

EDITORIAL



What conclusions can be drawn from the Stockholm III rectal cancer trial in the era of watch and wait?

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The main results from the Stockholm III trial have recently been published [1]. In the trial 840 intermediate risk (often designated locally advanced) rectal cancer patients were randomized to preoperative radiotherapy (RT) using the short-course schedule (5×5 gray (Gy) in one week) with immediate (3–7 days) or delayed (4–8 weeks) surgery or long-course conventionally fractionated RT (25×2 Gy) without chemotherapy and delayed surgery (4–8 weeks). In brief, the trial showed no difference in local recurrence rates, distant metastases, recurrence-free or overall survival between the three arms. In the two delay groups, 5–7% of the patients experienced grade III–IV toxicity (required hospitalization), with no difference between groups. Postoperative mortality was the same, but any postoperative morbidity (53% vs. 41%, $p = .001$) and surgical morbidity (36% vs. 28%, $p = .03$) were higher in the short-course RT with immediate surgery group compared to the delayed surgery groups. Reoperations did not differ between groups (15% vs. 14%).

In this issue of *Acta Oncologica*, Bujko et al report on the feasibility of using short-course RT in a watch and wait policy [2]. The starting point of their presentation is the results of the Stockholm III trial. They report on an unplanned interim analysis of a single-center study in which elderly patients with a primary nonmetastatic rectal cancer assessable to digital examination were treated with chemoradiotherapy (CRT) or short-course RT if not fit for CRT with the aim to avoid surgery or do a local procedure if a good response to RT/CRT was seen. If a clinical complete remission (cCR) was seen, patients were observed, whereas patients with persistent tumors were treated with transanal endoscopic microsurgery (TEM) or total mesorectal excision (TME). Median interval to the evaluation after RT was 10 weeks (interquartile range, IQR 8–13 weeks). The entire study only included 59 evaluable patients, of which 30 were treated with short-course RT. Six (20%) of these patients reached a cCR. Numerically more patients treated with CRT obtained a cCR (10 patients, 34%), but not based upon randomization. Local regrowth was seen in 1 of 6 patients treated with short-course RT and in 4 of 10 patients treated with CRT after a rather short follow-up. These results are not different from those in other patient series [3–5], reflecting that the tumors were generally not so advanced.

We authors of this Editorial were senior authors on the publication reporting the main results of the Stockholm III trial.

The trial was initiated in Stockholm under the lead of the surgeons Björn Cedermark (PI) and Torbjörn Holm. Patient recruitment started in October 1998. In an amendment from May 1999, when one of us (BG) became head of the Gastrointestinal Section, Department of Oncology at Radiumhemmet in Stockholm, the protocol was amended [1]. Uppsala joined the study and it became possible to randomize only between the two short-course groups (immediate vs. delayed) and between all three groups. The second author (AM) became PI for the study when Björn Cedermark retired in 2007 and she took over the leadership of the surgical research group at Karolinska Institutet.

Ever since the trial results were known, and the final publication became available we have at scientific meetings and informally noticed many different conclusions from the trial results. The conclusions drawn by us, BG as a clinical (radiation) oncologist and AM as surgeon also differ on certain points. We will pinpoint a few aspects, not fully covered in the publication that may help to draw conclusions from the trial of relevance when watch and wait, or organ preservation as it often is referred to, has become very popular. This is now also feasible using the short-course schedule as described by Bujko et al. [2].

Radiation kills cells when delivered, not during the delay

All tumor cell kill occurs during the radiation within the irradiated volume, in this case the dorsal part of the pelvis. It is thus maximal within a week after the first RT fraction after short-course RT and after 5 weeks long-course RT or CRT. There is no cell kill effect either during or after treatment at distal sites unless abscopal or bystander effects occur. These effects are controversial, and although there are publications telling that they do happen [6,7], they are likely of no or limited relevance for killing rectal cancer deposits at distant sites. Thus, unless other antitumor treatments are added, prior to or after the surgery, there are no possibilities for distant metastases, and thus overall survival, to differ between arms in the absence of any difference in loco-regional control. The trial showed that loco-regional control was excellent with a very low (2–3%) risk of local failure [1]. Theoretically,

the local recurrence risk could be higher after a delay, if repopulation of the primary tumors and the locoregional lymph node metastases occurs before surgery is done. Doses of 5 Gy but also of 2 Gy rapidly negatively influence the capabilities of solid tumor cells to proliferate and metastasize [8]. We have limited knowledge about when these capabilities return, but they likely take several weeks even in poorly responding tumors. However, in a study, FDG-PET uptake was increased in about half of the patients with early rectal cancers treated with CRT between 6 and 12 weeks, indicating that the time before surviving tumor cells proliferate and potentially metastasize is not too long [9].

In the Stockholm III trial, the time intervals to surgery tested were surgery within a week against delayed surgery after 4–8 weeks. Whether a longer interval (8–12 weeks) is preferable and of further gain for the patient was not studied. Yet, the question is highly topical and extensively debated. The gain from delaying surgery beyond the acute tissue radiation effect has subsided, which usually takes up to about 3–5 weeks, unless the tumor is not nonresectable upfront, is not clear. Surgical morbidity will probably not be lower but can be higher the longer the waiting time is because of radiation-induced fibrosis. The time point when this fibrosis will become a clinical problem is not known. The increased surgical difficulties and complication rates in a French trial comparing 7 and 11 weeks delay are an illustration of this [10], even if this has not been seen in any of the retrospective studies. Survival can thus not be better (only worse if the tumor cells in poorly responding tumors have regrown and metastasized before surgery) if surgery is delayed after RT/CRT. Down-staging and down-sizing in responding tumors will, however, be more pronounced the longer the delay, at least up to about 10–12 weeks [11–14]. This is an argument for further waiting with the possibility of organ-preservation in well-responsive tumors.

A delay to surgery can potentially deteriorate survival if adjuvant chemotherapy is provided

In the Stockholm III trial, only 15% of the patients received adjuvant chemotherapy; this was about 30% in stage III. It is possible to conclude that survival and risk of distant metastases will not be worse if the surgery is delayed for a reasonable time, in practice up to 4–8 weeks as in the Stockholm III trial, if adjuvant chemotherapy is not part of treatment. However, the subclinical deposits at distant sites may grow during the delay to a size that no longer can be eradicated by the presently available cytotoxic treatments. The effects of adjuvant chemotherapy in colon cancer are well established, whereas they are controversial in rectal cancer, particularly in preoperatively irradiated patients [15–17]. Much circumstantial evidence still tells that there is a gain from adjuvant chemotherapy in rectal cancer with a hazard ratio of about 0.8 or slightly below, that is, a 20% relative reduction in recurrence risk after fluoropyrimidine alone [16–18]. Since it has not been properly tested, the benefit of adding oxaliplatin is not known, although there will likely be additional benefit since oxaliplatin works in metastatic colorectal cancer

irrespective of primary location. In colon cancer, adjuvant chemotherapy can often start within 6–8 weeks after diagnosis and surgery, whereas it cannot start until weeks or even months later in rectal cancer due to firstly the time of the pretreatment and eventual delay, and secondly, a slightly longer postoperative recovery period. A rather limited benefit of adjuvant chemotherapy in rectal cancer (possibly a 30–35% reduction in recurrence rates if oxaliplatin is added as opposed to 40–45% in colon cancer), predominantly seen in tumors who moderately respond to the neoadjuvant treatment [19], may therefore be less or entirely abolished if it is initiated 6–8 weeks or longer after an intentional delay, a highly controversial issue.

In patients not fit for adjuvant chemotherapy, a reasonable delay (4–8 weeks) is not negative, only positive since the complications after surgery will be less, and a delay is uncontroversial. In fit young patients in good shape for both surgery (nonsmoker, physically fit) and adjuvant chemotherapy, you have to balance less surgical morbidity against less chance that an earlier initiated adjuvant chemotherapy may eradicate all subclinical tumor deposits, which may be present if the tumor is locoregionally advanced with risk factors for distant metastases, like node positivity, vessel or nerve infiltration or poor histology. This concern was also expressed by Bujko et al. [2]. The Stockholm III trial was not primarily powered to show any survival difference. Further, adjuvant chemotherapy was only given to 15% of the patients, more or less eliminating the possibilities to detect any difference in recurrence-free or overall survival between the short-course groups [1]. We have different opinions in this balance. If the patient has a desire to avoid surgery, that is, organ preservation, this of course tells that a delay is required. If the tumor at MRI indicates risk factors for recurrence, which are present if RT is motivated, the probabilities that the tumor will respond very well (persistent complete clinical remission, cCR) is not precisely known, but likely less than 15% [20]. Again, this should be balanced against less likelihood that he/she will be cured from an earlier initiated adjuvant chemotherapy.

Neoadjuvant chemotherapy in the delay is not yet evidence based

This is a very attractive and presently popular approach, sometimes designated total neo-adjuvant therapy and will entirely eliminate the concerns about delaying the start of adjuvant chemotherapy by delaying surgery in high-risk patients for developing metachronous metastases. It has also been the subject of randomized trials against preoperative CRT with or without adjuvant chemotherapy [21–23]. However, these trials have not yet been reported or matured sufficiently to tell whether this will be the new standard, even if the National Comprehensive Cancer Network (NCCN) guidelines recently have considered this as a viable treatment strategy [24]. Recurrences after rectal cancer surgery may occur late, in contrast to colon cancer where these are seldom seen. Promising and apparently logical treatments

have failed earlier. Until then, neoadjuvant chemotherapy must be considered experimental.

Long-course radiotherapy alone is obsolete

Long-course RT alone can be considered obsolete. It takes much longer time than short-course, has no advantage concerning less acute toxicity and less surgical morbidity and although no differences in outcome were detected, few patients participated in the three-armed comparison with very low power to exclude meaningful differences. If anything, the long-course arm did slightly (insignificantly) worse [1]. Besides, adding chemotherapy concomitantly increases antitumor efficacy with fewer local failures/better local control without any gain in the risk of distant metastases and overall survival [25–27], unless the tumor is nonresectable (local advanced/ugly) at diagnosis [28]. It however increases acute toxicity substantially meaning that many patients do not tolerate this treatment and, although not well recognized, also late toxicity is increased [29,30]. The fact that half of the patients in the Polish study [2] including consecutive patients tell that a substantial proportion above 70 years will not tolerate CRT. Although CRT has become routine therapy worldwide whenever preoperative (long course) RT is indicated, this is not the case in intermediate/bad risk tumors in Sweden where no downsizing/staging is required, but only in the non-resectable/ugly tumors [31,32]. The ongoing trials comparing CRT with short-course RT and neoadjuvant chemotherapy may tell whether this routine therapy since decades will become obsolete too.

Conclusions

The Stockholm III trial has shown that delaying surgery for 4–8 weeks after short-course RT, rather than operating immediately, can be a valid option in many patients with rectal cancer. In elderly and comorbid patients, it is recommended treatment since the risk of surgical morbidity is less, and tumor outcome does not appear negatively affected. In addition, the delay might open up for optimizing the patient in front of surgery that may further reduce the risk of surgical morbidity, an issue not studied within the scope of the Stockholm III trial. In younger and fit patients, a delay may also decrease postoperative morbidity and allow detection of a well-responding tumor potentially suitable for organ preservation but may worsen survival if the delay is long enough to see tumor repopulation and if adjuvant chemotherapy is part of routine when risk factors for recurrence are present. That balance is intricate, but seldom recognized although considered by Bujko et al. [2].

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