After proctectomy complete pathological response is associated with low rates of local recurrence and excellent long term survival. Several authors claim a less invasive surgery or a non operative policy in patients with partial or clinical complete response respectively, however to identify patients with true complete pathological response before surgical resection remains a challenge. Current imaging techniques have been reported to be highly accurate in the primary staging of rectal cancer, however neoadjuvant therapy course produces deep modifications on cancer tissue and on surrounding structures such as overgrowth fibrosis, deep stroma alteration, wall thickness, muscle disarrangement, tumor necrosis, calcification, and inflammatory infiltration. As a result, the same imaging techniques, when used for restaging, are far less accurate. Local tumor extent may be overestimated or underestimated. The diagnostic accuracy of clinical examination, rectal ultrasound, computed tomography, magnetic resonance imaging, and positron emission tomography using 18F-fluoro-2'-deoxy-D-glucose ranges between 25% and 75% being less than

60% in most studies, both for rectal wall invasion and for lymph nodes involvement. In particular the ability to predict complete pathological response, in order to tailor the surgical approach, remains low. Due to the radio-induced tissue modifications, combined with imaging technical aspects, low rate accuracy is achieved, making modern imaging techniques still unreliable in restaging rectal cancer after chemo-radiotherapy.

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Key words: Rectal cancer; Restaging; Neoadjuvant therapies; Diagnostic accuracy; Complete pathological response

Core tip: Neoadjuvant chemoradiotherapy has become the standard treatment for patients with advanced rectal cancer allowing reduction of local recurrences and increased sphincters' preservation. New trends have proposed the possibility to change the planned surgical resection after neoadjuvant treatment, in case of extensive tumor response, and several Authors claim limited resection or non operative "wait and see" policy. In this setting restaging plays a crucial role in identifying patients with complete response. The diagnostic accuracy in predicting tumor response of the currently available imaging techniques is extensively reviewed in order to determine the reliability.

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INTRODUCTION

In the last two decades the treatment of rectal cancer has been modified by virtue of the introduction of neoadju-

vant treatment^[1], better imaging techniques and improvement of surgery with total mesorectal excision (TME). The crucial goals reached by upgrading diagnostic techniques and therapeutic strategies accounts for reduction of local recurrence rate and increase of sphincter preserving surgeries.

Preoperative chemoradiation therapy (CRT) has become the standard treatment in the last decade^[1-3]. Advantage of neoadjuvant treatment is the downsizing/downstaging of the tumor thus allowing the preservation of the sphincter, in case of extremely distal rectal lesions, and, often, avoiding multiorgan resection in case of responding tumor that had involved other organs before the neoadjuvant regimen. The overall benefits of this therapeutic regimen are, eventually, the reduction rates of local recurrence and the improvement in survival^[4-7].

Reduction of local recurrence after surgery was first achieved with the introduction of complete excision of the visceral rectal mesentery, bringing up the concept that mesorectum harbors positive lymph nodes and tumor residues^[8]. Moreover, it has been highlighted that surgical local radicality has to be carried out by improving the control on radial margins tumor-spread other than distal and proximal ones^[9,10]. These findings have been demonstrated by pathological analysis of circumferential resection margin (CRM).

The key of neoadjuvant treatment and restaging of the tumor is, finally, the possibility of changing the planned surgical treatment and, in particular, the chance of providing a sphincter preserving procedure. In a more experimental way, new trends have proposed local resection in case of extensive tumor response^[11] or a non-surgical "wait-and-see course" in case of complete tumor regression^[12-15]. On the contrary, for non-responding or poor responding rectal tumors, more aggressive, traditional surgery, after restaging, is indicated. This decision depends mostly on the reliability of the imaging techniques provided by modern technology and the synergy between the radiologist and surgeon.

The main issue of re-staging after CRT with imaging techniques, is to discriminate cancerous mass from non malignant tissue because of the radio induced overgrowth fibrosis^[16]. Tumor tissue changes, during and within 6-8 wk after chemo-radiotherapy, account for deep stroma alteration. Fibrosis compresses the colon tissue and ends up in causing wall thickness and muscle disarrangement. Other variation are tumor necrosis, calcification, and inflammatory infiltration of lymphocytes and macrophages^[17].

The tumor regression grade (TRG) exactly reflects the ratio between residual tumor percentage and overgrowing fibrosis percentage. Thus the more reliable restaging technique has, eventually, the goal to predict TRG because it positively correlates with disease free and overall survival^[18]. Ideally, precise staging of rectal cancer has to define the tumor depth of invasion through the rectal wall, detect positive lymphnodes, and establish the resectability of locally advanced tumors.

Several techniques have been described to restage rectal carcinoma after CRT, the most predominantly used being computer tomography (CT) scan, rectal ultrasounds (RUS), and magnetic resonance imaging (MRI).

In the present study we revise the accuracy and reliability of current techniques, used to re-stage rectal cancer after neoadjuvant therapy, in terms of sensitivity, specificity, and diagnostic accuracy, compared with pathological findings after surgical resection. Special attention will be paid to the ability to predict complete response (cPR).

CLINICAL EXAMINATION

There is no doubt that clinical examination, comprising digital rectal examination (DRE) and proctoscopy, is the first and essential approach to patients with rectal cancer. Moreover, clinical assessment of response to CRT may provide important information regarding the surgical strategy. Nevertheless few studies evaluated the accuracy of clinical assessment in predicting tumor response after completion of CRT, and the majority of these studies were retrospective. Clinical assessment may underestimate^[19,20] or overestimate^[21] pathological response therefore most authors claim that clinical examination is inaccurate and should not be used as the unique mean to define the efficacy of neoadjuvant therapy.

Only 2 studies tried to answer the question whether clinical parameters are able to predict cPR. In the study by Perez *et al*^[22], 99 patients were prospectively examined, by the same experienced colorectal surgeon, after 12 wk from completion of CRT; 16 patients had a complete clinical response (cCR), 3 underwent local excision of a residual scar, and a cPR was confirmed; 13 patients were enrolled in a strict follow-up without radical surgery, only one patients subsequently developed a local recurrence after a mean follow-up of 42 months; moreover the cCR positively correlated with the PET results^[22]. On the contrary Hiotis *et al*^[23] retrospectively analyzed 448 patients and found that 75% of patients with cCR had residual cancer in the resected specimens: 60% having T2 or T3 disease, and 18% node-positive disease. In addition, in the group of patients with no residual primary tumor at histology (T0), the percentage of node positivity was 15%.

Habr-Gama *et al*^[24], in an effort to standardize the clinical findings, clearly defined clinical and endoscopic sign to define complete response as: whitening of the mucosa, with or without telangiectasia, or loss of pliability of the rectal mucosa, absence of deep or superficial ulceration, or palpable nodule or stenosis located in previously tumor bearing area. Nevertheless the likelihood of detecting occult nodal disease in patients with no residual primary tumor is highly unlikely.

In conclusion even if clinical parameters may predict tumor response, they are unable to distinguish cPR and to predict which patient does not require surgical excision following CRT.

RECTAL ULTRASOUNDS

The assessment of rectal tumor by means of ultrasonography is based on the evaluation of depth of invasion through the 5 layers of the bowel wall. With high resolution probes T1-2 tumors can be correctly diagnosed and even SM1, SM2 and SM3 tumors can be recognized^[25]. On the other hand the mesorectum and peritoneum cannot be visualized by endorectal probe thus limiting the use of ultrasound for the evaluation of CRM.

Endorectal ultrasound can visualize perirectal lymph nodes and nodes located in the mesorectum while lymph nodes along the mesentery or the upper pelvis are generally unreachable. Normal lymph nodes are usually not seen sonographically. Enlarged lymph nodes are considered benign if oval shaped, and thought to be inflammatory if hyper echoic with well defined margins. There is no agreement as when to consider a lymph node as pathological. Dimensional, morphologic, and echographic pattern are to be considered. Nodes greater than 5 mm, round shaped and with echogenicity similar to the primary tumor (hypoechoic), are usually considered as predictors of metastatic involvement by most, but not all authors, who may choose only one of the aforementioned parameters, in particular size is considered the most reliable feature.

Different probes are employed for imaging rectal cancer including transrectal rigid, rotating or non rotating probe, either two-dimensional or with three-dimensional reconstruction, flexible endoscope either radial or linear, miniprobe able to pass through the biopsy channel^[26], with frequency ranging between 5 and 10 MHz. No comparison of the performance of different instruments has been made up to now. Unlike other imaging modalities, the endorectal ultrasound in the different settings is performed by a radiologist, a gastroenterologist or a colorectal surgeon, and this could be a further confounding factor when examining the accuracy of the examination.

There is no consensus regarding the time that must elapse between CRT and evaluation. The majority of the authors re-examined the patients after 4 to 6 wk. However a better diagnostic accuracy for N staging has been reported by Huh when the patients are re-evaluated after 7 wk^[27] from completion of CRT.

Accuracy in T restaging ranges between 27% to 72%, with overstaging between 16% and 53%. In the majority of the studies T1-2 stage are more misdiagnosed than T3^[8,9,11-13,16,18,28-30]. When examining the accuracy to correctly diagnose T0 the figure drop to 0% to 60%^[31-33]. Gavioli *et al*^[29] studied the modification of morphology induced by radiotherapy in 29 patients. They found that fibrosis replacing tumor corresponded to hypoechoic pattern at ultrasound that was difficult to differentiate from the pattern related to the tumor itself, thus inducing overstaging. In some cases of complete pathological response the fibrosis caused persistent interruption of the 5 layers leading to misinterpretation of the examination.

The accuracy in restaging lymph nodal involvement is somehow higher than accuracy for primary tumor, ranging between 39% and 83% and being around 70% in most studies. For this parameter overstaging was only slightly more common than understaging (8%-39% *vs* 11%-28%). Correct identification of N0 varies between 70% and 80%^[8,9,11-13,16,18,28-30,34]. Moreover 13%-55% of patients with lymph nodal involvement were recognized as N0^[30,34,35].

When compared with other imaging techniques, namely CT and standard MRI, ultrasound resulted the most accurate in determining rectal wall infiltration and lymph node involvement in some studies^[31], while performed worse in others^[27].

It is of note that in the majority of the studies diagnostic accuracy is reported separately for T and N stage, thus preventing accuracy for complete pathological response (ypT0N0) to be determined. Kahn examined 25 patients with T0N0 tumors after preoperative radiotherapy and reported that endorectal ultrasound failed to detect the absence of disease in 83% of patients, with overstaging of T0 lesions diagnosed as T1 in 67% of cases and T2 in 16%. In the 25 patients' series of Maor, ultrasound correctly predicted postchemoradiation T0N0 stage in only 50% of cases. Radovanovic reported only one correct diagnosis out of 5 patients (20%) with cPR^[36]. While complete remission was not correctly predicted in any of the 11 patients by Huh *et al*^[27].

The occurrence of uT0 harboring microscopic foci of tumor at histology is also reported^[35].

In conclusion endorectal ultrasound is insufficient in detecting which tumors become T0N0 after neoadjuvant treatment to possibly undergo limited resection or non-operative treatment.

COMPUTER TOMOGRAPHY

CT is one of the preferred tools to evaluate tumor response, in relation to the tumor size modification, because of its high reproducibility and availability. Compared with the other commonly used techniques, CT scan is more largely accessible, faster, inexpensive and less operator-dependent. Also the unique advantage of CT is that a single scan provides staging for local tumor and distant metastasis. Therefore every re-staging techniques pattern usually includes a total body CT scanning.

Accuracy of CT scan in predicting T stage after neoadjuvant course is still debated in the literature and the results are often inconsistent or discordant^[17,27,37].

In a recent study, 90 patients with locally advanced rectal cancer were prospectively analyzed before and after neoadjuvant regimen. Accuracy of CT in predicting pathological T after radiotherapy was low (37%). However CT was reported to be accurate in the identification of involved CRM (71%)^[37]. Conversely, Lee *et al*^[17] have demonstrated, in a series of 91 patients undergoing CT restaging after neoadjuvant course, that T status positively correlated with pathological examination with an accu-

cy of 61%. Moreover they found a statistically significant correlation with CT downstaging assessment and TRG at pathology. However over staging was frequently found in patients with fibrosis and alteration in muscle dissarayment^[17]. In the study conducted by Huh *et al*^[27] on 80 patients, CT accuracy in restaging the depth of rectal wall invasion was poor (46.3%). CT was also found to more likely overstage T3 tumor and understage T2 ones^[27].

Finally CT scan is commonly considered an unreliable restaging technique to assess cPR^[17,38]. In none of patients retrospectively analyzed by Huh CT scan was able to predict cPR^[27].

Nodal involvement detection plays a crucial role in those selected cases which are candidates to receive a local excision after extensive tumor response. In a local excision setting, it is compulsory to be aware of any residual nodal disease risk. Moreover the size of lymph nodes “per se” is considered not satisfactory for the determination of presence of disease. It has been shown that also texture arrangement and nodes profile are prognostic factors for malignancy^[39,40]. However restaging lymph nodes after neoadjuvant course could also be more complex since radiotherapy has the ability to reshape and modify the size and the texture of the nodes.

In terms of nodal involvement CT has an accuracy of 82% by using a cut off of 10 mm^[37]. On the contrary, in a 5mm cut-off setting, accuracy has been reported to be 62%^[38]. In Huh series, with respect to nodal involvement, CT demonstrated a sensitivity of 56% and a specificity of 74%.

MAGNETIC RESONANCE IMAGING

MRI currently plays a crucial role in the primary staging of rectal cancer by leading the therapeutic management. MRI shows high accuracy in the assessment of CRM and sphincter invasion assessment^[3-4,41-43], and high resolution T2 weighted images are considered the standard sequences to evaluate rectal cancer^[44,45].

However, when it comes to restage rectal cancer, MRI utility remains debatable. Several Authors have reported a reduction of its accuracy after neoadjuvant regimen^[46,47]. Accuracy in predicting rectal wall invasion is 50% (sensitivity, 100%; specificity 35%) and nodal involvement is 65%^[48]. Prediction of CRM is reported to be 66%-85%^[37,43].

The disappointing accuracy of MRI imaging in restaging rectal cancer is due both to overstaging and understaging^[48]. Typically, overstaging, in the assessment of rectal wall invasion, occurs because after radiotherapy the responding tumors can be replaced by fibrosis, inflammatory and vascular proliferation^[7,48]. This often results in overstaging T1 or T2 tumors^[46,47] because tumors are surrounded by diffuse hypointense tissue infiltration^[48] and the thickness caused by fibrosis is overestimated by MRI. Another common cause of overstaging is radio-induced ulceration or proctitis^[48]. Understaging is usually due to the inability to detect a small residual tumor overwhelmed

by fibrotic tissue^[46,47]. To overcome this issue, Kim *et al*^[48] suggested that comparison of both pre- and post neoadjuvant course should be mandatory to improve the accuracy of MRI restaging. Position, extension, and signal intensity of the tumor are to be considered the key points to compare MRI images before and after neoadjuvant course^[48]. Measurement of tumor size by three dimensional MR volumetry can be effective to establish tumor downsizing and it has shown good correlation with ypT stage after neoadjuvant regimen^[49,50]. Perfusion MRI imaging is able to determine tumor vascularization which reflects aggressiveness of the tumor. The microcirculation enhancement could suggest an increased tumor angiogenicity. Thus this technique is reported to be effective in predict tumor response to neoadjuvant course^[51-53]. Moreover, in diffusion weighted MRI, apparent diffusion coefficient (ADC) could be a useful parameter to predict responsiveness of tumor to neoadjuvant treatment. ADC reduction has been associated to cell apoptosis and increased response to radiotherapy^[54,55]. It is crucial also to consider that some histological types of adenocarcinoma have different behavior under CRT and different appearance at MRI. For instance, mucinous adenocarcinoma is more aggressive than usual adenocarcinoma and its typical feature is the production of mucin. This histological type is considered poor responder to neoadjuvant and, noteworthy, the great amount of mucin leads to misinterpretation of MRI imaging^[56] because of its high signal intensity on T2 weighted images^[48,57].

Nodal staging by MRI usually relies on size criteria. Typically a lymph node is considered malignant when its short axis measure over 0.5 cm^[58,59]. It has been reported that also the examination of imaging features such as undefined edges, dissimilar signal enhancement within the node could increase the accuracy of MRI^[39,60]. Nonetheless, due to fibrosis, undefined borders might be detected after chemoradiotherapy in negative nodes^[48]. Therefore lymph nodes restaging often results in overstaging because, usually, alteration of nodes structure after radiotherapy is associated with tumor invasion^[46,47]. New promising strategies using lymph node specific paramagnetic nanoparticles have been reported to increase the accuracy in detecting micro metastasis^[61-63].

PET

Positron emission tomography using ¹⁸F-fluoro-2'-deoxy-D-glucose (FDG-PET) is a diagnostic modality that visualizes the cellular glucose metabolism; it exploits the enhanced glycolysis in tumor cells to distinguish cancer from surrounding tissue with normal metabolic activity. Nowadays functional PET images are coupled with anatomical computed tomography scan so that PET/CT is normally employed for better tumor localization and improvement of diagnostic accuracy^[64,65].

PET/CT has been used as noninvasive tool in rectal cancer patients, after neoadjuvant CRT, to detect metabolic activity in the residual tumor and to assess change induced by the treatment^[66,67]. There is however lack of

uniformly regarding several issues: time interval between end of treatment and examination, parameters used to evaluate tumor response, and criteria to define and measure response.

Radiotherapy and chemotherapy cause tissue inflammation with accumulation of FDG uptake^[68,69], since this reaction may last up to several months from the end of treatment, the choice of the time interval to perform the examination is of crucial importance. In addition radiotherapy and chemotherapy can produce a confounding effects called “stunning” a reversible phenomenon characterized by temporarily decrease of glucose metabolisms in viable tumor cells, lasting several weeks. Although the optimal time for the acquisition of PET images has not been established, the control is performed by most authors after 4-6 wk from the end of CRT; it seems that earlier restaging could underestimate tumor response^[70].

Different parameters can be used to evaluate tumor response: maximum standardized uptake value (SUV_{max}), absolute difference (Δ SUV_{max}), mean standardized uptake value (SUV_{mean}), percent SUV max difference (response index RI), and change in total lesion glycolysis (γ TLG). Depending on the adopted criteria sensitivity and specificity may vary widely. Moreover different cut off value are reported for each parameter producing different diagnostic accuracy. In the majority of the studies the evaluated end point is response to treatment, in relation to regression in T stage or TRG (tumor regression grade). It is important to underline that, for the reasons previously mentioned, and for the limited spatial resolution of PET, that ranges between a 0.4- and 1.0-cm^[71-74], it is almost impossible to distinguish major to complete pathological response and therefore to find out γ T0N0 tumors. Sensitivity and specificity of FDG-Pet in predicting response, irrespectively from criteria and cut off value, range between 45%-84.5% and 79%-81%^[73,75-79]. Few authors evaluated the relation between PET and complete pathological response. In the series of Cho *et al*^[64] 18F-FDG PET/CT correctly predicted three of the four patients with a pathologic complete response after preoperative CRT. While the only patient with complete response at histopathology was correctly detected by visual FDG-PET analysis by Denecke *et al*^[80].

In conclusion although FDG-PET can be considered a promising tool to assess metabolic response after neo-adjuvant treatment and to recognize patients more prone to respond to radio chemotherapy from non responders, its role in defining complete response to tailor the therapy is far to be reached.

CONCLUSION

Neoadjuvant course is effective in producing downstaging and downsizing of locally advanced rectal tumor. Tumor response to such treatment has been significantly associated with improved outcome after surgical resection^[81,82].

Enthusiasm about these findings has drove inves-

tigators to sphincter preserving and organ sparing surgery^[83,84]. In this setting, trans-anal resection of partial responder tumor with negative lymph node assessment by pelvic imaging could be considered as paradigm organ sparing resection.

Moreover the effects of cytoreduction, provided by multimodality treatment, can produce complete clinical response (absence of clinically detectable tumor) or complete pathological response (absence of viable tumor cells at pathology examination after cancer resection) in up to 30% of patients^[5,23,85-87]. Given that rectal resection is related to significant morbidity, several authors have recommended careful “wait and see strategy” in clinical complete response cases^[13,88-90]. In this setting rectal cancer restaging after multimodality treatment has been claimed to provide adjustment of the surgical conduct.

Current imaging techniques have been reported to be highly accurate in the primary staging of rectal cancer. On the other hand, radiotherapy and chemotherapy course produce deep modifications on cancer tissue and on surrounding structures. As a result, when used to restage rectal cancer after CRT, the same imaging techniques produce inconstant results. Indeed pathological T stage and lymph nodes status prediction has been shown to be far less inaccurate when compared to primary staging.

Overstaging is a basic issue of current imaging modality. The overstaging is commonly due to the inability of distinguish residual tumor from radio-induced desmoplastic reaction and overgrowth fibrosis in the surrounding tissue. False positive diagnosis can clearly lead to over treat patients that indeed could take advantage of organ sparing surgery such as local excision for γ T1 N0 tumors. Moreover this possibility could be considered for high surgical risk patients thus avoiding morbidity and mortality of rectal resection.

On the contrary, understaging could lead to consider local excision in patients with occult mesorectal positive lymph node, thus producing a non-oncological resection with consequent reduction of survival. Furthermore it has been reported that, after radiotherapy, local recurrence could be more aggressive than native tumor and the situation could be more concerning when leaving untreated patients with complete response without surgically removing the site of the tumor^[91].

However, Habr-Gama *et al*^[13] found no significant difference in terms of survival and disease free rate when comparing patients with complete clinical response undergoing “wait and see policy” and patients with histologically proven complete response after surgery. Interestingly this group, when assessing complete pathological response, mainly relies on direct endoscopic visualization of rectal mucosa and uses additional radiological studies only in case of recurrence suspicion^[24].

Although currently available imaging techniques display an overall low accuracy in restaging rectal cancer, CT scan and MRI are efficient in excluding tumor extent to adjacent organs (T4 tumor) and CRM invasion^[37].

Clear assessment of lymph node status should be provided when considering local tumor excision due to the risk of leaving positive mesorectal nodes. Prediction of lymph node positivity is reported to be still poor. Moreover there is no consensus about the standard criteria to define lymph nodes positivity. It is clear that the size measurement only is not reliable and analysis of nodal contour, shape and structure has to be considered to improve the accuracy of restaging.

In conclusion modern imaging techniques are unreliable in restaging rectal cancer after CRT given the low correspondence between pathological status prediction and actual pathological assessment. In our opinion imaging evaluation patterns are to be reexamined to reduce the false positive and false negative percentage and to broaden diagnostic accuracy.

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