Adjuvant Therapy for Salivary Gland Carcinomas

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Abstract. *Aim: We compared the clinical outcomes and toxicity profile among a retrospective cohort of patients with primary major salivary gland carcinomas (SGCs) treated with surgery followed by adjuvant radiation therapy (S+RT) versus surgery and adjuvant chemoradiotherapy (S+CRT). Patients and Methods: Twenty patients (71%) underwent S+RT and eight (29%) S+CRT at our Institution between 2006 and 2015. Microscopic positive margins were present in 54% of the patients. Results: The 3-year overall survival (OS) was 100% with S+RT and 87.5% with S+CRT (p=0.141) and locoregional control (LRC) was 95% with S+RT and 87.5% with S+CRT (p=0.383). There were no significant differences in the rate of acute (p=0.801) and late (p=0.714) toxicities. Conclusion: While we await randomized data, adjuvant CRT may be considered as a viable therapeutic option for patients at high-risk of local or regional recurrence, especially in those with a positive microscopic margin where further surgery may result in functional cranial neuropathies.*

Salivary gland carcinomas (SGCs) represent less than 5% of all new head and neck malignancies with an estimated global incidence range of 0.4-13.5 cases per 100,000 annually (1, 2). SGCs exhibit a broad spectrum of phenotypic, biological and clinical heterogeneity. The World Health Organization (WHO) classifies 24 subtypes of SGCs with mucoepidermoid carcinoma, adenoid cystic carcinoma and adenocarcinoma being the most common histological subtypes (3).

Definitive treatment of SGCs consists of surgical resection of the primary tumor in operable patients followed by adjuvant radiation therapy (RT), when indicated (4, 5). Indications for adjuvant RT include: undifferentiated and high-grade tumors, close or positive margins, presence of perineural invasion (PNI), lymphovascular space invasion, facial nerve dysfunction, deep lobe involvement, skin invasion and nodal involvement (6-9). Non-randomized studies have shown that adjuvant RT improves the overall local regional control rate from 59% to 82% among patients with high grade, T3/4, and inadequately resected SGCs (10). Distant metastatic rates are similar to local failure rates, remaining approximately at 20% with variable rates depending on histology and grade.

The use of adjuvant chemoradiotherapy (CRT) has significantly increased local control and overall survival (OS) for squamous cell cancers of the head and neck; however there are very limited data supporting its use in salivary gland malignancies. Several chemotherapy agents have been used in the management of SGCs with a modest response rate, ranging from 15% to 50%, with an unclear OS benefit (11-14). Small institutional retrospective studies, however, suggest a potential benefit of concurrent administration of adjuvant chemotherapy with postoperative RT in the management of SGCs (15, 16). The ongoing Radiation Therapy Oncology Group (RTOG) 1008 trial is currently assessing the feasibility of CRT in patients with resected SGCs. Until the results of the trial are available, the tolerability and efficacy of CRT remains unclear.

The benefit of adjuvant CRT in head and neck cancers was first shown by both similarly designed RTOG (17) and European Organization for Research and Treatment of Cancer (EORTC) (18) trials. Although the incidence of acute grade ≥3 toxicity is approximately twice as high with CRT, compared to RT alone, significant improvement in progression-free survival (PFS) and local control among these patients led to routine adjuvant CRT in high-risk head and neck cancer patients. These randomized clinical trials did not include any SGCs. However, a retrospective study based on Surveillance, Epidemiology, and End Results

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(SEER)-Medicare database analysis evaluated the efficacy and toxicity of CRT in older patients with SGCs and reported a significantly higher rate of treatment-related acute toxicity in the CRT group than in the RT group (72% *vs*. 27.3%; $p<0.001$) (19). Since the results of the RTOG 1008 may not be available for 2-3 years, the utility of CRT in the management of SGCs remains controversial as the toxicity profile of CRT remains unclear. In order to address this question, our study has analyzed acute and late treatment-related toxicities in patients with SGC treated with adjuvant CRT.

Materials and Methods

Patient population. We analyzed a series of patients with primary SGCs treated with adjuvant RT or adjuvant CRT at our Institution. Inclusion criteria were pathology results confirming a diagnosis of any SGC and use of adjuvant RT or CRT as part of the treatment plan at our institution. Patients treated by surgical resection alone or definitive RT or CRT were excluded from this study. Any patient with a history of primary squamous cell carcinoma of the skin was also excluded. SGCs were defined as a diagnosis of carcinoma of the major salivary gland of the head and neck region (89% parotid and 11% submandibular), such as adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, carcinoma ex-pleomorphic adenoma or acinic cell carcinoma. All patients received routine pre-treatment evaluations prior to therapeutic intervention by a medical oncologist, radiation oncologist and head and neck surgeon. Initial staging procedures consisted of a complete history and physical examination, computed tomography (CT) or positron emission tomography (PET) of the head and neck region, biopsy and/or tumor resection, chest X-ray or chest CT as clinically appropriate. Patients were examined weekly during treatments for potential adverse events associated with RT and CRT. Acute toxicities were recorded using RTOG/EORTC toxicity grading scale (20).

Patient data was obtained retrospectively through protocols approved by the Research Ethics Boards of Mount Sinai Hospital of New York, NY (ID numbers: 14-00457 and 14-1075(0001)) and research was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent.

Statistical analysis. Statistical analysis was performed using SPSS version 23 (SPSS, Chicago, IL, USA). Categorical variables were compared across end points using Chi-squared tests or Fisher's exact tests, where appropriate, while continuous variables were compared across endpoints using analysis of variance (ANOVA). The Kaplan-Meier method was used to evaluate 3-year survival outcomes. Significance level was set at p-value <0.05.

Results

Patients' characteristics. Twenty-eight patients (64% male and 36% female) met the inclusion criteria. Patients' characteristics are demonstrated in Table I. Twenty patients (71%) underwent S + RT and eight patients (29%) S + CRT. The mean follow-up time for the entire cohort was 33 months (37 months in S + RT group and 22 months in S + CRT group). Median age at diagnosis was 61 years (range=31-86). The most common histology type among all patients was mucoepidermoid carcinoma in both groups (45% in S + RT group and 50% in S + CRT group). Tumor size (p=0.138) and nodal involvement (p=0.430) was similar among the groups, although there were 4 T4 tumors in the S + CRT group (50%) and none in the S+ RT group. Margins were positive following surgery in 54% of all patients (45% in S + RT group *vs*. 75% in S + CRT group, p=0.066). The majority of positive margins were identified in parotid tumors (93%) in an attempt to spare the facial nerve. Extranodal extension (ENE) was present in 25% of patients treated with S + CRT *versus* none in the S + RT group (p=0.020). Muscle invasion was present in 20% of patients in the S + RT group *versus* 25% of patients in the S + CRT group (p=0.781). One patient (12.5%) in the S + CRT group had bone invasion.

Table I. *Patients' characteristics*.

Characteristics	S + RT Group (%)	S + CRT Group (%)	p-Value
No. patients	20 (71)	8 (29)	
Age (years)			0.021
Median	57	64	
Range	31-86	55-84	
Gender			0.473
Female	8 (40)	2 (25)	
Male	12 (60)	6 (75)	
T Stage			0.138
T1	7 (35)	1 (12.5)	
T2	5 (25)	1 (12.5)	
T3	8 (40)	2 (25)	
T4	0 (0)	4 (50)	
N Stage			0.430
N0	18 (90)	5 (62.5)	
N1	2 (10)	0 (0)	
N2	0 (0)	3 (37.5)	
Histology			0.257
MEC	9 (45)	4 (50)	
ACC	5 (25)	1 (12.5)	
Other*	6 (30)	3 (37.5)	
Primary site			0.275
Parotid	17 (85)	8 (100)	
SMG	3 (15)	0 (0)	
Positive margins	9 (45)	6 (75)	0.066
Close margins (<0.5 mm)	3 (15)	1 (12.5)	0.263
ENE	0 (0)	2 (25)	0.020
PNI	5 (25)	5 (62.5)	0.065
Muscle invasion	4 (20)	2 (25)	0.781

S, Surgery; RT, radiation therapy; CRT, chemo-radiation therapy; MEC, mucoepidermoid carcinoma; ACC, adenoid cystic carcinoma; SMG, submandibular gland; ENE, extranodal extension; PNI, perineural invasion. *Other histology types include acinic cell carcinoma, carcinoma ex-pleomorphic adenoma and adenocarcinoma

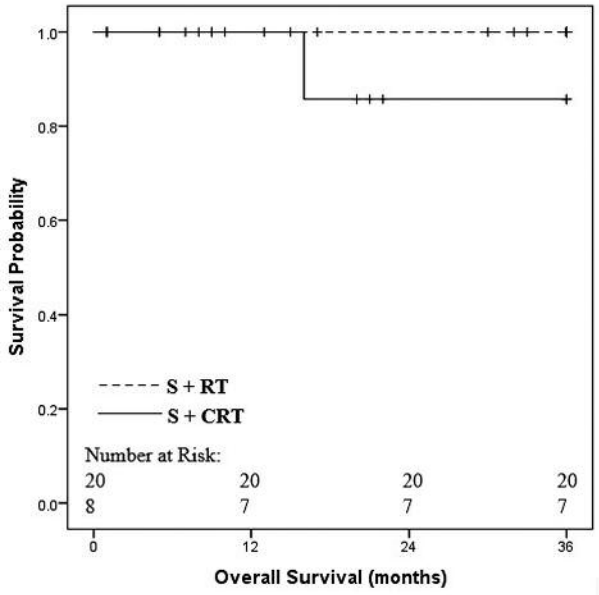

Figure 1. *Kaplan-Meier analysis of 3-year overall survival based on the type of adjuvant therapy (p=0.141).*

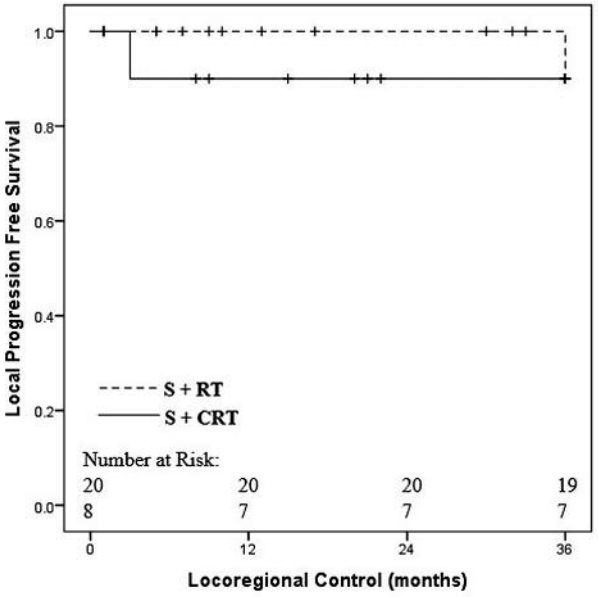

Figure 2. *Kaplan-Meier analysis of 3-year locoregional control based on the type of adjuvant therapy (p=0.383).*

Table II. *Radiation treatment.*

	S + RT Group (%)	S + CRT Group (%)	*p*-Value
Radiation dose (Gy)			
Median	60	66	0.912
Fraction size (Gy)			
Median	2	2	0.238
Radiation field			0.041
Primary	11 (55)	1 (12.5)	
Primary and neck	9 (45)	7 (87.5)	

S, Surgery; RT, radiation therapy; CRT, chemo-radiation therapy.

Treatment. All patients underwent surgical resection of the primary tumor. Neck dissection was performed in 14 patients (75% in the S + CRT group and 40% in the S + RT group) at the time of primary surgery. All surgeries were performed with a curative intent and with minimal cosmetic and functional scarification.

Median radiation dose was 60 Gy in the S + RT group and 66 Gy in the S + CRT group (Table II). In S + RT-treated patients, half also received treatment to the ipsilateral neck in addition to the primary site. In S + CRT-treated group, 87.5% of the patients had radiation to the primary site plus elective neck and 12.5% to primary site alone. RT was not interrupted secondary to hematologic toxicity; however, one patient in the S + CRT group had a RT break for 7 days due to dermatitis. Intensity-modulated radiotherapy (IMRT) was utilized in 90% of patients. The median time between the surgery and start of RT was 44 days. The treatment duration was not significantly different between groups (p=0.393).

Eight patients underwent chemotherapy concurrently with RT. Carboplatin and paclitaxel were the most commonly used chemotherapy agents in the S + CRT-treated patients (62.5%). Cetuximab was used in 37.5% of patients either alone or in combination with 5-fluorouracil (5-FU) and hydroxyurea or carboplatin and paclitaxel. Patients were examined weekly during treatments for potential adverse events associated with RT and CRT. Acute toxicities were recorded using RTOG/EORTC toxicity grading scale (20).

Treatment outcomes. In the S + RT group, one patient (5%) developed distant metastasis and one patient (5%) had local recurrence. In the S + CRT group, one patient (12.5%) developed both local and distant recurrence after completion of therapy and 2 other patients (25%) had distant recurrence. Lung and spine were the most common side for distant metastases. The 3-year OS was 100% with S + RT and 87.5% for S + CRT (p=0.141) (Figure 1) and PFS was 90% with S + RT and 62.5% with S + CRT (p=0.004). The 3-year locoregional control (LRC) was 95.5% with S + RT and 87.5% with S + CRT (p=0.383) as shown in Figure 2.

Toxicity outcomes. Acute toxicity outcomes are demonstrated in Table III. Grade 2 acute toxicities occurred in 61% of patients and Grade 3 acute toxicities occurred in 11% of patients. One patient (5%) in S + RT group had Grade 3

Table III. *Grade ≥2 toxicity outcomes.*

Characteristics	S + RT Group (%)	S + CRT Group (%)
Acute toxicity		
Mucositis		
Grade 2	7 (35)	2 (25)
Grade 3	0 (0)	1 (12.5)
Dermatitis		
Grade 2	5 (25)	3 (37.5)
Grade 3	0 (0)	1 (12.5)
Esophagitis		
Grade 3	1 (4.5)	0 (0)
Late toxicity		
Xerostomia		
Grade 2	5 (25)	1 (12.5)
PEG Tube	0 (0)	1 (12.5)
Hearing loss	1 (5)	0 (0)

S, Surgery; RT, radiation therapy; CRT, chemo-radiation therapy; PEG, percutaneous endoscopic gastrostomy.

acute esophagitis. One Grade 3 acute dermatitis (12.5%) and one Grade 3 acute mucositis (12.5%) were reported in S + CRT-treated patients. Carboplatin and paclitaxel were the chemotherapy agents used in this both Grade 3 acute toxicity cases. No patients had treatment held secondary to low blood counts. Grade 2 acute mucositis was experienced in 35% of S + RT-treated patients and in 25% of S + CRT-treated patients. Mild to intermittent hoarseness developed in 15% of patients in the S + RT group and in 12.5% of the S + CRT group. Overall, the acute toxicity rate among the groups was not significantly different (p=0.801). No patient developed Grade 4 or greater acute toxicity.

Late toxicity outcomes are demonstrated in Table III. Grade ≥2 late toxicities were reported in 24% of patients (25% of S + RT-treated patients *versus* 12.5% of S + CRT-treated patients, p=0.714). In the group treated with S + CRT, one patient (12.5%) required PEG tube placement after completion of the treatment. Carboplatin, paclitaxel and cetuximab were used in this patient. One patient (12.5%) with parotid tumor treated with S + RT developed late hearing loss likely related to RT toxicity.

Discussion

The management of SGCs remains a challenge due to its heterogeneous nature, diverse biological behaviors and low prevalence. The use of CRT has been shown to improve LRC and OS in many malignancies in specific settings. Particularly, in SCC of the head and neck, CRT resulted in a 10% increase in a 5-year OS in one randomized study (18). Depending on the presence of high-risk features, SGCs is currently managed *via* a multidisciplinary approach consisting of surgery followed by radiation or concurrent chemo-radiotherapy, even though the impact of CRT remains to be unclear in SGCs. Understanding of toxicity profile with adjuvant CRT in SGCs may allow us to improve treatment strategies of this group of malignancies.

There have been limited retrospective series evaluating the efficacy of adjuvant CRT for SGCs. Schoenfeld *et al.* reviewed 22 patients with SGCs treated with CRT with a median follow-up of 2.3 years (15). In this study, the distant metastasis-free survival and LRC rate were 83% and 92%, respectively. Although Schoenfeld *et al.* conveyed promising results, others reported conflicting outcomes (16, 19, 21, 22). An institutional study with a median follow-up of 42 months reported a 59% OS rate in 24 patients with SGC treated with postoperative CRT (21). Another recent study analyzed 741 patients through the SEER-Medicare database (1992-2009) and reported a 24-month mean OS among patients treated with adjuvant CRT and a 41-month mean OS among patients treated with adjuvant RT (19). In our study, with a mean follow-up of 33 months, the 3-year OS was 100% with S + RT and 87.5% for S + CRT (p=0.141). Low 3-year PFS rate in our study with S + CRT compared with S + RT (p=0.004) is likely due to metastases in this group. Due to the small sample size of patients in our study, it was inadequately powered to draw conclusions on the efficacy of CRT. The results of the RTOG 1008 trial will hopefully clarify the role of CRT in these patients.

Notably, 54% of patients in our study had a microscopic positive margin following surgery, while the local control rate remained similar to results from previous studies (15, 21). Rabatic *et al.* recently reviewed 62 patients with SGCs and PNI±other high-risk features (recurrent tumor, positive margins, multiple positive lymph nodes and extracapsular extension) treated with postoperative CRT with a median follow-up of 5 years (23). The LRC rate was 94% in this study further highlighting the potential benefit of adjuvant CRT in high-risk patients. Considering that the local control rate with adjuvant CRT remained excellent in our study despite the higher positive margin rate and T4 imbalance, a major benefit of adjuvant CRT may be in giving support to sparing the facial nerve during surgery in cases where it might otherwise have been sacrificed for a microscopic positive margin.

Acute toxicities associated with CRT in SGCs have been reported in very few institutional reports with a small number of patients. In a study of 24 patients with high-risk salivary gland tumors treated with surgery + CRT, by Pederson et al., 46% were found to have a Grade 3 acute mucositis and 33% Grade 3 acute hematologic toxicity rate (21). Long-term complications in this study also included 21% incidence of persistent xerostomia and 13% feeding tube placement rate. While Pederson *et al.* did not compare toxicity outcomes among S + RT treated patients, they also did not describe the extent of surgical procedures performed (21). In our study, acute toxicity rate was higher in S + CRT group but this did

not affect the tolerability of the treatment. Furthermore, in the S + CRT group only one patient had Grade 3 acute mucositis, one patient had persistent xerostomia and one patient had a feeding tube. In this study, the use of adjuvant CRT resulted in acceptable and anticipated acute and late toxicities when compared to the RT cohort.

There are several limitations of our study. First, its retrospective nature may have affected the quality of data collection. Second, the cohort included in this study was a heterogeneous group of patients with SGCs treated with S + RT or S + CRT and the number of patients included was small (n=28). The small sample size leaves the study underpowered to detect potential significant differences in both the acute and late toxicities between the treatment groups. Further limitations of this study may also include failure to control for additional factors associated with toxicity, such as diabetes or smoking history. Larger randomized trials are required to overcome such limitations in order to provide better insight into the development of toxicities in patients with SGCs.

In our Institution, as we await RTOG 1008 results, we do consider adjuvant CRT in cases of positive margins, ENE and a large primary or extensive nodal burden. Furthermore, we also consider androgen receptor (AR) and human epidermal growth factor receptor 2 (HER2) testing in patients with salivary duct carcinoma. HER2 overexpression is associated with a poor prognosis in SGCs and addition of trastuzumab to chemotherapy has been reported to improve disease-free survival (24-29). Based on these growing evidences, we also consider adding trastuzumab to chemotherapy if it is overexpressed.

Conclusion

Adjuvant CRT was well-tolerated and resulted in excellent local control despite the presence of adverse prognostic features. Until RTOG 1008 is published, these data suggest that adjuvant chemo-RT results in an acceptable toxicity profile and may be considered in select circumstances were the patient is at an elevated risk of local-regional failure.

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