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Clinical practice guidelines

Management of head and neck carcinomas with synchronous or metachronous oligometastatic disease: Role of locoregional radiotherapy and metastasis-directed radiotherapy

Radiothérapie des cancers épidermoïdes métastatiques de la tête et du cou synchrones ou métachrones oligométastatiques

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ABSTRACT

Head and neck carcinomas are initially metastatic in about 15% of cases. Radiotherapy is a cornerstone in the multimodal strategy at the locoregional phase. In patients with head and neck cancer, often heavily pretreated and with comorbidities, who relapse locoregionally or at distant sites, radiotherapy has also become increasingly important at the metastatic phase. Data on the optimal sequence of systemic treatments and metastasis-directed treatments including stereotactic irradiation are still lacking. Several randomized head and neck trials have been initiated that should provide important answers, including one recent GORTEC trial.

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RÉSUMÉ

Les carcinomes de la tête et du cou sont métastatiques d'emblée dans environ 15 % des cas. Chez ces patients souvent lourdement traités et atteints de comorbidité, la radiothérapie est une pierre angulaire de la stratégie multimodale, tant en phase locorégionale qu'en phase métastatique. Les données sur la séquence optimale des traitements et le rôle de l'irradiation stéréotaxique font encore défaut. Plusieurs essais randomisés sur les cancers de la tête et le cou ont été mis en place et devraient apporter des éléments de réponse, dont un essai récemment terminé du GORTEC.

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1. Introduction

Head and neck squamous cell carcinomas account for approximately 900,000 annual cases and over 400,000 deaths, worldwide [1]. Head and neck squamous cell carcinomas represent 4% of all malignancies [2,3]. Head and neck squamous cell carcinomas are typically diagnosed at a locoregionally advanced stage. The prevalence of synchronous distant metastases is estimated to be about 15% [4–7]. The median overall survival of metastatic head and neck squamous cell carcinomas patients is about 10 to 14 months [8–10]. Pulmonary metastases are the most frequent accounting for two thirds of distant metastases, followed by bone (about 20%) and liver (about 10%) metastases [11]. Specific metastatic patterns have been reported in Human papillomavirus (HPV)-related head and neck squamous cell carcinomas; more frequently disseminated intra-organ metastatic patterns and unusual metastatic sites have been reported [12].

We reviewed current evidence involving radiotherapy in the management of metastatic head and neck squamous cell carcinomas patients, especially oligometastatic disease with a controlled primary. Oligometastatic disease, defined as one to five metastatic lesions, represents an intermediate stage between local and widespread metastases [13]. This article also addressed polymetastatic disease treated with systemic therapies and a limited number of residual metastases, refractory or progressive metastases treated with stereotactic ablative radiation therapy, or synchronous locoregional and metastatic disease. We also briefly recalled the role of palliative radiotherapy in metastases.

2. Clinical rationale for the use of locoregional and metastasis-directed radiotherapy

The medical challenge is considerable in case of synchronous locoregional and metastatic disease. On one hand, symptoms associated with locoregional disease substantially alter patients' quality of life (dysphagia, dyspnea, pain, etc.) and on the other hand, response to current systemic treatments is overall poor, unpredictable and sometimes delayed [14]. The management of synchronous disease therefore relies on specific anticancer treatments (with supportive care) that aim at controlling both the locoregional tumor burden and metastases.

As for the locoregional treatment, pioneering what is being implemented in head and neck squamous cell carcinomas, locoregional radiotherapy for metastatic nasopharyngeal carcinomas has repeatedly associated with major survival improvement [15–18]. For example, in a phase III trial by You et al. of de novo metastatic nasopharyngeal carcinomas, the 24-month overall survival was 76% in the chemotherapy and locoregional radiotherapy group, and 54% in the chemotherapy-only group [15].

In addition to systemic therapies, local treatments directed at metastases are increasingly integrated in routine practice in the oligometastatic setting and are underreported as consolidative or salvage treatments in clinical trials (unpublished data). Intriguingly, trends for improved survival with time using a given protocol are observed over time (as for example, 10 months in EXTREME princeps publication versus 14 months in Checkmate 651 [9,19]). This might suggest that other interventions than just the systemic therapy might have contributed to improved outcomes. These interventions may include supportive care and local metastasis-directed treatments. Oligometastatic disease is relatively rare in metastatic head and neck carcinomas, but is of growing interest [20,21]. Consistently, recent multidisciplinary strategies, as in other tumor types, increasingly integrate local treatments directed at metastases in selected patients to maximize

metastatic control, progression-free survival and overall survival, such as in the GORTEC OMET (NCT03070366) trial.

Head and neck squamous cell carcinomas patients, particularly those with HPV-negative disease, often have severe comorbidities. They may have been heavily pretreated at the locoregional stage. Owing to their comorbidities and prior treatments, these patients may not be ideal candidates for systemic therapies. In contrast, they may be good candidates for highly conformal hypofractionated radiotherapy modalities, which have been associated with excellent tolerance and feasibility. Trials investigating the role of stereotactic ablative radiation therapy in oligometastatic head and neck squamous cell carcinomas have lagged behind other tumor sites; However, several trials specific to head and neck squamous cell carcinomas have now been designed and stereotactic ablative radiation therapy appears as a promising alternative to surgical metastasectomy in the oligometastatic setting or in addition to systemic treatments in the metastatic setting in general.

3. Biological rationale for the use of ablative radiotherapy in the metastatic setting

The new therapeutic standard of metastatic HNSCC disease includes immunotherapy when immune markers (such as intratumoral exhausted lymphocytes or their receptors on tumours, but the landscape of predictive biomarkers is moving continuously) are present. At the same time, the observation of some (anecdotal and mostly histology-prone) abscopal effects under radiotherapy alone were observed. Both the integration of immunotherapy and the observation of radiation immune effects renewed interest in using radiotherapy for its immune effects.

Radiotherapy variably induces the circulation of tumour antigens and tumour expression of programmed death ligand 1 (PD-L1) depending on its delivery/fractionation mode. It may increase the sensitivity to subsequently administered immunotherapy. The specific mechanisms by which radiotherapy may enhance immune response could occur through increased tumor antigen presentation, expression of major histocompatibility class I and antigen-presenting machinery components [22]. The dose and fractionation parameters influence the radiotherapy ability to design synergistic combinations with immunotherapy [23]. Manipulation of exposure in terms of fractionation to radiotherapy may sensitize to anti-programmed death 1 (PD1) treatment [24].

Moreover, manipulation of radiotherapy volumes might improve tumour response by favouring immune response. In a recent study, Darragh et al. determined whether nodal irradiation could be detrimental to the immune response generated by combining radiotherapy with immunotherapy. Nodal irradiation increased local and distant failure by decreasing the pool of systemic CD4 and CD8 effector T cells responsible for tumor control [25]. Reduced nodal volume irradiation could allow lymphocyte priming; this was the rationale of the recently terminated GORTEC 2018-02 Rewrite (NCT03726775) trial in non metastatic HNSCC patients.

4. The standard treatment of metastatic patients with head and neck squamous cell carcinomas relies on systemic combinations

Current therapeutic standards in metastatic patients with head and neck squamous cell carcinoma rely on systemic therapies. The "EXTREME" regimen has been the standard first-line regimen [9] until the recent integration of immunotherapy. The EXTREME regimen relies on continuous 5-fluorouracil administration, and severe acute adverse events occur in most of the patients (Table 1). In 2020, the Keynote-048 three-arm trial introduced pembrolizumab

Table 1
Summary of retrospective studies reporting treatment outcomes of oligometastatic head and neck squamous cell carcinomas.

Study	Local treatment	Number of patients	Treated metastases	Number of metastases per patient	HPV status	Metastasis location	Concomitant treatment	Median follow-up (months)	Overall survival	Treated-metastasis local control rate
Vincent et al., 2020 [28]	80% EBRT and 15% surgery	65	65	1	unknown	lung (82%)	unknown	unknown	40% at 5 years	55% after EBRT, 28% after surgery
Weissmann et al., 2021 [29]	90% SABR, 25% surgery, 3% interventional radiology	29	36	Median: 1 (range: 1-7)	unknown	lung (58%)	65%	65.2	Median: 23.0 months	90% at 1 and 2 years
Franzese et al., 2021 [30]	SABR	48	71	1 (46.5%), 2(19.7%)	unknown	lung (59.1%)	unknown	20.2	Median: NR	83.1% at 1 year, 70.2% at 2 years
Pasalic et al., 2020 [31]	SABR	82	107	NS	unknown	lung (100%)	34%	20	74.8% at 1 year, 61.6% at 2 years	97.8% at 1 year, 94.4% at 2 years
Bates et al., 2019 [32]	SABR	27	60	1: 44.1%, 2-3: 44.4%, >3: 11.1%	unknown	lung (73%)	none	19.2	Median: 22.8 months	75% at 1 year, 57% at 2 years
Bonomo et al., 2019 [20]	SABR	27	28	1: 96%, 2: 4%	HPV-(87.5%)	lung (100%)	75%	22	Median: 47.0 months	75% at 3 months
Oki et al., 2018 [33]	Surgery	77	77	1	unknown	lung (100%)	none	58	54% at 5 years	46% at 5 years
Shiono et al., 2009 [34]	Surgery	114	unknown	Median: 1 (range: 1-6)	unknown	lung (100%)	none	120	26.5% at 5 years	NR
Winter et al., 2008 [35]	Surgery	67	81	1: 37.3%, 2: 28.4%, >3: 34.3%	unknown	lung (100%)	Adjuvant chemotherapy (13.4%)	15.2	Median: 19.4 months	NR

NR: not reached; EBRT: external beam radiotherapy; SABR: stereotactic ablative radiation therapy; HPV: Human papilloma virus.

as the new first-line standard of care in patients with head and neck squamous cell carcinoma, either alone in patients with immunologically “hot” tumors (defined by a positive immune score) or in combination with chemotherapy using platinum, 5-fluorouracil in “colder” tumors [10,26]. The definition of tumor immunogenicity was evaluated by dividing patients using tumor expression of PD-L1 combined positive score (CPS) into groups with a score of at least 20 ($CPS \geq 20$), or at least 1 ($CPS \geq 1$), and total populations [10]. With a 4-year follow-up, first-line pembrolizumab and pembrolizumab-chemotherapy demonstrated survival benefit compared to cetuximab added to chemotherapy (EXTREME) for recurrent/metastatic head and neck squamous cell carcinomas. Patients responded well to subsequent treatment after pembrolizumab-based therapy [27]. In the CheckMate 651 trial comparing nivolumab plus ipilimumab to the EXTREME regimen, median survival was 13.9 months with immunotherapy and 13.5 months with EXTREME (hazard ratio [HR]=0.95) [19]. In patients with $CPS \geq 20$, the benefit was non-significant (14.6 versus 17.6 months, HR=0.78).

In routine practice, patients with null expression of combined positive score CPS are now advocated chemotherapy and targeted therapy. In patients with combined positive score-positive (> 1) head and neck squamous cell carcinomas, hyperprogressions characterized by an accelerated rate of tumor growth stimulated by immunotherapy were reported in 29% of patients and correlated with shorter progression-free survival. Hyperprogression occurred in 39% of patients with a locoregional recurrence (possibly in a previously irradiated area) and 9% of patients with distant metastases alone in the early years of immunotherapy [36], an observation that seems to yield less concern today. The exact prevalence of this phenomenon is unknown and predictive biomarkers of hyperprogression are currently lacking. In patients with combined positive score-positive head and neck squamous cell carcinomas who are to receive immunotherapy alone, the response rates are low and not accurately predictable, suggesting that in patients with significant tumor bulk, combination of immunotherapy and chemotherapy might be preferred. Identification of predictive biomarkers is an active area of investigations with tumor and immune cell scores, microsatellite instability, and HPV status are among the promising predictive biomarkers. Therefore, in patients with life-threatening locations, and in those with synchronous locoregional and metastatic disease, initiating treatment with chemotherapy and targeted therapy followed by immunotherapy in the second line might be a viable option.

5. Management of locoregional disease in the setting of synchronous head and neck squamous cell carcinomas

Locoregional radiotherapy has shown to provide a benefit on survival, and intensity-modulated radiotherapy may be used to improve mid-long term toxicity in patients expected to survive several months [37]. Several studies have demonstrated the benefit of combining locoregional treatment with systemic treatment. Notably, Rambeau et al. showed a median overall survival gain of 8.6 months ($n=65$ patients, $P<0.01$) compared to treatment with chemotherapy alone (platinum, 5-fluorouracil and cetuximab based regimen) [38]. Kabarriti et al. reported an overall survival gain of 2.3 months in a large retrospective study of 3516 patients [39]. Zumsteg et al. showed improvement in survival at 2 years (34 vs. 20.6%, $P<0.001$) in 3269 metastatic patients extracted from the National Cancer Data Base undergoing locoregional treatment (radiotherapy delivering at least 60 Gy or surgical treatment) or not [40]. Borson et al. showed no difference in progression-free survival (8.7 vs. 8.3 months) and survival (14.1 vs. 14.7 months) with chemoradiotherapy compared to surgery in patients with metastatic disease [41]. Patel et al., in a very large

study, showed a survival gain in patients treated with surgery or radiation (8.4 months in the absence of a locoregional treatment, 18.0 months with radiotherapy alone, 31 months if surgery alone and 40.0 months if surgery followed by radiotherapy) [42]. In all these retrospective studies, the improved survival of patients undergoing locoregional treatments may be difficult to interpret as it could be related to confounding factors including metastatic burden, patient general condition, use of systemic therapies, and not only to the use of locoregional treatments. Finally, aggressive management of locoregional disease in the setting of synchronous metastatic disease seems to be appropriate and to provide a benefit in some patients. Modalities of locoregional radiotherapy may be discussed to allow delivery of systemic therapies and preserve the quality of life. the PembroMetaRT trial (NCT04747054) has been initiated in this context.

5.1. Radiation target volumes

There are currently no recommendations for volume delineation of the locoregional disease in metastatic situations. The question of volume de-escalation, in particular the omission of large field prophylactic lymph node irradiation (as it is already done in case of reirradiation) is relevant in view of the acute toxicity of radiotherapy and the poor prognosis of metastatic disease. Preliminary experience in non-metastatic patients was shown feasible with no excess risk of relapse [43]. Given the metastatic context, it may be recommended to avoid large prophylactic irradiation in the neck and primary.

5.2. Timing of locoregional radiotherapy and metastatic treatments

The concomitant chemotherapy regimens given with radiotherapy are usually less dose intense than those given alone, due to toxicity issues. Different treatment sequences may be used depending on oligo/polymetastatic bulk and locoregional disease. However, retrospective studies do not report these differences between patients. Zumsteg et al. showed that aggressive local therapy had a stronger impact in the first 6 months after diagnosis (adjusted HR: 0.255, $P<0.001$) than after (HR: 0.622, $P<0.001$) [40]. In Rambeau et al.'s study, survival was slightly better with consolidative locoregional radiotherapy than initial radiotherapy (median overall survival 22.1 vs. 15.5 months, $P=0.11$). On one hand, such data might indicate that initial chemotherapy could identify good responders in whom a local treatment might be beneficial, but on the other hand, locoregional progression, not sufficiently controlled by systemic therapy alone, should prompt locoregional radiotherapy on a case-by-case basis [38]. In a trial by Borson et al., upfront (versus delayed) chemotherapy yielded similar progression-free survival (8.7 vs. 8.3 months) and improved overall survival without reaching statistical significance (27.5 vs. 13.7 months with $P<0.07$) [41]. Of note, these studies date back before the new standard first-line metastatic cancer using immunotherapy alone in patients with a high combined positive score. Delayed therapeutic responses to immunotherapy may be problematic in case of locoregional disease and in rapidly progressing tumours [10].

5.3. Fractionation of locoregional radiotherapy in case of synchronous metastases

Radiotherapy, along with other measures including chemotherapy, palliative care, and interventional procedures, has been studied extensively for its ability to relieve disease-related symptoms. When symptom alleviation is the goal, palliative radiotherapy is proposed according to various retrospective institutional studies and some small phase 2 trials [44,45]. Short courses of

3D- or intensity-modulated radiotherapy or stereotactic ablative radiation therapy have been used with no clear consensus [46]. In other situations where tumour control should be maximized, a Biologically Effective Dose (BED)₁₀ at least 72 Gy seems necessary [39]. Zumsteg et al. found no benefit in overall survival in patients receiving less than 60 Gy [40]. In 2019, Shuryak et al. showed that an optimized hypofractionated schedule of 18 × 3.0 Gy could substantially increase tumour control probability, particularly for advanced head and neck cancers (35% to 49% for advanced stage tumours) while decreasing high-grade late normal tissue complication probability (13 to < 2%), as compared with a standard 35 × 2.0 Gy protocol [47]. The choice of a standard fractionation or slightly hypofractionated and accelerated regimen is the result of complex clinical trade-offs.

5.4. Specific head and neck squamous cell carcinomas situations

5.4.1. HPV-positive head and neck squamous cell carcinomas

HPV-related oropharyngeal cancer patients have better survival and disease-free survival (DFS) than their HPV-negative counterparts [48]. Their 2–3 year survival rates at the metastatic stage vary between 7 and at least 20%, but this benefit was however abated in HPV+ polymetastatic patients [49–57]. A higher rate of disseminated metastases, involving more than two organs, or multiple lung metastases or unusual areas involved such as the skin, brain or intra-abdominal lymph nodes, has been reported in retrospective series but not confirmed in two large prospective series [49,52,53,58]. A better response to systemic treatment has been suggested in a post-hoc analysis of the EXTREME phase III trial and two large retrospective series [57,59,60]. Prolonged survival is reported in case of low metastatic burden or oligometastases confined to the lung and/or liver [49,61]. Median survival decreased from 41.2 months for one lesion, to 17.2 months for two to four lesions, to 10.8 months for five or more lesions ($P=0.007$) [62]. In HPV-positive patients with head and neck squamous cell carcinoma, stereotactic ablative radiation therapy may be considered owing to their relatively good prognosis, but their unusual metastatic sites (such as intrabdominal lymph nodes, metastases to the small bowel, cutaneous metastases, etc.) warrants investigations, and some metastases may not be optimally treated by this technique [63,64].

5.4.2. Elderly patients

Elderly patients usually have more comorbidity and should undergo oncogeriatric assessment. They are also more at risk of treatment toxicity and are less likely included in clinical trials [65]. In the metastatic setting when tumour bulk is limited, the risk benefit ratio may differ from that of younger patients. Tolerance to systemic therapies, such as chemotherapy, may be poor. Oligometastatic disease may represent an opportunity for metastasis-directed treatments such as stereotactic ablative radiation therapy, due to excellent tolerance and hypofractionation. In case of synchronous locoregional and metastatic disease, cautious planning should be applied to limit the severity of acute and late mucositis [66].

6. Management of metastases

In metastatic strategies, ablative treatment directed at metastases is increasingly discussed in all tumor sites. Ablative therapy using advanced forms of radiotherapy has become an attractive option in early (upfront oligometastases) and later lines of the management of metastatic disease. It has been integrated into the metastatic landscape as initial strategy to postpone initiation of systemic treatment using chemotherapy or to account for the delayed

response to immunotherapy on one hand. On the other hand, ablative therapy can also be used to enhance/consolidate the treatment response or as salvage therapy after partial failure or relapse to systemic therapies [67,68]. It is important to discuss patient's charts during the course of their metastatic disease at multidisciplinary staff meetings to identify windows of opportunities for ablative treatments of metastases in a careful patient-physician assessment of their quantity and quality of life [69].

This field is expanding in stereotactic ablative radiation therapy owing to its versatility (ability to treat complex and moving targets), excellence tolerance (below 5% severe toxicity) and flexibility (easy designs, severe hypofractionation). The possibility to perform stereotactic ablative radiation therapy plans rapidly has probably also contributed to their “popularity”. There is also room for intensity-modulated therapy, with fractionation regimens customized to the clinical condition and the locoregional bulk and aims.

6.1. Patients with oligometastatic head and neck squamous cell carcinoma

6.1.1. Definition of oligometastatic disease, and treatment approach

The oligometastatic concept has substantially evolved since its first description [70], and it is expanding rapidly. However, substantial debate still exists regarding whether metastasis-directed treatments do not postpone systemic treatments necessary to control disseminated disease and that aggressive local treatment exposes patients to futile toxicity. Patients with limited disease burden, viral-associated pharyngeal cancer (Epstein-Barr virus [EBV]-positive nasopharyngeal carcinoma or HPV-positive oropharyngeal carcinoma), metachronous metastases, or lung-only metastases have improved prognosis and might benefit most from aggressive ablative approach [58,71–73].

The more consensual definition of oligometastatic disease is one to five metastatic lesions; some studies have included patients with up to ten metastases [13,74]. To that extent, it is important to note that a multisite irradiation approach may be preferred in situations where an abscopal effect is unlikely, as it is the case in head and neck squamous cell carcinomas. It is also critical to identify biomarkers that could predict metastatic dissemination in patients having limited bulk disease who are proposed local metastatic treatments. In one randomized trial of patients with head and neck squamous cell carcinomas and multiple metastatic sites, administering stereotactic ablative radiation therapy to a single metastatic site in combination with immunotherapy (nivolumab) did not improve outcomes and local control in “off-target” lesions, compared with nivolumab alone [75].

For head and neck squamous cell carcinomas, most evidence to date for metastasis-directed local treatments has been based on surgery and data from oligometastatic trials of patients with head and neck squamous cell carcinomas have lagged other tumor sites. Randomized phase II trial results have suggested that metastasis surgery could improve survival in some patients with oligometastases, in particular, 5-year overall survival rates of 29% and up to 50% for patients with oligometastatic disease undergoing lung metastasectomy [33,76,77]. Better evidence was provided from the results of the randomized phase II SABR-COMET trial of 99 patients, with one to five metastases but only 10% of them had head and neck squamous cell carcinoma. Stereotactic ablative radiation therapy to all disease sites showed 5-year overall survival rate of 42% while it was 17% with the standard of care ($P=0.006$) [78].

Retrospective evidence supporting improved outcomes associated with stereotactic ablative radiation therapy for oligometastatic head and neck squamous cell carcinomas is limited to small studies [20,28–32] (Table 1). Compared to

Table 2
Ongoing studies of systemic treatment combination for oligometastatic head and neck squamous cell carcinomas.

Study title	Study name	NCT ID	Design	Concomitant therapy	Primary location	Primary outcome
NBTR3, radiation therapy, and pembrolizumab for the treatment of recurrent of metastatic HNSCC	x	NCT04862455	Phase II single arm	Pembrolizumab	Head and neck cancers	Tumor response
Stereotactic radiotherapy combined with chemotherapy or not for treatment of oligometastases in HNSCC	OMET (GORTEC 2014-04)	NCT03070366	Phase II randomized	Chemotherapy	Head and neck cancers	Overall survival rate without quality of life deterioration at 1 year
Stereotactic ablative radiotherapy for comprehensive treatment of oligometastatic (1–3 metastases) cancers	SABR-COMET-3	NCT03862911	Phase III randomized	Chemo-/immune-/hormonotherapy/none	Any primary site (including head and neck cancers)	Overall survival rate at 5 years
Stereotactic ablative radiotherapy for comprehensive treatment of 4–10 oligometastatic tumors	SABR-COMET-10	NCT03721341	Phase III randomized	Chemotherapy/none	Any primary site (including head and neck cancers)	Overall survival rate at 6 years
Stereotactic ablative radiotherapy for oligo-progressive disease refractory to systemic therapy in head and neck cancer	Suppress-HNC	NCT04989725	Phase II randomized	Continue current systemic therapy	Head and neck cancers	Progression-free survival rate at 5 years
Immunotherapy and SBRT or metastatic head and neck carcinomas	OZM-088	NCT03283605	Phase I-II single arm	Durvalumab/tremelimumab	Head and neck cancers	Acute toxicity rate at 3 months, progression-free survival rate at 6 months
Sintilimab combined with chemotherapy and SBRT in limited metastatic HNSCC	LM-HNSCC	NCT05136768	Phase II single arm	Sintilimumab/platinum-based chemotherapy	Head and neck cancers	Progression-free survival rate at 2 years
Durvalumab, tremelimumab, and hypofractionated radiotherapy in treating patients with recurrent or metastatic HNSCC	x	NCT03522584	Phase I-II single arm	Durvalumab/tremelimumab	Head and neck cancers	Safety and tolerability
Immunotherapy and SBRT for metastatic head and neck cancers	x	NCT03522584	Phase I-II single arm	Durvalumab/tremelimumab	Head and neck cancers	Progression-free survival rate at 6 months, acute toxicity
Stereotactic body radiotherapy in patients with rare oligometastatic cancers	oligoRARE	NCT04498767	Phase III randomized	Continue current systemic therapy	Any primary site (including head and neck cancers)	Overall survival rate at 7.5 years
Radiotherapy with pembrolizumab in metastatic HNSCC	IMPORTANCE	NCT03386357	Phase II randomized	Pembrolizumab	Head and neck cancers	Best response
Study on the efficacy of radiotherapy and pembrolizumab in newly diagnosed metastatic head & neck cancers	PembroMetaRT	NCT04747054	Phase III randomized	Pembrolizumab	Head and neck cancers	Progression-free survival rate at 3 years

HNSCC: head and neck squamous cell carcinomas; SBRT: stereotactic body radiation therapy.

Table 3
Guidelines for the management of head and neck cancers according to clinical situations.

Setting	Management of locoregional disease		Management of metastases	
	Dose and volume	Level of evidence	Dose and volume	Level of evidence
Oligometastatic	First line therapy, radiation dose and volume depend on tumor size and location, combined positive score, patient condition. Discuss omission of large field prophylactic lymph node irradiation	Level C	Depend on site of metastases: Lung metastases (GTV) treated with SABR (single fraction of 16 to 30 Gy, 3 fractions of 15-20 Gy, 8 fractions of 7.5 Gy or 5 fractions of 8 Gy for central locations) Hepatic metastases (GTV) treated with SABR with 3 fractions of 15 Gy Bone metastases (GTV) treated with SABR to control the oligometastatic disease Same as for oligometastatic disease	Level B
Oligoprogressive	First line therapy, radiation dose and volume depend on tumor size and location, combined positive score, patient condition. Discuss omission of large field prophylactic lymph node irradiation	Level C	Same as for oligometastatic disease	Level C
Oligopersistent	First and second line therapy depends on tumor size and location, combined positive score, patient's condition	Level C	Same as for oligometastatic disease	Level C
Palliative	Palliative short course 3D, IMRT, SABR to alleviate	Level C	SABR unless metastases involve many vertebrae, or the limbs, in which case, palliative hypofractionated IMRT or 3D irradiation may be preferred to alleviate symptoms	Level B

GTV: gross tumor volume; SABR: stereotactic ablative radiation therapy; 3D: three-dimensional; IMRT: intensity-modulated radiation therapy.

historical cohorts of metastatic head and neck squamous cell carcinomas, they provide favorable results. Mean survival rates are about 75% at 1 year and 50% at 5 years in patients with ablated lung metastases [31,33,77]. The largest cohort reported data from 82 patients, treated for 107 lung metastases, with 68.2% of oligometastases. With a median follow-up of 20 months, the survival rate was 74.8% and the treated-metastasis local control rate 97.8% at 1 year [31]. In 2021, Franzese et al. reported a cohort of 48 patients, where treated-metastasis local control rate was 83.1% and 70.2% at 1 and 2 years respectively, with a median follow-up of 20.2 months [30]. Primary stage, free interval since completion of locoregional treatments, metastatic bulk (size and number of metastases) are common prognostic factors. In a cohort of patients with oligometastatic disease from any primary tumor site treated with stereotactic ablative radiation, Rusthoven et al. showed a significant difference in 5-year overall survival for differently sized stereotactic ablative radiation-treated metastases, with a 5-year local control rate of 100% for smaller lesions compared to 77% for those larger than 3 cm [79]. Bonomo et al. reported advanced T-stage at diagnosis as the only predictor of decreased time to progression following stereotactic ablative radiation therapy [20]. The inherent selection biases of retrospective studies highlight the need for more robust prospective data in support of stereotactic ablative radiation therapy directed at all oligometastases as an initial or relapse event. The randomized phase II GORTEC 2014-04 NCT03070366 trial ÔMETwas designed to investigate whether could be proposed for oligometastatic patients (69 patients, one to three metastases, any site) with head and neck squamous cell carcinomas to omit or postpone initiation of a systemic approach and stopped inclusions in 2022 (ESMO proffered paper presentation 2023).

6.1.2. Radiation target volumes and doses

The volume and dose depend on the location of the oligometastatic lesions. Metastases limited in number and size to the lungs may be treated with stereotactic ablative radiation using gating/tracking guidance. Despite the great heterogeneity of sites, techniques, doses, and fractions, most studies of radiotherapy of pulmonary oligometastases have shown similar results, regardless of the proposed radiation regimens: a high local control rate, around 70 to 90% at 2 years, and little toxicity (5% G3 at 2 years)

[79,80]. Treatment protocols vary from a single session of 15 to 30 Gy to regimens of three fractions of approximately 15 Gy or five fractions of 8 Gy for central locations situated near (within 2cm) the mediastinal structures. Bone metastases may also be treated with stereotactic ablative radiation to control the oligometastatic disease. The dose is often extrapolated from first publications of vertebral irradiation and are in the order of three fractions of 8 to 9 Gy each. The dose is adapted according to the nearby medullary segment.

6.2. Oligoprogression and oligopersistent disease

Stereotactic ablative radiation therapy may also be used to treat residual metastases that could regrow following interruption of systemic treatments or have not responded to systemic treatments in routine practice and clinical trials. Indirect evidence from multidisciplinary staff meetings suggests that the use of stereotactic ablative radiation therapy has likely been underestimated in practice [69]. In a recent randomized phase III trial, McBride et al. did not observe abscopal effects from the combination of nivolumab alone compared to nivolumab and stereotactic ablative radiation therapy for metastatic head and neck squamous cell carcinomas (objective response rate [ORR] to nivolumab 34.5 vs. 29.0%, $P=0.86$) [75]. As a result of adding stereotactic ablative radiation therapy to nivolumab, Forner et al. reported persistent disease control in a patient with oligoprogression [81]. In the absence of abscopal effects in head and neck squamous cell carcinomas, stereotactic ablative radiation therapy cannot be recommended alone on selected oligometastases only but should rather be delivered to all visible oligometastatic sites, and synergies of immunotherapy and multisite stereotactic ablative radiation therapy should be investigated. The response rates of systemic treatments are relatively low, and response may be transient. Irradiating residual tumor sites may be used to prolong the response and possibly improve progression-free survival.

6.3. Palliative radiotherapy on metastases

Stereotactic ablative radiation is increasingly considered in the treatment of metastases, as it allows dose escalation compared to purely palliative or symptomatic radiotherapy. The

conceptual borders between palliative and stereotactic ablative radiation therapy may be fuzzy with this change of paradigm toward maximizing treatment in metastatic patients. Stereotactic ablative radiation therapy cannot, however, be proposed for all metastatic situations and it may not be relevant for highly symptomatic patients or those at risk for pathologic fracture. Bone metastases, the second-most frequent site of metastases, are associated with a poor prognosis of head and neck squamous cell carcinomas. They are increasingly treated with stereotactic ablative radiation unless they involve many vertebrae, or the limbs, in which case, palliative hypofractionated 3D irradiation may be preferred to alleviate symptoms [82–84]. Similar choices between radiotherapy techniques may be discussed on a case-by-case basis.

7. Ongoing trials

Several ongoing trials are assessing systemic treatment in combination with stereotactic ablative radiation therapy. Evaluating systemic treatment in combination with stereotactic ablative radiation therapy for oligoprogressive head and neck squamous cell carcinomas are needed to better clarify the benefits of radiation (compared to reinitiation or switch of systemic therapy) and the criteria on which to select patients. Table 2 summarizes the ongoing trials assessing combination of systemic therapy with stereotactic ablative radiation therapy. Three phase III randomized trials are assessing the benefit of stereotactic ablative radiation therapy on any oligometastatic primary sites (one to three metastases: SABR-COMET-3, NCT03862911; or four to ten metastases: SABR-COMET 10, NCT03721341), or for rare oligometastatic cancers (oligoRARE, NCT04498767) to assess overall survival at 5 years [74,85]. Other phases I–II single arm trial are evaluating the addition of stereotactic ablative radiation therapy specifically in metastatic head and neck cancers with combination of immunotherapy or chemotherapy (OZM-088, NCT03283605; LM-HNSCC, NCT05136768 NCT03522584 and NCT03522584), to assess progression-free survival or safety. Finally, three randomized phase II trials are measuring the addition of stereotactic ablative radiation therapy to systemic therapy for oligoprogressive, oligometastatic or metastatic head and neck cancers (Suppress-HNC, NCT04989725; OMET GORTEC 2014-04 and IMPORTANCE, NCT03386357). The endpoint of the OMET GORTEC 2014-04 (NCT03070366) is to assess overall survival with deterioration of the overall quality of life using stereotactic ablative radiation therapy alone compared to chemotherapy and stereotactic ablative radiation therapy in patients with head and neck squamous cell carcinoma with one to three metastases [86].

On the other hand, metastatic clinical trial protocols now integrate second line systemic treatments but most still omit the use of ablative therapies directed at metastases, although their effect might be significant. Finally, irradiating residual tumor sites is also being investigated in the ECOG-ACRIN 3211, a phase II/III randomized trial on immunotherapy and consolidative radiotherapy for oligometastatic head and neck squamous cell carcinomas, that will assess the role of consolidative radiotherapy.

About the management of the locoregional disease, Pembrol-MetaRT (NCT04747054), a randomised phase III trial, currently evaluates moderately hypofractionated locoregional radiotherapy of 54 Gy delivered in 18 fractions (with no prophylactic volumes) associated with immunotherapy in patients with a combined positive score at least 20. Chemotherapy may however be needed below a combined positive score of 20 and the Pembrol-MetaRT protocol has been changed accordingly [87,88].

Translational research and radiomics studies are being conducted to identify predictive biomarkers and assess the value of monitoring circulating DNA [89].

8. Conclusion

For head and neck squamous cell carcinomas, radiotherapy is a cornerstone of the treatment of locoregional disease but increasingly also of metastatic disease (Table 3). Multimodal treatments depend on synchronous/metachronous nature, and tumour bulk, as well as patient and immune profiles. The use of stereotactic ablative radiation therapy has substantially increased in these settings in the last 15 years but data specific to head and neck squamous cell carcinomas are rare. Several important trials are ongoing.

Disclosure of interests

Pr. Thariat is co-coordinator of the GORTEC 2014-04 trial. The other authors have no relationships/activities/interests.

Authors' contributions

M.T.: conceptualization, writing – original draft preparation, manuscript editing; R.N., A.L.: conceptualization, writing – original draft preparation; S.T., Y.P., P.B.: conceptualization, manuscript reviewing and editing; J.T.: conceptualization, supervision, manuscript reviewing and editing.

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