Radiotherapy and Oncology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

EURECCA consensus conference highlights about rectal cancer clinical management: The radiation oncologist's expert review

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ARTICLE INFO

Article history:
Received 18 September 2013
Accepted 20 October 2013
Available online xxxx

Keywords:
Rectal cancer
Radiotherapy
Combined modality therapy

ABSTRACT

Background and Purpose: Although rectal and colon cancer management has progressed greatly in the last few decades clinical outcomes still need to be optimized. Furthermore, consensus is required on several issues as some of the main international guidelines provide different recommendations. The European Registration of Cancer Care (EURECCA) drew up documents to standardize management and care in Europe and aid in decision-making.

Material and Methods: In the present section the panel of experts reviews and discusses data from the literature on rectal cancer, focusing on recommendations for selecting between short-course radiotherapy (SCRT) and long-course radio-chemotherapy (LCRTCT) as preoperative treatment as well as on the controversies about adjuvant treatment in patients who had received a pre-operative treatment.

Results: The starting-point of the present EURECCA document is that adding SCRT or LCRTCT to TME improved loco-regional control but did not increase overall survival in any single trial which, in any case, had improved with the introduction of total mesorectal excision (TME) into clinical practice. Moderate consensus was achieved for cT3 anyNM0 disease. In this frame, agreement was reached on either SCRT followed by immediate surgery or LCRTCT with delayed surgery for mesorectal fascia (MRF) negative tumors at presentation. LCRTCT was recommended for tumor shrinkage in MRF+ at presentations but if patients were not candidates for chemotherapy, SCRT with delayed surgery is an option/alternative. LCRTCT was recommended for cT4 anycNM0. SCRT offers the advantages of less acute toxicity and lower costs, and LCRTCT tumor shrinkage and down-staging, with 13–36% pathological complete response (pCR) rates.

To improve the efficacy of preoperative treatment both SCRT and LCRTCT have been, or are being, associated with diverse schedules of chemotherapy and even new targeted therapies but without any definitive evidence of benefit. Nowadays, standard treatment is fluoropyrimidine alone since alternative agents and regimens have not been shown to be more active, only more toxic.

Conclusions: The EURECCA panel summarized available evidence in an attempt to reduce variance in rectal cancer management. This is expected to benefit patients. Results from ongoing randomized trials will help clarify some of the issues that are still under debate.

Even though great progress has been made in rectal and colon cancer management over the past decades, clinical management and outcomes still need to be optimized. Consensus is required since some of the main international guidelines report few, albeit substantial differences in recommendations [1]. A step forward was taken with the publication of a consensus document on managing rectal cancer in 2009 [2]. It was followed by a position paper from the European Registration of Cancer Care (EURECCA) [3] which aimed at standardizing clinical management of colon and rectal cancer care in Europe, aiding doctors in multidisciplinary teams in decision-making and providing benchmarks to enhance the quality of treatment through audits and outcome analyses of population-based registries.

The present review will focus on recommendations for patients with rectal cancer especially for selecting between short-course radiotherapy (SCRT) and long-course radio-chemotherapy (LCRTCT) as preoperative treatment as well as on the controversies about adjuvant treatment in patients who received either SCRT or LCRTCT.

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0167-8140/$ - see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.radonc.2013.10.024

Preoperative radiotherapy treatment schedule: short versus long course

The EURECCA conference achieved moderate consensus for algorithms advocating preoperative RT for cT3 anyNM0 disease at presentation. In this frame, agreement was reached on SCRT followed by immediate surgery or LCRTCT with delayed surgery for a mesorectal fascia (MRF) negative presentation in any localization.

LCRTCT was recommended, despite lack of definitive evidence that it improved outcomes [4], for MRF+ presentations (irrespective of localization and nodal involvement), in order to achieve tumor shrinkage. For this group of patients, SCRT with delayed surgery should be proposed only if patients were not candidates for the combination with chemotherapy. LCRTCT was recommended for cT4 anycNM0.

Although North American guidelines describe LCRTCT as the option of choice for preoperative treatment of cT3-T4N+/− M0 [5], there is no European consensus on this issue [1]. The EURECCA document emphasized global reports of better survival for rectal cancer patients after the introduction of total mesorectal excision (TME) and increased use of preoperative RT [6]. Although an older study had reported a survival gain with SCRT [7], no single randomized trial has observed significantly increased overall survival (OS) after adding either SCRT or LCRTCT to TME. Both regimens improved loco-regional control to about the same extent and had similar effects on OS and long-term toxicity [3,8,9]. Compared with LCRTCT, SCRT is associated with less acute toxicity, and lower costs. LCRTCT has the potential for tumor shrinkage and downstaging, which led to pathological complete response (pCR) rates of 13–36% [10]. On the other hand downsizing, downstaging and even pCR, are seen when surgery is delayed after SCRT [11–13].

In the pre-operative RT setting, randomized trials evaluated administering SCRT followed by surgery vs surgery alone which was eventually followed by postoperative adjuvant RT ± chemotherapy for high-risk presentations [8,14]. The Dutch TME trial randomized 1861 patients to no pre-operative treatment or to SCRT (25 Gy in 5 fractions). At 11.6 years median follow-up, local control (LC) was significantly better in the SCRT group [15]. Even though postoperative RT was mandatory for patients who had received surgery alone and had circumferential resection margin (CRM) involvement of $\leqslant$1 mm (CRM+), only 47% were treated. The MRC C07 trial assigned patients to pre-operative SCRT versus primary surgery. Post-operative LCRTCT was administered to the surgery-alone group when CRMs were involved or threatened (<1 mm). Results showed local control and disease free survival (DFS) were significantly better in the SCRT group, OS did not differ between the groups (HR = 0.91; 0.73–1.13; $p = 0.40$) [14].

Randomized trials also compared pre- and post-operative LCRTCT administration. In 823 patients Sauer et al. (CAO/ARO/AIO-94) delivered 50.4 Gy in 28 fractions with concomitant chemotherapy to increase radiosensitivity with a boost of 5.4 Gy in the postoperative arm. At 11 years follow-up the preoperative LCRTCT approach was associated with higher LC, less toxicity and increased sphincter preservation in a subgroup [9,16].

Two randomized trials directly compared SCRT and LCRTCT. In 316 patients with palpable cT3 lesions above the anorectal ring Bujko et al. [4,17] observed no significant differences in LC, DFS and 4-year OS. LC rates were, however, numerically higher (16% vs 11%) in the LCRTCT group. LCRTCT was associated with significantly higher rates of acute toxicity (grade III–IV: 18.2% LCRTCT vs 3.2% SCRT) and pCR (16.1%-LCRTCT vs 0.7%-SCRT), and a lower CRM+ rate (4.4%-LCRTCT vs 13%-SCRT). In the Australia and New Zealand trial Ngan et al. [18] randomized 366 patients with cT3 any N lesions of the middle and lower rectum to SCRT or LCRTCT. Adjuvant chemotherapy was planned for both groups (6 courses in the SCRT cohort; 4 in the LCRTCT group, which was administered to 85% and 86% of patients, respectively). With a median 5.9 years follow-up, no significant differences were found in OS, late toxicity and distant recurrence rates. The 3-year local recurrence showed no significant difference between the groups (7.5 for SCRT vs 4.4% for LCRTCT; $p = 0.24$); for tumors at <5 cm from the anal verge there was a trend for reduced local recurrences with the LCRTCT approach (6/48 (12.5%) SCRT patients, and 1/31 (3.2%) LCRTCT; $p = 0.21$). Interestingly like Bujko et al. [17] pCR and downstaging rates were significantly higher in the LCRTCT group (15%- vs 1%-SCRT; $p < 0.01$; 45%- vs 28%-SCRT; $p = 0.002$ respectively). The authors concluded that "LCRTCT may be more effective in reducing local recurrence for distal tumors ... and it may be reasonable to suggest a policy that distal ... tumors be treated with LCRTCT." This conclusion was hotly debated [19,20], as it derived from an unplanned analysis, the results of which were not statistically significant. There are some limitations in the trials conducted by Bujko et al. [19] and Ngan et al. [18]. OS was not the primary end-point, and relatively few patients were accrued. An on-going German study (the so-called "Berlin study"), designed to compare SCRT followed by early surgery with LCRTCT, expects to enroll 760 patients with cT2N+/T3Nx disease. Adjuvant chemotherapy is mandatory for all to avoid potential bias [21].

Given the results to date, the EURECCA consensus document contains different viewpoints on preoperative schedules for low seated lesions.

In summary, when compared, SCRT and LCRTCT seem to provide similar OS, LC and DFS in patients with intermediate advanced rectal cancer, chiefly cT3MRF−. SCRT was associated with less acute toxicity. LCRTCT achieved more downstaging and better pCR and CRM-rates than SCRT with immediate surgery, which is the evidence for recommending LCRTCT for advanced-stage disease (cT3MRF+, cT4) where some degree of downsizing or downstaging is usually needed. Lack of definitive evidence precludes recommending one modality over the other in less advanced stages as consensus was moderate to minimum [3].

Two specific issues play a central role in the preoperative RT setting; pCR induction and CRM status. Response to preoperative treatment is widely debated. Some studies did not show any impact on outcomes [22]. Others reported that when pCR is achieved after preoperative treatment outcomes are greatly better with fewer local recurrences [23,24], and better OS and distant metastases rates, as highlighted by two recent meta-analyses [25,26]. Moreover, to aid the multidisciplinary team in decision-making when difficulties arise because of tumor heterogeneity, Valentini et al. [25] suggested pCR be incorporated as a response parameter into specific predictive nomograms. MRF status has an impact before and after preoperative therapy and may determine choice of schedule. Involved CRM ($\leqslant$1 mm) after surgery are associated with high risk of metastases and low survival rates [27,28], as first shown by the Dutch trial results [8,28]. In the Polish trial LCRTCT decreased the CRM+ rates, however, this did not result in lower local recurrence rates, which is likely related to different time intervals to surgery [17]. The Australian and New Zealand trial did not focus on that issue [18]. The consensus conference agreed on the need to distinguish pathological (CRM) and imaging (MRF) findings. Recent studies highlighted the efficacy of Magnetic Resonance Imaging (MRI) in determining MRF involvement at clinical staging [29] which is useful information for selecting the recommended preoperative modality in different situations.

Some studies are attempting to overcome some of the drawbacks of both preoperative approaches.

In patients with locally advanced rectal cancer, the international phase III trial Rectal Cancer and Pre-operative Induction Therapy Followed by Diligent Operation (RAPIDO) is testing SCRT

Please cite this article in press as: Valentini V et al. EURECCA consensus conference highlights about rectal cancer clinical management: The radiation oncologist's expert review. Radiother Oncol (2013), http://dx.doi.org/10.1016/j.radonc.2013.10.024