Could the surgeon trust to radiotherapy help in rectal cancer?

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When the surgeon analyzes the ongoing literature on the evidence of the neoadjuvant approaches to rectal cancer finds a true paradox: from one side they seem to offer a relative less relevant contribute through the time, in fact whereas in the Swedish trial preoperative radiation yielded a significant improvement of local control and survival, after the introduction of TME the contribution of preoperative chemoradiation is relegated to local control with no or poor influence on survival, even if the absolute 5-year survival rate moved from 40% of the '70 to 60-65% of the latest years. From other side the growing evidence of an incidence of pCR approaching to 30% seems to identify a subset of patients with more favourable prognosis to neoadjuvant treatments. Furthermore, the overall evidence that 30-35% of rectal cancer patients treated with multimodality therapy still die from cancer namely by distant metastases in spite of the 4-8% of absolute benefit of adjuvant 5Fu based adjuvant chemotherapy, seems to vanish the efforts of the further optimization of the local treatments (surgery and radiotherapy) and of the ongoing modality of delivery the chemotherapeutic agents.

We would like to address the main evidences from the literature and the main uncertainties that the surgeon could face to propose a combined treatment to his rectal cancer patient.

Key words: rectal cancer, radiotherapy, surgery

MAIN EVIDENCES

Loco-regional tumor control in rectal cancer surgery has improved during the past 10-15 years and started with the introduction of more exact surgery and precise procedures following embryonic planes: the Total Mesorectal Excision (TME). Using this technique, locally radical surgery can be achieved without compromising sphincter function. The efficacy of TME is closely related to the training and the case volume of each surgeon, who still represents one of the major prognostic factors in the treatment of rectal cancer.

The margins created by the surgeons can be involved by tumor spread at a variety of sites. The most well known are the proximal and distal margins of a resection. However surgeons are taught to avoid involvement of these margins and only 1-2% of cases in randomised trials show involvement. A further margin is the mesenteric margin where the surgeon devascularises the bowel. This is infrequently examined but we know that tumour is close to it in 8% of cases as involvement of the highest lymph node (stage Dukes C2) is recorded when reporting according to Dukes.

The margin created around the mesorectum is the most important. This margin can be interested by direct tumour spread but also by the incomplete removal of lymph nodes that lie just under the mesorectal fascia, and any small deviation from the correct surgical plane could enter them, potentially compromising cure. The evidence base for the importance of the surgical CRM is now established. Over 4,000 patients have been reported in a range of studies from audits, prospective interventions, and a randomised clinical trial. All report higher local recurrence rates and lower survival when clearance is less than 1 mm.

The recording of the frequency of involvement of the surgical CRM is important for feedback to radiologists for accuracy of prediction as well as to the surgeon and patient as an indicator of the quality of surgery. The Leeds group have produced evidence that reduction of the frequency of CRM involvement by improving surgical technique improves survival for a single surgeon.

Three to 5% of rectal cancers are early localized tumors (3-5%). They include small, exophytic, mobile tumors without adverse pathologic factors and can be adequately treated with TME or with a variety of local therapies to avoid the sphincter removal in case of low located tumors.
Locally advanced rectal cancers are tumours with penetration through the entire rectal wall or with evidence of positive pelvic nodes, but still a non threatened CRM based upon preoperative MRI and without distant metastases. For these patients, there are more than 15 randomized trials of preoperative radiation therapy alone with low to moderate doses of radiation: most of them showed a decrease in local recurrence. The Swedish Rectal Cancer Trial is the only one out of eight studies with more than 500 patients, which reported a survival advantage for the total treatment group. Three meta-analyses report conflicting results. All of them reveal a decrease in local recurrence.

However a survival advantage was reported in the analysis by Camma et al., whereas the analysis by Munro and Bentley did not. The Swedish Council of Technology Assessment in Health Care (SBU) performed a systematic review of radiation therapy trials. They analyzed data from 42 randomized trials and 3 meta-analyses, 36 prospective studies, 7 retrospective studies and 17 other articles, for a total of 25,351 patients.

The main conclusion was that preoperative radiotherapy at biologically effective doses above 30 Gy decreases the relative risk of local failure by 50-70%, and by 30-40% for postoperative radiotherapy at doses that are usually higher than those used preoperatively (similar to the Colorectal Cancer Collaborative Group) and that survival is improved by about 10% using preoperative radiotherapy. In the last years therefore, preoperative therapy has gained wide acceptance as standard therapy for rectal cancer.

Preoperative and postoperative therapy have been compared in four randomized trials. At the present time, given the improved local control, acute and long-term toxicity profile, and sphincter preservation rate reported in the German trial, patients with cT3 rectal cancer who require combined modality therapy should receive it preoperatively.

Unresectable tumours are the Adenocarcinomas of the rectum beyond potentially curative surgical resection (R0). The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as on the morbidity the patient is willing to accept. Unresectable rectal cancer is a heterogeneous disease and it is not unequivocally related to the involvement of pelvic organs or structures (cT4).

All patients with primarily unresectable disease should receive preoperative combined modality therapy in the range of 50–54 Gy plus 5FU-based chemotherapy to enhance R0 resectability.

More recently, the preliminary outcome of a randomized Scandinavian Trial on preoperative radiochemotherapy vs only radiotherapy in unresectable and recurrent patients showed a statistical advantage for combined therapy in disease-free survival (64% vs 50% at 5 years, p=0.012) and overall survival (72% vs 53% at 5 years, p=0.025), and seems to further support the role of preoperative radiochemotherapy.

**MAIN UNCERTAINTIES**

The question is whether the addiction of radiotherapy with modern techniques, in a neo-adjuvant setting, has further changed surgical philosophy, since many surgeons presently claim that more sphincters can be preserved, provided that preoperative chemo-radiotherapy is used. Unfortunately this idea is not supported in randomized trials.

Whether this change has anything to do with preoperative chemo-radiotherapy is actually not known; rather the change in surgical attitude is more important than the effects of any preceding radio-(chemo)therapy. As the Swedish Council of Technology Assessment in Health Care (SBU) pointed out, at this moment the literature is inconclusive in evaluating the role of preoperative radiotherapy alone or with concurrent chemotherapy in promoting sphincter-saving surgery in low-lying tumours.

Anyway, sphincter preservation with a bad function is of questionable benefit. It is apparently very difficult to interpret the literature on this topic, as cultural differences are enormous: many patients from the Mediterranean areas will accept bowel function in preference to a stoma, and also accept using diapers.

Although some series show no correlation, many series report that patients who achieve a pathological complete response (pCR) following preoperative radiotherapy ± concurrent chemotherapy have an excellent local control rates, independent of their initial clinical T and N stage.

The different incidence of pCR in radiochemotherapy arms did not affect the final outcome of the randomized studies. These data support the concept of heterogeneity between rectal cancers and the need to identify reliable markers to detect favourable patients who could be cured with less therapy.

Organ preservation represents one of the ongoing topics of surgical research: the experience with preoperative radiation + 5FU based concomitant chemotherapy followed by local excision is at its beginning. Most series are limited to highly selected patients with cT3 disease who are either medically inoperable or refuse radical surgery. Since most series limit this approach to those patients who responded to preoperative therapy there is a need to identify prognostic and predictive factors to better define patients who are suitable for limited surgery.

Ongoing trials are accruing patients. It can even be questioned if a local excision can be avoided if the tumour has regressed completely following radiotherapy. Intensive follow-up with the "wait-and watch" philosophy has been used with impressive results, similar to those seen after radiotherapy for anal carcinoma. This treatment policy has been adopted in patients where an abdominoperaireal resection has been the alternative procedure.

There are insufficient data on adjuvant postoperative chemotherapy after pre-operative treatment with (chemo)radiation to come to a conclusion about its use. Since single agent 5-FU with or without leucovorin is a rather weak chemotherapy with a small but significant effect on...
colon cancer, the potential of adjuvant combination chemotherapy should be investigated.

The 5-FU bolus or infused 5-FU as well as capecitabine has been combined in several phase II studies with oxaliplatin or irinotecan, in combination with radiation as well as adjuvant treatment after surgery and the ongoing trial will clarify their role.

Furthermore, the next generation of clinical trials is about to start now and will integrate the novel "targeted" drugs like bevacizumab and cetuximab in both preoperative and postoperative setting.

Analysis of pre-treatment biopsies using selected molecular markers such as VEGF, c-K-ras, thymidylate synthase, p27kip1, p53, apoptosis, DCC, and Ki-67 have had varying success in identifying patients who may best respond to preoperative therapy. Since these studies are retrospective and usually do not examine multiple markers, at present the need for combined treatment should still be based solely on T and N stage.

The main aim of clinical follow-up is to improve survival, but the value of following patients after radical resection for colorectal cancer is still controversial, mainly since scientific evidence supporting it remains sparse. Many cohort and case-control studies have supported the effectiveness of follow-up but, very few randomised controlled trials have been performed regarding follow-up and cancer mortality.

Moreover, the frequency of follow-up is still debatable. Nevertheless despite limited evidence, follow-up programmes are being used in most clinics treating colorectal cancer patients.

CONCLUSION

It may be the time for the surgeons to become aware that resectable rectal cancer is an heterogeneous disease inside each stage group, overall composed by 1/3 of patients, who die from distant metastases, receiving insufficient therapies, and by 2/3 of patients who have a benefit from loco-regional therapies alone, such as the combination of chemoradiation and surgery.

Moreover in this group of patients can be recognised a sub-population achieving a pathological complete response after preoperative chemoradiation, which demonstrated in a recent European joint analysis of 566 pCR patients treated with preoperative radio-chemotherapy a rate of local recurrence of 1.6%, with an incidence of 8.9% of metastases, and a 5-years cancer related survival of 94%, with a 5-years of disease-free survival of 85%.

The new landscape that we have to explore is to tailor the treatment according to the tumour characteristic and behaviour, which we should identify biologically or clinically. It could be the time to overcome the approach to treat all the resectable locally advanced rectal cancer with the same neoadjuvant approach, but we could design studies and promote evidence based on the modulation of treatments according to tumour characteristic and behaviour.

REFERENCES


