MINI REVIEW

Adjuvant radiotherapy for rectal cancer: Recent results, new questions

La radiothérapie adjuvante pour le cancer du rectum : résultats récents, nouvelles questions

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Summary  Many randomised studies have now well established the role of radiotherapy (RT) in rectal cancer: it decreases the rate of local relapse and improves survival for stage II and III. The benefit of RT remains even in case of total mesorectum excision. Preoperative strategy has a better tolerance and is more efficient than post-operative RT. Two schedules have been widely used: an hypofractionated (5 × 5 Gy) and a normofractionated (45–50 Gy by fractions of 1.8–2 Gy) schedule. Both have advantages and drawbacks. Patients with locally advanced tumours or low-lying cancer must benefit from a protracted schedule, which increases down staging and the number of sphincter-preserving surgery. Combined chemoradiotherapy with 5FU or capcitabine enhances local control without a clear benefit in overall survival or disease-free survival. Adjunction of oxaliplatin does not improve the pathological response rate significantly. Results with cetuximab are still disappointing. Bevacizumab seems to increase widely the radiation response, but more data are needed to confirm these preliminary results. With this modern approach, the rate of local relapse is lower than 10%; the main issue is now the occurrence of distant relapses in 25–30% of the patients. Neo-adjuvant chemotherapy (CT) seems the better way to address this issue, because post-operative CT could be done properly in only 50% of the patients. Large prospective trials using neo-adjuvant CT with or without targeted therapies must be designed taking distant relapses and overall survival as main end-points.

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Introduction

Colorectal cancer is the fourth most common malignancy in western world with a disease specific mortality of around 33% [1]. The rectum is located within the pelvis, with bony
constraints limiting the surgical access, leading to a higher rate of local recurrence than colon cancers. Total mesorectum excision (TME) is associated with a lower risk of rectal recurrence (from 40% 20 years ago to less than 15% nowadays) and is accepted as the standard surgical technique.

The role of adjuvant radiotherapy (RT)

Before the era of TME, adjuvant RT was proposed to decrease the local recurrence rate. In the US, post-operative radiotherapy improved local control, but not overall survival [2,3]. Combination of postoperative chemotherapy (CT) and RT improved not only local control but also survival and was considered as the standard of care for patients with stage II or III rectal cancer [2,4—6]. In Europe, some trials used a pre-operative short-course, high-dose therapy (5 × 5 Gy over one week). A large Scandinavian trial showed a local recurrence rate reduction by this approach (from 27 to 11%; P < 0.001) and an improved 5-year overall survival (58% versus 48%, P = 0.004) [7]. An update of this trial with a median follow-up of 13 years showed that the benefit in local control (9% versus 26%; P < 0.001) and overall survival (38% versus 30%; P = 0.008) was maintained [8]. A meta-analysis including 22 randomized trials comparing pre- or post-operative radiotherapy versus surgery alone showed a higher specific survival in case of preoperative radiotherapy delivered with high biological doses (> 30 Gy) [9].

In the era of TME, has RT any remaining role? A Dutch randomized trial, with a standardized TME procedure, demonstrated that, even in case of good TME, preoperative RT decreased the local recurrence rate from 10.9 to 5.6% (P < 0.001), with no differences in distant relapses or survival [10,11]. In the MRC and NCIC trial, the benefit of preoperative RT was observed regardless to the quality of surgery [12].

Preoperative RT could be biologically superior to postoperative RT due to well-oxygenated tissue. Preoperative RT was associated with a better treatment compliance and a reduced gastrointestinal toxicity. The rate of sphincter-preserving surgeries was also increased. A German trial randomized 823 patients to pre- or post-operative chemoradiotherapy (CT-RT) [13]. Patients randomized to preoperative RT received 50.4 Gy in 28 fractions with a 120-h infusion of 5FU at 1000 mg/m² the first and fifth weeks of RT. Preoperative RT led to superior local control with a better tolerance (40% versus 26% grade 3/4 toxicity) (Table 1). The rate of sphincter-preserving surgery was doubled. Therefore, preoperative RT is now considered as the standard approach.

One recent MRC/NCIC trial randomised 1350 patients to preoperative RT (5 × 5 Gy) or selective post-operative concomitant CT-RT if circumferential resection margins (CRM) were positives [14]. The rates of local recurrence were 4% and 11% for preoperative RT and selective post-operative CT-RT, respectively (P < 0.0001). The improvement in local control was observed for stage II and III and for tumours of the lower or middle third of the rectum. This trial confirmed preoperative RT as the standard of care for all stage II and III rectal cancers.

Who are the best candidates for preoperative RT? In the Swedish trial, a benefit in disease-specific survival was observed in all stages [8]. However, TME procedure was not regularly performed. On the other hand, in the Dutch trial, a significant decrease in local relapse rate was demonstrated only for stage III (N1 or N2 disease) and for cancers located in the lower and middle third of the rectum. Despite TME, the rate of local recurrence was 21% in case of positive nodes [11]. Therefore, all patients with positive nodes on the preoperative staging should receive neo-adjuvant treatment. An improvement was demonstrated for stage II disease (T3N0) in the Swedish and the MRC trials, but the role of preoperative RT for “small” T3N0 lesions is still discussed.

CRM was reported to be an important factor for local control. CRM was defined as positive when microscopic tumour was ≤ 1 mm from the radial margin [15]. In the Dutch trial, a margin ≤ 2 mm was associated with a local recurrence risk of 16% compared with 5.8% in patients with a wider CRM (P < 0.0001). Patients with a margin ≤ 1 mm had an increased risk of distant metastases. MRI may now evaluate more precisely tumour volume and predict CRM [16]. Preoperative radiotherapy may induce a down staging and increase the rate of negative CRM.

What is the best preoperative regimen?

Two types of preoperative RT schedules have been used in prospective trials: a short-course of five fractions of 5 Gy followed by surgery one week later; and a long course consisting of 45—50 Gy, given by fractions of 1.8-2 Gy during five weeks, with surgery planned four to eight weeks after RT. The importance of achieving a high total biological radia-

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<th>Arms</th>
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<td>EORTC 22921 [38]</td>
<td>Preop RT</td>
<td>5</td>
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<td>FFCD 9203 [26]</td>
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<td>German trial [13]</td>
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Radiotherapy of rectal cancer

Frequent local relapses were less frequent in the groups receiving CT patients allocated to post-operative CT did not receive it. Post-operative CT was delivered in four courses, at the Preoperative CT was given during Weeks 1 and 5 of RT. During five days combined with leucovorin (20 mg/m²). But the number of patients was small (n = 312) and surgeons were not encouraged to modify the type of surgery according to tumour response. How to choose between these two regimens? Preoperative short-course RT, in the Dutch trial or in the MRC/NCIC trial, did not reduce significantly the local recurrences rate in case of positive CRM (Dutch trial: 19.7% versus 23.5%; P = 0.393, with or without preoperative RT [11]: MRC/NCIC trial: 13.8% versus 20.7% [14]). Long-course RT, with delayed surgery four to six weeks after, increased down staging and pCR rate [19]. It seems logical, with such results, to propose a long course CT-RT when bulky tumours have been found on MRI to obtain a large tumour down staging and negative CRM. In the same way, if the aim is to transform a rectal amputation into a sphincter-preserving surgery, a long-course is needed. On the opposite, for frail patients with a ‘small’ T3N0 of the middle third of the rectum, short term preoperative RT could be used.

There is some theoretical background to combine CT and RT in order to increase the effects of RT and to act on distant relapses as well [20]. To compare different schedules, histological response (down staging) and pCR were more and more used as a surrogate marker, because they seem to be correlated to disease-free survival [21–23]. Hartley et al. reviewed 52 trials using CT-RT and showed that the median pCR rate was 13.5%. Factors associated with pCR were: administration of two drugs, continuous 5FU or capecitabine and radiation dose over 45 Gy [24]. The EORTC trial compared RT alone or associated with preoperative CT, post-operative CT or both. CT consisted in 5FU delivered as short intravenous infusion, 350 mg/m² during five days combined with leucovorin (20 mg/m²). Preoperative CT was given during Weeks 1 and 5 of RT. Post-operative CT was delivered in four courses, at the same doses and schedule. Twenty-seven percent of the patients allocated to post-operative CT did not receive it. Local relapses were less frequent in the groups receiving CT (P = 0.002). CT increased the pCR rate as well. Interestingly, the decrease in local relapses was of the same magnitude whether the CT was given before or after surgery (Table 1). There was no increase in disease-free or overall survival [25].

The FFCD trial randomised 762 patients between preoperative RT and RT-CT. Treatment regimens were similar to those used in the EORTC trial. Once again, the local control was better in the RT-CT arm (Table 1), so was the pCR [26].

In the post-operative setting, protracted infusion of 5FU was compared to intermittent bolus 5FU in a randomised phase III trial. The protracted regimen was associated with better progression-free and overall survivals [5]. Cetuximab may mimic the pharmacokinetics of protracted 5FU infusion without patient discomfort: it could replace 5FU in the future in association to RT [27,28].

Oxaliplatin is highly effective in colon cancer. Its role in association with radiation has been evaluated in some phase II and III trials. Recently, the ACCORD 12 trial compared capecitabine and 45 Gy (Cap45) to a combination of capecitabine, oxaliplatin and 50 Gy (Capox50) [29]. There was more toxicity in the Capox50 arm without any benefit in the rate of conservative surgery (75%). The pCR rates were 13.9% and 19.2% (P = 0.09). The small increase in pCR rate could be due to the drug but also to the higher radiation dose given in the Capox50 arm. In an Italian study with the same design, the pCR were identical in the oxaliplatin and control arms (16 and 15%) [30].

Cetuximab, a monoclonal antibody directed against the epidermal growth factor receptor (EGFR), has been used in phase II trials associated with 5FU or capecitabine. A pooled analysis of these trials suggested an overall pCR of 9.1%, comparable to the pCR rate seen with fluoropyrimidine-based chemoradiation (Table 2) [31]. These results could be considered as disappointing. However, K-ras mutations, which occurred in 30% of the rectal carcinomas [32,33], were more toxicity in the Capox50 arm without any benefit in the rate of conservative surgery (75%). The pCR rates were 13.9% and 19.2% (P = 0.09). The small increase in pCR rate could be due to the drug but also to the higher radiation dose given in the Capox50 arm. In an Italian study with the same design, the pCR were identical in the oxaliplatin and control arms (16 and 15%) [30].

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Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF) improves survival in stage IV colorectal disease. Preclinical data are in favour of a combination of anti-angiogenic drugs and radiation. Two phases II prospective studies evaluated the role of bevacizumab in combination with capecitabine or 5FU [36,37]. Some impressive response rates were obtained with pCR of

| Table 2 Pathological complete response rate (pCR) according to preoperative regimen in prospective trials using long schedules of preoperative RT and concomitant CT-RT. |
|---|---|---|---|
| Trial       | Regimen                          | No. pts | pCR (%) |
| EORTC 22921 [38] | 5FU + leucovorin — 45 Gy          | 506     | 13.7    |
| FFCD 9203 [26]    | 5FU + leucovorin — 45 Gy          | 375     | 11.4    |
| German trial [13] | 5FU — 50 Gy                       | 399     | 8       |
| ACCORD 12 [29]    | Capcitabine-oxaliplatin — 50 Gy  | 299     | 19.2    |
| STAR [30]         | Capcitabine-oxaliplatin — 50.4 Gy| 291     | 15      |
| Pooled analysis [31] | Cetuximab + 5FU + RT             | 316     | 9.1     |
| Willet et al. [37] | 5FU-bevacizumab — 50.4 Gy        | 32      | 16      |
| Crane et al. [36] | Capcitabine-bevacizumab — 50.4 Gy| 25      | 32      |
16 and 32%. Digestive toxicity and delayed post-operative wound healing are frequent but seemed manageable. More studies are needed to better define the place of these new agents in combination with preoperative RT.

Distant relapses

In the more recent trials, combining TME and preoperative RT or RT-CT, the local relapse rate was usually less than 10%. Obviously, some major advances have been obtained with this approach. Distant metastases are now the main cause of relapse, around 25 to 35% (Table 1). In the Swedish trial, at 13 years, the rate of distant metastasis was 34% and was not influenced by preoperative RT.

Use of adjuvant CT has not been properly evaluated in large randomised trials. The EORTC trial failed to demonstrate a significant impact of adjuvant CT on disease-free or overall survival [38]. The benefit of adjuvant CT was only found for patients with a tumour classified ypT0-2 on the surgical specimen [39]. In the Italian trial comparing neo-adjuvant treatment with or without oxaliplatin, there was a slight decrease in the rate of distant metastasis [30].

By analogy with colon cancer, many physicians prescribe an adjuvant treatment if positive nodes are found in the surgical specimen. The histological regression rate is an important independent prognostic factor, as shown in the analysis of the German study. A five-point tumour regression grading (TRG) was described. TRG 0 was defined as no tumour regression and TRG 4 as a complete absence of viable tumour cells [21]. The 5-year disease free survival was 63% for TRG 0 + 1, 75% for TRG 2 + 3 and 86% for TRG 4 (P = 0.006).

Compliance to adjuvant CT is usually poor after preoperative CT-RT and rectal surgery, with approximately 50% of patients unable to receive the planned post-operative CT [13, 26, 38]. One possible way to address this issue is to intensify the preoperative regimen, with CT given before and during RT. In a phase II randomized trial, comparing four cycles of capecitabine–oxaliplatin given before CT-RT or after surgery, the preoperative regimen had a better tolerance (grade 3/4 toxicity: 19% versus 54%; P = 0.0004) and a better treatment compliance (91% versus 54%; P < 0.0001), but the rate of pCR was similar in both arms (13% and 14%) [40].

Quality of life after RT and surgery

Anorectal dysfunction is observed in a high number of patients after treatment of rectal cancer and is increased by adjuvant RT [41, 42]. Bowel frequency, incontinence and stool fractionation can impact on daily activities. In the Swedish study, 30% of the patients had restricted social lives [41]. In the Dutch trial, 47% of the patients had reduced activities versus 37% in the arm without RT [42]. In the Polish trial, 20% of the patients complained of severe deterioration of their quality of life [43]. The rate of perineal wound complications was also increased after preoperative RT [43].

The risk of anorectal dysfunction is increased in patients with low canal anal anastomosis.

Hypofractionated regimens can increase theoretically late toxicities compared to classical fractionation. In the polish trial, comparing 5 × 5 Gy to protracted CT-RT, late toxicities and quality of life were equivalent in both arms, but there was no RT quality control [43].

One possible way of improvement is to use new techniques of RT, specifically intensity-modulated radiotherapy (IMRT) [44]. However, the target volumes must be clearly defined. The local sites of recurrences have been analysed in retrospective studies [45]. Most relapses were located in the lower two-third of the pelvis, below the S1-S2 interspace, in the dorsal part of the pelvis. Lateral lymph node areas could be excluded from the target-volumes; width of the fields could so be reduced. For tumours of the middle third of the rectum, irradiation of the anal canal may be avoided. The Radiation Therapy Oncology Group (RTOG) proposed an atlas to better delineate clinical target volumes [46]. The same has been made by the French society of radiation oncology (http://www.siria.de).

Conclusion

The role of preoperative CT-RT is now well established for stage II or III rectal cancers. The new challenges are:

- to improve our staging to better define who really benefits from the preoperative treatment;
- to decrease long-term toxicity by improving surgical or irradiation techniques;
- to clearly demonstrate the role of adjuvant or neo-adjuvant CT;
- to evaluate targeted therapies in this disease.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

References

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