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Research Article

Definitive Radiotherapy in Salivary Gland Carcinoma of the Head and Neck

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Abstract

Purpose: This study was conducted to evaluate the treatment outcomes of definitive Radiotherapy (RT) for Salivary Gland Carcinoma (SGC).

Material and methods: From January of 2010 till December of 2020, a total of 24 patients underwent definitive RT for SGCs arising in the head and neck region. The median Biologically Effective Dose (BED) prescribed to the GTV was 80.5 Gy_{10} (79.1~84.9 Gy_{10}) with dose-per-fraction of 1.8-2.2 Gy. Elective neck irradiation of the clinically uninvolved lymph node was not a mandatory.

Results: During the median follow-up duration of 31.9 months (range, 9.5-74.2 months), 11 patients (45.8%) showed disease progression with locoregional progression being the most common treatment failure (n = 10; 41.7%). The 3-year Locoregional Control (LRC) and overall survival (OS) rates were 59.4% and 95.4%.

Conclusion: The current study showed that definitive RT without ENI is a feasible strategy for inoperable SGCs.

Keyword: Definitive radiotherapy; Head and neck; Salivary gland carcinoma

Introduction

Salivary Gland Carcinomas (SGCs) are rare, accounting for 1-6% of all neoplasm of the head and neck, and diverse with respect to origin and histologic type, which is classified according to the World Health Organization (WHO) classification published in 2015 [1]. The most common histological types include Adenoid Cystic Carcinoma (ACC), mucoepidermoid carcinoma, and adenocarcinoma, followed by acinic cell carcinoma, salivary duct carcinoma, and carcinoma ex-pleomorphic adenoma [2]. Their biological and clinical behaviors are variable, depending on the histological subtype and grade, and the anatomic site [2]. Complete surgical resection, with adequate free margins, is currently the mainstay treatment [3]. Usually, Radiation Therapy (RT) is used as adjuvant therapy following surgery. Many previous studies demonstrated local control and survival improvement by adding adjuvant RT to surgery in the patients having risk factor [4]. But, patients with advanced or unresectable tumor tended to undergo definitive RT with or without systemic chemotherapy [5,6]. The rarity and heterogeneity in clinical behavior have made it difficult to establish the optimal strategies of definitive RT, including dose schedule, target volume, and use of additional systemic chemotherapy [7]. There have been several studies on these issues, but most of them included the patients who received RT in adjuvant therapy setting. Therefore, the clinical evidences from the previous studies are not sufficient. The purpose of this study was to evaluate the treatment outcomes following definitive RT in the patients with SGCs.

Methods

Patients and initial Evaluations

From January of 2010 till December of 2020, a total of 24 patients underwent definitive RT for SGCs arising in the head and neck region. Definitive RT has been optionally recommended to the patients who are with unresectable disease, based on the tumor

extent and/or location, or in poor general condition to undergo surgery. The pretreatment evaluations included complete history and physical examination, complete blood counts and blood chemistry profiles, biopsy of primary or metastatic lesion, Computed Tomography (CT) of the head and neck. Magnetic Resonance Image (MRI) of the head and neck was taken in 21 patients (87.5%) and whole-body 18^{F}-Fluorodeoxyglucose positron emission tomography with CT (PET-CT) was in 23 (95.8%). The clinical stage was assigned according to the 8th American Joint Committee on Cancer (AJCC) staging system. The grade of tumor was divided into high and low according to the histological types [8]: high grade types included adenoid cystic carcinoma, squamous cell carcinoma, high-grade mucoepidermoid carcinoma, and high-grade adenocarcinoma; and low grade types did acinic cell carcinoma, low-grade mucoepidermoid carcinoma, and low-grade adenocarcinoma, respectively.

Treatment

All patients underwent contrast enhancing CT scans with the thermoplastic mask for immobilization before RT plan. Among all, 3 patients (12.5%) were treated with 3-dimensional conformal radiotherapy (3D-CRT) and 21 (87.5%) were with Intensity Modulated Radiotherapy (IMRT). The same target delineation policy was applied to all patients. The Gross Tumor Volume (GTV) was defined as the volume of primary tumor and involved lymph node(s) based on all available clinical information. The Clinical Target Volume (CTV) of primary tumor was delineated by adding 3~5 mm margins in all directions from GTV of primary tumor, and the margins were optionally modified in accordance with the anatomic boundaries of the involved tumor location and/or the adjacent organs. The lymphatic CTVs were divided into two components: CTV at high risk was to include the immediately adjacent lymphatic level from the nodal GTV with 1.0-1.5 cm margins; and CTV at low risk was to include the distal lymphatic level (usually 2.0-2.5 cm) from the most distal nodal CTV at high risk, respectively. Elective neck irradiation (ENI) to include the remote and uninvolved lymphatic levels was not applied and was determined on the individual basis considering the estimated risk of metastasis based on the extent, location, histologic type, and grade of primary tumor. The dose schedules were different according to RT technique and the study period. The median Biologically Effective Dose (BED) prescribed to the GTV and CTV were 80.5 Gy_{10} (79.1~84.9 Gy_{10}) and 73.0 Gy_{10} (61.0~84.0 Gy_{10}) with 5 weekly dose of 2.0~2.2 Gy per fraction. The addition of systemic therapy was determined according to the physician's discretion and seven patients (29.1%) received chemotherapy. The most common chemotherapy regimen during RT was tri-weekly cisplatin 100 mg/m^2 (n=6).

Surveillance and Statistical Analysis

Regular post-RT surveillance was scheduled and included physical examination, neck CT and/or PET-CT at 3 months' interval for the first 2 years and at 6 months' interval thereafter. Treatment failure included any type of disease progression, and in-field loco-regional failure was defined as progression of persistent lesion or development of new lesion within the RT target volume. The survival durations were calculated from the first date of RT until the date of event, death or censoring. The rates of loco-regional control (LRC), distant metastasis-free survival (DMFS), disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and the comparisons between subgroups were done using the log-rank test. Cox proportional hazard regression analysis was used to determine the significance of independent prognostic variables. All the statistical analyses were done using the SPSS software (standard version 26.0, IBM Corporation, Armonk, NY, USA).

Results

The patients' characteristics are summarized in Table 1. The median age was 53 years (range, 22~71 years). The major and minor salivary glands were involved in 5 (20.8%) and 19 patients (79.2%), respectively. The most common sites of involvement were paranasal sinus in six (25.0%), parotid gland in five (20.8%), nasopharynx in three (12.5%), and nasal cavity in four (16.7%). ACC was the most common histology in 18 patients (75.0%), followed by mucoepidermoid carcinoma in three (12.5%). The reasons for choosing definitive RT, instead of surgical resection, included cT4 disease in 15 patients (62.5%), extents of primary tumor or locations where radical resection was difficult in 9 patients (37.5%). The majority of the patients (21, 87.5%) had cN0 disease. Most patients received RT alone (17, 70.8%). The remaining seven patients (29.2%) received RT with chemotherapy. The patients who received RT with chemotherapy had cT3-4 disease more frequently than those who received RT alone. During the median follow-up duration of 31.9 months (range, 9.5-74.2 months), 11 patients (45.8%) showed disease progression. The most common treatment failure was loco-regional (LR) progression, which was observed in 10 patients (41.7%), followed by distant metastasis in 4 patients (16.7%). Ten patients with LR progression had failure within the RT target volume. The most frequent distant metastatic organs were the lung in three patients, followed by the bone in one patient. The 3- and 5-year LRC rates were 59.4% and 52.0%. (Figure 1). The 3- and 5-year DMFS were 84.0% and 42.0%. Overall DFS rates at 3- and 5-year were 55.4% and 23.7%. A total of two patients (8.3%) died during the follow-up period. The 3- and 5-year OS rates were both 95.4% and 86.7%. According to regression analysis, patients with lymph node involvement showed

worse DFS (Table 2). All patients were assessable for toxicity. Mucositis was the most common acute adverse event, with grade 3 (n = 1) mucositis was observed (Table 3). Temporal lobe necrosis was observed in one patient (4.6%). Esophageal stricture was observed in one patient (4.6%).

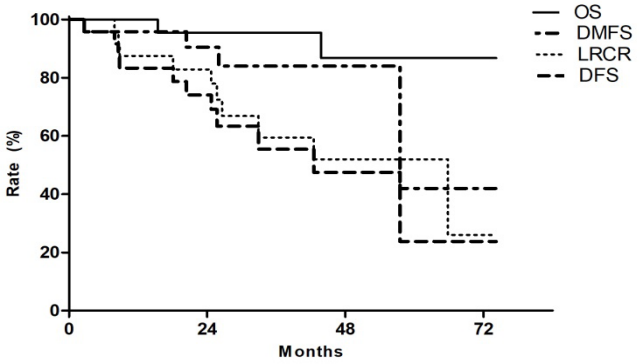

Figure 1: Treatment outcome.

Characteristics	Total (N=24)
Age (yr)	
Median	53
Range	22-71
Gender	
Male	9(37.5%)
Female	15 (62.5%)
Location	
Nasal cavity	4 (16.7%)
Paranasal sinus	6 (25.0%)
Nasopharynx	3 (12.5%)
Oral cavity	3 (12.5%)
Oropharynx	1 (4.2%)
Parotid gland	5(20.8%)
Larynx	2 (8.3%)
Histology	
Adenocarcinoma	3 (12.5%)
Adenoid cystic carcinoma	18(75.0%)
Mucoepidermoid carcinoma	3 (12.5%)
Grade	
Low	6 (25.0%)
High	18 (75.0%)
Clinical T stage	
cT1	6 (25.0%)
cT2	1 (4.2%)
cT3	2 (8.3%)
cT4	15 (62.5%)
Clinical N stage	
cN0	21 (87.5%)
cN1	1 (4.2%)
cN2	2 (8.3%)
Distant metastasis	
No	24(100%)
Yes	0 (0%)
Treatment	
RT alone	17 (70.8%)
RT with CTx	7 (29.2%)

RT: Radiation Therapy; CTx: Chemotherapy

Table 1: Clinical characteristics.

Characteristics	OS		LRCR		DMFS		DFS	
	Uni-	Multi-	Uni-	Multi-	Uni-	Multi-	Uni-	Multi-
	p	p	p	p	p	p	p	p
Gender								
Male vs. Female	.435	.645	.004	.004	.937	.904	.017	.010
Site								
Major Salivary gland vs. Others	.271	.997	.718	.183	.776	.888	.534	.111
Histology								
ACC vs. Non-ACC	.478	.953	.741	.862	.432	.996	.523	.934
Clinical T stage								
cT1-2 vs. cT3-4	.437	.947	.395	.587	.389	.976	.266	.392
Clinical N stage								
cN0 vs. cN1-2	.145	.887	.883	.636	.164	.822	.109	.041
Treatment								
RT vs. CTx + RT	.618	.955	.572	.219	.514	.794	.841	.266

ACC: Adenoid Cystic Carcinoma; RT: Radiation Therapy; Ctx: Chemotherapy; OS: Overall Survival; LRC: Locoregional Control; DMFS: Distant Metastasis Free Survival; DFS: Disease Free Survival

Table 2: Prognostic factors affecting survival outcomes upon regression analysis

Toxicity	No. of patients (N=24) (%)	
	Grade 3	Grade 4
Acute toxicity		
Anorexia	0	0
Nausea	0	0
Mucositis	1 (4.6%)	0
Chronic toxicity		
Temporal lobe necrosis	1 (4.6%)	0
Esophageal stricture	1 (4.6%)	0

Table 3: Toxicities after treatment.

Discussion

The standard of care for treatment of SGCs is complete surgical resection, with adequate free margins followed by postoperative RT when indicated. Some proportion of newly diagnosed patients are either not candidates for definitive resection or undergo limited procedures leaving behind gross residual disease. These patients are deemed inoperable because of locations of tumors where resection would result in a major functional and/or cosmetic deficit. Another subset of patients might have medical comorbidities or refuse surgical therapy. Regardless of the underlying reasons, primary RT has been recommended for these patients as the primary treatment of their SGCs. Some retrospective case studies have demonstrated that definitive RT is important in improving outcomes, despite of the heterogeneity and small number of patients [1,3,9,10]. Mendenhall et al. reported treatment outcome of definitive RT alone in 64 patients with SGCs [9]. After definitive RT with median dose of 74 Gy, the 10-year OS and LRC rates were 35% and 40%. Patients with T4 disease were less favorable with 10-year OS and local control rates of 21% and 24%. More recently, Spratt et al. reported a 5-year OS rate of 29% and 5-year LRC rate of 47%, for patients treated with definitive RT [3]. The current study showed comparable results with a 5-year LRC rate of 44.3%, even though the patients with cT4 stages accounted for more than half of the patients. Given the natural course of ACC, the current study showed an improved survival rate compared with previous studies, which was because more than half of the patients in the current study had ACC histology.

Despite the favorable outcome, when compared with surgical data, treatment results of definitive RT seem to be insufficient. Over 70% of patients ultimately developed recurrence or metastatic disease after RT. The common patterns of failure of SGCs are primary and/or distant metastasis [11]. Depending on the histological features, stages, and other characteristics of the studies, the patterns of failure may vary from study to study. Local recurrence was the most common treatment failure in the current study because majority of patients had cT4 stage and ACC histology which was characterized by local invasiveness. Local control is important when considering

the fact that most cases requiring definitive RT are locally advanced disease as in the current study. Various attempts have been made to improve tumor control. Usually, the higher the radiation dose, the better the local control. The optimal radiation dose for SGCs has been derived from multiple series [6]. Typically, a radiation dose equivalent to at least 66 Gy in 33 fractions (BED=79.2 Gy_{10}) to the primary tumor and involved nodes is recommended [10]. Some studies have reported the possibility of dose-response relationship for SGCs [5,12,13]. Chen el al. reported a statistically significant improvement in local control rate in patients treated with doses greater than 66 Gy [5]. In the University of Florida series, doses greater than 70 Gy resulted in better outcome than doses less than 70 Gy, particularly for ACC [13].

Hypofractionated Radiotherapy (HFRT) involves the use of high dose-per-fraction to achieve improved tumor control. Preclinical and clinical data showed that higher dose-per-fraction overcome the traditional radioresistance of certain histologies [14]. Despite promising tumor control, the risk of toxicity is increased as dose-per-fraction increased [14]. As IMRT is used more, high grade toxicities are expected to decrease further. More tailoring of dose and fractionation schedules to the individual patient can likely reduce the development of severe toxicities.

The limitation of the current study is small number of patients due to the rare incidence of SGCs. The results, therefore, are not statistically robust. Another major limitation is retrospective nature of this study. SGCs represent a significantly heterogeneous group of histological subtypes, and patients' characteristics are varied from study to study, making it difficult to compare studies and draw definitive conclusions. Large multi-centric studies should be conducted to further evaluate the optimal treatment strategy of SGCs. Lastly, more studies are needed to reduce the incidence of grade 3-4 toxicities. With the widespread adoption of more conformal techniques such as IMRT and image-guided RT, it is likely that the potential to reduce toxicity.

Conclusion

The current study showed that definitive RT is a feasible strategy for inoperable SGCs. Future studies should continue to focus on identifying the optimal dose and fractionation regimen for patients treated with definitive RT for SGCs.

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