Multidisciplinary Management of Radiation-Induced Salivary Gland Carcinomas in the Modern Radiotherapy Era

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Simple Summary: Etiopathogenesis of salivary gland cancers [SGCs] is largely unknown, even if exposition to ionizing radiation is a recognized risk factor for SGCs development. To date, exhaustive data to guide clinicians in managing patients with radiation-induced [ri] SGCs are scarce and their treatment remains challenging. The purpose of this work is to describe and to analyze clinical and histopathological features, delivered treatments, and outcome of a series of patients with ri-SGCs treated at two Italian cancer referral sites. Given the rarity of ri-SGCs, this retrospective analysis conducted on a case series of 13 patients adds further knowledge to the paucity of literature. The management of these malignancies is extremely complex requiring a multidisciplinary treatment approach.

Abstract: Clinical data of ri-SGCs patients treated between 2015 and 2019 at a tertiary cancer center and a national hadron therapy facility were reviewed. Latent time (LT) from first RT to ri-SGCs diagnosis, overall (OS), and disease-free survival (DFS) were assessed. Thirteen patients developed 14 ri-SGCs (one patient had 2 synchronous ri-SGCs), after a median LT of 23 years (range 16–34). Parotid was the primary site in 8 cases (57%) and salivary duct carcinoma was the most frequent
histotype (29%). Nine patients (69%) underwent surgery (Sx). Among them, 4 patients (31%) underwent Sx alone, 5 received post-operative treatments: 3 (23%) photon-based (X) reRT, one (8%) protons and carbon ions, one (8%) carbon ions only. One patient (8%) received definitive XRT. The remaining 3 patients (23%) received androgen deprivation therapy. With a median follow-up of 48 months (range 24–72), median OS and PFS were 74 and 24 months, respectively. In the subgroup of AR+ ri-SGCs, median PFS and OS were 12 and 74 months, respectively. Given the rarity of ri-SGCs, this work adds further knowledge to the paucity of literature. The management of these malignancies is extremely complex requiring a multidisciplinary treatment approach.

**Keywords:** Radiation induced cancer; salivary gland cancer; multidisciplinary management; radiotherapy; particle therapy; hormone therapy; surgery

### 1. Introduction

Malignant tumors of salivary glands (SGCs) comprise less than 0.5% of all cancers and constitute about 2–8.5% of head and neck cancers (HNCs) [1]. Worldwide annual incidence ranges from 0.4 to 2.6 cases over 100,000 [2] with a male to female ratio of 1.5:1, a higher prevalence in males compared to females during the 6th–7th decade for the salivary duct carcinoma (SDC), being exceedingly uncommon in children [1–3].

Etiopathogenesis of SGCs is largely unknown, even if exposition to ionizing radiation is a recognized risk factor for SGCs development. This was reported for the first time in Japanese survivors of the atomic bomb: the frequency of SGCs, mucoepidermoid carcinoma (MEC) in particular, was disproportionately high at high radiation doses. In Japanese survivors, out of 145 SGCs registered from 1950 to 1987, 41 were malignant and the proportion of MEC raised with the increasing of radiation dose ($p = 0.004$ for linear trend) [4]. However, even doses of 2 Gy could raise the risk of developing salivary gland tumors [4,5].

Further evidence supporting the role of radiation in salivary gland carcinogenesis derives from data of children treated with scalp irradiation for tinea capitis, or who received radiotherapy (RT) to the head and neck area to reduce the size of the tonsils and adenoids [6,7]. These children had a 4.5-fold incidence of SGCs compared to untreated people with a mean latency period until tumor development of 11 years [6].

Globally, the standardized incidence ratio of HNCs in survivors of childhood cancer is 13.6 and SGCs represent 65% of these cases [8]. The risk has been associated with the primary tumor type, gender, type of chemotherapy, etc. Radiation has been associated with an increased risk of all carcinomas, most marked for HNCs (SIR 18.5), and the site of the second tumor had arisen in a previous radiation field in 85% of HNCs. Besides, a large study on children survivors after RT (with or without chemotherapy) for a first cancer, showed a linear correlation between dose exposure and the risk of developing solid tumors including SGCs, with the second malignancy occurring at least eight years after the end of the first oncological treatment [9].

Exhaustive data to guide clinicians in managing patients with ri-SGCs are scarce and their treatment remains challenging, especially in the era of targeted systemic treatments and innovative radiation therapies, namely intensity modulated RT (IMRT) and hadron therapy [9–13].

Ideally, surgery with wide margins remains the mainstay of treatment followed by RT in high-risk cases [14,15]. However, radical salvage surgery is often not feasible, essentially because of technical difficulties when operating within an irradiated area [9,12,16] or due to the local extension of disease that prevents a radical resection.

In addition, further RT could be hardly given since normal tissues surrounding secondary SGCs have been generally treated to near their dose tolerance. Finally, in some cases, patients who suffer from secondary SGCs are young and potentially candidates to develop a third cancer, in particular in the presence of a genetic susceptibility [17]. In this scenario, modern RT techniques, including IMRT and particle therapy, may play a principal role in the management of these patients. Indeed, thanks to their physical properties, they have an excellent sparing of normal tissue outside the target and they are able to overcome an enhanced hypo-oxygenation that can also be present in ri-SGCs [14].
With the limitations of the descriptive nature of our work and the limited patient cohort, the purpose of our review is to describe and to analyze clinical and histopathological features, delivered treatments, and outcome of a series of patients with ri-SGCs.

2. Results

2.1. Patients’ Characteristics

Patients’ clinical characteristics at the first cancer diagnosis are listed in Table 1. Overall, we have identified 13 patients suitable for this analysis. One of these patients had two synchronous secondary SGCs after a LT of 34 years, for a total of 14 ri-SGC cases. Median age at diagnosis of primary tumor was 17 years (range 3–68), whereas median age at diagnosis of ri-SGC was 50 years (range 17–78), with a median interval between radiation exposure and diagnosis of the SGCs of 23 years (95% CI: 16–34).

Characteristics of the second SGCs were resumed in Table 2. Histology was quite heterogeneous: low grade MEC (n = 2), SDC (n = 4), low-grade polymorphous adenocarcinoma (n = 1), adenocarcinoma not otherwise specified NOS (n = 3), carcinoma ex-pleomorphic adenoma (n = 1), adenoid-cystic carcinoma (ACC) (n = 2), basal cell adenocarcinoma (n = 1). Eight tumors occurred in the parotid glands, five in submandibular glands, one in minor salivary glands of the oropharynx. Positive nodes (n = 3) have been detected in submandibular (n = 2) or minor salivary glands (n = 1) tumors whereas distant metastases were present in 2 cases. Median LT to ri-SGCs was not significantly different whether primary tumor was diagnosed in pediatric age (31 years, range 5–50) or in adult (33.5 years, range 18–68), even though in the former diagnosis of ri-SGCS appeared earlier after primary treatment compared to the latter.

Immunohistochemical (IHC) research of androgen receptor has been done only in cases with diagnosis of SDC, adenocarcinoma NOS, and carcinoma ex pleomorphic adenoma. Seven out of 8 patients had androgen receptors (ARs) overexpression. HER2 overexpression was not identified. NGS was performed in 6 out of 13 (46%) cases, in 3 cases somatic tumor mutations have been found: BRCA2 mutation in one SDC, TP53 mutation in one adenocarcinoma NOS, PIK3CA and HRAS mutations in another SDC.

Concerning the relationship with the previous treated volumes, data were available for 9 (64%) ri-SGCs (one patient had two synchronous ri-SGCs, Table 1). Six ri-SGCs developed within the previously treated volumes and in 5 of them, ri-SGC was marginal to high-dose volumes. Three ri-SGCs occurred within the initial target volume.

2.2. Treatment and Outcome for Secondary SGCs

Nine patients (69%) underwent surgery, either alone (n = 3), in combination with RT (n = 5), or with postoperative systemic treatment (n = 1); resection margins were positive in 8 cases. One patient received definitive RT. The remaining 3 patients received palliative treatment.

Seven patients (54%) out of 13 received RT as part of their multimodality treatment. Post-operative photon-based RT (XRT) (n = 3) doses ranged from 64 Gy to 70 Gy (median of 67 Gy); one patient received a palliative course of 30 Gy for an unresectable parotid gland tumor. Particle therapy was delivered in two cases: one patient was treated by post-operative Proton Therapy (PT) with a boost of Carbon Ion Radiotherapy (CIRT), receiving 6 Gy(RBE) with CIRT and 59.4 Gy with PT. The other one was treated with post-operative CIRT after microscopic residual surgery, with a total dose of 68.8 Gy(RBE). In the subgroup treated with post-operative RT, median age at primary tumor diagnosis was 12 years (range 3–27) and median LT was 17 years (range 5–41 years). The patient treated with radical RT was 8 years old at the time of the diagnosis of the primary tumor, with an LT of 37 years. With regard to acute toxicities, all of the patients who underwent post-operative RT developed mild to moderate xerostomia and oral mucositis (≤G2); as regards late toxicities, three patients treated with surgery and XRT developed buccal spasms (n = 1), fibrosis (n = 1), trismus and neuropathy of the facial nerve (n = 2). Both the 2 patients treated with post-operative particle therapy developed G1 trismus, G1 xerostomia, and G1 neuropathy of the facial and trigeminal nerve.
Table 1. Patient characteristics at diagnosis of primary cancer.

| Patient | Gender | Age at Primary Diagnosis | Year of First Diagnosis | Histology | Site and Stage | Treatment | RT Techniques/RT Volumes and Doses | Late Sequelae | Late Time between Primary Tumor and SGCs |
|---------|--------|--------------------------|-------------------------|-----------|---------------|-----------|-----------------------------------|--------------|----------------------------------------|
| Patient 1 | F | 10 | 2000 | Medulloblastoma | Cerebellar vermis T3M0 (Chang system) High Risk (>1.5 cm residual disease) | Sequential high dose CT + Sx + >RT Vincristine and CCNU-based maintenance therapy | IMRT Conventional XRT Hyperfractionated accelerated RT (HART) Craniospinal axis: 39 Gy Posterior fossa: 60 Gy | Neurocognitive impairment Hypothyroidism Bilateral hypoaacusia | 16 years |
| Patient 2 | M | 68 | 2008 | Undifferentiated carcinoma (EBER-negative HPV-positive) | Nasopharynx cT2N1c (AJCC VII ed) | Platinum-based CRT | Elective nodal volume: 50 Gy High risk volume: 70 Gy Conventional fractionation | Severe Xerostomia Dental alterations Moderate fibrosis | 10 years |
| Patient 3 | M | 18 | 1985 | Nodular lymphocyte-predominant HL | Neck Stage II A (Ann Arbor staging) | Neck Sx + >RT | Conventional XRT 40 Gy mantle field 45 Gy neck nodes | Chronic ischemic cardiomyopathy | 32 years |
| Patient 4 | M | 40 | 1992 | Squamous cell carcinoma | Oropharynx | Tonsillectomy + >RT | Conventional XRT Elective nodal volume: 45 Gy High risk volume: 60 Gy Conventional fractionation | Xerostomia Hypothyroidism | 25 years |
| Patient 5 | F | 27 | 1975 | Papillary thyroid carcinoma | Thyroid (stage not available) | Total thyroidecctomy > external beam RT | Conventional y photon-based RT (Co60) 45 Gy | Xerostomia Moderate fibrosis | 41 years |
| Patient 6 | M | 10 | 1997 | Sarcoma G3, NOS | Soft tissues of paramandibular area (locally advanced disease, stage not available) | 5x + CT(CEVAIE) + >RT (44.8 Gy, 1.8 Gy twice a day) | Conventional XRT | Moderate fibrosis | 19 years |
| Patient 7 | M | 8 | 1975 | HL | Neck Stage II (Ann Arbor staging) | CT + >RT | Conventional XRT | Moderate fibrosis | 37 years |
| Patient 8 | F | 17 | 1985 | Undifferentiated carcinoma (EBER unknown) | Nasopharynx (loco-regionally advanced disease, stage not available) | CT (Vincristine, Adriamycin and cyclophosphamide × 2 cycles) + concurrent adriamycin and cyclophosphamide × 4 cycles | Conventional XRT T and pathological nodes: 62 Gy Elective nodes: 40.2 Gy | Trismus Xerostomia Massive fibrosis Ipsilateral mandible | 34 years |
| Patient 9 | M | 19 | 1993 | Undifferentiated carcinoma (EBER unknown) | Nasopharynx T4N1 (AJCC VII edition) | Exclusive RT | Conventional XRT | Neck fibrosis Facial asymmetry Sinusosal synchiae | 22 years |
| Patient 10 | F | 12 | 2014 | HL | Neck Stage III (Ann Arbor staging) | CT (COPP/ABV × 6) + RT above and under diaphragm (total dose 14.4 Gy) | Conventional XRT T and pathological nodes: 62 Gy Elective nodes: 40.2 Gy | - | 5 years |
| Patient 11 | M | 3 | 1983 | HL | Neck Stage IV (Ann Arbor staging) for bone marrow infiltration | CT + >RT | Conventional XRT 20 Gy | - | 31 years |
| Patient 12 | M | 45 | 1993 | Undifferentiated carcinoma (EBER unknown) | Nasopharynx (stage unknown) | Induction cisplatin + 5-FU followed by exclusive RT | Conventional XRT | - | 19 years |
| Patient 13 | M | 13 | 1963 | Lymphoma NOS | Supraepiglottic lymph nodes | RT above diaphragm | Conventional XRT mantle field (unknown total dose) | - | 50 years |

Legend: 5-FU, 5-fluorouracil; ABV, Adriamycin, bleomycin, vindesine; AJCC, American Joint Committee on Cancer; CEVAIE, carboplatin, epirubicin, vincristine, actinomycin, ifosfamide, etoposide; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; CRT, concomitant chemoradiation; CT, chemotherapy; EBER, Epstein–Barr virus-encoded RNA; HL, Hodgkin lymphoma; NOS, not otherwise specified; RT, external beam radiotherapy; Sx, surgery; XRT, photon-based radiotherapy.
### Table 2. Patient characteristics at clinical presentation of radiation-induced SGC and at follow-up.

| Patient | Age at Secondary Diagnosis | Year of SGC Diagnosis | Site and Stage | SGCs Histology | Molecular Analysis | Relationship between SGC Volume and Previous RT Doses and Target Volume | Treatment of SGCs | Second Course of RT Techniques/RT Dose and Volume | Recurrence/Progression | Toxicity | Last Follow-Up Status | OS Time |
|---------|---------------------------|-----------------------|----------------|----------------|------------------|---------------------------------------------------------------|-----------------|------------------------------------------------|-------------------|----------|---------------------|---------|
|         |                           |                       |                |                |                  |                                                               |                 |                                                          |                   |          |                     |         |
| Patient 1 | 29                        | 2016                  | Parotid pT1    | Low Grade Polymorphous Adenocarcinoma | N.A. | Within initial treatment volume and marginal to high-dose volume | Sx (R1) → RT | Photon-based VMAT 40 Gy on parotid surgical bed | No | Bucal spasm | Alive | NED | 36 months |
| Patient 2 | 78                        | 2018                  | Parotid gland cT4 Unresectable disease | Salivary duct carcinoma AR+ | HRCA: p.17A5D2 exon 9 (50% of DNA) | Within elective volume and marginal high-dose volume | ADT → palliative RT | Photon-based VMAT 36 Gy to macroscopic parotid disease (3 Gy per fraction) | Local progression after 2 months | - | Dead | ED | 13 months |
| Patient 3 | 50                        | 2017                  | Right parotid gland cT4 Unresectable disease | Salivary duct carcinoma AR+ | HER-2 negative | Within initial treatment volume | ADT | Not delivered | - | Local progression and bone metastasis after 4 months | - | Alive | ED | 24 months |
| Patient 4 | 63                        | 2015                  | Right submandibular gland. Stage ptT1NS | Salivary duct carcinoma AR+ | HER-2 negative | Not applicable | Surgery for local disease. Al diagnosis of metastatic disease: Chemotherapy (CBDCA/paclitaxel), followed by ADT | Not delivered | - | Alive | ED | 48 months |
| Patient 5 | 48                        | 2016                  | Parotid pT3b (NP nodes radiologically positive) | Carcinoma ex pleomorphic adenoma AR+ | NR4A3 negative | Marginal to target volume | Sx | Photon-based VMAT-80Gy in 35 fractions 80 Gy on macroscopic disease 54 Gy RT nodules and I-II neck levels | No | Fibrosis Trismus Facial nerve disorder | Alive | NED | 38 months |
| Patient 6 | 27                        | 2015                  | Left parotid pT3 R2 | Low grade mucoepidermoid carcinoma | N.A. | Marginal to target volume | Sx | Photon-based VMAT-80Gy in 35 fractions 70 Gy on target disease 70 Gy on surgical bed | No | Trismus Facial nerve disorder | Alive | NED | 46 months |
| Patient 7 | 42                        | 2012                  | Submandibular tT4 (polateral mandibular nerve involvement) Unresectable disease | Adenocarcinoma =NOS AR+ | N.A. | Marginal to target volume | ET+ADT | Photon-based VMAT-80Gy in 35 fractions 70 Gy on target disease 70 Gy on surgical bed | No | Trismus Facial nerve disorder | Alive | NED | 38 months |
| Patient 8 | 50                        | 2019                  | Left submandibular gland pT3bN0M0HEX | Adenoid cystic carcinoma (solid variant) Basal cell adenocarcinoma | MIB negative (ACC) | Marginal to high-risk target volume, within elective volume | MIB marginal to high-risk target volume | Sx | Not delivered | Stable disease at both sides | - | Alive | ED | 4 months |
| Patient 9 | 41                        | 2016                  | Minor salivary gland (Submandibular gland) pT3N0M0HEX | Adenocarcinoma =NOS AR+ | ITPT: p.15H5 exon 6 (12% of DNA) | HER-2 negative | Not applicable | Sx → ADT | Not delivered | Bone metastases after 23 months from surgery | - | Dead | ED | 39 months |
| Patient 10 | 17                       | 2019                  | Left parotid pT3 R2 | Low Grade Mucoepidermoid carcinoma | N.A. | Marginal to high-risk target volume, within elective volume | Sx | CITRT 6 Gy -> Protein therapy (20 Gy) to parotid bed, 50.4 Gy to parotid and neck levels | No | Trismus Facial and trigeminal nerve disorder | Alive | NED | 15 months |
| Patient 11 | 34                       | 2016                  | Parotid pT3R1 | ACC | NGS: no mutations | ALK and NOS negative | Not applicable | Sx → RT | CITRT 60 Gy(IRR) (3.3 Gy(IRR) + 16 over 4 weeks) | Lung metastases 2 years after surgery | Trismus Xerostomia Facial and trigeminal nerve disorder | Alive | ED | 77 months |
| Patient 12 | 44                       | 2012                  | Left parotid M1 (lung) | Salivary duct carcinoma AR+ | NGS: BRCAl2-AR+EX2 (10% of DNA) | Not applicable | Chemotherapy | Not delivered | Bone, lung and brain progression | - | Alive | ED | 85 months |
| Patient 13 | 63                       | 2013                  | Right parotid pT4bN2bL | Salivary duct carcinoma AR+ | NGS: no mutations | Not applicable | Sx | Not delivered | Bone, lung and brain progression | - | Dead | ED | 74 months |

Legend: ACC, adenoid cystic carcinoma; ADT, androgen deprivation therapy; [bicatulam + LHRH analogue]; AR, Androgen receptor; AR+, Androgen receptor overexpression; CBDCA, carboplatin; CIRT, carbon ion radiation therapy; ED, evidence of disease; LHRH, luteinizing hormone releasing hormone; N.A., not assessed; NED, no evidence of disease; NGS, next generation sequencing; PR, partial response; RAI, radioactive iodine; RT, radiation therapy; RP, retropharyngeal node; S, surgery; SD, stable disease; SGC, salivary gland cancer; R1, microscopic residual tumor after surgery; R2, macroscopic residual tumor after surgery; ECS+, extracapsular spread.
Cut-off date was October 2019.
Median follow-up was 48 months (95% CI: 24–72). Median OS was 74 months (95% CI: 36.00–74.00). Median PFS was 24 months (95% CI: 6.00-upper limit not reached). Five-year OS and DFS were 67% and 26%, respectively. For the subgroup of AR+ SGCs, median DFS and OS were 12 months (95% CI: 2.00–25.00) and 74 months (95% CI: 13.00–74.00), respectively. In AR− SGC patients, median DFS and OS were not reached; 2-year DFS was 62.5% and 2-year OS 100%.

3. Discussion

We reported a small series of 13 patients with ri-SGCs with a more favorable outcome than previously published older series. Median PFS and OS were 24 months (95% CI: 6 months-not reached) and 74 months (95% CI: 36–74), respectively, despite high-grade histology in 77% of cases and advanced stage (III–IV) in 10 out 13 cases. These results are very encouraging, if we consider that 9 patients (69%) received surgery, 1 patient (8%) was treated with definitive XRT and concomitant androgen deprivation therapy (ADT), 1 patient (8%) received palliative XRT and subsequent ADT, whereas the remaining 2 patients (15%) received only systemic therapy. In the past, a 5-year OS higher than 90% was reported, however, mucoepidermoid was the most common histotype and almost all patients received surgery combined or not with RT [9,12]. In the analysis by Bhattacharyya et al., for example, patients with MECS exhibited a higher 5-year OS (81.5%), compared to other histotypes such as ACC (70.7%) and carcinoma ex pleomorphic adenoma (40.2%) [18]. On the other hand, Mallik et al. reported 47 submandibular gland cancers, mostly ACCs, with a 5-year DFS of 71.8%, 12.8% (n = 6) of loco-regional failure, and 12.8% (n = 6) of development of distant metastases. Compared to the past, availability of new effective systemic treatments (e.g., androgen deprivation therapy, ADT; anti-HER2 monoclonal antibody), improvement in the re-irradiation (reRT) [19] techniques and the opening of heavy ions facility in Italy in 2011 have offered new therapeutic opportunities.

If MEC was the most common histotype [3–7,9,11–13,16,20–25] in previous series, the SGC histotypes reported in our series are quite heterogeneous: 9 out 13 (69%) were high-grade with AR expression in 7 out of 9 cases. Of note, 38% received ADT with a median PFS and OS of 12 and 74 months, respectively. Activity of androgen blockade in AR expressing SGCs is already well known. Several papers [26–28] support the use of ADT in clinical practice and one randomized, prospective trial, is currently ongoing (NCT01969578). New potential druggable targets as HER2 [29], TRK [30], RET [31], BRAF [32] have been identified almost exclusively in high-risk histologies different from ACC, paving the way to active treatment approaches. Impressive results have been reported in the clinical practice with some tailored agents as trastuzumab emtansine [33], NTRK inhibitors [34,35], or RET inhibitors [36]. Activity of some antiangiogenic agents (e.g., lenvatinib) seems to be promising in ACC [37] even if structural disease shrinkage has been observed only in a few cases. Employ of checkpoint blockade (e.g., pembrolizumab) has been explored with a weak activity (ORR 12%) even if objective responses have been observed only in high-risk histotypes [38].

ReRT should be usually proposed as post-operative treatment, since it is related to prolonged survival rates, especially for ACC [39]: in our cohort, 5 patients out of 13 (38%) received a post-operative RT [any energy]. Indications for post-operative RT include advanced stage (T3, T4, n+), positive surgical margins, high tumor grade, perineural invasion, recurrent diseases [40,41]. Moreover, reRT should be taken into account whenever surgery is not feasible, even though no data from prospective randomized data are available in the literature. Nowadays, state-of-the-art RT techniques, such as IMRT and stereotactic body RT (SBRT) allow steep dose gradients with optimal coverage even for complex target volumes, while allowing a good spare of close healthy tissues. Following NCCN recommendations, reRT should take place at least 6 months after the end of the first RT course and target volumes should be taken as narrower as possible, avoiding elective nodes coverage. Results are encouraging: Karam et al. re-treated 18 consecutive patients with SBRT with a median dose of 30 Gy delivered in 5 fractions. With a median cumulative dose of 91.1 Gy, 2-years local control and OS were 53% and 39%, respectively, even if 4 patients eventually experienced soft tissue necrosis as a late severe toxicity [42].
In regards to IMRT, most of the experience in literature refers to mixed series where the number of SGCs is significantly lower than pharyngeal or laryngeal squamous cell carcinoma cases [19,43,44]. Recently, Orlandi et al. analyzed reRT outcomes on a cohort of 159 patients, of which 71 (45%) were not squamous cell carcinomas (in particular, 25 (16%) were ACC and 8 (5%) were affected by SGCs). With a median follow up of 49.9 months, 5-years OS and PFS were 43.5% (95% CI, 34.6–54.8%) and 20.9% (95% CI, 14.7–29.6%), respectively. It is hard to make comparisons with our current results, due to the limited number of patients and the mixed cohort of the cited study. To our knowledge, there are no data available in literature concerning reRT on an exclusive ri-SGCs cohort.

Treatment with hadrontherapy represents a new approach considering that most of these tumors arose in a previously operated and irradiated field. PT and CIRT seem to be a reasonable choice to overcome dosimetric thresholds in unresectable patients. Two patients (one teenager) received PT and CIRT (delivered doses: PT 59.4 Gy(RBE) + CIRT 6 Gy(RBE); CIRT 68.8 Gy(RBE)). The physical properties of PT can be exploited in pediatric patients. Through PT nearly the same physical dose of XRT can be delivered, with a neat fall of dose outside the target: Grant et al. reported a 53% of grade 2− grade 3 (G2-G3) dermatitis, 0% of G2-G3 dysphagia, and a 46% of G2-G3 mucositis in a cohort of 13 pediatric patients receiving 60 Gy(RBE), compared to 11 patients treated with XRT (60 Gy, 54%, 27% and 91% of toxicities rates, respectively). Takagi et al. compared PT and CIRT in a cohort of 80 pts treated for head and neck ACC: no differences were found in terms of local control (66% for PT, 68% for CIRT) for T4 unresectable cases when a dose of 65.0 Gy(RBE) was delivered. CIRT combines the ballistic properties and superior biological equivalent dose, allowing to retreat unresectable radio-resistant tumors. With a median CIRT dose of 51 Gy(RBE) (27 × 3 Gy(RBE)) delivered 61 months after the first radiotherapy course, Jensen et al. reported an objective response rate of 57% and a local control (median follow-up 14 months) of 70%; in that cohort, median cumulative dose was 128 Gy(RBE), with acceptable toxicity rates [45,46]. The Italian experience concerning reRT of SGCs with CIRT has been recently published [47]: from 2013 to 2016, 51 patients were treated with a median dose of 60 Gy(RBE) at 3–5 Gy(RBE) per fraction. After a median follow-up of 19 months, the local control rate was 41.2%; one-year OS and PFS were 90.2% and 71.7%, respectively.

In line with other papers, the treatment was well tolerated, with no G4 or G5 toxicities and only 17.5% of G3 events. Moreover, compared to other series with CIRT [46,48], reRT at CNAO did not suffer from soft tissue necrosis or carotid blow-out syndrome events [47]. This was probably related to the lower biologically equivalent doses (BED) delivered—155.2–167.4 Gy(RBE)—which could likely be increased in order to improve the outcomes. Interestingly, Vischioni et al. reported a shorter median LT, 6.33 years (range 1.08–20) compared to our results.

Despite the clinical challenges facing by any HNC specialist (i.e., radiation oncologist, head and neck surgeons, oro-maxillofacial surgeons, medical oncologist) Gs, a multidisciplinary approach is needed when dealing with ri-SC. This approach has been strongly recommended to achieve the best oncologic outcome and prevent or adequately treat any adverse effects [49–51]. Indeed, it should be considered as mandatory for SGCs as well [52]. In our series, most patients did not receive radical surgery; this is not an unexpected finding since post-treatment fibrosis and distortion of anatomy due to the treatment can increase the rate of positive margins. In this scenario, post-operative RT can almost double local control rate [53], and our results confirm that among 5 patients receiving marginal Sx and post-operative RT, 4 (80%) had no evidence of disease at last follow up; the remaining one did, but he actually received CIRT. Data on the radiobiological response to this type of RT are still being collected, and a stable disease does not always translate into treatment failure [54]. Nevertheless, all of our patients treated by Sx and post-operative RT were alive at last follow up. In this context, a dedicated pathologist is advisable as SGCs show the greater discrepancy between the initial and definitive pathological diagnosis [55]; moreover, pathology must guide systemic therapy by identifying druggable targets. This approach allowed almost half of our patients to benefit from ADT, warranting at least 12 months of survival even without a curative treatment. Lastly, a multidisciplinary approach allows late toxicities to be more promptly identified.
and managed; this could explain the low number of severe sequelae among our patients and could result in a better quality of life.

RT is a well-known causative agent in the development of secondary solid tumors and the issue of second cancers following therapeutic radiation for a wide variety of malignancies is currently receiving increasing attention. Indeed, it is well recognized that patients receiving radiation therapy have a higher long-term risk for developing secondary primary cancers compared with patients who do not [13].

In pediatric patients, who constitute most of the cases originally treated in this study, germline mutations and hereditary conditions may place one at risk for developing a secondary malignancy, and may not be related solely to chemotherapy [25]. Considering that 10 patients in our series received radiation and chemotherapy compared to 3 patients who received radiation alone, our series suggests that the association of chemo-radiation may increase the risk of second SGCs compared to radiation alone. This may lead to the idea of treatment-induced second SGCs, rather than simply radio-induced secondary malignancies.

The main limitations of our research are its descriptive nature and the limited patient cohort. Beal KB et al. reported 18 radiation-induced salivary gland tumors, 15 of which were ri-SGCs [11]. The main strengths of this work are central pathologic review of the 12 non-ACC tumor specimens, the prolonged follow-up, and the details about treatments for ri-SGCs.

4. Materials and Methods

We retrospectively analyzed clinical data of consecutive patients with ri-SGCs referring to Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy, and to Centro Nazionale di Adroterapia Oncologica (CNAO, National Center of Oncological Hadrontherapy), Pavia, Italy, between 2015 and 2019. Patients were managed by head and neck and pediatric multidisciplinary teams established at both the former Institutions and involving dedicated radiation oncologists. We considered as eligible adult and pediatric patients with a confirmed pathological diagnosis of SGC, who received for previous tumors curative RT in HN areas, lung, and upper mediastinum, with or without concurrent or sequential chemotherapy. Multidisciplinary discussion has been considered within the inclusion criteria as well. Patients with primary leukemia, benign lesions, and patients who received only chemotherapy as a curative treatment have been excluded.

Staging procedures included HN computed tomography (CT) and/or magnetic resonance imaging (MRI), thorax and abdomen CT scan, or 18-FluoroDeoxyGlucose (FDG) Positron Emission Tomography (PET) total body scan.

Patients’ characteristics, first tumor diagnosis, and secondary SGCs features, latent time (LT) from initial treatment to the development of SGCs, treatment, and outcome for secondary SGCs were analyzed.

Revision of all specimens was performed by a dedicated HN pathologist (PQ). Immunohistochemical (IHC) profile including androgen receptors and HER2 has been done in SDCs and adenocarcinoma not otherwise specified (NOS). Next-generation sequencing (NGS) has been performed on the tumor specimen until it was available for free (September 2019). RT plan of the primary tumor, when possible, was reconstructed on CT planning of the secondary SGCs with the aim of searching for a relationship between the dose distribution of the first RT and the second malignant tumor. Median overall survival (OS) and progression-free survival (PFS) and their 95% confidence interval (CI) were estimated using the Kaplan–Meier method. Further subgroup analyses were realized according to histological features of SGCs.

This study was approved on June 2020 by the Ethical Committee of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (internal study identification number: INT 127-20).
5. Conclusions

Our findings underline the benefit of a multidisciplinary approach and intraspecialty care for the management of this complex clinical scenario. This is realized through tailored treatments which are properly balanced between tumor control and toxicity, as to allow similar outcome to ex novo SGCs.

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