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REVIEW

Multidisciplinary treatment of rectal cancer in 2014: Where are we going?

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Abstract

In the present review we discuss the recent developments and future directions in the multimodal treatment of locally advanced rectal cancer, with respect to staging and re-staging modalities, to the current role of neoadjuvant chemo-radiation and to the conservative and more limited surgical approaches based on tumour response after neoadjuvant combined therapy. When initial tumor staging is considered a high accuracy has been reported for T pre-treatment staging, while preoperative lymph node mapping is still suboptimal. With respect to tumour re-staging, all the current available modalities still present a limited accuracy, in particular in defining a complete response. The role of short *vs* long-course radiotherapy regimens as well as the optimal time of surgery are still unclear and under investigation by means of ongoing randomized trials. Observational management or local excision following tumour complete response are promising alternatives to total mesorectal excision, but need further evaluation, and their use outside of a clinical trial is not recommended. The preoperative selection of patients who will benefit from neoadjuvant radiotherapy or not, as well as the proper identification of a clinical complete tumour response after combined treatment modalities,will influence the future directions in the treatment of locally advanced rectal cancer.

Key words: Rectal cancer; Cancer staging; Cancer re-staging; Neoadjuvant chemoradiation; Response; Treatment; Local control; Local excision; Complete pathologic response; Rectal cancer surgery

Core tip: There is a growing interest in the possibility of the preoperative identification of locally advanced rectal cancer patients who will or will not benefit from a preoperative chemoradiotherapy. This review evaluates the role of current available imaging techniques in this decision process and critically analyzes the results and future scenarios of the more limited surgical or observational approaches. In particular, the new trends following a pathologic complete response (*i.e.*, local excision, wait and see approach) are discussed on the basis of randomized trials and meta-analyses which form the basis for present treatment recommendations.

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INTRODUCTION

The treatment of rectal cancer has dramatically changed over time. Evidence exists from literature that up to 70% of patients with non metastatic rectal cancer present themselves as T3 or node positive rectal cancer[1]. This finding implies that major efforts should be directed in the cure of advanced rectal cancer. Current strategies in the management of rectal cancer are moving toward a tailored approach which is based on preoperative staging results, in their accuracy in re-staging the patient, determining how the patients have responded to the therapy,

and thus having a pivotal role in the selection of the different therapeutical options that could be potentially offered to a patient with locally advanced rectal cancer[2-7]. This is extremely fascinating since it represents the result of continuous research in rectal cancer biology, preoperative staging, surgical strategies including laparoscopic approach of rectal cancer and trans-anal surgery. The main progress in rectal cancer treatment, however is represented by the understanding that the overall five-year survival improvement which has been reported in the last two decades, could be only sustained by a multimodal therapy approach. This term means an interdisciplinary cooperation between surgeons, oncologists, radiologists and radiotherapists.

The present paper is directed to evaluate the state of the art in the multidisciplinary treatment of locally advanced rectal cancer and to evaluate which are the possible future scenarios in the treatment of locally advanced rectal cancer.

RECTAL CANCER STAGING

Preoperative staging is a crucial step in the multidisciplinary approach to rectal cancer, and it could be considered the base for a tailored approach to the tumour. The decision to submit a patient to preoperative chemoradiation (CRT) is mainly based on staging. Other factors include tumour histology, location, patient's morbidity, patient's age and medical diseases. Digital rectal examination, widely used in the past, for primary staging, can give information about the fixation of the tumour, sphincter involvement, distance from anorectal ring as well as to the size of the tumour, however it has a limited accuracy in establishing the depth of invasion which is approximately 65%[8].

The most common imaging modalities currently used in preoperative staging of rectal cancer are endorectal ultrasound (ERUS), magnetic resonance imaging (MRI) positron emission tomography (PET) scan and computed tomography (CT). This latter imaging technique however is mainly used to rule-out the presence of systemic metastasis, and it will be not discussed in the present review.

Pre-operative staging

ERUS: Data emerging from recent meta-analyses and cohort studies, showed that ERUS has an overall accuracy for T staging which ranges from 80% to 95%. In particular, the highest accuracy and specificity have been observed in the evaluation of early rectal cancer and in the assessment of tumour extent into the layers of rectal wall[9-14].

With respect to nodal staging, ERUS is less accurate, tends to overstage the patients with a reported overall sensitivity and specificity of 55% and 78%, respectively[10,11]. In particular data from a recent meta-analysis including 35 studies reported a pooled sensitivity and specificity of about 75%[14]. The sole size criteria used in the past for pathological node identification (*i.e.*, nodule of 10 mm or larger are certainly malignant) could be partially responsible for this wide variability in results. Wang *et al*[15] demonstrated that the majority of involved nodes following rectal cancer surgery has a diameter smaller than 5 mm and thus other factors are now considered in the determination of the nature of the nodule, such as roundness, border irregularity and hypoechoic nature. Even with these improvements, an overall false negative rate of 20% has been recently reported by Beets in a review article on this issue[16]. Other factors are potentially responsible for the reported wide variability in staging accuracy of ERUS: different probes, different professional figures (radiologist, gastroenterologist, colorectal surgeon performing the examination) and long learning curve[9,17,18]. Moreover an operator dependence has been reported with an inter-observer variation of 10% to 15% for T staging[10].

MRI: MRI has been demonstrated to be superior in imaging of the more advanced tumours, when compared to ERUS[16,19-22]. Moreover, another advantage of MRI, when compared to ERUS is the relatively small learning curve for the interpretation of the images, which could be more easily interpreted by other radiologists and clinicians[16,19]. This finding is of pivotal role when considering the multidisciplinary approach to rectal cancer. The main advantages of MRI have been reported to its ability in the identification of the mesorectal fascia, in particular in the threatened circumferential margin (CRM), while other diagnostic tools have showed low to intermediate accuracy in the evaluation of tumour penetration and involvement of the mesorectal fascia[19,23,24]. This correlates to its high accuracy in the preoperative identification of patients at risk of incomplete surgical excision[11,16,19,24,25].

Data from the multicenter, multinational MERCURY study group have demonstrated that MRI has an accuracy of 91% in predicting a clear CRM[26]. Recently, a meta-analysis on the same issue, reported figures in term of specificity in the prediction of an involved CRM ranging between 73% and 100% confirming the high accuracy of MRI in predicting CRM involvement[27]. Prognostic MRI features also include cancer less than 5 mm beyond the muscularis propria, mesorectal fascia more than 1 mm from the advancing edge of the tumour and absence of extramural vascular invasion. These features have been recently proposed to select patients who potentially do not need preoperative CRT[28]. Using these criteria, patients who underwent surgery alone had a local recurrence rate of 3% and a 5-year survival rate of 85%[29]. Phased-array MRI represents a step forward, in particular when an accurate assessment of tumor encroachment of the CRM is needed[25].

Current guidelines indicate pelvic phased-array coil as the most reliable tool in order to provide the most detailed depiction of the rectal wall and surrounding structures[24,30,31]. On the other hand, despite the continuous improvement in MRI technology, the use of new morphologic and signal-related criteria for lymph-node evaluation[32] and the introduction of lymph-nodes specific

MRI contrast agents, such as nano-paramagnetic particles of iron oxide[33], the accuracy of MRI in the preoperative identification of pathological lymph-nodes is still unreliable. Beaumont in a recent review of the role of MRI on rectal cancer staging has reported an overall accuracy of 69% and a sensitivity of 77% in the pathological lymph-node preoperative evaluation[24].

Positron emission tomography-CT scan: Positron emission tomography (PET)-CT scan has been recently proposed to be added to MRI for initial rectal cancer staging. However its role in T staging is low, due to its relatively low spatial resolution that ranges between a 0.4 and 1.0 cm and poor anatomical details[34]. The aforementionded limits also apply in the research of lymph-nodes micrometastases. Recent reports show that the accuracy of FDG-PET-CT in the evaluation of lymph-nodes is similar to the one of MRI with a reported sensitivity of 72%, and a specificity of 95%[34-37]. Nevertheless, FDG PET/CT maintains a consolidated role in M staging for rectal cancer and in detecting lymph-node at distant site, especially in the paraortic nodes[34,35]. Some reports have shown FDG PET/CT to detect 30% more distant lesions compared with CT scan, mainly in liver and lungs[11,37,38].

Re-staging modalities

As seen for the primary staging of the tumor, the accuracy in the restaging process after CRT is of paramount importance when deciding in favour of a more limited surgical procedure or when a non operative approach is contemplated. Both these new trends, in fact, are contemplated in case of extensive tumor response.

ERUS: With respect to ypT stage, ERUS shows an accuracy which varies between 27% to 72% with a high tendency to overstage the patient[39,40]. Figures within 0% to 60% have been variously reported when the accuracy to correctly diagnose a T0 is considered[39,41-44]. This low accuracy has been attributed to the difficulties in discriminating cancerous mass from desmoplastic reaction, peritumoral vasculopathy and radio-induced overgrowth fibrosis. This latter feature is particular difficult to differentiate at ultrasound for its hypoechoic pattern[45].

Better results have been reported when lymph nodal involvement restaging is considered, with figures ranging between 39% and 83%, resulting in a mean value of 70%[38,39,42,44]. For this parameter, overstaging was only slightly more common than understaging (8%-39% *vs* 11%-28%) as emerged in a recent review on this issue[43]. A higher diagnostic accuracy in N staging has been reported when patients were re-evaluated after 7 wk from the completion of CRT, compared to the 4-6 wk used by the majority of the authors, probably due to a reduction in the radio-induced fibrosis[46].

With respect to the accuracy in predicting a pathologic complete response (PCR), figures in term of accuracy ranging between 0% and 50% have been reported by means of small series and cohort studies[43,45-47].

MRI: The role of MRI in the restaging process is still sub-optimal[48,49]. A recent paper evaluating data from 5 institutional prospectively-maintained database demonstrated, using a sophisticated statistical method, the poor accuracy of MRI in predicting ypT, ypN, as well as the inability to predict a PCR or to discriminate a T4 disease[50]. Kim *et al*[51] reported an accuracy of 50% and 65% for rectal wall invasion and nodal involvement, respectively. Moreover, data from an Italian study, reported an accuracy in correctly identifying a ypT0 after neo-adjuvant therapy of 77% and of 65% for ypN0[52]. Radio-induced fibrosis, ulceration and proctitis might be responsible of this lack of accuracy[41,51,52]. This is particularly true for lymph-nodes restaging in which fibrosis makes it difficult to differentiate a metastatic lymph node and irradiated lymph node changes. In particular, a change in a lymph node with or without metastasis after neoadjuvant CRT is assumed to be associated with metastasis, resulting in lymph node overstaging[51]. The technical evolution of the MRI imaging with the introduction of the diffusion weighted MRI, perfusion MRI, lymph-nodes specific MRI contrast agents, seems to improve the accuracy of the imaging technique, in particular in the proper identification of a T0 lesion, however more data are needed to validate the role of these new imaging modalities[33,53-55]. Nevertheless, the actual prediction of a complete pathologic response is within the range of 66% to 85%[51,56,57].

PET: Concerning the role of PET in tumour response to therapy, some authors have suggested the complementary role of these imaging techniques to the most used MRI, CT scan and ERUS[34,58]. A growing interest among the scientific community in the potentiality of FDG PET/CT in evaluating the response of neoadjuvant therapy in rectal cancer has been reported, due to the promising results of the technique[59]. However, there is an urgent need for the standardization of the criteria used to measure the response[34,60]. Results, from recent reports, in fact, showed a wide range of values in term of sensitivity and specificity of FDG-PET in predicting a response after neoadjuvant therapy, which varies from 45% to 100% and from 59% to 96%, respectively. These results are related to different time-intervals in which the response is evaluated, different cut-off values and criteria used to define the response[34,59-62]. Moreover, with respect to the relation between PET and PCR, controversial results have been reported using 18-FDG-PET/CT[60,63-65]. These findings should be ascribed to the limit of the FDG PET/CT which has a spatial resolution of 5 mm, and it is not able to detect small cluster of cells, potentially limiting at present time its role in the prediction of complete response following CRT.

Conclusion: Staging rectal cancer

In Table 1 are summarized the pro and cons of each imaging technique in the staging and restaging process of

Table 1 Pro and cons of each imaging technique in the staging/restaging process

	Staging		Restaging	
	Pro	Cons	Pro	Cons
ERUS	High accuracy and specificity for early rectal cancer (T)	Tends to overstage N Operator dependent Long learning curve	High accuracy for persistent lymph nodal involvement	Low accuracy for T restage
MRI	Ability to evaluate CRM Best tool to select patients for neoadjuvant treatment High accuracy in advanced tumors	Low accuracy for lymph-nodes involvement	Good prediction for CRM involvement	Poor accuracy in predicting ypT0 and ypN0
PET	Confirmation of M and N at distant sites	Low accuracy for T staging	Detection of progression at distant sites	Lack of standardization of the criteria used to assess the response

MRI: Magnetic resonance imaging; ERUS: Endorectal ultrasound; PET: Positron emission tomography; CRM: Circumferential margin.

rectal cancer. An high accuracy has been reported for T staging using ERUS and MRI, while, despite the continuous technical progress in preoperative staging, preoperative lymph node mapping is still suboptimal with a false negative rate of 20%. PET scan is a promising imaging tool, but more data are needed to confirm its accuracy. With respect to the restaging process of rectal cancer following neo-adjuvant chemo- or radio-therapy (CT-RT), all the current available modalities still present limited accuracy, in particular when an accurate definition of clinical complete response is required.

In our opinion, the complementariness of these diagnostic tools should be kept in mind by the multidisciplinary team to obtain the most reliable information on the state of the tumour.

CURRENT ROLE OF PREOPERATIVE CT-RT

The current standard protocol in United States and Europe in patients with locally advanced cancer (T3, or any N1) is neo-adjuvant combined modality therapy (chemotherapy plus radiotherapy) prior to surgery[2,4-7,66,67]. Different randomized studies with high level of evidence were responsible for the adoption of this consolidated strategy[68-72].

The German CAO/ARO/AIO-94 trial, the Dutch TME trial, the MRC CR0//NCIC-CTG-C016 all demonstrated in patients who underwent preoperative CT/RT, a significantly lower local recurrence (LR) rate, a decreased toxicity, and increased sphincter preservation rate when compared with patients who underwent postoperative chemotherapy or surgery alone, while no significant difference was observed with respect to overall survival rate[68-70]. In contrast, data coming from another randomized controlled trial (RCT) trial, in which 240 patients with locally advanced cancer were enrolled, showed no difference in term of acute and late toxicity between preoperative and postoperative CRT, while a higher rate of sphincter preservation has been reported in patients who underwent preoperative CT (68% *vs* 42%)[72].

Sphincer preservation seems to have increased over time in the last 15 years. However, the role of preoperative CRT in decreasing the rate of abdomino-perineal amputation of the rectum (APE), thus resulting in an increased rate of sphincter preservation is still unclear and debatable. This issue has been recently addressed by Gerard *et al*[73] who analyzed the results of 17 trials randomizing close to 10800 patients. In this elegant analysis, none of the studies tested was able to demonstrate a beneficial effect of neo-adjuvant treatment on the rate of sphincter preservation. Other factors, such as the acceptance of progressive smaller distal margins, advances in surgical technology such as staplers, improvement in surgical techniques as inter-sphincteric resection could be responsible for the observed increased sphincter-saving reported by literature[7,74,75]. Another controversial issue is the role of neoadjuvant CT-RT in the management of unresectable rectal cancer (*i.e.*, palpably fixed lesion involving adjacent organ or structures, not amenable for primary surgical resection) which represented 15% of all rectal cancer at presentation. Chemoradiation aims for tumor shrinkage to allow radical resection. Two RCT trials demonstrated a higher resectability rate when chemoradiation was compared to radiation alone with figures in the range of 80%-85% for CRT *vs* 68%-75% for RT alone[76,77]. Moreover, the effect of boosted radiotherapy alone *vs* conventional neoadjuvant CRT on resectability has been recently evaluated by Engineer *et al*[78] in another RCT trial in which 90 patients with advanced or unresectable rectal cancer were included. Escalated radiation dose was not associated to a higher resectability rate, while it resulted in an increased wound infection and delayed wound healing. On the other hand preoperative short-course radiation could represent a valid alternative to CRT in elderly patients with primary unresectable rectal cancer unfit for preoperative chemotherapy due to severe co-morbidities[79].

The importance of adding chemotherapy to preoperative radiation was stressed in EORTC RCT trial published in 2006 (European Organization for Research and Treatment of Cancer). More than 1000 patients with locally advanced rectal cancer were recruited. A significant reduction of local recurrence from 17.1% to 8.7% was observed when chemotherapy was preoperatively added to 45 Gray (Gy) radiation delivered over 25 fractions[80]. The current recommended chemotherapeutic agent to use with preoperative radiation is capecitabine[81]. At

present time there is no consensus on which preoperative CRT scheme should be used; short or long-course CRT. Long-course scheme (LCRTCT) is the treatment of choice in North America and Canada[66]. In Europe, the scheme used to deliver preoperative CRT varies from country to country and different recommendations come from a panel of experts representing the most important European societies[82]. A moderate consensus to use short-course regimen (SCRT) was achieved for cT3 any NM0 disease. Agreement was reached on either SCRT followed by immediate surgery or LCRTCT with delayed surgery in patients with no CRM involvement. Moreover in patients not candidate for chemotherapy, SCRT with delayed surgery is an option/alternative. LCRTCT was recommended in patients with CRM involvement at presentations and in any cT4 any NM0. In this decision process, MRI prognostic features play a key role, in particular in the assessment of CRM involvement[67,82,83].

The main advantages of LCCRT over SCRT are tumour regression and downsizing as reported in the Polish and Trans-Tasman Group RCT trials which compare the two schemes[84,85]. In the Polish trial, a 16% complete pathologic response was reported for LCCRT, while it was 1% in the SCRT. Similar results were reported by the Trans-Tasman Group trial (15% *vs* 1% CR). No statistical difference was observed with respect of local recurrence and overall survival rate and late toxicity in both studies. A better downstaging response after long-course CRT when compared to short-course was also observed when a 6 wk interval to surgery was considered[86,87]. Data coming from the ongoing Stockholm Ⅲ trial will further clarify this issue. In this trial, three different randomization arms are considered; LCRT without concomitant chemotherapy, SCRT with immediate surgery or SCRT with surgery delayed for up to 8 wk in order to assess which treatment arm is more favourable in term of tumour regression, local recurrence rate and reduced toxicity[88]. An interim analysis of the Stockholm Ⅲ trial recently published, showed a close to 10% PCR rate, when SCRT followed by delayed surgery was considered, while figures of 0.4% and 2% were reported, in case of SCRT followed by immediate surgery and LCRT alone, respectively. Moreover SCRT followed by immediate surgery resulted in a higher complication rate when compared to the other treatment arms[88,89]. The use of SCRT and delayed surgery (6-8 wk after the completion of the treatment) has been recently proposed in patients with non resectable rectal cancer (synchronous/distant metastases) with contraindication to long-course CRT. These are patients in whom tumour regression and downsizing would not improve resection or sphincter preservation[90]. The results from this small series including 46 patients, show that delayed surgery was performed in all but nine patients, and that a complete pathologic response was obtained in 8.7% of the patients. The SCRT was well tolerated in the majority of the patients. Only one patients died due to sepsis with fever and neutropenia.

SELECTIVE USE OF PREOPERATIVE RADIATION

The well-recognized benefits of RT or CRT, in term of reduced local recurrence, increase rate of sphincter saving procedures, however need to be balanced against the risk of increased faecal incontinence, genitourinary disorders, impaired sexual function and bowel disorders[14]. Moreover, there is evidence in literature that TME surgery alone in the absence of preoperative radiation leads to local recurrence rates less than 10% and in a overall survival rate equivalent to preoperative radiation plus total mesorectal excision of the rectum (TME)[71,85,91].

Based on these results, several authors have focused their efforts to better identify the patients who are at low risk of local recurrence, and ideally may not benefit from neoadjuvant therapy[58,92,93].

Data from a Spanish institutional retrospective series on a population of 152 consecutive preoperatively stage Ⅱ or Ⅲ rectal cancer patients who underwent surgery alone, identified threatened mesorectal fascia at preoperative staging as the only independent preoperative factor associated with a significantly higher risk of local recurrence with a median follow-up of 39 mo[94]. This prognostic role of CRM was also confirmed by a Natgegaal and Quirke[95] on more than 17500 rectal cancer patient. Moreover data coming from NCRI colorectal cancer study group on 1156 patients identified the histological involvement of the circumferential margin as a powerful predictor of local recurrence, distant metastasis and survival rate[96]. On the basis of this evidence, it has been advocated the crucial role of CRM in the preoperative assessment of rectal cancer, in the light of neoadjuvant treatment, also suggesting that its assessment is more informative in treatment planning than the T stage[96-100]. Guidelines from an European consensus conference on rectal cancer, suggest that surgery alone is indicate in the early cT3N0 in presence of a clear circumferential margin assessed by MRI, unless the tumour is located at the level of the levators[67,82]. More recently, in a prospective single centre study, in presence of a good-quality TME, radiotherapy has been reserved only in patients with threatened or involved mesorectal margin irrespectively of the nodal status, with no adverse effect on local recurrence[99]. Guidelines from ESMO and EURECCA collaborative group proposed to sub-categorize rectal tumours in different subgroups (favourable, intermediate "bad group", advanced "ugly group") based on MRI findings in order to define the extent of surgery and whether neo-adjuvant CRT is required[101,102].

In summary, a predicted clear CRM as well as the other prognostic MRI features proposed by Heald *et al*[28] and stressed by others[25,29,30,67] already mentioned in this review (*i.e.*, absence of vascular invasion, upper third rectal cancer, absence of extramesorectal lymph-adenopathy, absence of neural or vascular invasion) seem to be able to identify patients at low risk, who will potentially not

beneficiate of preoperative radio and chemo-therapy. However, large randomized studies with high level of evidence are needed to implement this strategy.

Conclusion: Current role of preoperative CT-RT

According to these findings, one option could be to give neo-adjuvant therapy in the majority of patients, irrespective from their nodal status, leading to an overtreatment and its related consequences. The other future scenario is to reserve preoperative CRT only to patients with threatened CRM. This strategy should be indicated only by weighting the risk of unnecessary treatment against the possibility that these patients would ultimately require postoperative chemo-radiation which has a higher toxicity and it is less effective in term of local control when compared to preoperative CRT. However, this hypothesis is still awaiting, since more RCT trials and long-term follow-up studies are needed.

Which strategy following neo-adjuvant therapy

Current guidelines from the American Society of Colorectal surgeons indicate that radical surgery by means of TME with or without sphincter saving or partial TME depending on tumour localization should be offered to all patients following neoadjuvant treatment[66]. However, in light of the significant response rate that can be achieved with preoperative therapy, we have to consider and critically analyze the current role and implications of the new strategies proposed.

The benefits of neoadjuvant CRT have been well documented and include, among the others, tumour downstaging and tumour sterilization (*i.e.*, pathologic complete response) defined as the absence of cancer cells on histological examination in the resected specimen following radical surgery. PCR has been reported in 8%-40% of the patients either in phase Ⅱ/Ⅲ trials as well as in non-randomized trials as emerged in two recently published meta-analysis on this subject[103-105]. Different factors have been identified to influence the occurrence of PCR, such as the timing of response assessment, indicating that a longer interval between the completion of neoadjuvant therapy and surgery compared to the standard 4-6 wk adopted in the past by the surgical community, could increase the rate of PCR[106-108]. Moreover additional radiotherapy or dose escalation[109,110], novel chemotherapeutics agents and additional chemotherapy after preoperative CRT and before surgical resection have been variously documented to be able to improve PCR[104-106,110,111]. Patients who achieve a PCR have a favourable prognosis, with very low local recurrence rate (0%-1%) and 5-year survival rates greater than 95%[104,105,112-115]. Moreover there is evidence in literature that the risk of lymph-node metastases among patients with pathologic complete response is considerably low and frequently less than 5%[104,112,113,116,117]. A recent large series form Ireland, including 276 patients showed that in patients down-staged as ypT0/T1 the risk of nodal metastases was 2.3%[118]. This is in contrast with less radiosensitive tumours re-staged as ypT2-T4 in which the risk of harbouring nodal metastasis could be as high as 29%-64%[117]. According to the aforementioned findings, PCR may indicate a subset of patients associated with good outcome, but still at risk of lymph node metastasis, even low. This latter point is of crucial importance, since these patients could potentially beneficiate of a less invasive approach, avoiding a surgical procedure which is associated with a significant morbidity and long-term sequelae in term of sexual, urinary dysfunction and fecal incontinence[91,119-121]. According to these principles, a wait and watch approach has been proposed by Habr-Gama *et al*[122] from Brasil in patients in whom a clinical complete response (CCR: *i.e.*, absence of clinically detectable residual tumour) after neo-adjuvant therapy has occurred. CCR rates in the international literature range from 10.9% to 38.7% as recently reported in a review paper by Glynne-Jones *et al*[123], who evaluate the role of non operative approach after CRT in 650 patients. The Brasilian group has the largest experience on the non-operative approach to rectal cancer in patients who had a clinical complete response after neoadjuvant CRT. In their historical series published in 1998, of 118 patients with advanced low rectal cancer who underwent neoadjuvant therapy, 36 (30.8%) achieved a CCR. In these patients an observational approach was chosen with no immediate surgery, but a local recurrence which required a salvage resection occurred in 8 (27%) patients within 3 to 14 mo. Local recurrence and survival rate, however were similar to that of the patients with a PCR at surgery with a mean follow-up of 36 mo[122]. More recently published studies from the same institution, reported an early tumour regrowth (within one year) in approximately 17% of the patients[124,125]. However all the patients were amenable to salvage surgery with R0 resection, and the three-year overall and disease-free survival rate for patients with a sustained CCR was 94% and 75% respectively, with a median follow-up of 53 mo[125]. Authors from academic Institution from Holland and preliminary results from a phase Ⅱ clinical trial from England have recently reported their experience on the non operative approach to rectal cancer in patients with a complete clinical response reporting similar results in term of recurrence and overall and disease free-survival[126,127]. On the other hand, other studies, mainly of retrospective nature with inherent limitations in term of response assessment which was not standardized, reported disappointing results in term of local recurrence with figures ranging from 21% to 83% when a non-operative management following preoperative RT or CRT was considered[128,129]. The reproducibility of the results obtained by Habr-Gama *et al*[122], for the scientific community would be of fundamental importance for the wide application of a non-operative approach in patients with a clinical complete response following neoadjuvant treatment. Different variables should be considered in the interpretation of current available results. Major drawbacks are the definition of CCR which has evolved the course of published studies, in particular for

the Habr-Gama group series, the retrospective nature in the majority of published series, the absence of standardization in the methods used for determining response both in term of clinical and imaging modalities, the size of the tumour at initial evaluation, and the follow-up protocols which have been changed over time as underlined by Solanki *et al*[130] in a review paper on non operative management of rectal cancer after preoperative CRT. Another matter of criticism and caution in considering a non-operative approach, is represented by the fact that CCR does not necessarily correlate with PCR. A poor 25% to 30% concordance between clinical and pathological response has been reported by means of a large retrospective study from Memorial Sloan-Kettering Cancer Center and a review paper by Glynne-Jones in which 38 trials reporting data on complete/partial clinical response were analyzed[131,132]. Lastly, the rationale of the wait and see approach is based on an optimal restaging process following neoadjuvant treatment, but at present time, despite continuous technical advances in imaging techniques both with respect to MRI and PET-CT, restaging is still sub-optimal[33,56,57,60,63-65]. In summary, the need for a standardization both in definition of clinical complete response as well as in the follow-up procedure are of paramount importance, and only recently an expert consensus article has defined both clinical and endoscopic findings for CCR standardization that will be useful for future studies and their interpretation[133].

ROLE OF LOCAL EXCISION AFTER PREOPERATIVE CRT

Conventional TME is considered the standard of care following preoperative CRT. However, in selected patients in whom a significant tumour regression has occurred after neoadjuvant therapy, another surgical option is now represented by local excision. Moreover local excision using different surgical techniques has been recently proposed as a restaging biopsy, since both mucosal and submucosal endoscopic biopsies following CRT as well as digital examination should not be considered reliable procedures in the determination of a clinical complete response[3,39,68,134,135]. The main issue with respect to this approach, independently from the technique adopted; *i.e.*, transanal with retractors, TEM (trans-anal endoscopic approach)[136] or trans anal mini invasive surgery (TAMIS)[137] lies in the fact that only the rectal wall harbouring the tumour is removed without appropriate lymph-node dissection. Nevertheless, the rationale of proposing a local excision in patients who had a major response after CRT is based on the observation that the risk of nodal metastases depends from ypT status[62,138-140]. Different retrospective papers, small single series, have analyzed the role of local excision after major response to complete response following CRT[140-149]. In a recent pooled analysis by Borschitz *et al*[140] in which 270 patients were included, a strict correlation between local recurrence and pathological staging was reported. LR rate was 0% for ypT0 and 2% for ypT1, while for ypT2 figures between 6% and 20% were reported. According to the high recurrence rate reported in ypT2, the role of TEM in this sub-group of patients is controversial and there is no consensus on its use, at present time[116,145,146]. A recently published prospective multicenter phase Ⅱ study from Italy in which 63 patients with major clinical response after CRT were enrolled, reported a 0% LR rate after a mean follow-up time of 36 mo in the 43 patients who were ypT0 or ypT1/tumor regression grade (TRG) 2. Twenty patients resulted ypT > 2 or TRG > 3 or had positive margin following local excision; 11 underwent a TME, while 9 refused a TME. Among these latter 9 patients, a 22% LR was observed[147]. Similarly, another surgical group from Italy, found no local recurrence rate or distant metastases in patients in whom a PCR has occurred[148]. The interpretation of these data, however, needs some caution due to heterogeneity in staging as well in neoadjuvant regimens, to the inclusion of patients with high-co-morbidities or unfit for major surgery. Moreover, median follow-up times in the majority of published series, ranged from 19 to 56 mo[140]. This follow-up period has to be considered relatively short, since it has been demonstrated that pelvic recurrence following local excision may occur even after 5 years[146,147]. Finally, not in all studies, a sub-categorization of ypT1, ypT2 (*i.e.*, G1-2, *vs* G3, absence *vs* presence of lymphovascular invasion) has been reported[140]. The presence of lymphovascular invasion, as well as a poor tumour differentiation are well-known prognostic factors for risk of nodal metastases after neoadjuvant chemotherapy followed by TME and local excision and should be taken into account when considering a trans-anal excision[115,118,150]. Another matter of debate is the fact that local excision following radiotherapy increases postoperative morbidity in particular wound dehiscence[142,149]. Perez *et al*[145] comparing patients having CRT and TEM *vs* TEM alone, reported a 70% wound dehiscence in patients who underwent CRT and TEM *vs* 23% in patients who underwent TEM alone. A significant higher 30-d readmission rate was also reported in the same series, in the CRT plus TEM *vs* TEM alone (43% *vs* 7%, $P = 0.02$). A higher wound complication rate in the CRT plus TEM was also reported by others[143]. However in the majority of cases, they were treated conservatively as outpatients. Moreover, preliminary data from ACOSOG Z6041 trial also showed that preoperative CRT followed by local excision either by conventional transanal technique or TEM resulted in a persistent anal pain in 9% of the patients[151]. TEM excision can cause alteration or disruption of the surgical planes, resulting in a high risk of APE when a salvage or radical surgery is considered[152-154]. The true morbidity of TEM, postoperative quality of life as well as the risk of APE in case of salvage surgery need further investigation. The current CARTS (chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing trans-anal endoscopic microsurgery) multicentric trial still ongoing will probably further clarify this issue[155].

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