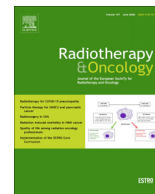




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Original Article

Concurrent cisplatin and dose escalation with intensity-modulated radiotherapy (IMRT) versus conventional radiotherapy for locally advanced head and neck squamous cell carcinomas (HNSCC): GORTEC 2004-01 randomized phase III trial



Yungan Tao^{a,*}, Anne Auperin^{a,b}, Pierre Blanchard^a, Marc Alfonsi^c, Xu-Shan Sun^d, Michel Rives^e, Yoann Pointreau^f, Joël Castelli^g, Pierre Graff^{e,h}, Stéphanie Wong Hee Kamⁱ, Juliette Thariat^{j,k}, Ovidiu Veresezan^l, Steve Heymann^m, Sophie Renard-Oldrini^h, Cédrik Lafond^f, Alexandre Cornely^a, Odile Casiraghi^a, Pierre Boisselier^{g,n}, Michel Lapeyre^{h,o}, Julian Biau^{o,1}, Jean Bourhis^{a,p,*}

^aGustave-Roussy Cancer Campus Grand Paris; ^bINSERM 1018, Villejuif; ^cInstitut Sainte Catherine, Avignon; ^dHopital Nord Franche-Comté de Montbéliard & CHRU de Besançon; ^eInstitut Claudius Regaud, Toulouse; ^fCentre Jean Bernard, Le Mans; ^gCentre Eugène Marquis, Rennes; ^hCentre Alexis Vautrin, Nancy; ⁱAP-HM Hôpital de la Timone, Marseille; ^jCentre Antoine Lacassagne, Nice; ^kCentre François Baclesse, Caen; ^lCentre Henri Becquerel, Rouen; ^mClinique Sainte Anne, Strasbourg; ⁿInstitut du Cancer de Montpellier; ^oCentre Jean Perrin, Clermont-Ferrand, France; and ^pCHUV Lausanne, Switzerland

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ABSTRACT

Background: Concurrent chemoradiotherapy (CRT) is the standard of care (SoC) in locally advanced (LA) head and neck squamous cell carcinomas (HNSCC). This trial was designed to test whether dose-escalated IMRT and cisplatin could improve locoregional control without increasing complications over 3D-radiotherapy.

Methods: Patients were randomized between 70 Gy/35F in 7 weeks with 3D-RT (Arm A) versus 75 Gy/35F with IMRT (Arm B). Both arms received 50 Gy in 25 fractions followed by a sequential boost of 20 Gy/10F in Arm A and 25 Gy/10F to gross tumor volume in Arm B, as well as 3 cycles of cisplatin at 100 mg/m² during RT. The primary endpoint was locoregional progression (LRP).

Results: 188 patients were randomized: 85% oropharynx and 73% stage IVa. P16 status was documented for 137 oropharyngeal tumors with P16+ in 53 (39%) patients; and 90% were smokers. Median follow-up was 60.5 months. Xerostomia was markedly decreased in arm B ($p < 0.0001$). The 1-year grade ≥ 2 xerostomia (RTOG criteria) was 63% vs 23% and 3-year 45% vs 11% in arms A and B, respectively. Xerostomia LENT-SOMA scale was also reduced in arm B. Dose-escalated IMRT did not reduce LRP with an adjusted HR of 1.13 [95%CI = 0.64–1.98] ($p = 0.68$). Survival was not different (adjusted HR: 1.19 [95%CI = 0.78–1.81], $p = 0.42$). No interaction between p16 and treatment effect was found.

Conclusion: Dose-escalated IMRT did not improve LRC in LA-HNSCC patients treated with concomitant CRT over standard 3D-RT. This trial reinforces the evidence showing IMRT reduces xerostomia in LA-HNSCC treated with radiotherapy.

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Concurrent chemoradiotherapy (CRT) is a well-established standard-of-care (SoC) in locally advanced (LA) head and neck squamous cell carcinomas (HNSCC) as shown in the update of

MACH-NC database (8% survival benefit at 5 years) [1–3]. The most commonly adopted standard CRT regimen is combination of conventional fractionated radiotherapy (70 Gy/7 weeks) with high-dose cisplatin (100 mg/m² every 3 weeks).

Intensity-modulated radiotherapy (IMRT) can spare major salivary glands [4] and other organs at risk (OAR), while conforming high doses to the shape of target volumes [5]. The phase III PARSPORT trial in HNSCC showed that IMRT significantly reduced the incidence of xerostomia and led to improvements in quality of life [6].

* Corresponding authors at: Department of Radiation Oncology, Gustave-Roussy Cancer Campus Grand Paris, 114 Rue Edouard Valliant, Villejuif, France (Y. Tao). Service of Radiation Oncology, Centre Hospitalier universitaire Vaudois, Bugnon 46, Lausanne 1011, Switzerland (J. Bourhis).

E-mail addresses: yungan.tao@gustaveroussy.fr (Y. Tao), jean.bourhis@chuv.ch (J. Bourhis).

¹ Co-last author, equally contributed.

IMRT could in theory improve locoregional control (LRC) compared with 2D radiotherapy (RT) or conformal 3D-RT by better conformation of irradiation to target volume [7]. While there is a well-established dose effect relationship for RT alone in these cancers, as suggested in randomized trials by the improvement in local control with hyperfractionation schedules [8], it is not known whether this also applies to concurrent CRT. If so, IMRT could be useful for dose-escalation [5]. Indeed, studies and meta-analyses have shown that 80 Gy in 7 weeks could improve the probability of tumor control by 15 to 20% compared with conventional RT of 70 Gy [9]. The absolute survival benefit associated with hyperfractionation was 8.1% at 5 years, similar to the benefit of concomitant chemotherapy [3]. Moreover, the vast majority of relapses occur in gross tumor volume (GTV), hence justifying the dose increase within GTV.

In this context, we designed a randomized phase III trial in LA-HNSCC treated by RT and concurrent high dose cisplatin to compare dose-escalated IMRT to standard-dose 3D-RT. The hypothesis was that IMRT could reduce OAR dose allowing tumor dose increase to obtain better tumor control, while decreasing side effects, in particular salivary sequelae.

Methods

Study design

GORTEC 2004-01 study was a randomized multi-center phase III trial performed in 11 centres/hospitals within French head and neck oncology and radiotherapy group (GORTEC). The study was performed in accordance with good clinical practice guidelines, the Declaration of Helsinki, and was approved by an ethics committee (Kremlin Bicêtre Hospital, France).

Patients

All patients provided written informed consent.

The main inclusion criteria were >18 years, Karnofsky Performance Status (KPS) 80–100, non-previously treated stage III-IV (T1-T4, N0-N2, M0 according to UICC TNM 2002) histologically proven squamous cell carcinoma (SCC) of oral cavity and oro/hypopharynx, regardless of HPV status, with indication to receive ≥ 50 Gy to bilateral neck. Patients had adequate liver, renal, cardiac functions and adequate hematological blood counts allowing administration of high-dose cisplatin.

HPV status was evaluated by p16 immunohistochemistry for oropharyngeal cancer (OPC) with a centralized evaluation [10].

Procedures

Patients were randomized between 70 Gy in 7 weeks with conventional 3D-RT with parallel opposed fields based on CT-simulation (arm A) and 75 Gy with IMRT (arm B). Randomization was done by minimization on centers, T (T0-2 vs T3-4), N (N0 vs N1-2), subsite (hypopharynx vs oropharynx vs oral cavity) and unilateral or bilateral character of GTV, with a probability of 0.80 to assign the treatment which minimizes the imbalance.

Randomization was done centrally at the biostatistics service of Gustave Roussy Cancer Campus (Villejuif, France) using TENALEA software (NKI Amsterdam). Neither the physicians nor the patients were blinded to treatment-group assignment Fig. 1a.

Radiotherapy was prescribed in two sequential phases (Figs. 1b and 1c): 50 Gy/25 fractions (F) and 5 weeks to prophylactic PTV1, followed by a sequential boost of 20 Gy to PTV2 including initial GTV in arm A (2 Gy/F) or 25 Gy in arm B (IMRT: 25 Gy/10F) during 2 weeks. In both arms, 3 cycles of cisplatin at 100 mg/m² were administered every 3 weeks during RT.

Work-up before enrollment included physical examination, blood tests, head and neck CT or MRI, chest CT, and an endoscopy examination. Patients were assessed 3 months after treatment completion with physical examination and imaging studies (CT-scanning +/- MRI) and then with physical examination every 3 months for two years, and every 6 months thereafter.

Radiotherapy quality assurance was carried out by GORTEC's QA team. The criteria checked were: (1) that PTV2 included GTV; (2) that the dose to PTV1, PTV2, brainstem, spinal cord, and for arm B the dose to the parotids complied with accepted constraints.

Statistical analysis

The primary endpoint was loco-regional progression (LRP), defined as the time from randomization to locoregional failure as first event (even if associated with distant progression). Secondary endpoints were progression-free survival (PFS), overall survival (OS), distant progression (DP). The second cancer was not considered as progression.

Acute and late toxicities such as xerostomia were scored according to RTOG radiation morbidity scoring criteria. Late xerostomia was also evaluated using patient-reported symptoms scored with LENT-SOMA scale (subjective part).

The LRP rate with standard CRT was expected to be 40% at 2 years, i.e. LRC rate of 60%. In order to detect a hazard ratio (HR) of 0.56 (for illustration of this HR value, it corresponds to decrease in 2-year LRP from 40% to 25%), observing 109 LRP was needed with 85% power, assuming a two-sided type I error of 0.05. A total of 109 LRP was expected out of 310 patients (155 per arm). No interim analysis of efficacy was planned.

Cumulative incidences of LRP and DP were estimated within the framework of competing risk analysis [11]. PFS and OS were estimated using Kaplan-Meier method and 95% confidence intervals (95% CI) of yearly rates were estimated according to the Rothman method.

Crude HR and adjusted HR for T stage (2 categories: T0-2 vs T3-4), N stage (3 categories: N0 vs N1-2b vs N2c), p16 status (OPC p16 positive vs OPC p16 negative vs others), unilateral or bilateral character of GTV and centers (4 categories: one for each site that included ≥ 20 patients, one category for all sites that included 10–20 patients and one for sites that included ≤ 10 patients) were estimated using Cox model for PFS and OS and using Fine and Gray model for LRP.

Median follow-up was estimated with the reverse Kaplan-Meier method.

We compared between the two treatment groups the late toxicities (xerostomia according to RTOG criteria and to LENT-subjective scoring, mucosal toxicity, subcutaneous tissue toxicity, laryngeal toxicity, dysphagia and bone toxicity) in two categories of grade (none or grade 1 versus grade 2, 3 or 4, assessed according to RTOG criteria and to LENT-subjective scoring) from 1 year to 5 years after end of treatment, with a generalised linear model for binomial variables with a logit link.

Analyses were done with SAS version 9.4 and with R version 3.6.1 for competing risk analyses.

Results

Between September 2005 and January 2015, 188 patients were randomized, 94 in each arm (Fig. 1a). The accrual rate was much slower than expected; due to the fact that IMRT became standard of care in a growing number of centers and was only allowed in Arm B in the trial. As a consequence, the trial was discontinued after inclusion of 188 patients.

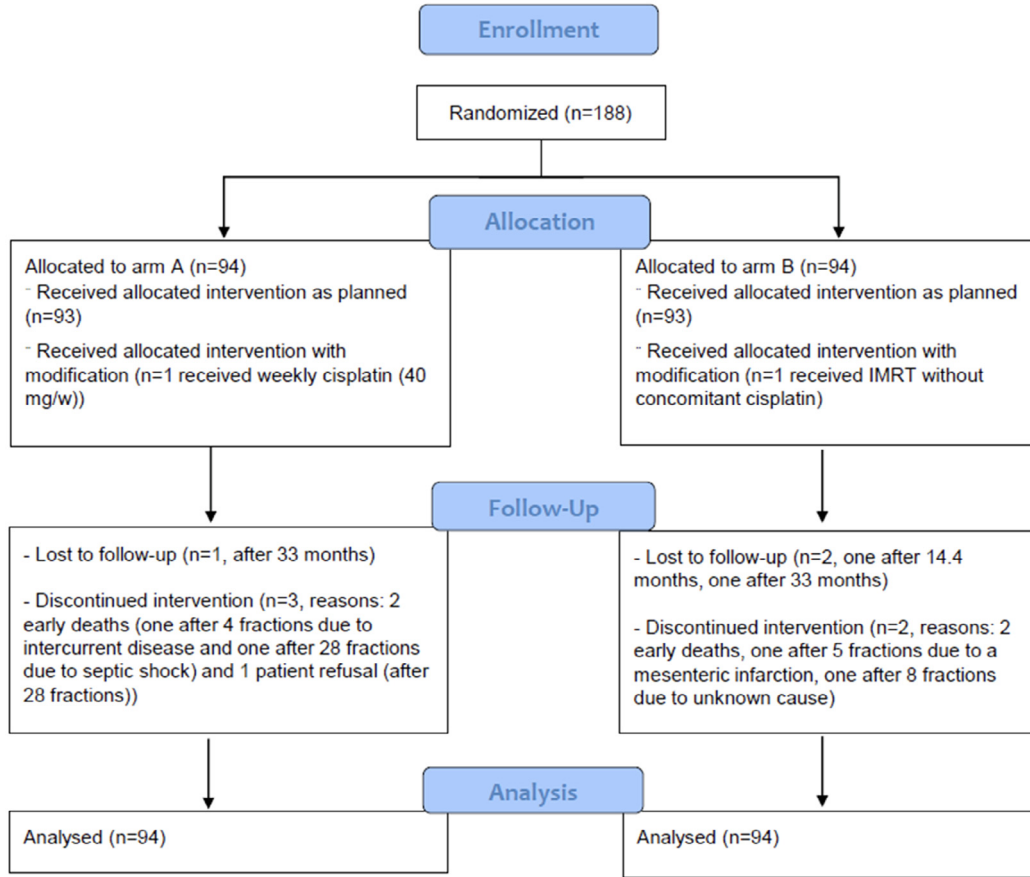


Fig. 1a. Trial profile.

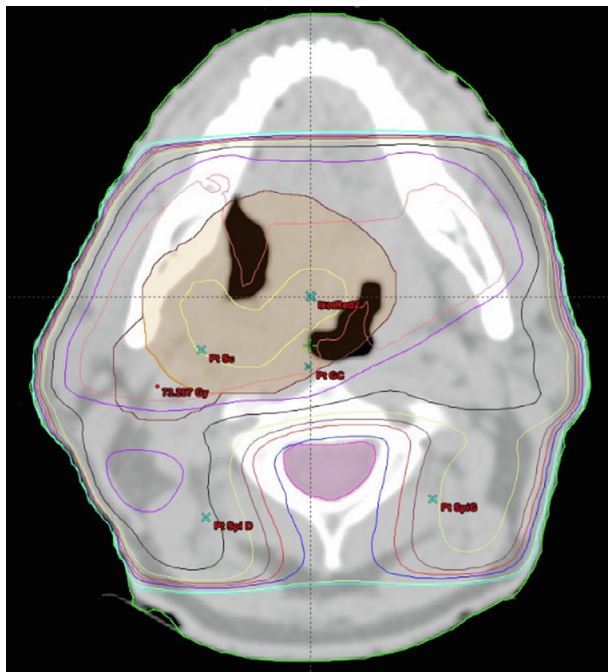


Fig. 1b. Dose wash of 3D-RT.

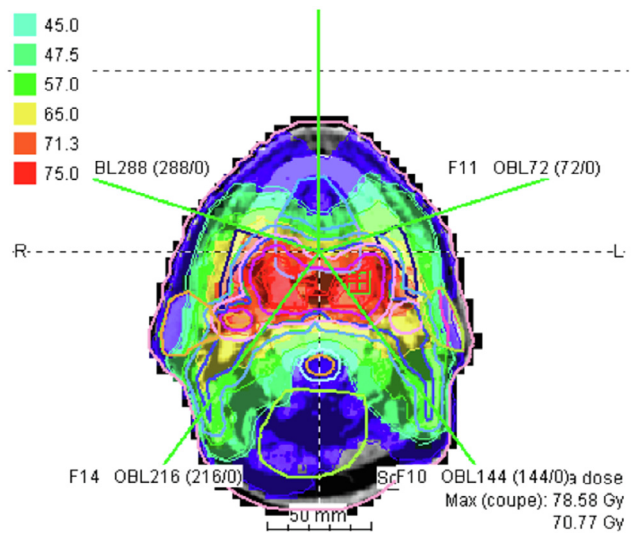


Fig. 1c. Dose wash of IMRT.

Initial characteristics of patients and tumor are presented in Table 1. 82% were males. Mean age was 59 years in arm A and 57 years in arm B. Tumor site was oropharynx in 85% of patients.

The majority of patients had stage IVa (72% in arm A and 73% in arm B). Overall, p16 was evaluable in 137 of 160 OPC (86%) patients (67/80 pts in arm A and 70/80 in arm B). P16 positive immunostaining (p16+) was found in 53 tumors (39%): 22/67 (33%) in arm A and 31/70 (44%) in arm B. Smoking status (pack-year: PY) was known for 148 of the 180 patients (82%). There were 54/61 (88%) smokers of >10 pack-year in arm A and 65/71 (76%) in arm B.

Table 1
Patient and tumor initial characteristics.

	Arm A 3D-RT (n = 94)	Arm B IMRT (n = 94)
Male	77 (82%)	78 (83%)
Female	17 (18%)	16 (17%)
Age (years) (mean, std, range)	59.1 (7.4) [42–73]	57.1 (7.3) [38–74]
<50 years	9 (10%)	14 (15%)
50–60 years	40 (43%)	54 (57%)
≥60 years	45 (48%)	26 (27%)
Karnofsky		
90–100	71 (86%)	72 (87%)
≤80	11 (13%)	10 (12%)
Unknown	12	12
Tobacco consumption		
Never	14 (15%)	8 (9%)
Yes, former	28 (30%)	33 (35%)
Yes, current	33 (35%)	38 (40%)
Unknown	19 (20%)	15 (16%)
Among smokers, number of PY	N = 61	N = 71
<10 PY	4 (7%)	3 (4%)
10–<20 PY	5 (8%)	7 (10%)
≥20 PY	49 (80%)	58 (82%)
Unknown	3 (5%)	3 (4%)
Tumor subsite		
Oropharynx	80 (85%)	80 (85%)
Oral cavity	3 (3%)	4 (4%)
Hypopharynx	11 (12%)	10 (11%)
Among oropharyngeal tumors		
p16 negative	45 (67%)	39 (56%)
p16 positive	22 (33%)	31 (44%)
p16 not available	13	10
Differentiation		
Well	45 (52%)	44 (48%)
Moderately	26 (30%)	29 (32%)
Poor	15 (17%)	19 (21%)
N stage		
N0	13 (14%)	14 (15%)
N1–2a	27 (29%)	27 (29%)
≥N2b	54 (57%)	53 (56%)
T stage		
T1–2	27 (28%)	26 (27%)
T3	40 (43%)	39 (41%)
T4	27 (29%)	29 (31%)
Stage UICC		
III	22 (23%)	22 (23%)
IVa	68 (72%)	69 (73%)
IVb	4 (4%)	3 (3%)
GTV		
Unilateral	45 (48%)	40 (43%)
Bilateral	49 (52%)	54 (57%)

The median follow-up was 60.5 months (range: 14.4 months–83.8 months), Inter Quartile Range = 51.4 months–63.5 months; similar in both arms: 59.8 months in arm A and 61.2 months in arm B.

The compliance to RT was not significantly different between the 2 arms: 84 (90%) of patients in arm A and 91 (97%) in arm B received at least 34 fractions ($p = 0.07$), with a mean overall treatment time of 50.6 days and 50.4 days, respectively ($p = 0.87$). The proportion of temporary RT interruption ≥7 days was 11% and 6% in Arm A and Arm B, respectively (Table 2). The number of cisplatin cycles received was not different between two arms ($p = 0.19$): 82 patients (88%) vs 86 (91%) received ≥2 cycles of cisplatin in arm A vs arm B, respectively; 52 patients (55%) vs 64 (68%) completed 3 cycles, respectively.

Acute toxicities are shown in Table 2. Similar incidence of mucositis and radiodermatitis was observed in the two arms. Acute salivary gland toxicity was decreased with IMRT: the rate of grade 3–4 was 8% in arm B versus 21% in arm A ($p = 0.015$). No difference of feeding tube use or loss of weight was found between the two arms. Hospitalization due to toxicity were significantly less frequent in arm B than in arm A (47% vs 30%, $p = 0.014$).

Table 2
Chemoradiotherapy compliance and acute clinical toxicity[§].

	Arm A 3D-RT	Arm B IMRT	P-value
Number of received fractions [§]			0.07
≤33	9	3	
≥34	84 (89%)	91 (97%)	
Definitive stop of RT	3* (3%)	2** (2%)	
Temporary RT interruption	73 (78%)	80 (85%)	
Duration of interruption			
1–6 days	63	74	
≥7 days	10	6	
Radiotherapy duration (days) (mean (std), median, [range])	50.6 (8.5) 50 [3–98]	50.4 (7.3) 50 [4–63]	0.87
Parotid gland irradiation	Data for 80 patients	Data for 90 patients	
Mean dose (Gy)			
Homolateral	63.1 (8.4) [32.9– 72.2]	43.2 (12.8) [20.7–67.5]	<0.0001
Controlateral	56.5 (8.9) [29.1– 73.2]	31.8 (8.1) [16.4–59.4]	<0.0001
Healthy oral cavity irradiation	Data for 70 patients	Data for 79 patients	
Mean dose (Gy)	47.1 (18.7) [0–72.5]	44.8 (10.5) [17.4–72.1]	0.35
% volume > 45 Gy	60.9 (30.8) [0–100]	45.5 (30.1) [0–100]	0.003
Number of cisplatin courses received [§]			0.19
0	0	1 (1%)	
1	11 (12%)	7 (7%)	
2	30 (32%)	22 (23%)	
3	52 (55%)	64 (68%)	
Mucositis			(grade 3–4 vs other) $p = 0.71$
No	1 (1%)	3 (3%)	
Grade 1	5 (5%)	8 (9%)	
Grade 2	42 (45%)	39 (42%)	
Grade 3	38 (41%)	36 (39%)	
Grade 4	7 (8%)	6 (6%)	
Salivary gland toxicity			(grade 3–4 vs other) $p = 0.015$
No	16 (18%)	21 (23%)	
Grade 1	19 (21%)	26 (29%)	
Grade 2	36 (40%)	37 (41%)	
Grade 3	18 (20%)	7 (8%)	
Grade 4	1 (1%)	0 (0%)	
Skin toxicity			(grade 3–4 vs other) $p = 0.38$
No	4 (4%)	5 (5%)	
Grade 1	24 (26%)	32 (34%)	
Grade 2	51 (55%)	46 (49%)	
Grade 3	12 (13%)	8 (7%)	
Grade 4	2 (2%)	2 (2%)	
Feeding tube	64 (69%)	59 (63%)	$p = 0.38$
Maximal % of weight loss during treatment (mean (std))	11.7% (6.0)	12.1% (6.7)	$p = 0.68$
Hospitalization due to toxicity	44 (47%)	28 (30%)	$p = 0.014$

[§]Grading according to RTOG scoring criteria.

^{§§}Missing for one patient of the Non-IMRT arm.

*2 deaths (one after 4 fractions due to a non-specified intercurrent disease and one after 28 fractions due to a septic shock) and 1 patient refusal after 28 fractions and 41 days..

**2 deaths: one after 5 fractions due to a mesenteric infarction, one after 8 fractions due to unknown cause.

[¶]One patient of the Non-IMRT arm received weekly carboplatin instead of cisplatin.

Five early deaths occurred during the treatment or within 3 months after end of treatment: 3 in arm A and 2 in arm B.

Late xerostomia was markedly decreased with IMRT at least until 4 years after the end of treatment (Table 3 and Fig. 2). According to RTOG scoring criteria, the grade ≥2 xerostomia rates were

Table 3
Late toxicity between one and five years after the end of treatment.

	1 year		2 year		3 years		4 year		5 years		p-value*
	3D-RT	IMRT	3D-RT	IMRT	3D-RT	IMRT	3D-RT	IMRT	3D-RT	IMRT	
Xerostomia RTOG											<0.0001
No	4 (6%)	17 (26%)	6 (11%)	16 (30%)	5 (11%)	20 (43%)	5 (16%)	19 (46%)	7 (26%)	8 (33%)	
Grade 1	19 (30%)	34 (52%)	13 (24%)	28 (53%)	19 (43%)	22 (47%)	16 (50%)	17 (41%)	12 (44%)	12 (50%)	
Grade 2	34 (54%)	13 (20%)	28 (51%)	8 (15%)	16 (36%)	5 (11%)	9 (28%)	4 (10%)	8 (30%)	4 (17%)	
Grade 3	6 (10%)	2 (3%)	8 (15%)	1 (2%)	4 (9%)	0 (0%)	2 (6%)	1 (2%)	0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Xerostomia LENT subjective											<0.0001
No	3 (5%)	13 (22%)	6 (11%)	12 (25%)	3 (8%)	16 (36%)	4 (14%)	16 (40%)	4 (17%)	7 (28%)	
Grade 1	14 (23%)	20 (34%)	11 (20%)	21 (44%)	11 (29%)	16 (36%)	7 (24%)	13 (32%)	7 (29%)	11 (44%)	
Grade 2	23 (37%)	16 (27%)	15 (27%)	9 (19%)	13 (34%)	9 (20%)	15 (52%)	9 (22%)	11 (46%)	4 (16%)	
Grade 3	22 (35%)	9 (15%)	23 (41%)	6 (12%)	9 (24%)	4 (9%)	3 (10%)	2 (5%)	2 (8%)	3 (12%)	
Grade 4	0 (0%)	1 (2%)	1 (2%)	0 (0%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Mucosal											0.55
No	66 (92%)	64 (86%)	55 (82%)	58 (92%)	47 (94%)	45 (90%)	33 (82%)	40 (89%)	27 (90%)	25 (93%)	
Grade 1	6 (8%)	9 (12%)	8 (12%)	4 (6%)	1 (2%)	4 (8%)	5 (12%)	3 (7%)	2 (7%)	1 (4%)	
Grade 2	0 (0%)	1 (1%)	2 (3%)	0 (0%)	1 (2%)	1 (2%)	2 (5%)	1 (2%)	0 (0%)	1 (4%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade 4	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade NE			0 (0%)	1 (2%)	1 (2%)		0 (0%)	1 (2%)	1 (3%)		
Subcutaneous tissue											0.47
No	59 (92%)	58 (78%)	42 (64%)	49 (78%)	40 (80%)	38 (76%)	26 (65%)	34 (76%)	22 (73%)	20 (74%)	
Grade 1	6 (8%)	11 (15%)	13 (20%)	11 (17%)	5 (10%)	8 (16%)	8 (20%)	6 (13%)	7 (23%)	5 (19%)	
Grade 2	5 (7%)	4 (5%)	10 (15%)	2 (3%)	5 (10%)	4 (8%)	6 (15%)	3 (7%)	1 (3%)	2 (7%)	
Grade 3	1 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	
Grade NE	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
			0 (0%)	1 (2%)			0 (0%)	1 (2%)			
Laryngeal											0.88
No	63 (88%)	67 (91%)	58 (88%)	58 (92%)	47 (94%)	46 (92%)	35 (88%)	44 (98%)	30 (100%)	26 (96%)	
Grade 1	5 (7%)	3 (4%)	4 (6%)	3 (5%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	0 (0%)	0 (0%)	
Grade 2	2 (3%)	4 (5%)	2 (3%)	2 (3%)	1 (2%)	2 (4%)	1 (2%)	0 (0%)	0 (0%)	1 (4%)	
Grade 3	1 (1%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	
Grade 4	1 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade NE							2 (5%)	0 (0%)			
Dysphagia											0.17
No	66 (92%)	72 (97%)	61 (92%)	61 (97%)	48 (96%)	48 (96%)	40 (100%)	45 (100%)	29 (97%)	24 (89%)	
Grade 1	4 (6%)	1 (1%)	2 (3%)	0 (0%)	1 (2%)	2 (4%)	0 (0%)	0 (0%)	1 (3%)	3 (11%)	
Grade 2	2 (3%)	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade 3	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Grade NE			1 (2%)	2 (3%)							
Bone											0.34
No	68 (94%)	71 (96%)	59 (89%)	56 (89%)	44 (88%)	47 (94%)	35 (88%)	42 (93%)	29 (97%)	27 (100%)	
Grade 1	1 (1%)	2 (3%)	4 (6%)	2 (3%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (3%)	0 (0%)	
Grade 2	0 (0%)	0 (0%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)	2 (5%)	2 (4%)	0 (0%)	0 (0%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	
Grade NE	3 (4%)	1 (1%)	2 (3%)	3 (5%)	3 (6%)	0 (0%)	1 (2%)	0 (0%)			

*Comparison between the two treatment groups of none or grade 1 versus grade ≥ 2 from 1 year to 5 years after end of treatment by generalised linear model. NE: not evaluate.

63% in arm A and 23% in arm B at one year and 45% and 11% respectively at three years. According to subjective LENT-SOMA scoring, the grade ≥ 2 salivary toxicity rates were 73% in arm A and 44% in arm B at one year and 63% and 29% respectively at three years. The other late toxicities were not different between the two arms (Table 3).

The use of dose-escalated IMRT did not transfer into a lower LRP incidence with a crude HR of 0.97 [95%CI = 0.56; 1.65] and an adjusted HR (on centers, T, N, GTV laterality, p16) of 1.13 [0.64–1.98] ($p = 0.68$). LRP occurred as first event in 26 patients in each arm, corresponding to 48% of the expected number of LRP. The cumulative incidence rates of LRP were 27.7% in arm A vs 23.5% in arm B at 3 years, and 27.7% vs 25.8% at 5 years, respectively (Fig. 3a).

PFS and OS were not significantly different between the 2 arms (Fig. 3b, c). The 3 and 5-year PFS rates were respectively 56.4% and 49.8% in arm A and 54.1% and 48.2% in arm B (Fig. 3b) with an adjusted HR of 1.26 [95%CI = 0.84; 1.90, $p = 0.27$]. The 3 and 5-year OS rates were respectively 60.6% and 51.6% in arm A and

61.4% and 51.2% in arm B (Fig. 3c) with an adjusted HR of 1.19 [95%CI = 0.78; 1.81, $p = 0.42$].

Metastasis alone as first event was observed in 7 and 10 of arm A and B, respectively. Cumulative incidence of metastasis was not significantly different between the two arms (adjusted HR of 1.47 [95%CI = 0.55; 3.92], $p = 0.44$).

A significant improvement in LRP, PFS and OS was found in p16 + compared to p16- OPC (all p -values <0.0004). Only 3 LRP were observed in p16 + OPC, one in arm A and 2 in arm B. The dose-escalation with IMRT did not improve outcomes in patients with OPC regardless of p16 status [non-significant interaction tests between p16 and treatment modality for LRP ($p = 0.96$), PFS ($p = 0.65$) and OS ($p = 0.45$)].

Discussion

This phase III trial confirmed a significant reduction of acute and late xerostomia for patients treated with IMRT and cisplatin

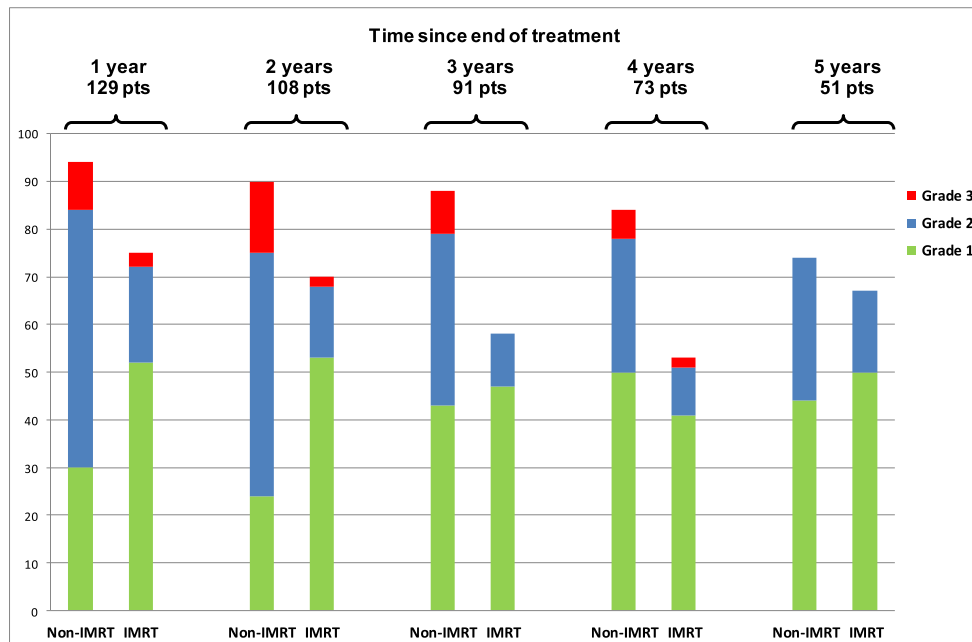


Fig. 2a. Late xerostomia grade according to RTOG scoring criteria: percentages of grade 1, 2 and 3 at years 1, 2, 3, 4 and 5 after the end of treatment. Comparison between the two treatment groups of none or grade 1 versus grade 2, 3 or 4 from 1 year to 5 years after end of treatment, $p < 0.0001$.

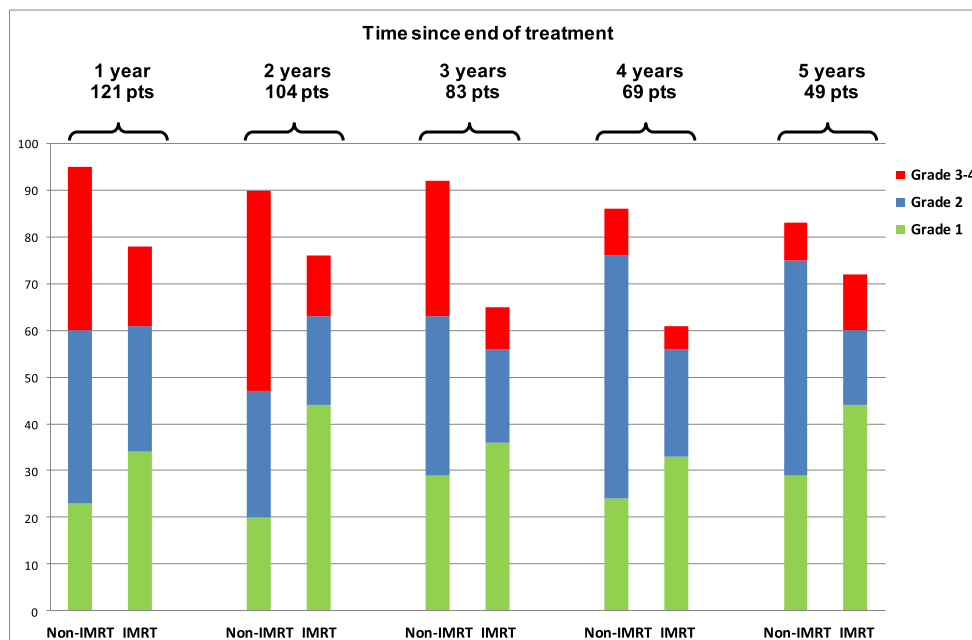


Fig. 2b. Late xerostomia grade according to LENT-subjective scoring: percentages of grade 1, 2, 3 and 4 at years 1, 2, 3, 4 and 5 after the end of treatment. Comparison between the two treatment groups of none or grade 1 versus grade 2, 3 or 4 from 1 year to 5 years after end of treatment, $p < 0.0001$.

compared with 3D-RT, which is consistent with other trials of IMRT in early stage of head and neck cancers [12] and with one systematic review [13]. We failed to show any benefit with dose escalation from 70 Gy to 75 Gy in terms of tumor control (in fact the equivalent dose is higher than 75 Gy since the last 25 Gy were given on an accelerated mode with 2.5 Gy/F and 12.5 Gy/week). To our knowledge, this is the first randomized phase III trial in LA-HNSCC, comparing IMRT vs 3D-RT in terms of LRP and also the first randomized trial showing the benefit of parotid-sparing

with IMRT vs 3D-RT in concurrent CRT setting with cisplatin for LA-HNSCC. The widespread use of IMRT after the trial was launched for LA-HNSCC patients was the main reason for slow enrollment and early closure of trial.

Although widely used in the treatment of LA-HNSCC, there is relatively limited Evidenced Based Medicine level 1 regarding the benefit of IMRT. IMRT is a tool markedly improving RT dose distribution to reduce normal tissues damages and/or to escalate radiation dose to GTV. Our study addressed these 2 issues and showed a

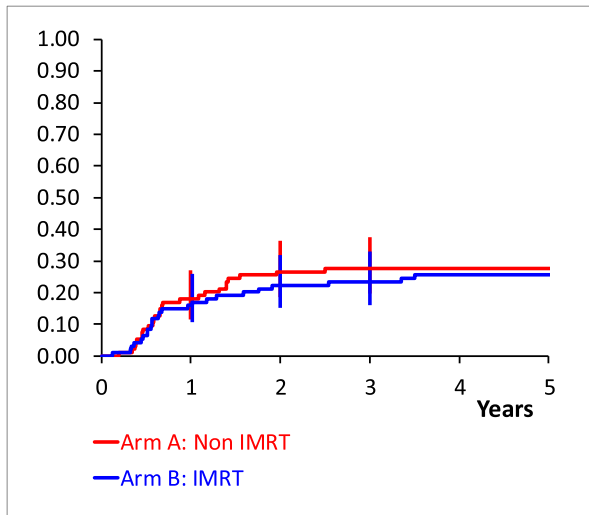


Fig. 3a. Cumulative incidence of loco-regional progression by treatment arm.

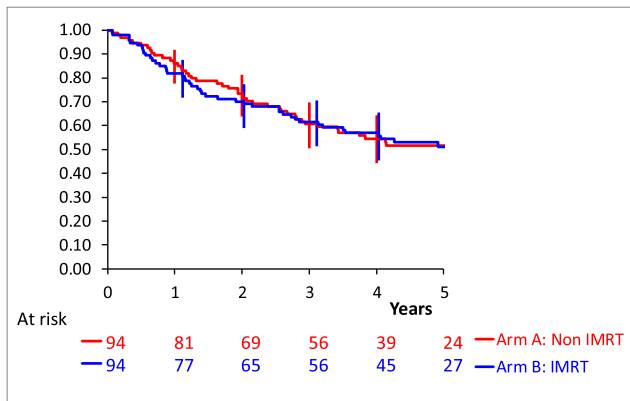


Fig. 3b. Overall survival by treatment arm.

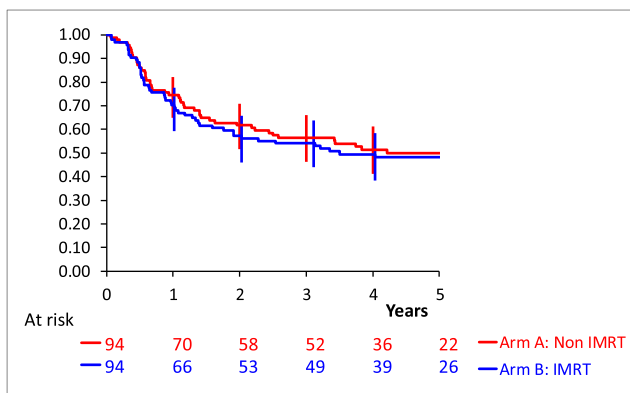


Fig. 3c. Progression free survival by treatment arm.

significant reduction of xerostomia as compared to 3D-RT in patients treated with CRT. This is consistent with the benefit demonstrated with IMRT for patients treated by RT alone. Our results show not only that xerostomia has been improved by IMRT, but also that the need of hospitalization due to toxicity has been decreased and the compliance to cisplatin was improved.

The second potential benefit of IMRT is related to the possibility to increase the radiation dose to GTV, which is of particular

importance in LA-HNSCC since most of relapses occur inside or close to GTV. Despite a relatively important dose increase (75 Gy versus 70 Gy) along with moderate acceleration for the boost (25 Gy/10F), no benefit was seen in terms of LRC or survival. The HR of 0.56 for loco-regional control in favour of dose-escalated IMRT was probably too ambitious. In the PARSPORT trial, there were slightly more locoregional recurrences in IMRT group than in conventional RT group (12 vs 7), although this difference was not significant. However, the population of patients included in this trial was quite heterogeneous (many patients with stage I/II), and treatment was quite different (>40% with neoadjuvant chemotherapy and >20% with surgery) [6]. Thus, it is impossible to draw any firm conclusion regarding tumor control with PARSPORT trial. In contrast, our trial included a homogenous population and patients were all treated with high-dose cisplatin-based CRT. One Indian randomized trial also showed that IMRT significantly reduced the incidence and severity of xerostomia compared to 3D-CRT and no difference in tumor control [14].

Interestingly, this is a relatively unique study showing that there is no dose effect relationship beyond 70 Gy if concurrent high dose cisplatin is used. It is in contrast to improved survival and tumor control by dose increasing when RT alone is used for example through hyperfractionated RT as shown in MARCH meta-analysis [11]. Why could dose increase in IMRT arm not be translated into improved tumor control? The first reason is use of cisplatin in both arms. This absence of radiation dose/time effect relationship when RT is associated with concurrent chemotherapy is similar to the GORTEC 99-02 in which we failed to show superiority of concurrent accelerated CRT versus conventional fractionated CRT [15,16]. The second reason could be that many patients with HPV/p16 + OPC probably do not need dose escalation as opposed to HPV/p16- patients [17], although this could not be explored in our study given the very small number of events in p16+ patients (3 LRP and 5 DP). Other biomarkers could also be important for the selection of patients who could potentially benefit from dose escalation. The third reason is that dose escalation may be only necessary in specific areas such as hypoxic regions in GTV and not in the whole GTV. We need also note that since many centers in the trial have switched IMRT technique during this trial, it could be an impact of learning curve with such outcome. Thus, these points could suggest that future dose escalation protocol could be more selective not only for different patients but also for different biologically-targeted zones in the tumor. Last, as the study was closed early due to slow accrual, its power to evaluate LRP as primary endpoint was low.

A potential concern of this dose escalation 75 Gy/7 weeks by IMRT was toxicity. In fact, in our trial, we did not find any difference of acute toxicities such as radiomucositis, radiodermatitis or use of feeding tube. Importantly, the patients in the dose-escalated IMRT arm were less likely hospitalized due to toxicities during RT. Furthermore, the patients in IMRT arm probably better tolerated concurrent cisplatin, with 68% vs 55% in 3D-RT arm completing 3 cycles cisplatin. The better tolerance in IMRT arm could partially be related to a higher rate of patients ≥ 60 years of age in 3D-RT arm (48% vs 27%); indeed, these older patients had slightly more adverse events grade ≥ 3 than younger patients (90% versus 80%) and more hospitalization (51% vs 31%).

The proportion of p16 positivity in oropharynx cancers in this trial was 39%, and this is consistent with recent randomized trials GORTEC 2007-01 [10] and 2007-02 [18] which showed about 20–30% OPC with p16+ and even less p16+ non-smokers. The large majority of patients are p16- /smokers. This is in contrast with population in North America where the proportion of p16+ cancers is generally higher [17 19]. In fact, recently, for low risk or intermediate risk HPV + OPC, clinical trials were designed to de-intensify the treatment such as reducing radiation dose or use of less toxic

chemotherapy; while treatment intensification is reserved for HPV– or high-risk HPV+ patients.

In conclusion, radiotherapy dose escalation to the GTV with IMRT did not improve loco-regional control in patients with locally advanced HNSCC treated with concurrent high-dose cisplatin and RT, while xerostomia and tolerance were improved by IMRT. This trial adds new evidence level 1 in favor of IMRT in LA HNSCC but does not support dose escalation to the entire GTV in patients treated by CRT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2020.05.021>.

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