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Original Article

Locoregional relapses in the ACCORD 12/0405-PRODIGE 02 study: Dosimetric study and risk factors ☆

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ABSTRACT

Purpose: The aim of this study is to correlate locoregional relapse with radiation therapy volumes in patients with rectal cancer treated with neoadjuvant chemoradiation in the ACCORD 12/0405-PRODIGE 02 trial.

Patients and methods: We identified patients who had a locoregional relapse included in ACCORD 12's database. We studied their clinical, radiological, and dosimetric data to analyze the dose received by the area of relapse.

Results: 39 patients (6.5%) presented 54 locoregional relapses. Most of the relapses were in-field (n = 21, 39%) or marginal (n = 13, 24%) with only six out-of-field (11%), 14 could not be evaluated. Most of them happened in the anastomosis, the perirectal space, and the usual lymphatic drainage areas (presacral and posterior lateral lymph nodes). Only patients treated for a lower rectum adenocarcinoma had a relapse outside of the treated volume. 2 patients with T4 tumors extending into anterior pelvic organs had relapses in anterior lateral and external iliac lymph nodes.

Conclusions: Lowering the upper limit of the treatment field for low rectal tumors increased the risk of out of the field recurrence. For very low tumors, including the inguinal lymph nodes in the treated volume should be considered. Recording locoregional involvement, treated volumes, and relapse areas in future prospective trials would be of paramount interest to refine delineation guidelines.

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The standard treatment of locally advanced (i.e. T3-T4 and/or N+) rectal adenocarcinoma is neoadjuvant radiation therapy followed by surgery with total mesorectal excision (TME) [1]. Indeed, the addition of radiation therapy to surgery reduces the local relapse rate [2–6]. The benefit of radiation therapy on local control is greater when given in the neoadjuvant setting [7,8]. Pathological complete response (pCR) rates have been further improved by addition of concurrent 5-fluorouracil (5FU) chemotherapy to normofractionated radiation therapy [9,10]. However, radiation therapy does not improve overall survival when total mesorectal excision is performed [6].

The addition of oxaliplatin to fluoropyrimidine-based adjuvant chemotherapy for colon cancer patients demonstrated a DFS and OS benefit, leading to study this combination concurrently with neoadjuvant radiation therapy for rectal cancer [11,12]. In this context, the ACCORD 12/0405-PRODIGE 02 trial was launched in 2005. Patients were randomized between neoadjuvant CAP45 and CAPOX50 before surgery with TME.

In a recent international consensus guidelines on CTV delineation in rectal cancer, the necessity of adapting radiation therapy volumes to locoregional extension have been highlighted [13].

This study intends to analyze local relapses in the ACCORD 12/0405-PRODIGE 02 trial and to identify risk factors.

Methods

ACCORD 12/0405-PRODIGE 02 trial

The ACCORD 12/0405-PRODIGE 02 trial included patients with histologically proven rectal adenocarcinoma, accessible to digital rectal examination, staged T2, if located in the distal anterior rectum, or T3-T4 N0-2M0 as assessed by endorectal ultrasound and/or magnetic resonance imaging. They were randomized (ratio 1:1) to receive either neoadjuvant CAP45 (radiation therapy at a total dose of 45 Gy in 25 fractions over 5 weeks with concurrent capecitabine 800 mg/m^2 twice daily delivered on each radiation day) or CAPOX50 (50 Gy in 25 fractions over 5 weeks with the last three fractions delivered only to the GTV and with concurrent capecitabine 800 mg/m^2 twice daily delivered on each radiation day and oxaliplatin 50 mg/m^2 administered once weekly for 5 weeks) before surgery with TME. Randomization was stratified by sex, treatment center, T-stage (cT2, cT3, cT4), and distance between the tumor and the anal verge ($\leq$6 versus >6 cm).

The radiation therapy protocol suggested a three-field (two lateral and a one posterior) prone technique, with a superior field limit set at the S2-S3 vertebral interspace or at the promontory depending on the tumor location. No elective inguinal, external iliac or anterior lateral irradiation was mandated. Surgery was to be performed six weeks after completion of neoadjuvant chemoradiotherapy. It could be either abdominoperineal amputation, anterior resection, or intersphincteric resection with TME. Modified Dworak score was used to assess tumor regression on pathological specimen [14]. Follow-up was carried out 3 months after surgery and then every 6 months for 5 years. The analysis of toxicities was carried out according to the National Cancer Institute Common Toxicity Criteria, version 3.0 [15]. Nice's Antoine Lacassagne Cancer Center's ethics committee had validated the protocol. The efficacy and toxicity results have been reported previously [16–19].

Inclusion criteria

We identified the included patients who presented a locoregional relapse in UNICANCER ACCORD 12 database. Relapse was classified as locoregional if it involved any of the following areas: rectal anastomosis, adjacent pelvic organs, lateral, presacral, and perirectal lymph nodes as well as inguinal and external iliac lymph nodes in case of anal canal or anterior pelvic involvement, respectively, as these would be considered locoregional (i.e. non metastatic) according to the 2018 AJCC TNM classification [20]. Patients whose relapses would be classified as metastatic (for instance para-aortic) were excluded from this analysis.

Patients had given their written consent for the use of their clinical and radiological data for further analyses when being included in the original ACCORD 12/0405-PRODIGE 02 trial. Patients who had since withdrawn consent were not included in the analysis.

Dosimetric analysis

As patients had been treated either with a two-dimensional (2D) technique or with three-dimensional conformal radiotherapy (3D), some dosimetric data could not be obtained as DICOMRT files. For these patients, we identified a patient who were treated at our institution with same gender, treatment position, similar height and weight to use as phantoms as it has been done in previous studies [21]. Beams were modeled on those patients' CT scans with the help of portal images and treatment file information (including angle, beam size, filters, and energy) on Philips Pinnacle3 Radiation Therapy System v.9.10.

The area of relapse was delineated on the Pinnacle software with the help of fusion with images of relapses (PET scans, CT scans, or MRI). Only the first known local relapse was included for analysis.

Both RTstruct and RTdose files were transferred onto Aquilab's *ARTIVIEW Plan Check* v.2.8.2 software for analysis [22]. Minimal, mean, and maximal doses received in the relapse volume as well as coverage by the 95% isodose were reported, according to ICRU guidelines [23,24]. Relapses were defined as in-field, marginal, or out-of-field if over 95%, between 20% and 95%, or less than 20% of the volume, respectively, were covered by the 95% isodose, as done in previous studies [25,26]. Patients were classified according to their least covered relapse.

Relapses were also classified according to the area they were located in according to both Roels's and Valentini's classification [13,27]. A single relapse could involve multiple adjacent locations. We then studied clinical characteristics and treatment factors to assess links between those and the location of the relapse.

Statistical analysis

Statistical analysis was performed with R v.3.3.1. Student t-test was used was used for quantitative data and χ^2 test for qualitative data. When underlying data did not meet the assumptions about the population sample to allow these tests to be used, non-parametric Wilcoxon-Mann-Whitney and exact Fisher tests for quantitative and qualitative data respectively were performed when appropriate [28].

Results

Out of the 598 patients included in the ACCORD 12/0405-PRODIGE 02 trial, 574 had surgery and 565 surgical samples were analyzed [16]. Forty-four patients (7.4%) had a local relapse reported in the UNICANCER database. Out of these, five were excluded from analysis because they did not have an actual locoregional relapse (one did not undergo surgery, one had a second colon primary, one had gangrene with no evidence of local relapse on the surgical sample, and two had metastatic lesions).

This left us with 39 patients (6.5%) who presented 54 locoregional relapses as nine patients had multifocal relapses. Twenty-two of the 39 patients had synchronous metastatic relapses. Six patients (15.3%) had no imaging available at the time of relapse, meaning that relapses could be classified in only 33 patients. Seven

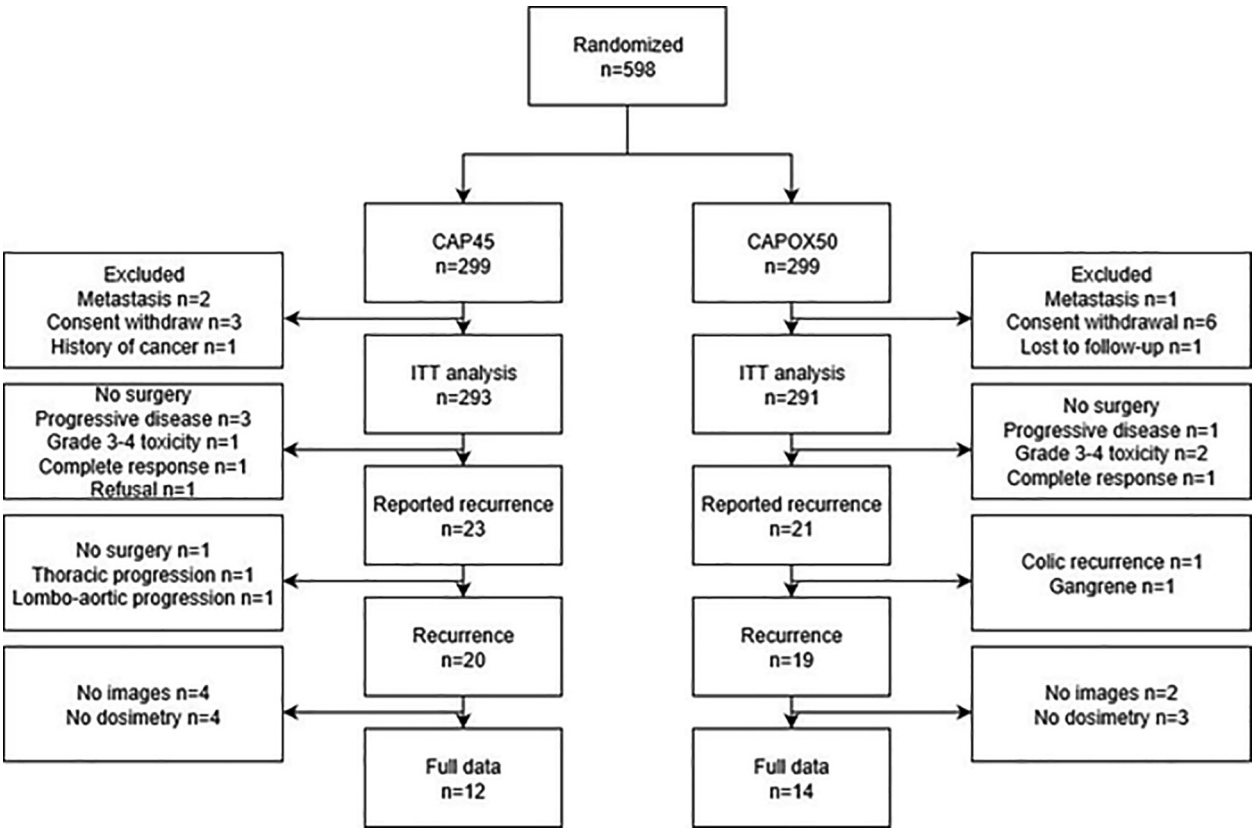

Fig. 1. Flowchart of the study.

patients' dosimetries (17.9%) had been lost. In total, 26 patients (66.6%) had enough data to complete the entire dosimetric study, including 19 (48.7%) in DICOMRT format (Fig. 1).

Adherence to the trial's radiation therapy guidelines was poor in patients who had locoregional relapse, with 61.5% of patients treated in supine position, 48.7% treated with an upper beam limit at the L5-S1 vertebral interspace, and 56.4% of patients treated with more than three beams. These data could not be compared to those of the whole population included in the trial as data for the patients who did not relapse were not always available. Compared to the whole trial population, in patients who had a locoregional relapse, ypT and ypN stages were higher ($p < 0.001$ and $p = 0.005$, respectively), tumor response was poorer ($p = 0.002$), R1 resection more frequent ($p < 0.001$), as well as circumferential resection margin <2 mm ($p = 0.002$), and abdominoperineal amputation ($p = 0.048$) [19].

The locations of relapses whose CT scan or MRI could be retrieved are shown on Fig. 2.

Patients were more likely to have been treated with an S2-S3 field limit if they had a lower rectal tumor ($p = 0.004$). T and N stage did not impact upper beam limit (Table 1).

Most of relapses were in-field ($n = 21$, 39%) or marginal ($n = 13$, 24%) with only six out-of-field (11%). For 14 relapses (26 %), the location of relapse according to treated volume could not be properly evaluated.

There was no significant difference in relapse location according to upper beam limit ($p = 0.76$). When looking at patients, three patients had relapses only above L5-S1 (8%), 15 only between L5-S1 and S2-S3 (38.5%), and 10 only below S2-S3 (25.5%). Three had relapses both below S2-S3 and above L5-S1 (8%) and four with relapses both below and above S2-S3 (10%). In four patients (10%), locoregional relapse could not be defined according to L5-S1 and S2-S3 vertebral interspaces due to lack of clinical and radiological information. When looking at individual relapses (as shown in Fig. 3), in total, 17 relapses were located above the field limit, of which 7 were located between S2-S3 and L5-S1 in patients with an S2-S3 beam limit.

Clinical and pathological parameters and their influence on location of the relapse are reported in Table 2. The only factor that significantly impacted the relapse location was the T stage ($p = 0.03$). No patient with an initial cT2-3N0 stage tumor had a local relapse outside of the radiation field. No patient with mid-rectum tumor had an out of the field relapse but this did not significantly differ from patients with a lower-rectum tumor.

When looking at the whole population, T stage (2 vs. 3 vs. 4, p-0.0073), TRG (0–1 vs. 2–3, $p = 0.018$) and resection margins (R0 vs. R1, $p = 0.010$) were predictive of relapses outside of the treated volume. Those results stayed true when excluding patient with relapses of unknown location (Supplementary Table 3).

Out-of-field relapses were located in inguinal area ($n = 2$, cT4N0 and cT4N1), ischioanal fossa ($n = 1$, cT4N0), posterior lateral lymph nodes ($n = 2$, cT4N0 and cT4N1), and presacral space ($n = 1$, cT4N0). The latter three occurred in patients with an S2-S3 upper beam limit.

In the CAPOX50 arm, only two relapses (6.5%) were found in the boost volume, eight (26.5%) were marginal, 14 (47%) were out of the boost volume, and six (20 %) were of unknown location.

Relapse locations according to Valentini's and Roels's classifications are reported in Supplementary Tables 1 and 2.

All four patients with an inguinal relapse (0.7% of the trial population, 1.7% of patient with a tumor that needed a sphincteric resection due to proximity or involvement of the anal canal and 10.2% of the patients with locoregional relapse) initially had a low-rectum tumor (cT3N1, cT3N2, cT4N0, and cT4N1) with one

Table 1
Upper beam limit according to clinical characteristics.

Characteristic		Upper beam limit, *n* (%)			*p*
		L5-S1	S2-S3	Unknown	
Tumor location	Lower rectum	10 (26)	13 (33)	6 (15)	0.004
	Mid rectum	9 (23)	0	1 (3)	
T stage	T2	1 (3)	1 (3)	1 (3)	0.81
	T3	14 (36)	11 (28)	6 (15)	
	T4	4 (10)	1 (3%)	0	
N stage	N0	5 (13)	5 (13)	1 (3)	0.58
	N+	14 (36)	8 (21)	6 (15)	

Abbreviations: n, number; T, tumor; N, nodal.

having an initially involved inguinal lymph node that was marginally covered (62% of the lymph node received at least 42.75 Gy) and one whose images could not be retrieved. None of them had successful surgical inguinal salvage lymphadenectomy. Both patients who presented with a relapse in the external iliac or anterior lateral lymph nodes (one of them in field, one of them marginal) had a T4 tumor, one of which had a proven anterior extension (right seminal vesicle), as there were 31 patients with T4 tumors in the study, this means that 6.5% of patients with T4 tumors had a relapse in the external iliac or anterior lateral lymph nodes (p = 0.002 for T4 vs. T2-3 as a risk factor for anterior relapse). Both patients with an abdominal presacral relapse initially had lymph node involvement (cT3N2 and cT4N1), one of which initially had presacral lymph node involvement.

Only patients with low-rectum tumors presented with relapses in the ischioanal fossa (n = 7, 1.2%) or the sphincter complex (n = 17, 2.8%), i.e. at the anastomosis. Neither the patient treated with intersphincteric resection nor the patient treated by local excision had relapse in the sphincter complex. They had perirectal and presacral relapses, respectively. However, among the 217 patients treated for low-rectum tumors with anterior resection, 11 (5.1%) had relapses with sphincter complex or anastomosis involvement with, among them, nine unifocal relapses and two patients relapsed in the ischioanal fossa..

Thirty-nine patients (6.5%) had R1 resection including 34 low-rectum tumors out of 388 (8.8%) and five mid-rectum tumors out of 197 (2.5%) (p = 0.004). Seven of them (18%) had locoregional relapses. For six of them, we had CT scan or MRI which allowed

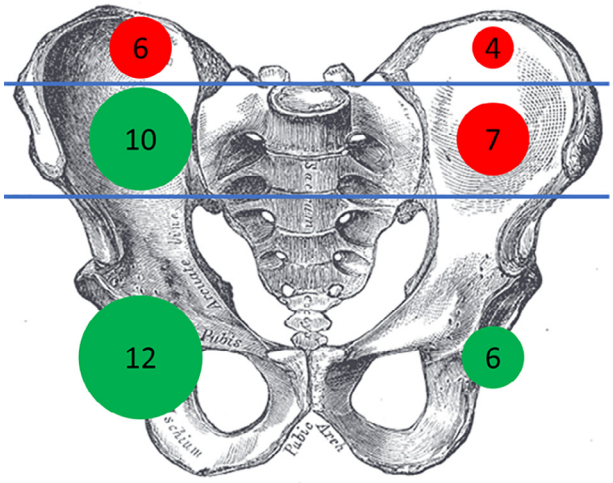

Fig. 3. Relapse location according to upper beam limit. Shown above are the relapses according the L5-S1 and S2-S3 spaces. On the left are relapses seen with an L5-S1 field limit, on the right seen with an S2-S3 field limit. The numbers in the circles refer to the number of individual relapses in each location (above L5-S1, between L5-S1 and S2-S3 and below S2-S3), a red circle means that the relapse is located above the field limit (50% isodose) and a green circle that it is located below the field limit. The precise location of the relapse was unknown in 5 cases, the upper beam limit in 7. Adapted from Henry Gray, Anatomy of the Human Body 20th edition.[47]

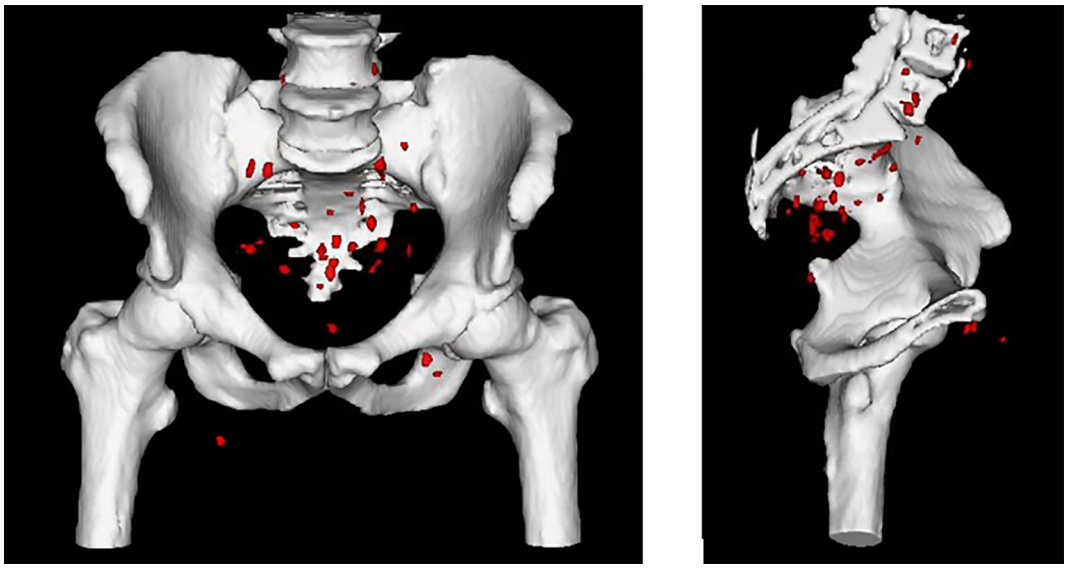

Fig. 2. Epicenter of locoregional relapses.

Table 2
Location of relapses according to clinical and pathological characteristics.

Characteristics		Relapse					*p*
		In-field	Marginal	Out-of-field	Unknown	Total	
T stage	T2	1	1	0	1	3	0.030
	T3	10	8	1	12	31	
	T4	0	2	3	0	5	
N stage	N0	2	5	2	2	11	0.46
	N+	9	6	2	11	28	
Tumor location	Lower rectum	10	6	4	9	29	0.10
	Mid rectum	1	5	0	4	10	
T2-3 N0	Yes	2	5	0	2	9	0.28
	No	9	6	4	11	30	
Modified TRG	1–2	8	8	3	12	31	1
	3–4	3	2	1	1	7	
	Unknown	0	1	0	0	1	
Margins	R0	10	9	2	11	32	0.31
	R1	1	2	2	2	7	
Adjuvant chemotherapy	Yes	6	6	2	9	23	1
	No	5	5	2	4	16	

Abbreviations: n, number; T, tumor; N, nodal.

us to locate the relapses as follows: abdominal presacral space, anastomosis, posterior lateral and rectovaginal spaces, pelvic presacral space, perirectal area, posterior lateral lymph nodes, and ischioanal fossa. The seventh patient, whose images we could not retrieve, had reported relapses in the ischioanal fossa, inguinal nodes, and prostate, meaning only two out of 39 R1 patients (5.1%) had anastomotic relapse.

Discussion

Locoregional relapses in the ACCORD 12 0405-PRODIGE 02 trial were rare and mostly involved the posterior and inferior pelvic areas. Most of them were either in-field or marginal relapses with out of field relapses involving only patients with low-rectum tumors and mostly T4 patients. These data are consistent with literature [27,29]. Valentini et al. offered guidelines for extending the treated volume according to locoregional extension (T4 tumors, positive lateral lymph nodes, numerous mesorectal nodes, anal canal, external sphincter, or lower vaginal involvement) [13]. Out of field relapses might have been avoided with such an extension of the treated volume as every single one of them happened when the initial extent of the tumor fulfilled at least one of those criteria. Additionally, when looking at the whole population T4 status was predictive of relapses out of the treated volume, strengthening the case for larger treatment volumes (possibly including anterior lymphatic drainage pathways).

We found similar results to those reported by Nijkamp et al. [30]. Patients with T2-T3N0 tumors had rarely relapses above the S2-S3 vertebral interspace, whereas patients with T4 tumors had a higher tendency to do so. Furthermore, patients with T2-T3N0 tumors never had out-of-field relapses. However, one should note that low tumors may also have higher pelvic relapses, as it has been previously reported [30]. Indeed, only patients with low-rectum tumors had out-of-field locoregional relapses, including two which were above the S2-S3 interspace meaning that lowering the upper beam limit must only be done after careful staging.

Our data is also consistent with the literature stating that patients with T4 tumors had a higher risk of lateral or external iliac lymph node relapse. Koda et al. reported that in patients with mid-rectal tumors, lateral or external iliac involvement could be found in 0% of patients with pT2 tumors, 1.4% of patients with pT3 tumors, and 7.1% of patients with pT4 tumors. These rates rose to 5.2%, 13.5%, and 18.8%, respectively, in patients with low-rectum tumors [31].

We found a low rate of inguinal relapse (0.7%). Risk of inguinal involvement has been reported to be rather low in rectal cancer, with below 1% involvement even in low rectal cancers [27,32–34]. Roels et al. and Valentini et al. recommend irradiation of this region only if there is an involvement of the lower vagina or an extensive involvement of the external sphincter [13,27]. Indeed, while it has been shown that elective inguinal irradiation was efficient at preventing local relapses, the toxicity of such an irradiation is rather high with older radiation therapy techniques and could even increase abdominal wound complications, especially compared to the low frequency of such a relapse [35–38]. Moreover, some reports show that some of those relapses could be salvaged by surgery although this was not the case in our study [38]. Improvements in radiation therapy techniques such as IMRT could reduce this toxicity. Indeed, Milano et al. reported no grade ≥ 3 non hematologic toxicities in anal canal cancer irradiation with IMRT including inguinal nodes with a median inguinal dose of 45 Gy [39].

Only patients with low-rectum tumors presented relapses in the sphincter complex or the ischioanal fossa. These results are consistent with a study by McDermott et al. showing an involvement of the inferior pelvis in 8% of patients with tumors lying below 6 cm from the anal verge, 3% of patients with tumors lying between 6 and 11 cm from the anal verge, and 0% of patients with tumors lying above 11 cm from the anal verge [40]. Conversely, our data is consistent with the fact that abdominal presacral relapse is rare in patients with no initial involvement of this region and may not warrant elective irradiation [13].

Our data is also consistent with studies led by Yu et al. and Sanfilippo et al., showing that most locoregional relapses in patients treated for rectal adenocarcinoma are situated inside the treated volume. Yu reported 65% of in-field and 16% of marginal relapses, Sanfilippo 70% and 20%, respectively [41,42]. In the present study, of the 40 relapses whose dose and location were known, 53% were in-field and 33% marginal. No prospective randomized study has compared a 45 Gy to a 50 Gy dose with the same chemotherapy regimen. Therefore, international guidelines offer the 5 Gy boost as an option [43–45]. However, it is important to note that only two relapses were in the boost volume, i.e. less than 1% of the patients randomized in the CAPOX50 group.

Our study has some caveats. First of all, even if the patients were included prospectively, it is unplanned and retrospective, and as such prone to bias. Some of the dosimetric and imaging data could not be retrieved. We also did not have the dosimetry of patients who did not relapse and therefore could not investigate relapse risk factors further and more accurately. Adherence to

radiotherapy guidelines were poor and radiotherapy protocols varied greatly between patients, which may also have impacted our results [46].

Our study also has some strengths. To our knowledge, it is the first to have studied dosimetries with a 3D reconstitution of dose for all patients as opposed to only using field limits to determine which relapse is in or out of field [30,41,42]. Such a method has been used in other dosimetric studies and while one may argue that such as process only approximates dose distribution in the actual patient (although less than by using only beam limits), hardly any relapse was close to the chosen limits (20% and 95% of the prescription isodose) and 48.7% of our patients had DICOMRT dosimetry files, making the risk of misclassification nearly inexistent [21]. We have also extensively studied risks factors for relapse depending on the relapse region and compared them to current international guidelines.

Conclusions

Locoregional relapses in patients treated with neoadjuvant chemoradiation tend to occur in field. The upper beam limit in patients with T4 tumors or dubious circumferential resection margin should not be lowered to S2-S3. Patients with T4 tumors may warrant more extensive elective nodal irradiation, notably including the anterior lateral and external iliac nodes. Inguinal irradiation remains debated and the patients who may benefit from it need to be more clearly selected.

Conflict of interest statement

Conflicts of interest, whether potential or actual, do not exist for any of the authors of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.06.006.

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