Original Article

Postoperative Radiotherapy in Salivary Gland Carcinoma: A Single Institution Experience

Öztun Temelli[1], Ersoy Kekilli[2], Ahmet Kızılay[3]

[1]Department of Radiation Oncology, [2] Department of Nuclear Medicine, [3] Department of Otolaryngology, School of Medicine, Inonu University, Malatya, Turkey

Abstract

Background: Salivary gland carcinoma are rare tumors and the main treatment is surgical. The addition of radiotherapy to surgery decreases locoregional relapses in high risk patients. Aim of our study is to retrospectively evaluate local control and survival and the factors affecting them in patients who received postoperative radiotherapy.

Materials and methods: The medical records of 30 patients with salivary gland tumors operated on and referred to our clinic for adjuvant RT between January 2004 and June 2015 were retrospectively evaluated. RT was applied to the primary tumor or its lymphatics in a median dose of 60 Gy (48–66 Gy) in 1.8–2 Gy/fraction. The number of patients receiving concomitant chemotherapy was 8 (27%) and 22 (73%), respectively.

Results: The mean duration of follow–up was 47 months (range: 3–132 months). The mean duration between surgery and RT was 51 days and mean duration of RT was 43 days. Tumors were located in the parotid gland in 25 patients (83%), in the submandibular gland in four patients (14%), and in the sublingual gland in one patient (3%). Histopathologically, the most common tumor was adenoid cystic carcinoma (27%), followed by mucoepidermoid carcinoma (20%), and skin SCC metastatic to the parotid gland.

Five–year overall survival (OS), five–year disease specific survival (DSS), and five–year disease free survival (DFS) were 50%, 50%, and 54%, respectively. Regional recurrence and distant organ metastasis developed in 5 (17%) and 9 (30%) patients, respectively. OS, DSS, and DFS were significantly decreased in patients with lymph node metastasis compared to the patients with no metastasis (p=0.002). DFS was better in Stage 1–2 patients compared to Stage 3–4 patients (p=0.019). OS and DFS were significantly in radiotherapy time in less than 45 days (p=0.01). A duration between surgery and radiotherapy of more than 42 days was associated with low DFS (p=0.042). No prognostic significance of age, gender, type of the salivary gland, T stage, tumor diameter, surgical margin, PNI, LVI, and extracapsular involvement was found among the other variables.

Conclusion: Adjuvant RT is an efficacious and safe method of treatment in high risk patients operated on for salivary gland tumor.

Keywords: Radiotherapy, salivary gland carcinoma

Introduction

Salivary gland tumors are seen quite rarely. The incidence in the western world is 2.5–3 in 100,000. Malignant salivary gland tumors comprise 0.5% of all cancers and 3–5% of head and neck cancers. Most of the patients are between 60 and 70 years old. There is a slight male preponderance (51%). [(1)]

The major salivary glands are the parotid, submandibular, and sublingual glands. Among the salivary gland tumors, about 70% of them originate from parotid gland; however, less than 50% of them are malignant. Submandibular gland tumors compose 10% of the salivary gland tumors and 50% of them are malignant. The remaining 20% originate from minor salivary glands and are generally malignant [(2)]. Of those, major malignant tumors are mucoepidermoid, adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Primary squamous carcinoma of the parotid gland is quite rare;

Corresponding author: Öztun Temelli, Assistant Professor, M.D., Department of Radiation Oncology, School of Medicine, Inonu University, 44280, Malatya, Turkey.
Telephone: +90 422 341 0660–5603,
Telefax: +90 422 341 0728.
Email: droztun@gmail.com

however, parotid gland is a region of frequent metastasis of skin cancers and thus it is difficult to distinguish from metastasis from squamous cell skin cancers. [3, 4] Primary treatment is surgical. The addition of radiotherapy to surgery decreases locoregional relapses in high risk patients. Postoperative indications of RT include positive or close margin (< 5mm), high grade cancer, skin, bone and nerve involvement, T3–4 tumors, and lymph node metastases. [5, 6]

Major prognostic factors are histological grade, tumor dimension, and local invasion. The risk of distant metastasis is higher in individuals with lymph node metastasis, skull base involvement, and high grade histology. The most frequent locations of metastasis are the lungs, liver, and brain [7].

We aimed to retrospectively evaluate the prognostic factors of patients who underwent radiotherapy following surgery.

Materials and methods

Thirty patients who received postoperative radiotherapy at the Department of Radiation Oncology between January 2004 and June 2015 were retrospectively evaluated. All patients were evaluated at a multidisciplinary council composed of an otolaryngologist, radiation oncologist, and medical oncologist prior to the treatment. Patients were re–staged according to the American Journal of Critical Care (AJCC) 7th 2011 edition criteria prior to the study.

Planning tomography was obtained in all patients in the supine position using a thermoplastic mask. Patients were treated using 2D conventional or 3D conformal radiotherapy until the year 2013 and using IMRT method in Helical Tomotherapy device. Treatment fields and normal tissues were defined on the computed planning system in patients who received 3D conformal and IMRT. The dose and fraction of RT applied to the primary tumor or lymphatics were a median 60 Gy (48–66 Gy) and 1.8–2 Gray (Gy)/fx, respectively. Patients with positive or close surgical margins received an additional dose of 6 Gy. Cisplatin 40 mg/m2 concomitantly to RT was added to the treatment in high risk patients (ECE, positive/close surgical margins, and presence of >2 lymph nodes).

Patients were invited for the first follow–up visit four to six weeks after radiotherapy. Follow–up examinations were performed at the multidisciplinary tumor council bi–monthly in the first year, in every three months in the second year, and in every six months after the second year.

In this study, the effects of variables such as age, gender, type of the salivary gland, tumor and nodal stage, lymph node involvement, extracapsular involvement, surgical margin, tumor diameter, duration of RT and duration between surgery and RT on survival and local control were evaluated. Overall survival and progression–free survival were calculated according to the Kaplan–Meier method from the histologic diagnosis. Progression–free survival was defined as disease progression or death from any cause. The Cox regression test was used in the multivariate analyses. The level of statistical significance was accepted as $p<0.05$.

Results

The median age was 55 years (range: 20–85) among the patients. The number of males was significantly higher (M:21, F:9). The tumor was located in the parotid gland, submandibular gland, and sublingual gland in 25 (83%), 4 (14%), and 1 (3%) patients, respectively. The most common histological types were adenoid cystic carcinoma (27%), mucoepidermoid carcinoma (20%), and skin SCC metastatic to the parotid gland in descending order of frequency. The characteristics of the patients are shown in Table 1.

The number of patients receiving concomitant chemotherapy was 8 (27%), while 22 patients received radiotherapy alone. Median duration of follow–up was 47 months (range: 3–132 months). The median duration between surgery and RT was 51 days and median duration of RT was 43 days. Neck dissection was performed in 18 (60%) patients, while 12 (40%) patients had no neck dissection. Elective nodal radiotherapy was performed in 21 (70%) patients, 12 of whom had bilateral neck nodal radiotherapy. Patients undergoing RT received a median dose of 60 Gy. Only two patients received <60 Gy (48 and 55.8 Gy); treatment was terminated early in one patient because of intolerance and the dose was intentionally kept low in another patient with Ewing's sarcoma. Treatment specifications are summarized in Table 2.

A total of 12 patients, one (3%) due to a second primary carcinoma of the urinary bladder, died during the follow–up. Five–year overall survival (OS), five–year disease specific survival (DSS), and five–year disease–free survival (DFS) were 50%, 50%, and 54%, respectively. Regional recurrence and distant organ metastasis occurred in five (17%) and nine (30%) patients, respectively. Among the patients with development of metastasis, two had lung, four had lung + bone, two had bone alone, one had liver + lymph node, and one had skin + soft tissue metastasis.

Tumor grading was excluded from the analysis because of some missing data. OS, DSS, and DFS were significantly decreased in patients with lymph node metastasis compared to those without lymph node metastasis ($p=0.002$). DFS was better in patients with stage 1–2

compared to the patients with stage 3–4 (p=0.019). OS and DFS were significantly in radiotherapy time in less than 45 days (p=0.01). A duration between surgery and radiotherapy of more than 42 days was associated with low DFS (p=0.042). No association of age, gender, type of the salivary gland, T stage, tumor diameter, surgical margin, PNI, LVI, and extracapsular involvement among other variables was found between OS and DFS. The results obtained in the univariate analysis could not be retrieved in the multivariate analysis due to the small number of patients. The association of the variables with OS, DSS, and DFS are shown in Table 3.

Discussion

This retrospective study was performed to evaluate the clinical and pathological properties and the treatment failures in patients that received postoperative radiotherapy. Salivary gland cancers compose a heterogeneous group. Therefore, it is quite difficult to define the prognostic factors. Histology, grade, and stage have been demonstrated as the most significant prognostic factors in some retrospective publications[8,9]. Other prognostic factors have been proposed to be positive surgical margin, extracapsular extension, bone invasion, or perineural invasion [2].

Five–year OS has been reported to be 49% and 55% in salivary gland tumors in various studies. [10, 11] The present study is compatible with the literature: five–year OS and DFS were 50% and 54%, respectively.

No randomized study has been published evaluating the efficacy of adjuvant RT in salivary gland tumors since the incidence of those tumors is low. Surgery alone provides a 10–year control in 85% of the cases in low grade (low grade mucoepidermoid carcinoma, acinic cell carcinoma, and low grade adenocarcinoma) and early stage tumors in which complete resection is possible, while adjuvant RT has been reported to improve the results in advanced stage and high risk patients (high–grade and advanced stage lesions, positive surgical margins, and skin and nerve invasion, as well as nearly all adenoid cystic carcinomas). [6, 12, 13]

In a study by Armstrong et al., five–year local control rate and cause–specific survival were both improved with adjuvant RT compared with surgery alone in stage 3–4 patients (51 versus 17 and 51 versus 10 percent, respectively) [6]. Similarly, in a study by Terhaard et al., postoperative radiotherapy was demonstrated to provide a significant improvement in 10–year local control compared to surgery alone in T3–T4 tumor, close surgical margin, incomplete resection, and bone and perineural invasion. Fu et al. demonstrated that PORT decreased local recurrence in cases with close/positive surgical margin [14].

Characteristics	No. of patients	%
Age(yr), median 55 (range 20-85)		
<60	14	46.7
≥60	16	53.3
Gender		
Male	21	70
Female	9	30
Location		
Parotid gland	25	84
Submandibular gland	4	13
Sublingual gland	1	3
Histopathology		
Adenoid cystic carcinoma	8	26.7
Mucoepidermoid carcinoma	6	20
Squamous cell carcinoma	6	20
Adenocarcinoma (NOS)	3	10
Salivary duct carcinoma	1	3.3
Lymphoepithelial carcinoma	1	3.3
Myoepithelial carcinoma	1	3.3
Epithelial myoepithelial carcinoma	1	3.3
Epithelioid Hemangioendothelioma	1	3.3
Mezenkimal tumors	2	6.7
T stage		
T1	3	10
T2	16	53.3
T3	5	16.7
T4	5	16.7
N stage		
N0	17	56.7
N1	8	26.3
N2	4	13.3
Stage		
1	0	0
2	11	36.7
3	11	36.7
4	7	23.3
Tumor size		
< 4 cm	21	70
≥4 cm	9	30
LVI		
Yes	4	13.3
No	26	86.7
ECE		
Yes	2	6.7
No	28	93.3
PNI		
Yes	12	40
No	18	60
Resection margin		
Close/positive	14	46.7
Negative	16	53.3

Table 1: Patients Characteristics

LVI: lymphovascular invasion
ECE: extracapsular extension
PNI: perineural invasion

In the present study, 14 patients had close or positive surgical margins and OS and DFS was found to be statistically similar in those patients and those with a negative surgical margin. OS and DSS were lower in patients with stage 3–4 compared to the patients with

stage 1–2; however, the difference was insignificant, while DFS was significantly lower in stage 3–4 patients compared to the patients with stage 1–2 (57 versus 27 months, p=0.019).

In a study by Teo et al., the most important prognostic factor was found to be nodal stage [15]. Postoperative radiotherapy was demonstrated to improve local control compared to surgery alone in N+ patients in a study by Terhaard et al. from the Dutch Head and Neck Oncology Cooperative Group (86% vs. 62%) [16]. In the present study, also, lymph node positivity was found to cause a significant decrease in OS, DSS, and DFS (p=0.002).

In the present study, 83% of the cases were located in the parotid gland, while 14% were in the submandibular gland. In a study by Renehan et al., in over 1000 patients, malignant salivary gland tumors were located in the parotid gland, submandibular, and minor salivary glands in 80%, 6%, and 14%, respectively [17]. Local control and its effect on survival was analyzed in the DAHANCA (Danish Head and Neck Cancer Group) study in which the prognostic effect of tumor location was evaluated and crude survival, disease–specific survival and recurrence–free survival were longer in minor salivary gland tumors[18]. No prognostic significance of the location of the tumor was found in the present study.

Histology is an important prognostic factor. The most common histological subtype was mucoepidermoid carcinoma in many studies, while adenoid cystic carcinoma (26.7%) followed by mucoepidermoid carcinoma (20%) were encountered most frequently in the present study, similar to some studies [17, 19]. Adenocarcinoma NOS and undifferentiated carcinoma had poorer prognosis, with 10–year relative survival of 55% and 44%, respectively [20]. No statistically significant difference was found between histological subtypes in this present study.

	N (%)
Surgery	30 (100%)
Neck dissection	
Yes	18 (60%)
No	12 (40%)
RT technique	
Conventional	4 (13%)
3 D conformal	19 (64%)
IMRT	7 (23%)
Elective nodal irradiation	21 (70%)
Bilateral	12
Unilateral	9
Concurrent Chemoradiotherapy	
Yes	8 (27%)
No	22 (73%)

Table 2: Treatment Characteristics

Advanced age has been demonstrated as a poor prognostic factor in some studies [8, 18, 21]. OS, DSS, and DFS were lower in patients of 60 years of age or older, though not statistically significant.

DFS was lower in patients with a duration between surgery and RT of more than 42 days in the present study (p=0.042). Ang et al. demonstrated that a duration between surgery and RT of more than seven weeks resulted in low locoregional control (p=0.03) and low survival (p=0.01) [22].

Prolongation of duration of RT is associated with decreased locoregional control in head and neck cancers [23]. In the present study, as well, duration of radiotherapy more than 45 days was demonstrated to result in decreased survival (57 versus 23 months, p=0.01), while decreased disease free survival also decreased (45 versus 19 months, p=0.067), though not statistically significant.

RT application can be performed in various techniques, while IMRT has been frequently used recently [24]. Neutron and heavy charged particle therapy provides a better local control in unresectable and inoperable patients compared to conventional photon radiotherapy (two–year control 67% vs. 17%, p<0.005) [25].

Elective nodal radiotherapy decreases incidence of nodal relapse in histological types of squamous, undifferentiated and adenocarcinomas [12]. In the present study, a total of 21 patients (70%), among which 12 received bilateral treatment, received elective nodal radiotherapy; however, this application was prognostically insignificant.

Insufficient information is present in the literature on adjuvant concurrent chemoradiotherapy in salivary gland cancers. Chemotherapy provided a significant increase in survival compared to radiotherapy alone in the study by Tatvenyanon et al. (three–year survival rates were 83% and 44%, respectively, p =0 .05) [26]. Adjuvant chemotherapy and adjuvant radiotherapy alone have been compared in the continuing RTOG clinical study 1008.

Systemic therapy with either chemotherapy or molecularly targeted agents may be used for palliation in advanced disease.

Clinicopathological factors (no. of cases)	OS (months)	p- value	DSS (months)	p- value	DFS (months)	p- value
Gender		0.287		0.3		0.839
Male	50		51		37	
Female	39		39		37	
Age, years		0.177		0.183		0.114
<60	56		56		45	
≥60	39		39		30	
Location		0.297		0.297		0.174
Parotid gland	50		50		41	
Submandibular gland	29		29		15	
Sublingual gland						
Tumor size		0.651		0.654		0.342
<4 cm	45		45		33	
≥4 cm	52		52		47	
T stage		0.0836		0.829		0.909
1-2	48		48		39	
3-4	50		50		36	
N stage		***0.002***		***0.002***		***0.002***
N0	64		66		53	
N+	26		26		17	
Stage		0.065		0.061		***0.019***
1-2	64		66		57	
3-4	39		39		27	
Resection margin		0.519		0.554		0.183
Negative	44		44		31	
Close or positive	51		51		45	
PNI						
Yes	43	0.719	43	0.736	29	0.553
No	50		50		43	
LVI						
Yes	40	0.737	40	0.728	24	0.562
No	48		48		39	
Extracapsular extension		0.105		0.111		0.406
Yes	13		13		13	
No	49		50		39	
Radiotherapy time (days)						
<45		***0.01***		***0.01***		0.067
≥45	57		58		45	
	23		23		19	
Surgery-Radiotherapy interval (days)		0.180		0.196		***0.042***
<42	55		56		50	
≥42	36		36		21	

Table 3. Univariate analysis of prognostic factors for Overall Survival (OS), Disease Specific Survival (DSS), Disease Free Survival (DFS)

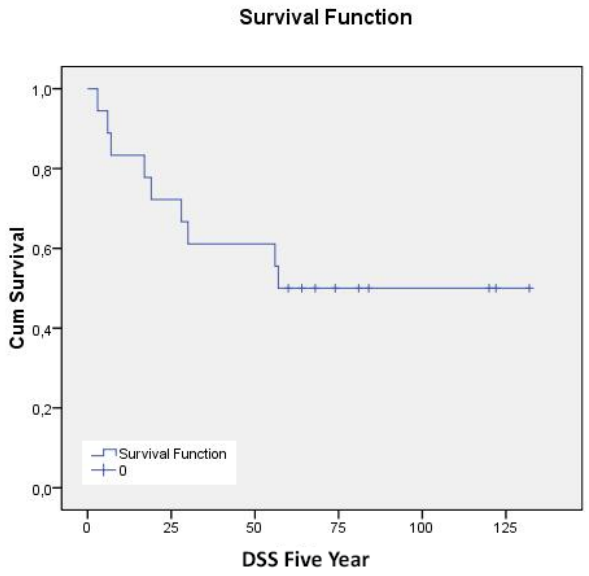

Figure 1. Five years DSS

Conclusion

Statistically, no effect of some prognostic factors on local control and survival could be determined due to the low number of patients in this study.

Salivary gland tumors comprise a rarely seen group of tumors. Efficacy of postoperative RT in high risk patients is overt on local control and survival; however, randomized prospective studies are needed.

The place of adjuvant chemotherapy should be defined by prospective studies since the rate of distant metastasis is high.

Conflicts of Interest

The authors declare no conflicting interest in the conduct of this study.

References

1. Speight PM, Barrett AW. Salivary gland tumours. Oral Dis 2002;8:229–240
2. Spiro RH. Salivary neoplasms: Overview of a 35–year experience with 2,807 patients. Head Neck Surgery 1986;8:177–184
3. Bron LP, Traynor SJ, McNeil EB et al. Primary and metastatic cancer of the parotid: comparison of clinical behavior in 232 cases. Laryngoscope 2003 ;113(6):1070–5.
4. Batsakis JG, McClatchey KD, Johns M et al. Primary squamous cell carcinoma of the parotid gland. Arch Otolaryngol 1976 ;102(6):355–7.
5. North CA, Lee DJ, Piantadosi S et al. Carcinoma of the major salivary glands treated by surgery or surgery plus postoperative radiotherapy. Int J Radiat Oncol Biol Phys 1990;18:1319–26.
6. Armstrong JG, Harrison LB, Spiro RH et al. Malignant tumors of major salivary gland origin. A matched–pair analysis of the role of combined surgery and postoperative radiotherapy. Arch Otolaryngol Head Neck Surg 1990;116:290–3.
7. Douglas JG, Koh WJ, Austin–Seymour M et al. Treatment of salivary gland neoplasms with fast neutron radiotherapy. Arch Otolaryngol Head Neck Surg 2003;129:944–948
8. Terhaard CH, Lubsen H, Van der Tweel I, et al. Salivary gland carcinoma: independent prognostic factors for locoregional control, distant metastases, and overall survival: results of the Dutch head and neck oncology cooperative group. Head Neck. 2004;26:681–92
9. Lima RA, Tavares MR, Dias FL, et al. Clinical prognostic factors in malignant parotid gland tumors.Otolaryngol Head Neck Surg. 2005;133:702–8
10. Demiroz Abakay C, ahintürk K, Türk A et al. Our results of postoperative radiation therapy in patients with salivary gland cancer. Kulak Burun Bogaz Ihtis Derg. 2014 ;24:316–23.
11. Feinstein TM, Lai SY, Lenzner D et al. Prognostic factors in patients with high–risk locally advanced salivary gland cancers treated with surgery and postoperative radiotherapy. Head Neck. 2011 ;33:318–23
12. Chen AM, Granchi PJ, Garcia J et al. Local–regional recurrence after surgery without postoperative irradiation for carcinomas of the majorsalivary glands: implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 2007;67:982–7.
13. Ghosh–Laskar S, Murthy V, Wadasadawala T et al. Mucoepidermoid carcinoma of the parotid gland: factors affecting outcome. Head Neck. 2011 ;33:497–503
14. Fu KK, Leibel SA, Levine ML et al. Carcinoma of the major and minor salivary glands: analysis of treatment results and sites and causes of failures. Cancer. 1977;40:2882–90.
15. Teo PM, Chan AT, Lee WY et al. Failure patterns and factors affecting prognosis of salivary gland carcinoma: retrospective study. Hong Kong Med J. 2000;6:29–36.
16. Terhaard CH, Lubsen H, Rasch CR et al. Dutch Head and Neck Oncology Cooperative Group.The role of radiotherapy in the treatment of malignant salivary gland tumors. Int J Radiat Oncol Biol Phys 2005;61:103–11.
17. Renehan A, Gleave EN, Hancock BD et al. Long–term follow–up of over 1000 patients with salivary gland tumours treated in a single centre. Br J Surg 1996; 83:1750–4

18. Bjørndal K, Krogdahl A, Therkildsen MH, et al. Salivary gland carcinoma in Denmark 1990–2005: outcome and prognostic factors. Results of the Danish Head and Neck Cancer Group (DAHANCA). Oral Oncology 2012; 48:179–85.

19. Jaafari–Ashkavandi Z, Ashraf MJ, Moshaverinia M. Salivary gland tumors: a clinicopathologic study of 366 cases in southern Iran. Asian Pac J Cancer Prev 2013;14, 27–30.

20. Wahlberg P, Anderson H, Biörklund A,et al. Carcinoma of the parotid and submandibular glands––a study of survival in 2465 patients. Oral Oncol. 2002 ;38:706–13.

21. Bell RB, Dierks EJ, Homer L, et al. Management and outcome of patients with malignant salivary gland tumors. J Oral Maxillofac Surg 2005;63:917–28

22. Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head–and–neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–8

23. Platek ME, McCloskey SA, Cruz M, et al. Quantification of the effect of treatment duration on local–regional failure after definitive concurrent chemotherapy and intensity–modulated radiation therapy for squamous cell carcinoma of the head and neck. Head Neck. 2013 ;35:684–8

24. Schoenfeld JD, Sher DJ, Norris CM Jr et al. Salivary gland tumors treated with adjuvant intensity–modulated radiotherapy with or without concurrent chemotherapy. Int J Radiat Oncol Biol Phys. 2012 ;82:308–14

25. Laramore GE, Krall JM, Griffin TW, et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG–MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. Int J Radiat Oncol Biol Phys. 1993 ;27:235–40.

26. Tanvetyanon T, Qin D, Padhya T, et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major salivary gland carcinoma. Arch Otolaryngol Head Neck Surg. 2009;135:687