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Impact of locoregional irradiation in patients with upfront metastatic head and neck squamous cell carcinoma

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ABSTRACT

Objective: To evaluate the frequency of use, modalities and potential interest of locoregional irradiation (LRT) in patients with upfront metastatic head and neck squamous cell carcinoma (HNSCC).
Methods: Retrospective multicentric study. Were included all patients presenting an upfront metastatic HNSCC treated by platin-5FU- cetuximab based regimen, from 2008 to 2016. Patients with past history of cervical irradiation or HNSCC within the 5 years before metastasis diagnosis were excluded.
Results: 65 patients were included. 25 patients (38%) presented a response or stable disease with chemotherapy. Forty-one patients (63%) underwent a locoregional irradiation: 5 patients before chemotherapy (upfront RT), 13 patients with stable disease or response after chemotherapy (consolidation RT), and 23 patients with progressive disease. Median overall survival (OS) was 11.6 months, median progression free survival was 7.9 months. OS was significantly improved for patients who underwent LRT (median OS 16.1 vs 7.5 months, $p < 0.01$). Among patients who received LRT, OS trended to be better if LRT was performed as consolidation RT compared to upfront RT (median OS of 22.1 vs 15.5 months, $p = 0.11$). Among patients with stable disease or response after chemotherapy, there was a non-significant better OS for the 13 patients treated by LRT (median OS 22.1 vs 11.8 months, $p = 0.21$)). Radical dose was not associated with better locoregional control compared to palliative dose ($p = 0.37$).
Conclusion: LRT is frequently performed during management of upfront metastatic HNSCC and associated with better OS. Non-progressive disease after firs-line chemotherapy seems a good way to select patients who would benefit from radical LRT.

Introduction

Each year more than 500 000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed worldwide [1]. Metastatic spreading occurs in 10% of cases at diagnosis [2], and up to 30% after treatment of a local disease. Distant metastases strongly impact prognosis with no survivors five years after diagnosis [3]. First-line treatment of recurrent/metastatic HNSCC (R/MHNSCC) is based on a polychemotherapy combining platinum salts, 5FU and cetuximab followed by cetuximab based maintenance for good responders (Extreme regimen) [4]. Using this regimen, progression free survival (PFS) is about six months in clinical trials. Nevertheless, clinical presentation of patients with HNSCC metastases is heterogeneous: patients presenting a recurrent disease were usually treated first by prior surgery and/or locoregional irradiation, while patients with upfront metastasos were not. However, in recurrent and metastatic HNSCC, locoregional treatment, and especially radiation therapy, may be proposed. In addition to systemic therapy, radiation therapy can be used for different goals: improving locoregional control and increasing progression-free survival in the event of stabilized metastases under chemotherapy, or palliating locoregional symptoms. Nevertheless, there are hardly any data on locoregional irradiation and its modalities in patients with upfront distant metastasis at diagnosis. The aim of this study was to assess the frequency of use and potential interest of locoregional irradiation in

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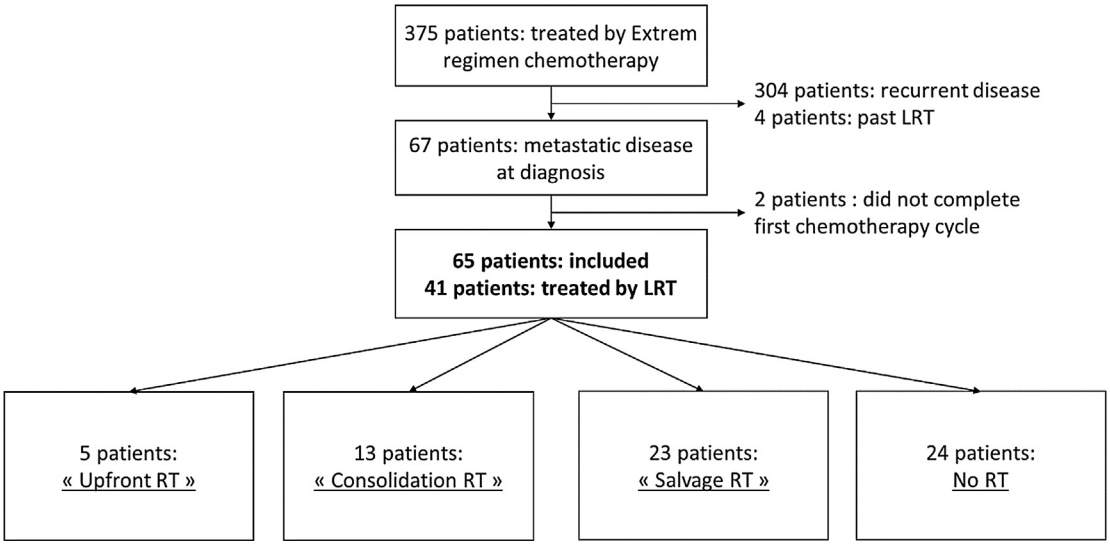

Fig. 1. Flow chart. *LRT: Locoregional RadioTherapy.*

metastatic HNSCC patients treated by polychemotherapy.

Methods

Objectives

The primary endpoint was to assess the frequency of use, indications and modalities of locoregional irradiation in patients with upfront metastatic HNSCC carcinoma. Secondary endpoints were to evaluate: progression-free survival (from diagnosis to first progression), progression sites and overall survival according to radiotherapy administration or not, description of progression sites and according to treatments.

Patients

This multicenter retrospective study included all consecutive patients with upfront metastatic HNSCC treated by a platin / 5FU / cetuximab regimen as first-line chemotherapy from 2008 to 2016. Upfront metastatic disease was defined as presence of distant metastasis at initial HNSCC diagnosis. Use of cisplatin or carboplatin was at the physician's discretion. Adapted regimens were included (without 5FU due to comorbidities or without cetuximab due to anaphylactic reaction). Patients who received less than one cycle of chemotherapy and those in poor general condition (WHO performance status 3–4) were excluded. Patients with a history HNSCC were included if they had no prior exposure to radiation therapy and no relapse of this first cancer for the last five years.

Recruitment was performed in 3 French hospitals: the Henri Becquerel comprehensive cancer center in Rouen, the François Baclesse comprehensive cancer center in Caen, and Caen University Hospital. This study was approved by the institutional review board of the center Henri Becquerel (N°1706B) and is in accordance with French laws regarding retrospective medical studies. Patients who were alive at study time were informed about the study, and none expressed opposition to inclusion.

Patients' characteristics collected from computerized medical files were age, sex, comorbidities assessed by Charlson index, alcohol and tobacco consumption, WHO performance status (PS), nutritional status, tumor location, TNM stage, metastatic sites and previous oncologic treatment. Oligometastatic disease was defined as 1 to 3 metastases without restriction on metastatic site. Malnutrition was defined by a body mass index (BMI) below 18.5 kg/m^2 or a weight loss of more than 10% of total body weight in the last three months [5].

Treatment and follow up

Patients who received locoregional head and neck irradiation were divided into three subgroups according to time of radiotherapy: before chemotherapy (Group "Upfront RT"), as consolidation in the event of stable disease or partial response after Extreme protocol (Group "Consolidation RT"), or as salvage in the event of locoregional progression after chemotherapy (Group "Salvage RT"). Patients who did not receive locoregional irradiation were part of Group "No RT". Total dose, number of fractions and intent of treatment (prolonged local control vs antalgic) was recorded. Irradiation was defined as radical in the event of locoregional irradiation planned dose of ≥ 60 Gy, and as palliative if < 60 Gy.

Chemotherapy regimen, number of cycles and doses were recorded. Data on treatment at progression were also collected.

Follow-up during treatment included at least a physical exam before each cycle of chemotherapy, and every three months after completion of chemotherapy with a cervicothoracic CT scan. Follow up was defined from time to diagnosis to last follow-up or death. Disease progression was assessed according to RECIST criteria. Progression-free survival (PFS) was determined from time of diagnosis or time of RT. Overall survival (OS) was determined from time of diagnosis.

Statistical analysis

Quantitative variables were described with median and range [min–max], while qualitative variables were described with numbers and percentages. Chi square or Fisher exact tests were used to compare categorical variables. PFS and OS were assessed using the Kaplan–Meier estimator and compared using a log-rank test. A stepwise regression of the Cox model was used for multivariate analysis. For all tests, a two-tailed P value less thanor equal to 0.05 was considered statistically significant.

Results

Population

The flow chart of the study is described in Fig. 1. Sixty-five patients were included. Patients characteristics at diagnosis are detailed in Table 1. Median age was 57 [41–78]. Of note, 39 patients (58.0%)

Table 1
Patients characteristics at diagnosis.

	n	%
Gender		
Male	56	86.0%
Female	9	14.0%
Smoking (n = 63)		
Yes	40	63.5%
Withdrawn	18	28.6%
Never	5	7.9%
Alcohol consumption (n = 64)		
Yes	33	51.6%
Withdrawn	20	31.2%
Never	11	17.2%
Primary tumor site		
Oral cavity	6	9.2%
Oropharynx	26	40.0%
Hypopharynx	19	29.2%
Larynx	6	9.2%
Unknown primary	8	12.3%
T stage (n = 64)		
1 & 2	12	18.8%
3 & 4	44	68.8%
No primitive	8	12.4%
N Stage		
0	1	1.6%
1	8	12.3%
2	32	49.2%
3	24	36.9%
Metastatic site		
Pulmonary	53	81.6%
Bone	12	18.5%
Extra-cervical lymph node	10	15.4%
Visceral	13	20.0%
Oligometastatic disease		
Yes	23	35.4%
No	42	64.6%
WHO Performans status at diagnosis (n = 63)		
0	12	19.0%
1	38	60.3%
2	13	20.6%
Nutritional status (n = 62)		
Malnutrition	29	46.8%
Good	33	53.2%

HNSCC: Head and neck squamous cell carcinoma. WHO World Health Organization.
Extra-cervical lymph node: axillary, hilar and/or retroperitoneal lymphadenopathy

presented at least one significant comorbidity. Median Charlson Index was 7 [6–11]. HPV status was not available.

First-line chemotherapy treatment

First-line polychemotherapy regimen was based on cisplatin for 47 patients (72%) and carboplatin for 17 patients (26%). One patient did not receive platin due to renal and vascular comorbidities. Three patients did not receive 5FU due to a vascular contraindication. Three patients discontinued cetuximab due to grade 3 anaphylactic reaction.

Median number of chemotherapy cycles administered was 5 (range 1–7). Forty patients (58%) showed disease progression during the first six cycles of chemotherapy. Twenty-five patients (38%) underwent a maintenance phase with cetuximab monotherapy after the first six cycles of chemotherapy. For these patients, median number of maintenance cycle was 7 (1–32). One patient had stable disease without cetuximab maintenance because of anaphylactic reaction during the first infusion. No patient underwent local treatment of metastasis in a curative intent (surgery or irradiation). Second line treatment is described in supplementary data.

Locoregional irradiation

Among the 65 patients included, 41 (63%) underwent locoregional irradiation after diagnosis. Treatment modalities were decided during a local multidisciplinary team meeting. Radiotherapy doses were radical for 28 patients (68%) and palliative for 13 patients (20%). Patients presenting an oligometastatic spread and/or no extrapulmonary metastasis were more likely to receive locoregional irradiation ($p = 0.016$ and $p = 0.014$ respectively).

Types of head and neck irradiations were: Upfront RT for 5 patients (14%), Consolidation RT for 13 patients (29%) and Salvage RT 23 patients (57%). Disease characteristics, irradiation modalities and concomitant medical treatment according to each group are detailed in Table 2.

Patients in the Upfront RT group were usually treated by platinum-based chemoradiotherapy for oligometastatic disease (4 out of 5 patients). All the patients received irradiation with a radical dose.

Among patients in the Consolidation RT group, locoregional irradiation was performed after 3 cycles of chemotherapy for 5 patients (38.5%) and after 6 cycles in 8 patients (61.5%). No concomitant treatment was administered in 54% of all patients. Patients in the Salvage RT group (treated after progression on polychemotherapy) received no concomitant treatment, and irradiation intent was palliative in 52% of cases. Locoregional radiotherapy was performed after first line chemotherapy in 22 patients (88%), and after second line chemotherapy in 2 patients (12%).

Survival outcomes

Median follow-up was 12.3 months [1–49]. Fifty-eight patients (89%) were dead at time of analysis. Overall median PFS from diagnosis among the 65 patients was 7.9 months. Median OS was 11.6 months.

In univariate analysis, OS was significantly longer in patients who received head and neck irradiation compared to those who did not (median OS respectively 7.5 vs 16.1 months, HR 0.38 95%CI [0.19–0.73] $p < 0.01$). Other prognostic factors in this cohort were: presence of extra pulmonary metastasis and carboplatin-based chemotherapy regimen, which were associated with significantly lower OS ($p < 0.01$ and $p = 0.04$ respectively). In multivariate analysis, OS was significantly longer in patients treated by LRT, a cisplatin-based chemotherapy regimen and with WHO Performance status 0–1 ($p < 0.01$, $p = 0.03$ and $p = 0.04$ respectively) (Table 3).

OS and PFS according to each group of RT are presented in Table 4 and Fig. 2. OS was significantly different according to RT group ($p = 0.0009$) PFS from the end of irradiation was significantly lower in the Salvage RT group ($p = 0.02$). Among patients treated by LRT, 16 out of 39 patients evaluated (41%) had a cervical progression despite locoregional treatment.

Among the 27 patients with stable disease or response after chemotherapy, 20 underwent LRT (13 patients as Consolidation RT, 7 patients with progressive disease under cetuximab maintenance as Salvage RT). A non-significant improvement in OS was observed among patients who underwent locoregional radiation (median OS 23.9 months) compared to those who did not (median OS 12.7 months), HR 0.53 [0.16–1.81] ($p = 0.21$). The same pattern of results was found regarding PFS between these two groups: median PFS 14.9 versus 9.8 months HR0.54[0.118–1.6] ($p = 0.18$) (Fig. 3). No significant difference in OS was found between patients treated by Consolidation RT (median OS 22.1 months) or by Salvage RT under cetuximab maintenance (median OS 25.9 months) (HR 0.95[0.34–2.65], $p = 0.92$). A non-significant improvement in PFS was observed among patients treated by Salvage RT in the event of progression under cetuximab maintenance (median PFS 20.6 months) compared to the patients treated by Consolidation RT (median PFS 13.2 months) (HR 0.64 [0.25–1.65], $p = 0.35$). OS tended to be longer in the Consolidation RT group than in the Upfront RT group, with a median survival from

Table 2
Disease characteristics and locoregional irradiation modalities according to subgroups.

	Group « Upfront RT » (n = 5)		Group « Conso RT » (n = 13)		Group « Salvage RT » (n = 23)		*p*	Group « No RT » (n = 24)	
	n	%	n	%	n	%		n	%
T							*0.456*		
1–2	0	*0%*	3	*23%*	5	*23%*		4	*17%*
3–4	3	*60%*	9	*69%*	15	*65%*		17	*71%*
0	2	*40%*	1	*8%*	2	*9%*		3	*12%*
NA					1				
N							***0.025***		
0	0	*0%*	0	*0%*	1	*4%*		0	*0%*
1	2	*40%*	3	*23%*	0	*0%*		3	*12%*
2	2	*40%*	9	*69%*	13	*57%*		8	*33%*
3	1	*20%*	1	*8%*	9	*39%*		13	*54%*
Oligometastatic							*0.240*		
Yes	4	*80%*	6	*46%*	9	*39%*		4	*17%*
No	1	*20%*	7	*54%*	14	*61%*		20	*83%*
Extrapulmonary metastasis							*0.999*		
Yes	2	*40%*	3	*23%*	5	*22%*		16	*67%*
No	3	*60%*	10	*77%*	18	*78%*		8	*33%*
Dose							***< 0.001***		
Radical	5	*100%*	12	*92%*	11	*48%*			
Palliative	0	*0*	0	*0*	12	*52%*			
NA			1						
Technique							***< 0.001***		
IMRT	4	*80%*	6	*50%*	0	*0%*			
Conformal	1	*20%*	6	*50%*	19	*100%*			
NA			1		3				
Split course	0	*0%*	2	*17%*	1	*4%*	*0.531*		
Concomitant treatment							***< 0.001***		
Platin	5	*100%*	1	*8%*	0	*0%*			
Cetuximab	0	*0%*	5	*38%*	3	*13%*			
None	0	*0%*	7	*54%*	22	*87%*			

Group Upfront RT: radiotherapy as primary treatment and before any chemotherapy / Group Consolidation RT: locoregional radiotherapy with stable disease or partial response after chemotherapy / Group Salvage RT: locoregional radiotherapy with progressive disease after chemotherapy. / Group No RT: no locoregional radiotherapy. P Value were calculated between the three groups treated by radiation therapy.
IMRT: Intensity – Modulated Radiation Therapy. NA: not available.

Table 3
Univariate and multivariate analysis of predictive factors of overall survival determined by Cox model.

Variable	Univariate analysis			Multivariate analysis		
	HR	95%IC	p Value	HR	95%IC	p Value
Age > 70	0.81	[0.39–1.67]	0.59	NI		
WHO PS 2	1.78	[0.82–3.85]	0.06	1.42	[1.02–2.00]	**0.04**
LRT	0.35	[0.16–0.74]	< **0.01**	0.30	[0.16–0.55]	< **0.01**
Malnutrition	1.54	[0.89–2.65]	0.09	NI		
Carboplatin-based regimen	1.81	[0.93–3.50]	**0.04**	2.01	[1.09–3.68]	**0.03**
Extrapulmonary metastasis	2.04	[1.13–3.69]	< **0.01**	NI		

HR: Hazard Ratio. CI: Confidence Interval. NI: Variable Not Included by the mod. WHO PS: World Health Organization Performance status.

diagnosis of 22.1 and 15.5 months respectively (HR = 0.426 [0.112–1.612], p = 0.11). No difference was found regarding PFS in these two groups (HR = 0.731 [0.211–2.532], p = 0.58). A radical dose was not associated with better locoregional control after RT compared to a palliative dose (p = 0.37).

Discussion

In this retrospective multicenter study of patients diagnosed at a metastatic stage of HNSCC, we investigated the use of locoregional irradiation. Metastatic spreading of HNSCC is usually associated with locoregionally evolved disease [6]. Interestingly, 63% of the patients in this study were treated by locoregional radiotherapy, so this treatment option is frequently used in that setting. A retrospective analysis of 6663 patients with distant metastatic head and neck carcinoma -but also including salivary gland, thyroid and sinusal primitives - reported comparable results with a 75% rate of surgical or radiation treatment within the head and neck region [7].

In the present study, irradiation was performed at radical doses in about 2 cases out of 3, despite the metastatic stage. Overall, use of locoregional RT in selected patients was associated with a clear improvement in OS in univariate analysis (HR 0.35 95%CI [0.16–0.74], p < 0.01) and multivariate analysis (HR 0.30 95%CI[0.16–0.55], p < 0.01). Regarding the population included, median OS and PFS from diagnosis were respectively 11.6 and 7.9 months. In the pivotal study by Vermorken et al. [4] of a metastatic and/or recurrent population pg HNSCC, OS and PFS were 10.1 and 5.6 months, but rates of locoregional irradiation was not described in the event of upfront metastatic disease. Such a difference in survival rate is unexpected, since our unselected population presented comorbidities and malnutrition that are more frequent than in prospective trials. Argiris also described better outcomes in the event of prior LRT in R/M HNSCC [8]. Thus, it can be hypothesized that the subgroup of patients with upfront metastatic disease had a slightly better prognostis than those with a recurrence. Of note, HPV status, which impacts outcomes in patients with recurrent or metastatic HNSCC [9], was unavailable in this retrospective study but is usually around 10% in our region [10] and could hardly have biased the results. Whatever the benefit in OS observed in this study, it is in line with two retrospective studies which reported an

Table 4
Outcomes according to radiation group.

	Group "Upfront RT" N = 5		Group "Consolidation RT" N = 13		Group "Salvage RT" N = 23		Group "No RT" N = 24	
Outcomes								
Death (all causes)	5	*100%*	9	*69%*	22	*96%*	22	*92%*
Cancer related death	4	*80%*	6	*46%*	16	*70%*	15	*68%*
Survival (months)								
OS	15.5 [5.7–25.5]		22.1 [6.5–49.0]		13.2 [4.6–48.0]		7.5[1–33,4]	
PFS from diagnosis	13.1 [5.4–23.3]		13.1 [6.5–35.6]		8.1 [2.9–32.0]		6.0 [1–33.4]	
PFS from RT	9.1 [2.3–20.9]		4.7 [0–28.7]		2.2 [0–7.5]		–	
1st progression site after RT								
Cervical	2	*40%*	1	*8%*	3	*14%*	7	*29%*
Metastatic	1	*20%*	4	*31%*	10	*48%*	4	*17%*
Cervical and metastatic	2	*40%*	4	*31%*	4	*19%*	6	*25%*
None	0	*0%*	3	*23%*	3	*14%*	5	*21%*
Death before evaluation	0	*0%*	1	*8%*	1	*5%*	2	*8%*
NA					2			

OS: overall survival. PFS: Progression-free survival. RT: radiotherapy.
Survival data are expressed as Median [Min-Max]. Outcomes and progression sites are expressed as numbers and percentage.
Group Upfront RT: radiotherapy as primary treatment and before any chemotherapy / Group Consolidation RT: locoregional radiotherapy with stable disease or partial response after chemotherapy / Group Salvage RT: locoregional radiotherapy with progressive disease after chemotherapy. / Group No RT: no locoregional radiotherapy.

improvement in OS among metastatic HNSCC patients treated with combined high-intensity local treatment and systematic therapy [7,11]. Obviously, retrospective analyses induce a selection bias and an immortal-time bias. Nevertheless, cumulative evidence suggests that local RT is benefical in selected patients.

The most appropriate timing and modalities of locoregional irradiation in metastatic patients are unclear regarding the few data available on this subject. Primary and nodal evolution often leads to detrimental symptoms. Pain, airway obstruction, dysphagia and bleeding are commonly described in the terminal phae [12–14]. Such symptoms can lead to proposing locoregional irradiation even in a terminal palliative setting. A Finnish study [14] of 60 patients in a palliative care unit showed that half of the hospitalized patients with HNSCC had undergone locoregional irradiation. In general, 30 Gy of radiotherapy was administered in 3 Gy fractions but some patients even received radical treatment despite the palliative intent. The aim of early radical locoregional irradiation is to improve survival and increase quality of life in the late phases by preventing the onset of severe symptoms. This approach may be used in the event of oligometastatic disease. Nevertheless, metastatic disease at diagnosis means that treatments can only have a palliative intent. Radiotherapy at radical doses leads to high rates of acute toxicity and can decrease quality of life [15]. Thus, it is mandatory to establish an appropriate benefit / toxicity ratio as well as to select patients who will benefit from radiotherapy.

Locoregional irradiation was administered in 63% of our population and in three settings: before chemotherapy, after stable disease or partial response to chemotherapy, and in the event of progressive disease after chemotherapy. Considering the patients treated by upfront radiotherapy, the first sit of progression was locoregional in 4 cases out of 5 and the benefit of early locoregional treatment seemed small both in term of OS and local control. On the other hand, there was trend in favor of proposing LRT in patients who had a response or stable disease after 6 cycles of chemotherapy with a median OS of 23.9 months, which is twice as long as would be expected in an overral metastatic / recurrent population. LRT could be given as a consolidation treatment after chemotherapy or at progression after cetuximab maintenance. Radical radiation therapy was not associated with better locoregional control than a palliative dose. This emphasizes the need of further data on this subject in order to homogenize standards of care in patients with upfront metastatic HNSCC.

Owing to a lack of power and biases due to its retrospective design,

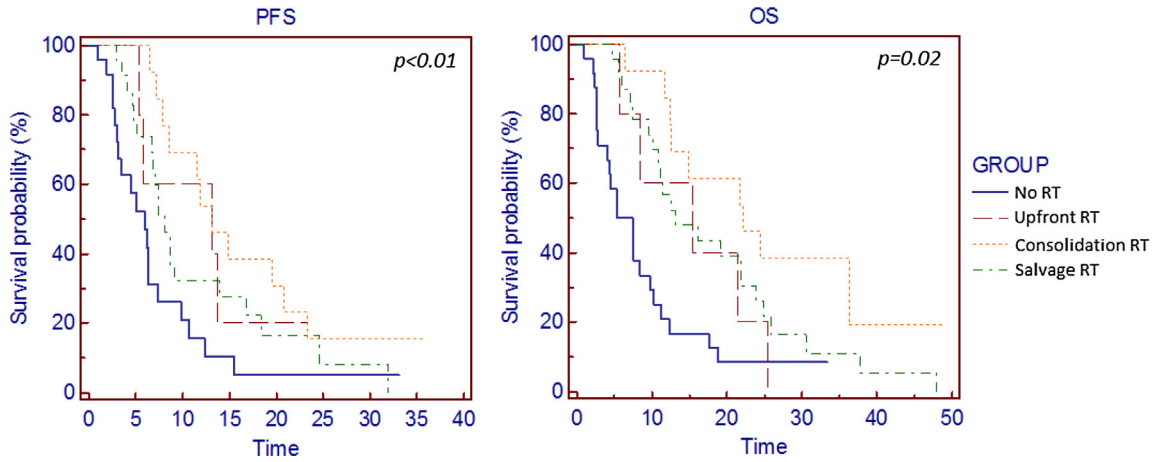

Fig. 2. A: Progression-Free Survival (PFS) and B: Overall Survival (OS) according to radiation group. *"Upfront RT": radiotherapy as primary treatment and before any chemotherapy / "Consolidation RT": locoregional radiotherapy with stable disease or partial response after chemotherapy / "Salvage RT": locoregional radiotherapy with progressive disease after chemotherapy. / "No RT": no locoregional radiotherapy.*

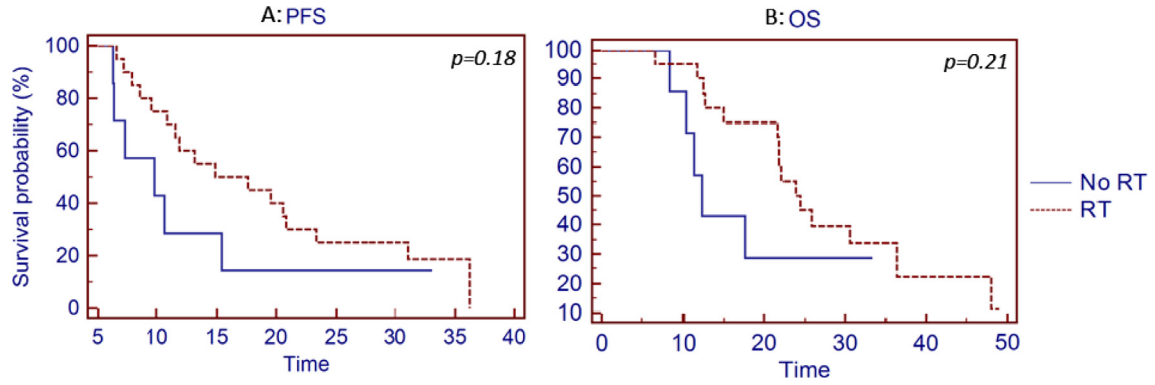

Fig. 3. A: Overall Survival (OS); B: Progression-Free Survival (PFS) among the 27 patients with stable disease after 6 cycles of chemotherapy and according to radiation therapy. *RT: locoregional radiotherapy.*

this study does not provide any definitive conclusion about the efficacy of locoregional irradiation in patients with metastatic disease at diagnosis. Nevertheless, our results can help in selecting patients, since: the response to first-line systemic treatment seems to indicative of who would benefit fromradical radiation therapy. It also helps to avoid administering radiotherapy to patients who will not respond to chemotherapy. A prospective study is now needed to explore whether locoregional irradiation affects survival outcomes with an acceptable level of tolerance in patients with metastatic HNSCC.

Conclusion

Locoregional irradiation is frequently administered in the event of metastatic HNSCC and is associated with a benefit on OS. While the timing and modalities of radiotherapy vary patients who are treated after stable disease or partial response to chemotherapy seem to be the best candidates for radical treatment.

Conflict of interest

None to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.04.005.

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