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EDITORIAL

What is most relevant in preoperative rectal cancer chemoradiotherapy – the chemotherapy, the radiation dose or the timing to surgery?

Chemoradiotherapy (CRT) is extensively used prior to rectal cancer surgery for at least the last 10 years when three randomized trials showed that concomitant administration of a fluoropyrimidine improved local control, however, at the expense of increased acute and potentially also late morbidity [1–5]. It was extensively used also prior to that date, extrapolating knowledge from trials using postoperative CRT. Postoperatively, CRT is seldom recommended today as preoperative therapy is more efficient and less toxic than postoperative treatment [6].

Rectal cancer subgrouping and indications for chemoradiotherapy

Rectal cancers are after staging with pelvic magnetic resonance imaging (MRI) best grouped into three major clinical groups, early or 'good', intermediate or 'bad' and locally advanced or 'ugly' [7–9]. Many groups, however, define rectal cancers besides the early cT1-2N0 tumors as locally advanced, a term that it is misleading because it usually tells that advanced therapy is required. Many of those patients can be handled with surgery alone if the risk of local failure is limited as in low cT3a(b)N0mrf– tumors or high cT3abN0-1mrf– tumors (mrf– means that the mesorectal fascia is not involved or threatened) or with short-course radiotherapy (scRT, 5×5 Gy in one week) prior to immediate surgery if the risk of local failure is higher, like in most low cT3b-dN0-2mrf– cancers and in most high cT3cdN0-2mrf– cancers. A very low cT2/T3a tumor may also be at risk of local failure unless proper surgery is done and preoperative scRT could be motivated. CRT is mainly indicated when there is a need of downsizing or downstaging prior to surgery in order to achieve a high probability of an R0 resection. These tumors are those with threatened or involved mesorectal fascia (mrf+) or cT4 tumors growing into non-readily resectable organs or structures (mainly cT4b according to TNM7 from 2010). A cT4a tumor with peritoneal involvement only or a cT4b tumor with involvement of, for example the uterus is usually easily resectable with limited risk of a local failure, again after proper surgery, and does not require any downstaging/sizing. Thus, scRT is sufficient, although it could be discussed whether surgery alone would be enough for some of them to obtain excellent locoregional control. It should be said that these guidelines are far from generally accepted, and CRT rather than surgery alone or preceded by scRT is recommended by many in spite of no need to downstage/size the tumor, as, for example reflected in a document after a recent EORTC consensus meeting [10].

Modifying the chemotherapy

The most commonly used preoperative CRT schedule is to deliver about 50 (46–50.4) Gy in 5–6 weeks in 1.8–2 Gy fractions together with a fluoropyrimidine, initially 5-fluorouracil (5-FU) as a bolus injection with leucovorin, as in the randomized trials showing superiority of CRT over the same RT alone [1–3], 5-FU as a continuous infusion, potentially superior to bolus 5-FU when given postoperatively [11] or more lately as oral capecitabine [12]. During several years, it has been extremely popular to add other drugs to the fluoropyrimidine and a large number of phase II studies have been performed. They have with few exceptions all claimed superior results, although it is likely that the apparently favorable results are ascribed to patient selection rather than treatment efficacy. The addition of oxaliplatin has been the topic of at least six randomized trials [13–18]. In comparison with the reports from the phase II studies, the randomized evidence is disappointing; the two trials showing some superiority of the combination all used different and likely less efficient and/or more toxic fluoropyrimidine schedules in the control arms [15,17]. It has also been popular to include a targeted agent, particularly bevacizumab or the EGFR inhibitor cetuximab. The latter has been the subject of one randomized study, the EXPERT-C trial, reporting improvements in secondary outcomes like tumor regression and overall survival, but not in the primary outcome pathological complete remission (pCR) rate or in progression-free survival [19].

Modifying the radiation

The other component of CRT is the radiation, being subject to much less interest than the drug component. This may many consider natural, as further development in oncology lies in new drugs and particularly in those with a specific target on the tumor cells or the tumor micro-environment. However, the radiotherapy has developed considerably during the past decades, and the radiation dose can today be better conformed to the tumor cell containing volumes with possibilities for increased doses without increased normal tissue complications than in the past [20,21]. The study by Hall et al. in this issue of Acta Oncologica [22] is then of great interest. It included data from 3298 patients treated at more than 150 US hospitals. All patients received a fraction dose of 1.8 Gy to a total dose of between 45 and 54 Gy, however, not based upon randomization. In multivariate regression analyses, radiation dose together with cT stage and time interval to surgery were significant predictors of pCR.

Further, radiotherapy dose was also together with cN stage and time interval predictive for node negativity, and all factors for downstaging to ypT0-2. Tumor burden (cT and cN stage) and the time interval to surgery (to be discussed further below) are well known to influence whether tumor regressions including pCR rates are seen. The study now adds further support that the radiation dose within a rather limited interval used clinically is of interest. The study population is large, the patient material properly collected and described and adequate statistical analyses used, why it is possible to conclude, in spite of the retrospective design, that the radiation dose within that limited range will be of relevance. Appelt et al. [23] found a clear dose-response relationship, likewise in a retrospective study where many patients received a brachytherapy boost, for rectal cancer in the range of doses between 50.4 and 70 Gy, for instance only partly overlapping the doses in the study by Hall et al. Further prospective evaluation is, however, desired. In the light of known difficulties to run radiotherapy trials, this may be a pious hope.

The importance of the radiation dose in rectal cancer has not been the subject to particularly many prospective clinical trials. In the Lyon R96-02 trial, a contact therapy radiation boost (85 Gy in 3 fractions) to external radiotherapy alone (3 Gy $\times$13) resulted in more complete clinical remissions (cCR) and improved sphincter preservation rates [24,25]. Other outcomes did not differ between groups. A similarly designed study randomized patients to CRT without or with a brachytherapy boost (10 Gy in 2 fractions). The primary endpoint, pCR rates did not differ (18% in both) but more tumor regressions were seen [26]. In spite of this, again no differences in other outcomes were seen [27]. These results do not exclude that a dose-response relationship is seen also for other and more relevant outcomes than immediate tumor regression. To kill the center of the tumor with an extra radiation dose makes no sense if the tumor anyhow is removed by surgery, although it may be important if you aim at organ preservation (to be discussed further below). It is at least in the most locally advanced cases more motivated to boost the periphery of the tumor in order to obtain radical surgery [28] although this may potentially increase acute and late toxicity [29]. Higher radiation doses than usual have also been given in other patient series with reported better outcomes, however, difficult to interpret due to confounding with different chemotherapy. The significant increase in pCR or near pCR in one of the trials evaluating the addition of oxaliplatin to the CRT is discussed by Hall et al. [22] in terms of an increased radiation dose in the oxaliplatin group, 50 Gy instead of 45 Gy in the capecitabine only group [13], referring to the chiefly negative results in the other trials evaluating the role of oxaliplatin with CRT (see above).

Modifying the time interval to surgery

The third component of relevance for evaluating the extent of tumor regression after CRT is the time interval to surgery. Tumor regression, either as downsizing or downstaging is particularly important when it can be anticipated that the surgery will not be radical, for instance in many of the 'locally advanced/ugly' tumors (cT3 mrf + or cT4b). Experience during recent decades tells that regression of an adenocarcinoma can be slow and not complete until after several months (see [30]). Several retrospective analyses have recently reported increasing pCR rates with longer time intervals [31]. For the patients more relevant outcomes as risk of recurrence, survival and toxicity have not differed according to the length of the interval. The time interval after CRT has now also been subject to randomized studies [32,33]. The two trials reached different results in pCR rates, being the primary endpoint in one of the studies, and secondary in the other. In the French study, no difference was seen in pCR rates in patients operated after seven or 11 weeks (15% vs. 17%, $p = .6$) [33]. Morbidity was increased and the quality of the mesorectal excision poorer in the longer interval group. In the British study, also including patients considered to be locally advanced (likely intermediate risk), tumor downstaging recorded with MRI (mrT) was higher in the group of patients having waited for 12 weeks rather than six weeks (58% vs. 43%, $p = .02$), as were the rate of pCRs (20% vs. 9%, $p < .05$) [32].

A major incentive to explore a longer interval than needed to allow for the acute radiation tissue reaction to subside has been to detect tumors that respond with a cCR, and then to avoid major surgery, for instance to preserve the organ [34,35]. Delaying surgery with the aim to detect excellent responders for organ preservation has become extremely popular and may be legitimate. However, to delay surgery to achieve more pCRs or to see more mrTRGs (tumor regression detected with MRT) and thus improve treatment outcomes with the motivation that both pCR and mrTRG are associated with (disease-free) survival is a leap of logic. This was, however, the conclusion in the British study [32] and has been a conclusion in most studies the past decade having explored the value of delaying surgery. The prognostic importance of pCR or mrTRG has been seen after CRT with a fluoropyrimidine to about 50 Gy. It is probably explained by an association between lack of metastatic capability and response to a moderate radiation dose. It is not established whether a similar association will be seen when, for example higher radiation doses have been used. For obvious reasons, the tumor cell killing occurs during the treatment and not during the delay. The tumor cell killing is not detected morphologically until later, but it is then irrelevant for risk of recurrence whether the surgery is delayed or not. Increasing the radiation dose from conventionally 45–50 Gy to 54 Gy or even higher, or adding chemotherapy in the interval may, however, improve outcome since more therapy is given. This has also been done by the group in Sao Paolo, Brazil pioneering organ preservation, to see more cCRs [36]. To add a brachytherapy boost to the center of the tumor, as explored by a Danish group, may also increase pCR rates (although this was not seen in the randomized trial [26]), but this will neither improve outcome after surgery. Although it may result in more cCRs and thus more organ preservation. In an observational study enrolling 55 patients, with cT2-3N0-1 tumors (early/intermediate, median diameter 2.8 cm), as many as 40 (78%) of 51 patients treated with a higher dose than usual,

60 Gy in 30 fractions with a fluoropyrimidine followed by a brachytherapy boost of 5 Gy reached a cCR [37]. The study supports the use of a higher dose than has been the case, although nine (23%) patients have had a local failure and three have metastasized after a comparably short follow-up. The collected experience tells that size of the tumor is most important for reaching cCR. In a recent large study including 620 patients, no clinical factors could, however, reliably predict ypCR or downstaging to ypT0-1N0 [38].

A delay to surgery in those who do not respond well will not be of any advantage for that patient; potentially rather the opposite. If a tumor does not respond may mean that it can become non-resectable, or metastasize during the waiting period, although this is likely not frequently seen during the first several months. Further, the start of adjuvant therapy will be delayed, and this may negatively influence survival even if the gains of adjuvant therapy in pretreated rectal cancer patients are controversial [39–41]. Thus, it is important that a first evaluation with MRI and endoscopy is done after about six weeks, with discussion at an MDT conference week 7 and with preparations so that surgery can be performed the week after. If the response is excellent or close to, the surgery can safely be postponed for another six weeks with the final discussion about whether a watch-and-wait program should start or surgery done. To skip the first evaluation will immediately save healthcare resources, but may be disadvantageous to some patients.

The role of radiation and radiation dose for palliation of inextirpable or recurrent rectal cancer has also been the topic of studies, two of which are included in this issue of Acta Oncologica [42,43]. In a systematic review of the literature, the group of authors behind a prospective study exploring the palliative value of external radiation to 30–39 Gy in 3 Gy fractions, could not find an optimal radiation dose or fractionation useful for palliation [44]. In the prospective study, most patients had major symptomatic relief of the treatment [42]. Survival was short, prompting abbreviated treatments. Whether a single fraction of about 8 Gy or the short-course schedule 5×5 Gy is the best schedule for palliation is not known, but 5×5 Gy when given to patients not eligible for surgery or with synchronous metastases, symptomatic relief has often been seen [45,46]. In selected patients, higher and potentially curative doses up to about 60 Gy can be safely given and may result in good tumor control [47]. Whether interstitial pulsed dose rate brachytherapy as a complement to external CRT in locally advanced/ugly or recurrent rectal cancers will improve outcome is not known [43]. The value of an external electron boost intraoperatively (IORT) for the same indication is questionable [48].

Besides the three articles about radiation therapy in rectal cancer discussed above [22,42,43], another five articles in this issue of Acta Oncologica also deal with colorectal cancer [49–53]. Four of them concern the prognosis of early stage colorectal cancer, also a very important topic where great uncertainties about which patients should be given adjuvant chemotherapy exist. Nomograms for prediction of recurrence risks after curative surgery can be of future clinical importance. In addition, the study by Hoshino et al. including 4167 patients operated at 22 Japanese hospitals is also interesting because only 13.5% of the patients have had a recurrence with five years, supporting notions that the results today are much better than they were in the past when the trials detecting the value of adjuvant therapy for colon cancer were running [54,55]. The possible absolute gains from adjuvant therapy, at least in stage II but likely also in stage III, are less than anticipated as fewer recurrences are seen. Results are similarly improved in rectal cancer, potentially also challenging routines developed based upon studies performed in the past. More intensive staging at diagnosis, better surgery, more careful pathological examinations and discussions at multidisciplinary team meetings all contribute to improved outcomes overall and in the separate stages, so called stage migration [56–58].

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