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Clinical outcome of stereotactic body radiotherapy for lung-only oligometastatic head and neck squamous cell carcinoma: Is the deferral of systemic therapy a potential goal?

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ABSTRACT

Objectives: Oligometastatic head and neck squamous cell carcinoma (HNSCC) is a rare entity with no evidence-based treatment recommendations available to support the use of local ablative therapies. The aim of our study was to report on the clinical benefit of stereotactic body radiotherapy (SBRT) for patients with lung-only oligometastases, defined by the presence of 1 to 5 pulmonary lesions.

Material and Methods: SBRT was applied in case of single lesions deemed amenable to local treatment only ("de novo" pattern) or after first line chemotherapy at time of disease oligoprogression ("induced" pattern). To assess the potential deferral of systemic therapy in both time points, we analyzed time to progression (TTP) defined as the time from the last day of SBRT to disease progression or death from any cause. Cox regression analysis was performed to identify predictive factors of better outcome.

Results: Twenty-seven patients were retrospectively evaluated. The majority (81.5%) had HPV negative disease and a "de novo" oligometastatic pattern (78.6%). The median maximum lesion diameter and target size were 1.5 cm and 22.7 cc, respectively. At a median follow-up of 22 months (range 6–73), the median TTP was 10 months (95% CI: 9.5–21.1), with 1- and 2-year rates of 56.2% and 35%, respectively. The objective response rate at 3 months after SBRT was 75%. At multivariate analysis baseline T3/T4 stage had a HR for worse outcome of 5.38 ($p = 0.033$). Acute toxicity was minimal (G1/G2 of 14.8%).

Conclusion: In properly selected oligometastatic patients, SBRT has potential for sustained deferral of systemic treatment.

Introduction

The diagnosis of head and neck squamous cell carcinoma (HNSCC) in a recurrent or metastatic stage portends a dismal prognosis. Unless the relapsed disease is deemed amenable to salvage surgery or re-irradiation, the intent of treatment is invariably palliative. With first line Cetuximab – based chemotherapy options, the median overall survival is of about one year [1–4]. Historically, the predominant pattern of failure is loco-regional [5]: uncontrolled tumor growth in the head and neck is cause of marked deterioration in quality of life and ultimately of death for most patients. In recent years, the competing risk of distant relapse as first event of disease progression has increasingly been recognized. In particular, in contrast to classical tobacco and alcohol – related HNSCC, HPV – driven oropharyngeal cancer is characterized by exquisite radio- and chemo-sensitivity [6], resulting in long-term loco-regional control for > 75% of cases [7]. However, for locally advanced HPV - related tumors, such as T4 or N3 disease, the survival rate is still suboptimal mainly due to distant spread [8]. Next to the rising incidence of HPV – positive HNSCC [9], the overall efficacy of aggressive multidisciplinary strategies in securing primary tumor control also for HPV negative tumors has contributed to make the pattern of failure of head and neck cancer more heterogeneous [10] than in the past. In this context, an "oligometastatic" state has been defined [11] as a disease entity with a still limited metastatic potential in terms of number and

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location of secondary lesions. For HNSCC, the occurrence of oligometastases has been rarely [12] reported, mainly in relation with lung metastatization. Among other local ablative treatments, stereotactic body radiotherapy (SBRT) is an effective strategy [13] supported by accumulating data for thoracic lesions from different primary tumors, but with only anecdotal evidence for head and neck cancer. Since the management of recurrent/metastatic HNSCC is still hampered by the availability of a limited array of systemic options [14], the possibility to defer the need of chemotherapy for selected patients by employing a local ablative treatment may be noteworthy. The aim of our work was to report on the clinical outcome of SBRT for lung-only oligometastatic HNSCC in terms of safety and efficacy.

Material and Methods

Patients' characteristics and inclusion criteria

Patients affected by histologically-confirmed HNSCC with lung oligometastatic disease treated with SBRT were considered in this retrospective study. In line with common definition [15], a lung-only oligometastatic disease was characterized by the presence of 1 to 5 pulmonary metastases. A multidisciplinary discussion was mandatory for every patient, in particular to rule out differential diagnoses such as inflammatory nodules or second primary lung cancer. The inclusion criteria for patients enrolled were as follows: receipt of curatively-intended treatment for primary disease; FNAB of index metastatic pulmonary lesion positive for HNSCC or pathologic FDG uptake; largest diameter of index lesion of maximum 5 cm; lesion deemed suitable for ablative SBRT; SBRT dose equivalent to BED $\geq 100\,Gy_{10;}$ minimum 6 months follow-up time after SBRT; PS (ECOG) 0–2; exclusion of surgical metastasectomy for solitary lesions due to clinical reasons or patient's refusal.

For the study purpose, we distinguished a "de novo" from an "induced" oligometastatic pattern based on the timing of consideration for SBRT in respect to systemic treatment: "de novo" oligometastases were solitary metastatic lesions deemed amenable to local treatment only, whereas "induced" oligometastases were initially managed with chemotherapy (CHT), with SBRT applied at time of disease oligoprogression. In all cases, the use of SBRT was envisaged to potentially defer the need of further systemic therapy rather than as a truly "curative" approach. In very selected patients with a "de novo" oligometastatic pattern, the solitary lung metastasis was detected in the frame of initial diagnostic workup for locally advanced HNSCC. For these cases, pending mandatory histologic confirmation through fine-needle aspiration biopsy (FNAB) and multidisciplinary discussion in favour of an aggressive, curatively-intended therapy notwithstanding the stage IVC disease, SBRT was proposed to the index lesion along with primary treatment to the head and neck.

Treatment features

SBRT was delivered with a standard linear accelerator (Elekta Synergy, Elekta, Crawley, UK, and Varian, Palo Alto, CA) through a volumetric modulated arc therapy (VMAT or RapidArc) or with a robotic machine (Cyberknife). Typically, target volume consisted of gross tumor volume (GTV) only. To take into account organ motion due to respiratory movement, a simulation 4D-CT was performed, allowing to generate an internal target volume (ITV). A further 3 mm margin was applied to create a planning target volume (PTV) for each case. As per standard practice, daily image-guidance was performed before every fraction. Based on the position (central vs peripheral) and size of the treated lesion, different ablative fractionations (BED $\geq 100\,Gy_{10}$) were chosen. The dose prescription modality (i.e,95% isodose or lower) was dependent on the RT technique which was employed.

Outcome measures and statistics

Local control of the irradiated lesion was assessed at 3 months after SBRT according to Recist criteria [16]. In order to take into account different timepoints in disease progression, we defined two distinct Progression-free survival (PFS) assessments. PFS 1 was defined as the time from the last day of primary treatment (surgery alone, surgery followed by adjuvant treatment, radiotherapy alone, concurrent chemo-radiation, induction chemotherapy followed by chemo-radiation, SBRT concurrent with primary treatment) to disease progression or death from any cause. PFS 2 was defined as the time from the last day of SBRT to disease progression or death from any cause. Time to progression (TTP) was defined as the time from the last day of any SBRT to disease progression or death from any cause. Overall survival (OS) was defined as the time from HNSCC diagnosis to death from any cause. Median PFS1, PFS2, TTP and OS were calculated. The relative estimates of PFS1, PFS2, TTP at 12 and 24 months were estimated by the Kaplan-Meier method. A log-rank test was employed to test whether age, primary site (oropharynx vs others), HPV status, initial disease stage, lesion size and oligometastatic pattern correlated with longer TTP. A multivariate Cox regression analysis was performed when multiple risk factors with a p value < 0.05 were identified in the univariate analysis. Toxicity of SBRT was graded according to CTCAE v.4.1 [17].

Results

Between January 2012 and December 2017, 27 HNSCC patients received SBRT for lung-only oligometastatic disease and were included in our analysis. Patients' characteristics are shown in Table 1. At HNSCC diagnosis, the median age of the patients' population was 67 years (range 37–85). Most subjects (81.4%) had an ECOG PS of 0–1, with a baseline median age-adjusted Charlson comorbidity index (CCI) of 5. Overall, the majority of patients were heavy smokers (59.2% had > 20 pack/years) and had HPV negative disease (81.5%). Treatment modality for primary disease was heterogeneous, with radiotherapy applied in 20/27 patients (74%) as a stand-alone modality or as backbone of post-operative or definitive treatment. In all but 2 cases, an IMRT technique was used. A total dose of 66 – 70 Gy with 2 Gy – 2.12 Gy fractionation was delivered to the head and neck, based on disease extent and treatment intent (adjuvant vs definitive). Concurrent chemotherapy was administered in 75% of cases: 3-weekly 100 mg/m^2 cisplatin, weekly 40 mg/m^2 cisplatin and Cetuximab were prescribed in 4, 8 and 3 patients, respectively. Moreover, TPF-induction chemotherapy preceded chemo-radiation in 3 patients. SBRT features are shown in Table 2. Of note, a patient was treated for two metachronous solitary lung metastases developed 18 months apart, counting therefore twice in our analysis for a total of 28 lesions. According to our prespecified definition, "de novo" and oligoprogressive metastatic patterns were reported in 22 (78.6%) and 6 (21.4%) cases, respectively. The median maximum lesion diameter and target size were 1.5 cm and 22.7 cc, respectively. Among the "de novo" group, 5 lesions (5/22, 22.7%) were synchronous solitary metastases treated with SBRT along with primary treatment. A sustained complete remission was observed in two of these cases with stage IVC disease, described here briefly. A 64-year old male was diagnosed with a T1N2bM1 HPV positive, base of tongue squamous cell carcinoma. The patient had a 10-pack-years tobacco exposure that was stopped 15 years before. During the staging workup, a baseline FDG PET scan showed a solitary hypermetabolic, 7 mm round nodule located in the apicoposterior segment of the upper left lobe which was histologically-confirmed as a metastatic lesion after FNAB (figure 1). The patient underwent 3 cycles of TPF-based induction chemotherapy followed by concurrent chemo-radiation (40 mg/m^2 weekly cisplatin together with IMRT delivering 70 Gy to the primary and nodal GTVs and 60 Gy to the bilateral elective neck in 35 fractions). The "de novo" metastasis (stable after TPF) was treated with 54 Gy to the 95% isodose in 3 fractions with VMAT SBRT over the third and

Table 1
Patients' characteristics. ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer 7th edition; RT, Radiotherapy; CT, Chemotherapy; RTCT, radio-chemotherapy; SBRT, stereotactic body radiotherapy.

Characteristic	No. of patients (%), n = 27
Median age	
years (range)	67 (37–85)
Sex	
Male	24 (88.9%)
Female	3 (11.1%)
ECOG Performance Status	
0	8 (29.6%)
1	14 (51.8%)
2	5 (18.6%)
Charlson Comorbidity Index (age-adjusted)	
< 4	4 (14.8%)
4–7	18 (66.6%)
≥8	5 (18.6%)
Smoking history (pack/years)	
0	5 (18.6%)
< 10	2 (7.4%)
10–20	4 (14.8%)
> 20	16 (59.2%)
Primary tumor	
Oropharynx	11 (40.7%)
Larynx	7 (25.9%)
Hypopharynx	5 (18.6%)
Other	4 (14.8%)
HPV status (OPC only)	
Positive	5 (45.5%)
Negative	6 (54.5%)
T stage at diagnosis (VIIth ed)	
x	2 (7.4%)
1	3 (11.1%)
2	6 (22.3%)
3	12 (44.4%)
4a	3 (11.1%)
4b	1 (3.7%)
N stage at diagnosis (VIIth ed)	
0	10 (37%)
1	4 (14.8%)
2a	1 (3.7%)
2b	11 (40.8%)
2c	1 (3.7%)
AJCC stage at diagnosis (VIIth ed)	
I-II	3 (11.1%)
III	8 (29.6%)
IVA	10 (37%)
IVB	1 (3.7%)
IVC	5 (18.6%)
Primary treatment modality	
Surgery	6 (22.3%)
RT	1 (3.7%)
Surgery + RT	3 (11.1%)
Induction CT + RTCT	3 (11.1%)
RTCT	9 (33.3%)
RT/RTCT + SBRT	4 (14.8%)
Surgery + SBRT	1 (3.7%)

fourth weeks of chemo-radiation (CTRT) (figure 2). A PS-1, 85-year old male was diagnosed with a cTxN2bM1 squamous cell carcinoma of unknown primary. He presented with a 5-cm bulk of enlarged lymph nodes in the second right level: FNAB was suggestive for a HPV/EBV negative squamous cell carcinoma. The diagnostic work-up, examination under general anesthesia and ipsilateral tonsillectomy could not detect a primary tumor. However, a synchronous 1-cm round nodule peripherally located in the left upper lobe was FDG-avid at baseline PET scan. Histologic confirmation was consistent with a squamous cell carcinoma of the head and neck. After multidisciplinary discussion, synchronous VMAT to the right neck (70 Gy to the nodal GTV and 60 Gy to the ipsilateral II-V lymph node basins) and lung SBRT (55 Gy to the 95% isodose in 5 fractions) were performed. Of note, no putative mucosal irradiation was prescribed to reduce treatment morbidity. Both

Table 2
Characteristics of treated lesions. FNAB, fine-needle aspiration biopsy; SBRT, stereotactic body radiotherapy.

Characteristic	No. of lesions (%), n = 28
Oligometastatic pattern	
De novo	22 (78.6%)
Oligoprogressive	6 (21.4%)
Diagnostic workup of index lesion	
FDG PET + FNAB	18 (64,3%)
FDG PET only	10 (35.7%)
Maximum lesion diameter	
≥ 1 < 2 cm	17 (60.7%)
≥ 2 < 3 cm	4 (14.3%)
≥ 3 < 5 cm	7 (25%)
Target size	
< 20 cc	12 (42.8%)
≥ 20 < 35 cc	10 (35.7%)
≥ 35 < 55 cc	6 (21.5%)
SBRT dose (total dose/dose per fraction/prescription isodose)	
54 Gy/18 Gy @95%	7 (25%)
54 Gy/18 Gy @70%	2 (7.2%)
55 Gy/11 Gy @95%	5 (17.6%)
50 Gy/10 Gy @95%	4 (14.3%)
50 Gy/10 Gy @80%	1 (3.6%)
52 Gy/6.5 Gy @95%	2 (7.1%)
45 Gy/15 Gy @95%	1 (3.6%)
45 Gy/15 Gy @85%	1 (3.6%)
36 Gy/12 Gy @70%	1 (3.6%)
60 Gy/8 Gy @95%	1 (3.6%)
56 Gy/7 Gy @95%	1 (3.6%)
26 Gy/26 Gy @70%	2 (7.2%)

patients are disease-free at 32 and 23 months after the end of primary treatment plus SBRT, respectively. The other 3 patients treated with upfront SBRT ultimately died from synchronous locoregional and distant failure, widespread metastatization and metachronous metastatic kidney cancer, after 37, 26 and 28 months, respectively. Considering the rest of the cohort, the most common first event of progression after primary treatment was lung-only distant failure (20/22 patients, 90.9%) whereas in 2 laryngeal cases (9.1%) a local failure was surgically salvaged with total laryngectomy before the subsequent development of lung oligometastases. In addition, two HPV positive OPC patients firstly underwent surgical metastasectomy for a solitary distant recurrence at 39 and 54 months from the end of CTRT, before further developing an isolated lung metastasis treated with SBRT after 47 and 42 months, respectively. Overall, the objective response rate (ORR) of the irradiated lesion at 3 months after SBRT was 75%, with 13 CR and 8 PR, respectively. The median PFS 1 was 16 months (95% CI: 13.1 – 26.2) with 1 - and 2- year PFS 1 rates of 66.6% and 21.6%, respectively. Of note, the median PFS for the 5 patients with an "ab initio" single metastasis was 16 months (95% CI: 6–29.9), as well. The potential benefit of SBRT to defer the need of further systemic therapy for a recurrent disease with limited metastatic potential could be better appreciated by the PFS 2 analysis (23 lesions). A median PFS 2 of 10 months (95% CI: 7.8–21.6) was reported, with 1- and 2- year rates of 55.6% and 33.3%, respectively. Considering only the 6 oligoprogressive lesions (21.4%), where SBRT was administered for limited lung progression during maintenance Cetuximab and Gemcitabine (2 hypopharyngeal, 2 laryngeal, 1 oral cavity and 1 nasopharyngeal primaries, respectively) on top of first line Extreme and Cisplatin-Gemcitabine regimens, the median PFS 2 was 6 months (95% CI: −5.5–28.1). To investigate the efficacy of SBRT to postpone disease progression in our cohort independently from its timing of delivery, we analysed TTP for 28 lesions according to our definition. The median TTP was 10 months (95% CI: 9.5–21.1), with 1- and 2- year rates of 56.2% and 35%, respectively (figure 3). To investigate the presence of potential predictive factors for longer TTP after SBRT, univariate and multivariate analyses were performed. At univariate analysis, only age > 70 years (p = 0.021) and T1/T2 initial stage (p = 0.047) correlated with better

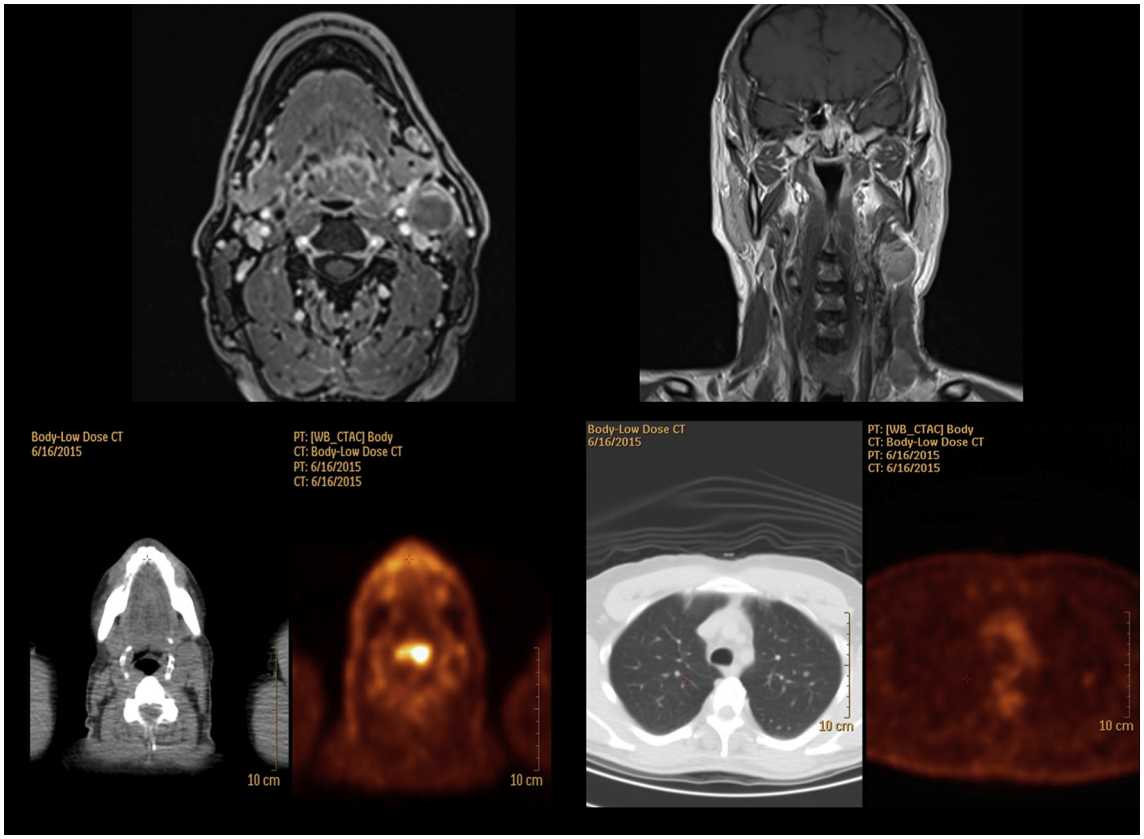

Fig. 1. Axial and coronal images of contrast-enhanced, T1-weighted MR showing a hypointense lesion of the base of tongue crossing the midline with left cystic lymph nodes at levels II and IV (upper row). FDG PET-CT images showing intense hypermetabolism of the primary tumor, rim accumulation of tracer at level II lymph node and a solitary lung lesion in the apicoposterior upper left lobe with moderate hypermetabolism (lower row). Morphology and FDG uptake in a 7 mm lung nodule were suggestive of neoplastic origin.

response after SBRT. No correlation was observed in respect with sex, CCI, PS, smoking history, primary tumor, HPV status, N stage, oligometastatic pattern, disease-free interval after primary treatment, lesion maximum diameter, lesion size and BED_{10}. At multivariate analysis, only initial T stage retained statistical significance: baseline T3/T4 stage had a HR for worse outcome of 5.38 (95% CI: 1.4–25.2, p = 0.033) (figure 4). At a median follow-up of 22 months (range 6–73), 18/27 patients are alive (66.6%), 11 of which are disease-free (40.7%), with a median OS of 47 months (95% CI: 46.8–75.2). The pattern of failure after SBRT was mainly distant dissemination (13/16, 81.2%), followed by local tumor regrowth (2/16, 12.5%) and simultaneous local and distant (1/16, 6.3%). SBRT tolerability was very good, with an acute toxicity rate of 14.8%, namely G2 esophagitis, G1 cough and G1 thoracic pain in 2 and one patient each, respectively. No severe adverse events were observed.

Discussion

In recent years, the concept of an oligometastatic state has been increasingly recognized and supported by clinical and biological data [11] for several malignancies. Oligometastatic HNSCC is still a relatively underreported entity [12]. In this scenario, the most extensive data come from small case series on surgical management of metastases published over 3 decades [18,19]. Apart from few reports on hepatic lesions, the majority of these retrospective studies refer to pulmonary metastasectomies. Scanty data have been published on therapeutical approaches on metastatic sites other than surgery. To our knowledge, our study is the largest to report on SBRT as the exclusive local ablative treatment used for lung-only oligometastatic HNSCC. Considerations about the potential effectiveness of the treatment of oligometastatic disease come from surgical series. Young and colleagues]20] performed a systematic review and *meta*-analysis to assess the impact of lung metastasectomy on the outcome of patients previously treated for primary HNSCC. Analyzing 11 articles for a total of 387 patients, the authors reported an absolute 5-year survival rate of 29.1%. In addition, the presence of advanced nodal disease at diagnosis, primary tumor from the oral cavity, incomplete pulmonary resection and multiple lung lesions were identified as poor prognostic factors. Thus, this study provided indirect evidence of potential long-term benefit for selected patients undergoing surgical ablation of metachronous lung metastases. However, it has to be taken into account that the retrospective nature of the included articles and their inherent selection bias limit to a large extent the generalizability of these findings. Additional insight was provided by a more recent single-center retrospective experience describing the pattern of distant failure in 66 oropharyngeal cancer patients. Sinha et al [21] showed that a remarkable 40% 3-year survival rate after the detection of metastases could be observed for a small group (n = 18) of oligometastatic p16 positive patients treated with pulmonary resection. The role of SBRT as the non-surgical treatment of choice for medically inoperable early stage lung cancer is increasingly accepted [22,23]. In the context of pulmonary oligometastases, large retrospective [24,25] and prospective studies [26,27] in colorectal cancer, non-small cell lung cancer and breast cancer have been published. Regarding HNSCC, very limited data are available. Analyzing the largest published reports on lung oligometastases from different primaries treated with SBRT (Table 3) [28–35], only 4.8% (30/613) of included cases originated from head and neck cancer. Since the publication of pivotal RTOG 0129 study by Ang and colleagues [6], several authors [36–44] sought to evaluate the evolving pattern of failure of locally advanced HNSCC in light of the rising epidemiologic impact

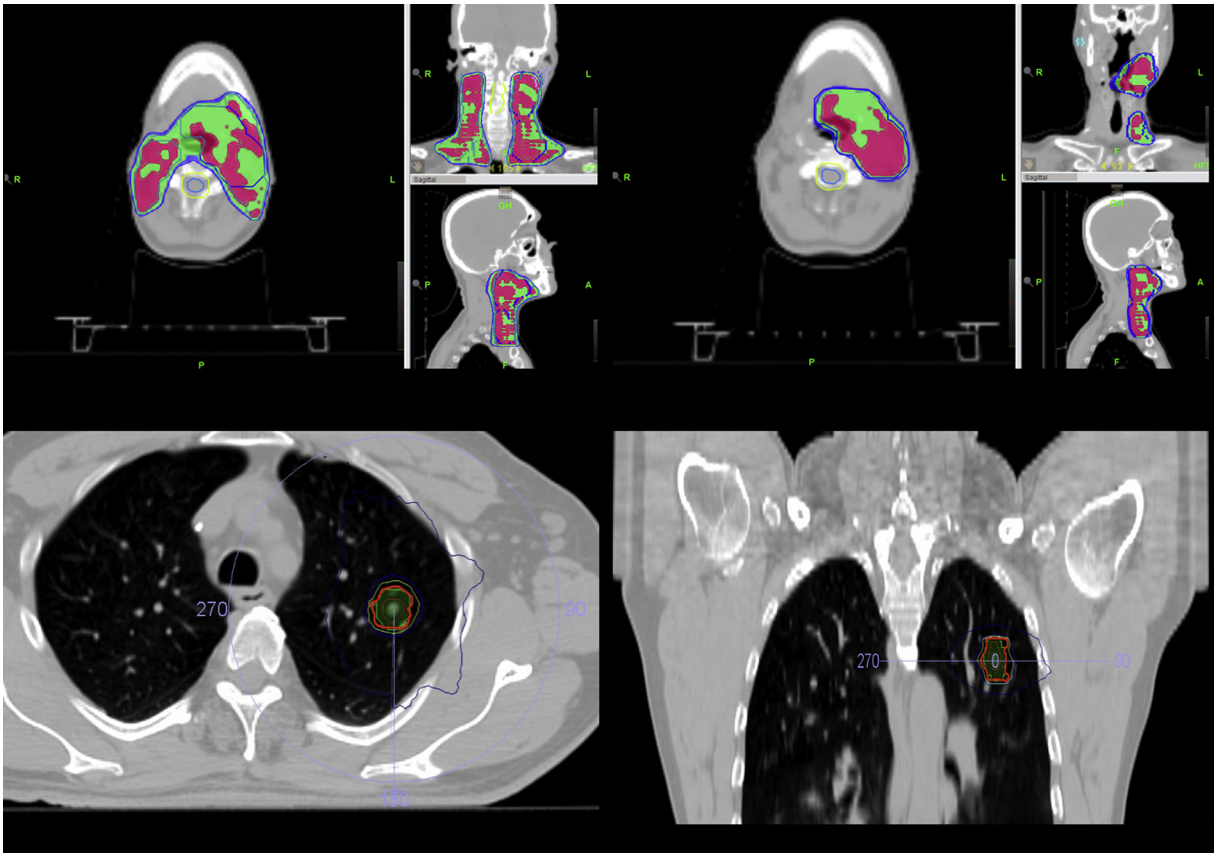

Fig. 2. Dose distribution of conventionally-fractionated IMRT: 60 Gy delivered to the bilateral elective neck (upper row, left) and 10-Gy boost to the primary and nodal GTVs (upper row, right). Blue, green and pink areas corresponding to 90%, 95% and 100% isodoses. Dose distribution of SBRT: 54 Gy delivered to the upper left lobe nodule (GTV drawn in light brown, PTV drawn as light green halo). Blue, green and red (thicker line) corresponding to 90%, 95% and 100% isodoses. The dark blue line at the periphery corresponds to the 20 Gy – isodose. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

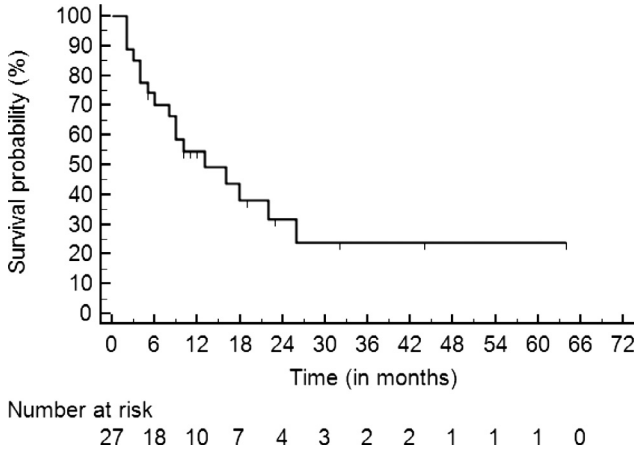

Fig. 3. Time to progression.

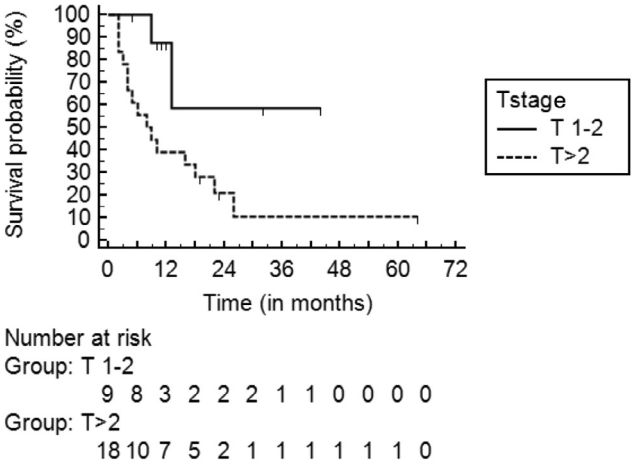

Fig. 4. Impact of T stage on time to progression.

played by HPV infection. Compared with HPV negative disease, retrospective analyses showed that HPV positive oropharyngeal cancer was associated with longer overall survival after disease progression [36], later manifestation of distant metastases [37,38] and possibly with an atypical metastatic behavior such as multi-organ dissemination and spread to unexpected sites [39]. In parallel, an indolent pattern of disease progression characterized by limited lung-only distant failure was also recognized [40,41] for both HPV positive and negative HNSCC. In a dual institution, retrospective analysis on 108 patients with oropharyngeal cancer, Guo et al [42] showed that surgical salvage for mainly pulmonary metastatic recurrence (n = 33) was associated with improved OS for both HPV positive and negative patients (p = 0.03 and 0.05, respectively). In a mono-institutional retrospective report on 38 HPV positive oropharyngeal cancer patients out of 506 (7.5%) developing distant failure after primary treatment, Albergotti et al [43] reported that the median OS of the oligometastatic group (n = 12) was significantly longer than that of the remaining "polymetastatic" cohort (45 vs 10 months; p = 0.00028). Mainly, the oligometastatic patients were surgically managed. Analyzing the outcome

Table 3
Outcome of SBRT for lung oligometastases. *: 36.6% lung oligometastases (miscellaneous); #: 41% lung oligometastases (miscellaneous); §: 36.3% lung oligometastases (miscellaneous).

Author (year) [ref]	Type of study (n: total/HNSCC)	SBRT dose	Main efficacy results
Norihisa Y (2008) [28]	Retrospective (n = 34/5)	60 Gy/12 Gy @ isocenter 48 Gy/12 Gy @ isocenter	2-year OS: 84.3% 2-year LC: 90% 2-year PFS: 34.8%
Rusthoven KE (2009) [29]	Phase I/II (n = 38/3)	48 to 60 Gy/16 to 20 Gy @ 80%-90% isodose	2-year LC: 96%
Inoue T (2010) [30]*	Retrospective (n = 41/6)	60 Gy/7.5 Gy @ isocenter	3-year OS: 39% 3-year LC: 80% 3-year PFS: 20%
Takeda A (2011) [31]	Retrospective (n = 34/7)	50 Gy/10 Gy @ isocenter	2-year LC: 94%
Milano MT (2012) [32]#	Prospective (n = 121/2)	50 Gy/5 Gy @ 80% isodose	2-year OS: 39% 2-year LC: 90%
Salama JK (2012) [33]§	Prospective (n = 61/5)	24 to 60 Gy/8 to 20 Gy @ 80–90% isodose	2-year OS: 56.7% 2-year PFS: 22%
Sharma A (2018) [34]	Retrospective (n = 206/0)	51–60 Gy/3 fx @ 70–90% isodose (peripheral lesions) 45–60 Gy/5–8 fx @ 70–90% isodose (central lesions)	2-year OS: 63% 5-year OS: 30%
Mazzola R (2018) [35]	Retrospective (n = 78/2)	#regimens @ 95% isodose	median OS: 19.6 months (12–47 months) median LC: 18 months (12–46 months)

after distant failure of 148 patients with both HPV positive and negative squamous cell carcinoma, Leeman et al [44] showed that a subgroup of 19 patients with a single metastasis had a 5-year survival rate of 39.1%, with 14/19 subjects undergoing either surgery or SBRT to the index lesion. To our knowledge, our study is the largest to report on SBRT as the exclusive local ablative treatment used for lung-only oligometastatic HNSCC, taking also into account that non-squamous histotypes were not included in our analysis. Moreover, the "de novo" group considered in our study (21 patients with 22 lesions) compares favorably with the "indolent" cases observed in the aforementioned studies. Taking our cohort as a whole, it can be observed that the clinical benefit of SBRT lies in its excellent toxicity profile, high local control rate (ORR of 75%) and

relevant deferral of need of systemic treatment, with a median TTP of 10 months in a heterogeneous population. Interestingly, in a single-center prospective study on 105 lung oligometastases treated with SBRT, Ahmed et al [45] evaluated their intrinsic radiosensitivity by assessing the radiosensitivity index (RSI) on tissue samples based on a validated 10-gene assay [46]: with an absolute RSI of 0.33, HNSCC metastases were in the lower range of radioresistance, being breast adenocarcinoma the least radioresistant with 0.29. In this perspective, the potential immunogenic interplay of SBRT and immune checkpoint inhibitors for recurrent/metastatic HNSCC is of extreme interest [47].

Several limitations have to be acknowledged in the interpretation of our results. First, the retrospective nature of our study and its intrinsic selection bias by reporting on very selected, heterogeneous patients limit the strength of our findings. Second, histologic confirmation of the metastatic nature of the lung lesions was not performed for over a third of the whole cohort: despite thorough multidisciplinary evaluation and clinical judgement, the potential occurrence of a second primary lung cancer [48,49] cannot be self-excluded. Third, taking into account our small sample size, we weren't able to demonstrate a differential benefit of SBRT for the "de novo" and "induced" oligometastatic subgroups, respectively. However, our finding of a better outcome for patients with a limited T stage at initial HNSCC diagnosis may fit well with the data reported by Young et al [20] in their *meta*-analysis, where two papers showed better 5-year survival rates following pulmonary metastasectomy in those patients with a baseline N0 stage (32% and 60% vs 13.8% and 24% if N-positive, p = 0.01 and 0.025, respectively). On the contrary, Sinha et al [21] were not able to detect an impact on survival after the diagnosis of lung metastases for the initial T1/T2 primaries. Nonetheless, it could be hypothesized that in selected cases a less advanced burden of disease at diagnosis may be associated with a higher likelihood of developing an indolent pattern of disease recurrence such as lung oligo-metastastization. Finally, the relatively short follow-up time of this study restrains us from ascertaining the potential long-term benefit of SBRT.

Conclusions

In the setting of lung-only oligometastatic HNSCC, consideration for a local ablative therapy may be justified on an individualized basis. In this perspective, SBRT is an effective, non-invasive treatment with an optimal therapeutic index. In properly selected patients such as those with "de-novo" single lung metastases, SBRT has potential for sustained deferral of systemic treatment. Prospective studies aimed to investigate the impact of SBRT as a stand-alone modality or in combination with standard of care systemic options should be warranted.

Conflict of interest

There is no conflict of interest.

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