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Original Article

Intensity-modulated radiation therapy of anal squamous cell carcinoma: Relationship between delineation quality and regional recurrence

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ABSTRACT

Background and purpose: Intensity-modulated radiation therapy (IMRT) is currently indicated to treat anal squamous cell carcinoma (ASCC). Conformal dose delivery and steep dose gradients may cause marginal misses. We analyzed patterns of locoregional recurrences (LRR) and delineation quality to determine IMRT-specific predictive factors.
Material and methods: Lymph node area delineation was classified as "compliant" or "non-compliant" according to experts' workgroup recommendations. The recurrence volume (V_{recur}) was delineated on initial planning-CT by recurrence imaging registration. The V_{recur} was determined to be "in-field" (IF), "marginal" (ML), or "out-of-field" (OF) in regard to the 95% isodose coverage.
Results: Out of 165 patients, 30 had LRR. Among the 27 local recurrences (LR), 20 (74%) were IF, 4 (15%) ML, and 2 (7%) OF. Fourteen patients had regional recurrence (RR), amounted to 33 separate recurrence sites (RS). RS were mostly localized in inguinal ($n = 12;36,4\%$), external iliac ($n = 7;21.1\%$), presacral ($n = 4;12.1\%$) and common iliac ($n = 3;9.1\%$) nodes. Eighteen (54.5%) RS were IF, 6 (18.2%) ML, and 9 (27.3%) OF. Performance status ≥ 2 ($p = 0.007$) and active smoking ($p = 0.025$) were predictors of LR. Immunodepression ($p = 0.012$), external iliac involvement ($p < 0.001$), and non-compliant delineation for ≥ 10 areas ($p = 0.005$) were predictors of RR.
Conclusions: New predictive factors for recurrences of ASSC treated with IMRT have been found, suggesting that the delineation accuracy is essential for regional control.

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Concomitant chemoradiotherapy with 5-fluorouracil (5-FU) and Mitomycin–C (MMC), is the standard of care for locally advanced anal squamous cell carcinoma (ASCC) [1–5]. Locoregional recurrences (LRR) occur in 20–30% of cases, mainly within the first 2 years after treatment [1,6,7].

Approved in 2005 for ASCC in France, Intensity-modulated radiation therapy (IMRT) delivers dose in a more conformational way than three-dimensional radiotherapy (3D-RT) with a better coverage and decreased toxicities [8–14].

IMRT requires clinical experience to achieve accurate and precise delineation [11]. The conformal dose delivery and the steep dose gradients may increase LRR. Marginal misses due to IMRT have been demonstrated in head and neck cancer [15,16] but to our knowledge not yet described for ASCC.

This retrospective study reports a series of patients treated by IMRT for ASSC in two French university hospitals. The primary objective was to describe the patterns of LRR and to search for predictive factors, focusing on delineation. Secondary objectives were to evaluate overall survival (OS), disease-free survival (DFS), and definitive colostomy incidence.

Materials and methods

Patients

Consecutive patients treated by IMRT for ASSC from the introduction of IMRT in two French centers were retrospectively included: from December 2006 at the Institut de Cancérologie de l'Ouest, Nantes, and from October 2009 at the Institut de Cancérologie de Lorraine, Nancy, to December 2016.

Inclusion criteria

Were included: patients with histological proof of anal canal or margin SCC, treated by IMRT, with curative intent, either alone or with concurrent chemotherapy.

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Exclusion criteria were: non-SCC histologies and visceral metastases.

Chemoradiotherapy

An experienced radiation oncologist, according to his center's recommendations, performed the delineation. The gross tumor volumes (GTV) were defined as GTVT for the primary tumor and GTVN for involved lymph nodes (LN). Two clinical target volumes (CTV) were delineated: CTV1 corresponding to the mesorectum and the prophylactic regional LN areas (PLNA), i.e. presacral, internal-external and common iliac, inguinal, ischio-rectal fossas and ilio-obturator LN; CTV2 created by adding a 5–15 mm margin around the GTV. Five to 10 mm margins were added to create the planned target volume (PTV).

IMRT procedures were volumetric arc-RT or helical Tomotherapy©, delivered in one course with a simultaneous integrated boost or in two courses with or without a two week gap. A gap was defined as a split between the two courses of treatment (planed in the majority of cases) whereas a break (temporary or definitive) was non-expected and occurred during a course.

The dose to the CTV1 was 45–50 Gy, with five 1.8 or 2 Gy daily fractions per week. A boost of 15–20 Gy was delivered to the CTV2 by external-beam RT or brachytherapy (BT). An additional intermediate dose level of 9 Gy could be delivered to the involved LN.

According to the French recommendations, patients with advanced ASSC (tumor $\geq$3–4 cm, or LN involvement) received concomitant chemotherapy, two cycles of MMC (10 mg/m^2) and a continuous infusion of 5-FU (1000 mg/m^2) from day 1 to day 5, on the first and the last weeks of the RT. Other chemotherapy regimens could be used, depending on patient comorbidities or ongoing clinical trials.

Follow-up

Clinical outcomes were evaluated by physical examination within three months after the end of the treatment, then every four months for two years, every six months for five years then yearly. Computed tomography (CT) and/or positron emission tomography (PET)-CT were performed to evaluate regional and distant responses, while endoscopic ultrasound and/or magnetic resonance imaging (MRI) were conducted for local response. Biopsies were performed for patients with partial response or progression.

Local recurrence (LR) was defined as the persistence or recurrence of disease within the anus and regional recurrence (RR) as the persistence or recurrence of disease elsewhere in the pelvis or in the inguinal nodes.

Endpoints

The delineation quality of each 14 right and left-side PLNA was analyzed and compared to the published contouring atlas [17–19] to be classified as "compliant" or "non-compliant" (Appendix 1). The compliance analysis was based on a qualitative variable, defined as follows:

Compliant delineation	Non-compliant delineation
The PLNA analyzed was *delineated* **AND** *All the delineation criteria* listed in Appendix 1 for the PLNA analyzed were respected	The PLNA analyzed was *not delineated*[*] **OR** *One or more* compliance criteria listed in Appendix 1 for the PLNA analyzed were not respected

[*]All PLNA had to be delineated whatever the disease stage.

For patients with a LRR, the recurrence imaging was integrated into the treatment-planning system (Eclipse®v11 in Nancy; Raystation® 5 in Nantes) and fused with the planning-CT, associating rigid and soft tissues registrations (protocol in Appendix 2).

The recurrence volume (V_{recur}) was then delineated on the planning-CT and determined to be "in-field" (if $\geq$95% was within the 95% isodose), "marginal" (if 20–95% was within the 95% isodose), or "out-of-field" (if <20% was within the 95% isodose).

Statistical analysis

Statistical analysis used SAS software (SAS Institute Inc., Cary, NC). Statistical significance was defined as $p < 0.05$.

OS was defined as the time between the first day of RT (D1) and the death (all causes). Surviving patients were censored at the date of last follow-up or five years after D1. Disease Free Survival (DFS) was defined as the date of local, regional or metastatic recurrence or death, whichever occurred first. Definitive colostomy incidence was defined as the time between D1 and the date of definitive colostomy occurrence. LRR incidence was defined as the time between D1 and the date of first local or regional recurrence. LR was defined as the time between D1 and the date of local recurrence. RR was defined as the time between D1 and the date of regional recurrence. Only the first recurrence occurring locally or in the same nodal site was analyzed.

Kaplan–Meier method was used to describe outcomes. The association between outcomes and prognostic factors was investigated using bivariate and multivariate Cox proportional hazard models. The results were expressed as a hazard ratio (HR) [95% confidence interval (CI)]. Quantitative variables were transformed into binary variables by assessment of known clinical significance. The proportional hazard assumption's validity was checked by determining the scaled Schoenfeld residuals. All variables with a p-value < 0.05 in the bivariate Cox model were introduced in a multivariate Cox model with backward selection at $p = 0.05$. Results of the final multivariate models are presented as the adjusted HR [95% CI].

Results

Patients and tumor characteristics (Table 1)

One hundred and sixty-five patients were included and analyzed. Fifty-two percent of the tumors were T3 or T4. Two patients with stage IV disease (periaortic LN involvement) were treated with curative intent. Sixty percent of patients were N1–N3, and 32.1%hadinguinal node involvement. The median number of involved LN per patient was 1 (from 0 to 9), and 37% had $\geq$2 involved LN.

Treatment and delineation characteristics (Tables 2a and 2b)

Median overall treatment time (OTT) was 63 days (15–194). One hundred and thirty (78.8%) patients had concomitant chemotherapy including 97 (74.6%) using MMC. The median prophylactic dose to the pelvis was 45 Gy (19.8–52.5) and the median dose to the primary tumor was 65 Gy [19.8–70]. A gap >3 days was performed for 124 (75.1%) patients, with a median time of 14.5 days [5–165]. Forty-seven (28.5%) patients received brachytherapy.

GTV T was delineated for 83 (74.8%) patients, excluding patients who received BT boost or who had initial surgical resection. The margin from GTV T to CTV2 T was $\leq$0.5 cm for 60.3% of patients. The margin from CTV2 T to PTV2 T was >0.5 cm for 73.9% of patients. GTV N was delineated for 55 (70.5%) patients, and the

Table 1
Patient and tumor characteristics at diagnosis (*N* = 165).

Characteristics		
Patient characteristics		
Female gender		130 (78.8%)
Age (years). Median (range)		62.33 (34.7–88.1)
<65 years		98 (59.4%)
≥65 years		67 (40.6%)
Performance status	0	79 (47.9%)
	1	76 (46.1%)
	2	9 (5.4%)
	3	1 (0.6%)
Immunodepression*		7 (4,2%)
Active smoking		43 (26.2%)
Tumor characteristics		
Tumor localization	Anal canal	147 (89.1%)
	Anal margin	18 (10.9%)
T stage	T1	21 (12.7%)
	T2	57 (34.6%)
	T3	52 (31.5%)
	T4	35 (21.2%)
N stage	N0	66 (40.0%)
	N1	29 (17.6%)
	N2	36 (21.8%)
	N3	34 (20.6%)
Topography of the involved LN	Mesorectum	68 (41.2%)
	Inguinal	53 (32.1%)
	Internal iliac	21 (12.7%)
	External iliac	21 (12.7%)
	Presacral	18 (10.9%)
	Common iliac	6 (3.6%)
	Obturator	6 (3.6%)
	Periaortic	2 (1.2%)
	Ischiorectal fossa	1 (0.6%)
Involved LN per patient, *median (range)*		1 (0–9)
Patients with ≥2 involved LN		61 (37.0%)
Tumor size (mm), *median (range)*		45 (10–112)
Ulcerated lesion		22 (13.3%)
Keratinization△	Yes	53 (42.7%)
	Moderate	42 (33.9%)
	No	29 (23.4%)
Differentiation△	Well-differentiated	45 (34.3%)
	Moderately differentiated	52 (39.7%)
	Poorly differentiated	34 (26.0%)
HPV Status	Positive (p16+)	60 (36.4%)
	Negative	4 (2.4%)
	Not investigated	101 (61.2%)

Results expressed as frequency and percentage, unless otherwise indicated.
*Immunodepression = HIV positive patients (*n* = 4) and immunosuppressive therapy (*n* = 3).
LN = Lymph Nodes. HPV: Human Papilloma Virus.
△Forty-one (24.9%) missing for keratinization. Thirty-four (20.6%) missing for tumor differentiation grading.

Table 2a
Treatment characteristics (*N* = 165).

Treatment characteristics	
Pretreatment colostomy	4 (2.4%)
Initial surgical resection	14 (8.5%)
R0 surgery	2 (14.3%)
R1 surgery	12 (85.7%)
Concomitant chemotherapy*	130 (78.8%)
5FU + MMC	86 (66.2%)
5FU + Cisplatin	23 (17.7%)
Capecitabine + MMC	10 (7.7%)
Carboplatin + 5FU	3 (2.3%)
Other**	8 (6.1%)
Completed chemotherapy treatment*	101 (77.7%)
Overall treatment time, *median (range)*	63 (15–194)
Gap (>3 days)	124 (75.1%)
Number of days, *median (range)*	14.5 (5–165)
Temporary breaks (>3 days)	19 (11.5%)
Number of days, *median (range)*	7 (4–46)
Definitive breaks	8 (4.8%)
Anal tumor boost using Brachytherapy	47 (28.5%)
Anal tumor total dose (Gy), *median (range)*	65 (19.80–70)
Prophylactic dose to pelvis (Gy), *median (range)*	45 (19.80 – 52.50)
Patients with boost to involved LN	78 (47.3%)
Involved LN total dose (Gy), *median (range)****	64.80 (54–67)

Results expressed as frequency and percentage, unless otherwise indicated.
*In 130 patients who had concomitant chemotherapy
**Capecitabine (*n* = 4); Capecitabine + Cisplatin (*n* = 1); 5-FU alone (*n* = 1); MMC alone (*n* = 1); 5FU + Cisplatin + Erbitux (*n* = 1).
***In 78 patients with a boost to one or more involved lymph node.
MMC = Mitomycin C.

Table 2b
Delineation characteristics (*N* = 165).

Delineation characteristics		
Initial tumor delineation△		
GTV T delineated		83(74.8%)
CTV2 T delineated		87 (78.4%)
GTV T to CTV2 T margin (cm)	0	31 (27.9%)
	0.1–0.5	36 (32.4%)
	0.6–1	29 (25.2%)
	>1	16 (14.4%)
CTV2 T to PTV2 T margin (cm)	≤0.5	29 (26.1%)
	>0.5	86 (73.9%)
Initial involved LN delineation		
Patients with involved LN not boosted	≥1 LN	35 (21.2%)
	≥2 LN	21 (12.7%)
GTV N delineated		55 (70.5%)
CTV2 N delineated		59 (75.6%)
GTV N to CTV2 N margin (cm)	0	19 (24.4%)
	0.1–0.5	39 (50.0%)
	>0.5	20 (25.6%)
CTV2 N to PTV2 N margin (cm)	≤0.5	23 (29.5%)
	>0.5	55 (70.5%)
Prophylactic lymph node area delineation		
Conforming for all PLNA		3 (1.8%)
NC for 1 or more PLNA		162 (98.2%)
NC for 10 or more PLNA		81 (49.1%)
Delineation's compliance		
	Presacral	117 (70.9%)
	Mesorectum	106 (64.2%)
	Internal iliac α	89 (54.4%)
	Inguinal α	75 (45.4%)
	External iliac α	53 (32.1%)
	Obturator α	53 (32.12%)
	Ischiorectal fossa α	46 (27.9%)
	Common iliac α	22 (13.3%)

Results expressed as frequency and percentage, unless otherwise indicated.
△One hundred and eleven patients analyzable for tumor delineation, excluding patients with a BT boost and initial surgical resection.
αTaking into account left-side and right-side PLNA.
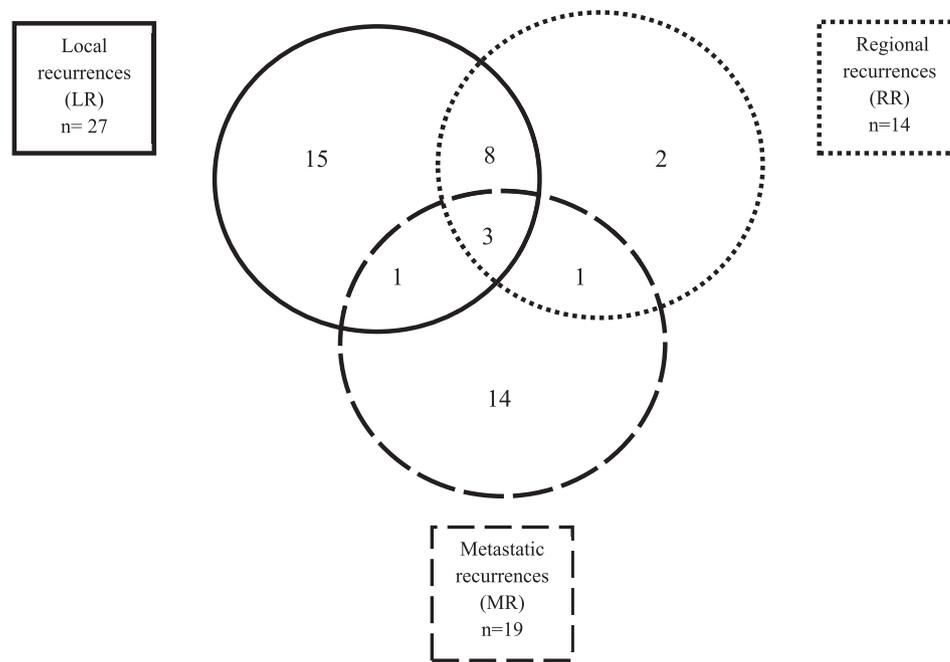LN: lymph node; NC: non-conforming; PLNA: prophylactic lymph node area.

margin to CTV2 N was ≤0.5 cm for 74.4% of patients. The margin from CTV2 N to PTV2 N was >0.5 cm for 70.5% of patients.

Three patients (1.8%) had the correct delineation for all of the PLNA as recommended and 81 (49.1%) patients had 10 or more PLNA that were non-compliant (NC) for delineation. Inguinal, external iliac, obturator, ischiorectal fossas, and common iliac areas were the PLNA that were most frequently NC.

Survival and clinical outcomes

The median follow-up was 33.8 months [9–111]. The two-and five-years OS were 81.5%, 95% confidence interval [74.2; 86.9] and 68.3% [59; 76] respectively, and cumulative incidence of colostomy were 13.7% [9; 20.5] and 15.9% [10.6; 23.4] respectively.

Fig. 1. Patterns of recurrences (*N* = 30 patients with local and/or regional recurrence, and 19 patients with metastatic recurrence). 30 patients presented a locoregional recurrence and 19 patients presented a metastatic recurrence: 27 patients presented a **local recurrence**: 15 isolated LR, 8 combining LR + RR, 1 combining LR + MR. 14 patients presented a **regional recurrence:** 2 isolated RR, 8 combining LR + RR, 1 combining LR + MR. 19 patients presented a **metastatic recurrence:** 14 isolated MR, 1 combining LR + MR, 1 combining RR + MR. 3 patients had a combination of the three types of recurrence.

The two- and five-years DFS were 70.9% [63.2; 77.3] and 60.8% [51.7; 68.7] respectively.

Distant metastases occurred in 19 (11.5%) patients. The two- and five-years cumulative incidences of metastasis recurrence were 10.8% [6.8; 16.8] and 12.8% [8.3; 19.5] respectively. Metastatic sites were liver (*n* = 12), lung (*n* = 8), and bone (*n* = 3).

Thirty patients developed LRR: 27locally and 14in pelvic nodes (Fig. 1). Of 27 LR, 21 were salvaged by abdomino-perineal resection. The two- and five-year cumulative incidences of LRR were 14.5% [12.9; 25.3] and 19.3% [13.7; 26.7], respectively. The median time from treatment to LRR was 9 months [3–60]. Of 30 LRR, 28 (93.3%) occurred in the first two years following the initial treatment.

Significant predictive factors of OS and LRR are presented in Table 3.All predictive factors are listed in Supplementary results 2. In multivariate analysis, predictive factors of poorer OS were age >65 years (HR 2.43 [1.29; 4.60]), and immunodepression (HR 5.05 [1.72; 14.80]). Performance status ≥2 (HR 3.82 [1.31; 11.09]) and active smoking (HR 2.31 [1.11; 4.82]) were predictors of a higher incidence of LRR. In the subgroup of patients with concomitant chemotherapy, MMC-based regimens were associated with better locoregional control in multivariate analysis (HR = 0.39 [0.17; 0.86]) after adjustment on performance status and smoking status.

Topography and predictive factors of local recurrence (LR)

Twenty-seven patients had LR: 15 isolated LR, 1 local and metastatic, 8 local and regional and 3 local, regional, and metastatic (Fig. 1). Two- and five-year cumulative incidences of LR were 16.4% [11.3; 23.3] and 17.5% [12.2; 24.8] respectively.

Of the 27 LR, 20 (74%) were in-field, 4 (15%) marginal, 2 (7%) out-of-field, and one treated with BT boost with iridium wires was not analyzable due to the absence of a planning CT.

The significant predictive factors of LR are presented in Table 3. In multivariate analysis, predictors of LR were a performance sta-

tus ≥2 (HR 4.48 [1.52; 13.19]) and active smoking (HR 2.43 [1.12; 5.28]). In the subgroup of patients with concomitant chemotherapy, regimens using MMC were associated with better local control in multivariate analysis (HR = 0.36 [0.16; 0.81]) in addition to the other predictive factors.

The margins applied from GTVT to CTV2 T and from CTV2 T to PTV2 T were not predictive factors for LR (see Supplementary results 3).

Topography and predictive factors of regional recurrence (RR)

A total of 14 patients developed RR, with a median of 2 regional recurrence sites (RS) per patient (from 1 to 6) corresponding to 33 RS. Geographical distribution of the RS is presented in Table 4. The two- and five-years cumulative incidences of RR were both 9.4% [5.7; 15.4].

The RS were mostly located in inguinal (*n* = 12; 36.4%), external iliac (*n* = 7; 21.1%), presacral (*n* = 4; 12.1%), and common iliac (*n* = 3; 9.1%) LN, representing 78.7% of the regional RS. Eighteen RS (54.5%) were in-field, 6 (18.2%) marginal, and 9 (27.3%) out-of-field.

Significant predictive factors of RR are presented in Table 3. In multivariate analysis, immunodepression (HR 7.25 [1.54; 34.20]), initial involvement of external iliac LN (HR 7.89 [2.54; 24.56]), and non-compliant delineation for ≥10 PLNA (HR 9.09 [1.96; 42.15]) remained significant.

Margins applied from GTVN to CTV2 N and from CTV2 N to PTV2 N were not predictive factors for RR (see Supplementary results 4).

Discussion

Feasibility of IMRT for ASCC treatment has been demonstrated, given similar survival outcomes with a favorable toxicity profile in comparison with 3D-RT [10,11,14,20]. However, an inaccurate delineation could increase the risk of failure due to target miss.

Table 3
Significant predictive factors of overall survival (OS), locoregional recurrence (LRR), local (LR) and regional recurrences (RR) in univariate and multivariate Cox proportional hazard models.

Parameters		Univariate analyses		Multivariate analyses	
		HR (95% CI)	p	HR (95% CI)	p
Predictive factors of OS					
Age (years)	<65				
	≥65	2.15 [1.16; 3.98]	0.015	2.43 [1.29; 4.60]	0.006
Immunodepression	No	1			
	Yes	3.70[1.30; 10.51]	0.014	5.05 [1.72; 14.80]	0.003
Definitive break	No	1			
	Yes	3.25 [1.15; 9.13]	0.025	-	
Anal tumor boost technique	External RT	1			
	Brachytherapy	0.42 [0.18; 0.95]	0.036	-	
Anal tumor total dose	<64 Gy	1			
	≥64 Gy	0.49 [0.25; 0.96]	0.038	–	
Predictive factors of LRR					
Performance Status	<2	1		1	
	≥2	3.01 [1.05; 8.66]	0.041	3.82 [1.31; 11.09]	0.014
Active smoking	No	1		1	
	Yes	2.22 [1.07; 4.61]	0.033	2.31 [1.11; 4.82]	0.026
Differentiation[Δ]	Poorly differentiated	1			
	Moderately differentiated	2.30 [0.62; 8.50]	0.211	-	
	Well differentiated	4.31 [1.25; 14.89]	0.021		
Chemotherapy agents[*]	No MMC	1		–	
	MMC	0.39 [0.17; 0.86]	0.021		
Predictive factors of LR					
Performance status	<2	1		1	
	≥2	3.46 [1.19; 10.07]	0.023	4.48 [1.52; 13.19]	0.007
Immunodepression	No	1			
	Yes	3.54 [1.06; 11.83]	0.040	-	
Active smoking	No	1		1	
	Yes	2.30 [1.06; 4.97]	0.034	2.43 [1.12; 5.28]	0.025
DifferentiationΔ	Poorly differentiated	1			
	Moderately differentiated	2.00 [0.53; 7.56]	0.304	-	
	Well differentiated	3.68 [1.05; 12.91]	0.042	-	
Chemotherapy agents[*]	No MMC	1		–	
	MMC	0.36 [0.16; 0.81]	0.014		
Anal tumor boost technique	External RT	1			
	Brachytherapy	0.28 [0.08; 0.95]	0.040	-	
Predictive factors of RR					
Immunodepression	No	1		1	
	Yes	4.46 [1.00; 19.97]	0.050	7.25 [1.54; 34.20]	0.012
Number of involved LN at diagnosis	<2	1			
	≥2	3.69 [1.24; 11.04]	0.019	–	
External iliac involvement at diagnosis	No	1		1	
	Yes	4.65 [1.55; 13.93]	0.006	7.89 [2.54; 24.56]	<0.001
Inguinal involvement at diagnosis	No	1			
	Yes	3.16 [1.10; 9.11]	0.003	–	
Keratinization[ΔΔ]	No	1			
	Yes	0.32 [0.11; 0.97]	0.044	–	
PLNA with NC delineation[α]	<10	1		1	
	≥10	5.77 [1.29; 25.78]	0.022	9.09 [1.96; 42.15]	0.005
Involved LN not boosted	0 or 1	1			
	≥2	3.30 [1.03; 10.52]	0.044	–	
Internal iliac delineation	Conforming	1			
	NC	4.20[1.17; 15.08]	0.027	–	

HR: Hazard ratio; 95% CI: 95% confidence interval; PLNA = prophylactic lymph node area; NC = non-conforming; MMC: Mitomycin C; LN = Lymph Nodes.
[*] In 130 patients who had concurrent CT, not included in multivariate analysis.
[Δ] Not included in multivariate analysis due to 34 (20.6%) missing values.
[ΔΔ] Not included in multivariate analysis due to 41 (24.9%) missing values.
[α] Distinguishing left-side and right-side of PLNA.

We tried to examine the patterns of failure obtained with IMRT, and to search for specific risk factors. We separately searched for local and regional recurrence risk factors, because the local and regional control challenges are different: a LR can benefit of salvage surgery, which offers remission in almost half of patients; whereas salvage treatment of RR is rarely successful and impacts on OS.

The two main studies (Das et al and Wright et al.) that reported the LRR topography are dated and used conformal-RT [6,7]. The lack of planning-CT did not permit to precisely estimate the dose delivered at the recurrence site at the time of treatment. Our study provides more precise information concerning the localization of

LRR against radiation fields; thanks to the soft-tissues registration that we have been able to perform between the recurrence imaging and the planning-CT. Table 5 compares our study to the literature. While the radiotherapy technic was different, the boundaries of radiation fields were relatively comparable to those of our study. According to theses limits, the whole pelvis included the external and internal iliac, obturator, mesorectal, presacral and ischiorectal fossas LN. When the superior border was placed at the L5-S1 inter-space, common iliac nodes were also included. Only the medial part of the inguinal lymph nodes was included. Furthermore, the doses reported in these articles to the whole pelvis, anal tumor

Table 4
Topography of recurrences sites (*N* = 33).

Type of recurrence				
Recurrence sites	In-field	Marginal	Out-of-field	Total (%)
Inguinal	7	2	3	12 (36.4%)
External iliac	5	1	1	7 (21.1%)
Presacral	2	2		4 (12.1%)
Common iliac		1	2	3 (9.1%)
Internal iliac	2			2 (6.1%)
Periaortic			2	2 (6.1%)
Mesorectum	2			2 (6.1%)
Obturator			1	1 (3.0%)
Ischiorectal fossa				0 (0%)
TOTAL (%)	18 (54.5%)	6 (18.2%)	9 (27.3%)	33 (100%)

Table 5
Comparison between locoregional recurrence characteristics in our study and in Literature.

Characteristics		Authors		
		Das and al (2007)	Wright and al (2010)	Our study
Number of patients		**167**	**180**	**165**
Radiotherapy technique		**Conventional**	**Conventional**	**IMRT**
Radiation fields boundaries∞				
Superior border		Bottom of sacroiliac joints before the year 1999, and L5-S1 interspace from 1999		NA
Inferior border		At least 3 cm below the inferior border of the tumor or the anal verge		NA
Lateral border		1.5–2.0 cm outside the pelvic brim		NA
Posterior border		Behind the sacrum		NA
Anterior border		0–2 cm behind the pubic symphysis		NA
Doses delivered				
Median dose to "whole pelvis" (Gy), Range#		30,6 (NA)	30,6(0–45)	45(19.80–52.50)
Median dose to "true pelvis" (Gy), Range#		50,4/45(NA)**	45(0–46,8)	–
Median dose to anal tumor (Gy), Range		55(NA)	45(30 – 59,4)	65(19.80–70)
Median dose to involved nodes N+ (Gy), Range		55(NA)	45(0 – 50,4)	64,8(54–67)
Locoregional recurrences. Number of patients (%)		**24 (14,4%)**	**45 (25%)**	**30 (18,2%)**
Local recurrences. Number of patients (% of LRR)		**18 (75%)**	**35 (77,8%)**	**27 (90%)***
	IF	15 (83,3%)	NA	20 (74%)
	M	2 (11,1%)	NA	4 (15%)
	OF	1 (5,6%)	NA	2 (7%)
Regional recurrences. Number of patients (% of LRR)		**6 (25%)**	**20 (44,4%)**	**14 (46,7%)**
Regional recurrence sites. Number of sites (%)Δ		6 (100%)	19 (100%)	33 (100%)
	IF	4 (66%)	14 (74%)	18 (55%)
	M	1 (17%)	3 (16%)	6 (18%)
	OF	1 (17%)	2 (10%)	9 (27%)

IMRT: Intensity modulated radiation therapy.
NA: not available.
IF: in-field; M: Marginal; OF: out-of-field.
∞Only for conformal-RT.
**Median dose to true pelvis: 50,4 Gy before the year 2003 and 45 Gy from 2003.
*One patient treated with BT boost with iridium wires was not analyzable due to the absence of a planning CT.
ΔConsidering all regional recurrence sites except ischiorectal fossa.
#Whole and true pelvis concept in conformal-RT only.

and involved nodes were significantly lower than in our study (Table 5). Our recurrence rates were broadly similar to the literature: 18,2% of patients presented a LR that remained mainly local (90% of recurrences). RR occurred in only 8% of patients, and were mostly following a LR.

The topographies of LR were also similar to those described by Das et al. and Wright et al. manuscripts, and remained mainly "in-fields", despite a higher median dose delivered to the primary tumor in our population. In addition, we did not find any relationship between margins applied around the target volume and local control rates, even when they were zero or very low, thereby suggesting the absence of a direct link with the IMRT technique. In view of these reports, the main question seems to remain the intrinsic tumor radiosensibility, more than the radiation dose. Indeed, the dose–response curve of ASCC is unknown, and there is actually no recommendation about the "right" dose to deliver. The radiation dose delivered to the tumor can significantly vary between countries, with, *a priori*, the same local control rates.

The UK ongoing phase III "PLATO" trial, consisting of 3 distinct anal cancer trials and analyzing different dose levels depending on the disease stage, will probably give us guidance. To improve local control rates, we need to understand how to improve biological effectiveness of RT. It could be assumed that biological effectiveness could be improved with higher dose by fraction, delivered by IMRT with simultaneous integrated boost technique. Furthermore, in our study, and in concordance with the literature [21,22], brachytherapy boost seems to increase local control for early stages as well as OS. Finally, the impact of immune status on local control highlighted by our study, associated to the frequent relation between ASCC and infection with oncogenic virus HPV, suggest the role of the immune environment in tumor response. As suggested by many studies emerging, the association of radiotherapy and immunotherapy could be promising for ASCC treatment. In any event, a close follow-up after treatment, combining physical examination and several imaging, endoscopic ultrasound, MRI et PET-CT, repeated every 4 or 6 months within the first 2 years, appears

essential to allow early diagnosis of local recurrences that can then be managed by salvage surgery.

RR occurred mainly in inguinal, external iliac, presacral and common iliac regions, as described in the literature [6,7]. However, while Das et al. and Wright et al. found respectively 34% and 26% of marginal and out-of-field RR, we observed an increased rate of 45%. We can then question the relationship that may exist between the topography of these recurrences and the delineation, i.e. IMRT precision. Indeed, with the IMRT technique, only delineated volumes are treated, unlike conformational-RT in which larger volumes received the prescription dose. This hypothesis is supported by the importance of PLNA's delineation for regional control highlighted by our study. We showed that not following the delineation recommendations seems to significantly increase the RR risk. In our series, almost half of patients had non-compliant delineation for ten or more PLNA, suggesting that the delineation's recommendations are not sufficiently followed. Furthermore, the detection of LN involvement at diagnosis also seems to be a determining factor for regional control. Indeed, we highlighted that the number and the topography of these involved LN could affect the regional control. In case of LN involvement, a higher dose or "boost" should be delivered to these LN. It can be difficult to affirm the LN involvement. It is commonly the case for small LN ($\leq$1 cm), or with low hypermetabolism in PET-CT, or when a near-complete regression is observed after the first time of pelvic irradiation. In our study, we demonstrated that not boosting these suspect LN could increase the RR rate. Despite the progress in radiology and the common use of PET-CT for the disease assessment, the early detection of infraclinic LN involvement remains problematic. PET-CT has a poor resolution and cytoponction has a poor sensitivity. Newest imaging techniques, such as sentinel LN technic or ultrasmall superparamagnetic iron oxide particles MRI (USPIO) should provide a better involved LN detection, but their routine feasibility needs to be demonstrated [23–29].

Our study has biases, mainly due to its retrospective nature. It has enabled us to obtain a population of 165 patients which is a significant number compared to the rarity of this disease. Furthermore, we did not take account of differences existing between the three experts groups when analyzing the delineation's compliance. Indeed, for AGITG, the inguinal nodes irradiation is optional for T1N0 stages. The same for Siriade, which proposes to reserve the presacral and common iliac irradiation to T3–T4 and N+ stages. Taking account of these features would have made the delineation analysis too complex and would have increased the risk of error.

In conclusion, the prognosis of ASCC resides in locoregional control improvement. Two mechanisms of regional recurrence are likely: tumor spreading from primary tumor and initial infraclinic node progression. Considering the first mechanism, management of local control remains necessary, probably by improving the radiobiological efficacy of treatments. Concerning the second mechanism, new predictive factors have been found highlighting that the delineation's quality of PLNA seems essential for regional control, associated with a complete and improved initial assessment.

Conflict of interest

The authors of this paper have no conflict of interest to declare.

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.10.021.

References

[1] Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer 2010;102:1123–8.

[2] Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997;15:2040–9.

[3] Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996;14:2527–39.

[4] Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB, et al. Long-term update of US GI intergroup RTOG 98–11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012;30:4344–51.

[5] James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. Lancet Oncol 2013;14:516–24.

[6] Das P, Bhatia S, Eng C, Ajani JA, Skibber JM, Rodriguez-Bigas MA, et al. Predictors and patterns of recurrence after definitive chemoradiation for anal cancer. Int J Radiat Oncol 2007;68:794–800.

[7] Wright JL, Patil SM, Temple LKF, Minsky BD, Saltz LB, Goodman KA. Squamous cell carcinoma of the anal canal: patterns and predictors of failure and implications for intensity-modulated radiation treatment planning. Int J Radiat Oncol 2010;78:1064–72.

[8] Vieillot S, Fenoglietto P, Lemanski C, Moscardo CL, Gourgou S, Dubois J-B, et al. IMRT for locally advanced anal cancer: clinical experience of the Montpellier Cancer Center. Radiat Oncol 2012;7:45.

[9] Vendrely V, Henriques de Figueiredo B, Rio E, Benech J, Belhomme S, Lisbona A, et al. French multicentre clinical evaluation of helical TomoTherapy® for anal cancer in a cohort of 64 consecutive patients. Radiat Oncol [Internet] 2015;10. Available from: http://www.ro-journal.com/content/10/1/170.

[10] Brooks CJ, Lee YK, Aitken K, Hansen VN, Tait DM, Hawkins MA. Organ-sparing intensity-modulated radiotherapy for anal cancer using the ACTII schedule: a comparison of conventional and intensity-modulated radiotherapy plans. Clin Oncol 2013;25:155–61.

[11] Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-c for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol 2013;86:27–33.

[12] Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: Toxicity and clinical outcome. Int J Radiat Oncol 2005;63:354–61.

[13] Chen Y-J, Liu A, Tsai PT, Vora NL, Pezner RD, Schultheiss TE, et al. Organ sparing by conformal avoidance intensity-modulated radiation therapy for anal cancer: Dosimetric evaluation of coverage of pelvis and inguinal/femoral nodes. Int J Radiat Oncol 2005;63:274–81.

[14] Chuong Michael D, Freilich Jessica M, Hoffe Sarah E, Fulp William, Weber Jill M, Almhanna Khaldoun, et al. Radiation therapy vs. 3d conformal radiation therapy for squamous cell carcinoma of the anal canal. Gastrointest Cancer Res 2013;6:39–45.

[15] Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol 2008;70:660–5.

[16] Eisbruch A, Marsh LH, Dawson LA, Bradford CR, Teknos TN, Chepeha DB, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol 2004;59:28–42.

[17] Ng M, Leong T, Chander S, Chu J, Kneebone A, Carroll S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. Int J Radiat Oncol 2012;83:1455–62.

[18] Myerson RJ, Garofalo MC, El Naqa I, Abrams RA, Apte A, Bosch WR, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiat Oncol 2009;74:824–30.

[19] Azria D. RCMI canal anal. In: Site Internet de radioanatomie et d'autoenseignement à la délineation (SIRIADE). Paris: Afcor,SFRO,SFJRO [Internet]. 2011; Available from: www.siriade.org.

[20] Dasgupta T, Rothenstein D, Chou JF, Zhang Z, Wright JL, Saltz LB, et al. Intensity-modulated radiotherapy vs. conventional radiotherapy in the treatment of anal squamous cell carcinoma: A propensity score analysis. Radiother Oncol 2013;107:189–94.

[21] Cordoba A, Escande A, Leroy T, Mirabel X, Coche-Dequant B, Lartigau E. Low-dose-rate interstitial brachytherapy boost for the treatment of anal canal cancers. Brachytherapy 2017;16:230–5.

[22] Hannoun-Levi J-M, Ortholan C, Resbeut M, Teissier E, Ronchin P, Cowen D, et al. High-dose split-course radiation therapy for anal cancer: outcome analysis regarding the boost strategy (CORS-03 Study). Int J Radiat Oncol 2011;80:712–20.

[23] Damin DC, Rosito MA, Schwartsmann G. Sentinel lymph node in carcinoma of the anal canal: a review. Eur J Surg Oncol EJSO 2006;32:247–52.

[24] de Jong JS, Beukema JC, van Dam GM, Slart R, Lemstra C, Wiggers T. Limited value of staging squamous cell carcinoma of the anal margin and canal using the sentinel lymph node procedure: a prospective study with long-term follow-up. Ann Surg Oncol 2010;17:2656–62.

[25] Nardi PD. New approach to anal cancer: Individualized therapy based on sentinel lymph node biopsy. World J Gastroenterol 2012;18:6349.

[26] Tehranian S, Treglia G, Krag DN, Kakhki VRD, Zakavi SR, Sadeghi R, et al. Sentinel node mapping in anal canal cancer: systematic review and meta-analysis. J Gastrointestin Liver Dis 2013;22.

[27] Wáng YXJ, Idée J-M. A comprehensive literatures update of clinical researches of superparamagnetic resonance iron oxide nanoparticles for magnetic resonance imaging. Quant Imaging Med Surg 2017;7:88–122.

[28] Will O, Purkayastha S, Chan C, Athanasiou T, Darzi AW, Gedroyc W, et al. Diagnostic precision of nanoparticle-enhanced MRI for lymph-node metastases: a meta-analysis. Lancet Oncol 2006;7:52–60.

[29] Wu L, Cao Y, Liao C, Huang J, Gao F. Diagnostic performance of USPIO-enhanced MRI for lymph-node metastases in different body regions: a meta-analysis. Eur J Radiol 2011;80:582–9.