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Preoperative radiotherapy or chemoradiotherapy in rectal cancer – Is survival improved? An update of the "Nordic" LARC study in non-resectable cancers

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ABSTRACT

The randomized "Nordic" LARC study compared preoperative long-course radiotherapy alone (RT) or with chemotherapy (CRT) in the most locally advanced/ugly rectal cancers. Despite significantly better local control in the CRT group, no overall survival benefit was seen after 10 years follow-up. The relations between local control and survival are discussed.

During the past 15 years, three randomized trials in what is designated locally advanced rectal cancer (LARC) have reported that conventionally fractionated radiotherapy (RT) given concomitantly with fluoropyrimidine chemotherapy, chemoradiotherapy (CRT), results in fewer local recurrences/better local control than when given alone [1–3]. Since some 10 years ago, CRT is the reference treatment in LARC, despite CRT giving significantly more acute, and in two of the studies also more late toxicity [4,5], and no overall survival (OS) benefit. All subsequent trials have used CRT with a fluoropyrimidine as control arm.

LARC is a heterogenous group of tumors, not often well defined. A fixed tumor with direct invasion of adjacent organs or structures, or with perforation of visceral peritoneum (clinical stage (c)T4a-b), is often referred to as primarily non-resectable, although they technically might be upfront resectable, but with a high risk of non-radical surgery or local recurrence. These tumors are best treated preoperatively with a delay to surgery to allow downstaging/-downsizing; CRT is then more effective than RT. Most clinicians and researchers include also less advanced tumours (cT3N0 or cT1-3N+), often easily resectable but with a risk of local failure, within the LARC group. In fact, in two of the three randomized trials showing better local control with CRT versus RT, only these tumours were eligible [1,2], whereas in the third [3], only non-resectable tumours (cT4 defined clinically or with computer tomography (CT)/magnetic resonance imaging (MRI)), however not reaching present standards, were included. More recently, three groups of rectal cancer have been introduced in literature, early, intermediate or locally advanced (the good-bad-ugly concept) [6,7]. The high-risk, "ugly" group traditionally constitutes 10–15% of all rectal cancers [8], but there are no updated studies using high quality MRI to confirm this percentage.

In the two trials [1,2] including intermediate advanced tumors, 5-year cumulative local recurrence rates were lowered by about 8% (from 16-17% to 8%), but there were no improvements in disease-free survival (DFS) or OS, not even after long-term follow-up [9], whereas in the trial including only the locally advanced/ugly tumors, cancer-specific survival (72% vs 55%, $p = 0.02$) but not OS (66% vs 53% at 5 years, $p = 0.09$) were significantly improved. In the trial, local control rates were significantly improved (82% vs 67% at 5 years, $p = 0.03$). To be able to balance gains and losses properly in different tumor presentations, long-term outcomes are important. For these reasons, we considered it important to update the "Nordic" LARC study.

Patients and results

In 2008 we presented the results of the randomized phase III trial comparing preoperative radiotherapy (2 Gy × 25) versus

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chemoradiotherapy (2 Gy × 25 + 5-FU/leukovorin, Nordic schedule) [3]. Two hundred and seven patients were included in Norway, Sweden and Poland between 1996–2003. The aim was to investigate if chemotherapy, within a combined modality treatment, could improve survival and reduce recurrence rates in primarily non-resectable rectal cancer. Patients with previously non-irradiated local recurrence were also included. Almost all patients fulfilled the RT as planned, while in the CRT group, 85% received all 3 cycles of concomitant chemotherapy. There was significantly more acute grade 3–4 toxicity in the CRT group (28%) compared to the RT group (4%). Late bowel toxicity was slightly worse [5], but quality of life did not differ.

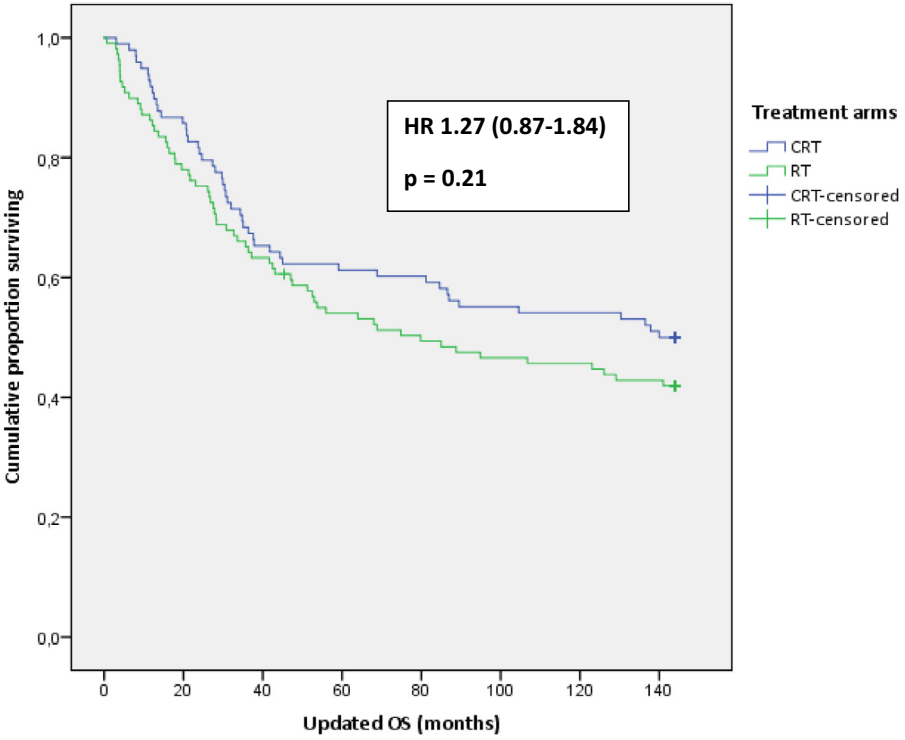
In this update we explored the difference in OS after observing all patients until death or for more than 10 years, median 12 years. At last follow-up, 41 patients (42%) were alive in the CRT group and 39 patients (36%) in the RT group. The difference in OS remained, being about 8% at 5 and 10 years. Using the Kaplan–Meier method comparing the difference in OS at ten years, the HR was 1,27 (0.87–01.84) and log-rank test showed a *p*-value of 0.21 (Fig. 1), still not statistically significant.

Discussion

The relatively few included patients (n = 207) may influence the possibility to show a statistically significant difference in OS between the two groups. Still this is the largest, and to our knowledge the only, randomized study to compare RT and CRT in the most locally advanced (ugly, *c*T4) rectal cancers. A clear and marked improvement in local control of approximately 15% after 5 years has apparently no significant impact on OS, likely because most patients die from distant metastases. Even if the two other trials comparing RT with CRT were much larger (773 and 1011 patients, respectively) [1,2], an absolute benefit of 8% in local recurrence rates from adding chemotherapy did neither improve OS (Table 1). Prolonged follow-up will not improve the chances to detect a difference. After about 5–8 years, all cancer related events have happened, and in a population with a median age of 60–70 years at inclusion, other deaths predominate, unless the treatments result in increased mortality with time. The latter is very unlikely; RT does e.g. not increase the risk of secondary malignancies [10].

It is also not surprising that no survival gain has been seen in randomized trials evaluating the value of adding RT to total mesorectal excision (TME) surgery despite significant relative gains of about 60% (absolute gains about 6%, from about 11% to 4–5% after 3–10 years, Table 1) [11–13] in local recurrence rates. A survival gain was seen only in the pre-TME era when the absolute gain at 10 years amounted to 17% (relative gain 65% or from 26% to 9% at 10 years) [14]. Population-based comparisons of many thousands of patients, where different use of RT/CRT has been practised, have neither been able to detect OS differences during time periods when local recurrence rates differed (about 4%, from 12% to about 8%) [15].

Considering the morbidity from uncontrolled pelvic growth, it is a legitimate goal of therapy to increase the possibilities to radically remove the primary and prevent local recurrences, and CRT is the reference treatment in ugly tumors, provided the patients tolerate



CRT	98	83	64	60	58	53	52	49
RT	109	85	68	57	53	49	48	45

Numbers at risk (n)

Fig. 1. Updated Kaplan–Meier curves comparing overall survival (OS) between the chemoradiotherapy (CRT) group and the radiotherapy-alone (RT) group in the "Nordic" LARC study.

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