

Salivary duct carcinoma: A clinopathological report of 11 cases

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Abstract. The aim of the present study was to summarize the clinicopathological and immunohistochemical characteristics of salivary duct carcinoma (SDC) and to evaluate the currently available treatment modalities. Between 2001 and 2011, 11 patients with SDC were diagnosed and treated at the Affiliated Hospital of Stomatology of Nanjing University (Nanjing, Jiangsu, China). The present study retrospectively reviewed the clinicopathological and immunohistochemical data of these 11 patients and the results indicated that the parotid gland was the most commonly affected site, followed by the submandibular gland and the palate. Furthermore, the mean age of onset was 58.8 years and all cases were treated with surgery, with 72.7% receiving post-operative radiation therapy. The range for the follow-up period was 10-89 months and of the 11 patients investigated, only two succumbed to the disease. In addition, the two-year overall survival rate was 75% according to Kaplan-Meier analysis and the mean overall survival time was 72.8 months. In conclusion, the present study determined that the site of the malignancy is the best predictor of survival in patients with the rare salivary malignancy SDC, while age, gender, T stage, N stage, American Joint Committee on Cancer stage, nerve paralysis, post-operative radiation, neck dissection, and protein expression levels of Ki-67, androgen receptor and human epidermal growth factor-2/neu are less influential factors.

Introduction

Salivary duct carcinoma (SDC) is a rare type of salivary malignancy which accounts for <10% of all salivary malignancies, and the majority of its histological characteristics are similar to those of mammary duct carcinoma (1-3). SDC exhibits characteristic ductal lesions and tumor cells are

often arranged in a 'Roman bridge' formation and cribriform architecture, with comedo necrosis (2). Due to the rarity of SDC, little data regarding its clinicopathological characteristics exists. The standard treatment for SDC is surgery in combination with radiotherapy, however, the prognosis of SDC is poor (4-7). Effective therapeutic strategies rely on a sufficient understanding of SDC and its prognostic factors, therefore, the aim of the present retrospective study was to summarize the clinicopathological characteristics of SDC and to evaluate the current treatment modalities currently used at the Affiliated Hospital of Stomatology of Nanjing University (Nanjing, Jiangsu, China).

Patients and methods

Patients. Between 2001 and 2011, 11 cases of histopathologically diagnosed with SDC, according to the 2005 World Health Organization classification of salivary gland tumors (2), were identified at the Affiliated Hospital of Stomatology. Subsequent to excluding any patients with distant metastasis or a previous history of head-neck surgery, all 11 patients primarily underwent surgical treatment, predominantly consisting of local extensive resection with neck dissection, followed by post-operative radiation therapy. All cases were followed up from the date of the surgical procedure to the date of mortality or the date patients were lost to follow-up. Clinical and histological data were reviewed (Table I).

Statistical analysis. All data were analyzed using SPSS software version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). Survival analysis was conducted and survival curves were constructed using the Kaplan-Meier method. Furthermore, the log-rank test was used to analyze the statistical differences and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Diagnosis and staging. The occurrence of only 11 cases of SDC in the head and neck during a 10-year period in a busy institution confirms the rarity of the cancer. In the current cohort, the male:female gender ratio was 7:4 and the mean age of the patients was 58.8 years. The parotid gland was the most commonly affected location (seven cases; 63.6%), followed by the submandibular gland (three cases; 27.3%) and the palate (one case; 9.1%). Furthermore, the majority of cases presented

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Table I. Patient and tumor characteristics.

Characteristic	Patients	
	n	%
Age, years		
38-60	6	54.5
≥61	5	45.5
Gender		
Male	7	63.6
Female	4	36.4
Mortality due to disease	2	18.2
Site		
Parotid gland	7	63.6
Submandibular gland	3	27.3
Palate	1	9.1
Nerve paralysis		
Yes	4	36.4
No	7	63.6
T stage		
1	2	18.2
2	2	18.2
3	2	18.2
4	5	45.5
N stage		
N0	5	45.5
≥N1	6	54.5
AJCC stage		
I	1	9.1
II	1	9.1
III	1	9.1
IV	8	72.7
Surgical margin		
Negative	10	90.9
Positive	1	9.1
Perineural spread		
Yes	5	45.5
No	6	54.5
Intravascular tumor emboli		
Yes	4	36.4
No	7	63.6
Neck dissection		
Yes	8	72.7
No	3	27.3
Post-operative radiation		
Yes	8	72.7
No	3	27.3
AR expression		
Negative	4	36.4
Positive	7	63.6
HER-2/neu expression		
Negative	2	18.2
Positive	9	81.8

Table I. Continued.

Characteristic	Patients, n	%
p16 expression		
Negative	5	45.5
Positive	6	54.5
p53 expression, %		
0-25	8	72.7
26-50	1	9.1
>50	2	18.2
Ki-67 expression, %		
0-25	6	54.5
26-50	4	36.4
>50	1	9.1
AJCC, American Joint Committee on Cancer; AR, androgen receptor; HER-2, human epidermal growth factor-2.		

with a painless mass in the early period of the disease, however, in the advanced stage, the majority of patients suffered from pain, and nerve paralysis was identified in four cases. All cases in the cohort were staged according to the American Joint Committee on Cancer (AJCC) staging system (8) and the majority (72.7%) of cases were determined to be stage IV. Six patients (54.5%) exhibited regional lymph node metastasis during routine neck dissection and only one patient exhibited a positive resection margin. In addition, 45.5 and 36.4% of patients presented with perineural spread and intravascular tumor emboli, respectively.

Treatment strategies. All cases were treated with local extensive resection, 72.7% of which simultaneously underwent neck dissection. Six patients (54.5%) exhibited an N stage of ≥N1, and all seven patients with tumors located in the parotid gland underwent parotidectomy, among which three cases were accompanied by resection of the facial nerve. Additionally, eight patients underwent post-operative radiation therapy of a moderate dose ranging between 50 and 60 Gy.

Immunohistochemistry. The results of the immunohistochemical analysis of the 11 samples are indicated in Table I. Examination of HER-2/neu protein expression revealed a high positivity rate of 81.8% (9/11 cases) in the examined tumor samples. Furthermore, androgen receptor (AR) expression was detected in seven of the tumor specimens (63.6%) and five cases (45.5%) were p16-negative. However, Ki-67 and p53 demonstrated >50% positive expression in only one and two cases, respectively (Fig. 1).

Follow-up. In the present study, the range for the follow-up period was 10-89 months and the mean overall survival time was 72.8 months. At the termination of the follow-up period, only two of the 11 cases had succumbed to the disease, while distant metastasis occurred in two patients, with the lung identified as the metastatic site.

Furthermore, the two-year overall survival rate was 75% according to Kaplan-Meier analysis (Fig. 2). The site of the

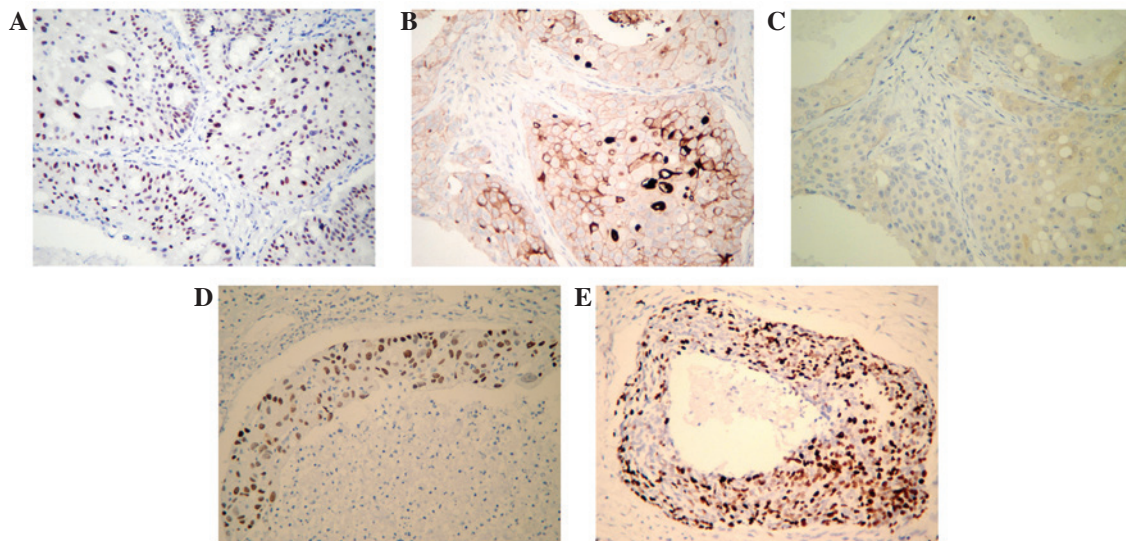


Figure 1. Immunohistochemistry demonstrating positive staining for (A) androgen receptor, (B) human epidermal growth factor-2/neu, (C) p16, (D) p53 and (E) Ki-67 (magnification, x200).

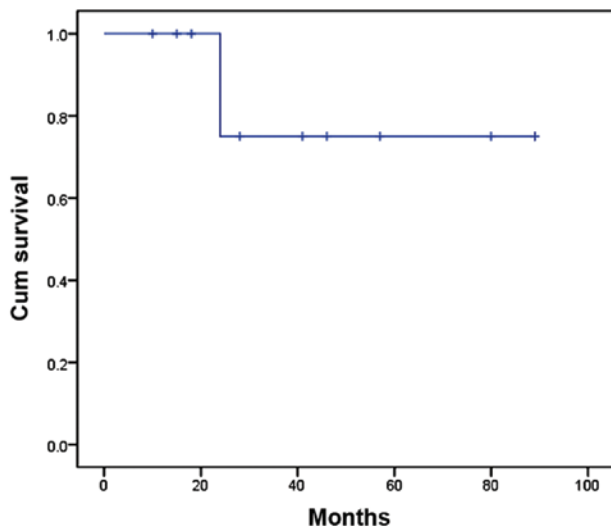


Figure 2. Overall survival of 11 patients with primary salivary duct carcinoma.

tumor ($P=0.049$) appeared to be significantly associated with a poor prognosis, whereas age, gender, nerve paralysis, post-operative radiation, T stage, N stage, AJCC stage, neck dissection, and expression of AR, Ki-67 and HER-2/neu did not appear to significantly affect the survival rate.

Discussion

SDC in the salivary gland region is a type of carcinoma that is histologically indistinguishable from mammary duct carcinoma, exhibiting intraductal and invasive components (2-5). SDC is rare and thus clinicians have relatively limited experience to aid in guiding the development of novel treatment strategies for the cancer. SDC has been reported to occur with a male predominance and an average age of onset of ≥ 50 years (2,6,7). The present study revealed similar results, with a preponderance of males and an average age

of 58.8 years. SDC typically presents with a painful or painless rapidly growing, firm tumor, and the symptom of nerve palsy is also common (1,2,9); in the present study, nerve palsy occurred in $>36\%$ of patients. Furthermore, the parotid gland was the most frequently involved site of SDC, followed by the submandibular gland, while only one case was located in the palate. These data are similar to those determined by previously conducted studies (2,3,5,6).

According to previous studies, SDC is typically characterized by aggressive behavior and a poor prognosis (2,3,5). Thus, the cases investigated in the present study were representative of typical SDC, as they demonstrated aggressive biological behavior. Furthermore, cervical lymph node involvement occurred in 54.5% of cases and nerve paralysis in 36.4%, and the majority of patients (72.7%) presented with AJCC stage IV disease. In addition, the incidence of intravascular tumor emboli and perineural spread were relatively high, at 36.4 and 45.5%, respectively.

For the majority of salivary malignancies at our institution, local tumor resection with a free surgical margin is a suitable treatment strategy, however, a more aggressive method is required for the treatment of SDC. For example, in the current cases from the Affiliated Hospital of Stomatology, the most commonly administered therapeutic strategy was local extensive resection with neck dissection. The present study evaluated the prognostic parameters for SDC and identified that the tumor site was a significantly predictive factor of SDC survival, whereas age, gender, nerve paralysis, post-operative radiation, T stage, N stage, AJCC stage, neck dissection, and the expression of HER-2/neu, AR and Ki-67 did not appear to significantly affect survival. Furthermore, SDC in the parotid glands was associated with an improved prognosis compared with that of the palate and submandibular gland. In the current series of patients, distant metastasis occurred in two patients, with the lung identified as the metastatic site. Distant metastasis is one of major clinical problems in the management of SDC and requires the development of a novel alternative strategy to the current treatment methods.

Notably, the present analysis determined a good short-term outcome for the patients with primary SDC, which was in disagreement with the findings reported in previous studies (2,3,6,7,10-13). Mortality in late-stage patients was 22.2% compared with 0% in early-stage patients with similar prognoses; however, N status did not appear to have a significant impact on the patient prognosis. The present findings differ from those of previous studies, in which an association was identified between tumor size/lymph node involvement and outcome (2,3,5,6,14). In the current study, it was identified that the two-year overall survival rate was 75% according to Kaplan-Meier analysis; only two patients succumbed to the disease within 24 months and no mortalities occurred during the two-year treatment period. The good prognosis in the present study may be attributed to the high number of patients administered with post-operative radiation (72.7%) and exhibiting negative surgical margins (10 cases). In validation of this proposal, a recent study demonstrated that post-operative radiotherapy was effective for SDC locoregional control (14); therefore, we hypothesize that complete resection combined with post-operative radiotherapy may be an effective treatment for SDC.

A number of previous studies demonstrated that HER-2/neu and p53 expression are statistically associated with SDC survival rates (3,15-20). However, in the present study, the protein expression levels of HER-2/neu, AR, Ki-67, p16 and p53 did not correlate with prognosis, although HER-2/neu, AR and p16 demonstrated a positive expression rate of >50%, which may contribute to the diagnosis for SDC.

The role of additional adjuvant therapy for SDC remains unclear. Due to the limited efficacy and severe complications of surgery and radiotherapy, a more systematic therapeutic approach should be analyzed in order to improve the prognosis of SDC. The present study demonstrated a high positivity rate for HER-2/neu and AR expression in SDC, indicating that SDC carcinogenesis may resemble that of breast ductal carcinoma or prostate cancer (4,7,11,13,15,18,21,22). As HER-2/neu blockers (trastuzumab) are effective in treating HER-2-overexpressing breast cancer, this agent may be useful for the treatment of SDC. Similarly, androgen deprivation therapy may be applied to the treatment of SDC. These two therapeutic strategies have achieved positive results in a small number of cases of head and neck SDC (11,15,22). Clinicians may expect monoclonal antibody treatments to be a promising adjuvant therapy for SDC, however, this field requires additional research prior to the application of such therapies.

In conclusion, the present study determined that SDC is a rare salivary malignancy with a peak incidence in the fifth and sixth decades of life, and a clear male preponderance. The parotid gland was the most commonly affected site and the majority of cases presented with a painless mass in the early stage of the disease. In the advanced stage, pain and nerve paralysis were common. All patients were treated with surgery and the majority underwent adjuvant post-operative radiotherapy. The range for the follow-up period was 10-89 months and the mean overall survival period was 72.8 months. At the completion of follow-up, only two of the 11 cases had succumbed to the disease, resulting in a two-year overall survival rate of 75% according to Kaplan-Meier analysis. Furthermore, the current data demonstrated that SDC in the parotid glands is

associated with a more positive prognosis compared with SDC in the palate and submandibular gland. However, the limitations of this study, which include its retrospective nature and the small sample size used, should be considered. The present study proposes that the development of a biological treatment strategy for SDC, targeting HER-2/neu or AR, may provide a more positive outcome for such patients.

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