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Radiation Therapy Updates In Rectal Cancer

Nabila Sellal, Mohamed El Hfid

1- Radiation Therapy Department- Mohammed VI University Hospital of Tangier
2- Faculty of Medicine and Pharmacy of Tangier- Abdelmalek Essaadi University- Morocco

Abstract:
The colorectal cancer is one of the most important causes of mortality and its incidence has been increasing. Radiation therapy (RT) is a major treatment in the management of locally advanced rectal cancer. For several years, neoadjuvant radiotherapy has been considered as standard of care for this cancer with either long course chemoradiation or short-course RT. Over the recent years, the management of rectal cancer was an active research area, especially the role of RT including indications, optimal radiotherapy regimens, therapeutic sequences and the organ preservation approaches. Authors summarize recent RT updates in the management of rectal cancer.

Key words: *Radiotherapy, rectal cancer, neoadjuvant therapy, guidelines, treatment*

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I. Introduction:

Colorectal cancer is the third most common cancer worldwide. Rectal adenocarcinomas represent about one-third of all colorectal cancers. The therapeutic management of this cancer is multidisciplinary. Radiation therapy (RT) is a major treatment of rectal cancer, especially the locally advanced stages. Last years have seen several advances in the management of this cancer, particularly the neoadjuvant treatment.

For many years surgery was the gold standard treatment for rectal cancer. But since 2005 multiple prospective trials have demonstrated that neoadjuvant RT decreases the risk of local recurrence, even in the era of total mesorectal excision (TME). With Conventional surgery, the rate of local relapse was nearly 45 % but the adjunction of RT to TME has reduced the rate of local relapse to 5%. Thus, RT in rectal cancer decreases the risk of local recurrence, increases downstaging and hence the chance of organ preservation [1], [2]. For these reasons, preoperative RT has widely been considered as standard of care for locally advanced rectal cancer; however, some questions remain about the role of RT in the rectal cancer.

Neoadjuvant Radiotherapy: Indications

In the latest American Society for Radiation Oncology (ASTRO) guidelines of RT for rectal cancer, it is noted that for patients with clinical stage II-III rectal cancer, there is a strong evidence to recommend neoadjuvant RT and the second strong recommendation is that when RT is indicated for rectal cancer, RT should be performed preoperatively rather than postoperatively because many data suggested a significant decrease in local recurrence and acute toxicity in the patients treated preoperatively. Furthermore, there is a conditional recommendation based on moderate evidence to omit neoadjuvant RT in favor of upfront surgery for patients in clinical stage IIA (cT3a/b N0) when the cancer is located more than 10 cm from the anal verge and there is a predicted circumferential resection margin 2 mm and the absence of extramural vascular invasion as determined by MRI with rectal cancer protocol. And based on expert opinion neoadjuvant chemo-radiation therapy (CRT) is conditionally recommended to improve the possibility of sphincter preservation for patients with clinical stage I (cT1-T2 N0) tumor in a distal location which could need an abdominoperineal resection. The evidence recommends strongly preoperative rather than postoperative treatment. Finally, based on expert opinion neoadjuvant RT is conditionally recommended when sphincter preservation is being considered for a patient with a clinical stage I (cT1-T2 N0) tumor in a distal location [3].

In Nice guidelines from UK for early rectal cancer, preoperative RT could be offered only in the context of a clinical trial and as ASTRO Guidelines, preoperative radiotherapy is recommended for patients with locally advanced rectal cancer cT1-T2, cN1-N2, M0, or cT3-T4, any cN, M0 (stage II and III) [4]

To summarize the indications of neoadjuvant RT according to latest European and American guidelines, preoperative radiotherapy is indicated for T3-T4 and / or N + cancers of the middle and lower rectum or for all tumors that on MRI are 1 mm or less from the fascia recti regardless on site and stage [3], [5], [6], [7].

Neoadjuvant regimens: short-course RT or chemoradiation

In 2004, neodjuvant CRT with concurrent 5-FU became the standard of care in rectal cancer, then in 2012, many studies confirmed that Capecitabine was not inferior to 5-FU in neoadjuvant ChemoRT and there was no benefit to the addition of oxaliplatin in chemo radiation protocol [8], [9], [10], [11], [12], [13]

The first randomized trial to compare the short regimen of RT with a long regimen was the Polish trial [14] and the second was the Australian [15]. In these studies, the short course consisted on 25 Grays in 5 fractions followed 1week later by surgery .The long course consisted on 50.4 Gy in 28 fractions with continuous infusion 5 FU followed 4 to 6 weeks later by surgery. They concluded that short-course Radiotherapy or long-course CRT are equivalent and both of them improve local control and have a similar efficacy and patient quality of life. In a subset analysis of distal tumors (< 5cm from the anal verge) in the TROG randomized trial, there were more local recurrences in the short course RT arm compared with the conventionally arm but this difference was not statistically significant [15].

Total neoadjuvant treatment

Until 2020, Neoadjuvant radiotherapy with concurrent chemotherapy or short course RT followed by surgery and adjuvant chemotherapy has been the standard of care for locally advanced rectal cancer. Despite this standard therapeutic sequence, overall survival does not exceed 75% and nearly 30% of patients still develop distant metastasis, which represents the main cause of treatment failure and death [16], [17]. Also there is a Poor compliance with adjuvant chemotherapy. Hence, to deal with these issues and to increase the tumor response with more patients eligible for organ preserving strategies, it was necessary to intensify the treatment. Indeed, the total neoadjuvant therapy (TNT) concept, in which all Chemotherapy and RT are delivered before surgery, has been evaluated in recent years to intensify the neoadjuvant treatment. There are two options for TNT; RT followed by Consolidation chemotherapy or Induction chemotherapy followed by RT. The most important studies that evaluated the TNT were "Rapido" and "Prodige 23" [18], [19]. Rapido trial is a multicenter randomised phase 3 trial which included 885 patients with high risk rectal cancer. Patients were randomized to the experimental arm which received short-course radiotherapy (5×5 Gy over a maximum of 8 days) followed by six cycles of CAPOX chemotherapy or nine cycles of FOLFOX4 with a chemotherapy-free interval between 2–4 weeks followed by TME, or to the standard of care arm with CRT on 25 fractions followed by TME and, optional adjuvant chemotherapy with 8 cycles of CAPOX or 12 cycles of FOLFOX4 [18). This study reported a significant lower probability of disease-related treatment failure (DrTF) at 3 years and lower distant metastases (DM) rate in experimental group. Also with TNT the pathological complete response rate was double compared to the standard of care group. There was no difference in post-operative complications, quality of life and Overall survival. At 5,6 years follow-up, the risk of locoregional recurrence was increased in the experimental group. However, the benefit in terms of DrTF and DM persisted after 5 years [20].

The Prodige 23 is one of the most important TNT studies. This trial randomized also patient with high risk rectal cancer to the experimental group that used 3 months of folforinox before chemoradiation and TME surgery folowed by 3 months of folflox after TME surgery compared to standard treatment (CRT followed by TME and 6 months of adjuvant chemotherapy). This trial showed that pathologic response grade is significantly greater when chemotherapy was delivered before CRT and surgery. Also, the TNT extends Disease-free survival with a manageable toxicity profile without impact on Overall survival [19].

The data regarding the optimal treatment sequence are not robust. A German Phase II trial compared 2 options of TNT; Induction chemotherapy followed by CRT (INCT-CRT) to the second option of TNT, CRT followed by consolidation chemotherapy (CRT-CNCT) and TME [21]. Authors concluded that in the consolidation arm there was more pCR (25% versus 17%). The OPRA trial, compared also INCT-CRT to CRT-CNCT and either TME or watch-and-wait according to tumor response. Patient with CNCT achieving greater rate of preservation compared to the group receiving INCT and this difference was statistically significant but without impact in survival [22].

According to these data, TNT became a new standard of care since 2020. It is recommended for tumors with Risk factors for increased recurrence including clinical T4 or N2 stage, low (≤5 cm) tumors, threatening of the CRM or presence of extramural vascular invasion as determined by MRI [3].

Interval before surgery

Traditionally, surgery was performed within 7 days of neoadjuvant short course RT for rectal cancer. The Stockholm III study randomised patients to three arms: SCRT (5x5 Gy) with surgery within one week, SCRT (5x5 Gy) with surgery after 4-8 weeks or long course radiotherapy (25x2 Gy) and surgery after 4-8 weeks [23], [24]. This trial concluded that SCRT with delayed Surgery (4-8 weeks) was similar to the others arms in terms of local recurrence, Metastasis and Overall Survival. The postoperative and operative toxicity were significantly reduced in the SCRT group with delayed surgery. Hence, this approach may be advantageous and useful.

After neoadjuvant chemoradiation, the interval of 6 to 7 weeks before surgery was established as a standard by The German rectal trial [8]. The GRECCAR-6 trial is a phase III, multicenter, randomized trial which included patients with locally advanced rectal cancer of the mid or lower rectum who received RCT with surgery either after 7 weeks or after 11 weeks. This study did not demonstrate an improvement in tumor pCR and morbidity was significantly increased in the 11 weeks' group (perioperative complications and worse surgical quality) [25]. Also there was no impact on 3- year OS, DFS or Distant and local recurrences in the update of this trial [26]

Organ preservation approaches:

Rectal surgery is associated with high postoperative morbidity (40 to 50%). In 10 - 25% of cases, a complete and sub complete tumor response was observed after CRT and a very low rate of residual lymph node metastases after neoadjuvant treatment was observed. For these reasons and to avoid a permanent colostomy, organ preservation has been an active area of research. [27], [28]

There are two Organ preservation approaches after completion of neoadjuvant treatment; Watch and wait (WW) strategy, in which surgery is omitted in patients who have achieved a clinical complete response (CR) and local excision (LE) approach.

The WW strategy was evaluated in small and retrospective studies. The first systematic comparative analysis and meta-analysis of WW versus surgery was published on 2017. For patients managed by WW strategy, the pooled 2-year local regrowth was 15.7%. Authors found no significant differences in non-regrowth cancer recurrence or overall survival in patients treated with WW versus surgery [29].

Hence, WW instead of surgery seems a safe and feasible treatment approach for patients achieving CR to neoadjuvant CRT but more prospective studies are mandatory to confirm long-term safety.

For LE approach, GRECCAR 2 was the first multicentre, randomised trial to compare LE with TME in downstaged low rectal cancer [30]. In this study, Patients with T2-T3 low rectal cancer, of a maximum size of 4 cm who had clinically good response after CRT (residual tumour ≤2 cm) were randomly assigned before surgery to either LE or TME. In the LE arm, a TME was performed if pathological tumor stage was ypT2–3. The 5-years results of this study confirmed no evidence of difference in oncological outcomes between LE and TME. LE can be an acceptable treatment in selected patients having a small T2-T3 low rectal cancer with a good clinical response after CRT.

The 2 organ preservation approaches were compared to radical surgery in a recent metanalysis. Eleven english studies with 1131 patients were included. There were 412 patients in Wait and See group (WS), 678 patients in radical surgery (RS) group, and 41 patients in LE group. WS group had a higher local recurrence rate than RS group. There was no significant difference in DFS and OS between the three groups [31].

Hence, Organ preservation can be recommended after multidisciplinary discussion in patients with rectal cancer who would have a permanent colostomy or inadequate bowel continence after TME and denied TME and accept a close multidisciplinary follow-up. [3]

II. Conclusion:

Radiation therapy is one of the most important treatments in the management of rectal cancer. Each case is specific and multidisciplinary tumor board is mandatory in all cases to get the optimal management of this cancer. Future studies will help to establish risk stratification groups, define the ideal regimen for rectal cancer in the neoadjuvant setting, identify the optimal sequencing of chemotherapy and radiation therapy in the TNT approach and select patients for organ preservation strategy.

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