REVIEW

Assessment of clinical and pathological complete response after neoadjuvant chemoradiotherapy in rectal adenocarcinoma and its therapeutic implications

SORIN TIBERIU ALEXANDRESCU[1], ADRIAN VASILE DUMITRU[2], RUXANDRA DOINA BABIUC[3], RADU VIRGIL COSTEA[1]

[1]Department of General Surgery, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2]Department of Morphological Sciences, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[3]Department of Internal Medicine I – Gastroenterology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Because almost one fourth of patients with rectal adenocarcinoma (RC) achieve pathological complete response (pCR) after neoadjuvant chemoradiation therapy (CRT), having significantly higher survival rates than those without pCR, the assessment of pCR represents a highly important challenge nowadays. Moreover, recent studies revealed that organ-sparing approaches could represent a reasonable alternative to radical surgery (RS) in patients with pCR, achieving similar long-term outcomes with lower morbidity rates and improved quality of life. Unfortunately, the decision of a rectum-sparing approach should be based only on clinical, endoscopic (with or without biopsy) and radiological methods, that must accurately predict the pCR after neoadjuvant CRT, in the absence of the pathological examination of the RS specimen. Thus, a surrogate parameter called clinical complete response (cCR) emerged, to assess the results of neoadjuvant CRT. The evolving accuracy of recent endoscopic and imaging methods in assessment of cCR and their predictive value for estimation of pCR achievement are presented. The usefulness of combining the results of these evaluation methods (resulting in the development of few nomograms) for a more accurate estimation of pCR, as well as the predictive factors for pCR achievement are also debated. Moreover, the changing landscape of therapeutic approaches based on cCR assessment is discussed, emphasizing the advantages and pitfalls of rectum-sparing approaches, compared to RS. Because there are no reliable methods to estimate with 100% accuracy the pCR, the only way to decrease as much as possible the risk of misleading treatment choices is the multidisciplinary team-based decision.

Keywords: rectal cancer, complete response, neoadjuvant chemoradiation therapy, local excision.

⊟ Introduction

Since the late '70s, rectal resection with total mesorectal excision (TME) became the standard surgical approach to rectal carcinomas (RCs) [1]. Even this surgical approach decreased the five-year local recurrence rates (LRRs) from 12–20% [2] to 8.5% in the series operated by Heald *et al.* between 1978 and 1987 [3], further decrease in the five-year LRR (3%) was achieved by the same authors between 1988 and 1997, probably due to the extent use of pre-operative radiotherapy (RT) [3]. Moreover, in 1999, Vauthey *et al.* revealed that the addition of chemotherapy to pre-operative RT significantly improved overall survival (OS) in patients operated for locally advanced rectal cancer (LARC) [4], although LRR was not influenced by the use of neoadjuvant chemotherapy. Moreover, a recent study revealed that the addition of chemotherapy to neoadjuvant RT was an independent predictor for better progression free survival in patients with cT1-2N0M0 RC [5]. Correspondingly, preoperative chemoradiation therapy (CRT) was able to induce down-staging of RC in 50–60% of patients [6–10] with LARC, leading to a significantly higher rate of sphincter-preserving operations [4].

In a series of 231 patients with cT1-2N0M0 distal RC treated by definitive RT or CRT, 135 (58.4%) patients experienced macroscopical disappearance of rectal tumor, so-called clinical complete response (cCR) (76.1% in cT1N0 patients and 51.2% in cT2N0 patients) [5]. Furthermore, neoadjuvant CRT determined a cCR in up to 26.8% of cT2-4N0-2M0 patients [8]. Moreover, among patients with incomplete clinical response, an additional pathological complete response (pCR) was observed in 8.3–16.6% of patients who underwent radical surgery (RS) with TME after neoadjuvant CRT [8, 11]. The OS rates achieved by surgical resection in patients with pCR were significantly higher than those observed in patients without pCR [6, 12]. These observations raised the question whether RS could be avoided in good responders (cCR/pCR) to neoadjuvant CRT, and which are the most appropriate selection criteria for treatment allocation. Thus, the accuracy of different diagnostic modalities to assess pCR is crucial to identify those patients who are most likely benefiting from organ-sparing approaches. Prognostic factors associated with pCR, as well as the influence of various types of neoadjuvant therapy on pCR rates are presented. Furthermore, alternative strategies to RS are discussed, reporting also their results and future modalities to improve both the short-term and long-term outcomes.

⊟ Definition and assessment of complete response

pCR represents the absence of malignant cells on the specimen of rectal resection in patients who were previously treated with neoadjuvant CRT. In most studies, this endpoint is reported as ypT0N0, according to the *Union for International Cancer Control* (UICC) or *American Joint Committee on Cancer* (AJCC). The same outcome (pCR) is reported in few studies [13] as equivalent with TRG4, according to the tumor regression grade (TRG) system developed by Dworak *et al.* (although in its seminal work Dworak did not find any patients with TRG4 among the 17 evaluated specimens) [14]. In a reduced number of studies [15], pCR was equivalent with grade 3 according to the histological criteria for the assessment of response to chemotherapy/RT released by the *Japanese Society for Cancer of the Colon and Rectum* [16]. Irrespective the grading/scoring system used for its assessment, pCR is a clear entity, characterized by the absence of viable tumor cells on the specimen of rectal resection, after neoadjuvant CRT (Figures 1–3).
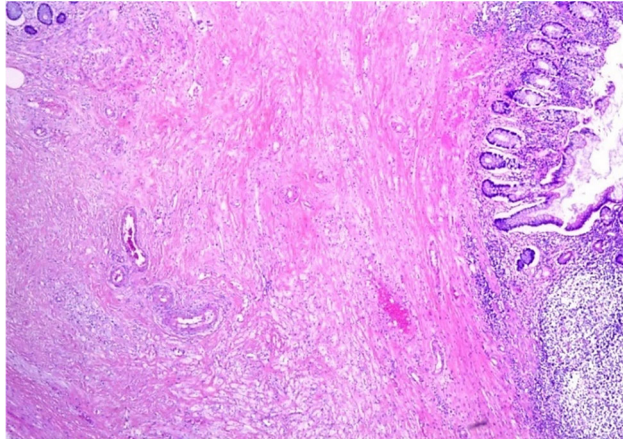

Figure 1 – *Complete tumor regression (TRG0/pCR). The absence of viable tumor cells is the highlight of the complete response after neoadjuvant therapy. The entire tumor bed is fibrotic and has multiple foamy macrophages. Observe the architectural distortion of the mucosa as well as its ulceration as a side effect of neoadjuvant treatment. HE staining, ×40. HE: Hematoxylin–Eosin; pCR: Pathological complete response; TRG: Tumor regression grade.*
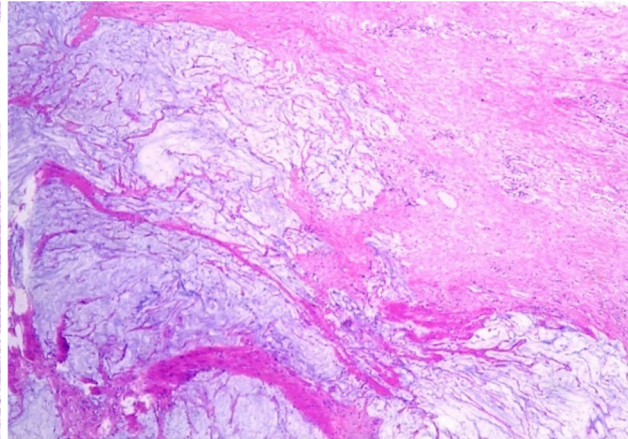

Figure 2 – *Complete tumor regression (TRG0/pCR) with extensive pools of extracellular, acellular mucin also known as colloid response. The presence of acellular mucin pools in pCR patients does not affect prognosis. HE staining, ×40.*
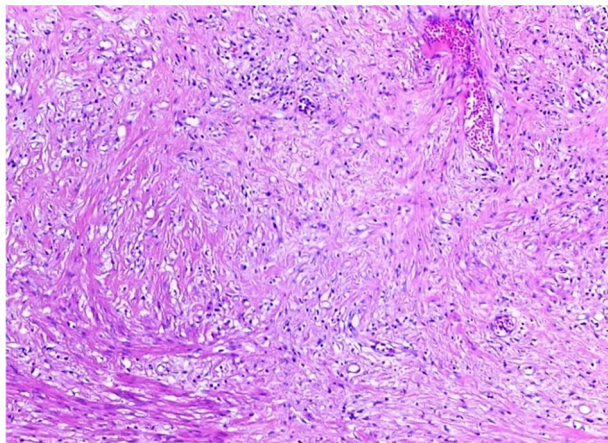

Figure 3 – *Microscopic features of the tumor bed in a patient with complete response after neoadjuvant treatment. The whole area is fibrotic with numerous fibroblasts, macrophages, lymphocytes, and blood vessels with thickened or distorted walls. HE staining, ×100.*

In a meta-analysis of 14 studies including patients that underwent RS after neoadjuvant CRT, the pooled prevalence of pCR was 16% [9]. The rate of pCR ranged between 8% and 29% [6, 7, 17–21], mainly depending on the initial clinical T (cT) stage and the type of neoadjuvant therapy.

Unfortunately, pCR cannot be established before rectal resection. Thus, the results achieved by neoadjuvant CRT are evaluated by digital rectal examination (DRE), rectoscopy (with or without biopsy) and radiological methods [such as computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or positron-emission tomography (PET)/CT]. The term that was coined for the disappearance or rectal tumor with virtual absence of viable malignant cells is cCR. cCR represents a surrogate parameter used mainly when rectum-sparing approaches are considered after neoadjuvant CRT [21–23].

Although many studies are discussing the management of patients with RC that experienced cCR after neoadjuvant CRT, there is a lack of consensus on the definition of cCR (Table 1).

Table 1 – *Criteria for assessment of cCR*

Study	DRE	Endoscopy	Biopsy	CT scan	MRI	ERUS	PET/CT	CEA
Habr-Gama *et al.* (2004) [8]	No evidence of tumor	No residual tumor or ulcer, only whitening of mucosa or telangiectasia	Negative	No disease	–	–	–	–
Li *et al.* (2015) [24]	No palpable tumor	No visible lesion other than flat scar	–	Similar to MRI (when MRI not performed)	No residual tumor	Similar to MRI (when MRI, CT not performed)	–	–

Study	DRE	Endoscopy	Biopsy	CT scan	MRI	ERUS	PET/CT	CEA
Dalton *et al.* (2012) [11]	Normal	No residual tumor or ulcer (even if biopsy finding negative). Only residual scar	Negative from previous tumor site/ residual scar	–	Significant tumor regression, with little evidence of residual tumor	–	No evidence of tumor	–
Smith *et al.* (2012) [25]	No palpable tumor	No other lesion than a flat scar	Selective biopsy (scar)	–	–	–	–	–
Glynne-Jones *et al.* (2017) [26]	No palpable tumor or irregularity	No other lesion than flat scar, telangiectasia, or mucosal whitening	Negative biopsy from the scar	–	No residual tumor at primary site or lymph nodes	Similar to MRI (when MRI not performed)	–	Normalized after CRT
Maas *et al.* (2011) [22]	No palpable tumor	No residual tumor or only a small residual erythematous ulcer or scar	Negative biopsies from the scar/ ulcer/former tumor location	–	No residual tumor or residual fibrosis only or residual wall thickening due to edema and no suspicious lymph nodes	–	–	–
Lai *et al.* (2016) [27]	No tumor, mucosal irregularity, or ulceration	No tumor, mucosal irregularity, or ulceration. Only mucosal whitening and telangiectasia	–	Similar to MRI (when MRI not performed)	No residual rectal disease or extrarectal disease	Similar to MRI (when MRI, CT not performed)	–	–

cCR: Clinical complete response; CEA: Carcinoembryonic antigen; CRT: Chemoradiation therapy; CT: Computed tomography; DRE: Digital rectal examination; ERUS: Endorectal ultrasound; MRI: Magnetic resonance imaging; PET: Positron-emission tomography.

Due to the different definitions of the cCR, the rate of this observation varies largely between different series. Irrespective the rate of cCR rates, it was hypothesized that most of these patients will experience pCR. Unfortunately, between 5% and 53% of patients with cCR had still viable tumor cells, depending on the modality of cCR assessment [28, 29]. By contrary, between 8.3–16.6% of patients who did not fulfill the criteria of cCR had pCR at pathological examination of the resected specimen [8, 11, 28, 29]. These data reveal that there is not an "overlapping" between cCR and pCR, mainly depending on the modality of cCR assessment [30–32].

Thus, in the studies that do not use biopsy assessment, up to 53% of patients with cCR do not have pCR on rectal resection specimens [29]. In a study of Habr-Gamma, which evaluated 360 patients with RC who received neoadjuvant CRT, out of 99 patients who were considered as having cCR based on DRE and rectoscopy, five (5%) were wrongly classified. By contrary, among 261 patients without cCR, 24 (9.1%) had pCR on histological examination of the resection specimen [28]. Thus, DRE associated with rectoscopy had a sensitivity of 79.6% in detecting pCR, and a specificity of 97%. A similar specificity (97%) of macroscopic assessment in prediction of pCR was reported by Smith *et al.*, but in their study the sensitivity of macroscopic evaluation was much lower (26%) [33]. Guillem *et al.* revealed that DRE and rectoscopy underestimated the response to neoadjuvant CRT in majority of their patients, being able to correctly identify pCR in only three out of 14 (21%) patients [30]. In 166 patients with LARC who were treated by neoadjuvant CRT followed by RS, rectoscopy after neoadjuvant CRT had a positive-predictive value of 88.2%, a negative-predictive value of 53.8% and an accuracy of 85.5% [34]. Patients in whom rectoscopy showed residual ulcers after neoadjuvant CRT had viable malignant cells at pathological examination of the resection specimen in 65% cases, while only 46% of those with fibrotic scars had residual tumor on pathology report [34]. Combining endoscopy with biopsy, the prediction rate for pCR increased to 77% [34].

Even in the studies that used biopsy from the residual scars/ulcers/tumors, up to 78% of patients with negative biopsies still have residual tumor on the resected specimen [34]. Although biopsy alone offered a positive-predictive value of 100%, its negative-predictive value was only 21.4% and accuracy 44.6% [34]. That could be explained by the fact that residual scar/ulcer area may not be representative for the potential residual tumor after neoadjuvant CRT. Thus, Hayden *et al.* demonstrated that among the patients without pCR almost 50% had malignant cells outside the visible ulcer margin (median distance was 1 cm) or in the absence of a residual ulcer [36]. Furthermore, only 13% and 56% of patients with ypT2-4 had residual malignant cells after CRT in mucosa and submucosa, respectively, while 98% had residual cells in the *muscularis propria* [37]. Because biopsy samples are frequently taken from mucosa and submucosa, the risk of a false-negative pCR is very high. Based on such information, as well as those derived from other studies [38, 39], a recent consensus released by experts in RC treatment did not recommend the routinely use of biopsy sampling to establish the pCR due to the risk of false-negative findings and a lack of evidence of value, especially when DRE, endoscopy and MRI criteria for cCR are all fulfilled [40–42].

Although pelvic MRI has an increased ability to correctly assess the T stage before treatment, its usefulness in evaluation of pCR after neoadjuvant CRT has been a subject of debate during the last decade. The main pitfall after neoadjuvant CRT is represented by the development of fibrosis which decreases the ability of MRI to differentiate between residual tumor and fibrosis. Moreover, tumor may still exist within a scar [43]. Thus, in a study published in 2011, Kuo *et al.* showed that MRI had a positive-predictive value of 86.4%, a negative-predictive value of 33.3% and accuracy of 82.5% in predicting pCR after neoadjuvant CRT [34]. Based on these results the authors stated that MRI

might not be a useful predictor of pCR after neoadjuvant CRT in patients with LARC [34]. During the last years, the addition of diffusion-weighted (DW) to MRI improved the ability of MRI to predict pCR [44, 45]. In a study published in 2018, Horvat *et al.* revealed that combined T2-weighted and DW imaging achieved a sensitivity of 84%, a specificity of 56%, a positive-predictive value of 30% and a negative-predictive value of 94% for pCR assessment [43]. In this study, MRI-based radiomics features of the primary tumor were also investigated to assess their predictive value in the diagnosis of pCR. Radiomics analysis involves computer-based extraction of a large number of quantitative features and has potential for aiding clinical decision making [43, 46]. In their study, radiomics features of the primary tumor were able to significantly increase the specificity (to 91%) and positive-predictive value (to 72%), while sensitivity and negative-predictive value for pCR were 100% [area under the curve (AUC) of 0.93] [43]. Moreover, recent studies revealed that MRI radiomics features of the mesorectum have also been associated with increased performance in predicting pCR [47, 48] after neoadjuvant CRT in patients with LARC. By using eight MRI radiomic features of the mesorectal fat, Jayaprakasam *et al.* were able to develop a predictive support vector machines model that achieved a diagnostic accuracy for pCR of 83.9%, a sensitivity of 78%, a specificity of 85.1%, a negative predictive value of 94.9%, a positive predictive value of 52.5% and an AUC of 0.89 [47]. Thus, in present, DW–MRI, associated with MRI-based radiomics of the primary tumor and mesorectal fat can predict pCR with high accuracy, representing an important complementary tool to the DRE and rectoscopy.

In an early, small sample size study exploring the usefulness of PET/CT in evaluation of pCR after neoadjuvant CRT, Martoni *et al.* found that Fluorodeoxyglucose (FDG)–PET/CT has limited predictive value for pCR achievement [13]. Similar to this study, Calvo *et al.* [49] and Capirci *et al.* [50] revealed that PET/CT could be seen only as a complementary tool in assessing the response to neoadjuvant CRT. More specifically, Vliegen *et al.* showed that although PET/CT may predict tumor response to neoadjuvant CRT, its accuracy in predicting pCR is limited [51]. A study from *Memorial Sloan-Kettering Cancer Center* published in 2013 which evaluated 121 patients with LARC treated with neoadjuvant CRT revealed that the absence of FDG uptake after neoadjuvant CRT has not been equivalent with pCR [21]. The PET/CT evaluation had a sensitivity of 54%, specificity of 66%, positive predictive value of 30%, negative predictive value of 84% and an AUC of 0.64 in predicting pCR after neoadjuvant CRT. The ability of CT scan in predicting pCR has also been low, with a sensitivity of 19%, specificity of 95%, positive predictive value of 50% and negative predictive value of 81% [21]. Consequently, the authors concluded that neither PET/CT, nor CT scan predict pCR with enough accuracy to be considered clinically useful for treatment decision after neoadjuvant CRT in patients with LARC [21]. A study published in 2019 by Sorenson *et al.* re-emphasized the decreased value of PET/CT (performed at baseline and 6–8 weeks after neoadjuvant CRT) in predicting pCR after neoadjuvant CRT in LARC patients [20]. In their study, PET/CT was rather useful in identification of poor responders to neoadjuvant CRT, since more than 85% of patients with

a post-CRT standardized uptake value (SUV)max higher than 4.3 will not achieve pCR [20]. They concluded that future multicenter prospective trials combining DRE with rectoscopy and PET/CT could provide more robust data about the usefulness of post-CRT PET/CT to select patients for RS or organ-sparing approaches [20].

Even the accuracy of histological examination of resected specimen in the detection of pCR was questioned by some authors. Thus, Chen *et al.* [52] extracted deoxyribonucleic acid (DNA) from 26 specimens deemed as pCR after pathological examination and used standard and highly-sensitive polymerase chain reaction (PCR) techniques to identify the presence of tumor-specific p53 and Kirsten rat sarcoma viral oncogene homologue (*KRAS*) mutations. They found evidence of residual tumor cells in 7.7% (2/26) of cases [52].

Because the currently available methods are not able to predict pCR with 100% accuracy even in patients with cCR, the assessment of factors that are significantly associated with the occurrence of pCR became tremendously important. Different clinico-pathological factors, neoadjuvant treatment schedules and molecular features have been reported to be associated with the response to neoadjuvant CRT. Prediction of pCR should take into account these variables, which are useful for advising patients on prognosis after neoadjuvant CRT and treatment options [7].

⊟ Prognostic factors for pCR

The most frequently reported clinical predictors of cCR were cT stage, tumor volume and the extent of rectum circumference involvement [53–56].

Clinical stage at baseline

Among the factors that were associated with the occurrence of CR, cT stage was an independent prognostic for both cCR and pCR. Thus, Peng *et al.* revealed that cT stage was an independent predictor for cCR [5] and the meta-analysis of Maas *et al.* showed that pCR was significant more frequently observed in cT1/T2 patients than in cT3/T4 patients [9]. Furthermore, Hasan *et al.* [6] evaluated the results of neoadjuvant CRT followed by surgery in 5086 patients with LARC, revealing that the lower cT stage, the significantly higher was the chance of pCR [cT1/T2 *vs.* cT3: odds ratio (OR) (95% CI) = 0.60 (0.41–0.87), *p*=0.01; cT1/T2 *vs.* cT4: OR (95% CI) = 0.25 (0.13–0.49), *p*<0.001]. In this study, cT stage was the strongest predictor of pCR in multivariate analysis [6]. In another study, cT stage was the only predictive factor independently associated with pCR achievement (in multivariate analysis), although clinical N (cN) stage and maximum diameter of the tumor have also been associated with pCR in univariate analysis (but not in multivariate analysis) [56]. So far, there are no strong evidence to support the predictive value of cN stage [9] and maximum tumor diameter at baseline for pCR achievement.

Tumor size at baseline

However, since the late '90s, it has been suggested that the volume of RC at baseline is as an even stronger predictor of tumor response to neoadjuvant CRT than cT stage [57, 58]. In a small study, which intended to evaluate the feasibility of a high-dose rate endorectal brachytherapy boost after external beam RT in elderly patients with rectal

cancer who were unfit for surgery, the volume of the RC and the thickness of the tumor at baseline were the only predictive factor associated with cCR in univariate analysis (p=0.005 and p=0.02, respectively) [55]. Moreover, patients whose tumor volume was lower than 20 cm^3 experienced a 74% sustained response rate at two years, significantly higher (p=0.007) than those observed in patients with larger tumors [55]. Recently, a larger study that included 187 patients with LARC treated by neoadjuvant CRT and RS, revealed that 44 (23.5%) patients had pCR on the resected specimen [59]. In multivariate analysis, the volume of RC less than 39.5 cm^3 was the only independent predictive factor for pCR occurrence (p<0.01 by logistic regression model and p=0.026 by Bayesian independent test) [59]. The degree of circumferential extension of the RC could also represent a surrogate parameter for the volume of the rectal tumor. In a paper published in 2007, Das *et al.* revealed that a circumferential involvement of the rectum less than 60% was independently associated with a higher rate of pCR [54].

In 2011, van Stiphout *et al.* developed a predictive model for pCR incorporating cT stage, cN stage and tumor length, which achieved an AUC of the receiver operating characteristic (ROC) curve of 0.61 in the training dataset and an AUC of 0.69 in the validation dataset [60]. By adding pre- and post-CRT PET/CT specific data as post-CRT SUV$_{max}$ and relative change of SUV$_{max}$ to the tumor length, they achieved a predictive model that performed significantly better in predicting pCR (AUC = 0.83; p<0.01 in training dataset and AUC = 0.86; p=0.056 in validation dataset) [60]. To identify the patients with highest chance to achieve pCR as early as possible, the same group developed a nomogram including the following parameters: cT stage, cN stage, intermediate maximum diameter, and response index of SUV mean; the latter two parameters were evaluated based on PET/CT performed before starting CRT and during CRT (15 days after its start) [56]. This model was able to divide the patients in three groups according to the chance of achieving pCR, based on the percentages released by the nomogram. Thus, patients with a higher than 53% score had a significantly increased probability of pCR occurrence, compared to those in the other two groups (100% *vs.* 21.3% *vs.* 7.35, respectively, in the training dataset, and 66.7% *vs.* 30.8% *vs.* 13%, respectively, in the validation dataset) [56]. These early estimation of pCR is important to avoid over-treatment of poor responders, that most probably do not have any benefit from intensified therapy.

Pathological type of RC

Pathological type of RC has recently been demonstrated as a predictor for pCR. Thus, a study that included patients with LARC (from three prospective clinical trials) assessed the predictive implication of mucinous adenocarcinoma (MAC) on the rate of pCR achievement after neoadjuvant treatment. Although in patients who received only neoadjuvant chemotherapy the rate of pCR was not significantly different between MAC group and non-MAC group (0% *vs.* 13.2%, respectively; p=0.11), among patients treated with neoadjuvant CRT (irrespective the chemotherapy regimen) the rate of pCR was statistical significantly higher in non-MAC group than in the MAC group (27.3% *vs.* 11%, respectively; p=0.03) [61].

Type of neoadjuvant therapy

Undoubtably, the regimen of neoadjuvant therapy plays an important role in the response rate of patients with LARC. Since the late '80s, it was observed that neoadjuvant RT is able to produce pCR in some patients with RC. Thus, a randomized trial, published in 1989, which evaluated preoperative RT (34.5 Gy divided in 15 doses) in patients with RC revealed that in the preoperative RT (followed by surgery) arm five out of 231 patients had pCR (2.1%) [62]. A slightly higher rate of pCR (4.4%) after neoadjuvant RT (31.5 Gy) was reported in 1990, by Horn *et al.*, in a similar randomized trial performed in Norway [63]. Moreover, in 1997, Berger *et al.* showed that higher doses of neoadjuvant RT, tumor differentiation and prolonged interval between RT and surgery were predictive factors for RC down-staging [64]. However, they were not able to identify the predictors of pCR, mainly due to the small number of patients (nine out of 167 patients – 5%) which experienced this outcome [64].

In the late '90s, it was hypothesized that the addition of concurrent chemotherapy to preoperative RT may improve outcomes in patients with LARC. In 1998, a retrospective study that evaluated the rate of postoperative complications after neoadjuvant RT (45 Gy in 25 fractions) and concurrent continuous infusion of 5-Fluorouracil (5-FU) followed by RS, reported the achievement of pCR in 27% patients with LARC [65]. A randomized trial whose results were published in 2006 that compared the outcomes of pre-operative RT alone (45 Gy in 25 fractions) to those achieved by the same RT regimen associated with 5-FU/Leucovorin reported similar results [66]. All the patients underwent RS 3–10 weeks after neoadjuvant treatment and subsequent adjuvant chemotherapy with 5-FU/Leucovorin [66]. A pCR was significant more frequently achieved in neoadjuvant CRT group than in neoadjuvant RT alone group (11.4% *vs.* 3.6%, respectively; p<0.05) [66]. Moreover, the five-year LRR was significantly lower after neoadjuvant CRT than after RT alone (8.1% *vs.* 16.5%, respectively; p<0.05), although the OS rates were similar in the two groups [66]. A randomized phase III clinical trial revealed that pre-operative RT associated with Capecitabine determined similar three-year LRRs, five-year disease-free survival (DFS) and OS rates as neoadjuvant RT combined with 5-FU continuous infusion [67]. In the same study, the addition of Oxaliplatin did not improve the long-term outcomes, but significantly increased the incidence of overall grade 3–5 toxicities [67].

To evaluate the long-term outcomes achieved by preoperative CRT *vs.* postoperative CRT, Sauer *et al.* performed a randomized clinical trial in which patients were randomly assigned to either preoperative RT (5040 cGy) and two cycles of continuous infusion 5-FU followed by RS (six weeks after CRT) and subsequent four cycles of continuous infusion 5-FU or RS followed by identical CRT [18]. Although the five-year OS rates were similar in the two groups (76% *vs.* 74%, respectively; p=0.80), the five-year cumulative incidence of local recurrence (LR) was significantly lower in the preoperative CRT group than in the postoperative CRT group (6% *vs.* 13%, respectively; p=0.006) [18].

Patients who received modified 5-FU, Leucovorin and Oxaliplatin 6 (mFOLFOX6) during the interval between

neoadjuvant CRT and surgery experienced significantly higher rates of pCR than those who received only CRT [68]. These initial results raised the question if total neoadjuvant therapy (TNT) could further improve the long-term outcomes in patients with LARC, as well as the rate of pCR.

The advent of TNT in the last decade, meaning the use of either induction chemotherapy before CRT or consolidation chemotherapy after standard CRT seems to increase the likelihood of achieving pCR. A recent meta-analysis reported a pooled pCR rate of 22.4% (95% CI: 19.4–25.7) in patients treated with TNT [69]. Based on the reported results of the 10 studies which compared TNT with standard neoadjuvant CRT, TNT increased by 39% the likelihood of pCR (1.40, 95% CI: 1.08–1.81, p=0.01) [69]. Moreover, the addition of six cycles of Folinic Acid (Leucovorin), 5-FU, Irinotecan, Oxaliplatin (FOLFIRINOX) before CRT significantly improved three-year DFS compared with CRT alone (76% *vs.* 69%, respectively; p=0.034) [70].

Interval between neoadjuvant CRT and surgery

Optimal time interval between the end of neoadjuvant CRT and the development of pCR has not been identified. A monocentric study published in 2009 assessed the predictive factors for pCR after neoadjuvant CRT, identifying extended time interval (more than eight weeks) between the end of CRT and surgery as the only independent predictor for pCR achievement [71]. An up-dated evaluation of patients from the same center revealed that a prolonged interval (more than eight weeks) between the end of CRT and RS was associated with a decreased three-year LRR, compared to those observed in patients operated after a shorter interval (less than eight weeks) (1.2% *vs.* 10.5%, respectively; p=0.04) [72]. Nevertheless, the optimal cut-off for the "prolonged" interval between CRT and surgery has been differently reported by other authors. A retrospective analysis of 23 747 patients with RC included in National Cancer Database (NCDB) between 2006 and 2011 found the time interval between the end of CRT and RS longer than six weeks as an independent predictor for the achievement of pCR, the highest rates of pCR being achieved in patients operated at more than eight weeks [7]. A Dutch study revealed that the highest incidence of pCR was achieved in patients operated 15–16 weeks after the start of neoadjuvant CRT [73]. Moreover, the use of TNT dramatically changed the interval between the start of neoadjuvant therapy and subsequent evaluation of CR. A phase II trial published in 2015 revealed that patients who received six cycles of mFOLFOX6 after neoadjuvant CRT had the highest rate of pCR (38%), being operated at 26 weeks after the start of neoadjuvant therapy [68]. Consequently, a recent consensus on key outcome measures for organ preservation after CRT in patients with RC considered that it is not possible to establish a specific time point for assessing cCR. However, because pCR cannot undoubtedly be established by pre-operative evaluation, in patients considered for rectum-sparing approaches the consensus recommended to evaluate the occurrence of cCR in a two-step manner. Thus, in patients with RC that might underwent an organ-sparing approach was recommended a first assessment at 12 weeks after starting of short-course RT or CRT and a subsequent evaluation at 16–20 weeks after the initiation of neoadjuvant treatment. Patients without down-staging at 12 weeks should be immediately referred for RS to ensure oncological safety. The good responders (identified at 12 weeks) should be re-evaluated 4–8 weeks later, recommending rectum-sparing approaches in those who achieved a cCR at that time point [40]. In patients treated with TNT, the optimal interval between the start of neoadjuvant therapy and the time of cCR assessment is still unclear, especially due to the various durations of different TNT schemes. However, an early response evaluation is needed to identify the poor responders that should be referred to RS for oncological safety reasons. For good responders, who might benefit from completing the scheduled TNT, the evaluation of cCR could be done at 4–8 weeks after the end of TNT, but even in these patients close monitoring during the neoadjuvant treatment is mandatory [40].

Molecular features of RC

Apart from clinic and pathological factors, molecular profile of RC is related with treatment response [74]. Most colorectal carcinomas are sporadic, but sometimes the appearance of these types of tumors in a syndromic context can be demonstrated by molecular surrogate immuno-histochemical (IHC) tests. Sometimes, colorectal carcinomas may demonstrate microsatellite instability (MSI), a functional manifestation of mismatch repair (MMR) protein deficiency. MMR IHC enables pathologists to assess the expression status of the four proteins [MutL homolog 1 (MLH1), PMS1 homolog 2, MMR system component (PMS2), MutS homolog 2 (MSH2) and MutS homolog 6 (MSH6)]. As a rule, the presence of all four proteins signifies a micro-satellite stable tumor, although exceptions exist; whereas staining loss indicates MMR deficiency with the pattern suggesting the defective gene. However, MMR IHC is not considered genetic testing since it evaluates protein expression. Most colorectal carcinomas are MMR stable (Figures 4–7) with retained nuclear expression for the MMR immunomarkers. A recent study showed that MSI status has been an independent prognostic factor for pCR in patients with LARC [6]. Among the 636 patients with MSI-positive RC the prevalence of pCR was 5.9%, statistical significantly lower than those observed in 4450 patients with MSI-negative RC (8.9%, p=0.01). The difference remained also significant even after propensity-score matching in multivariate analysis [OR (95% CI) = 0.65 (0.43–0.96)] [6]. This observation emphasizes the importance of initial testing for MSI status of patients with RC, especially when a rectum-sparing approach is considered (usually due to the advanced age and comorbid conditions of the patient).

Novel biomarkers that were associated with pCR were lower levels of circulating vascular endothelial growth factor receptor 3 (VEGFR3), epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2) in pre-treatment plasma samples of patients with LARC [75]. A combination of these three circulating biomarkers using logistic regression generated an AUC of 0.869 (with a sensitivity of 43% at 95% specificity) in prediction of pCR [75].

Clinical implication of pCR is of paramount importance because the survival rates achieved by RS in these patients are significantly higher than those observed in patients

without pCR [9, 76]. Moreover, recent studies suggested that in selected patients with pCR the long-term outcomes achieved by local excision (LE) or watch and wait (WW) approach are similar to those reported after RS.
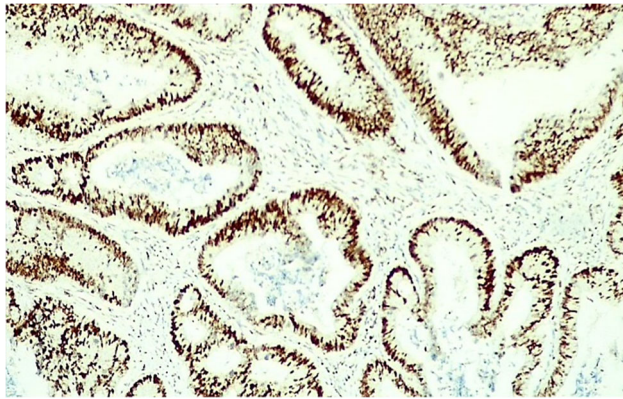

Figure 4 – *Colonic adenocarcinoma with strong, diffuse nuclear staining for MLH1. Anti-MLH1 antibody immuno-staining, ×200. MLH1: MutL homolog 1.*

Figure 5 – *MMR stable colonic adenocarcinoma with strong nuclear staining for PMS2. Anti-PMS2 antibody immunostaining, ×200. MMR: Mismatch repair; PMS2: PMS1 homolog 2, mismatch repair system component.*
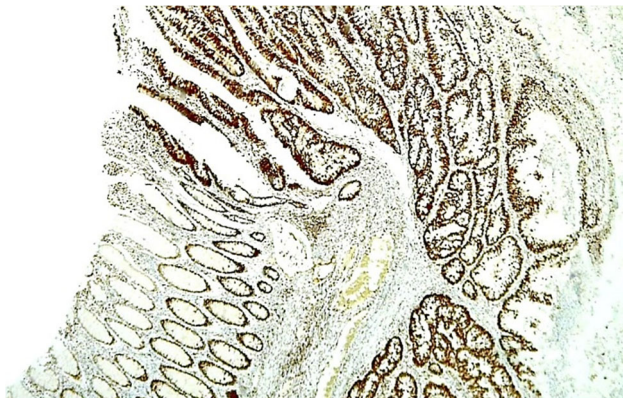

Figure 6 – *MMR stable colonic adenocarcinoma with retained staining for MSH2. The colonic mucosa in the vicinity of the neoplastic proliferation provides an ideal positive internal control. Anti-MSH2 antibody immuno-staining, ×100. MMR: Mismatch repair; MSH2: MutS homolog 2.*
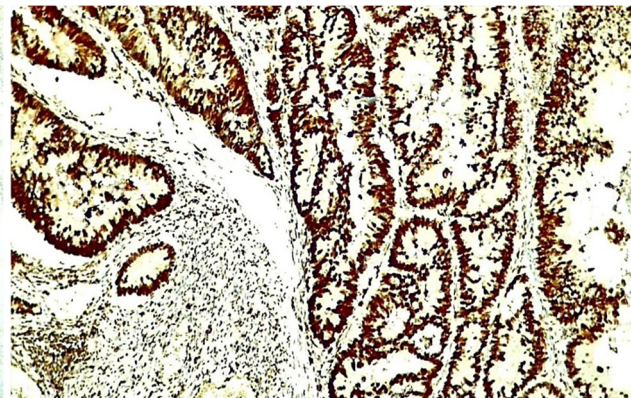

Figure 7 – *MMR stable colonic adenocarcinoma with retained staining for MSH6. Anti-MSH6 antibody immuno-staining, ×200. MMR: Mismatch repair; MSH6: MutS homolog 6.*

Because current clinical and paraclinical methods are not able to predict pCR with 100% specificity and sensitivity, the treatment strategy is chosen based on the parameters that define cCR. Thus, the accurate evaluation of cCR after neoadjuvant CRT is of tremendous importance, especially in patients who refuse RS, or having a poor performance status which is associated with high-risk RS. In such patients, the accurate evaluation of cCR is crucial, because alternative strategies consist in LE or WW approach, both of them omitting TME which is still considered the standard approach to RC. A recent international consensus on key outcome measures for organ preservation after (chemo)radiotherapy in patients with RC [40] has chosen the Amsterdam/ Maastricht criteria for defining cCR [22].

Although the current studies assessing the outcomes of organ-preserving strategies are heterogeneous in terms of selection criteria for different treatments and reported endpoints, thus limiting the accuracy of data interpretation and comparison between studies [40], international guidelines already allow less-radical management in selected patients with cCR after neoadjuvant CRT [26, 77, 78]. Further on are presented the results achieved by current approaches in patients with cCR after neoadjuvant CRT.

⊟ Treatment strategies in patients with cCR

In present, for patients who achieved cCR after CRT, three approaches could be considered: (*i*) RS meaning rectal resection with TME – is still considered the standard treatment; (*ii*) LE which consists in full-thickness excision of the tumor bed with a 1 cm safety margin and closure of the rectal wall – represents a surgical alternative to RS for selected patients; (*iii*) WW strategy consisting in close follow-up of these patients is a non-surgical approach for patients who achieved cCR after neoadjuvant CRT, aiming to avoid surgery in elderly or high-risk patients. Because there are few randomized clinical trials with various designs which compared the results of these strategies, the optimal approach for these patients is still unclear, each of these strategies having advantages, limitations, and drawbacks.

RS with TME

RS still represents the "gold standard" approach to RC patients.

Short-term outcomes after RS in patients with pCR

Although initially has been supposed that RS is associated with lower morbidity and mortality rates in

patients who achieved pCR after neoadjuvant CRT compared to those without pCR, the available data are still conflicting. In 2009, Stelzmueller *et al.* found a higher rate of major morbidity (Clavien–Dindo III–IV) in patients who experienced tumor down-staging after neoadjuvant CRT than in those without down-staging (26.6% *vs.* 8.8%, respectively; *p*<0.05), although the achievement of pCR was not correlated with significantly higher morbidity rates [79]. Maggiori *et al.* revealed that overall morbidity rates were not statistical significantly different between laparoscopically-resected patients who achieved pCR after neoadjuvant CRT and those who did not achieve pCR (36% *vs.* 51%, respectively, *p*=0.20) [29]. However, in patients with pCR the rates of clinical anastomotic leakage (9% *vs.* 29%, respectively; *p*=0.02) and major morbidity (6% *vs.* 22%, respectively; *p*=0.04) were significantly lower compared to those observed in patients without pCR [29]. On the other hand, neoadjuvant CRT itself increases the risk of anastomotic leakage [80]. Duldulao *et al.* did not find significantly different morbidity rates after RS between patients who achieved pCR and those without pCR, either for overall postoperative complications (41% *vs.* 35%, respectively; *p*=0.72), or major postoperative complications (18% *vs.* 8%, respectively; *p*=0.16) [81]. A study which evaluated 23 747 patients with RC who underwent neoadjuvant CRT and RS, revealed (after propensity-adjusted analysis) that mortality rates after RS in patients with LARC who experienced pCR after neoadjuvant CRT were similar to those reported in patients without pCR (0.7% for each group; *p*=0.119) [7]. The same analysis of patients included in NCDB between 2006 and 2011 found that length of hospital stay was slightly (but statistically significant) shorter in patients who experienced pCR than in those without pCR (7.26 days *vs.* 7.49 days, respectively; *p*=0.045 after propensity-adjusted analysis) [7]. In the study of Maggiori *et al.*, length of hospital stay was also significantly shorter in resected patients with pCR than in those without pCR (nine days *vs.* 12 days, respectively; *p*=0.01) [29].

Long-term outcomes after RS in patients with pCR

Even in the first decade of the third millennium few authors reported better local control, improved DFS and OS after RS in patients who achieved pCR following neoadjuvant CRT [82–84]. A meta-analysis of Maas *et al.* reported the results achieved by RS in patients operated after neoadjuvant CRT [9]. After a median follow-up of 46 months, the data about LR were available only for 455 patients with pCR; in these patients LR was observed only in 12 cases (five-year LRR was 2.8%). Out of 419 patients with pCR and available data about disease recurrence, the disease recurred in 61 patients (five-year DFS was 83.3%). In 465 patients with pCR and available data on OS, there were 53 death during follow-up interval, with a five-year OS rate of 87.6% [9]. In their counterpartners without pCR who underwent RS, both five-year DFS and OS rates were significantly lower (65.6% and 76.4%, respectively) than those observed in patients with pCR (*p*<0.0001). Furthermore, five-year LRR was significantly higher in patients without pCR (9.7%), than in patients with pCR (*p*<0.0001) [9]. In 2012, Kuo *et al.* published a retrospective analysis of 161 patients who

underwent RS after neoadjuvant CRT, revealing that no one patient with pCR developed LR after RS [34]. However, 8% of patients with pCR after neoadjuvant CRT developed distant metastases after RS, even in the absence of LR [34].

Local excision

LE could be performed by conventional transanal approach, by transanal endoscopic microsurgery (TEM) or by transanal minimally invasive surgery (TAMIS). A case-control matched-pairs analysis demonstrated that these modalities to perform LE resulted in similar results [85, 86]. The main advantages of LE (compared to RS) are the lower risk of postoperative morbidity [87, 88] and the avoidance of colostomy in a significant percentage of patients with low-RC.

Patients with early RC

LE was initially recommended in patients with cTis/T1N0M0 mid/low-RC. Theoretical assumption that supports this approach is the low risk of lymph node metastases or disseminated disease in such patients. By this reason, it was considered that for these patients TME might be unnecessary, as long as LE of primary tumor with a 1 cm safety margin could entirely remove primary tumor without jeopardizing long-term oncological outcomes [26, 86, 89].

A retrospective analysis of more than 10 000 patients with T1 RC included in NCDB between 2008 and 2016 revealed a significant increase in the use of LE approach over the time (from 52.69% in 2008 to 69.47% in 2016, *p*<0.001) [86]. Moreover, the 5-year OS rates were not significantly different in patients who underwent LE compared to those treated by RS (82.65% *vs.* 83.53%, respectively; *p*=0.639) [86]. Even earlier studies suggested that LE achieved OS and DFS rates similar to those accomplished by RS [90–93]. However, LRRs tended to be higher in T1N0M0 patients treated by LE than in those who underwent RS [90, 93, 94]. To better select patients for LE, some investigators evaluated the predictors for higher LRR and lower survival outcomes. The main reason for local or distant recurrence in patients with pT1 RC treated by LE with safety margin is the presence of metastatic LNs. A meta-analysis of 3621 patients with pT1 RC revealed that the independent predictors for LN metastases were lympho-vascular invasion, tumor invasion into submucosa deeper than 1 mm, tumor budding and poor histological differentiation [95]. The depth of submucosal invasion by RC was divided in three degrees: Sm1 – invasion of the upper third of submucosa, Sm2 – invasion in the middle third and Sm3 – invasion of the lower third. Morino *et al.* revealed that recurrence rate after LE was 0% in Sm1 and 22.7% in Sm2 or Sm3 [96]. If pathological evaluation of the resected specimen after LE reveal the presence of such high-risk factors, or incomplete resection margins (R1/R2), immediate RS should be recommended due to the high-risk of recurrence. The oncological outcomes achieved by RS after LE in patients with high-risk pathological factors seems to be similar to those of patients treated with up-front RS [97, 98]. Elderly or high surgical risk patients, as well as those who refuse RS might benefit from adjuvant (chemo)radiotherapy [26].

However, in pT2 patients who underwent LE, even the addition of adjuvant CRT was associated with significantly

lower survival rates than to those achieved by LE alone in patients with pT1 RC. Thus, Greenberg *et al.* revealed that 10-year OS and DFS were 84% and 75% for pT1 patients treated with LE, and 66% and 64% for pT2 patients treated with LE followed by adjuvant CRT [99]. Moreover, local and distant recurrence rates for pT1 tumors were 8% and 5%, while in pT2 patients were 18% and 12% even after adjuvant CRT [99].

A recent randomized study (TREC) evaluated the potential role of LE after neoadjuvant short-course RT in patients with early RC (T1-2N0M0) [100]. TREC study assessed the feasibility of randomly assigning eligible patients with early-stage RC to either RS without pre-operative RT, or LE after neoadjuvant short-course RT [100]. The study also contained a non-randomized registry including patients for whom randomization was considered inappropriate, due to a strong clinical indication for one of the treatment options (*e.g.*, elderly/frail patients with many comorbidities that were considered unsuitable for RS underwent RT and subsequent LE) [100]. The pCR was observed in 30% of patients randomized to neoadjuvant RT followed by LE and in 41% of non-randomized patients who underwent neoadjuvant RT and LE [100]. An intention-to-treat analysis revealed, in randomized patients, that incidence of serious adverse events was significantly lower in LE group compared to those in RS group (15% *vs.* 39%, respectively, *p*=0.04). Moreover, patient-reported quality of life (QoL) and function scores were improved in the group of patients randomly assigned to LE than in RS group [100]. Although TREC study has not been designated to compare the long-term outcomes achieved by the two therapeutic strategies, survival analysis revealed that although patients randomly assigned to RT followed by LE had lower OS and DFS rates compared to those assigned to RS, the differences were not statistically significant [100]. However, only 19 out of 27 (70%) patients randomly assigned to LE achieved organ preservation, the other eight (30%) patients undergoing RS (early-per protocol conversion in five patients and TEM difficulties in three patients) [100]. Due to the favorable short-term and functional outcomes achieved by rectum-sparing approach, TREC study supports further evaluation of short-term RT followed by LE in patients with early RC in the context of larger randomized clinical trials aiming to investigate the long-term outcomes of this organ-preserving approach.

Patients with LARC (cT3-4N0-2M0)

In patients with more advanced tumors (cT3-4N0-2M0) that achieved cCR after neoadjuvant CRT, LE was recommended (by most authors) only when important co-morbidities were present (such as obesity, or high-risk cardiovascular, pulmonary or neurological disease) and abdominoperineal resection or coloanal anastomosis with intersphincteric resection were required [101]. However, in patients with ypT2-4 and/or R1 resection and/or lympho-vascular invasion (on pathological examination of LE specimen) a salvage RS was recommended following LE, in most studies [101–104].

In the last decade, prospective trials have been undertaken to evaluate feasibility and outcomes of LE in patients with LARC who experienced cCR after neoadjuvant CRT. In most of these trials, ypT2-4 stage or R1 resection represented indications for immediate RS.

A phase 2 feasibility trial (CARTS study) reported that almost two thirds of patients with T1-3N0M0 RC enabled organ preservation with LE after neoadjuvant CRT [105]. In GRE3CCAR2 trial (a phase 3 randomized clinical trial), patients with cT2-3N0-1M0 stage at baseline received neoadjuvant CRT; those patients who achieved a good response after CRT (consisting in a smaller than 2 cm scar at DRE and rectoscopy) were randomly assigned to LE or RS. Patients assigned to LE who had ypT2-3 or R1 on pathological examination specimen were referred to completion TME (RS). All the patients were followed at four months for the next five years after surgery, and those who relapsed were treated according to the current clinical guidelines. By using this approach, per-protocol analysis revealed that 43 out of 81 (53%) patients eventually achieved organ preservation [106]. The study aimed to evaluate the potential superiority of LE over RS in good responders after neoadjuvant CRT, especially in terms of short-term outcomes, LR and side-effects (*e.g.*, colostomy, fecal incontinence or sexual dysfunction) [106]. Such superior outcomes have been suggested by earlier retrospective studies.

Thus, a case-matched study compared the outcomes of LE and RS in patients who achieved cCR after neoadjuvant CRT. Overall morbidity rate was significantly higher following RS (65%) than after LE (26%), although there was no significant difference between major morbidity rates in LE group vs RS group (3% *vs.* 4%, respectively) [101]. GRECCAR2 trial revealed that almost 46% of patients randomly assigned to LE after neoadjuvant CRT needed completion RS, which was associated with significantly higher rates of overall and major morbidity (78% and 46%, respectively), compared to LE (29% and 12%, respectively) or initial RS (38% and 22%, respectively) (*p*<0.01) [106]. By this reason, GRECCAR2 trial failed to demonstrate in an intention-to-treat analysis, as well as in per protocol analysis, that LE is associated with significantly lower morbidity rates compared to RS [106].

However, the strategy employed in GRECCAR2 trial seems to be oncologically safe, as long as in an intention-to-treat analysis the three-year DFS and OS rates achieved by LE (78.3% and 91.9%, respectively) and RS (76.1% and 91.5%, respectively) were not significantly different (*p*=0.45 and *p*=0.92 for DFS and OS, respectively). Similarly, a per-protocol analysis found similar three-year LRRs after LE or RS (6% *vs.* 3%, respectively; *p*=0.63) [106]. These results are in line with long-term outcomes reported in the literature for LE in patients who achieved cCR after neoadjuvant CRT. Calmels *et al.* showed similar oncological outcomes in the LE group and RS group: LRRs were 5% and 3%, respectively (*p*=0.601) and distant recurrence rates were 8% and 7%, respectively (*p*=1) [101]. Likewise, a prospective (CARTS) study reported that LE enabled a five-year LRR of 7.7%, as well as five-year DFS and OS rates of 81.6% and 82.8%, respectively [105].

Moreover, CARTS study reported better QoL in patients treated by LE, with improved emotional well-being during follow-up, compared to those managed by RS [105]. Also, a recent retrospective study revealed that patients who underwent a rectum-sparing approach (LE or WW) had better intestinal (*p*<0.01), sexual (*p*=0.04) functional and emotional status (*p*=0.02) compared to RS patients [107].

So far, most guidelines recommend LE only in cTis-T1 patients with low-risk pathological features [108]. In patients who achieved a cCR after neoadjuvant CRT, most guidelines still endorse RS as "gold standard" treatment [108]. *European Society for Medical Oncology* (ESMO), Italian and Netherlands Guidelines recommend LE of the tumor bed (after cCR), but aware about the need for thorough pathological evaluation [108]. In case of ypT2-3, patients should immediately undergo RS. *European Association for Endoscopic Surgery* (EAES) and French Guidelines proposed LE only within the setting of clinical trials [108]. In patients with high-risk pathological features on the specimen of LE (ypT2-3, R1, lympho-vascular invasion), current guidelines recommend immediate RS, unless the patients refuse or poor performance status [26]. In patients without cCR or having cN1-2 stage, RS is mandatory. For such patients, small retrospective low-quality studies evaluated the results of LE, reporting LRR ranging between 4% and 15%, three-year DFS rates up to 90% [109–111].

Watch and wait

The better functional results and improved QoL achieved by LE were the main reasons for exploring the safety and efficacy of non-operative management in patients who achieved cCR after neoadjuvant CRT. A Brazilian group led by Angelita Habr-Gama pioneered the WW approach, consisting in close follow-up of patients who achieved cCR after neoadjuvant CRT [8]. In the seminal study published in 2004, the authors compared the long-term outcomes achieved by WW approach in 71 patients who had cCR after neoadjuvant CRT to those of 22 patients with pCR observed on the specimen of RS. After more than 48 months follow-up, there have been two LRs in WW group and three distant recurrences in each group (*p*=0.02). Although five-year DFS rates were not statistical significantly different between WW and RS group (92% *vs*. 83%, respectively; *p*=0.09), the five-year OS rate enabled by WW was significantly higher than those achieved by RS (100% *vs*. 88%, respectively; *p*=0.01) [8]. In an updated evaluation, Habr-Gama *et al.* reported after a mean follow-up of almost five years a LRR of 5%, a distant metastases rate of 7.1% and a combined local and distal recurrence of 1% [112]. Small sample size studies suggested that WW approach is able to achieve long-term oncological outcomes similar to those observed after RS in patients with cCR [113]. However, larger retrospective studies and meta-analysis reported different results. A recent analysis of 880 patients with cCR after neoadjuvant CRT (enrolled in the *WW International Registry*) revealed a two-year local re-growth rate of 25.3%, with 77.6% of the recurrences treated by RS and the others by LE [114]. The five-year OS and DSS rates were 84.6% and 93.8%, respectively, for the entire group and 75.4% and 84%, respectively, in patients who developed local re-growth [114]. A meta-analysis of nine studies compared the long-term outcomes achieved by WW (348 patients) and RS (453 patients) [115] revealing that WW approach achieved two-year LRRs and five-year DFS rates similar to those observed in patients treated by RS, irrespective their pathological staging. Furthermore, five-year OS rate accomplished by WW was significantly higher than those achieved by RS in all the patients (*p*=0.046) [115]. However, compared to patients with pCR proved by pathological examinations

of the RS specimen, the two-year LRR was significantly higher in WW group, while five-year DFS and OS rates were significantly lower in WW group [115]. Based on this evidence, caution is recommended before offering this approach, whose application should be limited in present only to elderly, fragile (high-risk) patients or those refusing RS [26, 34, 116].

Nonetheless, when WW approach is chosen, close follow-up is mandatory, especially during the first three years, because local regrowth and distant metastases usually occur in this time interval after the end of CRT. A recent multicentric study showed that the probability of remaining free from local regrowth for an additional two years if a patient had a sustained cCR for three years was 97.3% and the probability of remaining free from distant metastasis for a further two years in patients without distant metastasis at three years was 97.8% [117]. A recent consensus recommended an intensified follow-up regimen in the first three years after CRT, consisting in serum carcinoembryonic antigen (CEA) evaluation every three months, DRE, rectoscopy and pelvic MRI every 3–4 months as well as chest and abdominal CT scan at six months. Since the fourth year after CRT, the follow-up regimen could be de-intensified, consisting in serum CEA evaluation, DRE, rectoscopy and pelvic MRI every six months and chest and abdominal CT scan at 12 months [40].

⊟ Conclusions

Patients with cTis-T1N0 M0 could be safely and efficiently treated by LE, avoiding RS. In more advanced RC, neoadjuvant CRT followed by RS is still the "gold standard" approach. However, pCR after neoadjuvant CRT could be achieve in up to 30% patients, depending mainly on the initial cT stage, tumor volume at baseline, type of neoadjuvant CRT, as well as pathological and molecular features of the tumor. In such patients, the oncological outcomes are better than those observed in patients without pCR. Moreover, in patients with pCR, LE enables potentially better short-term outcomes and QoL, compared to RS. Furthermore, long-term outcomes achieved by LE seems to be similar to those of RS in patients with pCR or low-risk ypT1. Unfortunately, evaluation of pCR is challenging, because cCR does not translate in pCR in all the patients. By this reason, the accurate evaluation of response to neoadjuvant CRT has paramount importance and the achievement of cCR should be estimated based on DRE, rectoscopy and novel imaging methods (especially MRI features). Caution should be recommended before the application of a watch and wait policy in patients with cCR. This approach is recommended in present only in elderly, high-risk patients, with limited estimated life-expectancy. For patients fit for RS, WW approach should be employed in the setting of clinical trials or in case of patients' refusal of RS.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

The authors contributed to the documentation process, conceptualization of the article, writing and corrections and they approved the final version sent to the Editor.

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Corresponding author

Ruxandra Doina Babiuc, Assistant Professor, MD, PhD, Department of Internal Medicine I – Gastroenterology, Emergency University Hospital Bucharest, Carol Davila University of Medicine and Pharmacy, 169 Independenţei Avenue, Sector 5, 050098 Bucharest, Romania; Phone +40721–837 070, e-mail: ruxandra.babiuc@umfcd.ro