Randomized clinical trial

Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer

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Background: **Neoadjuvant chemoradiotherapy does not alter anal sphincter preservation or postoperative complications compared with short-course radiotherapy alone in patients with clinical stage T3 or T4 resectable rectal cancer. The aim of this study was to compare survival, local control and late toxicity in the two treatment groups.**

Methods: **The study randomized 312 patients to receive either preoperative irradiation (25 Gy in five fractions of 5 Gy) and surgery within 7 days or chemoradiation (50·4 Gy in 28 fractions of 1·8 Gy, bolus 5-fluorouracil and leucovorin) and surgery 4–6 weeks later. The median follow-up of living patients was 48 (range 31–69) months.**

Results: **Early radiation toxicity was higher in the chemoradiation group (18·2 *versus* 3·2 per cent; $P < 0·001$). The actuarial 4-year overall survival was 67·2 per cent in the short-course group and 66·2 per cent in the chemoradiation group ($P = 0·960$). Disease-free survival was 58·4 *versus* 55·6 per cent ($P = 0·820$), crude incidence of local recurrence was 9·0 *versus* 14·2 per cent ($P = 0·170$) and severe late toxicity was 10·1 *versus* 7·1 per cent ($P = 0·360$) respectively.**

Conclusion: **Neoadjuvant chemoradiation did not increase survival, local control or late toxicity compared with short-course radiotherapy alone.**

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Introduction

Randomized trials have demonstrated superior local control, lower toxicity and better compliance of radiotherapy or radiochemotherapy administered before rather than after surgery[1–4]. Conventionally fractionated chemoradiation with delayed surgery or short-course irradiation (25 Gy in five fractions) with immediate surgery are probably the most frequent regimens in the preoperative treatment of patients with resectable rectal cancer[2,4,5–10]. Similar long-term survival, local control and late morbidity have been reported for both these methods in non-comparative studies[4,8–12]. The benefit of the short-course schedule is a lower rate of early toxicity than with chemoradiation[4,13–16]. In addition, short-course irradiation is less expensive and more convenient, especially in centres with a long waiting list. On the other hand, the use of high doses per fraction raises concern about late toxicity[17]. Conventionally fractionated chemoradiation might be better than the short-course radiation schedule at reducing local recurrences. Another advantage of chemoradiation is better sphincter preservation because the tumour bulk is reduced before surgery[17,18]. However, there is no firm evidence to support this[18].

A randomized study was conducted to determine whether greater tumour shrinkage after chemoradiation would result in an improved rate of sphincter-preserving surgery compared with short-course radiotherapy. The

aim of the current report is to evaluate the following secondary endpoints: long-term survival, incidence of local recurrence, distant metastases, late toxicity and permanent stoma.

Patients and methods

The details of the material and methods and early results have been reported previously[15,19,20]. In short, the trial had been approved by the ethic committees of participating centres. The criteria for entry were as follows: according to the tumour node metastasis (TNM) staging system, clinical (c) stage T3 or T4 resectable primary tumour, no evidence of sphincter involvement on digital rectal examination, lower tumour margin accessible to digital rectal examination and written informed consent. All circular or tethered lesions on digital rectal examination were determined as cT3 or cT4 tumours. Patients with freely movable tumours not involving the entire circumference of the bowel wall had endorectal sonography, pelvic computed tomography (CT) or magnetic resonance imaging (MRI) to exclude T1/T2 lesions.

Patients were randomized to receive either preoperative irradiation (five fractions of 5 Gy) with total mesorectal excision (TME) performed within 7 days or chemoradiation (50·4 Gy in 28 fractions of 1·8 Gy per fraction, plus bolus 5-fluorouracil and leucovorin) and TME 4–6 weeks later.

The irradiation technique was identical in the two groups and was based on textbook guidelines[21]. Patients in the chemoradiation group received two cycles of chemotherapy during weeks 1 and 5 of irradiation. The cycle consisted of leucovorin 20 mg/m^2 per day and, 10–20 min later, 5-fluorouracil 325 mg/m^2 per day, both administered as rapid infusion on 5 consecutive days. Postoperative chemotherapy was optional. The protocol called for 4 months of bolus 5-fluorouracil and leucovorin in the chemoradiotherapy group and 6 months of the same chemotherapy in the short-course radiotherapy group. Before the start of the study, workshops had been organized for the participating surgeons, radiation oncologists and pathologists. The final decision regarding sphincter preservation was to be based on the tumour status at the time of surgery, not before irradiation. The distal bowel margin had to be at least 1 cm macroscopically. The TME technique was to be used for low-lying cancers and subtotal mesorectal excision for midrectal cancers. For logistic reasons, there was no central quality control for simulator films, radiotherapy treatment plans, TME technique, pathological reports and chemotherapy; these procedures were standardized within the treating institutions.

Patients were followed at 6-month intervals for 3 years and then once yearly. Evaluation consisted of physical examination, abdominal ultrasonography or CT and chest radiography. Other examinations were performed for symptomatic patients. Local recurrence was defined as any reappearance of pelvic tumour mass located within the irradiated volume or in the perineum. Detection of local recurrence was performed by physical examination and/or pelvic CT or MRI. Histopathological verification of any recurrence was recommended. Early and late toxicity from skin, small or large intestine and bladder was recorded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (EORTC) scale[22]. Late toxicity from ureter was recorded according to the objective criteria of the late effects on normal tissues (LENT) subjective, objective, management and analytic (SOMA) scales and late toxicity from peripheral nerves (pain, motor function and sensory function) according to the subjective criteria of LENT SOMA scales[23]. The toxicity was scored as late if it occurred more than 30 days after surgery. Late toxicity was scored as severe when it met any of the following criteria: toxic death, grade III–IV or requiring major surgical intervention or hospitalization.

Statistical analysis

A sample size of 316 patients was planned to detect a difference of at least 15 per cent in sphincter preservation with a power of 80 per cent. Randomization was performed by telephone to the central trial office and was based on the minimization method. Patients were stratified by institution, tumour character (movable or tethered) and most likely type of surgery (anterior resection, abdominoperineal resection or ambiguous decision). Case report forms were collected at the central trial office. Audits were performed during the study period in each of the participating hospitals in order to check the reported data. The statistician who performed the analysis was not blinded to group assignment. All comparisons between groups were made on an intention-to-treat principle, except for comparisons of early radiation morbidity, postoperative complications and postoperative pathology variables, which were performed according to the actual radiotherapy administered. The χ^2 test was used to compare proportions and the Mann–Whitney U test to compare continuous variables. Actuarial curves were calculated by the Kaplan–Meier method and were compared by the log rank test. All tests were two

sided. Time intervals were calculated from the date of randomization. For the calculation of the actuarial disease-free survival, the events were death from any cause, local recurrence or distant metastases, whichever was observed first. Patients who did not undergo primary tumour excision or who had distant metastases detected before or at surgery were considered as treatment failures at the time of randomization. For the calculation of the actuarial cumulative incidence of local recurrence, the data from patients who were alive and free from local recurrence or who died without local recurrence were censored. When calculating the rate of permanent stoma, diverting stoma or stoma as a result of Hartmann's procedure was disregarded, if later stoma reversal was performed. The Cox's proportional hazards model was used to calculate the hazard ratios and 95 per cent confidence intervals (c.i.) in the univariable analysis. Statistical analyses were performed using SPSS® (version 10.0) for Windows (SPSS, Chicago, Illinois, USA).

Results

Between April 1999 and February 2002, 316 patients from 19 Polish hospitals were enrolled. *Fig. 1* shows the progress through the phases of the study including major deviations from the protocol. The reasons for major and minor deviations have been published previously[15]. Patients in both groups were well balanced with respect to pretreatment characteristics[15].

In the chemoradiation group, there were two sudden deaths due to cardiac arrest: one patient died during the second week of chemoradiation and the other 4 days after chemoradiation. The incidence of grade III–IV early adverse effects was 3·2 per cent for the short-course radiotherapy group and 18·2 per cent for the chemoradiotherapy group ($P < 0·001$). Better compliance was observed for the short-course radiotherapy schedule (97·9 per cent of patients) than the chemoradiation schedule (69·2 per cent)[15].

The rates of anal sphincter preservation were 61·2 per cent in the short-course group and 58·0 per cent in the chemoradiation group ($P = 0·570$)[15]. The rate and severity of postoperative complications did not differ significantly between the groups[19]. The rates of pathological complete response for the short-course and chemoradiation groups were 0·7 per cent *versus* 16·1 per cent; 39·5 *versus* 45·6 per cent in the yp (after radio- or chemotherapy) T1/2 category, 59·9 *versus* 37·7 per cent in the ypT3/4 category and 47·6 *versus* 31·6 per cent in the node-positive category respectively. A positive circumferential margin was more common in the short-course group than the chemoradiation group: 12·9 *versus* 4·4 per cent ($P = 0·017$)[15]. The length of distal intramural microscopic cancer spread in the bowel wall did not differ significantly between the groups[20].

Among patients who underwent tumour resection, who had no distant metastases at surgery and who were alive 30 days after surgery, postoperative chemotherapy was more common in the short-course group than the

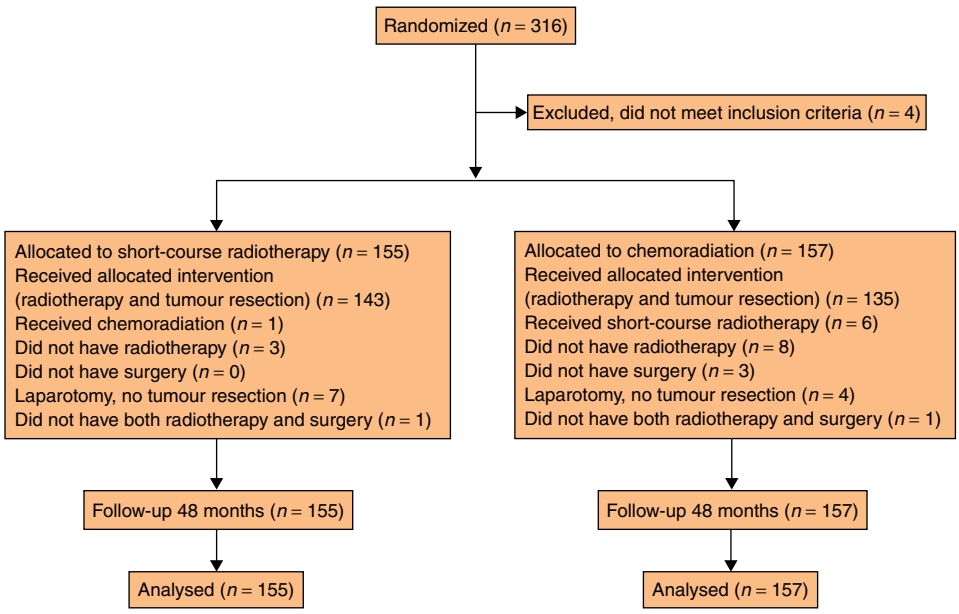


Fig. 1 CONSORT diagram of patient progress through the trial

chemoradiation group: 46·4 per cent (65 of 140) *versus* 30·1 per cent (43 of 143) ($P = 0·005$). The proportion of patients with positive nodal disease receiving postoperative chemotherapy was similar in both treatment groups: 68 per cent (43 of 63) in the short-course group and 67 per cent (30 of 45) in the chemoradiation group ($P = 0·860$). None of the 17 patients with a complete pathological response after chemoradiation received postoperative chemotherapy.

The median follow-up of living patients was 48 (range 31–69) months. Of these patients, 97·5 per cent (197 of 202) had a follow-up time of more than 3 years and 14·9 per cent (30 of 202) of more than 5 years. No patients were lost to follow-up with regard to vital status; three (1·0 per cent) were lost to follow-up with regard to relapses and 14 (4·5 per cent) with regard to late toxicity.

Survival

The events and reasons for death are summarized in *Table 1*. The actuarial 4-year (median follow-up) overall survival was 67·2 per cent in the short-course group and 66·2 per cent in the chemoradiation group ($P = 0·960$) (*Fig. 2a*). The hazard ratio of death in the short-course group compared with the chemoradiation group was 1·01 (95 per cent c.i. 0·69 to 1·48). The actuarial 4-year disease-free survival was 58·4 per cent in the short-course group and 55·6 per cent in the chemoradiation group ($P = 0·820$) (*Fig. 2b*). The hazard ratio of death or relapse in the short-course group compared with the chemoradiation group was 0·96 (95 per cent c.i. 0·69 to 1·35).

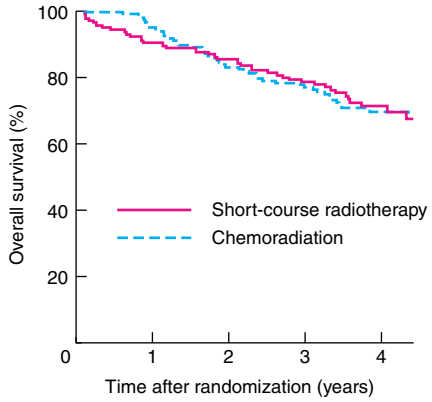
Local control

The rate of local recurrence was calculated in 295 patients who underwent resection without (R0) or with (R1) microscopic residual tumour. Of these, 43 (14·6 per cent) had non-radical resection, R1 in 26 and with distant metastases detected at surgery in 17. The crude rate of local recurrence was 9·0 per cent in the short-course group and 14·2 per cent in the chemoradiation group ($P = 0·170$) (*Table 1*). The actuarial 4-year cumulative incidence of local recurrence was 10·6 per cent in the short-course group and 15·6 per cent in the chemoradiation group ($P = 0·210$) (*Fig. 3*). The hazard ratio for local recurrence in the short-course group compared with the chemoradiation group was 0·65 (95 per cent c.i. 0·32 to 1·28). The crude incidence of local failure, defined as the incidence of local recurrence added to the incidence of R2 resection and added to the incidence of unresected tumours, was 14·4 per cent in the short-course group and 18·6 per cent in the

Table 1 Intention-to-treat analysis of events in 312 patients

	Short-course radiotherapy ($n = 155$)	Che-moradiation ($n = 157$)
Deaths		
Yes	52 (33·5)	53 (33·8)
Deaths related to rectal cancer	35	46
Deaths from treatment complications*	5	5
Deaths from causes not related to rectal cancer	8	1
Deaths from unknown causes	4	1
No	103 (66·5)	104 (66·2)
Local recurrences alone or with distant metastases†		
Yes	13 (9·0)	21 (14·2)
Local recurrences alone	2 (1·4)	9 (6·1)
No	131 (91·0)	127 (85·8)
Non-applicable, tumour not resected	8	8
Non-applicable, R2 surgery	1	0
No data	2	1
Distant metastases alone or with local recurrence		
Yes	48 (31·4)	54 (34·6)
Distant metastases alone	36 (23·5)	42 (26·9)
No	105 (68·6)	102 (65·4)
No data	2	1
Late complications		
Yes	39 (28·3)	38 (27·0)
Severe late complications	14 (10·1)	10 (7·1)
No	99 (71·7)	103 (73·0)
Non-applicable (tumour not resected or death within 30 days of surgery)	11	8
No data	6	8
Late permanent stoma		
Yes	87 (56·9)	81 (51·6)
Stoma after abdominoperineal resection	52	58
Stoma for palliation of uncontrolled local disease	9	10
Temporary stoma not reversed‡	18	9
Stoma because of late morbidity or poor anorectal function§	8	4
No	66 (43·1)	76 (48·4)
No data	2	0

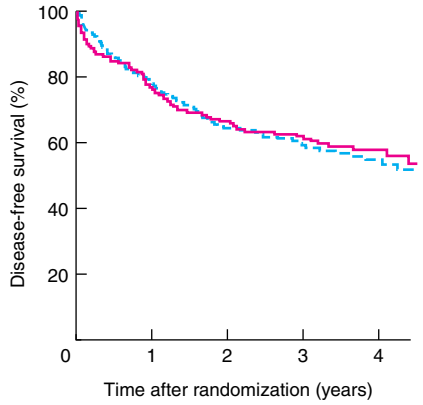
Values in parentheses are percentages. *Two deaths were due to early radiation toxicity, five occurred within 30 days of surgery and three were due to late toxicity (ileus, sepsis due to non-healing perineal wound and following surgery of hernia in abdominal postoperative scar). †Ten patients had both detected at the same time within 3 months of each other, seven had local recurrence detected more than 3 months before and six had local recurrence detected more than 3 months after the diagnosis of distant metastases, including two patients with distant metastases detected at surgery. ‡Non-reversed temporary stoma ($n = 27$) was performed for the following reasons: leak of anastomosis ($n = 12$). Hartmann's procedure ($n = 10$) and prophylactic diverting stoma ($n = 5$). Of these 27 patients, 16 were alive and free of disease more than 6 months after surgery. §Reasons for stoma because of late morbidity ($n = 12$) include poor anorectal function ($n = 4$), stenosis of anastomosis ($n = 3$), ileus ($n = 2$) and fistula ($n = 3$).



No. at risk

Short-course radiotherapy	155	135	125	110	50
Chemoradiation	157	145	125	110	56

a Overall survival



No. at risk

Short-course radiotherapy	155	119	104	91	43
Chemoradiation	157	122	102	89	48

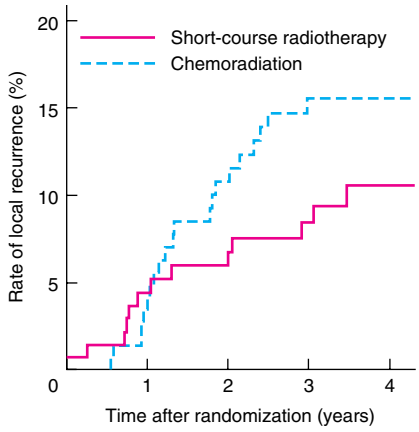
b Disease-free survival

Fig. 2 Intention-to-treat analysis of **a** actuarial overall survival ($P = 0{\cdot}960$) and **b** actuarial disease-free survival ($P = 0{\cdot}820$, log rank test)

chemoradiation group ($P = 0{\cdot}320$). The crude incidence of distant metastases was 31·4 per cent in the short-course group and 34·6 per cent in the chemoradiation group ($P = 0{\cdot}540$).

Late toxicity

The crude overall incidence of late toxicity was 28·3 per cent of patients in the short-course group and 27·0 per cent in the chemoradiation group ($P = 0{\cdot}810$) (*Table 1*). The relative risk of late toxicity in the short-course group compared with the chemoradiation group



No. at risk

Short-course radiotherapy	146	125	118	100	46
Chemoradiation	149	136	116	98	53

Fig. 3 Intention-to-treat analysis of actuarial cumulative incidence of local recurrence ($P = 0{\cdot}210$, log rank test)

was 1·05 (95 per cent c.i. 0·72 to 1·53). The crude incidence of severe late toxicity was 10·1 per cent of patients in the short-course group and 7·1 per cent of patients in the chemoradiation group ($P = 0{\cdot}360$) (*Table 1*). The relative risk of severe late toxicity in the short-course group compared with the chemoradiation group was 1·43 (95 per cent c.i. 0·67 to 3·07). Toxic deaths and severe late toxic effects are shown in *Tables 1* and 2.

Table 2 Intention-to-treat analysis of severe late toxic effects in 279 patients*

	Short-course radiotherapy ($n = 138$)	Chemoradiation ($n = 141$)
Small/large intestine†	7 (5·1)	2 (1·4)
Urinary bladder	2 (1·4)	1 (0·7)
Skin (non-healing perineal wound)	0	4 (2·8)
Urether	1 (0·7)	1 (0·7)
Nerves: motor function	3 (2·2)	2 (1·4)
Nerves: sensory function	1 (0·7)	1 (0·7)
Nerves: pain	0	1 (0·7)
Postoperative hernia requiring surgery	1 (0·7)	1 (0·7)
Fracture of femoral neck	1 (0·7)	0
Total complications	16 in 14 patients	13 in 10 patients

Values in parentheses are percentages. *The total number of patients does not include those for whom there were no data concerning severe late complications (six patients in the short-course radiotherapy group and eight in the chemoradiation group) or those who did not undergo tumour resection or died within 30 days of surgery (11 patients in the short-course radiotherapy group and eight in the chemoradiation group). †Of nine patients with severe complications from the small/large intestine, three had ileus, three had fistula and three had stenosis of the anastomosis.

Permanent stoma

The crude incidence of permanent stoma was 56·9 per cent for the short-course group and 51·6 per cent for the chemoradiation group ($P = 0{\cdot}350$). The relative risk of a permanent stoma in the short-course group compared with the chemoradiation group was 1·10 (95 per cent c.i. 0·90 to 1·35). It is noteworthy that, of 186 patients who had undergone sphincter-preserving surgery, as many as 39 (21·0 per cent) when last seen had a stoma for a cause not related to a local recurrence (*Table 1*).

Discussion

Differences in survival, local recurrence rate, incidence of distant metastases and late toxicity were not significant between patients who received short-course radiotherapy and those who received chemoradiotherapy. These results suggest that five preoperative fractions of 5 Gy with immediate surgery and preoperative conventionally fractionated chemoradiation with delayed surgery might be considered as alternatives for patients with resectable lesions. Based on the results of this and other trials[1,2,5–8,11–14], preoperative short-course irradiation is in use in Poland as the primary choice schedule for resectable rectal cancer because of its lower early toxicity, better compliance and lower cost than preoperative chemoradiation.

Limitations of the analysis of the current trial should be acknowledged. The study is unlikely to detect small differences, as it has been powered to detect differences of 15 per cent or more. The duration of follow-up is not long enough to assess late toxicity. Furthermore, postoperative chemotherapy was administered more often in the short-course group than in the chemoradiation group, which might be a confounding factor. This difference is probably related to the downstaging effect of chemoradiation which has, in consequence, resulted in decreasing the number of patients for whom this treatment was considered beneficial (those with node-positive disease). According to the protocol, only patients with cT3/T4 disease were eligible. However, in the short-course group, 39·5 per cent of patients actually had pathological (p) T1/T2 disease. This may have resulted partly from a downstaging effect of the short-course radiotherapy, observed if the time between the start of radiotherapy and surgery is more than 10 days[24] (12·7 per cent of patients in the present trial). Similarly, in the German rectal cancer study (CAO/ARO/AIO)[4], in which eligibility criteria also excluded patients with cT1/T2 tumours, pT1/T2 tumours were detected in 25 per cent of patients in the group who received immediate surgery. These findings reflect the difficulties of precise clinical staging in multicentre studies. The high rate of pT1/T2 tumours in the short-course radiotherapy group may imply that this group included more favourable cases. However, this is highly unlikely, as tumours were stratified by character, and movable and tethered tumours were equally distributed in both groups[15].

The local recurrence rate in the present trial is higher than in other randomized studies in which the TME technique has been used[4,9–11]. This technique was quite new for some surgeons, so one reason could be suboptimal quality of the TME. Since there was no pathological control of surgery quality, this hypothesis cannot be verified. Furthermore, there was no endoscopy and India ink tattooing to mark the distal edge of tumour extent before radiation to make sure that the tumour bed had been completely resected. Another reason for the high local recurrence rate could be that patients with high tumours were not eligible: a tumour had to be accessible to digital rectal examination. Inferior local control of low-lying tumours compared with high tumours is well documented[8,25]. Inadequate clinical staging and high local recurrence rate do not undermine the hypothesis of similar local efficacy of both radiotherapy schedules, as the relative efficacy of preoperative radiotherapy in reducing the risk of local recurrence is not much different for T1/T2 and T3/T4 resectable tumours or for TME and non-TME surgery[7,8,11].

The results of the present trial, which show no difference in the local recurrence rate between the radiotherapy-alone and chemoradiation groups, contrast with those of the EORTC[9] and the Foundation Francaise de Cancerologie[10] randomized trials. These trials compared conventionally fractionated preoperative irradiation with the same schedule plus chemotherapy in patients with resectable rectal cancer. They demonstrated a significant benefit in local control of adding chemotherapy to radiotherapy, although without significant differences in disease-free or overall survival. In these two trials, the chemoradiation protocol was similar to that of the present trial, but there were differences in the fractionation pattern and the interval between radiotherapy and surgery in the radiotherapy-alone groups. The design of an ongoing Australian study is similar to that used in the present trial (Joseph, personal communication). The ongoing Stockholm III trial compares five fractions of 5 Gy with immediate surgery, five fractions of 5 Gy with delayed surgery and conventionally fractionated 50 Gy with delayed surgery (B. Glimelius, personal communication). These two trials will provide more data about the efficacy of the short-course schedule compared with conventionally fractionated radiotherapy or radiochemotherapy.

The present trial demonstrated that tumour shrinkage after preoperative chemoradiation has not resulted in a higher rate of anterior resection. Two other randomized studies, the Lyon trials[26,27], have also been designed to assess whether tumour shrinkage following preoperative irradiation improves the rate of sphincter preservation. In one trial, the rate of anterior resection was not significantly different between groups. The second trial demonstrated a higher rate of sphincter preservation in the experimental group. However, this was not accomplished by a significant increase in the number of anterior resections, but was mainly the result of local excisions or additional brachytherapy boosts without surgery. The CAO/ARO/AIO study[4] compared preoperative chemoradiation with postoperative chemoradiation. The rate of anterior resection in a subgroup of patients, who were judged clinically by the operating surgeon to require abdominoperineal resection, increased significantly in the preoperative compared with the postoperative chemoradiation group (39 *versus* 20 per cent respectively; $P = 0{\cdot}004$). However, there was a higher rate of low tumours in the experimental group ($P = 0{\cdot}008$), so the randomization process did not ensure similar distribution of the variable crucial to evaluation of sphincter preservation. In addition, in the entire randomized group, the rate of sphincter preservation was 69 per cent in the preoperative chemoradiation group and 71 per cent in the postoperative chemoradiation group. Thus the evidence from randomized trials fails to show that preoperative irradiation improves the anterior resection rate.

The present trial demonstrated a downstaging effect, with higher rates of both complete tumour response and negative circumferential margin after chemoradiation compared with those observed after short-course irradiation. Since local control and survival were not statistically different between the groups, the degree of downstaging, rate of complete tumour response and rate of R0 surgery should not be used as surrogate endpoints to compare the efficacy of preoperative radiotherapy or radiochemotherapy regimens with schedules that have a different interval between the beginning of irradiation and surgery. This is because cancer cells damaged after radiotherapy need time to undergo necrosis[26], and non-viable cancer cells may look morphologically intact shortly after irradiation.[28]

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Appendix

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Snapshots in Surgery

Pulsatile scrotum

A 3-year-old boy presented with swelling of scrotum and left gluteal region that had increased in size since birth. A warm, erythematous pulsatile mass involved the scrotum (*Fig. 1*) and extended into the left gluteal region (*Fig. 2*). There was evidence of scrotal bruit and thrill, suggestive of arteriovenous malformation (AVM). Magnetic resonance angiography confirmed multiple, tortuous feeders from the left internal iliac artery, consistent with AVM. Treatment was a combination of super-selective angio-embolisation and surgical resection.

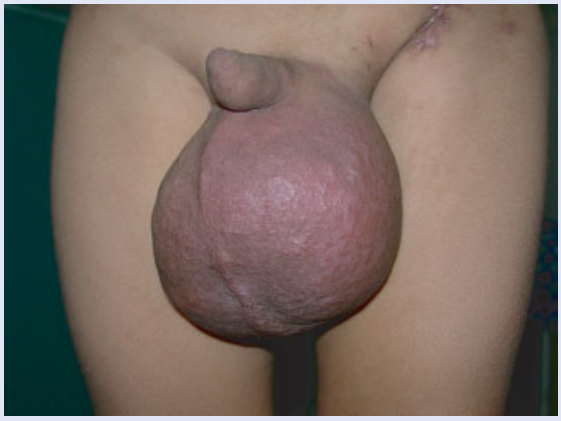

Fig. 1

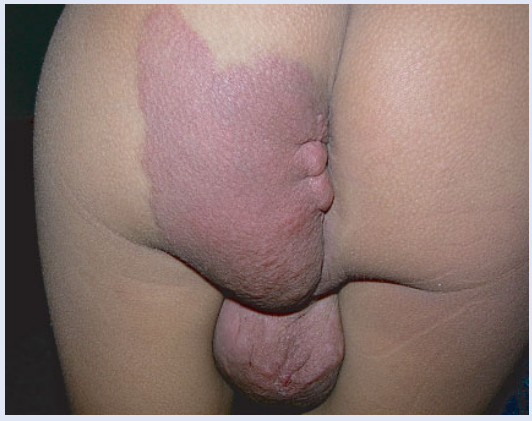

Fig. 2

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