ACTA ONCOLOGICA
2020, VOL. 59, NO. 5, 565–568
https://doi.org/10.1080/0284186X.2020.1730005

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Treatment outcomes of patients with salivary duct carcinoma undergoing surgery and postoperative radiotherapy

Dong Soo Lee[a], Chang Geol Lee[b], Ki Chang Keum[b], Seung Yeun Chung[b], Taehyung Kim[b], Hong-Gyun Wu[c,d,e], Jin Ho Kim[c], Myung-Whun Sung[f], Soon-Hyun Ahn[f], Kwan Ho Cho[g], Ki Mun Kang[h], Young-Taek Oh[i], Jin Hee Kim[j] and Min Kyu Kang[k]

[a]Department of Radiation Oncology, College of Medicine, The Catholic University of Korea, Seoul, South Korea; [b]Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, South Korea; [c]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, South Korea; [d]Cancer Research Institution, Seoul National University College of Medicine, Seoul, South Korea; [e]Institute of Radiation Medicine, Medical Research Center, Seoul National University, Seoul, South Korea; [f]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University College of Medicine, Seoul, South Korea; [g]Proton Therapy Center, Research Institute and Hospital, National Cancer Center, Goyang, South Korea; [h]Department of Radiation Oncology, Gyeongsang National University School of Medicine and Gyeongsang National University Changwon Hospital, Jinju, South Korea; [i]Department of Radiation Oncology, Ajou University School of Medicine, Suwon, South Korea; [j]Department of Radiation Oncology, Keimyung University, School of Medicine, Daegu, South Korea; [k]Department of Radiation Oncology, School of Medicine, Kyungpook National University, Daegu, South Korea

ARTICLE HISTORY Received 2 February 2020; accepted 11 February 2020

Introduction

Salivary duct carcinoma (SDC) is a rare, high-grade tumor arising from the ductal epithelium of the salivary gland. SDC comprises approximately 10% of all salivary gland malignancies and typically presents in older men, with the parotid gland being the most common primary site [1]. SDC is typically managed by similar treatment approaches as other high-grade salivary gland tumors [2–4]. Complete surgical resection of the involved salivary gland and neck dissection is recommended. Postoperative radiotherapy (PORT) to the tumor bed and ipsilateral neck is usually recommended. The role of systemic chemotherapy is unclear despite its evaluation in several clinical trials [5,6]. In the prior studies, 50–70% of the patients presented with regional lymph node (LN) metastasis at initial diagnosis, and 30–70% developed distant metastasis (DM) during follow-up, resulting in 50–70% of deaths by tumor-related causes [1,7–17]. However, data describing patterns of failure after surgery and PORT have been limited so far.

This study aimed to elucidate the treatment outcomes and the patterns of failure of SDC treated with surgery and PORT, among patients enrolled in the multi-institutional retrospective study of the Korean Radiation Oncology Group (KROG) 13-09.

Material and methods

Study population and patient eligibility

The eligibility criteria for the KROG 13-09 study were as follows: patients with pathologically proven salivary gland carcinoma in major salivary glands; patients without DM at the time of diagnosis; patients treated with surgery and/or RT for curative intent; patients without history of other malignancies; and patients who were treated between January 1999 and December 2008. Patients who did not complete the planned RT or who received palliative surgery before RT were excluded from this study.

Before study enrollment, all participating hospitals obtained ethical approvals from their respective institutional review boards. In each institution, the medical records of the enrolled patients were retrospectively reviewed for information about patient and tumor characteristics, treatments, and follow-up results. Among 272 enrolled patients from seven hospitals, the data of 27 patients with SDC were analyzed for this study.

Study endpoints

The study endpoints were overall survival (OS), disease-free survival (DFS), local control (LC), regional control (RC), and distant control (DC) rates. OS was calculated from the date of surgery to the date of death by any cause or the final follow-up. DFS was calculated from the date of surgery to the date of disease recurrence or last follow-up. LC, RC, and DC rates were defined as the proportion of control rates in the primary site, neck, and distant sites, respectively. In addition, we analyzed the primary patterns of failure, significant prognostic factors for each study endpoint, and failure patterns in relation to the RT field.

Statistical analyses

Survival curves were generated using Kaplan–Meier methods, and survival differences were compared using a log-rank test. The Pearson's chi-square test, Fisher's exact test, or

CONTACT Min Kyu Kang mkkang@knu.ac.kr Department of Radiation Oncology, Kyungpook National University Chilgok Hospital, 807 Hoguk-ro, Buk-gu, Daegu, 41404, South Korea; Chang Geol Lee cglee1023@yuhs.ac Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul, 03722, South Korea

Supplemental data for this article can be accessed here.

Mann–Whitney *U* test was used to compare quantitative and qualitative variables. Statistical analyses were performed using SPSS statistics version 18.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was defined as a $p \leq .05$.

Results

Patient and tumor characteristics

The patient and tumor characteristics are summarized in Supplementary Table 1. The median age was 61 (range, 23–78) years, and 22 patients were male. The tumor location was parotid gland in 21 and submandibular gland in 6, respectively. The majority had Eastern Cooperative Oncology Group performance status of 0–1 (96.3%). During operation, facial nerve invasion (FNI) was found in 12 (44.4%) patients. Pathological LN positivity was observed in 18 (66.7%) patients. Resection margin (RM) and perineural invasion (PNI) were positive in 9 (33.3%) and 16 (59.3%) patients, respectively.

Treatment characteristics

The treatment characteristics are outlined in Supplementary Table 2. The most common types of primary site surgery were total conservative parotidectomy (85.7%) for parotid gland cancer, and wide excision (83.3%) for submandibular gland cancer, respectively. Neck dissection was performed in 85.7% and 66.7% of patients in parotid gland and submandibular gland cancer, respectively, by either one of the following types of surgery; radical neck dissection, modified radical neck dissection, or supraomohyoid neck dissection. The most common types of RT techniques were three-dimensional conformal RT (51.9%), followed by two-dimensional RT (29.6%) and intensity-modulated RT (18.5%). The median PORT doses were 63 (range, 45–66) Gy for primary site and 54 (range, 41.4–66) Gy for neck. Most patients (92.6%) did not receive chemotherapy, and adjuvant chemotherapy was administered in only 2 patients.

Nodal metastasis and neck management

The details of nodal metastasis distribution are summarized in Table 1. Pathological nodal metastasis was positive in 71.4% and 50% of parotid gland cancer and submandibular gland cancer patients, respectively. Level II and III were the common metastatic sites, and other Levels (I, IV, and V) were positive in about 20%. All four parotid gland cancer patients with intraparotid or periglandular LN metastasis had nodal metastasis in other nodal stations. In parotid gland cancer patients, 64.3% had LN metastasis only in Level I–III, and no patient had isolated lower neck metastasis.

The mixture of neck dissection level and PORT field was very heterogeneous but could be simplified according to the nodal positivity. In nine patients with pN0 or pNx, four patients were treated with neck RT covering lower neck levels (up to Level IV or V). Three patients were irradiated to only the surgical field (upper neck), and two did not receive neck RT. In 18 patients with pN+, neck RT field covered lower neck levels in 12 patients and only upper neck levels in 6 patients. With these treatments, only 1 patient experienced regional failure (RF); he had single nodal metastasis in level II (pN1) and received neck RT covering the dissected area of Level II, but RF occurred in the ipsilateral supraclavicular node area (out-field).

Table 1. Distribution of neck node metastasis.

	Parotid gland	Submandibular gland
Status of node metastasis		
pN0 or pNx	6 (28.6%)	3 (50%)
pN+	15 (71.4%)	3 (50%)
Distribution of node metastasis (I)[a]		
Intraglandular	1 (5.3%)	
Periglandular	3 (15.8%)	
Level I	4 (21.1%)	1 (20%)
Level II	9 (47.4%)	2 (40%)
Level III	5 (26.3%)	2 (40%)
Level IV	4 (21.1%)	1 (20%)
Level V	4 (21.1%)	1 (20%)
Level VI	1 (5.3%)	0 (0%)
Distribution of node metastasis (II)[b]		
Level I–III (+) and IV–V (−)	9 (64.3%)[c]	1 (50%)
Level I–III (+) and IV–V (+)	4 (28.6%)	1 (50%)
Level I–III (−) and IV–V (+)	1 (7.1%)[d]	0 (0%)

[a]Denominators were 19 for parotid gland cancer and 5 for submandibular gland cancer after removing 3 patients who had nodal metastasis without information on involved nodal stations.
[b]Denominators were 15 for parotid gland cancer and 2 for submandibular gland cancer, which had complete information on involved nodal stations.
[c]One patient experienced regional failure in the supraclavicular node.
[d]One patient had single nodal metastasis in Level Va.

Survival outcomes and prognostic factors

The median follow-up duration was 57 (range, 4–141) months. During follow-up, 13 (48.1%) patients experienced recurrences, and 13 patients died of cancer progression ($n = 12$) or unknown cause ($n = 1$). The survival curves are shown in Figure 1. The 5-year OS, DFS, LC, RC, and DC rates were 63.4%, 47.4%, 72.7%, 96.3%, and 68%, respectively.

In univariate analysis, pN-stage and PNI showed a marginal significance for OS ($p = .06$ and .063) and DFS ($p = .076$ and .074). With regard to LC, pT-stage ($p = .017$) and FNI ($p = .026$) were the significant prognostic factors. There was no significant prognostic factor for DC. The statistical results of univariate analysis are summarized in Supplementary Table 3.

Patterns of failure

The distribution of relapses in all 13 patients was as follows: four local; one local and distant; one regional; and seven distant sites.

The patient, tumor, and treatment characteristics of 6 patients with local and regional recurrences are described in Supplementary Table 4. Local failures (LFs) occurred 14–44 months after surgery. All patients with LF had both FNI and pT4-stage. Recurrent patients received 45–66 Gy of PORT (66 Gy in patients with positive RM), and 2 patients had positive RM status. The LF sites were temporal bone, internal auditory canal, skull base, and neighboring skins.

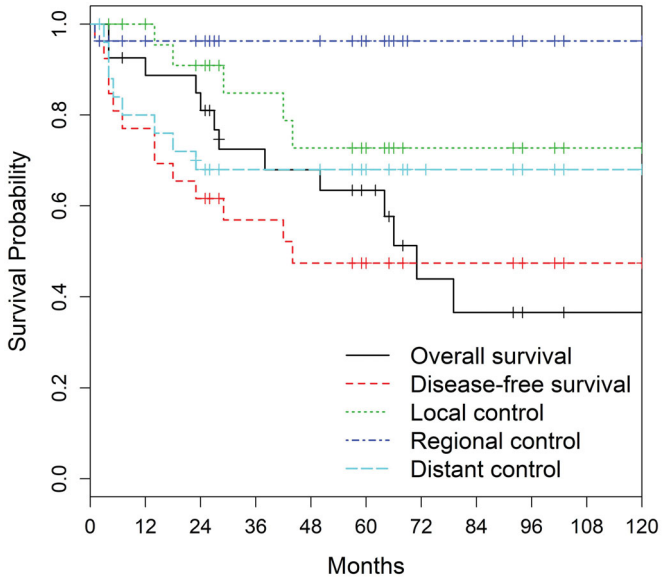

Figure 1. The Kaplan–Meier curves of overall survival, disease-free survival, local control, regional control, and distant control.

Four among five LFs occurred from the original PORT field (in-field). The total PORT dose was not statistically different between patients with and without LFs ($p = .656$). There was one RF, as described above in the section on nodal metastasis and neck management. The DM occurred in bone, lung, liver, adrenal, and spine in 8 patients, with a median elapsed time of 6 (range, 3–23) months.

Discussion

In this multicenter study of SDC in major salivary gland treated with curative surgery and PORT, overall treatment outcomes and patterns of failure were similar to those of previous studies [1,7,12,14–17].

In major salivary gland SDC, LF has been reported to be 10–30% after surgery followed by PORT [1,17,18]. In the present study, 5 patients experienced LFs; all had pT4-stage and positive FNI, and 4 patients had facial nerve paralysis at the time of diagnosis. LF at neighboring skin and internal auditory canal were also commonly observed. Johnston et al. [1] reported that 6 of the 8 patients with LFs presented with facial nerve paresis or paralysis. Shinoto et al. [17] described that PNI was a significant prognostic factor for LC. In our study, all out-field recurrences developed in patients with PNI, similarly in Shinoto et al. [17] These findings support that the clinical target volume should include the involved cranial nerves and the corresponding parts of the skull base in patients with positive PNI. With regard to RT dose issue, the median RT doses were 63 Gy for primary site in our study. Neither resection margin status nor RT doses significantly affected the LC rates in the subgroup analysis. Johnston et al. [1] also reported that the doses given to primary sites were 66–70 Gy in 4 patients with in-field LF and there was no dose–response relationship for LC. Since there have been no standard doses for PORT in SDC to date, PORT doses should be refined to improve LC, and new RT technologies such as particle therapy should be introduced.

With respect to neck management, previous studies described their own institutional treatment policies [17,18]. However, to our knowledge, no studies depicted the distribution of neck node metastasis and the extent of neck treatment. The current study categorized the study population according to the distribution of LN metastasis (Table 1) and treatment extent. LN metastasis was positive in 66.7% of patients, with Level II and III being the most commonly involved sites. There was no lower neck metastasis without upper neck metastasis. In nine patients with pN0 or pNx, there was no RF regardless of the extent of treatment. In 16 patients with upper neck metastasis, the lower neck node was positive in 5 patients. RF occurred in the lower neck in 1 patient who had Level II node metastasis and had been treated only to the upper neck. Despite the small sample sizes, these results provided some insightful viewpoints for RT field design as follows; ipsilateral upper neck for pN0 or pNx, and ipsilateral whole neck for pN+. Although contralateral neck node recurrence has been reported [1,17,18], the indication of contralateral neck RT is uncertain so far.

In terms of risk factors for DM, multiple pathological LNs, lymphovascular invasion, and extracapsular extension have been known to be major factors [1,18]. In the current study, no factors were statistically significantly associated with DM, which might be due to the limited sample sizes. Interestingly, 5 (4 distant and 1 regional) relapsed within 6 months after treatment. The development of disease relapses within the very early period, especially in distant sites, was also previously described [16,18]. Despite conflicting results among studies [15,19], human epidermal growth factor receptor-2 and androgen receptor are emerging as future potential therapeutic targets, owing to a good response of metastatic SDC to trastuzumab and anti-androgen drugs. In addition, programed death ligand-1 was reported to be expressed as high as 48% in SDC [20], whose expression allows tumor cells to elude the immune system. Considering the fact that DM is a major failure pattern of SDC, novel systemic therapies or immunotherapy, combined with surgery and PORT, is anticipated to improve DC, as well as LRC.

Although our study is limited by its retrospective nature and small sample sizes, the main strengths are the multicenter nature of the study and the detailed depiction of patterns in nodal metastasis. A multicenter study has less risk of bias than a single institutional study, and we proposed perspectives of neck management based on pathological nodal distribution, PORT fields, and patterns of failure.

In summary, the present study demonstrated that surgery followed by PORT was effective in LRC, but not in DC, in major salivary gland SDC. Optimization of radical surgery, proper RT field design based on this study's results, and application of novel systemic agents to minimize DM would be indispensable for future SDC treatment.

Disclosure statement

The authors report no conflicts of interest.

ORCID

Chang Geol Lee http://orcid.org/0000-0002-8702-881X
Min Kyu Kang http://orcid.org/0000-0002-7962-7054

References

[1] Johnston ML, Huang SH, Waldron JN, et al. Salivary duct carcinoma: treatment, outcomes, and patterns of failure. Head Neck. 2016;38(S1):E820–E826.
[2] Noh JM, Ahn YC, Nam H, et al. Treatment results of major salivary gland cancer by surgery with or without postoperative radiation therapy. Clin Exp Otorhinolaryngol. 2010;3(2):96–101.
[3] Cerda T, Sun XS, Vignot S, et al. A rationale for chemoradiation (vs radiotherapy) in salivary gland cancers? On behalf of the REFCOR (French rare head and neck cancer network). Crit Rev Oncol Hematol. 2014;91(2):142–158.
[4] Lim CM, Hobson C, Kim S, et al. Clinical outcome of patients with carcinoma ex pleomorphic adenoma of the parotid gland: a comparative study from a single tertiary center. Head Neck. 2015;37(4):543–547.
[5] Milano A, Longo F, Basile M, et al. Recent advances in the treatment of salivary gland cancers: emphasis on molecular targeted therapy. Oral Oncol. 2007;43(8):729–734.
[6] Nabili V, Tan JW, Bhuta S, et al. Salivary duct carcinoma: a clinical and histologic review with implications for trastuzumab therapy. Head Neck. 2007;29(10):907–912.
[7] Afzelius LE, Cameron WR, Svensson C. Salivary duct carcinoma–a clinicopathologic study of 12 cases. Head Neck Surg. 1987;9(3):151–156.
[8] Brandwein MS, Jagirdar J, Patil J, et al. Salivary duct carcinoma (cribriform salivary carcinoma of excretory ducts). A clinicopathologic and immunohistochemical study of 12 cases. Cancer. 1990;65(10):2307–2314.
[9] Delgado R, Vuitch F, Albores-Saavedra J. Salivary duct carcinoma. Cancer. 1993;72(5):1503–1512.
[10] Grenko RT, Gemryd P, Tytor M, et al. Salivary duct carcinoma. Histopathology. 1995;26(3):261–266.
[11] Lewis JE, McKinney BC, Weiland LH, et al. Salivary duct carcinoma. Clinicopathologic and immunohistochemical review of 26 cases. Cancer. 1996;77(2):223–230.
[12] Guzzo M, Di Palma S, Grandi C, et al. Salivary duct carcinoma: clinical characteristics and treatment strategies. Head Neck. 1997;19(2):126–133.
[13] Hosal AS, Fan C, Barnes L, et al. Salivary duct carcinoma. Otolaryngol Head Neck Surg. 2003;129(6):720–725.
[14] Weon YC, Park SW, Kim HJ, et al. Salivary duct carcinomas: clinical and CT and MR imaging features in 20 patients. Neuroradiology. 2012;54(6):631–640.
[15] Wee DT, Thomas AA, Bradley PJ. Salivary duct carcinoma: what is already known, and can we improve survival? J Laryngol Otol. 2012;126(S2):S2–S7.
[16] Salovaara E, Hakala O, Back L, et al. Management and outcome of salivary duct carcinoma in major salivary glands. Eur Arch Otorhinolaryngol. 2013;270(1):281–285.
[17] Shinoto M, Shioyama Y, Nakamura K, et al. Postoperative radiotherapy in patients with salivary duct carcinoma: clinical outcomes and prognostic factors. J Radiat Res. 2013;54(5):925–930.
[18] Kim JY, Lee S, Cho KJ, et al. Treatment results of post-operative radiotherapy in patients with salivary duct carcinoma of the major salivary glands. Br J Radiol. 2012;85(1018):e947–e52.
[19] Boon E, Bel M, van Boxtel W, et al.; PALGA Group. A clinicopathological study and prognostic factor analysis of 177 salivary duct carcinoma patients from The Netherlands. Int J Cancer. 2018;143(4):758–766.
[20] Mukaigawa T, Hayashi R, Hashimoto K, et al. Programmed death ligand-1 expression is associated with poor disease free survival in salivary gland carcinomas. J Surg Oncol. 2016;114(1):36–43.