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Metastatic salivary gland carcinoma: A role for stereotactic body radiation therapy? A study of AIRO-Head and Neck working group

Ciro Franzese[1,2] | Rossana Ingargiola[3] | Stefano Tomatis[1] | Nicola Alessandro Iacovelli[3] | Giancarlo Beltramo[4] | Pierfrancesco Franco[5] | Pierluigi Bonomo[6] | Isa Bossi Zanetti[4] | Angela Argenone[7] | Domenico Cante[8] | Domenico Attilio Romanello[3] | Daniela Musio[9] | Francesca De Felice[9] | Carlo Furlan[10] | Marta Scorsetti[1,2] | Ester Orlandi[11,3]

[1]Radiotherapy and Radiosurgery Department, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy

[2]Department of Biomedical Sciences, Humanitas University, Milan, Italy

[3]Radiation Oncology Unit 2, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

[4]Radiation Oncology, Cyberknife Center, Centro Diagnostico Italiano, Milan, Italy

[5]Department of Oncology, Radiation Oncology, School of Medicine, University of Turin, Turin, Italy

[6]Radiation Oncology, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

[7]Radiation Oncology Unit, Istituto Nazionale per la cura e lo studio dei tumori, Fondazione G. Pascale, Napoli, Italy

[8]Radiotherapy Department, Ivrea Community Hospital, Ivrea (Turin), Italy

[9]Department of Radiotherapy, Policlinico Umberto I "Sapienza" University of Rome, Rome, Italy

[10]Department of Radiation Oncology, Centro di Riferimento Oncologico di Aviano (CRO) IRCSS, Aviano, Italy

[11]Radiation Oncology Unit 1, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Correspondence
Ciro Franzese, Radiotherapy and Radiosurgery Department, Humanitas Clinical and Research Center IRCCS, via Manzoni 56, 20089 Rozzano (MI), Italy.
Email: ciro.franzese@hunimed.eu

Abstract

Objectives: The role of radiotherapy (RT) for oligometastases is currently established in different oncological settings but data on salivary gland cancer (SGC) are lacking. We evaluated the role of RT in oligometastatic SGC patients, focusing on stereotactic body radiation therapy (SBRT).

Materials and methods: We performed a retrospective, multicentric study of oligometastatic SGC treated with palliative RT or SBRT. Endpoints included response evaluation and local control (LC).

Results: Between 2006 and 2016, 64 patients were collected from 9 Italian Cancer Centers, on behalf of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) Head and Neck Working Group. 37 patients (57.8%) were suffering from adenoid cystic carcinoma (ACC) and 27 patients (42.2%) had non-ACC. Thirty-four patients underwent palliative RT (53,1%), and 30 received SBRT (46,9%). Most common metastatic sites were bone for palliative RT and lung for SBRT. Among patients treated with SBRT, an objective response or a stability was observed in all treated lesions. After a median follow-up of 29.2 months (range 2.3–117.1), LC at 12 months was 57.5% for patients treated with SBRT and was higher in ACC subgroup.

Conclusion: We confirmed the potential role of SBRT in the management of oligometastatic SGC patients to control limited burden of disease considering the absence of effective systemic therapies.

KEYWORDS

Head and Neck cancer, local control, metastatic adenoid cystic carcinoma, metastatic salivary gland carcinoma, oligometastatic, overall survival, SBRT, stereotactic body radiotherapy

Ciro Franzese and Rossana Ingargiola contributed equally.

1 | 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 terms of histology, biology, clinical behavior, and metastatic potential (Barnes et al., 2005).

Distant metastases are diagnosed in 25%–55% of SGCs patients, presenting with a variable clinical course, but with only 2% of patients still alive after 5 years. Adenoid cystic carcinoma (ACC) is the most common (60%) malignant histology observed in patients with metastatic disease, while less frequent subtypes are mucoepidermoid carcinoma, salivary duct carcinoma, adenocarcinoma not otherwise specified (NOS), and myoepithelial carcinoma. Metastatic ACC usually shows an indolent evolution, and this behavior leads to wonder if an early management of metastatic disease may be required or not. On the other side, high-grade non-ACC histologies have a higher likelihood of aggressive distant diffusion, requiring combined therapies. Overall, the presence of distant metastases is one of the strongest predictor of survival in metastatic SGCs but effective chemotherapy to manage this clinical situation are still scarce (Alfieri et al., 2017).

In metastatic setting, patients may require palliative external beam radiotherapy (RT) to obtain symptom relief or prevent complications from disease progression. Fractionation schemes for palliative RT commonly include 8 Gy in single fraction or fractionated regimens (20 Gy/5 fractions; 30 Gy/10 fractions), delivered with three-dimensional conformal techniques (3DCRT) or intensity modulated radiation therapy (IMRT). These approaches are 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 relatively low kinetic of metastatic progression (Weichselbaum, 2018). In these cases, ablation of limited metastatic lesions could potentially be curative. There is a relative consensus in defining oligometastatic state when ≤ 3–5 synchronous metastases in 3 or fewer different organs occur (Palma et al., 2014; Sun et al., 2018).

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 et al., 2004; Franceschini et al., 2019; Franzese et al., 2019; Gomez et al., 2016; Ruers et al., 2017). Among local treatments, stereotactic body radiation therapy (SBRT) is an advanced form of RT, characterized by the delivery of high doses per fraction, with a short treatment time (few fractions), implying a steep dose gradient and accurate localization systems (Potters et al., 2010). Recently, a randomized phase II trial including 99 oligometastatic patients reported SBRT to be associated with a significant improvement in terms of OS compared to patients receiving standard palliative care, although 4.5% of patients in the SBRT group experienced treatment-related death. A recent update of these data confirmed the impact of SBRT on 5-year OS rate, showing that it can give a durable over in time benefit (Palma et al., 2019, 2020).

The impact of SBRT for HNC patients has been reported anecdotally (Bonomo et al., 2019), and no report has been yet published regarding oligometastatic or oligorecurrent SGCs patients.

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

2 | MATERIAL AND METHODS

2.1 | Study population

We performed a retrospective, multicentric study of oligometastatic SGC patients treated with RT from 2006 to 2016 in 9 Italian Cancer Centers on behalf of the Italian Association of Radiotherapy and Clinical Oncology (AIRO) Head and Neck Working Group. We considered oligometastases as the presence at complete staging of a maximum of 3 metastatic lesions in up to two organs.

This study was approved by all Institutional Ethical Committees of the participating centers.

Patients were selected according to the following criteria: (a) histological diagnosis of high-grade SGC (ACC and non-ACC); (b) up to 3 metastases diagnosed synchronously or metachronously to primary tumor (c) controlled or resected primary tumor; (d) complete baseline staging of brain, thorax, and abdomen by mean of computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) scan; (e) treatment with palliative or ablative intent radiation; (f) first clinical and/or radiological evaluation response at 2–4 months after RT end; (g) eventual concomitant or adjuvant chemotherapy or target therapy; (h) no previous surgery on the same metastatic sites. Histological confirmation of the metastatic disease was not routinely required.

2.2 | Radiotherapy techniques

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

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

In case of palliative RT, target volume included the gross tumor volume (GTV) with an isotropic margin of generally 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. Palliative RT was delivered with 3DCRT or IMRT technique (including tomotherapy and volumetric-modulated arc therapy or VMAT). Most common moderately hypofractionated regimens were 3 Gy × 10 consecutive fractions, 4 Gy × 5 consecutive fractions or 8 Gy in single fraction.

SBRT treatments were delivered with CyberKnife, VMAT technique, or tomotherapy as already partially published together with other primary tumors (Franceschini et al., 2019).

In case of SBRT, target volumes and prescription doses were decided based on site, size, and number of lesions, together with the technology adopted. Multimodality imaging was used for target volume definition. 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 the PTV. Dose of SBRT 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.

2.3 | Statistical analysis

The primary end-point of this study was to define the pattern of response of metastatic lesions after palliative RT or SBRT. 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 1.1 (Eisenhauer et al., 2009). 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. The OS was calculated from the date of diagnosis of metastatic disease to death or last follow-up. The LC and OS rates were calculated using the Kaplan–Meier method.

Due to the absence of complete clinical data for part of the sample, we did not report on symptom control. Univariate and multivariate analyses were used to identify factors associated with LC and OS in the SBRT patients group. Univariate analyses were performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariable Cox regression analyses were done to evaluate the association between clinical factors and survival, with a significance level of $p < .05$.

Statistical calculations were performed using STATA, version 15.

3 | RESULTS

Sixty-four patients were eligible for the present study. Clinical characteristics of the study population are shown in Table 1. There were 44 males (68.7%), and median age was 56.5 years (range: 25–82 years). Thirty-seven patients (57.8%) were affected by ACC, and 27 patients (42.2%) had non-ACC primary tumor, that included adenocarcinoma NOS (10, 15.6%), ductal carcinoma (5, 7.8%), and high-grade mucoepidermoid carcinoma (4, 6.3%). In 78% of cases, major salivary glands were involved as primary tumor site. The most common non-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 tumor and synchronous metastases. Forty-eight (75%) patients were treated on a single

TABLE 1 Patients' and treatment's characteristics

	All patients (*N* = 64)
Age (years) at diagnosis of metastatic status	
Median (range)	56.5 (25–82)
Gender	
Male	44 (68.7%)
Female	20 (31.3%)
Histology	
ACC	37 (57.8%)
non-ACC	27 (42.2%)
Adenocarcinoma NOS	10 (15.6%)
Ductal carcinoma	5 (7.8%)
High-grade mucoepidermoid carcinoma	4 (6.3%)
Origin of tumor	
Major salivary glands	50 (78.1%)
Parotid	40 (62.5%)
Submaxillary gland and sublingual gland	10 (15.6%)
Minor salivary glands	14 (21.9%)
Time to metastasis	
Synchronous	10 (15.6%)
Metachronous	54 (84.4%)
Median time (months)	17.0
Number of treated lesions	
1	48 (75.0%)
2	12 (18.8%)
3	4 (6.2%)
Treatment performed for primary tumor*	
S/RT	35 (54.7%)
S	16 (25.0%)
S/RT/CT	6 (9.4%)
CT	5 (7.8%)
RT	2 (3.1%)

*S, Surgery; RT, Radiotherapy; CT, Chemotherapy; S/RT, combined Surgery and Radiotherapy; S/RT/CT, combined Surgery, Radiotherapy and Chemotherapy.

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 SBRT (46,9%). The most common metastatic sites were bone for palliative RT and lung for SBRT. Among patients treated with SBRT, 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 SBRT. In terms of biological effective dose (BED), median value was 39 Gy for palliative treatments (range: 14.4–78) and 81.6 Gy for ablative treatment (range: 35.7–151).

Patterns of response are shown in Table 3. Best overall response after RT was assessed 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 (including CR, RP, and *SD*) in all patients receiving SBRT, while all PD were observed in patients treated with palliative RT.

After a median follow-up of 29.2 months (range 2.3–117.1), LC at 12 months was 47.1% (95% CI 32.9–60.1) for the whole population (Figure 1), 57.5% (95%CI 35.1–74.6) for patients treated with SBRT, and 37.8% (95% CI 20.1–55.5) for palliative RT (Figure 2).

TABLE 2 Characteristics according to treatment group

	SBRT ($n = 30$)	Conventional RT ($n = 34$)
Histology		
ACC	18 (60.0%)	19 (55.9%)
non-ACC	12 (40.0%)	15 (44.1%)
Treatment site		
Lung (25)	16 (53.4%)	9 (26.5%)
Bone (20)	4 (13.3%)	16 (47.1%)
Brain (13)	10 (33.3%)	3 (8.8%)
Other (6)	0	6 (17.6%)
Treatment performed by		
3DCRT	1 (3.3%)	10 (29.4%)
VMAT/IMRT/ Tomotherapy	24 (80.0%)	20 (58.8%)
Cyberknife	5 (16.7%)	4 (11.8%)
Total Dose (Gy)		
Mean	33.6	31.6
Median	29	30
Range	20–54	8–60
Number fraction		
Median (range)	3 (1–5)	10 (1–25)
Dose for fraction (Gy)		
Median (range)	13.5 (5–28)	3 (1.8 – 8)
BED (Gy) (calculated with $\alpha/\beta = 10$ Gy)		
≤54 (32)	5 (16.7%)	27 (79.4%)
>54 (32)	25 (83.3%)	7 (20.6%)

The increasing number of treated metastases was found to be negatively associated with LC rates ($p \leq .01$) both in univariate (HR = 1.8) and multivariate tests (HR = 1.9).

Site of metastasis, RT dose and technique did not influence LC for the whole population. However, considering only ACC patients ($n = 37$), a significant benefit in time to local failure was observed for patients receiving SBRT compared to palliative RT technique, regardless of metastatic site ($p = .05$).

OS rates at 12 and 24 months were 84.9% (95% CI = 64.5–94) and 73.6% (95% CI = 49.4–87.5), respectively, for patients treated with SBRT and 96.9% (95% CI = 79.8–99.6), and 85.9% (95% CI = 66.6–94.5) for patients receiving palliative RT.

Two-year OS rate was 83% for ACC and 53% for non-ACC with borderline significance ($p = .066$). No difference ($p = .69$, univariate analysis) in terms of OS was observed in ACC patients between the SBRT compared to palliative RT (Figure 3).

4 | DISCUSSION

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

In the last years, several studies could be retrieved in literature about the role of SBRT but in oligometastatic patients from different primary tumors (Franzese et al., 2019; Hörner-Rieber et al., 2019; Sharma et al., 2020).

Recently, the ESTRO-EORTC collaboration (Guckenberger et al., 2020) produced a consensus recommendation classifying disease into oligometastatic subcategories, considering if oligometastatic disease is diagnosed during a treatment-free interval or on active chemotherapy, together with other disease or treatment characteristics. Palma et al. (Palma et al., 2019, 2020) conducted the first prospective randomized trial comparing standard of care with versus without SBRT in 99 oligometastatic patients, showing a median OS of 41 months versus 28 months, respectively.

Major advantages of SBRT on metastases include the possibility to control the limited burden of disease with potential delay of onset or intensification of chemotherapy. However, so far, very few data have been published on oligometastatic head and neck cancer patients (Bonomo et al., 2019; Jereczek-Fossa et al., 2013).

Regarding the clinical characteristics of our series, the majority of patients had ACC with lung metastases. Indeed, this is the most frequent presentation of SGCs managed by medical and radiation oncologists (Alfieri et al., 2017). Interestingly, due to its slow growth pattern and indolent evolution, at least for cribriform and tubular variants and in absence of NOTCH-1 activating mutation (Ferrarotto et al., 2017; Gao et al., 2013), 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 observed most commonly patients with

TABLE 3 Outcome for the whole group and according to the treatment

	All patients ($n = 64$)	SBRT ($n = 30$)	Conventional RT ($n = 34$)
Follow-up duration (months)			
Median (range)	29.2 (range 2.3–117.1)		
First radiological response			
CR	18 (28.1%)	9 (30.0%)	9 (26.5%)
RP	18 (28.1%)	12 (40.0%)	6 (17.6%)
SD	20 (31.3%)	9 (30.0%)	11 (32.4%)
PD	8 (12.5)	0	8 (23.5%)
Status at the last follow-up			
Alive	49 (76.6%)	24 (80.0%)	25 (73.5%)
Dead	15 (23.4%)	6 (20.0%)	9 (26.5%)

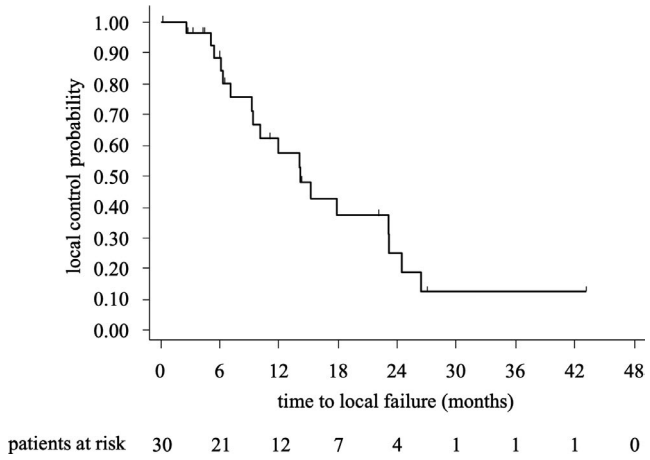

FIGURE 1 Kaplan–Meier local control probability for patients treated with SBRT

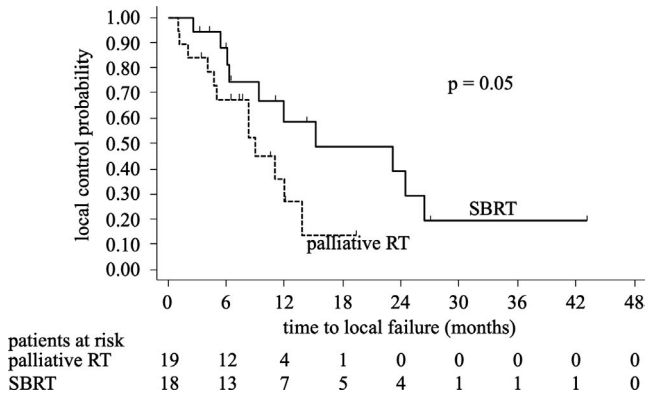

FIGURE 2 Kaplan–Meier local control probability for patients treated with SBRT (solid line) and palliative radiotherapy (dotted line) within the ACC histology patient group (37 cases)

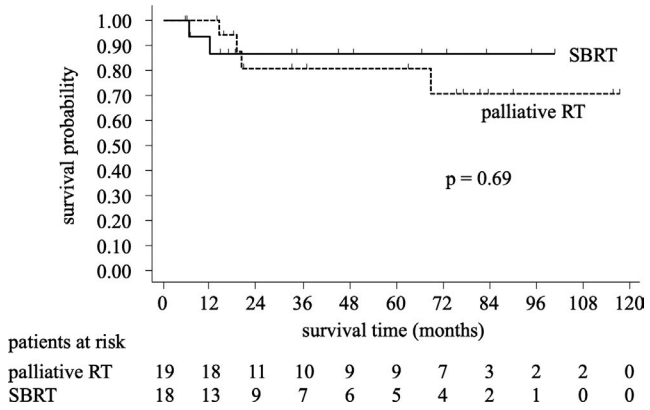

FIGURE 3 Kaplan–Meier overall survival estimates for patients treated with SBRT (solid line) and palliative radiotherapy (dotted line) within the ACC histology patient group (37 cases)

adenocarcinoma or salivary duct carcinoma, thus reflecting the epidemiological distribution of these cancers (Barnes et al., 2005).

Regardless of histological type, a clear evidence of benefits in using chemotherapy is still lacking (Alfieri et al., 2017), although multiple targets potentially useful for a tailored approach have been identified in the last few years (Cavalieri et al., 2019; Keam et al., 2020).

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

With respect to first radiological response of metastatic sites after RT, we found that all patients receiving SBRT obtained an overall clinical benefit (CR, PR and *SD*) with no cases of PD. In our study, the ablative treatment was equally effective on both lung and non-lung metastases.

We found a benefit in term of LC for ACC population receiving SBRT. Lungs are the most common site of distant metastasis of ACC, occurring in 70% of patients presenting with metastatic disease (Seok et al., 2019), with a better survival compared to the other subtypes of SGCs (Terhaard et al., 2004). Recently, a study by Cavalieri et al aimed to develop and validate a prognostic nomogram for metastatic ACC patients and found that patients with lung metastases had a more favorable outcome (HR = 0.547, 95% CL 0.317–0.944), compared to other sites such as liver (HR = 2.001, 95% CL 1.160–3.451) and bone disease (HR = 4.012, 95% CL 2.365–6.808) (Cavalieri et al., 2020). For this reason, resection of lung metastases could be taken into account to improve the outcomes in patients with metastatic ACC. Girelli et al. showed that in ACC patients, lung

metastasectomy was able to improve disease control when 2 conditions are met: (1) complete surgical resection and (2) time to pulmonary relapse after primary tumor resection longer than 36 months (Girelli et al., 2017). They reported OS of 69.5% at 5 years in case of complete surgical resection.

Considering the major criteria for an effective surgery, SBRT could be considered an alternative in case of difficult disease site, and/or presence of several comorbidities. These two characteristics could affect resectability and/or quality of life of patients. It remains to determinate the optimal dose and fractionation schedule, as well as identify the subset of patients who are most likely to benefit from this therapeutic approach. Radiosensitivity could be a relevant point considering the impact of primary tumor histology when treated with SBRT; thus, the concept of a personalized RT dose should be considered.

The correlation between LC and number of treated metastases was another relevant result in our study. We showed that a higher number of metastases, regardless of RT technique used, had a negative influence on LC.

While the prognostic role of disease's burden has been widely addressed for other primary tumors, no data have been published on oligometastatic SGC. Historically, the number of metastases as well as the diameter of lesions and organ localization represented a relevant prognostic factor in metastatic setting (Fode & Høyer, 2015; Tanadini-Lang et al., 2017). Hereupon, RT should be employed in the early phase of metastatic diffusion, mostly in patients with an expected long-term survival as for ACC histology.

The use of SBRT on isolated metastases could potentially prolong the efficacy of an ongoing line of systemic therapy by ablating more resistant metastatic foci, avoiding the need to discontinue, change, or intensify systemic therapy. This advantage could be relevant considering the lack of effective systemic therapies in metastatic SGCs, relying mostly on cisplatin-based chemotherapy.

We are aware of the limitations of our study which are mainly inherent to its retrospective nature, the small sample size, the heterogeneity of included patients and metastatic site, and the absence of a standard therapeutic approach as comparator. All these issues could potentially bias the results. However, we cannot ignore the absence of data in this setting, above all evaluating the potential synergic effect of SBRT with systemic therapy.

Further prospective studies are necessary to assess the real impact of SBRT in this setting and to define the optimal dose and fractionation schedule for ACC and no-ACC metastases. In addition, we need to explore, in future studies, the combination of SBRT with modern systemic therapies (immunotherapy or target therapy) in this clinical scenario to implement a personalized therapeutic approach.

5 | CONCLUSION

In our study, we showed that the use of RT, in particular SBRT, could have a role in the management of oligometastatic SGC patients. We observed an overall clinical benefit (CR, PR and SD) in all metastatic lesions when treated with SBRT. A benefit in terms of LC was observed for ACC histology if treated with SBRT compared to palliative RT. We hope that these results could stimulate the oncologic community toward prospective multicentric studies in this setting of patients.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Ciro Franzese: Conceptualization; Data curation; Writing-original draft. **Rossana Ingargiola:** Writing-original draft. **Stefano Tomatis:** Formal analysis. **Nicola Alessandro Iacovelli:** Resources. **Giancarlo Beltramo:** Resources. **Pierfrancesco Franco:** Resources; Writing-review & editing. **Pierluigi Bonomo:** Resources; Writing-review & editing. **Isa Bossi Zanetti:** Resources. **Angela Argenone:** Resources. **Domenico Cante:** Resources. **Domenico Attilio Romanello:** Resources. **Daniela Musio:** Resources. **Francesca De Felice:** Resources. **Carlo Furlan:** Resources. **Marta Scorsetti:** Conceptualization; Writing-review & editing. **Ester Orlandi:** Conceptualization; Data curation; Writing-original draft.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, CF, upon reasonable request.

ORCID

Ciro Franzese https://orcid.org/0000-0001-6893-6284
Francesca De Felice https://orcid.org/0000-0002-5119-8358

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