EDITORIAL

Colorectal Cancer

What more do we want from neoadjuvant treatment strategies in rectal cancer?

"There is a chance that radiation therapy may ultimately be omitted to a significant proportion of patients that respond well to chemotherapy alone and therefore may potentially avoid the long-term detrimental effects of radiation therapy."

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KEYWORDS

- complete clinical response
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- neoadjuvant chemotherapy
- rectal cancer

Radiation therapy (RT) delivered preoperatively has clearly shown to improve local disease control after radical surgery in rectal cancer [1–3]. In fact different options including short-course or long-course regimens have been extensively studied with similar good long-term local disease control [4–6]. Also, the addition of chemotherapy with fluoropyrimidine to radiation led to further improvement in local disease control of these patients [7,8]. At a first glance, the issue of local recurrence in rectal cancer had been solved with widespread introduction of preoperative RT with or without concomitant chemotherapy. So why do we keep searching for alternative treatment options for the already successful neoadjuvant approach? What are we looking for?

First of all, the observation that neoadjuvant chemoradiation (CRT) could result in complete tumor eradication, also known as complete pathological response is now considered one of the major advantages of neoadjuvant therapy in patients with rectal cancer [9]. Patients with complete pathological response (pCR) are associated with improved oncological outcomes [10]. Therefore, development of alternative neoadjuvant strategies that could maximize pCR rates is highly desirable.

Also, even though increased rates of sphincter preservation have been considered another advantage of the neoadjuvant strategy, none of the randomized studies have demonstrated any superiority in sphincter preservation rates in experimental arms of these studies [11]. However, in select patients with clinical and radiological evidence of pCR (complete clinical response [cCR]), alternative organ-preserving treatment strategies have been suggested [12,13]. Therefore, a substantial increase in pCR and cCR rates could benefit patients by improving oncological outcomes and truly affecting sphincter or even organ preservation rates [9]. Therefore, maximization of pCR/cCR rates is an excellent reason for the search of improved neoadjuvant treatment regimens.

But radiation therapy comes at a significant cost for patients, even though some

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patients may develop pCR/cCR. The long-term data from the Swedish trials using preoperative short-course radiation alone have clear indications that patients undergoing preoperative RT were at significant risk for the development of second primary cancers, small bowel obstruction and readmissions to the hospital [2,14,15]. Data from the Dutch trial also using preoperative short-course radiation showed that patients undergoing preoperative RT died less from cancer-related but more from unrelated causes [15]. Alternative neoadjuvant strategies that could spare patients from RT (with the similar benefits) would be highly attractive.

Also, even though local recurrence rates may have been significantly reduced with proper and standardized total mesorectal excision and judiciously use of preoperative RT (with or without chemotherapy), systemic disease control and survival have not. The lack of survival benefit among patients undergoing neoadjuvant treatment is quite disappointing and constitutes an important engine for the search of alternative neoadjuvant treatment strategies.

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Therefore, strategies that could both increase pCR/cCR, survival and could possibly spare patients from the detrimental effects of radiation are highly warranted.

Development of pCR seems to be associated with RT dose, addition of 5FU (and method of infusion) and with the interval between neoadjuvant completion and surgery [16,17]. Considering that RT is to be avoided, increasing RT dose is not an option. Another option would be the modification of specific chemotherapy regimens.

The observation of increased tumor response after the addition of 5FU to RT was a clear indication that chemotherapy also played an important role in tumor regression and possibly in pCR/cCR rates [18]. However, the inclusion of additional drugs to 5FU in the neoadjuvant setting with radiation therapy was somewhat disappointing. The addition of oxaliplatin resulted in significantly higher toxicity rates of CRT with no consistent benefit in pCR rates [19–21]. Also, the addition of targeted therapies, including anti-EGFR or anti-VEGF agents has been tested prior to or during CRT and even with chemotherapy alone (without RT). Even though the addition of these agents has demonstrated acceptable safety profiles, benefits in pCR rates are yet to be shown [22–25]. Understanding of exact underlying molecular and biological mechanisms associated with the effectiveness of these agents is expected to improve patient selection and allow definitive implementation of these targeted agents into personalized clinical practice.

In this setting, the use of additional cycles of chemotherapy (5FU-based) before, during and after RT is currently under investigation with promising preliminary data. Consolidation chemotherapy (when chemotherapy is delivered after RT and before surgery or assessment of response) has been investigated in a nonrandomized study that allocated patients to different treatment arms. Patients were allocated in groups with CRT followed by progressively longer interval periods between CRT and surgery. However, during these progressively longer intervals, systemic chemotherapy was delivered to patients using FOLFOX. Even though the study was not randomized and addressed 2 issues at the same time potentially increasing pCR rates (interval and consolidation chemotherapy), patients receiving consolidation chemotherapy were more likely to develop pCR [26]. Long-term survival data are still unavailable, but are expected to favor patients undergoing prolonged intervals and additional cycles of consolidation chemotherapy prior to radical surgery.

Another strategy has been suggested by the incorporation of additional chemotherapy not only during RT but also during the interval between RT completion and surgery or assessment of response. By implementing these additional cycles using exclusively 5FU-based chemotherapy this treatment regimen led to a substantial increase in complete response rates, allowing avoidance of surgery in selected patients with cCR in up to 51% of patients after a considerably long follow-up (≥48 months) [27].

Another strategy would be delivery of chemotherapy prior to CRT, also known as induction chemotherapy. The rationale of this regimen using chemotherapy alone, then chemoradiation and finally surgery is to deal with micrometastatic disease of patients at higher risk for systemic dissemination with systemic chemotherapy upfront (in addition to adjuvant chemotherapy after radical surgery) [28]. Different induction chemotherapy regimens with capecitabine/oxaliplatin (CAPOX) or cetuximab + CAPOX (CAPOX-C) have been studied in this setting. In one of the first studies using this treatment strategy offered to patients at higher

risk for systemic recurrence, pCR rates were not substantially improved. Even though patients undergoing induction chemotherapy with CAPOX-C did show improved tumor response, pCR rates were not significantly increased, even among *KRAS/BRAF* wild-type tumors [29]. A recent update of 5-year follow-up, reported that the addition of cetuximab was not associated with a statistically significant improvement in survival regardless of *KRAS/BRAF* status [30]. In a similar study recently reported using upfront FOLFOX followed by standard CRT in a broader patient population (not exclusively restricted to high-risk patients) resulted in surprising 38% complete response (either pathological or clinical response). This considerably high pCR and cCR rates led the authors to suggest that this regimen could be the ideal platform for an organ-preserving strategy [31].

However, none of these studies dared to remove radiation from neoadjuvant therapy. The role of radiation therapy in the neoadjuvant setting had to be challenged in patients with rectal cancer. The understanding of the effects of systemic chemotherapy alone on primary rectal cancer in the absence of RT led to the idea of a Phase II trial with neoadjuvant chemotherapy alone without the use of preoperative radiation. In a recent preliminary report of this study, after six cycles of FOLFOX + bevazicumab followed by radical surgery, the observed pCR rate was 25% [32]. These findings supported the idea that perhaps radiation therapy could be omitted in selected patients. This particular issue is currently under investigation in a prospective randomized trial (PROSPECT) where patients are randomized to CRT versus chemotherapy upfront and selective CRT for poor-responders. There is a chance that RT may ultimately be omitted to a significant proportion of patients that respond well to chemotherapy alone and therefore may potentially avoid the long-term detrimental effects of RT.

Ultimately, the question should be 'what do we want from neoadjuvant therapies in rectal cancer?'. Local disease control has clearly become an almost resolved issue after proper total mesorectal excision and selective use of neoadjuvant RT with or without chemotherapy. If long-term survival is to be improved, there is a hope that early exposure to chemotherapy may deal with micrometastatic disease either prior to or after RT (prior to surgery or assessment of response). However, if organ-preserving strategies are to be pursued among these patients, combination of RT and systemic chemotherapy may offer the ideal platform to its wide spread implementation. In this setting induction chemotherapy followed by selective CRT (particularly for poor-responders) or CRT followed by consolidation chemotherapy will become highly attractive alternatives for these patients. Future trials will definitely have to approach these alternatives in order to improve rectal cancer management in the near future.

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