Selective non-operative management of distal rectal cancer: The Watch & Wait Protocol

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Rationale for a non-immediate surgical approach

The observation of improved local disease control with the use of preoperative chemoradiation (CRT) for locally advanced rectal cancer established this treatment strategy as one the preferred initial approaches for this disease. Interestingly, the benefits of preoperative CRT were not restricted to local recurrence rates but also included reduced toxicity rates compared to postoperative CRT, significant tumor downstaging and downsizing, greater rates of sphincter preservation, and better functional results [1, 2].

In some cases tumor regression was so significant, that no residual cancer could be detected in the pathological specimen, a phenomenon known as complete pathological response (pCR).

Even though radical surgery (with TME) is still a cornerstone in the treatment of rectal cancer, it is associated with significant immediate morbidity and mortality. Anastomotic leak is probably the most important complication and is reported in up to 12% of cases [2, 3]. Perioperative mortality may reach 3% and is significantly higher, reaching up to 13% when an anastomotic leak is present among patients who do not undergo temporary diversion [4, 5]. Considering the fact that temporary stoma is almost always required, additional morbidity or even mortality related to stoma creation and take-down should be considered in the cumulative morbidity of rectal cancer management [6]. Also, even though nerve-preserving technique is now standard, the rates of urinary and sexual dysfunctions are quite significant. Finally, even though sphincteric function and quality of life among patients undergoing ultra-low anterior resections are acceptable, results are far from perfect. In a recent report of patients undergoing ultra-low anterior resections, the median fecal incontinence score rate was 11 with nearly half of patients with significant fecal incontinence [7].

In addition, final pathologic disease stage (after CRT) is the most significant prognostic factor in patients with rectal cancer [8]. Patients that develop complete tumor regression (pCR) seem to be associated with improved oncological outcomes [9]. In this setting, it seems appropriate that those patients with no residual cancer, that are associated with the best oncological outcomes would benefit the most from avoiding radical surgery and its associated morbidity and mortality rates.

The question that emerges is: *Is it justified to make our patients undergo a morbid and sometimes mutilating procedure when not even a single cancer cell is collected?* In this setting, identification of patients with complete tumor regression determined by clinical, endoscopic and radiological assessment has been proposed in order to avoid immediate TME in a significant proportion of patients at high risk for developing pCR.

More than providing a radical change in the management of rectal cancer, this approach consists of close surveillance of a select group of patients with a high suspicion of complete tumor response without immediate radical surgery. In one hand, patients with no residual cancer may have a chance to be spared from a major surgical procedure while on the other hand, patients with minimal residual disease and suspected for complete response will have surgery slightly postponed or delayed without any oncological compromise.

Response assessment

In order for such an approach to be feasible, tumor response assessment must be accurate and efficient. Unfortunately, there is still no perfect and definitive tool for this purpose. Instead, a combination of different modalities may be

R. Schiessel et al. (eds.), *Intersphincteric Resection for Low Rectal Tumors*

useful in identifying those patients more likely to harbor no residual cancer. Considering very stringent criteria of these different modalities, such patients have been considered complete clinical responders (cCR).

Clinical assessment

Residual symptoms after CRT should be considered with caution as indicator of a complete response. Even though they may subside in patients with cCR, most patients will present symptom relief despite the presence of residual cancer.

However, clinical assessment including digital rectal examination and proctoscopy by an experienced colorectal surgeon is definitely one of the most important tools in assessment of tumor response. Even though studies have reported disappointing results regarding sensitivity and specificity of this modality in identifying pCR patients, a few considerations may be worthwhile mentioning. First, standardization of what a complete clinical response was and is still unavailable. Also, patients were assessed in these studies using rather short intervals from CRT, a well-known factor that may considerably affect response rates. Finally, the fact that examinations were performed by different surgeons with different experiences, could also have influenced results [10].

In an effort to provide unification and standardization of clinical and endoscopic findings among patients with complete clinical response, our group has recently reported commonly observed features among these patients as well as findings that should warrant prompt surgical action. Not only these findings may aid surgeons in identifying individual patients that are likely to present complete tumor regression, they also may provide a basis for standardization of cCR in order to allow future clinical trials interested in investigating the role of alternative treatment strategies in such patients [11].

According to the stringent criteria provided in that report, patients with the following findings at digital rectal examination and proctoscopy (that can be performed either using rigid or flexible scopes) may be considered as complete clinical responders:

1. Whitening of the mucosa in an area of the rectal wall may be frequently observed in patients with cCR (Fig. 1).
2. Teleangiectasia (small derogative blood vessels seen on the rectal mucosa at the area previously harboring the primary cancer) is also frequently observed in complete clinical responders, even in long-term follow-up.
3. A subtle loss of pliability of the rectal wall harboring the scar; usually observed during manual insufflations at proctoscopy with light stiffness of the wall. In the context of no additional positive findings of residual cancer, this may also be considered as a feature of cCR
4. Whenever a tumor cannot be felt or seen, patients should be considered as complete clinical responders.

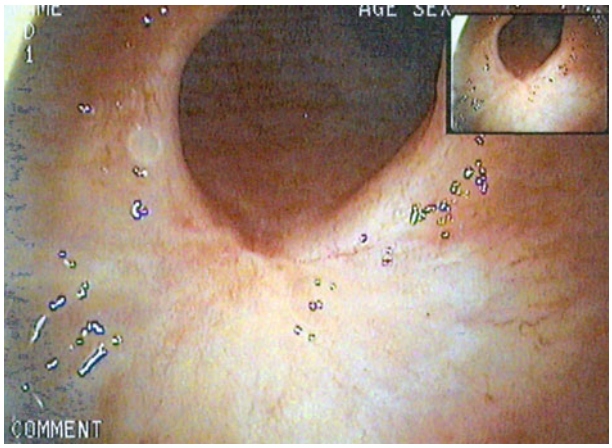

Fig. 1. Endoscopic view of a patient with Clinical Complete Response

Alternatively, the following findings should be considered as incomplete clinical response and therefore warrant immediate surgical action. Even though this may lead to a proportion of patients with pCR despite clinical findings of persistent cancer, it seems to be the safest procedure.

1. Any residual deep ulceration with or without a necrotic center.
2. Any superficial ulcer, irregularity, even in the presence of only mucosal ulceration.
3. Any palpable nodule, easily defined by digital rectal examination, even in the presence of mucosal complete integrity.

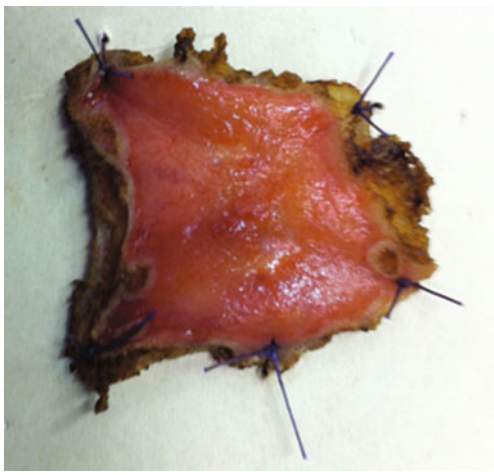

Fig. 2. Surgical specimen of a patient with significant tumor downzising operated by transanal endoscopic microsurgery (TEM)

These endoscopic and clinical findings should be considered of great risk for the presence of residual cancer. In any of these situations, a surgical action is warranted, at least for diagnostic purposes. A non-surgical approach in this scenario is not recommended (Fig. 2).

Radiological studies

Magnetic Resonance Imaging (MRI) and Endorectal Ultrasound provide appropriate primary staging of rectal cancer. Information on T-level classification and distance of the tumor to the mesorectal fascia correlate well with final pathological findings of these patients. Nodal staging is less accurate irrespective of staging modality.

However, after CRT, accuracy of T-level classification has been disappointing and in the range of 50% [12, 13]. If nodal staging seems rather inaccurate even without neoadjuvant CRT, after such treatment, precision may be even worse. Even highly experienced radiologists seem to be better off distinguishing tumors that are restricted to the rectal wall (ypT0-2N0) from those that penetrate through the wall or harbor lymph node metastases (ypT3 or ypN+) instead of providing exact post CRT ycT and ycN staging.

Rectal tumor volumetry on standard T2-weighted MR images was studied by some authors for the assessment of response after CRT with conflicting results. One report did not find difference in tumor volume reduction rates between patients with pCR and those with residual cancer [14]. Confronting this result, a more recent report found that a tumor volume reduction rate of more than 75% was associated with the development of pCR [15].

The introduction of diffusion-weighted (DW) MRI has attracted new interest on the matter. A recent multicentric study, reviewed 120 patients by three trained radiologists comparing standard MRI with DW MRI. Surprisingly, all of them found improvement in sensitivity and specificity rates for the detection of pCR [16]. This imaging modality was able to accurately predict pCR in 94% of the cases. Another recent report showed that post-CRT volumetry on DW-MR images were significantly more accurate than on T2-weighted MR images to assess a CR after CRT [17]. Although promising, more evidence is needed before these tools could be incorporated into routine clinical practice.

In our practice, MRI and/or endorectal ultrasound (ERUS) probably are best suited for the diagnosis of residual extrarectal disease, such as a mesorectal enlarged nodes or masses than for the diagnosis of a cCR. The presence of some thickening of the rectal wall, presence of small perirectal nodes (less than 5 mm) or densification of the perirectal fat, should not prompt any specific or immediate surgical attention, particularly when endoscopic and clinical assessment are normal. These findings are commonly seen in patients with cCR. Alternatively, the presence of highly suspicious perirectal nodes should prompt radical resection. Even though the presence of residual metastatic nodes in the setting of complete tumor regression (ypT0N+) is not frequent, it has been reported in up to 7% of the cases.

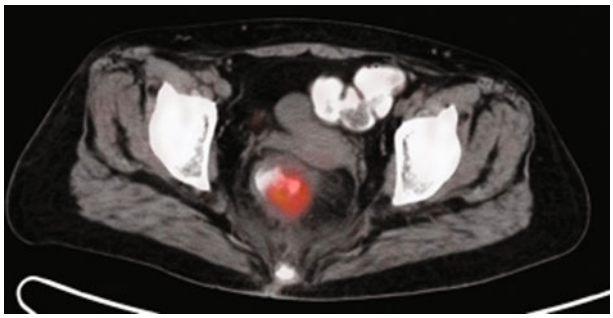

Fig. 3. 12 week PET/CT Scan of a rectal cancer patient treated with neoadjuvant chemoradiation. Metabolic active lesion at rectal wall suggesting incomplete response to therapy

Many expectations have been put in PET/CT in this setting since it provides metabolic information of a given tumor in addition to the structural anatomical findings. This study also provides an objective parameter of tumor metabolic activity by the maximum *Standard Uptake Value* (SUVmax), that can be measured (Fig. 3).

One study of 25 patients with rectal cancer compared the results of baseline PET-CT with a second PET-CT performed after 6 weeks from CRT completion. All patients included in the study experienced a decrease in maximum standard uptake values (SUVmax) between baseline and 6-week PET-CT scans. Also, the final SUVmax obtained at 6 weeks was significantly associated with primary tumor downstaging (patients with tumor downstaging exhibited significantly lower SUVmax) [18]. In another study from Memorial Sloan Kettering Cancer Center including 15 patients undergoing baseline PET followed by a second PET 6 weeks after CRT completion, a visual response score was shown to provide superior prediction of tumor downstaging in addition of the extent of pathologic response to CRT compared to standard CT [19].

These results although promising, should be carefully evaluated since only a small number of patients were included and as will be discussed later, the tumor response was assessed rather shortly (6 weeks) after CRT completion. In another study, 30 patients with locally advanced rectal cancer treated with CRT and surgery were assessed by pre and post-CRT PET-CT for tumor response after 7 weeks from CRT. PET/CT correctly identified six of eight patients with pCR (specificity 75%); unfortunately

sensitivity was only 45 percent and accuracy 53 percent. The positive and negative predictive values were 83 and 33 percent, respectively. The authors concluded that PET/CT could not predict the pathological response in locally advanced rectal cancer [20].

More recently, we were able to conclude a prospective study using PET/CT for the detection of complete tumor regression (pCR or cCR) in considerably larger sample size. After including 99 patients, PET/CT at 12 weeks from CRT completion was able to detect residual cancer with an overall accuracy of 85% and significantly better specificity and sensitvity rates. Even though assessment with PET/CT alone was not superior to clinical assessment alone (accuracy of 91%), it could have potentially corrected "mistakes" made by clinical assessment improving overall accuracy to 96% [21].

CEA

Determination of CEA levels before and after CRT may be useful during assessment of tumor response. In one study with over 500 patients undergoing neoadjuvant CRT, low baseline (before CRT) CEA levels were significant predictors of ypCR after radical surgery in univariate analysis [25]. Curiously, another retrospective report of patients undergoing different CRT regimens showed that a pre treatment CEA level <2.5 ng/dl was predictor of ypCR [22].

An increase in CEA levels or persistence of at least 70% from baseline levels has also been suggested as a significant predictor of worse outcome in patients with CEA levels >6 ng/ml at baseline [23]. Also, different cutoff values have been considered for patients undergoing CRT when compared to standard colorectal cancer patients. A retrospective analysis of 109 patients undergoing neoadjuvant therapy, identified a cutoff value for CEA <2.7 ng/ml at 4 weeks from RT completion to be a statistically significant and independent predictor of tumor regression [24].

Among our own series of patients undergoing, we found no correlation with both pre-treatment CEA and variation between pre and post treatment CEA levels with tumor response and oncological outcomes. On the other hand, a post CRT level <5 ng/ml after at least 8 weeks from CRT completion was a favorable prognostic factor for rectal cancer associated with increased rates of earlier disease staging and complete tumor regression [25].

Endoscopic biopsies after CRT

During endoscopic evaluation of a residual lesion, forcep's biopsies are frequently performed and considered by many to be useful in assessement of tumor response. Even though a positive result implies obvious persistence of residual tumor, negative results may warrant cautious interpretation.

In a retrospective review of patients undergoing post-CRT biopsies, the negative predictive value was as low as 36% [26]. However, it should be noted that these were unselected patients being assessed significantly earlier than 8 weeks from CRT completion.

In a retrospective review of patients undergoing neoadjuvant CRT restricted to patients with significant tumor downsizing, and therefore who were at increased risk to have possibly developed pCR, post-CRT biopsies resulted in a negative predictive value of 21% [27]. In this setting, a negative biopsy of a clinically detectable lesion, even after significant tumor downsizing was not useful for ruling out residual disease and should not prevent surgeons from performing surgical resection. In select cases, excisional biopsy (through a full-thickness local excision) may be considered either as a diagnostic or therapeutic procedure for definitive information on tumor response to CRT.

Factors associated with tumor response after CRT

Tumor response to CRT is not uniform and many factors may play a role. CRT regimen as well as time for assessment of response appear to be as important as tumor and patient characteristics. In this section, the most significant factors are reviewed.

Chemoradiation regimen

Fractionated long course chemoradiation followed by surgery after 6–8 weeks or pelvic short-course irradiation with 25 Gy in five fractions followed by immediate surgery (short-course) are the two most used regimens in the preoperative treatment of patients with resectable T3-4 rectal cancer. Benefits in local disease control seem to be equivalent between them, but there are significant differences in terms of tumor downstaging [28].

The rates of pCR are significantly lower in patients undergoing short-course RT, when compared with those undergoing long-course. At first glance, the long-course regimen includes chemotherapy and this could be determinant for that difference. It should also be considered that damaged cancer cells need time to undergo necrosis after radiotherapy and usually patients undergoing short-course RT, surgery is performed 1 week after RT completion whereas long-course CRT is followed by radical surgery after at least 6–8 weeks.

Indeed, the addition of chemotherapy has been shown to improve rates of tumor downstaging as well as local disease control (i.e. lower recurrence rates) [29, 30]. In a randomized trial of patients undergoing RT with or without 5-FU– based chemotherapy, patients in the CRT group more frequently had a complete pathologic responses less lymph node metastases as well as vascular invasion. Additionally, patients treated by CRT had fewer overall lymph nodes recovered in the resected specimens and decreased tumor size [29].

A review of phase II and III studies using different neoadjuvant CRT regimens for rectal cancer identified several predictive factors for complete pathologic response, including the dose of radiation therapy delivered, the method of 5-FU infusion, and the use of additional drugs to standard 5-FU based regimens. After reviewing over 4000 patients in 71 studies treated with different regimens, complete pathologic response ranged from 0% to 42% and was significantly associated with the delivery of radiation doses higher than 45-Gy, 5-FU regimens with continous infusion, and the use of a second drug, most frequently oxaliplatin [31].

The association of higher rates of pCR and the addition oxaliplatin to the traditional scheme of 5-FU has been strongly questioned in light of the results of a recent prospective randomized trial that showed that this addition was not associated with better rates of pCR. Moreover, patients treated with oxaliplatin experienced significantly more treatment-related toxicities [32].

Targeted biological drugs used for metastatic disease, such as bevazicumab and cetuximab, were included in phase I and II protocols in combination with other drugs with the hope of increasing response rates. However, these expectations were not fulfilled in any of the studies among patients undergoing this 'triple' therapy (5-FU, oxaliplatin, and cetuximab). A review of these trials also suggested a subadditive interaction between capecitabine, oxaliplatin, and cetuximab as reflected by decreased rate of pCR (9 *vs.* 16%) and significant decrease in tumor regression grades (more than 50% of tumor regression) among surgical specimens from these patients when compared with patients undergoing treatment with capecitabine and oxaliplatin alone CRT regimens [33]. It is not clear whether the inclusion of patients according to the K-ras status could have any influence in response to neoadjuvant CRT with this triple approach [34].

Time for tumor response assessment

The Lyon Trial randomized 201 patients with distal rectal cancer T2-3Nx before radiotherapy (39 Gy in 13 fractions) into two groups. The short interval group had surgery performed within 2 weeks after completion of radiation therapy compared to 6 weeks in the long interval group. After a median follow-up of 33 months, no differences in local relapse, morbidity and short-term survival between the two groups could be observed. On the other hand, improved clinical tumor responses ($p = 0.007$) and pathologic downstaging (10.3% *vs.* 26% $P = 0.005$) were observed in the long interval group [35]. These results provided the only prospective evidence, up to present day, to support an interval period of at least 6 weeks from CRT completion before surgery in order to obtain maximal or optimal tumor downstaging.

Recent retrospective studies were able to provide evidence that longer periods after CRT completion could be associated with higher rates of tumor downstaging. These studies have shown that patients managed by radical surgery 7 to 8 weeks after CRT completion had increased rates of complete pathological responses [36, 37]. In another retrospective review from the Cleveland Clinic of patients managed by neoadjuvant CRT, a steep increase in complete pathological response rates was observed when surgery was performed after 7 weeks from CRT. Also, the rates of complete response seem to stabilize only after 12 weeks, suggesting no additional benefit in terms of tumor downstaging after this time [38]. Another study prospectively compared patients with rectal cancer undergoing neoadjuvant CRT followed by radical surgery after 6 or 12 weeks from CRT. Although this study was not randomized and the 12-week group had significantly more advanced disease at baseline (as determined by primary tumor extension), there was a higher rate of pCR rate in this latter even though without statistical significance. Interestingly, the authors showed no increase in postoperative surgical complications among the longer interval group (12 weeks) [39].

The fear of potential metastatic dissemination when tumor is left in place for prolonged periods was used as an argument in favor of an early surgery (<8 weeks) after CRT completion. Noteworthy, tumor cell death seems to be related to a process induced by ionizing radiation. It is thought that after exposure to a dose of 44 Gy, metastatic potential of these tumors might decrease significantly because of the potential decrease in the overall number of surviving cells [40]. In recent studies it was found that prolonged intervals (>8 weeks) from CRT to surgery may not have any associated negative oncologic impact. In addition, these patients undergoing delayed surgery were actually associated with less postoperative morbidity, further supporting the safety of assessing tumor response at longer intervals [41, 42].

Tumor features and biology

Several aspects of the primary rectal cancer such as tumor height, extension and initial disease staging, have been considered to be predictors of tumor response or complete pathological response to neoadjuvant treatment. Even though very few studies have included patients with cT2N0 rectal cancer treated by neoadjuvant CRT, so far there has been no data to support that these tumors would develop pCR more frequently. Still, as experience increases with these earlier tumors being treated with CRT, there is still a chance that baseline stage is indeed a predictor of response to CRT.

In one retrospective study of over 500 patients tumor extension was an independent predictive factor of pCR after neoadjuvant CRT. In this study, circumferential tumor extent of $<60\%$ was significant predictor of pCR. Even though tumor distance from the anal verge was not a predictor of pCR, tumors located in the distal 5 cm of the rectum were more likely to develop greater tumor downstaging [43].

There is a hope that molecular biology will have a significant role in providing additional information and perhaps predicting tumor response to neoadjuvant CRT. Until now, only a few studies have addressed the role of gene expression in predicting response to CRT [44–46]. These studies generally compared "good" to "bad" responders. The problem is that while some of them considered only patients with pCR (as "good" responders), others grouped together patients with significantly different ypTNM stage classification

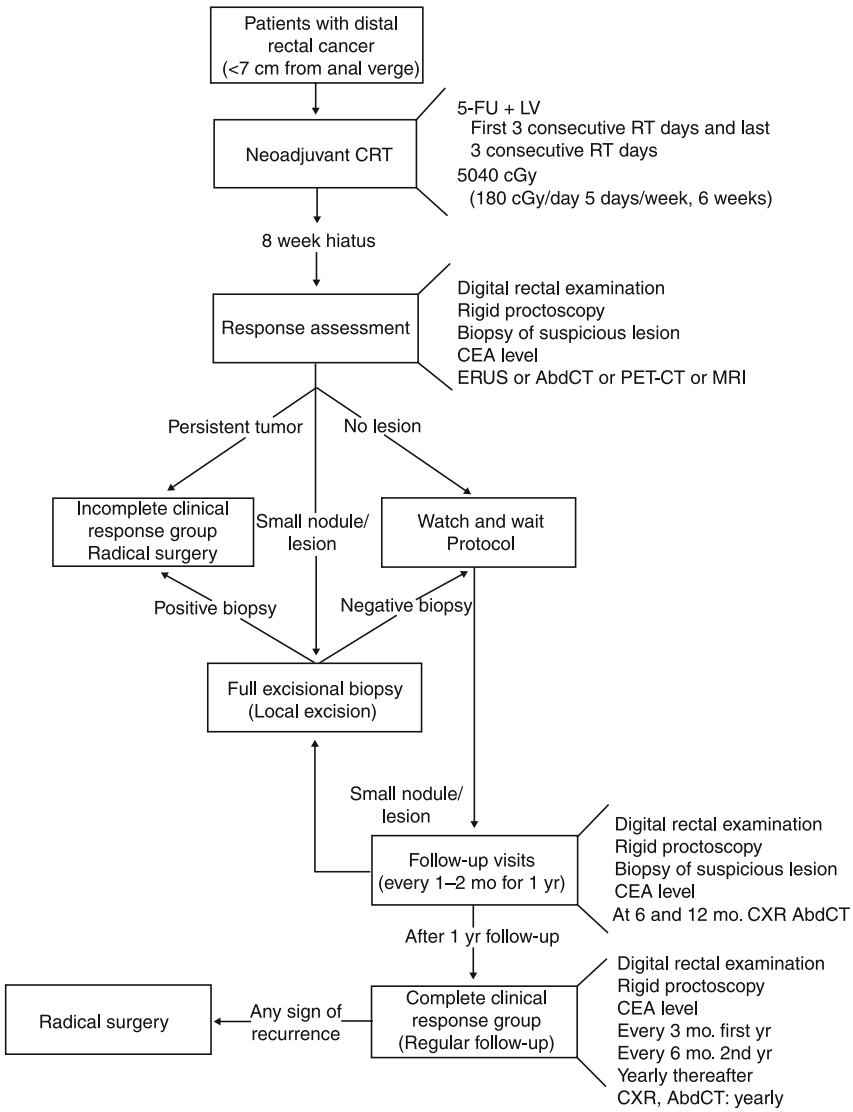

Fig. 4. The Watch & Wait Algorithm

as long as less than 10% of tumor cells were present ("good" response was based on tumor regression grading systems). The end-result is that all three studies suggested a set of genes capable of predicting a "good response" without a single gene in common between them [47]. More recently, it has been observed an strong association with some genes mutation (k-ras, p53 and others) and the absence of pCR [48]. Further studies using more advanced technologies in gene expression analysis are warranted in order to provide more definitive and useful information.

The Watch & Wait Protocol

Patients with complete clinical response, either after clinical assessment or after transanal local excision with complete primary tumor regression (ypT0), are enrolled in a strict follow-up program with no immediate surgery (Fig. 4). Adherence to the program is critical because distinguishing between complete and near-complete responses may sometimes be difficult and final decision might only be possible after a few follow-up visits. This is why an empirical 12-month probation period has been suggested where only patients that sustain a complete clinical response are considered as true cCR's [49].

The algorithm includes monthly follow-up visits with digital rectal examination and rigid proctoscopy in every visit for the first 3 months and every two to three months during the rest of the first year. CEA levels are determined every 2 months. Other radiological studies, including pelvic CT scans or magnetic resonance imaging, are performed at the time of initial tumor response assessment, and then every 6 months if there are no signs of tumor recurrence. Again, the main objective of these radiological studies is to rule out any sign of residual extrarectal disease, such as residual nodal disease that would require further investigation or even radical resection. The use of PET CT has not yet been standardized in the protocol, even though the metabolic information provided by it is useful in some cases.

Patients are fully informed that complete clinical regression of their primary tumor may be temporary and disease recurrence or tumor regrowth may occur at any time during follow-up. In the case of obvious recurrence or tumor regrowth, radical surgery is strongly recommended. Small nodules or scars may develop over time and can be managed by full-thickness transanal excision (either standard or Transanal Endoscopic Microsurgery), primarily as a diagnostic approach.

After 1 year of sustained, complete clinical response, patients are recommended for follow-up visits every 3 months, using the same clinical assessment tools used at initial patient assessment.

This treatment strategy has evolved since the beginning of our experience in 1991. Our accuracy in clinical assessment of tumor response has probably improved significantly with growing experience. At the beginning of our experience, patients were more frequently followed without immediate surgery when a near-complete clinical response was considered expecting that time would lead to a complete clinical response. More recently, these patients have been better assessed using full-thickness local excision (FTLE) as a diagnostic procedure, and according to the pathologic report they are then either managed by strict observation or referred to immediate radical surgery. Availability of surgical techniques such as TEM has also lowered the trigger for FTLE in the presence of questionable residual lesions.

Results

Many patients in our series have still been operated on and found to have ypT0N0 (absence of residual tumor) after radical surgery. It is possible, that incorporation of TEM (Transanal Endoscopic Microsurgery) for diagnostic or assessment of tumor response purposes would lead to a significant decrease in the rates of pCR following radical operations. Still, this is yet to be demonstrated.

In order to understand if there was any oncological benefit of radical surgery in the setting of complete tumor regression, a retrospective study was carried out at our Institution where patients with complete pathological response (pCR) managed by radical surgery were compared to patients with cCR managed non-operatively [50].

Patients managed by observation alone had similar outcomes to those managed by radical surgery in terms of long-term survival. Local recurrences were higher in the observation group. However, all recurrences were confined to the rectal wall and amenable to surgical salvage. No exclusive pelvic relapses without endorectal component was observed.

Five-year overall and disease-free survival rates were associated to disease final stage (clinical or pathological) and were 88% and 83% in pCR group and 100% and 92% in cCR group. These excellent survival rates in patients stage pCR and cCR were significantly better than those observed in patients ypII and ypIII. Patients with stage ypI had intermediate results.

An interesting observation is that in our series, systemic recurrences in cCR patients occurred considerably earlier than local recurrences. Besides intrinsic tumor behavior, this could be partly explained by the

staging inaccuracy of the different available imaging modalities, which were probably not capable of detecting microscopic foci or metastatic disease at initial presentation.

Also, local recurrences were observed in 10% of patients managed nonoperatively after a cCR and developed considerably later during follow-up. This has also been observed in other series, where more than one third of patients who develop local recurrences after neoadjuvant CRT and radical surgery, did so after 5 years of follow-up. In contrast, 75% of patients that develop local recurrences after radical surgery alone, do so within 2 years of follow-up. This information may have implications when considering follow-up and surveillance strategies [51].

Up to now, all local recurrences in patients with cCR after neoadjuvant CRT were amenable to salvage therapy. These recurrences and their salvage procedures were performed at considerably long intervals after CRT completion (mean > 50 months). In almost half of the cases an abdominoperineal resection (APR) was performed. Also, a third of these patients presented with low and superficial recurrences, amenable to full thickness transanal excision [51].

A significant subgroup of patients, presented early tumor regrowth (within 12 months from CRT completion). These patients were most commonly misdiagnosed as cCR and had their definitive surgical treatment postponed for variable periods of time. This raised the question whether these patients could have been harmed from an oncologic standpoint by delaying definitive surgical resection. However, long-term data revealed that they fared no worse than patients with incomplete clinical response and managed by radical surgery after 8 weeks from CRT completion. Noteworthy, final pathology in this group revealed significant tumor downstaging and even lower rates of lymph node metastases, further supporting the idea that downstaging is a time-dependent phenomenon. The fact that these patients were more frequently managed by APR, could reflect a motivation (both by the surgeon and the patient) to delay final decision on radical resection, knowing that tumor regression could be still going on [42].

Evolution: The extended chemoradiotherapy regimen

In order to increase the rates of tumor response, the delivery of chemotherapy during the waiting or resting period between radiation completion and tumor response assessment has been implemented in our Institution. This regimen consists of 45 Gy of radiation delivered by a three-field approach with daily doses of 1.8 Gy on weekdays to the pelvis, followed by a 9-Gy boost to the primary tumor and perirectal tissue (54 Gy total). Concomitantly, patients receive three cycles of bolus 5FU (450 mg/m^2) and a fixed dose of 50 mg of leucovorin for three consecutive days every three weeks. After completion of radiation, patients receive three additional identical cycles of chemotherapy every three weeks (21 days) during nine weeks. Tumor response assessment is performed immediately at 10 weeks from radiation completion (Fig. 5).

In a preliminary report of our series including T2/T3 distal rectal cancers, the sustained complete clinical response rate (>12 months) was 65% with no significant increase in chemotherapy-related toxicity rates [52].

Perspectives

Many are the aspects in the management of complete clinical response after neoadjuvant CRT that remain unresolved and that should be focus of future research.

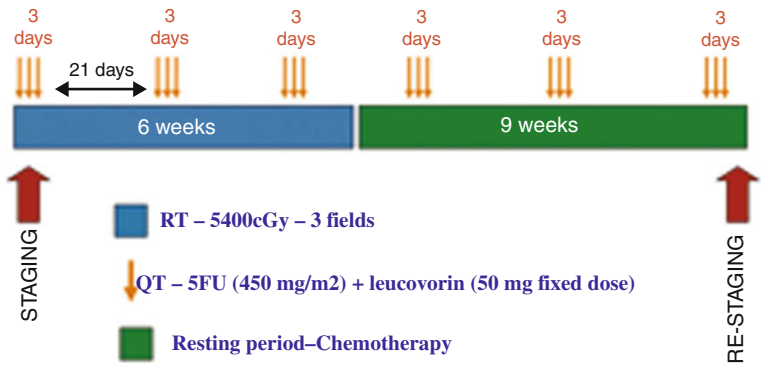

Fig. 5. The Extended Chemoradiation Regimen

Ongoing prospective randomized trials comparing different intervals between CRT completion and tumor assessment may provide additional information regarding this particular issue in rectal cancer management. Also, perhaps data from PET/CT imaging at different intervals from CRT completion may indicate kinetics of tumor metabolism as function of time in these patients.

Novel radiation therapy regimens including alternative radiation doses, delivery methods, and technical variants to maximize radiation-related tumor cell death and minimize side effects is an area of special interest. Moreover, improved chemotherapy regimens might lead to an increase in the rate of complete clinical response and, maybe, improve survival rates. Some investigators have suggested the use of aggressive induction chemotherapy before the delivery of radiation to provide immediate treatment of undetected microscopic foci of metastatic tumor cells in addition to the primary tumor. These regimens are currently under investigation in controlled trials to provide data on safety and long-term benefits [53].

Finally, development of next generation gene sequencing technology may allow further understanding of molecular genetic events relevant to sensitivity or resistance to neoadjuvant CRT. Identification of gene signatures may allow improvement of patient selection leading to true individualized management decisions. There is hope that studies using RNAseq technology may provide more definitive information in the near future.

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