The Right Study Design Is Needed to Find out which Patients Benefit from Preoperative Chemoradiotherapy for Intermediate Staged Rectal Cancer

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Surgery remains the main important treatment of rectal cancer, nevertheless the management of this disease has evolved to become multidisciplinary [1]. After 2000 a number of important European randomized studies have been published. They have examined a variety of preoperative approaches and most have required the use of total mesorectal excision (TME).

In order to shape clinical practice based on best scientific evidence from literature, the International Conference on ‘Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus’ (EURECA-CC2) was organized in Italy under the endorsement of the European Society of Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO), and the European Society of Therapeutic Radiation Oncology (ESTRO). The goal of this consensus conference was to help develop future programs, investigational protocols, and guidelines for staging and treatment of rectal cancer throughout Europe [2].

Intermediate tumors are defined as neoplasms extending beyond the rectal wall (c/pT3–4 or N1–2 M0) but without unresectable infiltration to surrounding organs (all cT4). There are two treatment approaches for patients with resectable intermediate stage rectal cancer. The first approach is preoperative radio(chemo)therapy followed by surgery and then postoperative chemotherapy can be considered. The second is initial surgery followed by postoperative combined modality therapy if the tumor is pT3–4 and/or N1–2 [1].

The main advantage of postoperative radio(chemo)therapy is better selection of patients since it can be based on pathologic staging. The primary disadvantages include increased toxicity related to the amount of small bowel in the radiation field, a potentially more radio-resistant hypoxic postsurgical bed and, if the patient has undergone an abdominal perineal resection, the radiation beams have to be extended to include the perineal scar. Preoperative and postoperative therapy have been compared in randomized trials [3–5]. Two trials (Intergroup 0147 and NSABP R-03) closed early due to lack of accrual. The completed trial, the German Rectal Cancer Trial [4] showed fewer local recurrences and less acute and late toxicity, but no survival benefit with preoperative therapy. In one trial where short-course preoperative radiation was compared with long-course postoperative RT alone [5] and in another trial where it was compared with long-course postoperative chemoradiation [3] for the subsets with a high risk of recurrence, more favorable results were seen in the preoperative groups. Postoperative therapy was a common approach in North America, however, since 2004 this is no longer the case.

At the present time, given the improved local control, and acute and long-term toxicity profile, patients with cT3 rectal cancer who require additional therapy to surgery (chemoradiation or short course radiotherapy) should receive it preoperatively [3–6]. It was agreed that short course radiotherapy definitively reduces the local recurrence risk for patients with most rectal cancers. The relative risk reduction may actually be higher the lower the absolute risk of a local failure is. The largest absolute gains in the trials have been seen in patients with extramural spread and node positive disease [3, 7]. For patients with positive circumferential resection margin, there is a reduction in local failure rates after short-course radiation although the magnitude of benefit is not considered sufficient for routine use [7]. After standardization of TME there is no evidence of overall survival benefit in the single short course randomized trial, the TME-trial [7]. However, population based studies have demonstrated that since standardization of rectal cancer surgery with TME and the implementation of preoperative radiotherapy there has been a survival benefit [8].

Two recent randomized trials have shown an improvement in the results of preoperative radiation in patients with intermediate stage rectal cancer when 5-FU based chemotherapy is added to radiotherapy. A statistically significant decrease in
local recurrence as well as an increased rate of pathological complete response (pCR) was observed in patients receiving chemotherapy. 5-year overall survival was not changed by chemotherapy, but the trials were underpowered to detect a 5% difference in overall survival [9, 10]. After preoperative radiochemotherapy a variable percentage of pCR specimens has been reported. Although some series show no correlation [11], many series report that patients who achieve a pCR following preoperative radiochemotherapy have improved long-term outcomes in terms of excellent local control rates and this is independent of their initial clinical T and N stage [12, 13].

To increase the efficacy of bolus or infused 5-FU or capecitabine these agents have been combined, in several phase II studies, with oxaliplatin or irinotecan plus radiation. The apparently positive results of these studies have supported many ongoing phase III studies. At the present, infused 5-FU as well as oral fluoropyrimidines remain the standard agents to combine with preoperative radiotherapy [1]. Two studies have recently reported early results from randomized phase III trials evaluating the role of adding oxaliplatin to chemoradiotherapy with 5-FU. Neither the Prodigie 2-ACCORD 12/0405 trial [14], nor the STAR-01 trial [15] could report any significant benefit in pCR rates.

There is insufficient evidence on the benefit of adjuvant postoperative chemotherapy after preoperative chemoradia-
tion to come to a consensus about its use [1]. Exploratory posthoc subgroup analyses suggest that only patients who respond and are downstaged from cT3–4 to ypT0–2 benefit from 5-FU based adjuvant chemotherapy [16]. These data support that – as shown in other trials such as the QUASAR trial [17] or the Japanese trial investigating 5-FU/FA or UFT, respectively – a significant survival benefit of 3–4% with 5-FU based chemotherapy. The role of adjuvant treatment strategy after preoperative chemoradiation is still being investigated.

Sphincter preservation is usually considered when the tumor is found in the lower third of the rectum. It has been claimed, mainly based upon historical controls, that radio-
therapy and preferably chemoradiotherapy with delayed surgery will increase the number of preserved sphincters due to a downsizing effect on the tumor by induction treatment. Unfortunately, there are no randomized trials supporting this idea. Cultural differences are significant. For example a stoma may be more disastrous for the patient than a local failure in southern parts of Europe and the Arabic world. Therefore, many patients from the Mediterranean areas will accept poor bowel function in preference to a stoma, and will also accept using diapers [18].

Retrospective data has suggested that a subset of patients with pT3N0 disease may not require adjuvant therapy. Reports from a US pooled analysis have identified favorable subsets of patients with pT3N0 disease who, following surgery alone, have a 10-year actuarial local recurrence rate of 10% [19]. Their data suggest that patients with upper rectal cancers who undergo a TME, have at least 12 nodes examined, and have stage pT3N0 disease with an adequate radial resection margin likely do not need radiation therapy. The 4–5% benefit in local control with radiation may not be worth the risks. Furthermore, about 20% of cT3N0 patients are overstaged and have cT1–2N0 disease and would therefore be overtreated with preoperative radiochemotherapy. However, an even larger number would be understaged since following preoperative radiochemotherapy 22% will have ypN disease. These data illustrate the weaknesses of nodal staging by imaging [20].

Won Sup Yoon and colleagues [21] performed a retrospective matched pair analysis on patients treated with preoperative or postoperative radiochemotherapy in locally advanced rectal cancer with the aim to identify the features of the subgroups of patients which had more benefit from a neo-adjuvant approach. The manuscript unfortunately failed in this aim, because study design and methodological aspects didn’t support their conclusion. However, the aim of identifying subgroup features for tailoring treatments is relevant and further efforts are needed to look for reliable evidence before moving away from consolidate knowledge.

References

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