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Clinical Trial

Comparison of short course radiotherapy with chemoradiotherapy for locally advanced rectal cancers in the elderly: A multicentre, randomised, non-blinded, phase 3 trial

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Abstract ***Background:*** There is no specific guideline for the treatment of locally advanced rectal cancers in the elderly. Here we compared R0 resection rate and degradation of autonomy based on the instrumental activities of daily living score between neoadjuvant, short course radiotherapy and chemoradiotherapy in this specific population.
Patients and methods: Patients ≥75 years with resectable T3–T4 rectal adenocarcinoma within 12 cm of the anal verge or T2 of the very low rectum were randomised between short course

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radiotherapy (5 × 5 Gy in one week) and chemoradiotherapy (50 Gy, 2 Gy/f, 5 weeks with capecitabine: 800 mg/m^2 twice daily, 5 days per week), with delayed surgery 7 ± 1 weeks for the two arms.

Results: One hundred and three eligible patients were enrolled between January 2016 and December 2019 when the trial was closed due to poor accrual. The R0 resection rate (first co-primary objective) was 84.3%; confidence interval 95% [73.26–94.18] in the short course group and 88%; confidence interval 95% [77.77–96.60] in the chemoradiotherapy group (non-inferiority p = 0.28). The deterioration of the instrumental activities of daily living score was not different during the pre-operative phase, it was significantly more deteriorated in the chemoradiotherapy group at 3 months post-operative (44.8% versus 14.8%; p = 0.032) but was not different at 12 months post-operative (second co-primary objective). During pre-operative phase, 9.8% of patients in short course group and 22% of patients in chemoradiotherapy group presented a serious adverse event, but we observed no difference during the post-operative phase between the two groups.

Conclusion: Although the main objectives of the study were not achieved, the short course radiotherapy followed by delayed surgery could represent a preferred treatment option in patients ≥75 years with locally advanced rectal cancer; a new study must be performed to confirm the improvement in overall and specific survival results.

1. Introduction

There is no specific guideline for the treatment of rectal cancers in the elderly even though above 40% of patients are over 75 years of age at the time of their rectal cancer diagnosis [1,2]. Chemoradiotherapy is the standard of care for locally advanced rectal cancer, although more toxic in the elderly and associated with decreased surgical excision [3]. The alternative option is short course radiotherapy (5 × 5 scheme) with immediate surgery [4]. Of note, no significant difference was observed between these two schemes, even if the downsizing is significantly greater with a combined treatment [5,6]. Recently, two phase III studies have demonstrated the benefit of total neoadjuvant treatment [7,8] in locally advanced rectal cancer. However, this intensification is poorly adapted to the most fragile patients, especially the elderly, because of poorer tolerance and the risk of decompensation of comorbidities. Registry data show that elderly patients have not benefited from the advances in neoadjuvant treatments for many years [9]. Although the post-operative death rate has improved significantly in recent years [10], the one-year survival remains poor for locally advanced tumours [11]. Short course radiotherapy is often proposed to elderly patients but without clear assessment of its risk-benefit balance. Therefore, we conducted a phase III study comparing neoadjuvant chemoradiotherapy with short course radiotherapy with delayed surgery in both arms to select the best strategy taking into account the oncology outcome and preservation of patient autonomy. We proposed to combine short course radiotherapy with delayed surgery to improve the comparison between both arms and because of the results that showed a downstaging and an improvement in the R0 resection rate with this regimen [12]. The interest of this scheme was confirmed by the Stockholm III study [13].

2. Patients & methods

PRODIGE 42/GERICO 12 study is a multicentre, open-label, phase III study, randomised and stratified according to centre, initial stage (T2/T3 versus T4) and age (≤80 versus >80 years). The study sponsored by Unicancer was conducted at 27 sites in France from January 2016 to December 2019. In accordance with French regulations, it was approved by the Sud Méditerranée IV ethics committee on 13th October 2015. This study is registered with www.clinicaltrials.gov (NCT02551237). All participating centres approved the protocol and written consent was obtained from each patient.

2.1. Patients

Eligible patients had to have histologically proven adenocarcinoma of the rectum; resectable T3 or T4 assessed by magnetic resonance imaging (MRI) and/or endorectal ultrasound. T2 tumours of the very low rectum could also be included. To note, lymph node involvement was not an inclusion criteria. The inferior margin of the tumour had to be located within 12 cm of the anal verge. Patients had to be at least 75 years old; have a 0–2 performance status; neutrophils ≥1.5 × 10^9/L, platelets ≥100 × 10^9/L, haemoglobin ≥100 g/L, bilirubin, transaminases and alkaline phosphatases ≤1.5 times the upper limit of normal and creatinine clearance ≥30 mL/min (Cockcroft and Gault). Patients were excluded if they had a metastatic disease, a local recurrent tumour or a significant serious disease that could prevent treatment from being performed.

2.2. Assessments

Prior to randomisation, patients had a complete physical examination with digital rectal examination as well as a complete colonoscopy in the absence of stenosis. The primary tumour was assessed by endorectal ultrasound and pelvic MRI; the general assessment by a computed tomography of thorax, abdomen and pelvis scan. A biological assessment evaluating the haematological, hepatic and renal functions was systematically performed. The multi-parametric geriatric assessment included an analysis of instrumental activities according to the instrumental activities of daily living (IADL) score and activities of daily living, gait speed, mini-mental state examination, geriatric depression scale-15, mini nutritional assessment, ONCODAGE and Charlson scores assessed during the inclusion assessment, before surgery, then 3, 6 and 12 months after surgery.

2.3. Study plan and treatments

Eligible patients were randomised (1:1), using Clinsight® software following the minimisation method, between chemoradiotherapy (arm A) comprising 25 fractions of 2 Gy over 5 weeks combined with oral capecitabine at a dose of 800 mg/m^2 twice daily, 5 days per week, and short course radiation therapy (Arm B) for a total of 25 Gy in five fractions administered in one week. The two neoadjuvant treatments were followed by surgery 7 ± 1 weeks later. The radiotherapy was delivered by a linear accelerator producing photons of at least 10 MV; the dose per session was prescribed on the International Commission on Radiation Units point. The radiation clinical target volume (CTV) was to include the mesorectum with the primary tumour and relevant regional lymph nodes. For long-term radiotherapy, the CTV was reduced after 44 Gy to the gross tumour volume with a margin of approximately 1 cm. For arm B, the 5 fractions were delivered on the CTV without volume reduction. We strictly followed the radiotherapy procedure described in the study protocol. This procedure has already been reported in the literature for the Partenariat de Recherche en Oncologie Digestive (PRODIGE 2) [14] and PRODIGE 23 [7] clinical trials. All centres participating in the present study enrolled patients in PRODIGE 2 and PRODIGE 23 studies; therefore, radiotherapy quality assurance and dummy run were not replicated in the PRODIGE 42 trial.

Surgery was scheduled for 7 ± 1 weeks after the end of the neoadjuvant treatment. Patients were followed up with clinical examination and laboratory assessment at 3, 6 and 12 months and then annually for up to 5 years after surgery. A multidimensional geriatric assessment was scheduled at each visit for the first post-operative year. A computed tomography scan and pelvic MRI were scheduled 6 months post-operatively and then annually until 5 years post-operative.

2.4. Outcomes and end-points

The two main outcomes analysed according to a closed-testing procedure (controls α risk of 5%) were to compare in first step, the efficacy according to the R0 resection rate and, in a second step, the maintenance of autonomy according to the IADL score between the two arms. The secondary objectives were to assess overall survival, disease-free survival, specific survival, loco-regional recurrence-free survival, safety and the rate of post-operative ostomy at 6 and 12 months. The first co-primary end-point was the comparison of R0 resection rates between arms in terms of non-inferiority. R0 resection rate was defined as tumour boundaries $\geq$1 mm from circumferential or distal margins. The second co-primary end-point was the comparison of the percentage of patients with autonomy deterioration between both arms measured by the variation (from baseline to 12 months post-operative) in the IADL score.

2.5. Statistical analysis

The needed number of patients was calculated considering both co-primary objectives. We expected R0 resection rate equal to 90% of patients in both arms. The limit of non-inferiority was set to 7.5%. To show the non-inferiority between arms under these hypotheses, with a one-sided α risk of 5% and a power of 80%, each treatment group must be composed of 200 patients. Moreover, we had assumed that the percentage of patients showing deterioration in autonomy would be 45% in arm A and 30% in arm B. Therefore, for the superiority comparison of arm A, a sample size of 163 patients/group was needed for a power of 80% with a two-sided α risk of 5%. Consequently, this study planned to enrol 210 patients/group (420 patients) taking into account patient dropout. Non-inferiority would be proven if the upper bound of the confidence interval (CI) of the difference in proportions did not cross over the pre-specified margin of 7.5% (95% CI: 1.8%–13%), one-sided. If the lower bound was above 0, then superiority would be assessed using Fisher's exact test. The study was considered positive if the two co-primary objectives were achieved (non-inferiority for the R0 rate and superiority for the preservation of autonomy). Patients who were randomly assigned but did not receive chemotherapy or radiotherapy or who have withdrawn their consent were excluded. The remaining participants who received any study treatment were included in the modified intention-to-treat (mITT) population. The per-protocol (PP) population was defined as subpopulations of mITT population excluding patients who did not received surgery. Efficacy analysis was performed in PP and mITT populations; safety analysis was done in patients who received at least one dose of the assigned treatment. All survival curves were estimated with 95% CI using the Kaplan–Meier method. Patient's characteristics were compared using the $\chi 2$ or Fisher's exact tests for

categorical data and the Student's test or Mann–Whitney test for continuous variables. The median follow-up and its 95% CI were calculated using the Schemper method [15]. Median follow-up and survival curves were compared using Log-Rank test. Data entry and management were performed on Clinsight® software. All statistical analyses were performed with R 3.6.0 software.

3. Results

3.1. Clinical and tumour characteristics

Between January 2016 and December 2019, 105 patients were included in this study by 27 centres. Despite efforts to increased enrolment, the accrual rate remained low and the study was closed following the independent data monitoring committee recommendation. Overall, 103 patients were randomly assigned, 52 in the chemoradiotherapy group (arm A) and 51 in the short course radiotherapy group (arm B) (Fig. 1). Two patients (2%) in arm A withdrew consent without receiving any study drug or surgery. Finally, 101 patients (98%) were included in the mITT population (50 in arm A [49.5%] and 51 in arm B [50.5%]). Ninety-five patients were included in the PP population (arm A 46; Arm B 49). MRI was performed in 100% of patients and endorectal ultrasound in 53.4% of them. Except for tumour differentiation, patient characteristics were well balanced across the two treatment groups (Table 1). Overall, the median age at inclusion was 80 years old (range 75–91 years). 26 patients in arm A and 23 in arm B had 39 (including 16 cardiovascular, 9 diabetes and 5 pulmonary) and 38 (including 20 cardiovascular, 6 diabetes and 6 pulmonary) comorbidities, respectively. The median follow-up was 26 months (95% CI: 23.2–27.1). 43 patients (86%) received full neoadjuvant therapy (6 patients (12%) did not received the boost and two (4%) did not receive capecitabine) in arm A, and all patients received the planned radiotherapy in arm B. Surgery was performed in 46 patients (92%) (1 patient refused surgery, 2 patients died before surgery, 1 patient had extensive tumour residue) in arm A and 49 (96%) (1 patient refused surgery, 1 contraindication to surgery) in arm B. Among the 46 patients of arm A, one patient was treated according to the short course radiotherapy scheme. This patient was classified in short course group for the PP analysis. No significant difference was measured in terms of operative technique between the two groups ($p = 0.57$). Nine patients (19.6%) in arm A and 14 (28.6%) patients in arm B had abdominoperineal resection; sphincter sparing surgeries represented 80.4% ($n = 37$) and 72.4% ($n = 35$) in

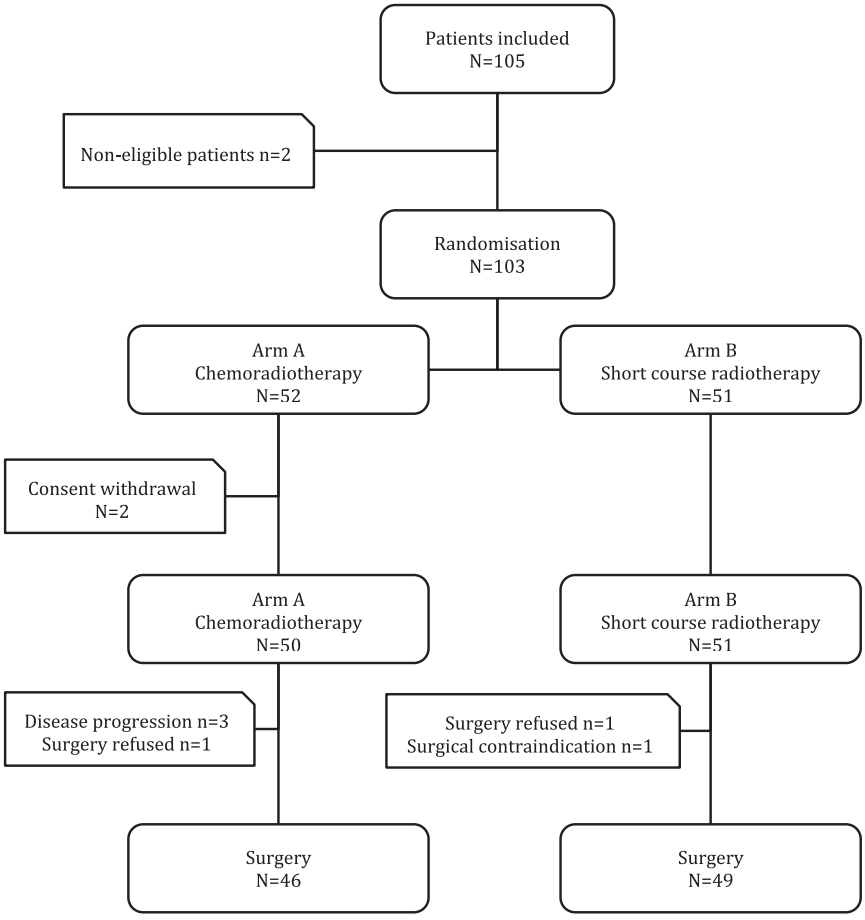

Fig. 1. Flow chart.

Table 1
Characteristics of the patients at study entry.

	Arm A: chemoradiotherapy (n = 50)	Arm B: short course radiotherapy (n = 51)	P value
Age (years); median (range)	80 (75–91)	80 (75–91)	0.959
Sex M/F; n (%)	34 (68)/16 (32)	25 (49)/26 (51)	0.083
PS; n (%)			0.387
0	16 (32)	17 (33.3)	
1	27 (54)	31 (60.8)	
2	7 (14)	3 (5.9)	
Charlson score;			0.822
Median (range)	2 (2–6)	2 (2–7)	
T Stage; n (%)			0.355
T2	3 (6.0)	7 (13.7)	
T3	43 (86.0)	40 (78.4)	
T4	4 (8.0)	4 (7.8)	
N Stage; n (%)			0.895
0	16 (39)	11 (33.3)	
1	20 (48.8)	18 (54.5)	
2	5 (12.2)	4 (12.1)	
Tumour differentiation; n (%)			0.048
Poorly	2 (6.2)	2 (5)	
Moderately	12 (37.5)	26 (65)	
Well	18 (56.2)	12 (30)	
Distance of lower border from anal verge (mm); mean (SD)	51 (23.9)	52.9 (27.7)	0.760

arm A and B, respectively. A permanent or temporary ostomy was performed in 41 (89.2%) and 46 patients (93.9%) in arm A and B, respectively. No significant difference was demonstrated for the rate of ostomy at 12 months (arm A: 32.5% [95% CI: 18.6–49.1], arm B: 39.1% [95% CI: 25.1–54.6]). Eight patients (17.4%) in arm A and 3 (6.1%) in arm B had a pathological complete response (p = 0.16) (Table 2). For the first co-primary end-points analysis, in the PP population, the R0 resection rate was 95.6% ([95% CI: 84.9–99.5]; n = 43) in arm A and 88.0% ([95% CI: 75.7–95.5]; n = 44) in arm B (non-inferior p = 0.49); Δ = 7.5% [95% CI −1.5% to 16.5%]. In mITT population, 87 complete resection were recorded; 44 patients (88% [95% CI: 77.77–96.6]) in arm A, 43 (84.3% [95% CI: 73.26–94.18]) in arm B (non-inferior p = 0.28, Δ = 3.7% [95% CI −7.5% to 15%]). In an exploratory objective, we found no difference between arms A and B in mITT ($\chi 2$ test; p = 0.8) and PP analysis ($\chi 2$ test; p = 0.27). Regarding autonomy preservation, there was no difference in the deterioration rate during the pre-operative phase between arms A and B with 15.4% and 17.1%, respectively (p = 1). At 3 months post-operative, for the 56 patients who had a score evaluation, a significant difference in the degradation rate was noted (arm A: 44.8%, arm B 14.8%; p = 0.032). However, for the second co-primary, no significant difference in the degradation of the IADL score between baseline and M12 was demonstrated in any arm, 14 patients (28.6% [95% CI: 16.6–43.3]; n = 49) in arm A and 14 (29.2% [95% CI: 17–44.1]; n = 48) in arm B (Table 3). Within the 36-month follow-up period, 9 (18%) and 3 patients (6%) died in arm A and B, respectively. Overall and specific survival were significantly improved in arm B (hazard ratio [HR] = 0.28 [95% CI: 0.07–1.00], p = 0.05 and HR = 0.21 [95% CI: 0.04–0.97], p = 0.027) (Fig. 2a and b). In terms of recurrence-free survival (Fig. 2c) and local recurrence-free survival (Fig. 2d), no statistical difference was demonstrated between the two arms (HR = 0.99 [95% CI: 0.47–2.09], p = 1.00) and HR = 1.7 [95% CI: 0.3–9.1], p = 0.55). During the pre-operative phase, 22% and 9.8% of patients presented a serious adverse event in arms A and B, respectively (Table 4), and one death was related to treatment in the chemoradiotherapy group (acute cholecystitis). Sixteen adverse event in arm A and 11 in arm B were Grade 3–5. During the post-operative phase (M3), treatment-related adverse event were identified in 9 patients (19.5%) in arm A and 10 (20.5%) in arm B. One death was related to treatment in arm A during this phase (Heart disorders).

4. Discussion

The management of rectal cancer in the elderly is not as standardised as that of young subjects and must take into account, more than for other groups of age, the quality of life and the impact of treatment on loss of autonomy. This is why organ preservation seems interesting in this population. In elderly patients with complete clinical response after radiotherapy or chemoradiotherapy, a watch and wait strategy seems promising with a 88% survival without local regrowth and 97% overall survival at 3 years [16]. However, the percentage of patients with a complete clinical response is low. Indeed, in a series of 59 patients over the age of 70, Bujko *et al.* reported a complete response rate of only 20% [17]. Therefore, this type of strategy can only be suitable for highly selected patients. In presence of locally advanced rectum cancer, total mesorectal excision surgery preceded by neoadjuvant treatment is considered the standard of care for fit patients. However, complications due to neoadjuvant treatment are more common in elderly patients [3] and although the results have improved significantly in recent years with post-operative mortality now very similar to that of young patients [10], significant progress must be made in order to choose a therapeutic decision based on the best balance benefit-risk. To investigate this question, we involved patients ≥75 years of age with locally advanced rectal carcinoma, in a study with co-primary objectives combining non-inferiority for the R0 resection rate and superiority for the preservation of autonomy for the 5 × 5 Gy radiotherapy regimen. We selected the R0 resection rate to have a primary objective immediately available and to allow an easier association with autonomy preservation. The R0

Table 2
Pathological results.

	Arm A: chemoradiotherapy (n = 46)	Arm B: short course radiotherapy (n = 49)	P value
ypT Stage; n (%)			0.09
0	8 (16.32)	3 (6.12)	
is	1 (2.04)	1 (2.04)	
1	3 (6.12)	0	
2	14 (28.57)	14 (28.57)	
3	19 (38.77)	26 (53.06)	
4	1 (2.04)	5 (10.20)	
ypN Stage; n (%)			0.62
0	33 (71.73)	31 (63.26)	
1	10 (21.71)	11 (22.44)	
2	2 (4.39)	6 (12.24)	
X	1 (2.17)	1 (2.04)	
pCR[a]; n (%)	8 (17.4)	3 (6.1)	0.16
PP[b] Resection; n (%)			0.43
R0	44 (95.6)	43 (87.7)	
R1-R2	2 (4.3)	6 (12.2)	
ITT[c] Resection; n (%)			0.27
R0	44 (89.8)	43 (86.0)	
R1-R2-non resection	5 (10.2)	7 (14.0)	

[a] pCR: pathological complete response.
[b] PP: Per-Protocol.
[c] ITT: Intent To Treat.

resection rate in the short course radiotherapy arm did not indicate the non-inferiority compared to chemoradiotherapy in PP or mITT analysis. Our first co-primary objective was not meet; however, we performed an exploratory statistical analysis that did not show any difference in R0 resection rate either in PP ($\chi 2$ test; p = 0.27) or in mITT ($\chi 2$ test; p = 0.8). Another prospective study compared short course radiotherapy and chemoradiotherapy (50 Gy + 5 Fluorouracil-folinic acid in bolus) with delayed surgery in all cases [18]. As in our study, the R0 resection rate was 83.8% in the short course radiotherapy arm and 88.9% in the chemoradiotherapy arm (p = 0.382). In contrast, the Polish study [5] demonstrated a worse rate of R0 resection in the short course radiotherapy group (87 versus 96%, p = 0.017); however, surgery was performed immediately after radiation therapy with a median-free interval of 8 days. In our study, as for the Trans-Tasman Radiation Oncology study 01.04 [6] or the Polish study [19], the local recurrence rate was not different between the two arms (HR 1.7 [95% CI: 0.3–9.1], p = 0.55). Regarding the local impact of neoadjuvant treatment, Latkauskas *et al.* [18] did not reported a significant difference in the histological complete response rate (4.4% for short course radiotherapy and 11.1% for chemoradiotherapy; p = 0.112), a result was also observed in our study. As classically reported by the literature, no difference in surgical technique was observed in our study [6,18,19]. Overall, short course radiotherapy is not associated with poorer local results; moreover, it improves compliance since 100% of our patients received all of the neoadjuvant treatment in the radiotherapy arm alone against 86% for the chemoradiotherapy arm. In the Polish study, there was 2% deviation from the planned treatment in the 5 × 5 group and 11% in the chemoradiotherapy group. Overall, a 98% of compliance was observed in the 5 × 5 Gy group compared with only 69% in the chemoradiotherapy group [5]. As expected, the lower compliance in the chemoradiotherapy arm is related to an increase in ≥Grade 3 side-effects (21.6% versus 32%) and in serious adverse events (9.8% versus 22%) in our study. Bujko *et al.* [5] had reported the better tolerance of hypofractionated radiotherapy compared to chemoradiotherapy (Grade III–IV toxicities 3% versus 18%). To note, in the Stockholm III study, 7% of patients treated with 5 × 5 Gy regimen with delayed surgery required hospitalisation for toxicity [13].

The second co-primary objective was to assess autonomy through the evolution of the IADL score from baseline to 12 months post-operative. Overall, there is no difference in the deterioration of IADL score between the two groups. On the other hand, a greater deterioration of the 3-month post-operative IADL score was noted in the chemoradiotherapy group (44.8% versus 14.8%, p = 0.032). Although the vast majority of our patients recovered their autonomy at 12 months in both arm, these results clearly show the risk of geriatric decompensation induced by oncological treatments. It may be thought that these results would be even more important in a less selected geriatric population. Indeed, an altered IADL score is associated to decreased overall survival in metastatic colorectal cancers [20] and increase of chemotherapy toxicity.

The main weakness of our study is the limited number of patients included, which is lower than expected. The

Table 3
Evolution of the IADL score compared to the baseline.

Phases	Evolution	Arm A chemoradiotherapy	Arm B short course radiotherapy	P value
Pre-operative; n (%)	Deterioration	6 (15.4%)	7 (17.1%)	1.000
	Stable or improvement	33 (84.6%)	34 (82.9%)	
M3; n (%)	Deterioration	13 (44.8%)	4 (14.8%)	0.032
	Stable or improvement	16 (55.2%)	23 (85.2%)	
M6; n (%)	Deterioration	7 (28.0%)	10 (29.4%)	1.000
	Stable or improvement	18 (72.0%)	24 (70.6%)	

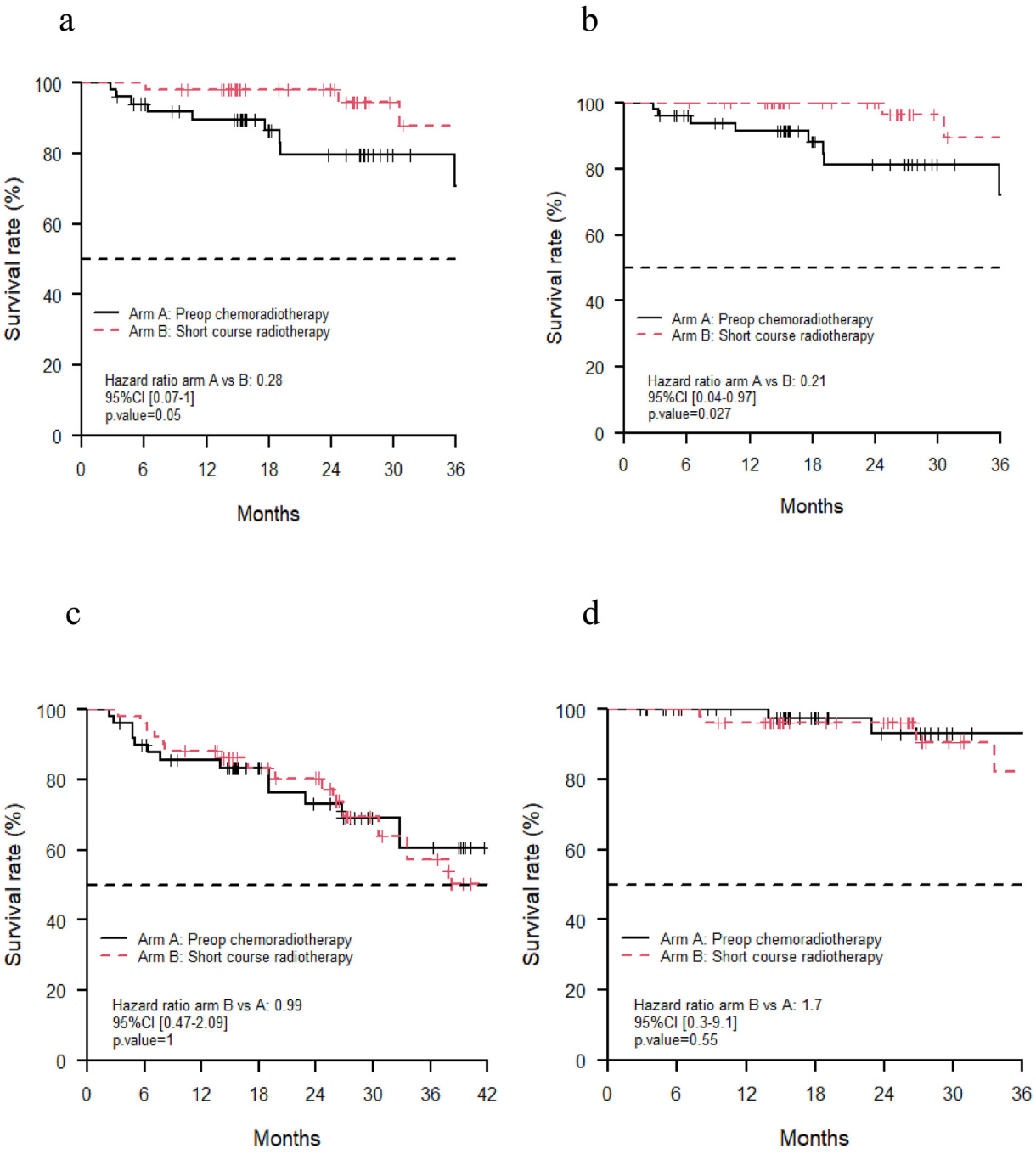

Fig. 2. Survival results. (**a**): Overall survival, (**b**): Specific survival, (**c**): Recurrence-free survival, (**d**): Local recurrence-free survival.

slowness of recruitment is partially explained by the high frequency of comorbities that prevented inclusion in the study; moreover, some patients were not included in the study and had short course radiotherapy to limit the number of trips. Although elderly patients are numerous, their frailties and comorbidities largely exclude them from clinical studies and prevent many of them from receiving all or part of the therapeutic strategy. In our study, even if more than 50% of the patients had comorbidities, this percentage is still too low compared to population-based registries which use less stringent selection criteria [21]; however, our population with the diversity of its comorbidities is a fairly faithful representation of the elderly population. Finally, we stopped the recruitment following IDMC recommendations. Overall survival (HR = 0.28 [95% CI: 0.08–1.00], p = 0.05) and specific survival (HR = 0.21 [95% CI: 0.04–0.97], p = 0.027) were significantly improved in the 5 × 5 Gy arm. On the other hand, recurrence-free survival was not different between the two groups (HR = 0.99 [95% CI: 0.47–2.09], p = 1). These results should be taken with caution because the size of our study was not suitable for a comparison of overall survival or recurrence-free survival and because the limited

Table 4
Tolerance.

	Arm A: chemoradiotherapy (n = 50)	Arm B: short course radiotherapy (n = 51)
Pre-operative phase		
All grades Toxicities; n (%)	39 (78.0)	29 (56.9)
Grade 3–5 Toxicities; n (%)	16 (32.0)	11 (21.5)
Cutaneous	2 (12.5)	0
Digestive	5 (31.3)	9 (81.8)
Thrombo-embolic event	0	2 (18.2)
Haematological	2 (12.5)	0
General condition	3 (18.8)	0
Others	4 (25.0)	0
Serious adverse events; n (%)	11 (22.0)	5 (9.8)
Cardiac	0	1 (20.0)
Cutaneous	1 (9.1)	0
Digestive	2 (18.2)	3 (60.0)
Thrombo-embolic event	1 (9.1)	1 (20.0)
Infections	1 (9.1)	0
Anorexia	1 (9.1)	0
Others	5 (45.4)	0
	Arm A: radiochemotherapy (n = 46)	Arm B: hypofractionated radiotherapy (n = 49)
Post-operative phase		
Grade 3–5 Toxicities; n (%)	16 (34.7)	13 (26.5)
Cardio-vascular	3 (18.8)	1 (7.7)
Renal/urinary	1 (6.3)	0
Digestive	3 (18.8)	1 (7.7)
Fistula	2 (12.5)	2 (15.4)
Haemorrhages	0	1 (7.7)
Infections	1 (6.3)	4 (30.8)
Pulmonary	1 (6.3)	0
Others	5 (31.3)	4 (30.8)

recruitment in our study. In the long-term follow-up of the Polish study, no difference in overall survival or recurrence-free survival was observed [19]. Despite the lack of power of our study preventing to meet the co-primary end-points and requiring to cautiously interpret the survival results which are in favour of short course radiotherapy, associated with better compliance and tolerance, we can foresee the advantage of a strategy of short course compared to a long course pre-operative chemoradiotherapy approach.

In conclusion, our study failed to meet its co-primary end-points. However, in patients $\geq$75 years with locally advanced rectal cancer, the 5 $\times$ 5 Gy radiotherapy followed by delayed surgery seems to present a good option due to a better tolerance and similar local recurrence-free survival. Further studies will need to confirm these data, especially overall survival. In addition, new strategies such as non-operative management must be tested in the light of the latest data from TNT studies to promote therapeutic de-escalation.

Author contribution

E François: Conception and design, Data acquisition, Data interpretation, Analysis, Manuscripts writing, Final approval.

De Bari, P Ronchin, E Nouhaud, I Martel Lafay, P Artru, P Clavere, V Vendrely, V Boige, D Gargot, C Lemansky, M Pernot, N Magné: Data acquisition, Data interpretation, Analysis, Final approval.

J Gal: Design, Data interpretation, Analysis.

N De Sousa Carvalho: Supervision, Project administration, Funding acquisition, Final approval.

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Conflict of interest statement

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