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Guidelines

Rectal cancer - French intergroup clinical practice guidelines for diagnosis, treatment, and follow-up (TNCD, SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, SFP, RENAPE, SNFCP, AFEF, SFR, and GRECCAR)☆

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ABSTRACT

Background: This article summarizes the French intergroup guidelines regarding rectal adenocarcinoma (RA) management published in September 2023, available on the French Society of Gastroenterology website.

Methods: This work was supervised by French medical and surgical societies involved in RA management. Recommendations were rated from A to C according to the literature until September 2023.

Results: Based on the pretreatment work-up, RA treatment was divided into four groups. T1N0 can be treated by endoscopic or surgical excision alone if there is no risk factor for lymph node involvement. For T2N0, radical surgery with total mesorectal excision is recommended, but rectal conservation is possible for small tumors (<4cm) after complete/subcomplete response following chemoradiotherapy. For T12N+ or T3+any N, total neoadjuvant treatment (TNT) followed by radical surgery is the gold standard, but rectal conservation is possible for small tumors after complete/subcomplete response following TNT. T3N2 or T+any N are an indication for TNT followed by radical surgery. Immunotherapy shows promise for dMMR/MSI RA. For metastatic tumors, recommendations are based on less robust evidence and chemotherapy plays a major role.

Conclusion: These guidelines aim at providing a personalized therapeutic strategy and are constantly being optimized. Each case should be discussed by a multidisciplinary team.

1. Introduction

This document focuses exclusively on rectal adenocarcinoma (neuroendocrine tumors, lymphomas, and melanomas are excluded). In France, around 14,000 new rectal adenocarcinomas are observed every year [1].

These guidelines are the result of collaborative work supervised by most of the French medical societies involved in the management of these tumors. This 2024 version is based on the previous one published in 2017 [2]. A writing committee composed of 17 physicians (colorectal surgeons, pathologists, radiation oncologists, medical oncologists, radiologists, and gastroenterologists) was designated to review the literature published until September 2023. The initial document was reviewed and modified after further interactive discussions and writings by a review committee. The last version was validated by the entire panel. Evidence levels were determined according to standard definition (grade A: large metanalysis or large randomized trial; grade B: small, randomized trials; and grade C: prospective non-randomized study). Recommendations were divided into three categories (A to C) based on their evidence level, or relied on expert agreement only (agreement or not) when no scientific evidence was validated (Table 1). The present article is a summary of the French intergroup guidelines published in September 2023 on the SNFGE society website (www.snfge.org/tncd) [3]. All statements in the present article completely match the original guidelines, with no additional data or comments.

2. Classification

2.1. Anatomical classification

The most reliable examinations to differentiate the three rectum levels are digital rectal examination (DRE), rigid rectoscopy (better than flexible sigmoidoscopy), endorectal ultrasound (ERUS), and magnetic resonance imaging (MRI), especially in the sagittal view [4] which is the reference exam for tumor localization.

The most robust origin level for such measurements is the anal verge (AV) or the anal ring, which is preferable for assessing the possibility of sphincter preservation [5]

- Low rectum: 0–5cm from AV
- Middle rectum: >5cm–10cm from AV
- Upper rectum: >10cm–15cm (recto-sigmoid junction: >15cm from AV)

2.2. Pathological classification

The Union for International Cancer Control – Tumor Node Metastasis (UICC–TNM) classification, 8th edition (2017), was used (Table 2) [6].

- Regional lymph nodes (LNs) of the rectum are rectal nodes (located in the mesorectal fat), internal iliac nodes, presacral nodes, and inferior mesenteric nodes (quite far from the

Table 1
Grade of recommendations.

A	Strongly recommended based on highly robust scientific evidence
B	Usually recommended based on scientific presumption
C	Option according to expert opinion based on weak scientific evidence
No scientific evidence	Only expert opinion

Table 2
Tumor node metastasis (TNM) classification.

T0	No detectable tumor
Tis	Carcinoma in situ: intra-epithelial or lamina propria invasion
T1	Tumor invading submucosa
T2	Tumor invading muscularis propria
T3	Tumor invading subserosa or non-peritonealized perirectal tissues
T4	Tumor directly invading other organs or structures and/or perforating visceral peritoneum
T4a	Tumor perforating visceral peritoneum
T4b	Tumor directly invading other organs
N0	No detectable metastatic lymph node (LN)
N1	Metastases in one to three regional lymph nodes
N1a	Metastases in one LN
N1b	Metastases in two to three LNs
N1c	Tumor deposit in perirectal fat or sub-serosa without LN metastasis
N2	Metastases in four or more regional LNs
N2a	Metastases in four to six LNs
N2b	Metastases in seven or more LNs
M0	No metastases
M1	Distant metastases
M1a	Metastases in only one organ (liver, lung, ovary, LN other than regional) without peritoneal metastases
M1b	Metastases in more than one organ
M1c	Metastases in peritoneum with or without metastases in other organs

rectum and never included in radiotherapy fields). Obturator and external iliac nodes are not considered as regional nodes but, if invaded, as distant metastases. At least 12 regional LNs must be retrieved during surgery, sometimes fewer after chemoradiotherapy (CRT). Even if there are fewer LNs, zero node involvement is staged as pN0. The Surveillance, Epidemiology, and End Results (SEER) registry has highlighted a complex relationship between nodal and tumoral status, with pT2 N1 having a better 5-year overall survival (OS) than pT3 N0 [7].
- Tumor margins must be specified after surgery (distal and, most of all, circumferential rectal margin [CRM]). A margin ≤1mm is classified as R1 and a CRM <2mm is a poor prognostic factor [8].

R1 resections present a higher risk of distant metastases than of local relapse [9]. In case of neoadjuvant treatment, the pathological classification is expressed using ypTNM. The macroscopic aspect of the mesorectum after proctectomy must be carefully assessed by the pathologist and scored according to Quirke's recommendations [10], as the preservation of a regular, smooth, shiny rectal specimen (no breach and no visible muscularis propria) has an important prognostic value for local and distant control. Pathological response can be evaluated using a tumor regression grade (TRG). Different TRGs have been proposed and encompass four or five grades. The most frequently used are the Dworak grade and the AJCC/CAP TRG modified Ryan system, which is used to evaluate cancer cell sterilization level on the pathological specimen [11–12].

2.3. Molecular tests

The MMR (MisMatchRepair) status must be assessed, preferentially on initial diagnostic biopsies by immunohistochemistry (IHC) from paraffin-embedded tissue. Molecular techniques, and more precisely Pentaplex PCR, can also be used, and should be performed in case of loss of one or more proteins observed on IHC. Although deficient (d)MMR/microsatellite instability is rare in rectal cancer (1–3%), the impact of this biomarker is major at the diagnostic level for Lynch Syndrome screening, and at the predictive level, with the increasing use of immunotherapy, notably in neoadjuvant trials. In case of metastases, *RAS, BRAF,* and *MMR* status should also be determined from paraffin-embedded tissue to guide treatment as part of precision medicine [13].

3. Pretreatment work-up

Recommendation:

A complete clinical history must be taken, including familial history. A biopsy is usually necessary at the time of colonoscopy for diagnosis and precision medicine. If the tumor is accessible to finger, DRE remains the most important clinical examination, as it enables the assessment of the distance of the lower tumor pole from AV, the clockwise extension, as well as tumor location, mobility, and consistency. Assessing tumor response after neoadjuvant treatment is essential. Indeed, DRE is probably the most useful examination ("bioprobe of L Pahlman") to help the surgeon decide which surgery to perform.

Three complementary examinations are mandatory:

- A complete colonoscopy, which allows biopsies to be taken, tumors to be localized in the rectum, their gross morphology to be observed (polypoid sessile, superficial, or deep ulceration, etc.), and synchronous lesions to be detected.
- Pelvic MRI, which is mandatory in all cases. An optimized technique is needed with high-resolution, small field of view, and thin axial slices perpendicular to the different rectal segments, especially at the tumor level. Diffusion-weighted images are now recommended both for initial staging and post-neoadjuvant treatment evaluation. A standardized report by a dedicated radiologist must mention the tumor location (clockwise and distance from AV), circumferential extension, and dimensions. T and N stages are then recorded. For T3 tumors, the subclassification (mrT3a, b, c, and d) according to tumor penetration level in the perirectal fat in millimeters should be detailed (Table 2). The CRM, defined as the shortest distance between the most peripheral tumor part and the fascia recti, should be measured. Its reliability remains weak for nodal involvement. LNs are considered as metastatic if their smallest diameter is >9mm, or between 5 and 9mm with at least two of the following morphological features: spherical, irregular border, or inhomogeneous signal intensity [14]. The presence of extramural venous invasion (EMVI) or tumor deposit should be evaluating as they are poor prognostic factor. After neoadjuvant treatment, MRI is required to evaluate tumor response including complete response (ymrCR) or TRG1 (or TRG2: good response, with dense fibrosis [>75%] and no obvious or minimal residual tumor).
- Thoraco-abdominal computed tomography (CT) scan is systematic for detecting distant metastases.

Options:

- Endorectal ultra sonography (EUS): In France, EUS is performed by dedicated gastroenterologists and is considered to be the most reliable examination to evaluate early (T1-2) tumor local spread, especially in the distal rectum. The classification (uTN) uses the same system as the UICC TNM classification, i.e., four T categories. In the case of superficial tumors, chromoendoscopy, and/or narrow banding imaging are recommended to evaluate deep tumoral infiltration [15,16].
- Liver MRI may be performed in case of equivocal CT scan results or metastases.
- Fludeoxyglucose-18 (FDG) positron emission tomography (PET) scan can be useful in some ambiguous situations.
- FDG-PET scan or MRI can be combined with the planning CT scan to improve accurate delineation of the target volumes for radiotherapy (RT) planning.
- Carcinoembryonic antigen (CEA) serum level, if elevated, may be indicative of distant diseases.

4. Treatments

4.1. Endoscopic treatment of superficial lesions (pTis-T1N0)

Early rectal cancer considered not at risk of LN involvement (CONNECT IIC or IIC+) should be offered local excision either by endoscopy or transanal surgery. If R0 resection is achieved, the treatment can be considered as curative if the pathological examination presents the following characteristics:

- pTis (adenocarcinoma *in situ*): LN involvement risk <1% [16]
- pT1 with submucosal invasion ≤1,000µm, without vascular or neural invasion, budding ≥2, or high grade (poorly or undifferentiated tumor): LN involvement risk <1% (16)
- pT1 with submucosal invasion >1,000µm, without vascular or neural invasion, budding ≥2, or high grade (poorly or undifferentiated tumor): LN involvement risk <4%. Resection can also be considered curative but required closer follow-up [17]

In case of vascular or neural invasion, tumor budding ≥2, high grade (poorly or undifferentiated tumor), or R1 resection, radical surgery with LN dissection is recommended. Hence, for frail patients with high post-operative complication risk or patients refusing radical surgery, adjuvant chemoradiotherapy can be proposed as an alternative treatment (expert agreement).

4.2. Surgery

4.2.1. Operability

Physiological age, with onco-geriatric evaluation if appropriate, is crucial depending on frailty and comorbidities. After 85 years, surgical trauma should be limited [18]. Obesity, especially in men with a narrow pelvis, must be considered. Using the American Society of Anesthesiology (ASA) score is recommended and should be evaluated before any surgery. Anorectal (mainly continence) and sexual functions must be investigated in both genders. In case of significant operative risk, alternative strategies must be discussed with the patient and within the multidisciplinary team (MDT).

4.2.2. Resectability

- Preoperative: DRE performed by a specialized surgeon, combined with digital vaginal examination in women, is highly informative in evaluating tumor resectability. Pelvic MRI is the reference examination to assess invasion of the fascia recti, inter-sphincteric planes, and surrounding organs. The tumor is considered non-resectable or at high risk of incomplete resection (R1, R2) if other organs are invaded and if the CRM is $<$1mm on MRI. The baseline non-resectable status must be reevaluated and can be modified depending on tumor response after neoadjuvant treatment. The surgeon must examine the patient at baseline and 5 to 7 weeks after completion of neoadjuvant treatment. Then, surgery must be planned in the coming weeks. A clinical complete response (cCR) is defined by the absence of residual tumor, a soft rectal wall or the presence of a small and flat rectal scar or some superficial ulcerations assessed by clinical exam (DRE and rectosigmoidoscopy) and mTRG 1 pattern on MRI. Patients with cCR after neoadjuvant treatment (especially if elderly, frail, or refusing surgery) can be discussed in MDT for a conservative strategy such as local excision or “watch and wait” [19–21].
- During surgery: if the exploration highlights unexpected extension precluding resection and if no preoperative treatment has been delivered, the surgery must be interrupted with a view to neoadjuvant treatment. If a residual extension is observed despite neoadjuvant treatment (sacrum, latero-pelvis, bladder, uterus, vagina, prostate, etc.), an R2 resection should not be performed. An extensive R0 resection must be done and technical arrangements have to be prepared in advance using, when necessary, bowel or urinary diversion.

4.2.3. Surgical techniques

For infiltrative rectal cancer, radical surgery is the cornerstone of curative treatment. Moreover, resection quality is a key prognostic factor. The specialization level of the surgeon is critical. Surgery type depends on tumor location and stage, but also on the general condition and desire of the patient.

Total proctectomy by extra-fascial excision of the mesorectum (so-called TME, as described by Heald and Ryall) [22] can decrease the local relapse risk and protect pelvic nerves, thus reducing urinary and sexual side-effects (grade C recommendation). In upper rectal tumors, mesorectum resection must be performed 5cm below the lower tumor pole. In middle or distal rectal locations, the whole mesorectum must be removed. The distal security margin must be $\geq$1cm [23]. Lymphadenectomy of the inferior mesenteric vessels is justified, ensuring that one centimeter of artery is left to spare the superior hypogastric plexus. Latero-pelvic lymphadenectomy is not recommended. In case of suspicious positive external iliac node, adenectomy is performed and a fiducial marker is positioned to help further irradiation targeting. An initial perineal approach is possible, especially if a manual coloanal anastomosis is performed in a narrow pelvis. The laparoscopic approach is recommended in experienced centers with oncological results identical to open surgery but better post-operative outcomes [24] (grade A recommendation). A robotic approach is also recommended in experienced centers with similar results to laparoscopy (grade A recommendation) [25].

Two main surgical procedure types are proposed:

- Anterior resection (AR) with sphincter preservation: AR can be performed in upper rectum tumors, usually without protective derivation. In middle rectal tumors, AR is performed with a derivative stoma. Low AR with coloanal anastomosis and protective stoma is often recommended. If recommended, the stoma is closed after 2 or 3 months without interfering with adjuvant chemotherapy. In distal rectal tumors, a low AR can be performed if the distal margin is $>$1cm and, optionally, using inter-sphincteric dissection for very low tumors.
- Abdomino-perineal resection (APR): in case of lower rectum tumor invading the external sphincter, or if a margin of 1cm is not obtained, an APR is performed and requires a permanent stoma. In case of pre-operative incontinence without anal sphincter involvement, low AR with coloanal anastomosis is not recommended, and Hartmann operation is an alternative option to APR.

4.3. Neoadjuvant treatment

4.3.1. RT and CRT

Neoadjuvant RT decreases the local relapse rate [26]. CRT increased the pathological complete response (pCR) rate compared with RT in previous studies [27,28]. Preoperative CRT has been demonstrated to be more active and less toxic than post-operative CRT to reduce local relapse [29] and is considered a standard approach by most guidelines. Oxaliplatin combined with 5-FU or capecitabine during RT failed to increase the rate of tumor sterilization or local control but increased acute toxicity [30–32]. Capecitabine appears to have the same efficacy as 5-FU when combined with RT and does not require intravenous infusion [32]. Head-to-head comparison between short-course RT and long-course CRT has not shown any significant difference regarding local recurrence or survival [33]. The choice of the most efficient regimen for local rectal adenocarcinoma control is still controversial [33,34]. None of these pre-operative radiation regimens improved survival because they did not modify the distant metastasis risk.

Recommendations:

Concurrent CRT with 5-FU and a total radiation dose of 45 to 50Gy remains a reference in many guidelines with grade A recommendations. In most French randomized trials, a CAP 50 regimen was adopted as the control group: RT 50Gy in 25 fractions over 5 weeks (2Gy/fr) with concurrent capecitabine (825mg/m^2 twice a day on radiation days). Preoperative CRT is recommended for T3-T4 and/or N+ cancers of the middle and lower rectum or for tumors measuring $\geq$1mm from the fascia recti on MRI, regardless of location and initial staging. This option must be discussed at the multidisciplinary tumor board (grade A recommendation). Time to surgery after neoadjuvant CRT varies between 6 and 8 weeks [35,36].

Rules for standard RT quality: RT must be performed with high energy photons ($\geq$6Mv), CT scan planning, and organ at risk (OAR) protection. Intensity modulation RT (IMRT) offers better OAR protection and reduces acute toxicity compared with conformal 3D technique. As most local relapses are located below the S2/S3 junction level, it is usually recommended not to extend the irradiated volume (CTV: clinical target volume) above this level in node-negative patients. The irradiated volume should usually not exceed 1,000cm^3. The anal canal, obturator, or external iliac nodes should

only be included in case of anal sphincter invasion or extension to the vagina or prostate.

Options:

Short-course RT (25/5) is well-suited to elderly patients or M1 tumors. Brachytherapy techniques can be used with three different approaches: (1) contact X-ray brachytherapy (CXB) 50kV for tumors <5cm and less than 10cm from AV, as a boost (90Gy/three fractions/4 weeks) in association with external beam RT (EBRT); (2) iridium 192 endoluminal high-dose rate or as a boost with EBRT; or (3) interstitial iridium 192 implant for very low rectal cancer extending into the anal canal [37]. A dose escalation up 60 Gy can be used in case of locally advanced tumor (T4 at risk of R1-R2 resection or T3N2) [38].

4.3.2. Neoadjuvant chemotherapy

Total neoadjuvant treatments (TNTs), which associate chemotherapy and (C)RT, were evaluated in different studies. The PRODIGE 23 study evaluated for T3-4+any N rectal adenocarcinoma (<15cm from AV) the combination of six cycles of FOLFIRINOX before CAP50 chemoradiotherapy. This TNT was followed by surgery and six cycles of FOLFOX adjuvant chemotherapy. An improvement of disease-free, metastasis-free, and overall survivals were observed compared with the standard arm (CAP50 followed by surgery and 12 cycles of adjuvant chemotherapy) [39]. This TNT is now considered as the reference for T3-T4 any N middle and low rectal adenocarcinoma (grade A recommendation). Then, the RAPIDO study studied in locally-advanced rectal cancer (LARC) patients (with at least one of the following criteria: cT4, extramural vascular invasion, cN2, CRM<0, enlarged lateral lymph nodes) and compared a TNT with a short-course radiotherapy (5 × 5Gy) followed by consolidation chemotherapy (six CAPOX or nine FOLFOX4) before surgery with standard of care (CAP50, surgery and optional adjuvant chemotherapy) [40]. The study was initially positive, but the significant local recurrence increase after a 5-year follow-up no longer allows us to recommend this therapeutic strategy [41].

The PROSPECT trial evaluated the non-inferiority of a neoadjuvant chemotherapy with FOLFOX and the selective CRT CAP 50 omission in patients responding to FOLFOX compared with CAP50 neoadjuvant CRT for middle or high rectal adenocarcinoma T2N1 or T3N0-1 with a CRM ≥3mm. This study demonstrated its non-inferiority in term of DFS or OS after surgery. However, the acute toxicity rate was higher in the chemotherapy arm. Neoadjuvant FOLFOX can be proposed as an alternative to CAP50 or TNT in patients too frail to receive TNT or in young women in order to preserve fertility [42] (grade B recommendation).

4.3.3. Rectal conservation

Despite progress in surgery and peri-operative care, radical TME is still associated with a high risk of post-operative morbidity and long-term digestive, sexual, or urogenital dysfunctions. After neoadjuvant treatment, 10% to 28% of pathological complete response (ypCR) was observed. In recent years, several teams have attempted to avoid radical surgery and proposed rectal conservation after complete or subcomplete response to neoadjuvant treatment. Two rectal conservation strategies have been studied: “watch and wait” or planned rectal conservation.

Watch and wait

This strategy involves monitoring patients with cCR after CRT or TNT. Since the work of A. Habr Gama, several studies have reported interesting results regarding rectal preservation with local recurrence rates varying from 5% to 25%, and 5-year DFS and OS rates of 52% and 85%, respectively [43]. Yet, an international study has shown that over 25% of patients in complete response will experience local recurrence within 3 years, with a prolonged risk beyond that period and a high likelihood of distant metastases (24.1%) [44]. The best treatment sequence between chemotherapy and CRT is still debated to enhance rectal preservation. The OPRA trial has experimented induction and consolidation neoadjuvant chemotherapy with CRT and compared both arms with and historical control group receiving CRT and TME. This phase II trial observed negative results for its primary endpoint (DFS). Despite interesting results regarding rectal preservation (3-year TME free survival: 41% with induction chemotherapy vs 53% with consolidation chemotherapy), long-term follow-up is necessary and data are currently insufficient to recommend this strategy [45]. The main problem of the “watch and wait” strategy is response evaluation after neoadjuvant therapy. Even with a combination of examinations (digital examination, endoscopy, MRI, or PET-CT), it is still difficult to assess a complete response. A “watch and wait” strategy can be proposed in expert centers if all the examinations show a complete response, if a local excision is not possible, or if the patient refuses radical surgery (expert agreement).

Planned rectal conservation strategies

The GRECCAR 2 trial was the only randomized study which compared in patients with initial T2-T3N0-1 <4cm rectal cancer local excision (LE) with TME in good responders after CRT [20,21]. The study showed that LE led to equivalent oncological results to TME in good responders, but induced significant morbidity when a complementary TME was needed. This strategy allowed rectal preservation in 46% of patients. Another way to perform a planned rectal conservation is using endocavitary brachytherapy. The OPERA study [46] evaluated radiotherapy intensification using the contact therapy technique (90Gy/three fractions) combined with CRT. The authors reported a significant advantage regarding organ preservation at 3 years. For tumors <3cm, the 3-year organ preservation rate was 97%, with 5% risk of local regrowth.

In conclusion, rectal preservation strategies after CRT or TNT can be proposed in cases of complete or subcomplete response, in expert centers and in selected patients: small tumors at baseline (T2-T3 <4cm and limited nodal involvement N0 or ≤3 mesorectal nodes <8mm); frail patients with a high mortality risk after radical surgery; patients refusing radical surgery, complete response and initial indication of abdominoperineal resection.

4.4. Adjuvant chemotherapy

In most recent phase III trials assessing neoadjuvant CRT, distant metastasis rate remained significant, between 32% and 38% [29,47]. There is a clear need to find a medical treatment capable of improving these figures.

The positive effect of adjuvant chemotherapy has been well established in patients with stage III colon cancer. In rectal cancer, adjuvant chemotherapy benefit is still controversial.

Adjuvant chemotherapy using 5-FU/folinic acid has demonstrated in previous studies a survival benefit in absence of neoadjuvant CRT [48,49]. When neoadjuvant CRT was performed, adjuvant chemotherapy using 5-FU/folinic acid had no impact on survival except, perhaps, for upper rectal tumors [50,51]. After CRT and surgery, adjuvant chemotherapy using fluoropyrimidines and oxaliplatin was compared with fluoropyrimidines in three phase III trials. Conflicting data were published, with positive [52–54] and negative phase III trials [30]. Adding oxaliplatin to capecitabine led to inconclusive results [55–56]. One of the main reasons leading to inconclusive results in these trials was the low compliance to adjuvant treatment. Across all the studies less than 50% of patients completed the planned adjuvant chemotherapy with the only exception of the PROCTOR SCRIPT trial reaching 72% [50]. Thus, no strong recommendation can be proposed. As for stage III colon can-

cer, a FOLFOX regimen may be discussed for patients with stage III after surgery.

In case of TNT with induction FOLFIRINOX and CRT (PRODIGE 23), according to the protocol, adjuvant chemotherapy with six FOLFOX cycles is recommended even if the compliance may be also low (grade A recommendation). However, due to the favorable prognosis, adjuvant chemotherapy can be omitted for ypT0-2N0 patients (expert agreement).

Targeted biotherapy

Anti-epithelial growth factor receptor (EGFR, cetuximab) and anti-vascular endothelial growth factor (VEGF, bevacizumab) must not be combined with neoadjuvant CRT. So far, they have no indication in the adjuvant setting.

4.5. Immunotherapy

Three studies have demonstrated very encouraging results with immunotherapy for dMMR/MSI rectal tumors with complete response and rectal conservation varying from 88% to 100% [56–58]. Despite the small patient number and short follow-up duration in these studies, each patient with dMMR/MSI rectal cancer should be discussed in MDT meeting for immunotherapy treatment (expert agreement). In case of metastatic disease, immunotherapy is recommended (grade A recommendation) [59–61].

5. Treatment strategy

The strategy depends on many different factors related to the tumor (site, stage, and size) and to the patient (comorbidity, age, and refusal of mutilating surgery). The surgeon should examine the patient before any decision and MDT discussion is necessary. If neoadjuvant treatment is performed, tumor response evaluation (clinical and imaging) is mandatory and can lead, in agreement with the expert colorectal surgeon, to a modification of the initially foreseen surgical approach. Currently, the two main approaches for improving outcome are to reduce the distant metastasis risk and to diminish radical surgery morbidity (either permanent stoma or low anterior resection syndrome) with minimal toxicity in (neo-) adjuvant treatments. Local control is still an issue in some LARC patients.

5.1. T1N0 (Fig. 1)

These are very early tumors of excellent prognosis with a sometimes equivocal initial biopsy regarding the malignancy level and nodal involvement risk <10% [56,57].

Recommendations:

- Local excision (transanal surgical [TEM] or endoscopic submucosal dissection) (grade C recommendation). Meticulous pathological examination of a non-fragmented specimen is mandatory.
- In case of incomplete excision (CRM ≤1mm) or unfavorable findings (vascular or neural invasion, tumor budding ≥2, high grade) a TME proctectomy is immediately indicated (grade B recommendation).

Options:

- Contact therapy ± CRT may be an option if local resection is not possible (grade C recommendation)
- In high surgical risk patients, or patient refusing surgery when a complementary TME is needed, a post-operative CRT may be discussed (recommendation grade: expert agreement). Low AR, as described in Section 4.2, is a standard treatment (grade C recommendation).

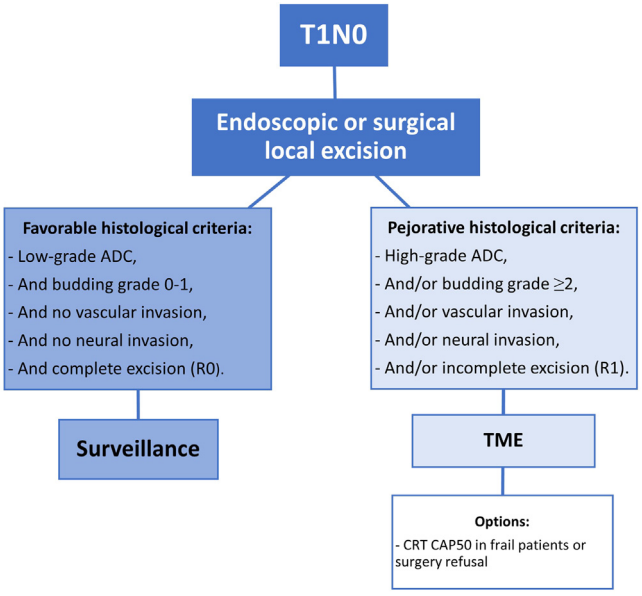

Fig. 1. Treatment strategy for T1N0.
Abbreviations: ADC: adenocarcinoma; CAP50: long-course chemoradiotherapy 50Gy with capecitabine; CRT: chemoradiotherapy; TME: proctectomy with total mesorectal excision

5.2. T2N0 (Fig. 2)

Recommendations:

- AR (TME) without neoadjuvant treatment (grade B recommendation).
- If classified pN1-2 or R1, postoperative treatment according to Sections 5.3.2
- For T2 with CRM <2mm on MRI, neoadjuvant CRT (CAP50) may be indicated (grade A recommendation).
- For T2 with a diameter <4cm, rectal conservation can be proposed and, in this case, neoadjuvant CRT CAP50 is recommended (grade A recommendation).

Options:

- In frail and elderly patients, short-course preoperative RT alone (25Gy/5) in a limited volume can be proposed if a neoadjuvant treatment is indicated (expert agreement).
- If neoadjuvant CRT is recommended and RT is contra-indicated, or in women of reproductive age, perioperative chemotherapy with FOLFOX can be proposed (grade B recommendation).
- For T2 <3cm of the middle and distal rectum, contact RT and CRT (CAP50) can be proposed for rectal conservation (grade B recommendation).
- If complete response on MRI and endoscopy after neoadjuvant treatment, the “watch and wait” strategy can be discussed (expert agreement).

5.3. T3 or T1-2N+ (Fig. 3)

These tumors defined by MRI present an intermediate risk of local or distant recurrence. The chance of organ preservation is limited and proctectomy (TME) is the main treatment, usually after neoadjuvant treatment.

5.3.1. Neoadjuvant treatment

Recommendations:

- Middle and distal rectum:

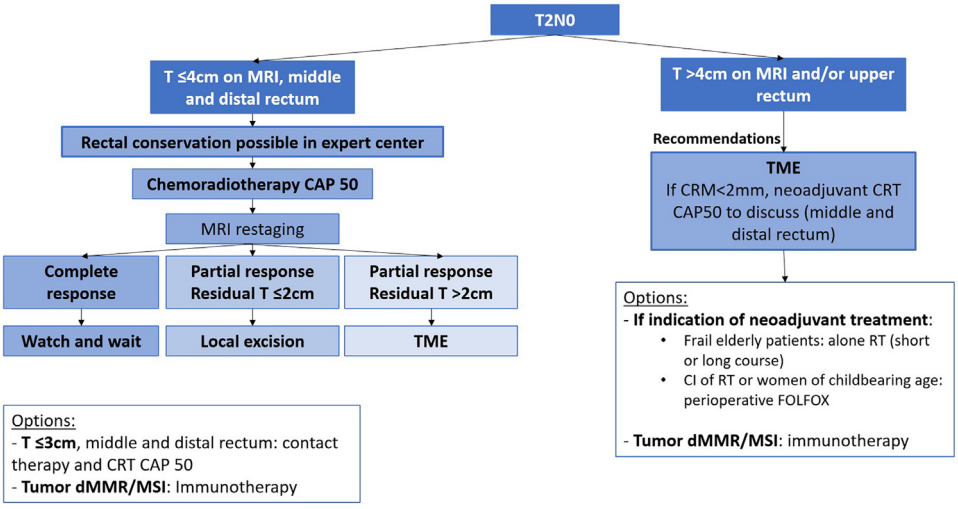

Fig. 2. Treatment strategy for T2N0.
Abbreviations: CAP50: long-course chemoradiotherapy 50Gy with capecitabine; CI: contra-indication; CRM: circumferential resection margin; CRT: chemoradiotherapy; dMMR/MSI: deficient mismatch repair or microsatellite instability; RT: radiotherapy; T: tumor; TME: proctectomy with total mesorectal excision; MRI: magnetic resonance imaging.

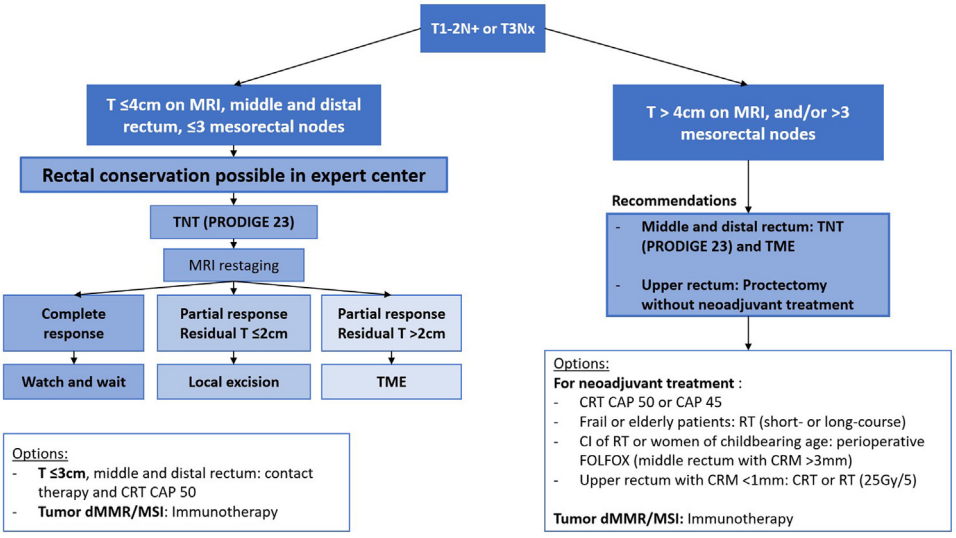

Fig. 3. Treatment strategy for T1-2N+ or T3Nx.
Abbreviations: CAP50: long-course chemoradiotherapy 50Gy with capecitabine; CAP45: long-course chemoradiotherapy 45Gy with capecitabine; CI: contra-indication; CRM: circumferential resection margin; CRT: chemoradiotherapy; dMMR/MSI: deficient mismatch repair or microsatellite instability; RT: radiotherapy; T: tumor; TME: proctectomy with total mesorectal excision; TNT: total neoadjuvant treatment; MRI: magnetic resonance imaging.

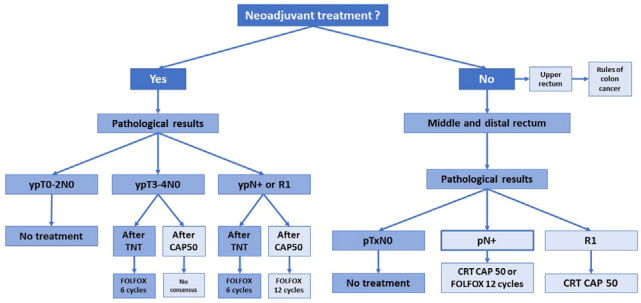

Fig. 4. Treatment strategy for T3N2 or T4Nx at risk R1/R2.
Abbreviations: CAP50: long-course chemoradiotherapy 50Gy with capecitabine; CRT: chemoradiotherapy; TNT: total neoadjuvant treatment.

- TNT using as reference six FOLFIRINOX cycles before CAP50 CRT (grade A recommendation).
- For T3 <4cm of the middle and distal rectum (with rectal nodes <3 nodes and <8mm), rectal conservation can be proposed, and TNT is also indicated (expert agreement).

• Upper rectum: proctectomy first with mesorectal excision up to 5cm below the lower tumor pole (expert agreement).

Options:

• For middle and distal rectum: CAP50 (grade A recommendation) or CAP45 (45Gy + capecitabine 825mg/m^2 twice a day on radiation days [grade A recommendation]) [24].
• In frail or elderly patients, neoadjuvant RT alone (25Gy/5, or 45 or 50Gy/5 weeks) in a small volume is possible.
• In the case of patients under 70 who are too frail to receive TNT, contra-indication to RT, or woman of reproductive age, perioperative chemotherapy with FOLFOX can be proposed (grade B recommendation).
• Middle rectum: if tumor extension into the mesorectum is limited with lateral extension >1mm from fascia recti, RT alone may be proposed (possibly a 25/5 regimen) [29]. Proctectomy

alone is still the subject of undergoing research and needs MDT discussion only if tumor is N0 and located in the posterior pelvis with no pejorative sign, such as extramural vascular invasion (EMVI) and distance from fascia recti >2mm (expert agreement).
- Upper rectum: neoadjuvant CRT or RT alone (25Gy/5) in case of invasion of fascia recti (expert agreement).
- For T3 <3cm of the middle and distal rectum (with rectal nodes <4 nodes and <8mm), contact XB and CRT (CAP50) can be proposed for rectal conservation (grade B recommendation)
- If complete response on MRI and endoscopy after neoadjuvant treatment, the "watch and wait" strategy can be discussed (expert agreement).

Clinical trials:

- NORAD01-GRECCAR 16 Phase III trial: cT3N0 or cT1T3N+, for tumors with CRM >2mm: neoadjuvant chemotherapy by FOLFIRINOX vs TNT.
- GRECCAR 14 Phase III trial: for locally advanced tumors, CRM <2mm; T3c-d N0– N2; T4a-b; EMVI: six cycles of FOLFIRINOX and depending on the response: immediate surgery vs CAP50 and surgery.
- TRESOR Phase III trial: T3b-c-d, 3.5 to 6cm (<2/3 circumference) N0 or N1, <75 years old: TNT versus TNT + contact XB (90Gy/3f) before CRT. Re-evaluation 5 weeks from the end of TNT for "watch & wait" strategy, local excision, radical surgery, or contact XB.
- GRECCAR 17 Phase III trial: selective vs systematic use of the diverting stoma after TME for rectal cancer.

5.3.2. Post-operative treatment (Fig. 4)

Post-operative treatment depends on the analysis of the operative specimen and the neoadjuvant treatment given. All rectal cancer cases must be discussed within the MDT before and after surgery. A good efficacy/toxicity balance must be explained to, understood, and accepted by the patient.

- Upper (supra-peritoneal) rectum: these tumors should be considered as colon cancer and adjuvant chemotherapy must be given accordingly (grade B recommendation).
- Middle-distal rectum

a) Patients having received neoadjuvant CRT or RT

Recommendations

After TNT as PRODIGE 23

- ypT0-2N0: no adjuvant treatment (recommendation grade: expert agreement).
- ypT3–T4N0 or ypN1–N2: adjuvant chemotherapy: six cycles of mFOLFOX6 (or four Capecitabine cycles) (grade A recommendation)

After CRT or RT alone:

- ypT0N0: no adjuvant treatment (expert agreement).
- ypT1–T2N0: no adjuvant treatment (grade A recommendation)
- ypT3–T4N0: no consensus can be achieved after analysis of the literature (expert agreement)
- ypTx N0: no chemotherapy (expert agreement)
- Patients <70 years of age and ypN+: adjuvant chemotherapy by FOLFOX 6 months (expert agreement). If there is persistent neurological sensory toxicity between two cycles, oxaliplatine should be interrupted because of the lack of evidence of effectiveness, and the patient should continue with LV5FU2 alone.
- Patients >70 years of age and ypN+: FOLFOX 6 months or fluoropyrimidine alone to be discussed only after geriatric evaluation (expert agreement). If there is persistent neurological sensory toxicity between two cycles, oxaliplatine should be interrupted because of the lack of evidence of effectiveness, and the patient should continue with LV5FU2 alone.

T with R1 resection (TNT or not): Salvage APR is not recommended

- Patients <70 years of age: adjuvant FOLFOX 6 months (expert agreement).
- Patients >70 years of age: FOLFOX 6 months to be discussed after geriatric evaluation (expert agreement)

b) Patient having received no neoadjuvant CRT or RT

Recommendations

- pT1-4N0 R0: no post-operative treatment (grade A recommendation)
- pN1-2:
  - Patients <70 years of age: CRT (grade A recommendation) or adjuvant chemotherapy using FOLFOX 4s (6m) for 6 months or CAPOX (expert agreement).
  - Patients >70 years of age: CRT (grade A recommendation) or adjuvant chemotherapy using FOLFOX 4s (6m) for 6 months after geriatric evaluation. (expert agreement)
- R1 resection or perforated tumor: CRT using RT 50.4Gy with concurrent fluoropyrimidine (grade A recommendation). Salvage APR is not recommended in case of R1 distal margin.

Options

- In case of contra-indication to post-operative CRT: adjuvant chemotherapy using simplified LV5FU2 or capecitabine or modified FOLFOX 4s (6m) or CAPOX during 6 months or post-operative RT alone (expert agreement).
- Even if there is no study in rectal cancer to support a systematic adjuvant chemotherapy for the rare situation of pT4N0R0, as it is practiced for colon cancers an adjuvant chemotherapy FOLFOX 6 months can be discussed (expert agreement).

5.4. T4 at risk of R1 or R2 resection or some T3 N2 with threatened margins

These tumors are often described as "locally advanced". They expose to an increased risk of local recurrence but also of distant metastases.

Recommendations:

- TNT: six FOLFIRINOX cycles before chemoradiotherapy CAP50 followed by surgery and six FOLFOX cycles (or four capecitabine cycles) adjuvant chemotherapy, performance status (PS) 0-1, 18-75 years old (grade A recommendation)
- In case of regional extension in a fit young patient and if no distal LN is found, extended surgery (using resection of the genito-urinary organs or sacrum) must be discussed on an individual basis if an R0 resection can be expected (grade C recommendation).
- If tumor excision is impossible, RT will be given to a total dose of 60Gy (45Gy pelvis and boost 60Gy tumor). Complementary treatment as endoscopic treatment (prosthesis, hemostasis) or derivative stoma can be performed, if necessary (expert agreement).
- Postoperative treatment if R1 or R2, or pN1-2: (expert agreement)
  - No neoadjuvant treatment: CRT followed by chemotherapy (FOLFOX or CAPOX during 6 months) (expert agreement)
  - Neoadjuvant treatment: FOLFOX during 3 months (6 months if only neoadjuvant CAP50) (expert agreement)
  - Rescue APR is not recommended in case of R1 distal margin.

Options: (expert agreement)

- CRT CAP50
- CRT with a 60Gy dose (45Gy pelvis and boost 60Gy tumor).
- Alternative concurrent chemotherapy with RT: 5-FU—folinic acid, continuous infusion of 5-FU.
- Intra-operative RT in case of R2 resection, if the technique is available.
- In case of inoperable patient for medical reason, CRT or RT alone can be proposed as a palliative measure.
- In case of pT4 and/or pN1-2 not known before surgery and not receiving any neoadjuvant treatment: post-operative CRT is recommended
- If CRT is contra-indicated, RT or chemotherapy alone can be proposed, or even therapeutic abstention
- In case of complete response ypT0N0: adjuvant chemotherapy must be discussed within the MDT

Clinical trials:

- GRECCAR 14 Phase III trial: for locally advanced tumors: CRM <2mm; T3c-d N0– N2; T4a-b; EMVI: six FOLFIRINOX cycles and depending of the response: immediate surgery vs CAP50 and surgery.

5.5. Tumors staged M1

5.5.1. Tumors with synchronous metastasis which can be removed surgically

The aim is to give the best treatment to the primary tumor and the metastases with a curative goal.

Recommendations:

- There is no universally-agreed standard. Each case must be discussed within the MDT.
- For dMMR/MSI: immunotherapy (expert agreement).

Options:

- Neoadjuvant CRT followed by one-stage surgery of the primary T and metastasis.
- Neoadjuvant CRT followed by sequential surgery first of the metastasis followed by primary T resection.
- Neoadjuvant chemotherapy using four or six cycles.
- Short-course RT (25/5) followed by chemotherapy targeting the metastasis, followed 3 months later by surgery to remove the metastasis and primary T, followed again by adjuvant chemotherapy for a total duration of 6 months.
- Peri-operative chemotherapy, followed by surgery of metastasis, followed by rectal tumor treatment

5.5.2. Tumor with non-resectable synchronous metastasis

Recommendations

- Some limited metastases may become resectable after chemotherapy. Such cases must be discussed before and after chemotherapy within the MDT.
- Such tumors have a poor short-term prognosis and quality of life is often the main treatment goal to avoid mutilating surgery (APR) and painful pelvic evolution.
- No prospective randomized trial provided a robust reference standard treatment.
- Chemotherapy is the main treatment. Other treatments (surgery or RT) may depend on the efficacy and tolerance of the medical treatment. Surgery can be proposed if the metastases become resectable. Surgery and/or RT can be proposed on the primary tumor if the aim is to cure or improve quality of life. Short-course RT (25Gy/5) is well-suited to such situations.
- In case of symptomatic primary tumor (pain, bleeding): FOLFIRINOX during 6 months can be proposed (expert agreement)
- For dMMR/MSI: immunotherapy (expert agreement)

5.6. Treatment of loco-regional recurrences (expert agreement)

- Loco-regional recurrences may be saved by a curative resection, especially after local excision or organ preservation, but also AR.
- A derivative stoma may be necessary and may sometimes be avoided using endorectal prosthesis.
- Chemo/radiotherapy is sometimes the only palliative treatment for locoregional recurrences.
- Chemotherapy using oxaliplatin and irinotecan combined with 5-FU may be useful to calm symptoms, FOLFIRINOX can be proposed if the patient has of PS score 0-1.
- Surgery with tumor deposit excision and hyperthermic intra peritoneal chemotherapy may be proposed in case of peritoneal recurrence.

6. Post-treatment follow-up

6.1. Diagnostic tools

There are numerous diagnostic tools: clinical exam, biological tests including CEA serum levels (with a non-robust sensitivity or specificity level), various imaging techniques, and endoscopy. A biopsy can be performed in some situations.

6.2. Follow-up strategy

Recommendations

No follow-up for cancer recurrence is needed for Stage I tumors.
For Stage II and III tumors:

- Follow-up is mainly of interest for patients able to tolerate a new procedure or chemotherapy/RT.
- After 5 years: no monitoring is recommended (expert agreement). Recurrence risk is low and there is no evidence that prolonged monitoring beyond 5 years improves patient prognosis.
- During the first 5 years after treatment: clinical exam and abdominal ultrasound every 3 months during 3 years, then every 6 months during 2 years. Chest X-ray every 6 months during 3 years then every year during 2 years.
- No CEA monitoring (PRODIGE 13). If pre-operative CEA was high, its normalization should be monitored 6 to 8 weeks after surgery. If still high: probable persistence of tumor remnants requiring morphological assessment.

Colonoscopy: (all stages)

- If complete and of good quality before surgery: colonoscopy should be performed at 1 year (grade B recommendation), 3 years, and 5 years, if the previous colonoscopy was normal (grade C recommendation)

If incomplete or of poor quality before surgery: an additional colonoscopy should be done 6 months after surgery (grade C recommendation).

Options: for stage II or III

- Thorax-abdomen-pelvis (TAP) CT-scan replacing ultrasound and chest X-ray if the patient is obese or the recurrence risk is high (CRM+, ypT4, ypN+).
- EUS if suspicion of local recurrence (transvaginal in female patient)
- Pelvic MRI if APR or organ preservation
- PET-CT: for localization of recurrence if invisible on TDM TAP with high CEA

Conflict of interest

F. Bibeau: Amgen, Astra-Zeneca, BMS, GSK, Incyte, MSD, Pierre Fabre, Sanofi, and Servier.

O. Bouché: Amgen, Apmonia Therapeutics, Bayer, Deciphera, Merck KGaA, MSD, Pierre Fabre, and Servier. E. Cotte: Intuitive and Takeda. F. Huguet: Amgen, Merck, MSD, and BMS.

All other authors have reported no conflicts of interest.

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