ORIGINAL ARTICLE

A retrospective outcome study in the elder patient with locally advanced rectal cancer treated with hypofractionated or conventional preoperative radiotherapy

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Abstract

Background: Neoadjuvant chemoradiotherapy is considered the standard approach for T3-4 M0 rectal cancer; however, the optimal dose remains undefined for the elderly. We performed a retrospective analysis to compare conventional (C) and hypofractionated (HF) schedules in elderly patients. We compared survival rates, local control and morbidity.

Methods: From 2000 to 2008, 177 patients older than 65 years with T3-4 M0 rectal cancer received preoperative radiotherapy according to either a conventional protocol (45 to 50.4 Gy in 1.8-2 Gy daily fractions) or a hypofractionated (39 Gy in 3 Gy daily fractions) protocol. Fifty-five patients in the conventional group and none of the patients in the hypofractionated group received concomitant chemotherapy. Both groups were equivalent in terms of their characteristics. The median follow-up was 36 months.

Results: The occurrence of early grade 3-4 radiation toxicity was equivalent between the 2 groups (7%). Surgery was performed in 98% of the patients in the HF group versus 92% in the conventional (p=0.08). The delay between radiotherapy and surgery was 22 days in the HF group versus 45 days in the conventional group (p=0.0021). The downstaging rates were 39% in HF group and 45% in the C group (p=0.53). For lower rectum tumors, the conservative surgery rates were 43% in the HF group and 35% in the C group, (p=0.52). The postoperative death rates at 30 days were equal between the two groups (3%). The 5-year local control rates was 87.3% in group C and 91.7% in group HF (p=0.5). Based on a Kaplan-Meier analysis, the 1-, 3- and 5-year overall survival rates were 88%, 67% and 45%, respectively, in the C group and 84%, 60% and 39%, respectively, in the HF group (p=0.28). In a multivariate analysis, the prognostic factors for overall survival were a Charlson index < 2 (p=0.0034 HR=0.3), pT stage $\leqslant$2 (p=0.0042 HR=0.16), pN0 stage (p=0.0072 HR=0.388), and downstaging (p=0.0498 HR=0.651). Radiation schedule and concomitant chemotherapy had no impact.

Conclusion: In this series, the local control rates and the overall survival results are equivalent for patients treated with HP and C radiation schedules. As hypofractionated radiotherapy is more convenient for elderly patients and has equivalent morbidity, additional prospective studies with this population could be of great interest.

Key words

Rectal cancer, Radiotherapy, Elderly, Dose fractionation, Hypofractionated

1 Introduction

The management of rectal cancer conventionally uses three modalities: radiotherapy, chemotherapy and surgery. For the last several years, the role of preoperative radiotherapy has been clearly established through randomized studies and meta-analyses [1, 2]. The association of radiotherapy and chemotherapy has been studied in randomized trials. Chemotherapy is conventionally performed with 5-fluorouracil (5FU) or an equivalent treatment. The addition of platins, such as oxaliplatin, is more recent and has produced potentially interesting results [3]. The combination of radiotherapy and chemotherapy before surgery provides important benefits and has improved the results of radiotherapy alone [4]. The radiation dose delivered is conventionally between 45 and 50.4 Gy with 1.8 to 2 Gy daily fractions and 5 fractions per week. Hypofractionated schedule, with 25 Gy in five consecutive fractions of 5 Gy, has been used with comparable results as conventional treatment but with probably more late complications. A more effective fractionation has not been clearly established. Although recent studies similar results in groups receiving two different fractionation protocols, the optimal regiment is still not established [5].

The benefit of preoperative radiotherapy has been demonstrated in the elderly [1, 2] however, its use decreases with age because it has been suggested that treatment is less well tolerated in this population [6, 7]. Furthermore, fatigability due to displacement should be taken into consideration when determining the number of fractions to be given to elderly patients. Here, we present the results of two schedules, 39 Gy in 13 fractions of 3 Gy and 45 Gy in 25 fractions of 1.8 Gy in order to do what to compare overall, survival, local control and downstaging rates, and to analyze morbidity between the two regiments of treatment.

Table 1. Patient characteristics

		Total N=177	**%**	**C**	**%**	**HF**	**%**	***P***
Age	<75	97	55%	61	59%	36	49%	0.2
	≥75	80	45%	43	41%	37	51%	
Gender	Male	110	62%	59	57%	51	70%	0.08
	Female	67	38%	45	43%	22	30%	
BMI median		25.7 (18.5-41.3)		25.9 (19.6-41.3)		25.6 (18.5-36.2)		NS
PS WHO	0	106	60%	61	59%	45	61%	0.75
	≥1	70	40%	42	41%	28	38%	
Charlson Score	0-2	151	86%	89	86%	62	85%	0.82
	>2	25	14%	14	14%	11	15%	
Tumor Location	Mid/High	72	41%	33	32%	39	53%	0.005
	Low	105	59%	71	68%	34	47%	
T	T3	151	86%	87	84%	64	90%	0.27
	T4	24	14%	17	16%	7	10%	
N	N0	81	63%	46	56%	35	74%	0.04
	N+	48	37%	36	44%	12	26%	
Mucinous component	Yes	16	9%	9	9%	7	9%	1
CA 19.9	Normal	126	85%	69	83%	57	88%	0.49
	Abnormal	22	15%	14	17%	8	12%	
CEA	Normal	110	70%	59	63%	51	78%	0.053
	Abnormal	48	30%	34	37%	14	21%	

N: Number of patients; C: Conventional; HF: Hypofractionated

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2 Materials and methods

2.1 Patients

We performed a retrospective analysis of patients over 65 years of age who were treated with preoperative radiotherapy for locally advanced rectal cancer between January 2000 and December 2008. All patients' characteristics are reported Table 1. All the tumors were T3-T4 with or without lymph node involvement. More patients > N0 are in the group C than in the group HF, 44% and 26% respectively. Patients who were treated with exclusive radiochemotherapy or postoperative radiotherapy and patients with metastasis were excluded from the analysis. All the tumors were considered as resectable. The patients had received no previous treatment for the rectal tumor, except for a derivation colostomy.

Two radiotherapy schedules were used: the classical (C) schedule, which delivered a dose of 45-50 Gy in 1.8 to 2 Gy daily fractions with 5 fractions per week, and the hypofractionated schedule (HF), which delivered a dose of 39 Gy in 13 fractions of 3 Gy with 5 fractions weekly. A total of 177 consecutive patients who fulfilled the inclusion criteria were included in this study: 104 patients received the C schedule, and 73 received the HF schedule. For all the patients, the median age was 74 years (range: 65 to 87.6 years). In group C, the median age was 73.2 years (range: 65 to 87.6 years, mean 73.8 years), and in group HF, it was 75 (range: 65 to 86.8 years, mean 75.4 years) (p=0.053). The study sample was comprised of 62% men and 38% women. The two groups were equivalent in terms of their general condition (60% of the patients had a WHO PS score equal to 0), their comorbidity score (86% of the patients had a Charlson score less than or equal to 2) and their median BMI at the time of diagnosis (25.7). Overall, the tumors were more frequently localized in the lower rectum (61%), although there was a difference between the two groups: 68% of the tumors in group C were in the lower rectum compared to 47% for the group HF (p=0.005). The pathology of the tumors was confirmed as adenocarcinoma in all the cases, with a mucinous component in 9% of the cases.

2.2 Classification

The TNM classification used was the UICC 2002 [8]. The spread of each tumor was assessed through a locoregional clinical examination that included a rectal examination and imaging (rectal ultrasonography, CT or pelvic MRI). The staging included a thoraco-abdominal-pelvic CT or a chest radiograph and an abdominal ultrasound. In cases of disagreement between the clinical findings and the imaging results regarding the tumor stage, the worst stage was used. cT3-stage tumors were found in 84% of the patients in the C group and in 90% of the patients in the HF group (p=0.27). There was a difference between the 2 groups in terms of the N stage: in the C group, 56% of patients were staged at cN0 compared to 74% in the HF group (p=0.04). In our evaluation of biological tumor markers, we found that CEA was normal in 63% of the patients in group C and in 78% of the patients in group HF, or 70% overall. CA 19-9 was normal in 83% of the group C patients and in 88% of the group HF patients, or 88% overall.

2.3 Treatment

In all the cases, the radiotherapy was a three-dimensional conformational radiotherapy using photons of 6 MV or more produced by linear accelerators. For all patients the same field technique has been performed using three photons fields, two lateral fields left and right and one posterior. All fields were treated every day. The target volume of radiotherapy was the macroscopic tumor or GTV (Gross Tumor Volume) defined by the CT-scan and the increased size of the lymph nodes. Information provided by other imaging modalities (ultrasonography, MRI, TEP-FDG) was taken into account for the delineation of the target volume. The CTV (Clinical Target Volume) included the mesorectum, the presacral area, and the anal canal, depending on the location of the tumor. Volumes were equal for the both groups.

For chemotherapy, 55 patients (31%) received concurrent chemoradiotherapy with 5FU; among them, 73% received *per os* chemotherapy, and 59% were given oxaliplatin. Only the patients following the conventional fractionation schedule had concurrent chemotherapy. Two patients of this group did not receive a combined treatment. More patients initially, > N0

received chemoradiation than N0 patients, 42% and 34% respectively. Thirty-one patients received adjuvant chemotherapy with 5FU, leucovorin and oxaliplatine, 18 patients in the group C and 13 patients in the group HF.

Surgery was performed in 95% of the patients: one patient died during concurrent radio chemotherapy, one died before surgery due to comorbidity, two had distant metastases detected after the combined therapy, and four died for unknown reasons. The median interval between the completion of radiotherapy and surgery was 41 days for the patients in groups C and 11 days for the patients in group HF.

2.4 Follow-up

The follow-up was continued until the date of death or as part of the study until December 2010. The overall median follow-up period was 35.7 months (1 to 118.9 months). It was 34.1 months (1.5 to 118.9) for the patients of group C and 39.1 months (1 to 118.4 months) for the patients of group HF (p=0.1).

3 Statistical analysis

Chi-squared test or Fisher's exact test were used for the analysis of qualitative variables, and ANOVA or a t-test was performed for quantitative variables. The survival rates were calculated by a Kaplan-Meier analysis. The survival time was the period between the date of the first irradiation and the date of death or the date of the last follow-up. The period of survival without recurrence was the period between the date of the first irradiation and the date of the first relapse (local or metastatic), the date of death or the date of the last follow-up.

A univariate analysis was performed to identify prognostic factors [age, gender, tumor classification, schedule of radiotherapy, concomitant radiotherapy, adjuvant chemotherapy, chemotherapy drugs, time between RT and surgery, OMS performance status, Charlson score, BMI class, characteristics of pathology (margins, angioinvasions, adenopathy...)]. The variables that were considered significant in the univariate analysis (p<0.05) were included in a multivariate analysis. The multivariate analysis of the prognostic factors was performed using the Cox regression model with proportional rates to calculate a hazard ratio (HR) and the 95% confidence interval (CI). All the tests were performed using the software StatView v5.0 (SAS Institute Inc., Cary, NC).

4 Results

A conventional fractionation protocol was administered in 59% of the cases (104 patients). For the patients in the C group, the median dose was 46.8 Gy (range: 23.4 to 56 Gy, mean 47.4 Gy) and the mean duration was 40 days (SE=0.76). For the patients in the HF group, the median dose was 39 Gy (range: 36-39 Gy, mean 38.9 Gy) and the mean duration was 19.8 days (SE=0.27). The radiotherapy was completed as expected for 99% of the patients in the HF group and 96% of the patients in the C group (p=0.65). The treatment duration was more than 20% longer than the theoretical target for 16% of the patients in group C and 27% of the patients in group HF (p=0.09).

4.1 Chemotherapy

The patients in the HF group did not receive concurrent chemotherapy. Among the patients in group C, 55 patients (52% of patients) received concurrent chemoradiation. The indications for chemotherapy included a younger age (OR=0.163 CI95%=0.045-0.590, p=0.0057) and higher a pN stage (OR=6.255 CI95%=2.080-18.816; p=0.0011).

4.2 Surgery

Overall, 95% of the patients underwent surgery, including 98% of the patients in group HF and 94% of the patients in group C (p=0.08). The mean delay between completion of radiotherapy and surgery were 22 and 45 days for group HF and group C, respectively (p=0.0021). A downstaging was obtained for 41% of the patients in group HF and 45% of the

patients in group C (p=0.74). According to the multivariate analysis, a delay between the end of radiotherapy and surgery more than 6 weeks (OR=3 CI95%=1.341-7.662, p=0.0088) and a T4 stage (OR=0.27 CI95%=0.086-0.825, p=0.0218) were favorable prognostic factors of downstaging. The rates of complete pathological response (pT0) were 6.7% and 1.4% (p=0.14) for groups C and HF, respectively. For tumors of the lower third of the rectum, the sphincter preservation rates were 34% and 38% for groups C and HF, respectively (p=0.82) For the other locations, these rates were 66% and 81%, respectively (p=0.26).

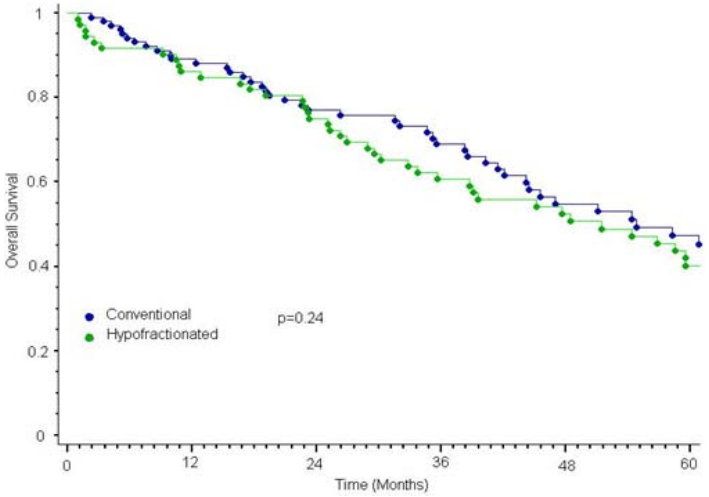

Figure 1. Overall survival curves according to the radiotherapy schedule

4.3 Local control

There was no difference of local or regional (nodes) control rates between the two groups. Median times of loco-regional control were not reached in the both groups. There were 9 locoregional relapses in the C group and 4 cases in the HF group. The 1-, 3- and 5-year local control rates were 96.5, 89.3 and 87.3% in the C group and 98.3, 91.7 and 91.7% in the HF group. No prognostic factor was retrieved.

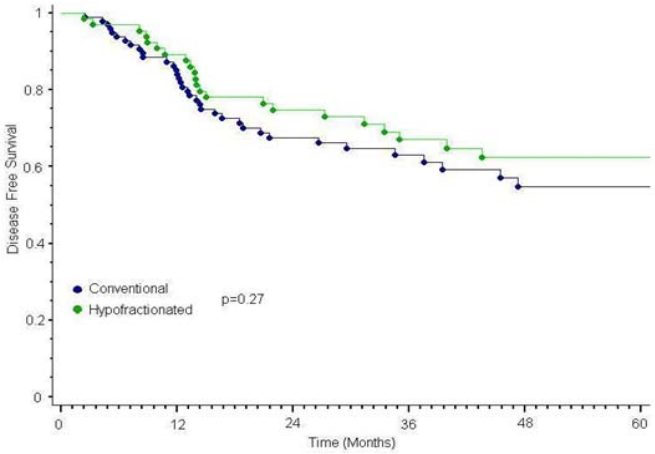

Figure 2. Disease-free survival curves according to the radiotherapy schedule

4.4 Survival

There was no difference in disease-free survival (DFS), and overall survival (OS), between the two schedules of radiotherapy, p=0.73 and p=0.97, respectively (Figures 1 and 2).

Overall, the 1, 3 and 5-year OS rates were 86.7%, 64.4% and 41.9%. For the C group, the rates were 88%, 67% and 45%, and for the HF group, the rates were 84%, 60%, 39%, respectively (p=0.28) (Figure 1). In the multivariate analysis, preoperative favorable prognostic factors for OS was a Charlson score < 2 (HR=0.3 CI95%=0.137-0.674, p=0.0034) Table 2). Postperative favorable prognostic factors for OS were pT stage ⩽ 2 (HR=0.16 CI95%=0.045-0.561, p=0.0042), stage pN0 (HR=0.388 CI95%=0.194-0.774, p=0.0072) and downstaging (HR=0.651 CI95%=1.001-7.695; p=0.0498) (Table 3). There was no treatment-related predictive factor for DFS (Table 4).

Table 2. Preoperative predictive factors for overall and disease-free survival

		Overall Survival				Disease-Free Survival			
		N	**EVT**	***P* (Uni)**	***P* (Multi)**	**N**	**EVT**	***P* (Uni)**	***P* (Multi)**
Age	<75	97	46	0.034	NS	95	35	0.73	NS
	≥75	80	46			78	24		
PS WHO	0	106	56	0.041	NS	105	37	0.58	NS
	≥1	70	36			67	22		
Charlson Score	0-2	151	73	0.0005	0.0034	149	51	0.42	NS
	>2	25	19			23	8		
T	3	151	78	0.5	NS	148	47	0.033	NS
	4	24	13			23	11		
N	0	81	32	0.084	NS	80	15	<0.0001	NS
	1-2	48	27			47	26		
Location	Mid/high	72	39	0.64	NS	71	20	0.12	NS
	Low	105	53			102	39		
Mucinous component	Yes	16	11	0.51	NS	16	7	0.44	NS
	No	161	81			157	57		
CA 19.9	Normal	126	65	0.3	NS	123	43	0.025	NS
	Abnormal	22	16			22	12		
% weight loss	<10%	116	60	0.56	NS	115	42	0.8	NS
	>10%	22	9			21	6		

N: Number of patients; EVT: Number of events, U: Univariate analysis; M: Multivariate analysis; NS: no significant; RT: Radiotherapy; CT: Chemotherapy

Table 3. Postoperative predictive factors for overall and disease-free survival

		Overall Survival				Disease-Free Survival			
		N	**EVT**	***P* (Uni)**	***P* (Multi)**	**N**	**EVT**	***P* (Uni)**	***P* (Multi)**
pT	0-2	59	16	0.0004	0.0042	59	8	<0.0001	NS
	3-4	102	63			100	46		
pN	0	118	45	<0.0001	0.0072	117	28	<0.0001	NS
	1-2	56	45			53	29		
Angioinvasion	Yes	11	9	0.008	NS	10	6	0.0036	0.036
	No	88	41			87	24		
Resection margin	R0	149	74	0.41	NS	147	49	0.19	NS
	R1-R2	9	6			9	5		
Downstaging	Yes	69	22	0.0018	0.0498	69	13	0.0007	NS
	No	90	56			88	40		

N: Number of patients; EVT: Number of events, U: Univariate analysis; M: Multivariate analysis; NS: no significant; RT: Radiotherapy; CT: Chemotherapy

For The DFS, 56 events have been observed. Overall, the 1, 3 and 5-year DFS rates were 84.5%, 64.0% and 57%. For the C group, the rates were 82.4%, 63.1% and 54.7%, and for the HF group, the rates were 87.7%, 65.7%, 60.3%, respectively (p=0.28) (Figure 2). There was no preoperative favorable prognostic factor for DFS (Table 2). The postoperative favorable prognostic factor for DFS was the absence of angio-invasions (HR=0.181 CI 95%= 0.037-0.89, p=0.0356) (Table 3). There was no treatment-related predictive factor for DFS (Table 4).

Table 4. Treatment-related predictive factors for overall and disease-free survival

		Overall Survival				Disease-Free Survival			
		N	**EVT**	***P* (Uni)**	***P* (Multi)**	**N**	**EVT**	***P* (Uni)**	***P* (Multi)**
Curative Surgery	yes	166	84	0.0001	NS	163	55	0.08	NS
	no	9	7			9	3		
RT – surgery Delay	< 6 weeks	114	66	0.33	NS	112	39	0.9	NS
	≥ 6 weeks	47	15			46	13		
Therapeutic schema	RT	101	56	0.83	NS	99	30	0.13	NS
	RTCT	76	36			74	29		
Fractionation schedule	C	104	45	0.24	NS	102	37	0.27	NS
	HF	73	47			71	22		
Radiotherapy lengthening	<20%	140	74	0.77	NS	137	48	0.9	NS
	>20%	37	18			36	11		

N: Number of patients; EVT: Number of events, U: Univariate analysis; M: Multivariate analysis; NS: no significant RT: Radiotherapy; CT: Chemotherapy

4.5 Toxicity

There was no significant difference in the acute grade 3 or 4 toxicities between the 2 schedules (7%). In the multivariate analysis, pretreatment loss of weight less than 10% was a favorable prognostic factor of toxicity (HR 0.914 CI95%=0.845-0.988, p=0.0243). Age, general condition, comorbidities, fractionation of radiotherapy and concomitant chemotherapy were not prognosticators. For either iatrogenic deaths (5%) or postoperative mortality at 30 days (3%) and 6 months (8%), there was also no difference between the 2 regimens.

5 Discussion

The standard treatment of locally advanced rectal tumors combines preoperative radiotherapy and concurrent chemotherapy, followed by surgical resection [9]. Complete removal of the tumor remains a determinant of the survival of elderly patients. The benefit of preoperative radiotherapy has been demonstrated in the elderly [1, 2]. A Swedish trial showed an improvement of local control irrespective of age [10], and studies have shown that pelvic radiotherapy is clearly achievable in elderly patients [6]. However, its use decreases with age because it has been suggested that treatment is less well tolerated in this population [11].

In a retrospective study of 534 patients, Ayanian et al. [12] showed that the rates of radiotherapy use, for patients aged < 55, 55-74, 75-85 and ⩾ 85 year-old, were 81.7%, approximately 70%, less than 50% and 14.3%, respectively. A combination of radiochemotherapy was prescribed more frequently for patients less than 55 years old than for older patients [12]. Similarly, a study by Jung et al. [7] that included 15,104 patients showed a decrease in the use of radiotherapy from 67% for patients less than 75 years old to 34% for patients older than 75 years. Furthermore, radiotherapy use has been shown to improved quality of life [13].

The question of dose and fractionation remains controversial. Hypofractionation has already been used for elderly with high efficiency and tolerance [14]. Two classical radiotherapy schedules, a protocol that delivers 45 to 50 Gy with conventional fractionation and the Swedish protocol consisting of 25 Gy given in five consecutive fractions, provided similar results in terms of local control. The short course was associated with a low rate of acute toxicity [15], while the long course appeared to decrease the rate of late toxicity [9]. In the Stockholm I trial [16], the monitoring data from patients who received 25 Gy in 5 fractions showed an increase in the occurrence of late complications. However, due to differences in the techniques used between our study and the previous investigation, the relationship between late complications and the radiotherapy protocol remains unclear. In our study, local control rates are comparable between the both groups. There was no difference of patient's characteristics between the two groups. It could be concluded that the HF treatment can be proposed to elderly. With only 13 locoregional relapses our results are equivalent to those obtained by others studies [9, 15, 16]. Furthermore, OS and DFS are comparable between both groups. In their study Bujko et al. compared the Swedish and the classical radiotherapy protocols in patients with locally advanced rectal tumors that were T3-T4 and resectable (patients mean age: 60). The grade 3 and 4 acute toxicity rates were higher in the chemoradiotherapy group (18.2 vs. 3.2% $p<0.0001$), but the late severe toxicities rates were comparable. In terms of efficacy, OS and DFS at 4 years were not statistically different in the 2 groups (67% and 56%, respectively) [17]. In our study, the rate of grade ⩾ 3 toxities remained low at 7%. This could be explained by the low use of chemoradiation. However, the lonely prognostic factor of complication was loss of weight. If this factor may seem intuitively easy to understand, no study has found that data as a prognostic factor for complications. However, it is a data that is perhaps not systematically analyzed because it may initially seem irrelevant. In fact, weight loss is rare in patients with rectal cancer. Bujko et al showed that the tumor response was significantly improved by the combination chemoradiotherapy (16% vs. 1% $p<0.0001$), but the authors did not find significant differences in the rates of local recurrence, which were 9% for the short course and 14% for the classical course ($p=0.170$) [17]. In our study, chemoradiation was not a prognostic factor neither for OS nor for DFS. However, the downstaging is slightly higher in the C group, but the reason is probably less in the fractionation of the treatment than in the time between end of radiotherapy and surgery, longer in the C group. This was in concordance with the results of the 90-01 Lyon trial [18]. Compliance with the short course was 98% compared to 69% for the classical schedule. Radiochemotherapy has not increased the rate of sphincter preservation compared to the short schedule, with rates of 61% and 58% ($p=0.57$), respectively [19]. In our study, there was no difference of sphincter preservation, but the treatment was not performed for this goal. The same hypofractionated protocol (39 Gy in 13 fractions) has been previously used in the Lyon trial with this objective but failed to prove its superiority comparatively to le conventional schedule [18]. In practice, elderly patients are usually excluded from prospective trials [20], and most studies that have analyzed the role of chemoradiation found a benefit in terms of local control and downstaging, but not overall survival [4, 17, 21-23].

The possibility that hypofractionated radiotherapy protocols could eliminate the need for preoperative chemotherapy makes this type of schedule an attractive option in the elderly. In conclusion, this retrospective study showed that the use of hypofractionated irradiation for the treatment of rectal cancer in the elderly is well tolerated with no negative impacts in terms of overall survival or local control. Prospective studies should be performed to investigate the use of hypofractionation in this population because many questions remain about the optimal strategy.

Conflict of interests

The authors declare that they have no conflict of interests.

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