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Original article

Preoperative radiotherapy and local excision of rectal cancer: Long-term results of a randomised study

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ABSTRACT

Background and purpose: It is uncertain whether local control is acceptable after preoperative radiotherapy and local excision (LE). An optimal preoperative dose/fractionation schedule has not yet been established.

Material and methods: In a phase III study, patients with cT1-2N0M0 or borderline cT2/T3N0M0 < 4 cm rectal adenocarcinomas were randomised to receive either 5 × 5 Gy plus 1 × 4 Gy boost or chemoradiation: 50.4 Gy in 28 fractions plus 3 × 1.8 Gy boost and 5-fluorouracil with leucovorin bolus. LE was performed 6–8 weeks later. Patients with ypT0–1R0 disease were observed. Completion total mesorectal excision (CTME) was recommended for poor responders, i.e. ypT1R1/ypT2-3.

Results: Of 61 randomised patients, 10 were excluded leaving 51 for analysis; 29 in the short-course group and 22 in the chemoradiation group. YpT0–1R0 was observed in 66% of patients in the short-course group and in 86% in the chemoradiation group, $p = 0.11$. CTME was performed only in 46% of patients with ypT1R1/ypT2-3. The median follow-up was 8.7 years. Local recurrence incidences and overall survival at 10 years were respectively for the short-course group vs. the chemoradiation group 35% vs. 5%, $p = 0.036$ and 47% vs. 86%, $p = 0.009$. In total, local recurrence at 10 years was 79% for ypT1R1/T2-3 without CTME.

Conclusions: This trial suggests that in the LE setting, both local recurrence and survival are worse after short-course radiotherapy than after chemoradiation. Because of the risk of bias, a confirmatory study is desirable. Lack of CTME is associated with an unacceptably high local recurrence rate.

Full-thickness local excision (LE) of rectal cancer is an attractive treatment option. Compared with total mesorectal excision (TME), LE allows stoma avoiding and reduces severe postoperative morbidity and mortality, including anorectal, sexual and urinary dysfunction [1]. Indications for LE alone are confined to favourable T1N0 tumours [1]. Evidence suggests that preoperative radio (chemo)therapy may broaden the applicability of LE to more advanced cancers [2–8]. However, the oncological safety of this treatment is uncertain.

Two randomised studies within a TME setting compared preoperative short-course radiotherapy with preoperative chemoradiation and demonstrated similar efficacies [9,10]. Short-course radiotherapy is preferable in many Polish institutions because early toxicity, cost and convenience favour this schedule. It is

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however unknown whether efficacy of these two radiotherapy schedules remains similar in a LE setting. A randomised trial was conducted to evaluate this issue and early results have already been published [11–13]. There were two main aims: (i) To compare short-course radiotherapy with chemoradiation delivered before LE and (ii) To evaluate whether preoperative radiotherapy and LE assure local control similar to that reported in the literature after TME for comparable stages of the disease. The current article aims to present the long-term outcomes. At present the literature does not provide clear answers to the following questions: (i) In the event of clinical complete response (cCR) is it better to perform LE of the scar tissue or to observe the patient without surgery (watch-and-wait)? (ii) In the event of a residual tumour, is it better to perform LE with selective completion TME or to proceed straight to TME? To evaluate these two issues, unplanned analyses were performed to guide future strategies.

Material and methods

Material and methods have been previously described [11,12] but are summarised here for convenience. The study received ethics committee approval. All patients signed their informed consent. Eligibility criteria included G1-2 adenocarcinomas smaller than 4 cm (actually most centres used the 3 cm limit). Patients with sessile cT1N0M0, cT2N0M0 or borderline cT2/T3N0M0 (irregular outer margin to the muscularis propria but no obvious mesorectal fat invasion) tumours were eligible. We believed that for sessile cT1 tumours preoperative radiotherapy is needed because this type of cancer growth shows worse prognosis compared to cT1 exophytic lesions [14]. Patients with the cN+ category were ineligible. LE with free surgical margins after radiation was deemed possible at baseline in all patients. The tumour was evaluated by endorectal ultrasound or CT; MR was not performed. Patients were randomly allocated using the minimisation method to either preoperative short-course radiotherapy or chemoradiation. Randomisation was done by telephone to the central trial office. Stratification was performed by institution. In the short-course radiotherapy group, patients received 25 Gy in 5 fractions over one week plus a 1×4 Gy boost after one week interval. In the chemoradiation group, patients received 50.4 Gy in 28 fractions plus a 3×1.8 Gy boost and three 2-day cycles of bolus leucovorin 20 mg/m^2 per day and 5-fluorouracil 400 mg/m^2 per day delivered during the 1st, 3rd and 5th week of irradiation. In both groups, a 6–8-week interval between radiation and surgery was planned. Such an interval provides time for tumour downstaging, both in the short-course group [7,15–17] and in the chemoradiation group [9,11]. Tumour imaging and endoscopy were not performed before LE after radiotherapy. LE had to be performed in all patients regardless of the clinical tumour response. A diagnosis of cCR was not mandatory in the protocol. For the unplanned analysis, we assumed the presence of cCR when a tumour was not palpated upon digital rectal examination and when the macroscopic evaluation described in pathological report of the LE specimen showed only scar or normal mucosa. The latter was considered as a proxy of diagnosis performed by an endoscopy. Full-thickness LE was performed with 0.5–1 cm margins around the tattoos which were put in place before radiotherapy. The resection was not attempted to reach the mesorectal fascia. A good tumour response (GTR) was defined as a pathological complete response (pCR) or ypT1 disease without any adverse factors (positive margin, G3, perineural, venous or lymphatic vessels involvement). An unfavourable tumour response was defined as ypT1 combined with the above adverse factors or ypT2-3 disease. The residual tumour size was measured macroscopically by pathologists in the postoperative specimen. Patients with GTR were observed. Conversion to TME was planned for patients with an unfavourable tumour response. Patients who could not be randomised were prospectively registered. Clinical examination, pelvic CT or endorectal sonography, rectoscopy and a serum carcinoembryonic antigen test were performed at 3-month intervals during the first 2 years of follow-up, at 4-month intervals during the third year and twice a year thereafter. The late toxicity was reported according to RTOG/EORTC scoring [18].

The study hypothesised that chemoradiation is superior to short-course irradiation in terms of GTR (the primary endpoint). Assuming a 50% rate of GTR after short-course irradiation, an $\alpha = 0.05$ and a power of 80%, 102 patients were needed to detect $\geq$25% difference between the two radiotherapy schedules. The secondary endpoints were: early, postoperative and late complications, anorectal and sexual dysfunctions, incidence of local recurrences, overall survival and disease-free survival. Comparisons between randomised groups were performed using the intention-to-treat principle. The chi-square test or Fisher's exact test was used to compare proportions and the Mann–Whitney *U* test to compare continuous variables. The Kaplan–Meier method was used to calculate survival. Local failure, distant failure or death was the event used for calculating disease-free survival. The Cox model was used for calculating hazard ratios (HR). The cumulative incidence of local recurrence was reported accounting for death or occurrence of distant metastases as competing risks; differences were compared by Gray's test. Competitive risk analysis was used to evaluate mortality from rectal cancer or from other reasons. All time intervals were measured from the first day of radiotherapy. All tests were two-sided. Data analysis was performed using IBM SPSS Statistics version 23 and R software (www.r-project.org).

Results

Previous reports have detailed acute toxicity, postoperative complications, anorectal and sexual dysfunctions and early oncological outcomes [11–13]. In summary, due to poor accrual, the study was terminated prematurely. Between 2003 and 2010, 104 patients were enroled from nine Polish centres. Of these, 43 patients were non randomised, mostly because of comorbidity precluding the use of chemotherapy and 61 patients were randomised. Ten randomised patients were excluded leaving 51 for analysis; 29 being assigned to short-course radiotherapy and 22 to chemoradiation (Fig. 1). Patient characteristics were well balanced between the randomised groups (Table 1). The median distance between the lower tumour edge and the anal verge was 5 cm in the short-course group and 4 cm in the chemoradiation group, $p = 0.43$. In total, there were 29% of patients with cT1, 53% with cT2 and 18% with cT2/T3. Twenty-two percent of patients did not receive any radiotherapy boost. The median interval between completion of radiotherapy and LE was 6.4 (interquartile range[IQR] 5.6–8.1) weeks in the short-course group and 6.3 (IQR 5.4–7.9) weeks in the chemoradiation group. The corresponding figures for the interval between start of radiotherapy and LE were respectively 8.0 (IQR 7.1–10.3) and 12.4 (IQR 7.8–14.0) weeks. All patients underwent LE. There were 8% ($n = 4$) of patients with cancer at the lateral surgical margin. In one additional patient, the lateral margin was only 0.7 mm. In none of the patients was a positive deep margin (mesorectal site) reported. All patients with GTR were observed after LE without a further treatment. Postoperative chemotherapy was not given. No patient was lost from follow-up; vital status was obtained from the national registry before analysis. The median follow-up was 8.7 (IQR 7.3–10.3) years. The 10-year mortality from rectal cancer was 14% (Table 2, Supplementary Fig. 1). More patients died from intercurrent diseases. In total, 22% ($n = 11$) of patients experienced local recurrence, including 7%

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