Clinical outcome and toxicity after simultaneous integrated boost IMRT in head and neck squamous cell cancer patients

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ABSTRACT

Introduction: A simultaneous integrated boost (SIB) intensity modulated radiotherapy (IMRT) in patients with head and neck squamous cell carcinoma (HNSCC) allows to irradiate different target volumes to different dose levels within a single treatment session without increasing the toxicity.

Aim: To analyze the outcome and toxicity of patients treated by definitive or postoperative SIB IMRT for HNSCC.

Material and methods: 106 patients with HNSCC of the oral cavity (OC), oropharynx (OP), larynx (L) and hypopharynx (HP), consecutively treated at our cancer center between 3/2012 and 3/2014 were retrospectively analyzed. The prescribed SIB IMRT doses were in the postoperative setting (group A) 60–66 Gy and 53 Gy in 30–33 fractions for PTV high risk and PTV elective, respectively; and 70 Gy and 56 Gy in 35 fractions for PTV high risk and PTV elective, respectively when given as primary treatment (group B). Toxicity was consistently graded according to RTOG/EORTC scale.

Results: Median follow-up duration was 31 months. Thirty (28%) patients were postoperatively irradiated (group A) and 76 (72%) patients received definitive IMRT (group B).

At 3 years, loco-regional control, distant control and overall survival were 78%, 78%, 57% and 64%, 76%, 52% in the postoperative (group A) and the definitive SIB IMRT group (group B), respectively. The observed acute grade 3 toxicities were dysphagia (44%), oral and/or oropharyngeal mucositis (40%) and dermatitis (21%). Late toxicity was predominantly clinically significant xerostomia (42%), dysgeusia (23%) and dysphagia (8%).

Conclusion: SIB IMRT is feasible, safe and effective in the treatment of HNSCC patients.

Introduction

The treatment of head and neck squamous cell carcinoma (HNSCC) depends on the primary tumor location and its extension [1–4]. In early stage (I–II) disease, both surgery and radiotherapy (RT) give similar loco-regional control. Locally advanced (LA; stage III and IV) HNSCC, on the other hand, is treated by surgery followed by postoperative RT or by post-operative chemoradiotherapy (CRT) in case of high risk factors (extracapsular extension and/or R1 resection). Definitive CRT is indicated when the patient is inoperable, in case of organ preservation or when surgery is considered to be too mutilating. In general, in case of LA-HNSCC primary surgery is indicated in patients with operable oral cavity tumors and bulky laryngeal/hypopharyngeal tumors in which organ preservation is not estimated.

Despite the advances in therapeutic approaches which have increased the survival of patients with locally advanced tumors, HNSCC remains a disease with a poor prognosis and high rates of recurrence. At the same time acute and late toxicity remain a major problem [5]. Intensity modulated RT (IMRT), developed to reduce this toxicity, is actually considered a standard of care based on level I evidence of reduction of xerostomia [6–10].

Compared with sequential IMRT where the treatment is delivered in two phases, i.e. initially the whole (elective and boost) volume followed by the boost volume, a simultaneous integrated boost (SIB) IMRT allows the irradiation of different targets at different dose levels within a single treatment session. The majority of studies comparing SIB IMRT and

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sequential IMRT are dosimetric reports. The dose distribution seems to be more conformal with SIB IMRT than with sequential IMRT [11,12]. In the latter, a vast part of the dose has already been delivered in the elective phase, which makes it more difficult to obtain a high level of dose conformation with the remaining fractions in the IMRT-boost phase. Regarding the sparing of organs at risk (OAR), some dosimetric studies suggests that SIB IMRT provide better sparing of the inner ear and parotid glands, while sequential IMRT lowered maximal doses to the spinal cord and brainstem [12,13].

In the present study, we will analyze the clinical outcome and toxicity of patients treated in our institution by definitive or post-operative SIB IMRT for early and LA-HNSCC.

Material and Methods

Patient selection

One hundred and six patients with HNSCC of the oral cavity (OC), oropharynx (OP), larynx (L) and hypopharynx (HP) consecutively treated at our cancer center between 3/2012 and 3/2014 were retro-spectively analyzed (nasopharyngeal tumors excluded from analysis).

Pretreatment evaluation

The diagnostic evaluation included a complete anamnesis, physical examination, complete blood test, panendoscopy with biopsies, radi-ologic evaluation by computed tomography scanner (CT-scan) and/or magnetic resonance imaging (MRI) of the head and neck region. Screening for distant metastases was done by CT-scan and/or positron emission tomography (PET)-CT scan.

Treatment outlines

Radiotherapy planning

A contrast-enhanced planning CT-scan with 3 mm slice thickness was obtained in the treatment position using an individual head support and a customized 5 points thermoplastic mask (Orfit Industries America, Wijnegem, Belgium). The registration and fusion of planning CT-scan with the patient's diagnostic images (CT-scan, MRI and Pet-CT scan when available) were performed. The Gross Target Volume (GTV), Clinical Target Volume (CTV) and organs at risk (OARs) were deli-neated by a specialized head and neck radiation oncologist according to uniform guidelines [14,15]. The GTV of the primary tumor and mac-roscopic suspicious lymph nodes was delineated and the CTV high risk was defined as GTV + 5 mm. The CTV elective included GTV + 10–15 mm (with correction for air and anatomical barriers) and regional elective lymph nodes dependent on nodal status (Fig. 1). To obtain the planning tumor volume (PTV) a margin of 5 mm was added around each CTV to take into account patient set-up uncertainties [16]. The prescribed SIB IMRT doses in the postoperative setting (group A) were 60–66 Gy and 53 Gy in 30–33 fractions for PTV high risk and PTV elective, respectively, and 70 Gy and 56 Gy in 35 fractions for PTV high risk and PTV elective, respectively, when given as primary treatment. Delineation and plan optimization were performed using the Varian Treatment Planning System.

Treatment delivery

Patient position was verified with daily online KV imaging using the On-Board Imager and position was adjusted accordingly. IMRT-SIB was delivered on Varian linear accelerator with dynamic multilieaf colli-mation. Patients were reviewed weekly by the radiation oncologist. Patients with acute grade ≥ II oral mucositis received twice or three times per week low level laser therapy (LLLT). Salvage nasogastric tube or PEG placement was recommended for body weight loss > 15%.
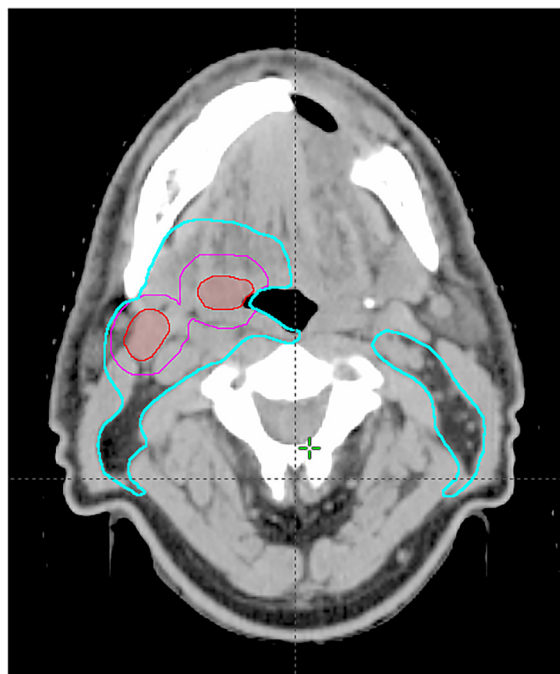

Fig. 1. Delineation of target volumes. GTVs are shown in red, the CTV high risk in pink and the CTV elective in blue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Toxicity evaluation

All patients were clinically assessed weekly during the radiation therapy and 1 month after the treatment. Subsequently, the schedule of the follow up was: every 2–3 months for the first 2 years, every 3–6 moths in 3rd, 4th and 5th years and then yearly further on.

The toxicity was defined as acute when occurring during RT and/or in the following 6 months and graded by a specialized head and neck radiation oncologist using the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and treatment of Cancer (EORTC) scores [17]. The evaluated acute side effects were oral-or-opharyngeal mucositis, dermatitis, dysphagia, xerostomia and dys-geusia. The late toxicities assessed at 6, 12 and 24 months were xer-ostomia, dysgeusia and dysphagia. Dysphagia was graded according to the RTOG/EORTC Late Radiation Morbidity Scoring, xerostomia was reported as clinically significant or not significant and dysgeusia as present or absent.

Clinical outcome evaluation

Response assessment was based on imaging data performed by CT scan/MRI and PET-CT scan at 6 and 12 weeks respectively, following the end of RT. Classification of early response was made in accordance with the Response Evaluation Criteria In Solid Tumors (RECIST) [18].

Statistical analysis

Standard descriptive statistics were used to analyze data and dis-tributions of categorical variables were reported using absolute and relative frequencies. The Kaplan-Meier method was used to estimate overall survival (OS) defined as the period from date of diagnosis to date of death or last follow up visit. The same analysis was used for loco-regional control (LRC) and distant control (DC) defined as the period from date of diagnosis to date of loco-regional relapse and dis-tant metastasis, respectively or last follow up visit. The distributions of time-to-event variables were summarized by actuarial medians and rates at 2 and 3 years (together with 95% confidence intervals). In addition, predictors (age, gender, smoking, alcohol, tumor site, stage,

Table 1
Patient and treatment characteristics.

		Group A	Group B	Total
Number of patients		30	76	106
Age (years)	Min-max	44–80	40–89	40–89
	Median	59	63	62
Gender	Male	24 (80%)	51 (67%)	75 (71%)
	Female	6 (20%)	25 (32%)	31 (29%)
Smoking	Heavy (≥20 CPD)	13 (43%)	29 (38%)	42 (40%)
	Intermediate(10–19 CPD)	5 (16%)	9 (11%)	14 (13%)
	Light (1–9 CPD)	2 (6%)	1 (1%)	3 (3%)
	Not quantifiable smokers	6 (20%)	22 (28%)	28 (26%)
	Never	3 (10%)	11 (14%)	14 (13%)
	Unknown	1 (3%)	4 (5%)	5 (5%)
Alcohol	Drinkers	15 (50%)	32 (42%)	47 (44%)
	Non-drinkers	10 (33%)	27 (36%)	37 (35%)
	Unknown	5 (17%)	17 (22%)	22 (21%)
Tumor site	Oral cavity	14 (47%)	13 (17%)	27 (25%)
	Oropharynx	8 (27%)	32 (42%)	40 (38%)
	Larynx	5 (17%)	15 (19%)	20 (19%)
	Hypopharynx	3 (10%)	16 (21%)	19 (18%)
TNM 7th edition stage	I-II	3 (10%)	16 (21%)	19 (18%)
	III-IV	27(90%)	60 (79%)	87 (82%)
Modalities	CCRT	14 (47%)	39 (51%)	53 (50%)
	ICT → RT	2 (6%)	0	2 (2%)
	ICT → CCRT	0	4 (5%)	4 (4%)
	RT	14 (47%)	33 (44%)	47 (44%)

RT: radiotherapy (SIB-IMRT); CCRT: concomitant chemoradiotherapy; ICT: induction chemotherapy; CPD: cigarettes/day.

treatment modalities regarding CRT and time of diagnosis to treatment initiation) for overall survival were studied using Cox regression models. First a simple Cox model was fitted for each covariate, covariates with p-value < 0.03 were then entered in the multiple Cox regression model. P-value of less than 0.05 was considered as statistically significant.

Results

Patients

Details of the 106 patient's characteristics and treatment modalities are presented in Table 1.

The oropharyngeal site was predominant with 40 patients (38%): 14 patients (35%) with human papilloma virus (HPV) positive status, 3 patients (8%) HPV negative status and for 23 patients (57%) the status was unknown.

Median follow-up duration was 31 months.

Treatment

Thirty patients (28%) were treated with IMRT-SIB after surgery (group A) and 76 patients (72%) as primary treatment modality (group B), with or without induction and/or concomitant chemotherapy. In 59 (56%) cases, systemic treatment by chemotherapy or targeted therapy was given. Concomitant cisplatin high dose based chemotherapy (100 mg/m2, administered with 3 week intervals) was given to 40 (68%) patients. 18/40 patients (45%) received 3 cycles, the other 22 (55%) only tolerated 2 cycles. Concomitant cisplatin weekly dose based chemotherapy (40 mg/m2, once a week, 1–7 cycles) was given to 11 (19%) patients. 4/11 patients received 7 cycles and 7 underwent 5–6 cycles. Two (3%) patients received concomitant cetuximab. Induction chemotherapy (platinum based) followed by concomitant cisplatin (weekly) was given to 4 (7%) patients, of whom 2 (3%) patients

received one cycle of Afatinib according to the EORTC 90111–24111-NOCI-trial. Ninety three (88%) patients had bilateral neck irradiation, nine (9%) had unilateral neck irradiation and the lymph nodes of four (4%) patients were not irradiated. Median duration of a course of RT was 48 days (range 42–70 days) and 49 days (range 44 to 59 days) in groups A and B, respectively. Ten patients (9%) had a prolongation of their treatment of 6 days or more due to holidays and/or machine maintenance. One patient in the postoperative group had a prolongation of 24 days due to a postoperative wound complication.

Treatment toxicities

Acute toxicity occurred in the majority of patients and the addition of chemotherapy further increased the adverse events. The observed acute grade 3 toxicities for whole cohort were dysphagia (44%), mucositis (40%) and dermatitis (21%). Mucositis and dermatitis were limited to the high dose volume. No Grade 4 was observed.

Forty-four (42%) and 38 (36%) patients presented clinically significant xerostomia at 12 and 24 months, respectively. The mean dose to the contralateral and ipsilateral parotid glands was 20.3 (SD 8.3) Gy and 31.6 Gy (SD 13.9), respectively. The mean dose of the contralateral and ipsilateral parotid glands in patients who did (44; 42%) and who did not (62; 58%) reported clinically significant xerostomia at 12 months was 21.7 Gy (SD 7.7) and 19.4 Gy (SD 8.7), p = 0.17 and 34.8 Gy (SD 11.5) and 29.3 Gy (SD 15.1), p = 0.045, respectively.

Twenty four (23%) patients complained of late dysgeusia: 20 patients had oral cavity or oropharynx as primary tumor site and four patients had laryngeal/hypopharyngeal tumors. Eight patients (8%) reported grade 3 late dysphagia: two in the postoperative group (1 oral cavity and 1 oropharynx); and six patients in the definitive SIB IMRT group (1 oral cavity, 3 oropharynx, 1 larynx and 1 hypopharynx). Thirty nine (37%) patients had either a laryngeal or hypo-pharyngeal cancer with 31/39 (79%) cases being treated by definitive SIB IMRT, of whom a significant proportion (24/31; 77%) presented with stage III/IV disease. At last follow up, 5/24 (21%) patients in this subset group had laryngectomy for tumor progression and another 4/24 (17%) presented a poor functional outcome. Two (8%) of them had vocal cord fixation, one requiring tracheostomy due to airway fixation, and the other two (8%) developed recurrent aspiration pneumonia of which 1 patient even died. Twenty seven (25%) patients had oral cavity cancer with 13/27 (48%) cases being treated by definitive SIB IMRT, of whom a significant proportion (10/13; 78%) presented with stage III/IV disease. In this subset of patients, the rate of osteoradionecrosis (ORN) was 7% (2/27) and none of the patients developed trismus.

The most common toxicities are presented in Tables 2 and 3 for the groups A and B respectively.

In the postoperative SIB IMRT settings (group A) there was no treatment interruption due to chemoradiation toxicity. Two patients treated by definitive SIB IMRT (group B) failed to complete the recommended full course of RT. The reasons for the interruption of treatment were grade III dermatitis for the first patient (received 30 fractions of 35) and grade 4 gastrointestinal toxicity due to the chemotherapy, with hospitalization for the second patient (received 30 fractions of 35).

Fifteen (50%) patients in group A and 31 (41%) in group B underwent preventive PEG, defined as placement prior or within the first week of (chemo) radiation. During the treatment, eight patients (11%) in the definitive SIB IMRT group lost ≥ 15% of their initial body weight. Three patients (10%) in group A and 10 (13%) in group B required a salvage percutaneous endoscopic PEG tube or total parenteral nutrition during the RT due to significant weight loss. Two patients in the definitive SIB IMRT group developed later feeding tube dependency with enteral alimentation at 12 month after the treatment.

Table 2
Toxicity outcomes for the group A.

Group A N = 30	RT No chemotherapy	RT with chemotherapy
	N patients (%) 14 (47%)	N patients (%) 16 (53%)
Acute toxicity		
Oral-oropharyngeal mucositis		
Grade 2	4 (29%)	5 (31%)
Grade 3	6 (43%)	5 (31%)
Dermatitis		
Grade 2	5 (36%)	7 (44%)
Grade 3	1 (7%)	4 (25%)
Dysphagia		
Grade 2	3 (21%)	6 (38%)
Grade 3	6 (43%)	6 (38%)
Xerostomia		
Clinically significant	10 (71%)	13 (81%)
Non clinically significant	4 (29%)	3 (19%)
Dysgeusia		
Yes	9 (64%)	15 (94%)
No	5 (36%)	1 (6%)
Late toxicity at 12 months after RT		
Xerostomia		
Clinically significant	5 (36%)	9 (56%)
Non clinically significant	9 (64%)	7 (44%)
Dysgeusia		
Yes	4 (29%)	6 (38%)
No	10 (71%)	10 (62%)
Dysphagia		
Grade 3	1 (7%)	1 (6%)

Table 3
Toxicity outcomes for the group B.

Group B N = 76	RT No chemotherapy	RT with chemotherapy
	N patients (%) 33 (43%)	N patients (%) 43 (57%)
Acute toxicity		
Oral-oropharyngeal mucositis		
Grade 2	7 (21%)	11 (26%)
Grade 3	12 (36%)	19 (44%)
Dermatitis		
Grade 2	5 (15%)	13 (30%)
Grade 3	8 (24%)	9 (21%)
Dysphagia		
Grade 2	10 (30%)	8 (19%)
Grade 3	15 (45%)	20 (47%)
Xerostomia		
Clinically significant	25 (76%)	38 (88%)
Non clinically significant	8 (24%)	5 (12%)
Dysgeusia		
Yes	27 (82%)	37 (86%)
No	6 (18%)	6 (14%)
Late toxicity at 12 months after RT		
Xerostomia		
Clinically significant	10 (30%)	20 (47%)
Non clinically significant	23 (70%)	23 (53%)
Dysgeusia		
Yes	8 (24%)	6 (14%)
No	25 (76%)	37 (86%)
Dysphagia		
Grade 3	2 (6%)	4 (9%)
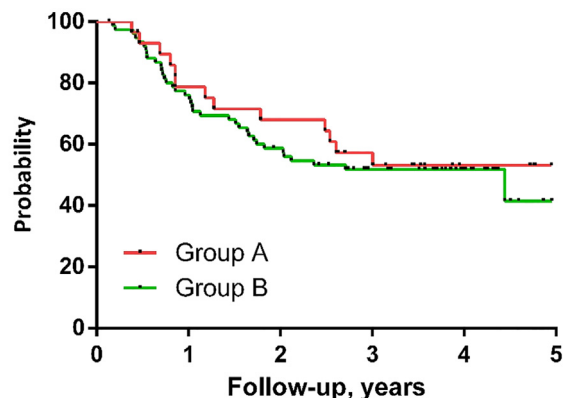
Fig. 2. Overall survival in the postoperative setting (*group A*) and in the definitive SIB IMRT group (*group B*). 2 year OS in the groups A and B: 68% (95% CI 47–82), 59% (95% CI 47–69), respectively. 3 year OS in the groups A and B: 57% (95% CI 37–73), 52% (95% 40–62), respectively.

Treatment outcomes

At 3 years, loco-regional control, distant control and overall survival were 78% (95% CI 58–90), 78% (95% CI 55–91), and 57% (95% CI 37–73), in the postoperative setting (*group A*) and 64% (95% CI 49–75), 76% (95% CI 63–85) and 52% (95% CI 40–62); in the definitive SIB IMRT group (*group B*), respectively (Figs. 2–4). The subset analysis restricted to LA HNSCC in the definitive SIB IMRT group (60 patients; 79%) revealed a 3-year loco-regional control at 61% (95% CI 45–74), a 1-year distant control at 77% (95% CI 64–87) and a 2.5-year overall survival at 52% (95% CI 39–64). The results of a simple and a multiple Cox regression model in function of overall survival can be found in Table 4. The alcohol consumption and time of diagnosis to treatment initiation (DTI) are significant prognostic factors in the univariate analysis but only the prognostic meaning of the alcohol consumption was retained in the multivariate model. In the group A, the DTI defined as the time from surgery to the initiation of postoperative RT was
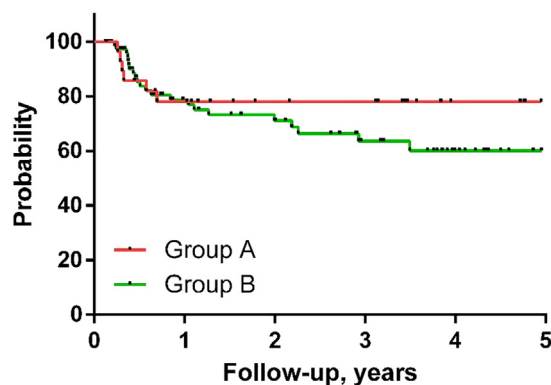
Fig. 3. Loco-regional control in the postoperative setting (*group A*) and in the definitive SIB IMRT group (*group B*). 2 year LRC in the groups A and B: 78% (95% CI 58–90), 71% (95% CI 58–81); respectively. 3 year LRC in the groups A and B: 78% (95% CI 58–90), 64% (95% CI 49–75), respectively.
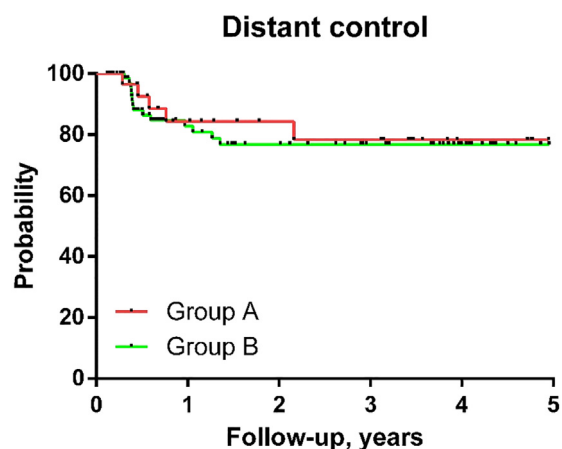
Distant control

Patients at risk

Group B	76	42	32	24	12	0
Group A	30	19	14	12	4	0

Fig. 4. Distant control in the postoperative setting (*group A)* and in the definitive SIB IMRT group *(group B)*. 2 year DC: in the groups A and B: 84% (95% CI 63–94), 76% (95% CI 63–85), respectively. 3 year DC : in the groups A and B: 78% (95% CI 55–91), 76% (95% CI 63–85), respectively.

≤ 6 weeks in eight (27%) patients and > 6 weeks in 22 (73%) patients (HR 1.20; 95%CI 0.33–4.36; p = 0.79). The DTI defined as the time from biopsy to the initiation of RT in the definitive group, was ≤ 6 weeks in 29 (38%) patients and > 6 weeks in 47 (62%) patients (HR 0.32; 95%CI 0.15–0.71; p = 0.004).

Recurrence

Group A: Six (20%) out of 30 patients failed loco-regionally, 3 (10%) only local and 3 (10%) local and regional. There was no isolated regional failure. Two of the regional recurrences occurred unilaterally on the same side as the initial primary disease and one was bilateral in the elective volume. Five patients developed a distant recurrence at a median time of 6 months (range 3 to 24 months). For three patients the metastatic site was the lung, for one it was the liver, and one patient presented skin metastases. In three patients, recurrence was both loco-regional and distant.

Group B: 21 (28%) out of 76 patients failed loco-regionally. Ten (13%) patients failed only locally, 2 (3%) only regionally and 9 (12%) patients failed both locally and regionally. The majority of failures occurred within the high risk isodose, 19 local and 6 regional. There were four failures within the prophylactic volume (isodose 95% PTV low risk) and one out-field regional recurrence. Fifteen patients developed a distant recurrence. In 7 patients, recurrence was both loco-regional and distant. Eight patients developed distant metastasis in the lung, 2 in the liver, one in the bones and 4 patients in multiple sites. Two patients developed a second head and neck primary tumor after RT, one at 25 months, the second at 33 months.

Survival

At the time of analysis 13 (43%) patients had died in the *group A*: 7 (23%) from a tumor progression, one (3%) from a treatment related death (carotid artery blowout after laryngectomy) and 5 (17%) from non-tumor related causes.

In the *group B*: 36 (47%) patients had died at the time of analysis, 22 (29%) from a tumor progression, one (1%) was from treatment related event (tracheotomy for vocal cord paralysis, dysphagia and decline of general condition) and 13 (17%) were non-tumor related causes.

Table 4
Simple and a multiple Cox regression model in function of overall survival.

			Simple Cox regression model			Multiple Cox regression model*		
			HR	95%CI HR	P	HR	95%CI HR	p
Age (years)	Min-max	40–89	1.01	0.99–1.04	0.34			
	Median	62						
Gender	Male	75	1.07	0.59–1.94	0.818			
	Female	31						
Smoking	Heavy (≥ 20 CPD)	42	1.25	0.70–2.21	0.46			
	Intermediate(10–19 CPD)	14						
	Light (1–9 CPD)	3						
	Not quantifiable Smokers	28						
	Never	14						
	Unknown	5						
Alcohol	Drinkers	47	0.44	0.22–0.88	**0.019**	0.44	0.22–0.88	**0.019**
	Non-drinkers	37						
	Unknown	22						
Tumor site	Oral cavity	27	1.9	0.9–4.1	0.089			
	Oropharynx	40	1					
	Larynx	20	2.22	1.01–4.9				
	Hypopharynx	19	2.16	1.17–5.7				
TNM 7th edition stage	I-II	19	0.90	1.42–1.92	0.78			
	III-IV	87						
Modalities	CCRT	53	0.82	0.46–1.46	0.31			
	ICT → RT	2	1.04	0.14–7.74				
	ICT → CCRT	4	2.6	0.77–8.7				
	RT	47	1					
DTI	≤ 6 weeks	37	0.45	0.23–0.47	**0.018**			
	> 6 weeks	69						

HR: hazard ratio; CI: confidence interval; RT: radiotherapy (SIB-IMRT); CCRT: concomitant chemoradiotherapy; ICT: induction chemotherapy; CPD: cigarettes/day; DTI: time of diagnosis to treatment initiation; * Multiple Cox regression model selected based on simple models (p < 0.30 is included in model).

Table 5
Incidence of Grade ≥ 3 oral mucositis in selected published series including our own study.

Study	Grading systems	N patients/treatment	CCRT (%)	Mucositis (%) Grade ≥ 3
Studer et al. [25]	RTOG	80 definitive SIB-IMRT 34 postop SIB IMRT	78	15
Montejo et al. [21]	CTCAE v.3	43 definitive SIB-IMRT	100	30.2
Mazzeo et al. [23]	RTOG	28 definitive SIB-IMRT	71	25
Franzeee et al. [51]	CTCAE v.3	122 definitive SIB-IMRT	91	11
Rastogi et al. [24]	RTOG	30 definitive SIB-IMRT	0	56.67
Our study	RTOG	76 definitive SIB-IMRT 30 postop SIB IMRT	56	40

CCRT concomitant chemoradiotherapy.

Discussion

Given the poor prognosis of locally advanced HNSCC due to the high loco-regional recurrence rate, optimizing radiation therapy remains an important goal. In the present series we report our experience with SIB IMRT combined with multimodality treatment.

Disease control

With a median follow up of 31 months, the estimated 2- and 3-year loco-regional control were 78% and 78% in the postoperative setting *(group A)* and 71 and 64% in the definitive SIB IMRT group *(group B)*, respectively. The 2- and 3-year overall survival rates were 68% and 57%, and 59% and 52% in group *A and group B,* respectively. These numbers are somewhat lower than the overall survival results reported in the literature being 83% to 90% in the postoperative [19,20] and 65% to 83% in the definitive SIB IMRT setting [21–23,3,24]. This can be explained by the high proportion of stage III-IV HNSCC (27/30 (90%) in the postoperative group and 60/76 (79%) in the definitive group). Moreover, there is also the important number (25%) of oral cavity tumors in our study, of whom half of them is treated by (C)RT; the majority for advanced unresectable disease or for being medically unfit for surgery. Studer et al. reported a 2-year overall survival rate of 85% in a mixed cohort of 34 postoperative patients and 80 patients treated by definitive SIB-IMRT [25]. Chao et al. found a 2-year loco-regional control of 79% and 90% in 74 patients undergoing adjuvant SIB-IMRT and 52 patients undergoing exclusive SIB-IMRT, respectively [19]. At the analysis of the pattern of failure with SIB-IMRT in our series, we observed that 80% and 89% of failures occurred in the high risk dose in patients in group B and A, respectively. These results are concordant with previously published studies reporting most failures to occur in high dose regions [26,19]. The explanation of our slightly worse data is the high proportion of stage III-IV HNSCC (27; 90% in the postoperative group and 60; 79% in the definitive group) and the absence of patients with nasopharyngeal cancer.

The distant control in our study was acceptable, 78% in group A and 76% in group B. In total, 20 (19%) patients developed distant metastasis, while only half of these patients developed a loco-regional recurrence, indicating early development of occult metastasis. The prevalence of distant metastasis seems somewhat higher in our series than in other studies, being 8% to 13.7% [27–29]. Duprez et al. reported a 2- and 5-year actuarial rates of distant control of 84% and 80% in a cohort of 1022 patients with HNSCC [29].

A number of studies shows overall treatment time (OTT) to be a critical predictor of the clinical outcome in HNC patients with the main explanation being the fast tumor cell repopulation [30,31]. Gonzalez et al. reviewed sixty-five articles confirming a large deleterious effect of prolonged OTT on local control and overall survival [32]. In these studies, the authors found that the delays in RT can result in an average loss of loco-regional control (LRC), ranging from as low as 1.2% per day to as high as 12–14% per week. In our study, a prespecified DTI threshold of 6 weeks was evaluated given the results reported by Ang

et al. [33]. They found that a > 6-week interval between surgery and RT was detrimental in patients receiving the 7-week schedule and that completing the therapy in a cumulative time of > 13 weeks yielded a highly significantly lower local control and survival. The importance of DTI on survival results in our cohort, especially in the definitive SIB IMRT group is consistent with previously published data in which delayed initiation of radiation therapy resulted in decreased patients' outcomes [34]. The majority of patients (98%) in our cohort received their IMRT without chemoradiation related toxicity interruptions. Ten patients (9%) had a prolongation of 6 days or more due to holidays and machines maintenance and one patient in the postoperative group had a prolongation of 24 days due to a postoperative wound complication. Based on these observations, we initiated a multidisciplinary collaboration to prioritize head and neck cancer patients and a priority process to avoid therapeutic interruptions. This process implies to either switch patients to another machine or to treat them twice a day later that week, in case of maintenance or breakdown.

Toxicities

The most important RT-related acute toxicity (≥ grade 3) in the postoperative and definitive SIB IMRT groups was dysphagia, followed by mucositis and dermatitis. Forty seven (44%) of our patients developed grade 3 dysphagia during treatment. This is somewhat higher than the findings of Mazzeo et al. who reported a 30% dysphagia in their series [23]. Rastogi et al. used the same RTOG/EORTC scoring system and reported 27% grade 3 dysphagia in the patients treated with definitive SIB-IMRT [24]. Oral-oropharyngeal mucositis at different degree is a common and treatment limiting toxicity of RT in the HNC patients. The maximum grade of acute mucositis reported in our series was grade 3, seen in 42 (40%) patients and spontaneous healing was observed at a mean of 8 weeks (6–12) after CRT completion. This incidence is in concordance with other published studies using IMRT-SIB technique (Table 5).

With regards to the specific measures, in order to prevent malnutrition and dehydration following treatment side effects often experienced by HNC patients some centers perform percutaneous endoscopic gastrostomy (PEG) tubes placement prophylactically. The preventive role of PEG tube is debated in literature. Some published data suggest that patients with HNC who undergone multimodality treatment have benefited from a prophylactic PEG which limits malnutrition, dehydration and loss of weight during the treatment [35]. Almost half of the patients in our study benefited from a preventive PEG. Despite of this approach, another three patients (10%) in group A and 10 (13%) in group B required a salvage PEG tube or total parenteral nutrition during RT due to significant weight loss. On the other hand, the preventive PEG tube may negatively affect swallowing physiology with long term PEG dependence, swallowing function and quality of life. In our study, only two patients in the definitive SIB IMRT group developed late feeding tube dependency.

Grade 3 dermatitis localized in the high dose volume area was experienced by 22 (21%) patients. This is closely comparable to the

findings of Rastogi et al. who reported almost 30% grade 3 dermatitis [24]. Studer et al. reported only 5% grade 3 dermatitis [25]. It is noteworthy that in case of cutaneous infiltration by pathological lymph nodes a bolus has been applicated in our series. We observed a clinically significant (grade ≥ 2) acute xerostomia in the majority of our patients (86; 81%).

The late toxicity in our study was tolerable in the majority of patients. The most prevalent for both groups was xerostomia followed by taste impairment.

At 12 months, 44 (42%) patients still complained of clinically significant xerostomia. The result at 12 months is in the same range as found in the IMRT arm of the PARSPORT prospective trial aimed to compare the incidence of severe xerostomia between IMRT and conventional RT [6]. They reported 38% LENT-SOMA subjective, grade 2 or worse xerostomia at 12 months in patients treated by IMRT with mean doses of 25.4 Gy and 47.6 Gy to the contralateral and ipsilateral parotid glands, respectively. The mean dose of contralateral glands in our cohort was lower than in the PARSPORT cohort (20.3 Gy vs. 25.4 Gy). The difference in the median dose of ipsilateral glands was even more pronounced (31.6 Gy vs. 47.6 Gy). Despite the above, 36% of our patients still reported late xerostomia at 24 months in comparison with 29% of patients in the PARSPORT trial. However, the comparison of toxicity scores coming from different grading systems is complicated, as concordance between the assigned grades can be weak. We highlight that our study bears some uncertainties regarding toxicity scores collected retrospectively and the lack of objective measurement of the xerostomia with our results based on subjective clinical data only.

The relatively high late dysgeusia (23%) is caused by the fact that 20/24 (83%) patients were treated for an oral cavity or oropharyngeal tumor with significant irradiation to the taste system.

We report grade 3 late dysphagia in 8 patients (8%) with 2 patients in the definitive SIB IMRT group suffering from feeding tube dependency with enteral alimentation at 12 months after treatment. In a group of 115 patients, Studer at al. observed 3 cases (3%) of late dysphagia grade 3/4 [27]. In a cohort of 50 patients with oropharyngeal cancer treated by IMRT at Memorial Sloan-Kettering Cancer Center, De Arruda et al. reported 8 cases (16%) of pharyngeal grade 3 toxicity with cases of esophageal stricture requiring dilatation [36]. In a subset of patients with stage III/IV laryngeal/hypopharyngeal cancer treated by definitive SIB IMRT group, a functional larynx was observed in 63% of the patients at the time of last follow up. Aspiration was observed in 8% of patients and a tracheostomy in 4%. In our study, mainly the complaining patients were reported, comparing to other studies which assessed all patients including non-symptomatic, who reported higher incidence of poor functional outcomes [37–39]. In a subset of patients with oral cancer treated either by postoperative or definitive SIB IMRT, 2/27 (7%) cases of ORN were documented. A similar rate (5%) was reported by Gomez et al in a cohort of 35 patients from Memorial Sloan-Kettering Cancer Center receiving postoperative IMRT for oral cavity cancer [40]. In a cohort of 75 patients from the same center treated definitively by (C)RT, 6.8% developed ORN [41]. However, some series reported worse results –ranging from 18.4 to 20.7% ORN [42–44]. Radical (C)RT for an oral cavity tumour remains a challenging treatment. High doses are required to treat target volumes in close vicinity to normal tissues such as the mandible, teeth and salivary glands. Some reports indicate that IMRT could reduce these toxicities. Ben-David et al found no ORN in 176 patients treated with IMRT for HNC [45]. They attributed the absence of ORN to the more conformal dose distribution limiting the high doses to the mandible and to the use of the prophylactic dental care. The latter because it has been shown in previous studies that dental extraction after RT is a risk factor for development of ORN [46,47]. We strongly recommended our patients to continue a long term dental follow up and give them advice regarding dental extractions or implantations.

At present, there are several chemotherapy regimens used in the treatment of HNSCC. The three weekly schedule of cisplatin on locally advanced HNSCC has been established by multiple clinical trials, while the toxicity remains important and only a part of the patients receive the complete 3-cycle treatment [3,48,49]. Although a weekly schedule has been used to decrease toxicity, the latest data comparing the two regimes suggest the superiority of the three weekly schedule in terms of locoregional control. In our retrospective analysis 59 patients (56%) received concomitant chemotherapy. In the 3-weekly group (40; 68% patients) more than half of the patients (55%) were not able to receive all three planned doses of cisplatin but all patients received at least 2 cycles . This is less than the 63–70% receiving all three cycles of cisplatin reported by other studies [4,48].

It is clear that our study suffered from some limitations. First and most important is its retrospective character. We determined that we may have underreported and underscored toxicity, especially the late toxicity. Furthermore, no patient reported quality of life data has been collected. HPV status was unknown in the majority of our patients. As most of our patients had oropharyngeal tumors, the knowledge of HPV status can affect the interpretation and comparison of the results, although most of our population at the time of the study had a smoker's profile. Generally, comparison of the data to prior results has some limitations because patient population in the reported studies is very heterogeneous and the assessment and scoring of toxicities is variable [50]. However, despite all these shortcomings our study reflects the daily life in a middle-sized European RT department and therefore our data is valuable to confirm safety and feasibility of SIB-IMRT for HNSCC outside clinical trials. Prospective data collection for all HNSCC IMRT patients is now in place at our institution.

Conclusions

Our findings demonstrate the safety and feasibility of SIB-IMRT for HNSCC, with acceptable toxicity rates and an excellent treatment compliance with 98% of patients receiving RT as prescribed. Prospective analysis with more accurate toxicity assessments combined with patients reported outcomes should be conducted to assess this treatment approach in more detail.

Ethics approval

The study was approved by the Jules Bordet Hospital Ethics Committee (Protocol_v_1.0 2016/06/17).

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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