Clinics and Research in Hepathology and Gastroenterology (2011) 35, 17—22

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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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Available online 24 December 2010

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 capecitabine 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.

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

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0399-8320/$ - see front matter © 2010 Published by Elsevier Masson SAS.
doi:10.1016/j.gcb.2010.07.017

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 preoperative 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 post-operative 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/m^2 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 (5×5Gy) 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 $\leq$1 mm from the radial margin [15]. In the Dutch trial, a margin $\leq$2 mm was associated with a local recurrence risk of 16% compared with 5.8% in patients with a wider CRM ($P < 0.0001$). Patients with a margin $\leq$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-

Table 1 Local control in recent randomized trials with preoperative (preop) radiotherapy (RT) or chemoradiotherapy (CT-RT).

Trial	Arms	Follow-up (yrs)	Local relapses (%)	Distant relapses (%)
EORTC 22921 [38]	Preop RT	5	17.1	34.4
	Preop RT + post-op CT-RT		9.6	
	Preop CT-RT		8.7	
	Preop CT-RT + post-op CT		7.6	
FFCD 9203 [26]	Preop RT	6	16.5	21.8
	Preop CT-RT		8.1	
German trial [13]	Preop CT-RT	5	6	36
	Post-op CT-RT		13	38