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LETTER TO THE EDITOR

The feasibility of short-course radiotherapy in a watch-and-wait policy for rectal cancer

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The Stockholm III randomized trial showed that short-course radiotherapy and delayed surgery can be used routinely for resectable tumours [1,2]. The interim analysis of this trial demonstrated pathological complete response (pCR) in 11.8% of patients after such treatment [2]. However, a clinical complete response (cCR) rate cannot be inferred from the above data because fibrous tumours persist in some patients with pCR [3]. Thus, a question arises whether short-course radiotherapy with delayed evaluation of tumour response can be used for watch-and-wait policy.

We launched a prospective single-centre study on organ preservation (watch and wait or local excision) in elderly patients undergoing preoperative radio(chemo)therapy (ClinicalTrials.gov NCT01863862). Because some elderly patients cannot tolerate chemotherapy, we used for them short-course radiotherapy with delayed evaluation of tumour response. The aim of this unplanned interim subgroup analysis was to evaluate the feasibility of short-course radiotherapy in a watch-and-wait policy. We decided to publish our results despite the low number of patients because, to our knowledge, this issue had not yet been reported in the literature.

The design of the study, methods and preliminary results were described previously in details [4]. Shortly, entry criteria were as follows: age $\geq$70 years or an American Society of Anaesthesiologists fitness grade III and a small ($\leq$5 cm and $\leq$60% circumferential involvement) cT1-4 N0-3 M0 rectal adenocarcinoma accessible to digital rectal examination. Patients had to be eligible either for local excision [transanal endoscopic microsurgery (TEM)] or total mesorectal excision. Patients received 50 Gy in 2 Gy per fraction over 5 weeks concomitantly with the Nordic schedule of chemotherapy that consisted of 5-Fu 400 mg/m^2 bolus and leucovorin 100 mg in short infusions on day 1, 2, 14, 15, 28 and 29. Those considered unfit for chemotherapy received short-course radiotherapy (5 $\times$ 5 Gy over 1 week). Patients with cCR were observed. Those with persistent tumours underwent TEM or total mesorectal excision. cCR was diagnosed when no tumour or bowel narrowing were palpable by the attending radiation oncologist and only a white scar or no abnormality were seen at endoscopy by a gastroenterologist. Near cCR was diagnosed when not palpable superficial ulceration was seen at endoscopy; then re-evaluation was scheduled after 1 month. Pelvic MRI was mandatory to confirm cCR, although this was carried out a few weeks after clinical evaluation due to a long waiting list. The trial received ethical committee approval at our institution.

Between September 2012 and October 2016, all 60 consecutive patients who met entry criteria entered the study. One patient who refused further treatment and follow-up visits after radiotherapy was excluded from analysis. The remaining 59 patients were analysed. Patients' characteristics are presented in Table 1. The median age was 77 years. Short-course radiotherapy was given to 30 patients (51%), 3 of these additionally received a 4 Gy boost in one fraction a week after completing 5 $\times$ 5 Gy which constituted a protocol violation. Chemoradiation was given to 29 patients (49%), 6 of these received reduced chemotherapy doses due to toxicity ($n = 5$) or due to logistical reasons ($n = 1$). Grade III + acute toxicity was not observed in any of the patients receiving short-course radiotherapy. The median interval between completing radiotherapy and evaluation of response was 10.3 weeks [interquartile range (IQR) 7.8–12.9 weeks] after short-course radiotherapy and 8.9 weeks (IQR 8.4–10.6 weeks) after chemoradiation. For the whole group, 13 patients achieved cCR and 6 a near cCR. Of patients with near cCR, subsequent evaluation showed cCR in three and a persistent ulcer in the other three. Thus, in total, 27% [95% confidence interval (CI) 16–38%] of patients ($n = 16$) achieved cCR; 20% (95% CI 6–34%) ($n = 6$) in the 5 $\times$ 5 Gy group, and 34% (95% CI 17–51%) ($n = 10$) in the chemoradiation group. Of six patients with cCR from the short-course group, there were three patients with cT2N0 and three with cT3N0 cancers; tumour size varied between 1.5 and 5 cm; all patients received 5 $\times$ 5 Gy. All patients with cCR agreed to observation without surgery and signed informed consent.

Of those with cCR, the median follow-up calculated from the start of radiotherapy was 21 months (range 2–37) in the

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Table 1. Patients' characteristics.

	Short-course RT[a] N = 30	Chemoradiation[a] N = 29	Total N = 59
Sex			
Female	10 (33)	14 (48)	24 (41)
Male	20 (67)	15 (52)	35 (59)
Median age (IQR), years	79.1 (73.9–84.9)	75.6 (72.8–80.4)	76.5 (73.0–81.9)
WHO performance score			
0	2 (7)	7 (24)	9 (15)
1	9 (30)	18 (62)	27 (46)
2	17 (57)	3 (10)	20 (34)
3	2 (7)	1 (3)	3 (5)
Median distance between tumour and the anal verge in cm (IQR)	4.0 (3.0–5.0)	4.0 (3.0–4.0)	4.0 (3.0–5.0)
Pre-treatment imaging			
Magnetic resonance	14 (47)	14 (48)	28 (48)
Endorectal ultrasound and computer tomography	11 (37)	10 (35)	21 (36)
Computer tomography	5 (17)	5 (17)	10 (17)
Median size of the tumour in the largest diameter in cm (IQR)	4.0 (2.4–5.0)	3.5 (3.0–4.0)	3.8 (3.0–4.9)
Median percentage of circumferential involvement (IQR)	40 (30–50)	40 (30–40)	40 (30–50)
cT-category			
T1	0	2 (7)	2 (3)
T2	18 (60)	16 (55)	34 (58)
T3	12 (40)	10 (35)	22 (37)
T4	0	1 (3)	1 (2)
cN-category			
N0	28 (93)	24 (83)	52 (88)
N+	2 (7)	5 (17)	7 (12)
Median CEA (IQR)	3.4 (1.7–5.0)	2.6 (1.6–4.9)	3.1 (1.6–5.0)
No data	2	1	3

Data in the table denote the number of patients (%) unless otherwise stated.
IQR: interquartile range; RT: radiotherapy.
[a]Chemoradiation – 25 × 2 Gy with concurrent bolus 5-Fu, leucovorin; short-course RT – 5 × 5 Gy (three patients additionally received 4 Gy boost).

short-course radiotherapy group and 19 months (range 10–43) in the chemoradiation group. Local re-growth was observed in 31% of patients (5 of 16); 1 of 6 after short-course radiotherapy and 4 of 10 after chemoradiation. Of the five patients with re-growth, four without distant metastases underwent R0 rescue surgery and the remaining one with distant metastases underwent palliative chemotherapy. There were no patients with distant metastases as the only site of failure. Twelve patients were alive. One patient died because of rectal cancer and three because of comorbidity.

Watch-and-wait policy after chemoradiation is gaining momentum [5–9], although it is still not considered as a standard in the recommendations. The present evaluation showed that cCR was achieved in 20% of patients after short-course radiotherapy. This proportion is within the range of pCRs reported after short-course radiotherapy and delayed surgery [2,10–12] Because patients were selected for 5 × 5 Gy instead of chemoradiation based on comorbidity and on general condition status, the rates of cCR after short-course radiotherapy and after chemoradiation cannot be reliably compared. In addition, the results are based on an unplanned analysis of subgroups. Moreover, the number of patients is small and follow-up is short. The strength of our study is the lack of selection bias within our institution because all patients who were referred to our centre and who met the entry criteria participated in the study.

Concluding, our findings suggest that watch-and-wait policy can be used, not only after chemoradiation, but also after 5 × 5 Gy. The results of the Stockholm III trial allow changing clinical practice from immediate surgery to delayed surgery after short-course radiotherapy [1]. The possibility of watch-and-wait policy is an argument in favour of the latter option. However, when organ preservation is not a real option, delayed surgery might not be safe because it may decrease survival due to delay in starting of the adjuvant therapy [13,14].

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