Early Rectal Cancer: Radiotherapy? Against

By

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Why against?

I. Definition of early rectal cancer.

II. Literatures about adverse effects of irradiation.

III. Clinical Trials.

IV. Guidelines and consensus.

I- Definition of early rectal cancer:

- The European Association of Endoscopic Surgery and the European Society of Coloproctology defined early rectal cancer as;

"a rectal cancer with good prognostic features that might be safely removed preserving the rectum and that will have a very limited risk of relapse after local excision" (Morino M etal., *Surg Endosc,* 2015).

- Only 2-12% of patients with early rectal cancer experience local or distant recurrence.

II- Adverse effects of irradiation in rectal cancer treatment:

- Adverse effects of neoadjuvant CRT, which can be severe, causing significant patients disability and potentially outweighing the benefits. This is of particular concern in patients with a low risk of local recurrence when treated with surgery alone. It can be;

Acute adverse effects :

wound healing, gastrointestinal, genitourinary, and neurologic complications

Late adverse effects:

occur in the urinary tract and skin and in the gastrointestinal, vascular, and skeletal systems

preoperative radiotherapy and quality of life:

- Several Studies evaluated quality of life using different scales (Sebag-Montefiore et al 2009; van Gijn et al 2011). Both previous studies concluded that sexual dysfunction occurred more in the preoperative radiotherapy group; results for fecal incontinence were mixed; and irradiated participants tended to resume work later than non-irradiated participants between 6-12 months, but with no difference after 18 months. So patients with early-stage tumors have not been shown to benefit from RT in terms of local control and preoperative RT may not result in sphincter preservation.

-Also, (Florian et al, 2014) observed that stool incontinence and sexual dysfunction occur in a considerable percentage of patients received neoadjuvant CRT and thus affect their quality of life.

III- Clinical Trials:

- The French GRECCAR 2 trial (*the lancet*. 2017),

- was a prospective, multicenter phase 3 trial that randomized patients with cT2/3 N0-1 tumors after radiochemotherapy (RCT) into an local excision (LE) group versus total mesorectal excision (TME) group.

- Subgroup of patients with TME completion surgery after LE (R1, ypT2/3, ypN+) performing particularly poorly in the cumulative score of surgical complication rates, poorer long-term functional outcome and a higher rate of definitive colostomy rates than primary TME after 2 years. .

- Thus, the concept of neoadjuvant RCT followed by LE and possibly followed by TME completion surgery represents a potentially significant overtreatment for patients with early rectal cancer.

Completion TME after primary LE without neoadjuvant CRT:

Local recurrence rates for completion TME after LE of pT1-2 rectal cancer was 4.1% for high-risk pT1 tumors and 4.3% for pT2 tumors (Van Oostendorp S.E etal,2020).

Although completion TME procedures are considered to be more difficult due to the compromised resection plane and fibrosis, the postoperative complication rate is acceptable and leakage rates seem to be comparable to primary TME resections (X. Serra-Aracil, *etal*, 2021; K. Levic Souzani, *etal*, 2021)

So, the French GRECCAR 2 trial failed to show superiority of LE over TME, because many patients in the LE group received a completion TME that probably increased morbidity and side effects, and compromised the potential advantages of LE.

- TME Dutch trial, (*N Engl J Med*,2001);

- Concluded that, despite CRT + LE group and TME group have comparable oncological outcomes for distal T2N0 rectal cancers, considerable proportion of CRT + LE patients experienced significant CRT toxicity and TME patients presented better overall health-related quality of life (HRQOL) scores 1 year after treatment; conversely, CRT + LE had worse scores.

- (ACOSOG Z6041) trial, (*Lancet Oncol;* 2015);

- Suggested that neoadjuvant CRT followed by LE might be considered as an organ-preserving alternative in carefully selected patients with clinically staged T2N0 tumors patients who refuse, or are not candidates for transabdominal resection.

- (ACOSOG Z6041) trial versus TME Dutch trial;

- Recently, a cohort of patients in the ACOSOG Z6041 trial with cT2N0 tumors treated with neoadjuvant CRT+LE were compared to a cohort of low pT2N0 tumors treated with upfront TME in the Dutch TME trial,
- Although, HRQOL decreased in the CRT+LE group and improved in TME patients, when considering anorectal function, results were worse than baseline in both groups (Patricio et al; *Annals of Surgery*, 2021).

- The CARTS study, (*JAMA Surg*. 2019);

- Included patients (cT1-T3 tumors) treated with long course CRT followed by organ-sparing (LE) and despite the favorable oncological outcomes, functional results in this study revealed that 50% of patients rectal preservation experienced major low anterior resection syndrome (LARS).

- Furthermore, one-third of the initially included patients with low-risk rectal cancer required TME surgery and hence underwent unnecessary radiotherapy (overtreatment).

Guidelines and consensus:

- Generally guidelines do not recommend neoadjuvant therapy for patients with stage I disease, given that the rate of local recurrence is low and the benefit of adjuvant chemoradiation therapy is very small.

While the benefit of neoadjuvant therapy is very clear for stage III disease, its benefit for stage II patients is less clear, and further investigation is needed.

- The Research Committee of the European Society of Coloproctology , performed a systematic review of 24 national and international guidelines which was published after 2010.

I. European Society of Coloproctology:

Original article

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Organ preservation in rectal cancer: a synopsis of current guidelines

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A- Treatment based on clinical stage (cTNM):

I- cT1N0M0

> Local excision is a safe approach for cT1N0M0 rectal cancer.
> Consensus: highest level of evidence 1b.

II- cT2N0M0

> For cT2N0M0 rectal cancer, TME should be considered standard of care.
> Consensus: highest level of evidence 2b.
> Local excision following neoadjuvant therapy can be offered in trial setting, or for patients who are not fit for or those refusing major surgery.
> Consensus: level of evidence 2b.

B- Treatment based on pathological stage (pT):

1- pT1 Low risk (well to moderately differentiated, no venous invasion, no lymphatic invasion, < 3–4 cm, SM1–2)

> For pT1 low risk, local excision is deemed sufficient.
> Consensus: highest level of evidence 1b.

2- pT1 high risk (poor differentiation, or venous invasion, or lymphatic invasion, or R1, or >3–4 cm, or SM3)

> The recommended treatment following local excision/polypectomy of a high-risk pT1 is a completion TME.
> Consensus: level of evidence 2b.
> Adjuvant (chemo)radiotherapy may be an alternative to completion TME within a clinical trial setting, or for patients unfit for surgery.
> Controversy: highest level of evidence 3b.

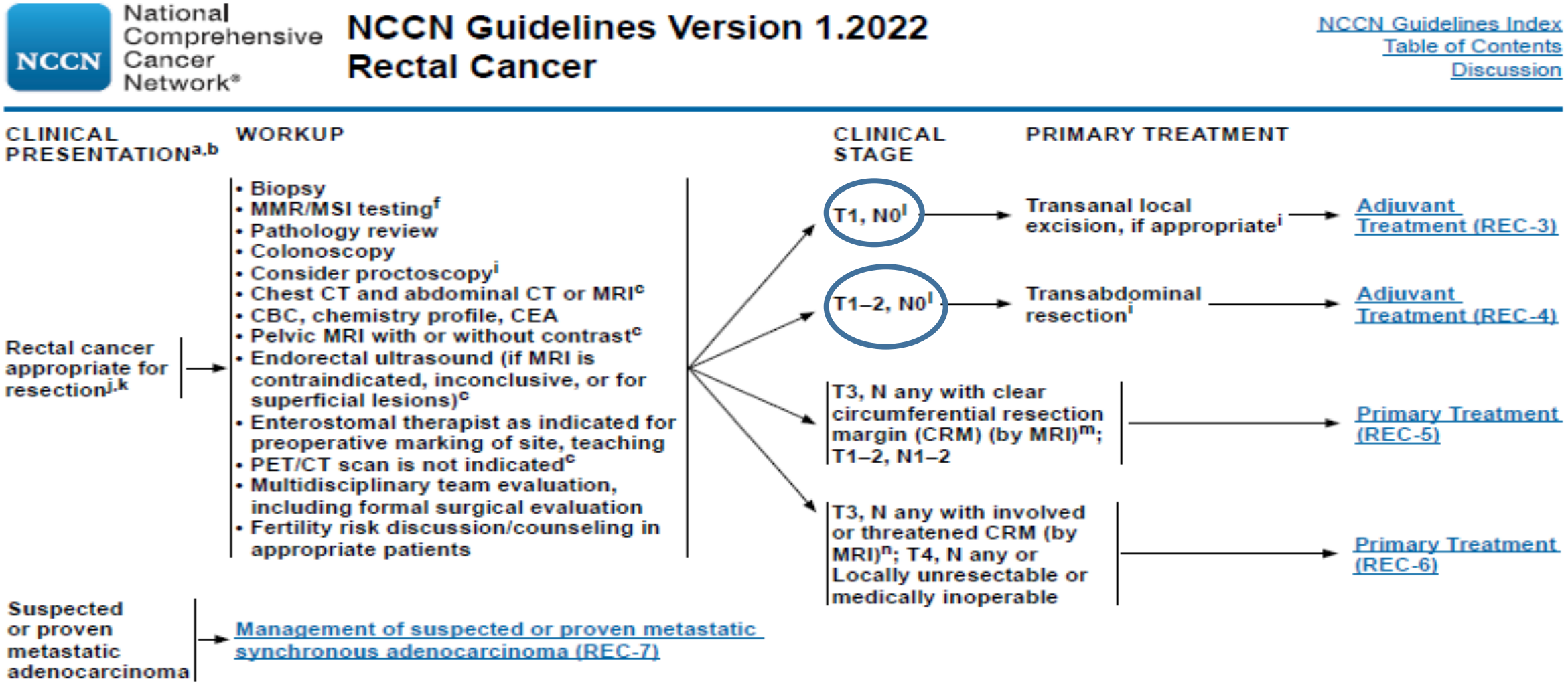
3- pT2

> Standard care after local excision of pT2 rectal cancer should be completion TME.
> Consensus: level of evidence 2b.
> Adjuvant (chemo)radiotherapy following local excision for pT2 rectal cancer is an alternative for completion TME within the setting of a clinical trial, in patients unfit for surgery or in those who have declined surgery.
> Controversy: level of evidence 3b.

C- Treatment strategy for complete clinical response to neoadjuvant treatment:

> W&W for ycCR with intensive surveillance by an experienced team can be considered for patients unfit for and declining surgery, but should be undertaken in the setting of a clinical trial. Local excision of the scar or small residual disease following (chemo)radiotherapy can be considered as alternative to TME surgery, with close surveillance for ypT0–1.
> Controversy: highest level of evidence 3b.

II. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Version 1.2022



significantly higher in patients receiving a laparoscopic resection compared with those receiving an open resection.[271]

Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection.[272-276] Comparable results are generally seen between the approaches in conversion to open resection, TME quality, postoperative complications, and quality of life.

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,[244,245] whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.[246,247] The panel defined principles by which minimally invasive resection of rectal cancer can be considered: the procedure can be considered by an experienced surgeon, should include thorough abdominal exploration, and should be limited to lower-risk tumors, as outlined in the guidelines. An international group of experts has defined standards for the technical details of laparoscopic TME.[277]

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy for stage II (T3–4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer usually includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases since this disease is characterized by lower rates of local recurrence.

Although radiation therapy (RT) has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities) relative to surgery alone.[133,278,279] It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.[83,280,281] However, 22% of 188 patients clinically staged with T3, N0 rectal cancer by either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens according to results of a retrospective multicenter study,[282] suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative treatment for patients with T3, N0 disease.

Combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), and chemotherapy is recommended for the majority of patients with stage II or stage III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. The current guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy. The total duration of perioperative therapy, including chemoRT and chemotherapy, should not exceed 6 months.

Preoperative Versus Postoperative Radiation

Several studies have compared the administration of RT preoperatively versus postoperatively for stage II/III rectal cancer.[283,284] A large, prospective, randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer.[283] Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs. 13%; P = .006) and treatment-associated toxicity (27% vs. 40%; P = .001),

although OS was similar in the two groups. Long-term follow-up of this trial was later published.[285] The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively ($P = .048$). OS at 10 years was again similar between the groups (59.6% and 59.9%, respectively; $P = .85$), as was DFS and the occurrence of distant metastases.

Interestingly, a recent SEER database analysis of 4724 patients with T3, N0 rectal cancer found that radiation given after resection was associated with a significant decrease in risk for cancer death compared to surgery without any radiation (HR, 0.69; 95% CI, 0.58–0.82; $P < .001$), while radiation given before resection was not (HR, 0.86; 95% CI, 0.72–1.04; $P = .13$).[286] Another SEER database review found that a cancer-specific survival benefit with adjuvant RT differed with the risk stratification of analyzed patients (patients with high-risk disease benefited from adjuvant RT while those with low-risk disease did not).[287]

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.[283,284,288] First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in patients with rectal cancer,[283,284] this conclusion is not supported by two meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[289,290] Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected).

One disadvantage of using preoperative RT is the possibility of overtreating early-stage tumors that do not require adjuvant radiation.[283,291] Improvements in preoperative staging with pelvic MRI have allowed for more accurate staging, but the risk of overstaging disease has not been eliminated.[282] The phase II QuickSilver trial investigated whether certain patients selected as having good prognosis by MRI imaging may avoid chemoRT by having primary surgery.[292] Of the 82 patients who were identified as candidates for primary surgery, only 4.9% were found to have a positive CRM following surgery, demonstrating the feasibility of this approach. However, more data are needed for this approach to be adopted into clinical practice.

Weighing these advantages and disadvantages, the panel recommends preoperative chemoRT for patients with stage II/III rectal cancer. Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen.

Concurrent Chemotherapy with Radiation

A number of randomized trials have evaluated the effectiveness of the addition of concurrent chemotherapy to radiation administered either preoperatively following clinical evaluation/staging (eg, T3–4 by EUS) or postoperatively following pathologic staging of rectal cancer as pT3 and/or N1–2.[293] Putative benefits of the addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases). Preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation.

In a study of patients with T3–4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative

III. ASTRO Clinical Practice Guideline for Radiation Therapy for Rectal Cancer (Practical Radiation Oncology, 2021) :

Table 2 Recommendations for neoadjuvant RT indications

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	Strong	Moderate [3-6]
2. For patients with stage II-III rectal cancer, neoadjuvant RT is recommended.	Strong	High [7-14]
3. For patients with stage II rectal cancer at lower risk of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended after discussion with a multidisciplinary team. Implementation remark: Lower risk is defined as a cT3a/b N0 tumor that is >10 cm from the anal verge* and with mrCRM ≥2 mm and no mrEMVI.	Conditional	Moderate [5,6,11,15]
4. For patients with cT1-2N0 rectal cancer who may need an APR, neoadjuvant chemoradiation is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Expert opinion [16-18]
5. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High [8-10,16-18]

Abbreviations: APR = abdominoperineal resection; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; RT = radiation therapy.
* cT3a/b = 1 to 5 mm extramural tumor spread; tumor height should be surgeon defined.

Expert Opinion*
Consensus of the panel based on clinical judgment and experience, due to absence or limitations in evidence.

Obstacles for omission of surgery in patients with cCR after neoadjuvant CRT:

- Patients with initially resectable tumors might develop irresectable regrowth or lesions that require abdominoperineal resection while low anterior resection would have been sufficient in the first presentation.
- The development of distant metastases that do no longer allow curative treatment.
- Patients need to be informed about the still experimental character of this treatment modality.
- Clinical examination, endoscopy and MRI to identify patients with cCR and to detect local regrowth during close follow-up require a high level of expertise and should be restricted to centers with special experience in multimodal diagnosis and therapy of rectal cancer.

Conclusion:

In early-stage rectal cancer (cT1-2N0M0), surgery remains the optimal treatment method, but a small group of patients who are not suitable for surgical resection like medically unfit for surgery or refuse to undergo colostomy for tumors located in the lower rectum. For those, Another treatment options can be introduced


Thank you