

Introduction

Salivary gland cancers (SGCs) are rare diseases accounting for 2–6.5% of all head and neck cancers (HNC), with a considerable heterogeneity in histology, biology, clinical behavior and metastatic potential (Barnes 2005).

Distant metastases are diagnosed in 25-55% of SGCs patients, conditioning a clinical variable course with overall, only the 2% of patients are alive after 5-years. Adenoid cystic carcinoma (ACC) is the most common (60%) malignant histotype observed in patients with metastatic disease, while the other are rarer, such as mucoepidermoid carcinoma, salivary duct carcinoma, adenocarcinoma not otherwise specified (NOS), and myoepithelial carcinoma. . ACC usually shows an indolent evolution and this leads to wonder if a prompt management of metastatic disease may be worthwhile or not. On the other side, high grade non-ACC histologies have a higher likelihood of aggressive distant metastases, requiring such type of management (Alfieri S, 2017).

Overall, the presence of distant metastases is one of the strongest predictor of survival (Alfieri S, OO 2017) of metastatic SGCs but effective systemic treatments to manage this setting are lacking (Alfieri S, OO 2017).

In metastatic scenery, patients may need palliative external beam radiotherapy (RT) with the aim to obtain symptom relief or anticipate complications from disease progression. Fractionation schemes for palliative RT commonly ranged from 8 Gy in one single fraction to 30 Gy delivered in 10 fractions using three-dimensional conformal technique (3DCRT) or intensity modulated radiation therapy (IMRT). These schemes seem to be effective in terms of symptoms control with an acceptable toxicity profile.

However, as demonstrated also for other primary tumors, the burden of metastatic disease for SGCs can be limited in terms of number and locations of the lesions, with a relative low kinetic of metastatic progression (Weichselbaum RR, JCO 2018). In these cases, ablation of the limited metastatic lesions could potentially be the cure for the whole burden of disease. There is a relative consensus in defining oligometastatic state

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when ≤ 3 -5 synchronous metastases in 3 or fewer different organs occur (Sun XS, Future Oncol 2018 Palma, D.A.; Nat. Rev. Clin. Oncol. 2014).

Nowadays, limited evidence is available to support the hypothesis that local treatment for cranial or extracranial oligometastases is effective in terms of overall survival (OS) (Andrews DW, Lancet 2004, Ruers, J. Natl. Cancer Inst. 2017, Gomez, DR, Lancet Oncol 2016, Franceschini, IJROBP 2019). Among local treatments, stereotactic ablative body RT (SABRT) is an advanced form of RT, characterized by delivering high doses per fraction, shorter time period (few fractions), and an accurate tumor targeting system (Potter I, IJROBP 2010). Recently, a randomized phase II trial including 99 oligometastatic patients reported that SABRT was associated with a significant improvement in OS compared to patients receiving standard palliative care, although the 4.5% of patients in the SABRT group experienced treatment related death (Palma DA, Lancet 2019).

The impact of SABRT for HNC patients is based on deductions (anecdotal) (Bonomo P, Oral Oncology 2019, Gao M 2013) and no report have been published on oligometastatic or oligorecurrent SGCs patients yet.

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The purpose of this study was to investigate the outcome of patients treated with RT on metastatic sites derived from SGCs, with a focus on SABR technique, dose, volume and site of metastases.

Material and Methods

Study population

We performed a retrospective, multicentric analysis of oligometastatic SGC patients treated with modern RT techniques from 2006 to 2016 in 9 Italian Cancer Centers on behalf of the Italian Association of Radiation Oncology (AIRO) Head and Neck Working Group. This study was approved by every Institutional Ethical Committee.

Patients were selected according to the following criteria: 1) histological diagnosis of high grade SGC (ACC and non-ACC); 2) one or more metastases (≤ 3) diagnosed synchronously or metachronously to primary

tumor 3) controlled or resected primary tumor; 4) baseline distant staging with brain-thorax-abdomen computed tomography (CT) and/or PET and/or magnetic resonance imaging (MRI); 5) treatment with palliative or ablative intent ; 3) first clinical and/or radiological evaluation response at 2-4 months after RT end; 4) concomitant or adjuvant chemotherapy or target therapy were allowed; 5) no previous surgery on metastatic sites. Histological confirmation of the metastatic disease was not routinely required.

Radiotherapy techniques

All patients were simulated with a CT slice thickness of 3 mm and immobilization devices according to the lesions location. In case of simulation for SABRT, contrast medium was used for visceral metastases and respiratory motion control was adopted for moving target, such as lung and liver. A thermoplastic mask or vacuum bags to prevent rotational movement (when needed) were used.

The SABRT was commonly chosen in patients with good performance status (PS), with indolent or paucisymptomatic 1 to 3 metastases, and an overall estimated life expectancy of at least 6 months.

In case of palliative conventional RT, target volume included the gross tumor volume (GTV) with an isotropic margin of about 1-2 cm to obtain Clinical Target Volume (CTV) and further 3-6 mm to define the Planning target Volumes (PTV). Organs at risk were contoured according to the anatomical area in which metastatic lesions were located. In case of a palliative intent, RT was delivered with 3CRT or IMRT technique (including tomotherapy and volumetric modulated arc therapy or VMAT). Most common moderately hypofractionation regimens were 3 Gy x 10 consecutive fractions, 4 Gy x 5 consecutive fractions or 8 Gy in single fraction.

The SABRT treatments were delivered with CyberKnife, VMAT technique, or Tomotherapy and in part previously published together with other primary tumors ([Franceschini D, Int J Radiat Oncol Biol Phys. 2019.](#) [Franzese C, Radiother Oncol. 2019\).](#)

In case of SABRT, target volumes and dose prescription were established according to site, size and number of lesions and adopted technology. Considering target volume definition, a simulation CT scan was commonly registered with other imaging for an accurate localization. The macroscopic tumor was defined

as GTV and was equal to CTV. In case of fixed target, an isotropic margin of 5 mm was used to create the PTV. In case of moving lesions, an internal target volume (ITV) was defined on 4DCT and a further expansion of 5-7 mm was adopted to create PTV. Dose of SABRT ranged from 20 - 28 Gy in single fraction, to 21 – 54 Gy delivered in 3 to 5 fractions.

Chemotherapy was additionally prescribed in both settings based on a case-by-case decision.

The first radiological response was assessed at 3-4 months after the end of RT. Thereafter, clinical and radiological follow-up was performed every 3-6 months according to patients' conditions, disease progression and institutional policy.

Statistical analysis

The first end-point of this study was to define pattern of response of metastatic lesions after conventional palliative RT or SABRT. Radiologic tumor response was classified according to European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumours (EORTC-RECIST) criteria.

version 1.16. In addition, we assessed local control (LC) of metastatic lesions, defined as the time from the beginning of RT to the progression of treated lesion or last follow-up. Overall Survival (OS) was calculated from the date of diagnosis of metastatic disease to death or last follow-up. Due to the absence of data for a percentage of the sample, we did not report the symptom control. Univariate and multivariate analysis were used to identify factors associated to LCM and OS in the SABRT patients group. Univariate analysis were performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariable Cox regression analysis were done to evaluate the association between clinical factors and survival, with a significance level of $p < 0.05$.

Statistical calculations were performed using STATA, version 15.

RESULTS

Sixty-four patients were eligible for the present study. Clinical characteristics of the study population are shown in Table 1. Briefly, there were 44 males (68.7%) and median age was 56,5 years (range, 25-82 years).

Commento [o2]: biblio

Commento [FDF3]: dati su volume della metastasi? Dose totale ricevuta? Tipo di lesione? (Inf, parenchima, osso)
Inizio cht sistemica? Ritardato?

Thirty-seven patients (57.8%) were affected by ACC and 27 patients (42.2%) had no-ACC. In 78% of cases major salivary glands were involved as primary tumor site. The most common no-ACC histologies were adenocarcinoma NOS and salivary duct carcinoma. Fifty-four (84.4%) patients had diagnosis of metachronous metastases with controlled or resected primary tumor, after a median time of 28.0 months from initial diagnosis. Ten (15.6%) patients were diagnosed with primary tumour and synchronous metastases. Forty-eight (75%) patients were treated on a single metastasis while 16 (25%) patients on 2 (18,8%) or 3 sites (6,2%) of disease.

Treatment patterns for the whole population are shown in Table 2. Thirty-four patients underwent palliative RT (53.1%) and 30 patients had SABRT (46,9 %). The most common metastatic irradiated site were bone for palliative RT and lung for SABRT. Among patients treated with SABRT, 18 (60%) were affected by ACC. Median total dose was 30 Gy delivered in 10 fractions for palliative RT and 29 Gy in 3 fractions for SABRT.

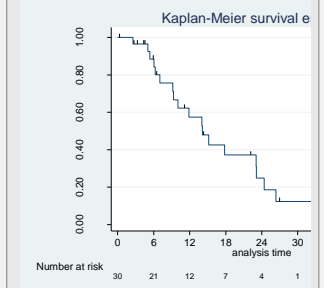
Patterns of response are shown in Table 3. Best overall response after RT was classified as complete radiological response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) in 18 (28.1%), 18 (28.1%), 20 (31.3%) and 8 (12.5%) cases, respectively. In detail, we observed an overall clinical benefit (CR, RP, SD) in all patients receiving SABRT, while all metastatic site progressions (PD) were observed in patients treated with conventional RT.

After a median follow-up of 29.2 months (range 2.3-117.1), LC at 12 months was 57.5% (95%CI 35.1 - 74.6) for patients treated with SABRT (Figure 1).

Univariate and multivariate analyses did not show any specific association with LC except for the number of metastases, regardless of RT technique. This quantity was found to be highly significant ($p \leq 0.01$) both in univariate (HR = 1.8) and multivariate tests (HR = 1.9).

Site of metastasis and RT technique did not influence LC for the whole population. However considering only ACC patients (n=37), -a significant- LC benefit could be observed for patients receiving SBRT compared to conventional RT technique, regardless of metastatic site ($p=0.05$).

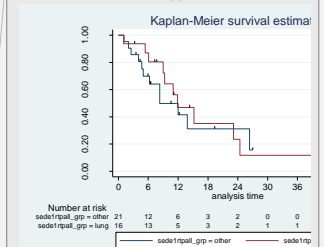
Commento [ST4]: Metto tutte le figure in bella copia (Qui sotto la figura 1 in "brutta"). Devo fare un file word a parte con tutte le figure? E le didascalie? Magari la versione beta la facciamo con le figure direttamente nel testo. Fatemi sapere. Grazie.



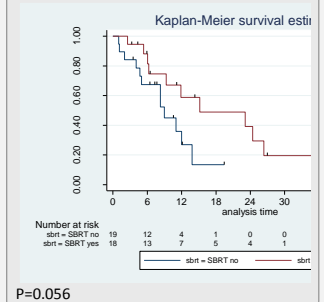
Commento [OE5]: stresserei questo

Commento [FDF6]: se arrotondi è 0.06 → no significant

Commento [ST7]: veramente per lung non c'è tutto sto vantaggio...



P=0.672 (non è significativo per niente!)
Mentre per SBRT siamo quasi significativi...



P=0.056

OS rates at 12, 24 and 48 months were 84.9%, 73.6% and 73.6% respectively for patients treated with SABRT and 96.9%, 85.9% and 71.4% was found, respectively, for conventional RT. 2-years OS rate was 83 % for ACC and 53 % for NON-ACC. Non differences were observed in ACC patients between the SABRT compared to conventional RT.

[Univariate and multi](#)

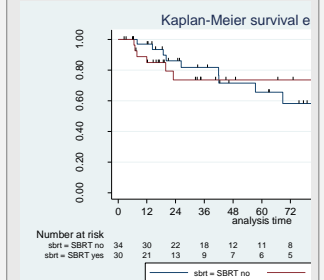
Discussion

The present study evaluates the role of RT in the management of metastatic SGC, focusing the attention on the outcome after SABRT. In the last years, several studies were published on the role of SABRT in the oligometastatic setting from different primary tumors ([Radiother Oncol. 2020 Mar;144:23-29. doi: 10.1016/j.radonc.2019. xxxx Clin Lung Cancer. 2019 Nov;20\(6\):e667-e677. doi: 10.1016/j.clc.2019.06.024. xxxxx Radiother Oncol. 2019 Apr;133:220-226. doi: 10.1016/j.radonc.2018.10.024.](#))

Palma et al. ([Lancet. 2019 May 18;393\(10185\):2051-2058. doi: 10.1016/S0140-6736\(18\)32487-5.](#)) conducted the first prospective randomized trial comparing standard of care with or without SABRT in 99 oligometastatic patients, showing a median OS of 41 months vs -28 months, respectively. Recently, the ESTRO-EORTC collaboration ([Lancet Oncol. 2020 Jan;21\(1\):e18-e28. doi: 10.1016/S1470-2045\(19\)30718-1](#)) produced a consensus recommendation classifying disease into oligometastatic subcategories, considering if oligometastatic disease is diagnosed during a treatment-free interval or on active systemic therapy, and other diseases or treatments characteristics.

Major advantages of SABRT on metastases include the possibility to control the limited burden of disease with potential delay of onset or intensification of systemic therapies. However, very few data have been published on oligometastatic head-neck cancer patients yet ([Bonomo P 2019, Jereczek-Fossa BA, 2013](#)).

Commento [ST8]: Per informazione, il grafico OS per questi numeri è il seguente.



La tabella cruda è questa

os_c	SBRT	
	SBRT no	SBRT yes
alive	25	24
dead	9	6
Total	34	30

In fondo i morti SABR (6) sono meno dei convenzionali (9) ...

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To our knowledge, this is the first multicentric study, although retrospective, focusing exclusively on oligometastatic SGCs patients treated with the more advanced RT techniques.

Regarding the clinical characteristics of our series, the majority of patients had ACC with lung metastases. Indeed, this is the most frequent form of SGCs with medical and radiation oncologists deal (Alfieri OO 2017). However, due to its slow growth pattern and indolent evolution, at least for cribriform and tubular variants and in absence of NOTCH-1 activating mutation (Gao M 2013; Ferrarotto R JCO 2017), distant spread can be limited and slowly evolving.

Distant spread from other non-ACC histologies is less frequent even if this clinical behavior can be very aggressive with a dismal prognosis. In our study, we found most commonly patients with adenocarcinoma or salivary duct carcinoma, thus reflecting the epidemiological distribution (Barnes 2005) of these cancers (Barnes 2005).

Regardless of histological type, a clear evidence of benefits in using chemotherapy is still lacking (Alfieri 2017), although multiple targets potentially useful for a tailored approach have been identified in the last few years (Cavalieri S 2019).

In this context the use of RT, in particular SABRT as metastases directed therapy, may have a role to improve patients final outcome.

With regard to first radiological response of metastatic sites after RT, we found that all patients receiving SABRT obtain an overall clinical benefit (CR,PR and SD) in all treated lesion with no cases of PD.

In our analysis, the ablative treatment was equally effective on lung and non-lung metastases.

However, we found a benefit in term of LC for –ACC population applying SABRT. Lungs are the most common site of distant metastasis of ACC, occurring in 70% of patients with metastatic disease, with a better survival than the other subtypes of salivary glands tumors. For this reason,–, surgery of pulmonary metastases can improve the outcomes in patients with metastatic ACC.

Commento [R9]: Jungirl Seok MD1 2019 – Lung metastasis in ACC

Commento [R10]: Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival - 2004

Girelli et al. [et al.](#) showed that in ACC patients, lung metastasectomy was able to improve LC disease when 2 conditions are met: (1) complete surgical resection is feasible and (2) the time to pulmonary relapse after primary tumor treatment greater than 36 months (GirelliXXX) with an OS of 69.5% at 5 years in case of complete surgical resection.

Considering these major criteria for an effective surgery, SABRT could be considered an option in case of difficult disease site, presence of patients comorbidities. These two characteristics could affect resectability and/or quality of life of patients. It remains to determinate optimal dose and fractionation schedule, as well as identify the subset of patients who are most likely to benefit from this therapeutic approach. Several studies have reported the impact of primary tumors histology in the outcome of lung metastases treated with SABRT, in term of radiosensitivity. Therefore, it is necessary to move towards a personalization of radiation dose.

Another important data that we found in our work was the correlation between LC and number of treated metastasis. We showed that number of metastasis, regardless the RT technique used, influences negatively LC with a high significance.

While the prognostic role of burden disease has been widely addressed as regards other primary tumors (biblio), no data have been published on oligometastatic SGC patients. Historically, the number of metastases well as diameter of lesions and organ localization, represent a prognostic factor in the metastatic disease (biblio). Hereupon, RT could be employed in an early phase of metastatic disease, mostly in those with an expected long survival such as ACC histology.

Moreover, the use of SABRT in treating single metastases could be used to prolong the on-going lines of systemic therapy by ablating more resistant metastatic foci, avoiding the need to discontinue or change systemic therapy. This because, there is a lack of effective systemic therapies in metastatic setting of SGCs, based primary on chemotherapy with Cisplatin alone or combined with other agents and considering the development of new promising target therapy. We are aware of the limitations of our study which are manly inherent to the retrospective nature, the small sample, the heterogeneity of patients and

Commento [i11]: Radiosensitivity of Lung Metastases by Primary Histology and Implications for Stereotactic Body Radiation Therapy Using the Genomically Adjusted Radiation Dose
Kamran A. Ahmed, MD

Commento [i12]: Survival and prognostic factors in 321 patients treated with stereotactic body radiotherapy for oligo-metastases
Mette Marie Fode [↑](#), Morten Høyer [↑](#)

Nomogram based overall survival prediction in stereotactic body radiotherapy for oligo-metastatic lung disease S. Tanadini-Lang

metastatic site and the absence of standard therapeutic approach. All these issues could potentially explain the lack of correlation between RT on metastatic sites and OS, as reported in several other oligometastatic disease instead.

However, we cannot ignore the absence of data that evaluate the potential synergical effect of SABRT and systemic therapy.

Further prospective studies are necessary to assess the real impact of SABRT in this setting and to define the optimal dose and fractionation schedule for ACC and non-ACC metastases. In addition, we need to explore, in future studies, the combination of SABRT with the modern systemic therapies (immunotherapy or target-therapy) in this clinical scenario that moves on a personalized therapeutically approach.

Formattato: Inglese (Stati Uniti)

CONCLUSION

In our analysis, we showed that the use of RT, in particular SABRT, could have a role in the management of oligometastatic SGC patients. We observed an overall clinical benefit (CR, PR and SD) in all metastatic lesion treated with SABRT. We showed a benefit in term of LC mostly for ACC histology between lesions treated with SABRT compared to conventional RT. However we demonstrated, in line with how is showed for other primary tumors, that the number of metastasis influenced negatively LC. Treating single metastasis is better than multiple. Even if several issues affect this paper, including the retrospective nature of the analyses and the heterogeneity of the patients and lesions included, we think that this results are an important novelty in the current literature and could be a push to focalize the attention on prospective studies including this setting of patients.