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HEAD AND NECK

Management and outcome of salivary duct carcinoma in major salivary glands

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Abstract Salivary duct carcinoma (SDC) is a rare and aggressive malignancy with poor prognosis. Its histomorphology is distinctly reminiscent of the ductal carcinoma of the breast. We reviewed the treatment and outcome of SDCs at a single tertiary care centre. Twenty-five cases of SDC of major salivary gland origin, diagnosed and treated at the Department of Otolaryngology, Head and Neck Surgery, Helsinki University Central Hospital, Helsinki, Finland, during a 14-year period from 1997 to 2011, were reviewed retrospectively. Survival outcome was analyzed for 18 patients with a minimum follow-up of 24 months. There were 16 male (64 %) and 9 female (36 %) patients with a median age of 61 years (range 36–82 years). The majority of the cases occurred in the parotid gland ($n = 21$, 84 %) followed by the submandibular gland ($n = 4$, 16 %). The primary treatment consisted of surgical resection in all cases and 17 (68 %) patients also underwent neck dissection. Most of the patients ($n = 18$, 72 %) were treated with postoperative radiotherapy. Seven patients (28 %) had a disease recurrence within a median follow-up time of 15 months (range 3–27 months). In the group ($n = 18$) with a minimum follow-up time of 24 months, the 2- and 5-year overall and disease-specific survival rates were 66, 41 % and 75, 55 %, respectively. These results confirm the aggressive nature of SDCs in major salivary glands. Diagnostics and management of these tumours need to be centralized in experienced surgical Head and Neck Oncology Centres, and new treatment strategies should be investigated.

Keywords Head and neck cancer · Tumour grade · Survival · Surgery · Radiation

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Introduction

Salivary gland carcinomas (SDCs) are a histologically highly heterogenous group of malignancies. In Finland, they compose approximately 0.2 % of all human malignancies [1] and 4–6 % of them are SDCs [2].

Salivary gland carcinoma is an aggressive disease entity with a poor prognosis. The histological picture greatly resembles that of ductal carcinoma of the breast [3]. cERBB2 protein and its encoding gene HER-2/*neu* (human epidermal growth factor 2) are expressed in a large proportion of SDCs [4–8]. This characteristic occurs also in many cases of the ductal carcinoma of the breast, and the receptor antagonist of cERBB2 trastuzumab is used as a targeted therapy. Similarities of SDC with ductal carcinoma of the breast offer an interesting route to explore new

treatment modalities in addition to surgery and chemoradiation. So far, three cases of SDC with successful treatment using trastuzumab have been reported [9–11].

Due to the low incidence of SDC, there are only a limited number of reports on treatment outcome. Lewis et al. [12] studied 26 patients with SDC at the Mayo clinic in 1996. A similar study with 15 patients was performed by Hosal et al. [13] in Pittsburgh in 2003. The largest study by Jaehne et al. [6] presents clinical data of 50 patients. In these studies, 56–77 % of the patients presented with cervical lymph node metastasis at the time of diagnosis, and 51–77 % had died of tumour-related causes at the time of evaluation [6, 12, 13]. Development of locoregional recurrences (19–48 %) and distant metastases (43–48 %) has been frequent [6, 13, 14].

The purpose of this study was to analyze the treatment modalities used and the outcome of SDC at our institution during a 14-year period.

Materials and methods

A retrospective review was performed of all patients ($n = 25$) with SDC diagnosed and treated at the Department of Otolaryngology, Head and Neck Surgery, Helsinki University Central Hospital (HUCH), Helsinki, Finland, between January 1997 and January 2011. All original SDC diagnoses in the present study were reviewed and confirmed to be true SDCs by an experienced head and neck pathologist with special interest in salivary gland tumours (I.L.). The histopathologic diagnostic criteria at each time point were those of the respective most recent WHO classification (WHO, 1991 and WHO, 2005). The tumours were staged according to the International Union Against Cancer (UICC 2009, 7th edition) tumour-node metastasis (TNM) classification. Data on patient characteristics, clinical and histological features of the tumour, and treatment and outcome parameters were recorded. The study design was approved by the Institutional Research Ethics Board.

The dates and causes of death were provided by Statistics Finland. Overall survival (OS) was defined as the interval between the time of diagnosis and the last follow-up or death, and estimated using the Kaplan–Meier method. Only the patients ($n = 18$) with a minimum follow-up time of 24 months were included in the survival analyses. Statistical analyses were conducted using the SPSS software (Version 12.0.1, Chicago, IL, USA). A P value of less than 0.05 was considered statistically significant.

Results

The patient characteristics of 25 cases of SDC are presented in Table 1. Fifteen (60 %) out of 25 patients were otherwise healthy or had only minor comorbidities (hearing aid, mild hypertension and spinal stenosis) at diagnosis. Five patients (20 %) had a history of another malignancy (lung, cervix, colon, mammary, prostate and pancreas). A neck lump was the initial symptom for most of the patients ($n = 23$, 92 %) and the median time for disease history was 27 months (range 1–240 months). Two patients presented with facial nerve paresis. Nearly all patients ($n = 24$; 96 %) underwent ultrasound examination and fine needle biopsy of the tumour before planning their treatments. Cytological evaluation showed a malignancy ($n = 22$) or a suspicion of it ($n = 3$) in all cases. Other preoperative investigations were MRI ($n = 18$, 72 %), chest radiograph ($n = 11$, 44 %), CT scan of body/chest ($n = 10$, 40 %) and CT scan of neck ($n = 1$, 4 %).

T1 (40 %, $n = 10$) and T4a (36 %, $n = 9$) were the most common T classes. The average tumour size evaluated by pathologists was 23 mm (range 5–60 mm). One case was classified as a carcinoma in situ, probably originating from pleomorphic adenoma. Fourteen patients (56 %) had cervical lymph node metastasis. Only one patient had distant disease in spinal column at the time of diagnosis. More than half ($n = 14$, 56 %) of the patients presented with Stage IVA disease.

Table 1 Characteristics of patients with salivary duct carcinoma

Patient characteristics	Total $n = 25$
Male	16
Female	9
Median age (years)	61
Age range (years)	36–82
Tumour site	
Parotid gland	21
Submandibular gland	4
T-status	
Tis	1
T1	10
T2	5
T3	
T4a	9
N-status	
N0	11
N1	2
N2b	12
N3	
Tumour stage	
I	7
II	1
III	1
IVA	14
IVC	1

All the patients underwent surgery. Almost half (48 %, $n = 10$) of the patients with a tumour in the parotid gland underwent total or near total parotidectomy. Six patients (29 %) underwent radical parotidectomy including mastoidectomy and killing of the facial nerve. Superficial parotidectomy was performed on five patients (24 %), and based on the final histomorphology in two cases it was later (1–3 weeks) extended to total parotidectomy. Also, in all patients with submandibular gland involvement surgery was the primary treatment. In addition, 17 patients (68 %) underwent neck dissection. All cases were discussed at a multidisciplinary tumour board meeting for possible additional treatment after the primary surgery with the final histopathological data available. Eighteen patients (72 %) received postoperative radiotherapy and the most frequently administered dose on the operated area was 50–60 Gy. All the patients ($n = 7$) who did not receive postoperative radiation therapy presented with Stage I disease. Adjuvant chemotherapy was given to six of the patients.

Follow-up time varied from 5 months to 14 years. Disease recurrence was found in 7 patients (28 %) within a median follow-up time of 15 months (range 3–27 months). Three of these had locoregional failures in the parotid area and neck, and six had distant metastases. Bone ($n = 4$) was the most common site for metastasis followed by the lungs ($n = 3$). The 2- and 5-year disease-free survival (DFS) rates were 79 and 56 %, respectively. No correlation was found between disease recurrence and TNM classification of the primary tumour. All patients with disease recurrence had undergone surgery and postoperative radiotherapy. Adjuvant chemotherapy was primarily given to three of these patients.

Data on survival and on local and regional recurrences were available for all of the 25 patients. OS and disease-specific survival (DSS) of 18 patients with a minimum follow-up of 24 months were analyzed. In this group the 2- and 5-year OS rates were 66 and 41 %, respectively (Fig. 1). The 2- and 5-year DSS rates were 75 and 55 %, respectively (Fig. 2). DSS according to Stage distribution (Stage I vs. Stage IVa) is presented in Fig. 3.

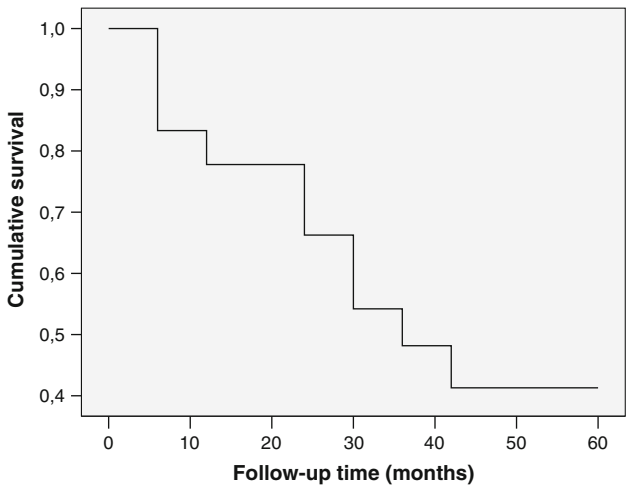

Fig. 1 Overall survival of 18 SDC patients with a minimum follow-up time of 24 months

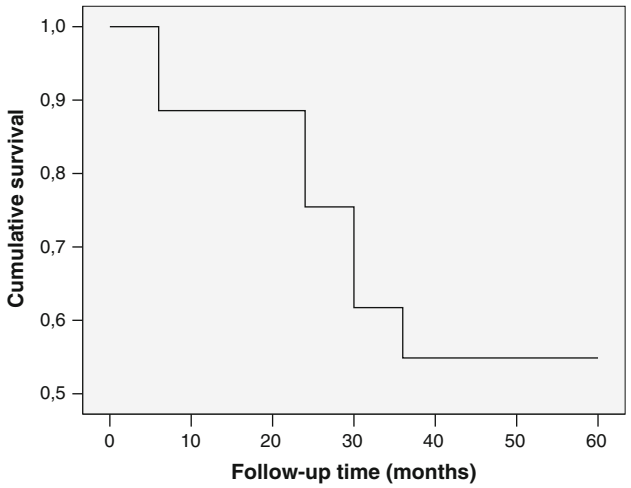

Fig. 2 Disease-specific survival of 18 SDC patients with a minimum follow-up time of 24 months

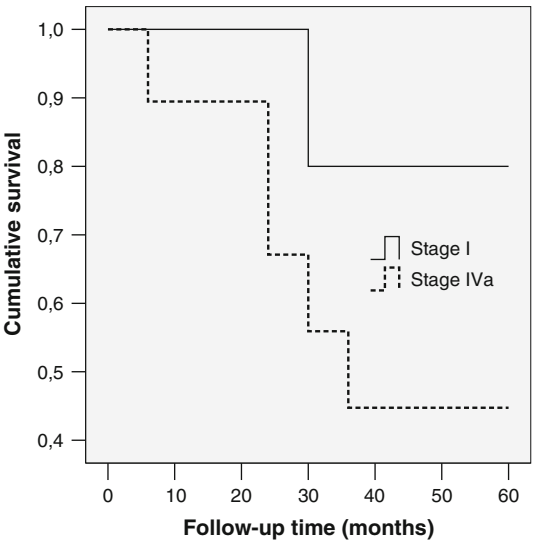

Fig. 3 Disease-specific survival in patients with Stage I and Stage IVa disease

Discussion

This is a single-institution review of 25 SDC patients treated during a 14-year period. Our results confirm the aggressive nature of this disease. Although the preoperative

investigations and the administered treatment were consistent with current guidelines for management of SDC, the prognosis of this particular patient group remains poor.

In accordance with earlier studies [6, 12–14], a typical patient in our series was a male in his later adulthood with a median age of 61 years. The tumour occurred most often in the parotid gland (84 %) and less frequently in the submandibular gland (16 %). None of the cases of SDC were found in minor salivary glands. The average history ranged from 1 month to several years. The patients typically (92 %) presented with a neck lump and the most common associated symptoms were facial nerve paresis (22 %) and pain (17 %). Two patients showed facial nerve paresis as the initial symptom, thus the total occurrence of facial palsy was 28 %. Guzzo et al. [14] reviewed 86 cases of SDC in the literature finding that the most common presenting sign of disease was a painless mass in the parotid area, and 29 % of the patients presented with facial nerve paresis. This is closely similar to the present results.

A total of 56 % of our patients had cervical lymph node metastasis and a Stage IVA disease. In previous studies, nodal involvement was found in more than 50 % of the patients [6, 13, 14] and the primary tumour was most often more than 2 cm in the greatest dimension [4, 6, 13–15]. In the present study the median size of the tumour was 2.3 cm with 56 % classified as T2 or higher. SDC may also develop in a pleomorphic adenoma [6, 13, 14, 16] as was encountered in one patient in our series.

Surgery and postoperative radiation therapy are still the main treatment modalities of SDC. In the present series, all primary tumours were operated and 68 % of the cases underwent neck dissection. Eight patients with N0 disease underwent only resection of the primary tumour and the parotid gland. Postoperative radiation therapy was given to 72 % of patients. This treatment was congruent with the Finnish National Guidelines for treatment of salivary gland cancer, but nevertheless the patient outcome remained poor. Almost one-third (28 %) of the patients developed a recurrence of their disease. The 2- and 5-year DFS rates were 79 and 56 %, respectively. This corresponds well to the reported survival outcome for salivary gland cancers in general. Feinstein et al. [24] analyzed the outcome of 74 patients with locally advanced salivary gland cancers registered in the University of Pittsburgh database from 1990 to 2006. These patients were treated with surgery and postoperative radiation therapy and 45 % of them experienced disease recurrence. The probability of 5-year DFS was 49 % and the 5-year OS was 55 %. In our study the 2- and 5-year OS rates were 66 and 41 %, respectively, and the DSS rates were 75 and 55 %, respectively. The reported survival rates for SDC are even poorer. Approximately 44–77 % of patients with SDC have died of disease-related causes [6, 12–14, 19] and the 5-year OS rates have been 20–44 % [19, 23]. Therefore, the importance of a consistent treatment protocol including at least radical resection of the primary tumour, neck dissection and postoperative radiation therapy has been emphasized [6, 13, 14, 23]. Our results further support these recommendations.

The recent literature regarding the management of SDC has focused on the immunohistological and molecular characteristics of the tumour. This is due to the histomorphological resemblance between SDC and the ductal carcinoma of the breast, and the frequent expression of HER-2 oncoprotein. These cancers frequently have amplification of the HER-2/*neu* oncogene and they overexpress the epidermal growth factor receptor (EGFR) [25]. HER-2/*neu* is a protooncogene located on chromosome 17q. Amplification of HER-2/*neu* and overexpression of its protein product occurs also in breast cancer. Although the histomorphology of SDC shows similarities with the ductal carcinoma of the breast, SDC usually lacks oestrogen and progesterone receptors, but is almost uniformly positive for androgen receptors [7, 15, 17–19]. Both the similarity with breast carcinoma and the expression of androgen receptors have been assessed for new treatment modalities [9–11, 20, 21]. Some reports have evaluated other cell cycle regulators and oncogenes [4, 6, 22, 23]. However, there is currently no evidence for these factors as prognosticators or as targets for future treatment modalities.

There is no widely tested standard chemotherapy regimen for the treatment of advanced or metastatic SDC. Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of the HER-2 tyrosine-kinase receptor and is widely used both in adjuvant postoperative treatment of breast cancer and in the treatment of metastatic breast cancer. The overexpression of HER-2 may provide a rationale for targeted therapy with trastuzumab also in SDC. A recent study by Williams et al. [8] suggested that overexpression of HER-2 and its gene amplification defines a group of patients who may benefit from targeted therapy with trastuzumab. In the same study, mutations also in exons 18 and 19 of the EGFR gene were detected suggesting that tyrosine-kinase inhibitors such as erlotinib may provide targeted therapeutic options in a subset of SDC patients [8]. However, a recent review regarding current management options for salivary gland cancers emphasizes a more sophisticated approach needed for useful clinical applications of the targeted therapy [25–27].

The rarity of SDC makes it difficult to conduct clinical studies aiming to develop optimal combinations of surgery, radiation, targeted cancer therapies and chemotherapy. The combinations of trastuzumab and chemotherapy found to be effective in breast cancer should probably be tested also in the management of SDC based on the biological

similarity of these two tumours. Diagnostics and management clearly need to be centralized in experienced multidisciplinary Head and Neck Oncology Centres, and new treatment strategies for SDC should be developed.

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Conflict of interest None.

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