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Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study

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Background: Improvements in local control are required when using preoperative chemoradiation for cT4 or advanced cT3 rectal cancer. There is therefore a need to explore more effective schedules.

Patients and methods: Patients with fixed cT3 or cT4 cancer were randomized either to 5 × 5 Gy and three cycles of FOLFOX4 (group A) or to 50.4 Gy in 28 fractions combined with two 5-day cycles of bolus 5-Fu 325 mg/m^2/day and leucovorin 20 mg/m^2/day during the first and fifth week of irradiation along with five infusions of oxaliplatin 50 mg/m^2 once weekly (group B). The protocol was amended in 2012 to allow oxaliplatin to be then foregone in both groups.

Results: Of 541 entered patients, 515 were eligible for analysis; 261 in group A and 254 in group B. Preoperative treatment acute toxicity was lower in group A than group B, $P = 0.006$; any toxicity being, respectively, 75% versus 83%, grade III–IV 23% versus 21% and toxic deaths 1% versus 3%. R0 resection rates (primary end point) and pathological complete response rates in groups A and B were, respectively, 77% versus 71%, $P = 0.07$, and 16% versus 12%,

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$P = 0.17$. The median follow-up was 35 months. At 3 years, the rates of overall survival and disease-free survival in groups A and B were, respectively, 73% versus 65%, $P = 0.046$, and 53% versus 52%, $P = 0.85$, together with the cumulative incidence of local failure and distant metastases being, respectively, 22% versus 21%, $P = 0.82$, and 30% versus 27%, $P = 0.26$. Postoperative and late complications rates in group A and group B were, respectively, 29% versus 25%, $P = 0.18$, and 20% versus 22%, $P = 0.54$.

Conclusions: No differences were observed in local efficacy between 5 × 5 Gy with consolidation chemotherapy and long-course chemoradiation. Nevertheless, an improved overall survival and lower acute toxicity favours the 5 × 5 Gy schedule with consolidation chemotherapy.

Clinical trial number: The trial is registered as ClinicalTrials.gov number NCT00833131.

Key words: rectal cancer, preoperative chemoradiation

introduction

Tumour excision may not always be possible in treating advanced cT3 or cT4 rectal cancers and the likelihood of R1-2 resection is high. Preoperative long-course chemoradiation, aimed at tumour shrinkage, is used to achieve R0 resection. Such treatments showed that there is room for local control improvement [1] and thus more effective schedules of preoperative treatment need to be explored.

Polish and Australian randomized studies have compared preoperative short-course irradiation (5 × 5 Gy) and immediate surgery with long-course preoperative chemoradiation and delayed surgery in resectable rectal cancer [2, 3]. Both trials showed no difference in long-term outcomes. A Stockholm III randomized study compared preoperative 5 × 5 Gy and immediate surgery with 5 × 5 Gy and delayed surgery. An interim analysis showed tumour downstaging in the delayed surgery group [4]. Based on these findings and other literature data [5, 6], it was concluded that if surgery is delayed after 5 × 5 Gy and consolidation chemotherapy is added between 5 × 5 Gy and surgery, such a combination might thereby be superior to long-course chemoradiation. In addition, when 5 × 5 Gy and consolidation chemotherapy is given, the chemotherapy is delivered in higher doses compared with long-course chemoradiation [5, 6]. This treatment was tested in a randomized trial and results are hereby presented.

materials and methods

The trial received ethical committee approval and is registered as ClinicalTrials.gov number NCT00833131. Eligibility criteria were as follows: primary or locally recurrent rectal cancer involving or abutting adjacent organs or structures (cT4) or a palpably fixed cT3 lesion, pathologically proven adencarcinoma, ≤75 years of age, WHO performance status ≤2 in patients fit for major surgery and chemotherapy along with informed written consent signed by patients. The involvement of mesorectal fascia as diagnosed by MRI was not used as the entry criterion, because of the long waiting time for pelvic MRI in Poland. Exclusion criteria were as follows: distant metastases, active coronary artery disease, cardiac arrhythmia, congestive heart failure, history of peripheral neuropathy and a history of cerebral stroke. Work-up included colonoscopy or rectoscopy, pelvic MRI or CT, CT of the abdomen, chest CT or radiography, blood count and biochemistry.

treatment

Patients were randomly assigned to receive either preoperative 5 × 5 Gy irradiation over 5 days with consolidation chemotherapy consisting three cycles of FOLFOX4 (group A) or preoperative long-course chemoradiation consisting 50.4 Gy in 28 fractions of 1.8 Gy concomitantly with oxaliplatin and boluses of 5-fluorouracil and leucovorin (group B). Oxaliplatin was used because at the time of protocol writing, a retrospective study suggested that oxaliplatin increases efficacy in cT4 rectal cancer [7]. In group A, three cycles of FOLFOX4 were chosen to keep the overall preoperative treatment time similar in both groups. Boluses of 5-fluorouracil and leucovorin in the group B were chosen because this schedule was routinely used in Poland; capecitabine and continuous infusions of 5-fluorouracil not being eligible for reimbursement. Details of the irradiation, surgical and pathological techniques as well as chemotherapy have been previously described [8]. The first cycle of FOLFOX4 in group A was planned a week after completing 5 × 5 Gy. However, upon radiation toxicity, the onset of chemotherapy had to be postponed until recovery. Whenever the second or third FOLFOX4 cycle was delayed, the interval between the first and last dose of chemotherapy was limited to 7 weeks. Patients allocated to group B received two 5-day cycles of 5-fluorouracil 325 mg/m^2/day and leucovorin 20 mg/m^2/day via intravenous bolus during the first and fifth week of irradiation. Additionally, five 1-day infusions of oxaliplatin 50 mg/m^2 were given once a week at 1, 8, 15, 22 and 29 days of irradiation. During the patients' accrual, randomized trials had been published that demonstrated no benefit of oxaliplatin addition to preoperative chemoradiation [9, 10]. However, one retrospective study demonstrated a benefit of using oxaliplatin for cT4 tumours [7]. Therefore, from 2012, oxaliplatin use in the two groups was left to the discretion of the local investigator. The schedules for delivering 5-fluorouracil and leucovorin remained unchanged. The NCI CTCAE v. 3 scale was used for evaluating acute toxicity.

Tumour resection should be attempted regardless of clinical response. Resection was categorized as R1, when cancer cells were seen within 1 mm from the surgical margin. Macroscopical non-radical surgery (R2) had to be confirmed by a pathologist because evaluation at surgery of whether gross cancer is left behind might be misleading; after chemoradiation, part of the gross tumour may contain only inflammatory/fibrous tissue. Postoperative complications were defined as those occurring within 30 days after surgery. Evaluating the quality of mesorectal excision and excision of the sphincters/levator region was carried out according to guidelines [11]. Centralized quality control for radiotherapy, chemotherapy, surgery, and pathology was not carried out.

follow-up

Delivering postoperative chemotherapy and its schedule was left to the discretion of treating physicians. Patients were followed at 3-month intervals for 2 years and then at 6-month intervals. Evaluations consisted of physical examination and measuring blood CEA levels. Abdominal, pelvic and chest CT (or chest radiography) was recommended at 1 and 2 years after treatment. Late complications, defined as those occurring later than 1 month after surgery, were graded using the RTOG/EORTC scale [12].

statistics

A R0 resection rate was chosen as the main end point, because in the randomized study, this rate had been correlated with both the type of preoperative treatment and the disease-free survival (DFS) [1]. In calculating sample size, it was assumed that an R0 resection rate after conventional chemoradiation is 75%. To detect at least a 10% benefit, 540 patients were needed, when using a two-sided test with a significance level of 0.05 and 80% power. The secondary end points were overall survival, DFS, acute toxicity of preoperative treatment, incidence of postoperative complications, pathological complete response (pCR) rate, locoregional and distant failure rate and rate of late complications. Time intervals were calculated from the date of randomization. Acute toxicity and compliance with

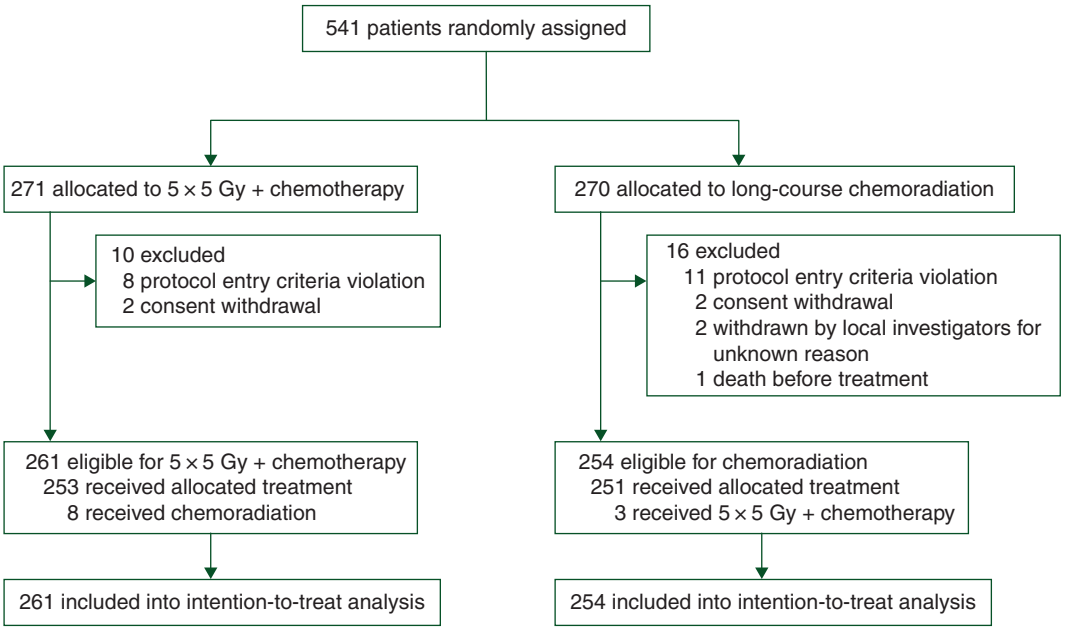


Figure 1. Trial profile.

Table 1. Patients' characteristics

	5 + 5 Gy + chemotherapy ($n = 261$)	Long-course chemoradiation ($n = 254$)
Gender		
Female	78 (30)	85 (33)
Male	183 (70)	169 (67)
Age in years, median (IQR)	60 (54–66)	60 (56–65)
Pelvic MRI		
Yes	172 (66)	164 (65)
No	88 (34)	89 (35)
No data	1	1
Type of tumour		
Primary fixed cT3 (diagnosed on MRI)	88 (34) [57 (33)]	83 (33) [59 (36)]
Primary cT4 (diagnosed on MRI)	165 (63) [112 (65)]	163 (64) [101 (62)]
Recurrent (diagnosed on MRI)	8 (3) [3 (2)]	8 (3) [4 (2)]
Who performance score		
0	129 (49)	126 (50)
1	120 (46)	115 (45)
2	11 (4)	13 (5)
3	1 (0.5)	0
Distance between tumour and anal verge (cm)		
0–5	148 (57)	138 (55)
>5–10	106 (41)	99 (39)
>10–15	7 (3)	16 (6)
No data		1

Numbers in the table denote number of patients (%) unless otherwise stated.

preoperative management were measured as treated. All other analyses were carried out according to the intention-to-treat principle. We compared categorical data by the χ^2 test or Fisher exact test and continuous data by the Mann–Whitney *U*-test. The χ^2 test stratified for oxaliplatin use was applied to compare the R0 resection rates. Survival was calculated by the Kaplan–Meier method and compared with the log-rank test stratified for oxaliplatin use. Local failure, distant failure or death, whichever occurred first, was an event used for DFS calculation. The Cox's proportional hazards model was used to calculate the hazard ratios (HR) and 95% confidence intervals (CI). Analysis of local or distant failure was reported as the cumulative incidence accounting for death as a competing risk; differences were compared by the Gray's test. Relative risk of local or distant failure was defined as the ratio of cumulative incidence function for group A to group B at 3 years. For calculating DFS and cumulative incidence of local failure, we assumed that in those patients having their pelvic tumour unresected, local failure occurred at the time of randomization. All tests were two-sided. The data were analysed with IBM SPSS Statistics software version 20 for Linux (IBM Inc., New York, NY, USA) and R software (www.r-project.org).

Randomization was carried out by telephone to a datacentre independent from investigators. Patients were stratified according to the institution and the type of tumour (cT3, or cT4, or recurrent). Randomization was based on the minimization method. The statistician who analysed the planned end points was blinded to the preoperative treatment assignment.

results

patients' characteristics

Between 2008 and 2014, 541 patients from 39 Polish institutions were randomly assigned either to group A or group B. Twenty-six patients were excluded for reasons given in Figure 1, leaving 515 patients for analysis; 261 patients in group A and 254 in group B. Patients in both groups were well balanced with respect

Table 2. Acute toxicity and adherence to the preoperative treatment; analysed as treated

	5 × 5 Gy + chemotherapy, *n* = 256 (%)	Long-course chemoradiation, *n* = 259 (%)	*P*-value
Oxaliplatin use			0.062
Yes	183 (72)	166 (64)	
No	72 (28)	93 (36)	
Preoperative chemotherapy not given	1		
Grade of toxicity			0.006
0	65 (25)	45 (17)	
1	72 (28)	59 (23)	
2	57 (22)	94 (36)	
3	49 (19)	42 (16)	
4	10 (4)	12 (5)	
Toxic deaths[a]	3 (1)	7 (3)	
Radiotherapy dose reduction (<5 × 5 or <50 Gy)	0	20 (8)[b]	<0.001
Radiotherapy time prolongation ≥1 week due to toxicity	0	12 (5)	<0.001
Chemotherapy dose reduction			
Yes, because of toxicity	51 (20)	66 (26)	0.15[c]
Yes, because of organizational or unknown reasons	5 (2)	5 (2)	
Yes, because cancer progression	1 (0.5)	0	
No	197 (77.5)	188 (73)	
Chemotherapy not given	1	0	
No data	1	0	
Chemotherapy cycle delay without dose reduction		Not applicable[d]	
Yes, because of radiotherapy or chemotherapy toxicity	43 (17)		
Yes, because of organizational or unknown reasons	13 (5)		
No	198 (78)		
Chemotherapy not given	1		
No data	1		
Radiotherapy and/or chemotherapy dose reduction and/or delays because of toxicity			0.40
Yes	95 (37)	87 (34)	
No	161 (63)	172 (66)	

[a]In the short-course irradiation group, two patients died probably due to myocardiac infarction, and in the third patient, the cause of death was unknown. In the long-course irradiation group, two patients died probably due to a thromboembolic event, one due to myocardiac infarction, one due to the pneumonia, one due to the gastrointestinal complications, one due to deterioration of general condition and in the seventh patient, the cause of death was unknown.

[b]In the patients having radiotherapy dose reduction, the dose ranged from 18.6 to 46.8 Gy, median 43.6 Gy.

[c]This *P*-value compares the rates of patients in whom chemotherapy dose was reduced because of toxicity.

[d]According to the protocol, chemotherapy not given during irradiation should be missed.

to the pre-treatment characteristics (Table 1). The majority had cT4 and low-lying tumours; locally recurrent cancers were recorded in only 3% of patients. Pelvic MRI was carried out in 66% of patients.

The median interval between the start of irradiation and surgery was 12.4 [inter-quartile range (IQR) 11.6–13.4] weeks in group A and 12.4 (IQR 11.3–13.6) weeks in group B. The corresponding results for the median overall time of preoperative treatment were, respectively, 6.6 weeks (IQR 6.3–7.5) versus 5.5 weeks (IQR 5.4–5.7), $P < 0.001$. The median interval between completion of 5 × 5 Gy and the start of consolidation chemotherapy was 9 days (IQR 8–11). One patient did not receive chemotherapy because of a deteriorating general condition after 5 × 5 Gy. Of the remaining patients, in the intention-to-treat analysis, oxaliplatin was given to 70% of patients in group A and to 66% of patients in group B, $P = 0.40$; in the per-protocol analysis, the corresponding figures were 72% and 64%, $P = 0.062$.

patients' compliance and toxicity

The acute toxicity was lower in group A than in group B, $P = 0.006$; any grade being, respectively, 75% versus 83%, grade III–IV 23% versus 21% and toxic deaths 1% versus 3% (Table 2). Diarrhoea was less common in group A than in group B, $P < 0.001$ (supplementary Table S1, available at *Annals of Oncology* online). Neutropenia was more common in group A than in group B, $P = 0.032$. Neutropenic fever was observed in 2% group A patients and in 3% in group B. In group A, most of the toxicity occurred during consolidation chemotherapy (supplementary Table S2, available at *Annals of Oncology* online). The toxic effect of short-course radiation appeared more often during the interval between irradiation and chemotherapy than during irradiation. In 8% of patients, consolidation chemotherapy was delayed for a few days until acute postradiation symptoms resolved. Adherence to the radiotherapy schedule was better in group A (Table 2). Radiotherapy and/or chemotherapy dose reduction and/or delays because of toxicity were required in 37% of patients in group A and 34% in group B, $P = 0.40$.

Late complications did not differ between group A and group B, $P = 0.54$ (Table 3). The rate of all toxic deaths (because of preoperative treatment, 30-day surgery or late complications) was 2% in group A and 5% in group B, $P = 0.09$ (Tables 2–4).

surgery and pathology

Pelvic tumours were not resected in 16% of group A and in 19% of group B (Table 4). Intraoperative irradiation was not given to either group. Of patients who underwent tumour excision, adjacent organs were resected in 21% of patients in group A and in 25% in group B, $P = 0.28$. There were no differences in postoperative complications (Table 4).

The median number of lymph nodes found in the postoperative specimen was 9 (IQR 5–13). The distribution of ypT and ypN categories did not differ between treatment-assigned groups (Table 4). The pCR rate (ypT0N0) in patients having tumour resection was 16% in group A and 12% in group B, $P = 0.17$.

Table 3. Oncological outcomes and late complications; intention-to-treat analysis of events

	5 × 5 Gy + chemotherapy, $n = 261$ (%)	Long-course hemoradiation, $n = 254$ (%)	*P*-value
Locoregional status			
No tumour resection or R2 resection	42 (16)	54 (22)	
Pelvic recurrences after R0–1 resection (as first event)	35 (13) [17 (7)]	18 (7) [12 (5)]	
Locoregional control	184 (70)	179 (71)	
No data, lost to follow-up		3	
Distant metastases			
Yes (as first event)	75 (29) [60 (23)]	62 (25) [58 (23)]	
No	186 (71)	189 (75)	
No data, lost to follow-up		3	
Late complications			0.54
Death because of complication[a]	1 (0.5)	2 (1)	
Grade 3–4 complications	15 (8)	10 (6)	
Grade 1–2	19 (11)	25 (15)	
No complications	143 (80)	135 (79)	
No data	5	7	
N.a., no tumour resection, R2 resection, local recurrence or 30-day postoperative death	78	75	
Deaths	64 (25)	84 (33)	
In patients with cancer	52	67	
From treatment complications	6	13	
From intercurrent disease	4	2	
Unknown cause	2	2	

n.a., not applicable

[a]Small bowel damage—1; late pelvic abscess—1; postoperative death after stoma closure—1.

Table 4. Surgery and pathology; intention-to-treat analysis of events

	5 × 5 Gy + chemotherapy, *n* = 261 (%)	Long-course hemoradiation, *n* = 254 (%)	*P*-value
Surgery			
Not carried out[a]	17 (7)	19 (8)	
Exploratory laparotomy; pelvic tumour was still non-resectable	19 (7)	24 (10)	
Exploratory laparotomy; distant metastases were found at surgery	5 (2)	6 (2)	
R2 resection	1 (0.5)	5 (2)	
R1 resection[b]	17 (7)	20 (8)	
R0 resection	202 (77)	178 (71)	0.07[c]
No data about surgical margin in resected tumour	0	2	
Type of surgery			0.76
Anterior resection	110 (50)	100 (49)	
APR	82 (37)	83 (41)	
Hartmann's procedure	22 (10)	19 (9)	
Resection of locally recurrent tumour	6 (3)	3 (2)	
N.a., no tumour resection	41	49	
Postoperative complications			0.18
Postoperative deaths 30 days (postoperative deaths 90 days)	0 [6 (3)]	4 (2) [7 (4)]	
Anastomotic dehiscence requiring re-operation	13 (6)	8 (4)	
Other complications requiring re-operation	18 (8)	14 (7)	
Treated conservatively	31 (15)	23 (12)	
No complications	152 (71)	149 (75)	
No data	6	7	
N.a., no tumour resection	41	49	
Quality of meserectal resection			0.61
The mesorectal plane	137 (79)	134 (83)	
The intramesorectal plane	28 (16)	20 (12)	
The muscularis propia plane	9 (5)	8 (5)	
No data	40	40	
N.a., no tumour resection or resection of recurrence	47	52	
Quality of sphincters/levator region resection in the case of APR			0.93
The levator plane	41 (84)	30 (83)	
The sphincteric plane	6 (12)	5 (14)	
The intersphincteric plane	2 (4)	1 (3)	
No data	33	47	
N.a., no tumour resection or other than APR resections	179	171	
ypT category			0.21
T0 (complete response)	37 (17)[d]	24 (12)	
T1	3 (1)	5 (3)	
T2	47 (22)	53 (26)	
T3	110 (51)	92 (46)	
T4a (involvement of peritoneum)	4 (2)	9 (5)	
T4b (involvement of adjacent organs)	15 (7)	19 (9)	
Residual cancer after resection of recurrence	4	3	
N.a., no tumour resection	41	49	
ypN category			0.86
N0	150 (69)	136 (68)	
N1	43 (20)	37 (19)	
N2	26 (12)	27 (14)	
No data	1	5	
N.a., no tumour resection	41	49	

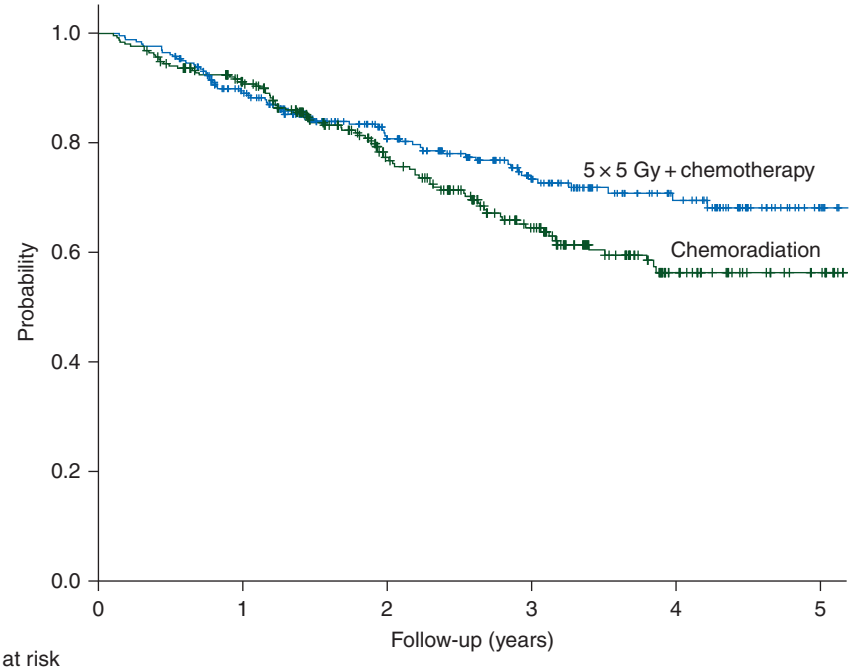
n.a., not applicable; APR, abdominoperineal resection, extralevator type was required by the protocol.

[a]Surgery was not carried out for the following reasons: 12—toxic death or complications after chemoradiation, 12—no patients' consent, 7—metastases found before surgery, 3—co-morbidity, 3—other reasons.

[b]Circumferential resection margin <1 mm in 35 patients and positive distal bowel margin in two patients.

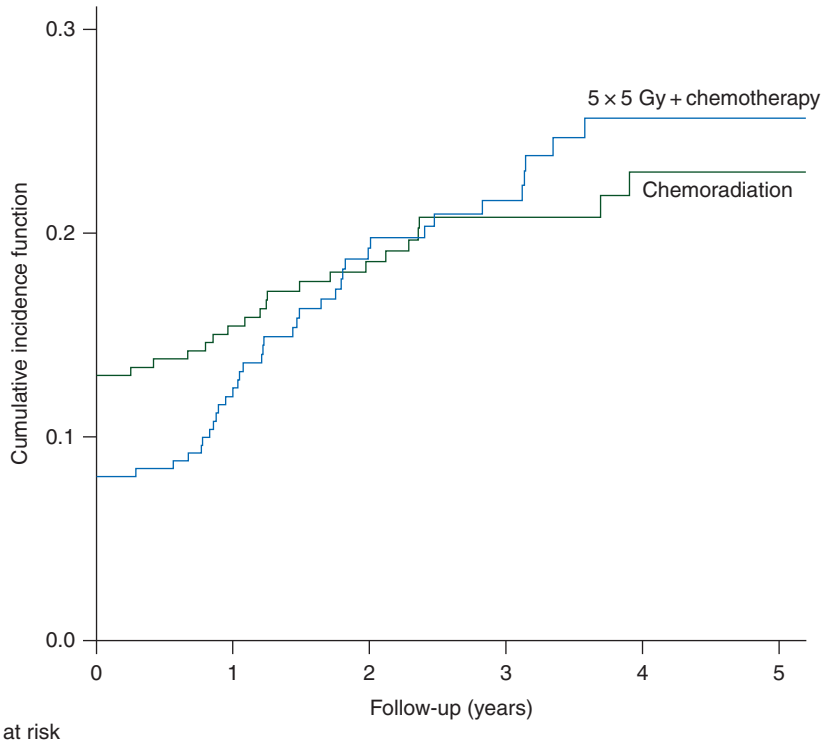
[c]This *P*-value compares the rates of patients having R0 resection.

[d]Metastases in mesorectal lymph nodes were found in one patient.



Number at risk						
5 × 5 Gy + chemotherapy	261	218	154	103	56	21
Chemoradiation	254	217	148	93	46	23

Figure 2. Overall survival.



Number at risk						
5 × 5 Gy + chemotherapy	261	186	130	90	48	18
Chemoradiation	254	174	124	79	41	19

Figure 3. Cumulative incidence of local failure.

oncological outcomes

The R0 resection rate was 77% (95% CI 72%–82%) in group A and 71% (95% CI 65%–76%) in group B, $P = 0.07$ with an odds ratio of 1.42 (95% CI 0.96–2.12). In patients after R0–1 resection, the rate of those who received postoperative chemotherapy was identical in the two treatment-assigned groups, namely

39%; oxaliplatin-based chemotherapy was given to 15% in group A and 11% to group B. The median follow-up for living patients was 35 months (IQR 21–50). None of the patients were lost to follow-up regarding vital status, but three patients were lost to follow-up regarding locoregional status. The raw data are given in Table 3. At 3 years, overall survival rates and DFS rates in group A and in group B were, respectively, 73% versus 65% (HR = 0.73, 95% CI 0.53–1.01, $P = 0.046$) (Figure 2) and 53% versus 52% (HR = 0.96, 95% CI 0.75–1.24, $P = 0.85$) (supplementary Figure S1, available at *Annals of Oncology* online). At 3 years, cumulative incidence of local failure (defined either as no tumour resection, R2 resection or local recurrence after R0–1 resection) and cumulative incidence of distant metastases were, respectively, 22% versus 21% (relative risk = 1.04, 95% CI 0.67–1.38, $P = 0.82$) (Figure 3) and 30% versus 27% (relative risk = 1.21, 95 CI 0.59–1.15, $P = 0.25$) (supplementary Figure S2, available at *Annals of Oncology* online). The rate of patients who underwent radical rescue surgery, either for local or distant failure, was 6% in group A and 5% in group B.

We carried out separate analyses of primary and secondary outcomes for 499 patients with primary tumours, i.e. after exclusion of 16 patients with recurrent pelvic cancer (supplementary Figure S3, available at *Annals of Oncology* online). The results were not much different from that observed in the whole patients' material, although the difference in the overall survival between the two treatment-assigned groups was statistically insignificant ($P = 0.078$).

discussion

This trial showed no difference in the R0 resection rate, DFS, local failure rate, distant metastases rate, postoperative complications and late complications between the two treatment-assigned groups. Better overall survival was observed in group A than in group B. To evaluate overall survival further, we carried out the competing risk analysis of cumulative incidence of death in patients having local or distant failure and separately in patients who died due to non-cancer reasons. At 3 years, the cumulative incidence of death in patients having local or distant failure was 23% in group A and 31% in group B, $P = 0.049$ (relative risk = 0.752, 95% CI 0.471–1.19) (supplementary Figure S4, available at *Annals of Oncology* online). The corresponding rates for the cumulative incidence of non-cancer death were 3% and 4%, $P = 0.946$. Reason for the difference between the two treatment-assigned groups in death rates in patients having local or distant failure is unclear bearing in mind that the rates of distant metastases and local failure were similar in the two groups. This shows that more patients with recurrences were alive in group A when compared with group B. An explanation could be that large irradiation fractions activate antitumour immune responses during the long interval to surgery [13]. Longer follow-ups are thus needed for elucidating this issue. Higher rates of acute preoperative treatment toxicity and a worse adherence to the radiotherapy schedule were observed in group B than in group A. A reason for this phenomenon could be that in group A, radiotherapy and chemotherapy were given sequentially, so that overlapping toxicities were avoided. Moreover, there was more flexibility in the chemotherapy delivery to this group; the start of consolidation chemotherapy and delivery of second or third cycle could be delayed because of toxicity, providing that the overall chemotherapy time was kept within 7 weeks. Whereas, in group B, all chemotherapy had to be given simultaneously with irradiation. Most of the acute toxicity of short-course irradiation was delayed for a few days after its completion (supplementary Table S2, available at *Annals of Oncology* online). Such toxicity is not observed when surgery takes place immediately after 5 × 5 Gy because the rectum (the organ at risk) is excised before damage occurs.

Limitations of the study should be acknowledged. We delivered 5-fluorouracil in a bolus, whereas currently continuous infusion or capecitabine are being used. Two large randomized trials showed no difference in local efficacy between 5-fluorouracil bolus and continuous infusion of 5-fluorouracil used in postoperative chemoradiation [14, 15]. This suggests that results of the present trial can be generalized for patients receiving continuous infusion of 5-fluorouracil. A threat to the surgical margin status diagnosed on MRI would be an optimal entry criterion for our study. However, pelvic MRI was not mandatory for economic reasons. Tumour fixation was used as the entry criterion. This not always reflected a high risk of R1-2 resection because this sign may be caused by a tumour bulk without threatening the surgical margin. Nevertheless, this drawback equally affected the two treatment-assigned groups, so comparison of the methods remains unbiased. Another weakness is the short follow-up, thus making an evaluation of long-term outcomes uncertain. A further limitation of the study is due to the imbalance in oxaliplatin use in the two treatment-assigned groups. This imbalance was however rather small (4% difference). Moreover, four of five randomized studies did not show any benefit of adding oxaliplatin to neoadjuvant chemoradiation in advanced rectal cancer [9, 10, 16–18]. Other weaknesses were the delivery of oxaliplatin as mono-chemotherapy without 5-fluorouracil in weeks 2–4 of radiotherapy and evaluation of postoperative complications without using formal tools for their classification and grading.

A PubMed searching was carried out using the terms 'rectal cancer', and 'short-course radiotherapy', or '5 × 5 Gy'. The results of 5 × 5 Gy and consolidation chemotherapy found in the present trial are consisted with results of three small prospective phase II trials [19–22] and three small retrospective studies [5, 6, 23] conducted in patients with stage II–III or IV rectal cancer. Prospective trials reported 25% and 26% rates of pCR [16, 17]. Using match pair analysis, one trial demonstrated improved DFS and distant metastases-free survival compared with long-course chemoradiation [22]. An ongoing RAPIDO trial [24] has a similar design to our study, but the main difference is that the RAPIDO trial explores whether, in the short-course arm, neoadjuvant therapy improves DFS by eradicating occult distant disease. For this reason, longer chemotherapy (17 weeks) after 5 × 5 Gy was used in this trial compared with our study (5 weeks).

The present trial is negative regarding primary end point. Nevertheless, better short-term overall survival and lower acute toxicity (including numerically lower toxic death rate—1% versus 3%) favours 5 × 5 Gy with consolidation chemotherapy. In addition, delivery of five radiotherapy fractions instead of 28 fractions makes short-course irradiation with consolidation chemotherapy cheaper and more convenient than long-course

chemoradiation. There were no differences in postoperative complications. Therefore, short-course radiotherapy with consolidation chemotherapy can be considered as an effective option for preoperative management in very advanced rectal cancer, especially in countries with low health-care budgets or long waiting lists for radiotherapy.

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disclosure

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appendix

The following doctors took part in the study: J. Albiński, R. Banaś, E. Chmielowska, W. Bal, J. Baszczyk-Mnich, M. Bialas, T. Borowiec, M. Bujko, A. Cencelewicz, K. Chomik, M. Chwaliński, I. Ciepela, D. Dupla, A. Florek, A. Górnicki, K. Jeziorski, W. Józwicki, J. Kobiela, M. Koda, P. Kołodziej, P. Kruszewski, M. Kryj, G. Kuciel-Lisiecka, R. Kwiatkowski, A. Lachowski, P. Liszka-Dalecki, A. Majewski, W. Majewski, T. Majsak, D. Maka, M. Malka, A. Mazurkiewicz, J. Morawiec, E. Nogal, M. Olejniczak, D. Olkowski, K. Ostrowska-Cichocka, M. Pietruszka, G. Piotrkowski, M. Plewicka, D. Porzuczek-Zuziak, J. Reszke, A. Rychter, J. Sadowski, A. Salata, K. Serkies, E. Srutek, B. Szóstak, T. Tuziak, D. Tyralik, J. Skoczylas, E. Wachua, P. Wandzel, B. Winkler-Spytkowska, P. Wojtasik, K. Wroński, M. Zemal, I. Zygulski.