The 2017 Assisi Think Tank Meeting on rectal cancer

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Debate

The 2017 Assisi Think Tank Meeting on rectal cancer: A positioning paper ☆

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ABSTRACT

Background and purposes: To describe current practice in the management of rectal cancer, to identify uncertainties that usually arise in the multidisciplinary team (MDT)'s discussions ('grey zones') and propose next generation studies which may provide answers to them.

Materials and methods: A questionnaire on the areas of controversy in managing T2, T3 and T4 rectal cancer was drawn up and distributed to the Rectal-Assisi Think Tank Meeting (ATTM) Expert European Board. Less than 70% agreement on a treatment option was indicated as uncertainty and selected as a 'grey zone'. Topics with large disagreement were selected by the task force group for discussion at the Rectal-ATTM.

Results: The controversial clinical issues that had been identified within cT2–cT3–cT4 needed further investigation. The discussions focused on the role of (1) neoadjuvant therapy and organ preservation on cT2-3a low-middle rectal cancer; (2) neoadjuvant therapy in cT3 low rectal cancer without high risk features; (3) total neoadjuvant therapy, radiotherapy boost and the best chemo-radiotherapy schedule in T4 tumors. A description of each area of investigation and trial proposals are reported.

Conclusion: The meeting successfully identified 'grey zones' and, in the light of new evidence, proposed clinical trials for treatment of early, intermediate and advanced stage rectal cancer.

Introduction

Patient and tumour heterogeneity, different therapeutic approaches, clinical outcomes and/or treatment toxicities in rectal cancer, justify setting-up a large database and developing predictive models for decision support systems inside the new personalized medicine concept [1–3]. Modern clinicians need to weigh up extensive information about demographics, patients' QoL, patient and physician/surgeon preferences as well as analyse data from images, pathology reports, blood tests, biomarkers, genomics and proteomics.

Medical imaging technologies has switched from being primarily a qualitative, diagnostic tool to a quantitative one. In the last

Abbreviations: ATTM, Assisi Think Tank Meeting; ESTRO, European Society for Radiotherapy & Oncology; RT, radiation therapy; MDT, multi disciplinary team.

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decade, several studies have been conducted to identify quantitative imaging features that can discriminate patients with different prognosis so as to avoid over-treatment in some patients or inadequate therapy in others [4–6]. Texture parameters (kurtosis, skewness, entropy and mean value of positive pixels) derived from T2 weighted MRI were reported to act as imaging biomarkers of tumoral response to neoadjuvant CRT [4,7,8]. Metabolic and textural features from pre-treatment 128FDG PET/CT scans were assessed as potential predictors of neoadjuvant CRT response [6]. However, the potential for radiomic cohorts and feature dimensions is still under investigation, reflecting the high uncertainty [9–11] that still lingers on quantitative imaging analysis.

Following several Multidisciplinary Consensus Conferences on rectal cancer in Perugia [12,13], the ''Assisi Think Tank Meeting" (ATTM) on Rectal Cancer was held on 19–21 March 2017, in Assisi, Italy, under the auspices of the European Society for Radiotherapy & Oncology (ESTRO). The meeting was designed to identify current practice in management of rectal cancer and propose the next generation of studies which may provide answers to uncertainties that usually arise in multidisciplinary team (MDT) discussions ('grey zones').

Therefore, the possibility to have an easy access to a high-quality large database will reduce subjectivity in decision-making and facilitate tailored therapies, which are crucial in rectal cancer as the same treatment could lead to different outcomes in individual patients.

Like the very successful 2016 ATTM on breast cancer [14], the 2017 ATTM on rectal cancer (Rectal-ATTM) was planned as 3 days intensive brainstorming on current therapeutic approaches for T2, T3 and T4 rectal cancer. Clinical challenges were identified by means of in-depth, evidence-based discussions. Here we report the Rectal-ATTM's methodology, the outcome of discussions, final conclusions and proposals for future studies.

Methodology

To identify trials to reduce areas of uncertainties, the so called 'grey zones', a three-step process was adopted.

Before the meeting

(1) *Identification of grey zones in the management of rectal cancer*
   (a) The Scientific Organizers (VV, CA, CM) selected an Expert European Board on the basis of clinical and research experience in rectal cancer, as indicated by their scientific profiles and participation in clinical trials, research projects and guidelines.
   (b) Together with the Scientific Organizers, a task force (CC, KH, FP, KB, GB, MAG, CvdV, CR, AC, BDB, HR, RGJ) designed a questionnaire to elicit controversies in T2, T3 and T4 rectal cancer which was distributed to the Rectal-ATTM Expert European Board. Less than 70% agreement on a treatment option was indicated as uncertainty and selected as a 'grey zone'.
   (c) Grey zone topics were selected by the task force for discussion at the Rectal-ATTM.

(2) *Literature scanning and ongoing trials on the grey zones*
   (a) Members of Rectal-ATTM were divided into 3 groups (group 1: T2, group 2: T3, group 3: T4). Each group included two Chairs and a Secretary. The Chairs identified speakers to review the main evidence from the literature, highlight state-of-the-art data graded according to evidence level, and analyse on-going clinical trials in depth. Chairs would also wrap-up the debates and review the final conclusions.

At the meeting

Day 1: Day one was reserved only for experts (organizers and expert board members).

Each of the 3 groups met separately to present reviews of the grey zones in respectively T2, T3 and T4 rectal cancer, examine evidence from literature, discuss on-going trials and make proposals for trials to address uncertainties.
The two chairs selected the main trial proposals to report and discuss on the following 2 days.

Day 2: The Main Meeting was open to all physicians and surgeons who were involved in rectal cancer management. Current evidence, on-going clinical trials and study proposals, related to the grey zones were explored in a general, free for all, discussion. An interactive voting system, prepared at the end of day one, enabled participants prioritize proposals.

Day 3: The Expert Board and Scientific Organizers drew up protocol proposals for each disease stage and the main ''Position Paper" features.

After the meeting

A writing committee, organizer and secretary, wrote the first draft of the ''Position Paper" which was circulated among the experts for their comments before the organizers' final review.

Results

Survey results (questions and answers) are summarised in the Appendix 1.

The area of investigation, description and trial proposals are reported for each clinical issue (T2–T3–T4).

Clinical issue 1: T2 cancer

The experts agreed that 'T2 tumors' are not a single disease and the treatment varies greatly in respect of the low, middle- and high- location and of the N involvement (N0 and N1 tumors). Neo-adjuvant treatment is controversial, especially in low cT2 and N1 tumors, as well as adjuvant treatment in tumors with unfavorable histological features after resection.

During the Rectal-ATTM, a strong need emerged for new (chemo)-radiotherapy (CRT) strategies and optimized RT techniques to reduce morbidity and mortality and improve quality of life and the chances of pathological complete response (pCR) and organ preservation.

Table 1 summarizes the clinical and therapeutic aspects that reached under 70% agreement. The discussions focused particularly on the role of neoadjuvant therapy and organ preservation on cT2-3a low-middle rectal cancer.

It is sometimes argued that patients should be offered CRT even in the absence of standard indications or clinical trial participation so as to access organ preserving treatment. The GRECCAR2 trial [15] randomized patients with cT2-3N0-1 low rectal cancer and good response to CRT to receive local excision or total mesorectal excision (TME). Composite endpoints included death, recurrence, major surgical morbidity (grade III-IV Clavien Dindo) and severe complications (definitive colostomy, anal incontinence, impotence). Although around 10% of patients in the local excision group were assumed to achieve a poor pathological response requiring TME, the number was much higher than expected as were related morbidity and complication rates. This discrepancy accounted for the surprising overall outcome of 56% *vs* 48% in favor of TME. Even though local excision was confirmed as safe and feasible in most

Table 1
Summary of the questions that did not achieve at least 70% of agreement amongst the experts in the therapeutic approach to the cT2-3a clinical case. TME (total mesorectal excision); PME (partial mesorectal excision); RT-CT (long course radiochemotherapy); CT (chemotherapy); FUP (follow-up).

Issue	Question
Low cT2 N1	
Primary therapeutic approach	– RT + Surgery vs RT + Organ Preservation
cT2N0 medium and high	
Neoadjuvant treatment	– RT schedule: RT-CT vs 5 × 5 Immediate Surgery vs 5 × 5 Delayed Surgery
cT2N0-1	
Neoadjuvant treatment	– RT-CT for organ preservation: boost vs no boost
Restaging	
Time after neoadjuvant treatment	– 6 weeks vs 10 weeks vs 6 and 10 weeks
cCR post neoadjuvant treatment	
Adjuvant treatment	– WW vs LE of the scar
Post local excision, high risk features	
Adjuvant treatment	– TME vs RT-CT vs RT-CT + TME
Post TME pN1	
Adjuvant treatment	– CT vs RT-CT vs FUP
Post neoadjuvant RT (long course or 5 × 5), pN1	
Adjuvant treatment	– None vs CT

patients, the study illustrated the risks of implementing experimental treatment before evidence showing the necessity of well-designed and conducted randomized clinical trials (RCTs).

Areas of investigation

Is there any room for preoperative treatment in early rectal cancer?

Neo-adjuvant treatment of these early tumors is controversial [12,16]. T2 tumors, especially small ones, have a higher chance of reaching clinical CR (cCR) after neoadjuvant therapy than more advanced stage tumors [17–20]. However, the risk of local recurrence is low, and CRT does not provide a survival advantage while it is associated with a substantial risk of acute and late toxicity and even mortality.

Furthermore, should oncologists opt for neo-adjuvant treatment, the best schedule has yet to be established. When CRT is used, conventional schedule includes 25 fractions of 2 Gy delivered with standard RT fields and 5-FU based chemotherapy. In a dose-escalation strategy a total dose of 54 Gy (27 fractions of 2 Gy/daily) were reached in association with 5-FU-based chemotherapy [20]. CRT followed by delayed surgery (6–10 weeks) usually downstaged the disease [21,22]. Another option is short course radiotherapy (SCRT) which delivers 1 fraction daily of 5 Gy for 5 days. When followed by surgery within 1 week no downstaging was observed [23,24] but when surgery was delayed tumors were down-staged [25–27]. In fact, the Stockholm III trial found an 11.8% pCR rate after SCRT and delayed surgery *vs* 1.7% with immediate surgery [28].

Although designed for local advanced rectal cancer, a third option is 5 × 5 Gy followed by FOLFOX as in the Polish 2 trial [29]. No differences were observed in local efficacy between 5 × 5 Gy with consolidation chemotherapy and long-course CRT.

Can organ preservation be promoted in early tumours?

The on-going phase II, 3-arm STAR-TReC trial is investigating SCRT and delayed surgery and CRT (long course RT concurrent with Capecitabine: 825 mg/m^2 orally) in organ preservation strategies for early stage rectal cancer [30]. To reduce the risk of toxicity, radiation fields are small and include only the mesorectum, without other elective lymph node areas. Capecitabine is only given on days when irradiation takes place. Patients with cT1-3bN0M0 disease (up to 5 mm extramural spread) are randomized to receive standard TME (control) or one of the two organ saving approaches. To avoid timing biases, the first assessment is held 11–13 weeks after starting RT in both experimental arms. Response to treatment, as assessed by endoscopy and magnetic resonance imaging (MRI) for the tumor regression grade, will determine the next treatment step. Non-responders will undergo TME while responders will be reassessed by endoscopy at 16–20 weeks. Whoever achieves cCR may progress directly to active surveillance; those who do not, will undergo a full thickness excision biopsy with transanal endoscopic microsurgery (TEM). In several years' time, the STAR-TReC trial will show which RT ± CT schedule best provides organ preservation and disease control and whether smaller mesorectal radiation volumes are less toxic and oncologically safe.

Another issue in organ preservation in early stage rectal cancer is dose-escalation to the primary tumor as adding a boost might increase pCR rates. In fact, in locally advanced rectal cancer, Appelt et al. showed a significant dose–response relationship for tumor regression after preoperative CRT (50.4–70 Gy) [31] and reported a higher percentage of major response (TRG 1–2) in patients treated with a brachytherapy boost after CRT (44% *vs* 29% CRT only) [32]. Unfortunately, the higher major response rate did not lead to a higher pCR rate. Delaying surgery beyond 8 weeks after CRT might have allowed more downstaging and consequently, more CR. Even though the brachytherapy boost was safe and feasible, it is highly specialized treatment that is not widely available.

What is the best follow-up strategy in an organ preservation program?

The need for a standardized evaluation and follow-up strategy in all organ preservation approaches was discussed. Since strategies are different in most studies, comparisons are difficult. To overcome the problem, a centralized data-base would be helpful. A good start is to use the EURECCA international watch & wait database to collect at least all organ preservation patients prospectively and to build up outcomes from diverse approaches [33].

Trial proposal

The T2 case working group proposed the Preoperative Radiotherapy for Organ Preservation in Early Rectal cancer (ATTM. PROPER) trial. This blinded clinical trial is designed to optimize CRT with the aim of achieving a higher organ preservation rate, less toxicity and good functional outcome in early low and middle rectal cancer. Target volumes will be smaller and the RT dose higher than the standard 50 Gy (Fig. 1).

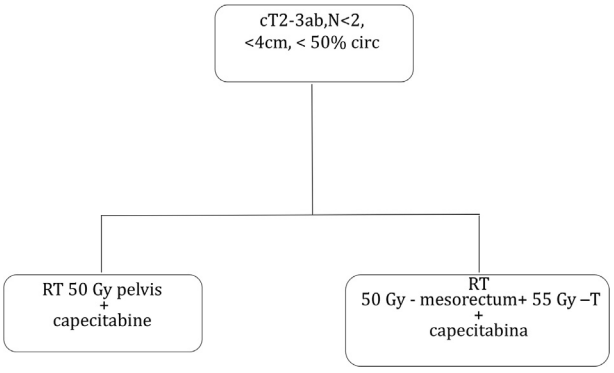

Fig. 1. cT2 rectal cancer: trial design ATTM PROPER.

Trial design

Patients will be randomised to standard 50 Gy RT with conventional radiation volumes vs experimental 50 Gy RT only to the mesorectal volume plus a simultaneous integrated boost (SIB) to the primary tumour and lymph nodes if involvement was demonstrated by multiparametric imaging. All patients will receive oral capecitabine (or 5-FUic depending on the on RT days). As the number of fractions is the same in each arm, the study will be blinded. Response evaluation and follow-up strategy will be in line with the STAR-TReC trial [34]. 11–13 weeks after starting CRT, patients will be restaged and those in cCR or major response will proceed to a second evaluation 6 weeks later. After this, patients with a cCR will be allocated to a 'watch and wait' strategy, patients with minor residual disease will undergo local excision; all others will receive a TME.

Inclusion criteria

- cT2-3a/b, as defined by MRI.
- <cN2 located peri-tumoral and not extra-mesorectal.
- no mesorectal fascia invasion.
- no extramural venous invasion (EMVI).
- distal tumor border located maximally 5 cm from the anorectal junction on sagittal MRI.
- maximum tumor size 4 cm.
- maximum 50% of circumference involvement.

Endpoints

The primary endpoint is a composite endpoint including 2-year organ preservation rate, functional outcomes and QoL; a 10% improvement is expected. A scoring system for functional outcome in organ preservation patients, like the LARS score, should be used.

Secondary endpoints include toxicity, surgical complications, pelvic failure rate, 2 years disease free (DFS) and overall survival (OS) rates.

Recommendation

Patients should be included in the watch and wait database (IWWD) [33].

Clinical issue 2: T3 cancer

Introduction

Neoadjuvant therapy followed by TME is today standard treatment for cT3 rectal cancer. The survey results and live discussion during the meeting, clearly showed that cT3 encompasses a broad spectrum of tumor presentations, with different long-term outcomes.

The panel focused the discussion on the so-called 'low-intermediate risk T3 tumors', which were defined as located in the mid-rectum, with fat infiltration up to 5 mm, not reaching the mesorectal fascia, with fewer than 3 positive nodes (cN0-1), non-mucinous and EMVI negative.

Survey results were evenly split, with half of the experts supporting any kind of neoadjuvant therapy and the other half advocating immediate TME (Fig. 1). Thus, the panel decided to review the role of neoadjuvant therapy in this sub-group of patients and search for potential trials.

Table 2 summarizes the clinical and therapeutic aspects that reached under 70% agreement. The discussions focused on the role of neoadjuvant therapy in cT3 low rectal cancer without high risk features.

Table 2
Summary of the questions that did not achieve at least 70% of agreement amongst the experts in the therapeutic approach to the cT3 clinical case. TME (Total Mesorectal excision); RT-CT (long course radiochemotherapy).

Issue	Question
cT3a-b, N0, no risk factors	
Primary therapeutic approach	– TME vs preoperative treatments
cT3a-b, N0, 1 risk factor (EMVI+ or cN1)	
Primary therapeutic approach	– TME vs chemoradiation (classicor RAPIDO-like)
cT3c-d, N0, no risk factors	
Neoadjuvant treatment	– chemoradiation vs 5 × 5 immediate surgery vs 5 × 5 delayed surgery 5 × 5 D
Post TME, 1 risk factor (EMVI+ or pN1)	
Adjuvant treatment	– Adjuvant CT vs Adjuvant RT-CT
After neoadj, 1 risk factor (CRM+ or EMVI+)	
Adjuvant treatment	– Adjuvant CT vs none

Areas of investigation

What is the role of neoadjuvant radiotherapy?

The role of neoadjuvant RT was assessed in several randomized trials [21–24,35]. SCRT and long course CRT both produced 5-year local recurrence rates below 6%, although no advantages in DFS and OS were obtained in any single trial. Similar results were seen after longer follow-ups [36–39]. Despite very good local control with this multimodal approach, distant failure still remained an issue, with 10–15% of patients dying from metastatic cancer.

Accurate assessment of pathological specimens identifies a wide spectrum of tumor responses after neoadjuvant CRT. Patients are classified as excellent, good or no responders with response directly correlating with long-term outcomes. In fact, complete responders showed better local control and better overall survival [1,18] while non-responders or patients with positive CRM had worse outcomes [40]. These disease profiles cannot be observed after SCRT and immediate surgery, due to the brief time lapse.

With the aims of increasing tumor response and improving long-term oncological outcomes, several trials attempted to intensify (neo)adjuvant treatment (e.g. concomitant drugs, dose escalation, adding post-operative chemotherapy, complete neoadjuvant therapy). However, due to the high heterogeneity of the schedules, patient populations and outcome parameters, no firm conclusions were reached. Consequently, at present standard treatments remain either SCRT or long course RT in combination with 5-FU based chemotherapy [41–43].

Despite the advantages of a preoperative approach, CRT or SCRT significantly increased the rate and intensity of surgery-related urinary, rectal and sexual dysfunction, thus worsening QoL in long-term survivors [44]. Although surgery is the major contributor for sexual and defecation dysfunction [44], short course radiotherapy was associated with detriments to anorectal, and sexual functions [37,45,46]. Fecal incontinence, anal blood and mucus loss occur significantly more frequently in irradiated, than in non-irradiated, patients. Preoperative RT had a negative effect on sexual functioning in both sexes, manifesting as erectile dysfunction and ejaculation disorders in males and vaginal dryness and dyspareunia in females. A multi-center prospective longitudinal study evaluated bowel function, fecal incontinence and QoL in rectal cancer patients who underwent neoadjuvant CRT. At the 2-year follow-up, 78% of patients had stool fractionation, 72% had the feeling of incomplete defecation, 49% used pads and 38% had both urgency and three or more bowel motions per day. Only 14% of patients had excellent fecal continence [47]. These results demonstrated that the decision to apply neoadjuvant RT for low-intermediate risk cT3 tumors should not be taken lightly. Data about the risk of second malignancies is not conclusive [48].

Is there any room for surgery alone?

Some groups omitted preoperative RT in patients whose preoperative MRI indicated a high probability of achieving clear surgical margins. The surgery-alone approach did not appear to decrease local control or disease-free survival [49–52]. The quality of surgery became crucial in this setting. In fact, several studies demonstrated that the majority of local recurrences derived from inadequate mesorectal resection and that about half of patients with local recurrences had residual mesorectal fat on MRI [53,54]. Consequently, the surgical specimen should have an intact mesorectum, with minor irregularities over a smooth surface and no defect deeper than 5 mm, no coning and with a smooth circumferential resection margin on slicing, as established by Quirke et al [55,56].

Is neoadjuvant chemotherapy an option for preoperative treatment?

Since adjuvant chemotherapy provided good results in colon cancer, postoperative chemotherapy was studied in stage III rectal cancer patients who had received neoadjuvant RT. As initial expectations of improved DFS and OS were not satisfied, several factors were investigated to account for the discrepancy (e.g. long interval before starting adjuvant chemotherapy, effect of poor compliance on treatment, tumour biology modification from chemoradiation) [57]. Furthermore, a small advantage might not have reached statistical significance [58].

Chemotherapy alone was proposed in some clinical trials as the only preoperative treatment in rectal cancer since it reduced local failure and distant metastases, which are nowadays the main site of failure [1,38]. Moreover, response to neoadjuvant chemotherapy may be an indication of tumor biological behavior [59,60]. Additionally, neoadjuvant chemotherapy can be administered before CRT with the aim of increasing the pCR and reducing the distant metastasis rates.

As neoadjuvant chemotherapy (NACT) alone, FOLFOX with or without bevacizumab was investigated in feasibility and retrospective studies. pCR rates ranged from 7% to 35%. Since patient cohorts were small and the studies were non-randomised, with short follow-ups, they were unable to show any impact on metastatic disease or local recurrence [61–64]. However, the proof of principle encouraged many current studies to explore neoadjuvant chemotherapy.

The ongoing PROSPECT randomized trial is testing the role of neoadjuvant FOLFOX [65] in patients with early-intermediate rectal cancer (T2N1, T3N0-1) and an indication to surgery. They are randomized to receive chemotherapy alone (followed by selective CRT in non-responders) versus standard CRT. Results are expected in 2021.

What role does imaging play in risk stratification?

Several advances in rectal cancer staging have been made with the routine use of pelvic-MRI. As the standard imaging modality, it sub-classifies T3 tumors into three groups that correlate with different prognoses [66].

Pelvic MRI accurately defines tumor extension into mesorectal fat, mesorectal fascia infiltration, extra-mural venous invasion and mucinous tumor.

Tumor extension into mesorectal fat and mesorectal fascia infiltration

Tumor invasion of mesorectal fat was associated with poorer survival. Independently of nodal involvement, a cut-off of 5 mm invasion was linked to more than 30% difference in OS [67]. The MERCURY Study Group reported on MRI accuracy in identifying the mesorectal fascia and in producing results that were comparable with histological analysis [68]. cT3 tumors were sub-classified into cT3a <1 mm, cT3b between 1 and 5 mm, cT3c between 5 and 15 mm and cT3d more than 15 mm. Furthermore, the Study Group showed that using a 1 mm cut-off on MRI a negative histological CRM could be predicted. For example, <1 mm distance between tumor and MRF predicts a high probability of a positive CRM. The 2016 ESGAR recommendation on MRI in rectal cancer suggested dividing and reporting tumors at least as T3ab <5 mm or T3cd >5 mm [69].

EMVI

Pathological extramural vascular invasion (EMVI), which is an independent poor prognostic factor in rectal cancer [70], is easily detected on MRI.

A recent metanalysis showed that 34.6% of rectal cancer patients had EMVI at diagnosis. EMVI on the diagnostic MRI was associated with a more than 5-fold chance of metastases at presentation and a 4-fold probability of developing distant metastases during follow-up [71].

Mucinous tumor

Mucinous tumors are correlated with worse outcomes as tumor response, local control, the metachronous distant metastasis rate [72] and overall survival were all worse than non-mucinous tumors. MRI is highly accurate in identifying mucinous tumors as high signal T2 weighted imaging. The percentage of mucin identified on MRI correlated with prognosis, with worse outcomes when the mucinous component was over 50%.

Trial proposal

The T3 working group proposed setting up an International **CO**hort study evaluating **R**adiotherapy T3 **RECT**al cancer (**ATTM. CORRECT)**, which was designed to assess whether neoadjuvant treatment is needed in T3 tumors at low/intermediate risk (Fig. 2).

Low-intermediate T3 tumors were defined as located in the mid-rectum, with fat penetration up to 5 mm (T3ab), no mesorectal fascia infiltration, negative or up to 3 positive nodes (N0-1), no positive extramesorectal nodes and no EMVI.

Trial design

Patients will be randomized to either TME or neoadjuvant therapy. Each participating centre will use one of the following neoadjuvant therapy schedules:

- SCRT (5 × 5 Gy) and delayed surgery.
- CRT (45–50 Gy combined with Capecitabine).
- neoadjuvant chemotherapy alone (Folfox 6 cycles), depending on PROSPECT results.
- brachytherapy (4 × 6.5 Gy) [73].

Patients will be re-staged 12–13 weeks after the beginning of neoadjuvant treatment.

Good/major or complete responders will be re-evaluated at 16–20 weeks and if major or complete response is maintained, patients will be candidates for organ preserving strategies (Fig. 2).

Data will be collected in a multiple cohort RCT design [74].

Endpoints

Primary: equal DFS at 3 years.

Secondary

- HRQL at 2 years, measured with LARS score, EORTC-C30 and CR29 and the newly developed CTCAE pro for rectal cancer [75].
- Validation of MRI based staging in the surgery only arm.

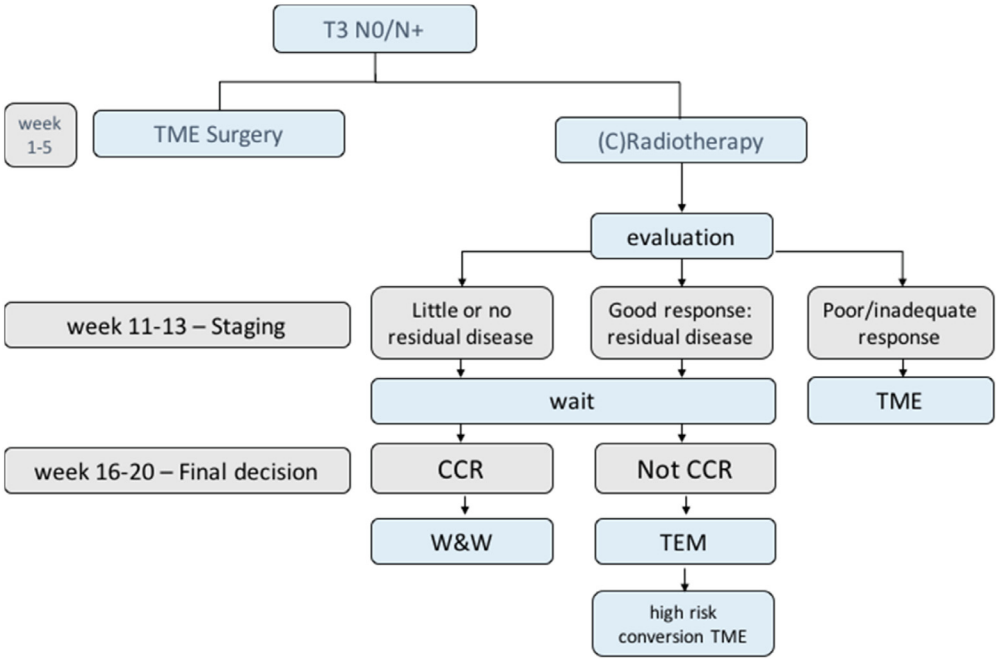

Fig. 2. cT3 rectal cancer: trial design CORRECT.

- Influence of Quality of Surgery on DFS.
- Influence of Quality of Radiotherapy on DFS and functional outcomes.
- pCR rate after different neoadjuvant strategies.
- 3 year local recurrence rate (including pelvic failure after organ preservation).
- 3 year distant metastasis rate.
- 3 year stoma free survival.

Patient selection

Patients will be selected according to MRI criteria.

Inclusion criteria

- cT3ab, <cN2.
- Mid-rectal tumors sited between the peritoneal reflection and at least 3 cm above the anal-rectal junction. Measurement should be on sagittal MRI for the lower border.

Exclusion criteria

- Mucinous/signet ring tumors on histology or MRI.
- Circumferential tumors.
- Threatened MRF on MRI.
- Presence of EMVI.
- cN2 disease.
- Suspected extra-mesorectal lymph node involvement.
- M1 disease.

Clinical issue 3: T4 cancer

Introduction

T4 tumors infiltrate surrounding structures or organs and form a subset of the larger group of heterogenous locally advanced rectal cancers (LARC). Indeed, some patients are at higher risk of local relapse (mostly T4N0-1, EMVI), while others have a greater risk of metastatic spread (mostly T4N2, EMVI+). As the underlying biology clearly differs in these two groups, diverse therapeutic approaches are required.

Despite the lack of randomized clinical trials, total neoadjuvant therapy (TNT) is an emerging option especially for patients with a high risk of metastases (clearly positive-node disease, high risk of a margin-positive resection or a diseased mesorectal fascia). Shifting systemic therapy delivery (RCT and subsequent chemotherapy) to the neoadjuvant setting might improve compliance rates, reduce toxicity and decrease rates of distant metastases [76–78]. In addition, TNT might impact beneficially on the CR rate, thus facilitating a non-operative strategy with the potential to increase the pool of patients with LARC who are eligible for organ preservation. Long-term follow-up will determine if these findings translate into improved survival.

T4 rectal cancers are classified as resectable or unresectable. Unresectable rectal cancers [41,43,79–81], which account for 10–15% of all tumors, are large immobile tumors or are fixed to non-removable structures (proximal sacrum, pelvic side wall, pelvic floor, prostate, or the urinary bladder base). Their management is complex, requiring a multidisciplinary approach. Few studies, often with small samples, have focused on the treatment of unresectable tumors and the role of CRT was assessed in only one randomized trial [80]. Although some large randomized studies assessed the role of neoadjuvant CRT in LARC cohorts which included both T3 and T4 cancer, the number of patients with T4 cancer is too small to clarify the role of neoadjuvant treatment for them.

Consequently, no firm conclusion can be drawn on the optimal treatment of T4 rectal cancer patients [29,41,43,79,80].

Table 3 summarizes the clinical and therapeutic aspects that reached less than 70% agreement. The discussions focused particularly on the role of TNT, RT boost and the best CRT schedule in this clinical setting.

Areas of investigation

Is neoadjuvant chemotherapy with or without CRT feasible for LARC?

Several studies [36,82] showed that neoadjuvant CRT was standard of care for patients with clinically staged T3 or T4 or node-positive disease [21,83]. Braendengen et al. randomized 207

Table 3
Summary of the questions that did not achieve at least 70% of agreement amongst the experts in the therapeutic approach to the cT4 clinical case. TME (total mesorectal excision); PME (partial mesorectal excision); RT-CT (long course radiochemotherapy).

Issue	Question
cT4	
Type of surgery	– TME vs PME
Neoadjuvant RT-CT	– Irradiation of the iliac external nodes – Role of dose escalation
Neoadjuvant chemotherapy	– Number of cycles
Restaging/response	– Best timing of restaging – Management of clinical complete response (TME vs organ sparing)
pT4N0 after neoadjuvant CT	
Role of adjuvant treatments	– None vs adjuvant RT-CT

patients with non-resectable cT4 or recurrent lesions to long-course RT alone or RT combined with chemotherapy including 16 weeks adjuvant chemotherapy. CRT increased R0 resection rates (84% vs 68%, $p = 0.009$), pCR (16% vs 7%, $p = 0.04$), 5-year local control (82% vs 67%, $p = 0.03$), and 5-year cancer-specific survival (72% vs 55%, $p = 0.02$) [80]. Several trials studied the impact of an intensified CRT schedule by adding mainly oxaliplatin to 5-FU. Although controversial, the results were encouraging [84]. Some studies showed that oxaliplatin prolonged DFS, but the OS benefit remained unproven. Moreover, any benefits need to be counterbalanced against the risk of increased toxicity [41,85–87].

The role of neoadjuvant chemotherapy before, or instead of, neoadjuvant CRT remains controversial. The rationale for this approach is treatment of micro-metastatic disease while avoiding the risk of radiation-induced pelvic toxicity. In addition, response to neoadjuvant chemotherapy may be an indication of tumor biological behavior [59,60]. The randomized PRODIGE 23 trial is testing the role of neoadjuvant Folfirinox [88] in patients with resectable LARC who were randomized to preoperative CRT alone or neoadjuvant chemotherapy followed by preoperative CRT. Accrual has been completed, and results are expected in 2022.

Another issue in LARC is the role of SCRT (5×5 Gy) followed by neoadjuvant chemotherapy. One international phase III study (the Rectal Cancer and Pre-operative Induction Therapy Followed by Diligent Operation RAPIDO-trial) is testing SCRT followed by 6 cycles of capecitabine plus oxaliplatin followed by TME vs CRT followed by TME and optional adjuvant chemotherapy with 8 cycles of capecitabine plus oxaliplatin [89]. Accrual has been completed and results are expected in 2020. A similar trial was performed in Poland. [29]. Patients with fixed cT3-4 rectal cancer were randomized either to 5×5 Gy and three cycles of FOLFOX4 or to 50.4 Gy in 28 fractions combined with two 5-day cycles of bolus 5-FU (325 mg/m^2/day) and leucovorin (20 mg/m^2/day) during the first and fifth weeks of irradiation plus one weekly infusion of oxaliplatin 50 mg/m^2 for 5 weeks. Although no differences were observed in local control, the 5×5 Gy schedule followed by consolidation chemotherapy was associated with better OS and lower acute toxicity rates.

Could dose escalation increase R0 resection?

R0 resection is a crucial issue in rectal cancer treatment. Pathology studies clearly demonstrated worse long-term outcomes in tumors resected with positive margins. Achieving a clear resection margin depends on multiple factors such as tumor infiltration, extent of the operation the surgeon is able to perform and what morbidities the patient is willing to accept.

With the goal of increasing R0 resectability neoadjuvant treatment included RT at 50–54 Gy plus 5-FU-based chemotherapy [80,90,91]. Braendengen et al., showed significant higher R0 resection rates after neoadjuvant CRT compared with RT alone (84% vs 68%, $p = 0.009$) [80]. Administering chemotherapy in the waiting time between the end of SCRT and surgery, achieved similar results as long course neoadjuvant CRT, with a R0 resection rate of above 75% [29].

A dose–response mathematical model, derived from clinical data, as developed by Appelt et al. [31], and a metanalysis of 18 studies and 1106 patients [92] demonstrated a significantly higher tumor response rate for doses above or equal to 60 Gy in T3 cancer. Positive evidence of the role of higher dose in unresectable tumors has yet to be confirmed in randomized studies.

In most studies of neoadjuvant CRT or RT alone rectal cancer patients were treated with a 3D technique which was long the standard RT modality. The advanced, intensity modulated radiotherapy (IMRT) technique provides concave dose distribution and a simultaneous integrated boost, thus increasing the daily and total dose to the tumor without significantly increasing toxicity. Consequently, IMRT appears to be the ideal technique for treating rectal cancer (and indeed is currently widely used) due to the horseshoe-shape of the pelvic CTV and the clear correlation between dose and tumor response. In addition, advanced image guided radiotherapy (IGRT) technologies, which directly visualize the tumor and the organs at risk even during treatment delivery, enable less expansion around the CTV, further helping to reduce the risk of toxicity. These advances in RT delivery and monitoring, encouraged radiation oncologists to design studies on dose escalation, which in the coming years will provide results on tumor response in general and R0 resection in particular.

Trial proposals

The T4 case working group proposed setting up two clinical trials.

(1) The ATTM.NEO-EXTREME (NEOadjuvant EXended Treatment for REctal cancers before total Mesorectal Excision) trial: a phase III randomized trial comparing neoadjuvant chemotherapy with short- or long- course RT before surgery in T4 resectable rectal cancer (Fig. 3).

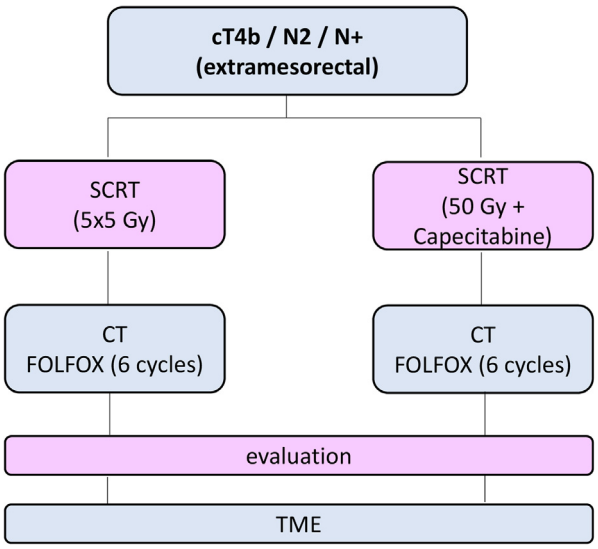

Fig. 3. cT4 rectal cancer: trial design NEO-EXTREME.

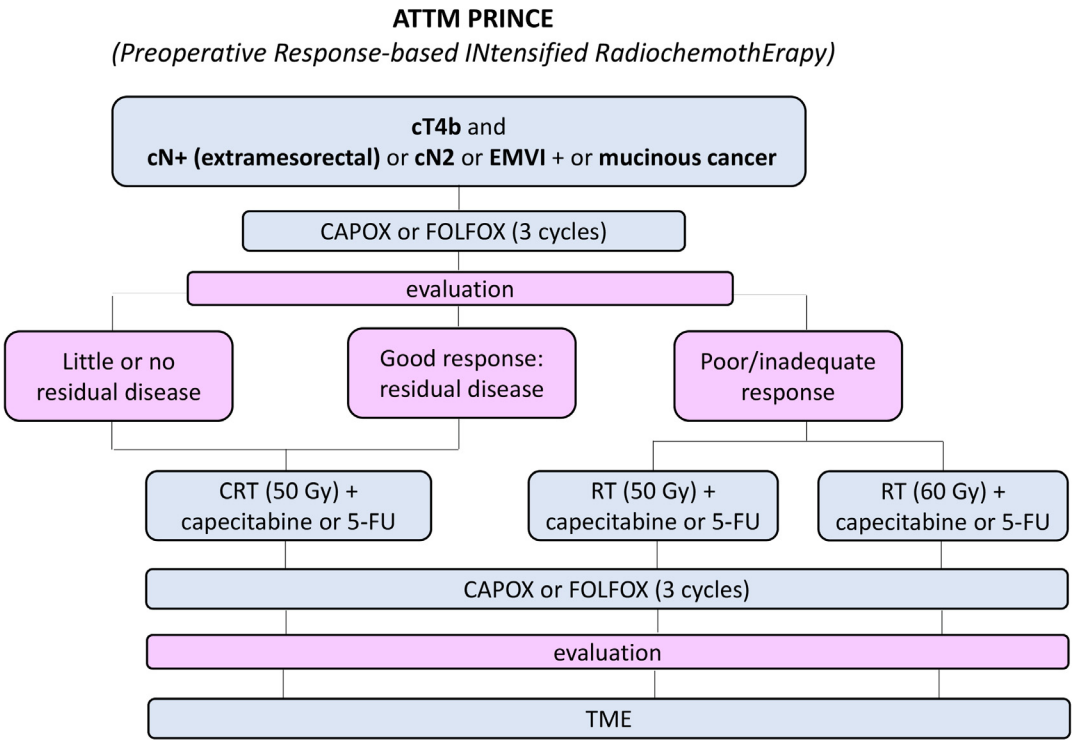

Fig. 4. cT4 rectal cancer: trial design PRINCE.

Trial design

Patients will be randomized to receive SCRT (5 × 5 Gy) or CRT (50 Gy + capecitabine). Both groups will receive chemotherapy with FOLFOX in the interval before surgery, starting two weeks after the end of RT. The SCRT group will receive 6 cycles and the CRT group 4. At week 15 from the beginning of RT, all patients will be re-evaluated to undergo TME surgery which will be performed from week 17 onwards. During the meeting a control arm with CRT alone was suggested as a potential treatment option but the proposal was not accepted due to the necessity of having a larger accrual.

Endpoints

The primary endpoint is an expected 5% increase in 3-year DFS in the CRT group compared with the SCRT (from 53% to 58%).

Secondary endpoints will be:

- 3-year OS.
- 3-year LC.
- 3-year metastases-free survival (MFS).
- toxicity.
- QoL.

Patient selection

This trial will include non-metastatic patients with at least one of the following features:

- resectable cT4.
- cN2 disease.
- suspected-involved extra-mesorectal nodes.
- EMVI.
- threatened mesorectal fascia.

(2) The ATTM.PRINCE (Preoperative Response-based INtensified RadiochemothErapy) Rectal trial: A randomized phase II trial exploring intensification of preoperative treatment for rectal cancer patients according to response after 3 cycles of neoadjuvant chemotherapy. (Fig. 4)

Trial design

Patients will receive 3 cycles of neoadjuvant chemotherapy with CAPOX or FOLFOX, followed by local and systemic restaging. Responders will receive 50 Gy. Non-responders will be randomized to receive 50 Gy or 60 Gy. All patients will receive 3 more chemotherapy cycles with concomitant oral capecitabine or i.v. 5-FU before surgery. After a second restaging, all patients will undergo TME.

Endpoints

The primary endpoint is an expected 5%increase in the R0 resection rate, compared with data from the Braendengen et al. trial [69]. We thus expect an R0 resection rate of 89% in non-resectable patients who received intensified treatment.

Secondary endpoints will be the 3-year DFS, OS, LC, MFS, as well as toxicity and QoL.

Patient selection

The trial will enroll non-metastatic patients with cT4b locally advanced rectal cancer and at least one of the following features:

- Suspected extra-mesorectal lymph node involvement.
- cN2 disease.
- EMVI.
- Mucinous cancer.

Conclusions

Rectal cancer has a broad spectrum of subtly different presentations. Advances in knowledge have improved outcomes leading to demands for better bowel, urinary and sexual function and quality of life. Consequently, the aims and practice of rectal cancer treatment have moved from treatment-to-stage therapy to an adapted multimodality therapy, creating in turn new uncertainties which we called ‘grey zones.

The ATTM was organized to explore controversies and potential areas of investigation and to envisage the future of RT in patients

with non-metastatic rectal cancer. Discussions among experts in the field successfully identified 'grey zones' and, in the light of new evidence, led to proposals for clinical trials investigating treatment for early, intermediate and advanced stage rectal cancer.

It is be hoped the ATTM findings will become a tool for national and international multidisciplinary groups to help them design research proposals and strategies and participate in the ones we have proposed here.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.07.001.

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