Treatment results of post-operative radiotherapy in patients with salivary duct carcinoma of the major salivary glands

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Objective: Salivary duct carcinoma (SDC) is a rare malignancy of high-grade pathological type. We evaluated clinical outcomes and prognostic factors in 35 patients with SDC treated post-operatively with adjuvant radiation.

Methods: We retrospectively assessed overall survival, locoregional control and disease-free survival in 35 patients with SDC of the major salivary glands who underwent surgery and were subsequently treated with radiotherapy. The evaluated prognostic factors included gender, age, symptom duration, tumour site, tumour size, TNM classification, and the following pathological features: perineural invasion, lymphovascular invasion, extraparenchymal invasion and resection-margin status.

Results: Of the 35 patients, 30 (85.7%) were male. Median age at initial diagnosis was 62 years (range 38–75 years). The parotid gland was the main site affected in 22 patients (62.9%). 18 patients (51.5%) had pathological T3/T4 tumours, and 26 (74.3%) showed pathological nodal involvement. Actuarial 5-year locoregional control, disease-free survival and overall survival rates were 63.3%, 47.4% and 55.1%, respectively. The cause-specific death rate was 31.4% ($n=11$). Pathological nodal involvement was correlated with distant metastasis ($p=0.011$). Lymphovascular invasion was significantly prognostic for distant metastasis-free survival ($p=0.049$), locoregional control ($p=0.012$) and overall survival ($p=0.003$) in a Cox proportional hazard model, whereas perineural invasion was only significantly prognostic for overall survival ($p=0.005$).

Conclusions: Surgery and post-operative radiotherapy were effective for locoregional control. Lymphovascular invasion and perineural invasion were significant prognostic factors in patients with SDC.

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Salivary duct carcinoma (SDC) is a rare high-grade tumour arising from the ductal epithelium of the salivary gland. Histologically, SDC strongly resembles intraductal and invasive mammary duct carcinoma, which is why it was named SDC [1]. Since first described in 1968, only approximately 400 cases of SDC have been reported in the English-language literature and the reported incidence of SDC varies between 1% and 3% of all malignant salivary tumours [2–5]. The tumour is clinically characterised by rapid progression, with early nodal involvement and high rates of local recurrence, distant metastases and tumour-related deaths [6–8]. The incidence of distant metastasis has been reported from 30% to 70%, and most patients die of disseminated disease [2, 3, 5, 7, 9]. Although several studies have attempted to identify clinical and immunohistochemical prognostic factors in patients with SDC [3, 7, 10–14], these studies have included small numbers of patients. This has made

it difficult to determine the role of post-operative radiotherapy, to assess treatment outcomes and to identify prognostic factors in patients with SDC.

We therefore investigated clinical outcomes and prognostic factors in 35 patients with SDC of the major salivary glands who were treated through surgery and post-operative adjuvant radiation treatment (RT).

Methods and materials

Patients

Between January 1998 and July 2010, 35 patients with SDC were treated at the Asan Medical Center. Their demographic data, past history and initial symptoms and signs, as well as information on tumour site, pathological findings and TNM classification [15] were obtained through review of pathological, radiological and surgical records.

All patients underwent complete surgical resection (for example, total parotidectomy or total submandibular gland resection). The type of surgery performed

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depended on the primary tumour site. Of 22 patients with tumours of the parotid gland, 16 (73%) underwent facial nerve resection. Neck dissection was performed in 31 (88.6%) patients. In our institution, neck dissection was recommended for patients with pre-operatively diagnosed high-grade tumours of the salivary gland [13]. Of the four patients who did not undergo neck dissection, two were not pre-operatively diagnosed with high-grade salivary tumours and the other two were referred from other hospitals after undergoing surgical resection. All patients received post-operative adjuvant RT to the tumour bed and ipsilateral neck nodes. The median prescribed dose was 59.4 Gy (range 50.4–71.4 Gy), with one patient receiving a maximum dose of 39.6 Gy because of poor tolerance. Three patients received concurrent cisplatin-based chemoradiation treatment, and one patient received pre-operative chemotherapy.

Follow-up and statistical analysis

The median follow-up period was 43 months (range 7–155 months). All clinical and pathological data were analysed statistically using SPSS for Windows (v. 17.0; SPSS Inc., Chicago, IL). Evaluated factors included gender, age, symptom duration, tumour site, tumour size, TNM classification and the following pathological features: perineural invasion, lymphovascular invasion,

extraparenchymal invasion and resection-margin status. Pathological node involvement, lymphovascular invasion and perineural invasion were compared according to the presence of distant metastasis using Fisher's exact test. Rates of overall survival, locoregional control and disease-free survival were estimated using the Kaplan–Meier method. Univariate analyses of prognostic values were performed using the log-rank test, and a Cox proportional-hazards model was used to analyse variables shown to be significant ($p < 0.05$) in univariate analyses. p -values < 0.05 were considered statistically significant.

Results

Clinicopathological features

The 35 patients comprised 30 males (85.7%) and 5 females (14.3%). Their clinical and demographic characteristics are summarised in Table 1. Median age at initial diagnosis was 62 years (range 38–75 years). Tumours originated from the parotid gland in 22 patients (62.9%), from the submandibular gland in 12 (34.3%) and from the sublingual gland in 1 (2.8%). All 35 patients presented with a palpable mass at initial presentation. 9 (25.7%) experienced pain and 27 (77.1%) showed clinical cervical lymph node involvement at the time of

Table 1. Clinical characteristics of salivary duct carcinoma of the major salivary gland ($n=35$)

Characteristics	<i>n</i>	%
Gender		
Male	30	85.7
Female	5	14.3
Age [mean (range), 59.5 (38–75) years]		
Location		
Parotid	22	62.9
Submandibular	12	34.3
Sublingual	1	2.8
Symptoms/findings		
Salivary mass	29	82.9
Cervical mass	7	20.0
Oral ulcer	1	2.9
Facial nerve dysfunction	2	5.7
Pain in the face/neck	9	25.7
Symptom durations [median (range), 5 months (20 days to 50 years)]		
Pathological TNM stage [15]		
T classification		
T1/T2/T3/T4	6/11/15/3	17.1/31.4/42.9/8.6
N classification		
N0/N1–2	9/26	25.7/74.3
M classification		
M0/M1	35/0	100/0
Pathologic findings		
Size of primary tumour [mean (range), 3.35 (0.8–10) cm]		
Lympho-vascular invasion	18	51.4
Perineural invasion	12	34.3
Extraparenchymal invasion	23	65.7
Resection margin	17	48.6
Initial treatment		
Surgery + RT	31	88.6
Surgery + RT + CT	4	11.4
Neck dissection (yes/no)	31/4	88.6/11.4
Follow-up period [mean (range), 48 (4–155) months]		

RT, radiation treatment.

diagnosis. The median duration of symptoms before diagnosis was 5 months (range 20 days to 50 years). In six patients, painless masses had remained stable for many years and had then begun to grow rapidly. Two patients had facial nerve paralysis, but none had distant metastasis.

The median pathological tumour size was 3.0 cm (range 0.8–10 cm). 18 patients (51.5%) had pathological stage T3/T4 tumours, and 17 (48.5%) had pathological stage T1/T2 tumours. Pathologic nodal involvement was observed in 26 patients (74.3%), with a mean number of metastatic nodes of 18.0 (range 2–68). 15 (57.7%) of the 26 node-positive patients had extracapsular spread. Lymphovascular invasion was observed in 18 patients (51.4%), and perineural invasion in 12 patients (34.3%).

Treatment outcomes and prognostic factor analysis

We found that the 5-year actuarial locoregional control rate was 63.3% (9 events), the 5-year disease-free survival rate was 47.4% (15 events) and the 5-year overall survival rate was 55.1% (12 events; Figure 1). Correlation analysis revealed that only pathological node metastasis was correlated with distant metastasis ($p=0.011$). Univariate analysis showed that lymphovascular invasion and T classification were prognostic for distant metastasis-free survival, locoregional control and overall survival ($p<0.05$). Perineural invasion was a prognostic factor for distant metastasis-free survival, overall survival and, in males, better locoregional control ($p<0.05$). Patients with submandibular gland involvement tended to have a poorer prognosis than those with parotid gland involvement. However, the difference was not significant

($p>0.05$; Figure 2). In multivariate analysis, lymphovascular invasion was a significant prognostic factor for distant-metastasis-free survival ($p=0.049$), locoregional control ($p=0.012$) and overall survival ($p=0.003$). Perineural invasion was a prognostic factor for overall survival ($p=0.005$), whereas gender was prognostic for disease-free survival ($p=0.018$) and locoregional control ($p=0.011$).

Patterns of failure

Treatment failures occurred in 15 (42.9%) of the 35 patients. In the four patients with local failure, recurrence was accompanied by distant failure (Figure 3). Nodal recurrence was observed in nine patients at between 3 and 57 months (median 16 months). All nodal metastases developed on the contralateral or undissected ipsilateral neck. Consequently, there was no neck node failure following post-operative radiation treatment after neck dissection. One patient who showed metastasis in a single regional neck node at 47 months after initial treatment underwent salvage surgery and has remained disease-free to date.

Distant metastasis developed in 14 patients (37.8%) after a median of 13 months (range 3–43 months), with the most common site being the lungs, followed by the bones and liver. 11 patients (31.4%) died of disease-related causes, all these cases being distant metastases. Three other patients (8.6%) with distant metastases remained alive with stable disease after palliative chemotherapy. At the time of evaluation, 19 patients (59.3%) were alive with no evidence of disease, and 2 (7.2%) had died of other diseases.

Figure 1. Actuarial locoregional control (LRC), disease-free survival (DFS) and overall survival (OS) in 35 patients with salivary duct carcinoma.

Figure 2. Univariate analyses of prognostic values in 35 patients with salivary duct carcinoma. Lymphovascular invasion, perineural invasion and T classification were significant prognostic factors ($p < 0.05$).

Discussion

The clinical characteristics of our patients were similar to those of other series and reviews [3, 6, 7, 11]. We found that SDC occurred most frequently in males aged 60–70 years (median 62 years). The most frequent site was the parotid gland, followed by the submandibular gland, although we found involvement of the latter to be more frequent than has been reported previously [5, 6, 9, 12]. Clinically, SDC has an aggressive course, with a high rate of cervical nodal involvement at the time of diagnosis, as well as early metastasis, local recurrence and a significant mortality rate [6, 7, 10–12, 14]. Our clinical review of 35 patients confirmed the aggressive clinical behaviour of SDC. We found that 74.3% of patients had cervical

nodal metastasis at the time of diagnosis, and distant metastasis occurred in 14 patients (37.8%) at a median 13 months (range 3–43 months) after initial treatment. We also recorded a death rate of 37.1% ($n=13$), which was lower than previously reported rates (45–77%; Table 2) [2, 3, 5–7, 9–12, 14, 16, 17]. In agreement with previous findings, we found that the most common cause of treatment failure in SDC was distant disease dissemination (11 of 14 patients) [2, 5, 9, 11, 12, 14]. Because of the high death rates caused by distant failure, previous studies have suggested the importance of effective systemic treatment in SDC. However, malignant salivary gland tumours show poor response to chemotherapy [18, 19]. There are significant pathological similarities between SDC and ductal carcinoma, and some authors

Figure 3. Treatment failure pattern in 35 patients with salivary duct carcinoma. Four cases of locoregional–distant failure, four of regional–distant failure, six of distant failure and one of regional failure were observed (in a total of 15 patients).

[20, 21] have reported good outcomes in patients with recurrent SDC who were treated with both docetaxel and trastuzumab, an established combination treatment for the advanced breast cancer. The overall survival rate for patients with distant failure may have been increased by active palliative chemotherapy, but prospective studies

are needed to identify more effective systemic treatments for SDC.

Nodal involvement at initial diagnosis has been reported to be prognostic for locoregional control, disease-free survival and overall survival rates in patients with SDC [9, 11–14]. We found that 74.3% of our patients showed pathologic nodal involvement, a higher rate than those reported previously [7, 11, 12, 14]. Correlation analysis revealed that pathological node metastasis was correlated with distant metastasis. However, univariate analysis showed that nodal metastasis did not have prognostic significance for local control, distant metastasis-free survival or overall survival. In the present study, despite a high nodal involvement rate, the locoregional recurrence rate was 25.7%, lower than the rate of 45–66% reported previously (Table 2) [2, 3, 5–7, 9–12, 14, 16, 17]. Moreover, all nodal recurrence was at the level of the undissected neck or the contralateral neck. These findings indicate that aggressive treatment through neck dissection and post-operative locoregional radiotherapy may lead to successful locoregional control, as well as a lower distant metastasis rate (37.8%).

Multivariate analysis showed that unfavourable prognostic factors were lymphovascular invasion, perineural invasion and male gender. Perineural and lymphatic invasion are common histological features in SDC [2, 5, 22]. The authors of previous studies [2, 5] proposed that high incidence of these findings may reflect the high-grade nature of this tumour. However, those studies did not include statistical analyses. We found that lymphovascular invasion was an independent prognostic factor for all treatment results, including distant metastasis,

Table 2. Review of literature for treatment outcomes in the salivary duct carcinoma of salivary gland

Series	Cases (n)	Age (Mean)	Gender (M:F)	Parotid (%)	Node+ (%)	PORT (%)	LR failure (%)	Distant metastasis (%)	Survival (%)
Luna et al (1987) [9]	30	63	3.2:1	83	66	–	66	66	30
Afzelius et al (1987) [15]	12	67	1.4:1	100	44	100	25	50	42
Brandwein et al (1990) [12]	12	61	4.9:1	100	72	33	45	54	55
Colmenero Ruiz et al (1993) [2]	9	66	3.6:1	89	34	89	56	34	33
Delgado et al (1993) [6]	15	59	4:1	87	13	60	33	40	47
Barnes et al (1994) [16]	13	92	2.0:1	77	67	–	58	25	66
Grenko et al (1995) [10]	12	64	2.0:1	100	77	58	58	62	23
Guzzo et al (1997) [7]	26	62	1.8:1	80	58	65	44	48	46
Lewis et al (1996) [11]	26	66	1.8:1	88	73	50	57	43	43
Hosal et al (2003) [5]	15	65	1.5:1	80	73	93	57	43	43
Jaehne et al (2005) [3]	50	62.5	1.9:1	78	56	72	48	48	66
Ko et al (2010) [14]	27	58.5	3.6:1	78	37	70	33	56	44
Present study	37	59.5	6.1:1	63	74	100	26	38	70

F, female; LR, locoregional; M, male; PORT, post-operative radiation treatment.

locoregional control and overall survival, suggesting that information about lymphovascular invasion should be included in a pathology report for clinicians. The very low incidence of SDC is a limitation in this kind of study. Only modest retrospective analysis was possible. Also, this study had limited statistical power. Although the number of patients was too small to achieve statistical significance, the clinicopathological analyses of 35 patients provided clinical information on managing patients with SDC so as to achieve a better treatment outcome.

Several studies [3, 12–14, 23] have attempted to identify molecular biomarkers that are predictive of outcomes in patients with SDC. In the largest study of patients with SDC, the expression of HER-2/neu and p53 was significantly associated ($p < 0.05$) with early local disease recurrence, distant disease metastasis and survival rates [3]. However, a more recent study [14] found that c-erb-B2, androgen receptor, vascular endothelial growth factor and epidermal growth factor receptor did not have prognostic significance in patients with SDC. Furthermore, neither hypoxia biomarkers [13] nor mitotic checkpoint proteins were prognostic in patients with SDC. Therefore, studies of predictive molecular biomarkers should be refocused to investigate therapies for preventing lymphovascular invasion, which we showed to be prognostic for survival and locoregional control, rather than the expression of molecular markers. Several lymphatic markers, including vascular endothelial growth factor receptor 3, Prox-1, LYVE-1 and podoplanin, have been investigated in human malignancies [24]. Investigating antibodies directed against lymphatic markers could lead to the identification of antilymphangiogenic compounds that reduce proliferation of the primary tumour.

In conclusion, we have shown that pathological nodal involvement was correlated with distant metastasis in patients with SDC and that lymphovascular invasion, perineural invasion and male gender were unfavourable prognostic factors. Aggressive treatment consisting of surgery followed by post-operative adjuvant radiotherapy to the tumour bed and ipsilateral neck nodes is effective in achieving both regional and local control.

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