Oral Oncology 74 (2017) 40–48

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Salivary duct carcinoma: An aggressive salivary gland malignancy with opportunities for targeted therapy

Nicole C. Schmitt[a,b,*], Hyunseok Kang[c], Arun Sharma[d]

[a] Integrative Therapeutics Program, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, United States
[b] Department of Otolaryngology – Head and Neck Surgery, Johns Hopkins University, Bethesda, MD, United States
[c] Department of Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD, United States
[d] Division of Otolaryngology – Head and Neck Surgery, Southern Illinois University, Springfield, IL, United States

ARTICLE INFO

Keywords:
Salivary duct carcinoma
Salivary malignancy
ErbB2

ABSTRACT

Salivary duct carcinoma (SDC) is a rare, aggressive salivary malignancy that is often diagnosed at an advanced stage. Previously, little was known about outcomes of this disease due to its rarity. In the past several years, much has been learned about salivary duct carcinoma after publication of outcomes from several large single-institution series and national database searches. Recent studies of genomic alterations have helped elucidate the biology and pathogenesis of this aggressive disease. Here we review outcomes of the disease, effects of treatment, prognostic factors, and genomic alterations in SDC. Studies of targeted therapy and promising future directions are also discussed.

Introduction

Salivary duct carcinoma (SDC) was originally described by Kleinsasser and colleagues in 1968 as a salivary malignancy that histologically resembles ductal carcinoma of the breast [1]. It occurs more commonly in the parotid gland than in the submandibular or minor salivary glands [2–6]. SDC has a propensity to metastasize early to regional lymph nodes and distant sites, as well as a high rate of recurrence [3–5,7–12]. The mainstay of therapy includes surgery and radiation; use of systemic therapy has been explored in some case series and small clinical trials [9,13,14]. Survival is poor, with most patients surviving only about three years after diagnosis [7,12,15–17].

Epidemiology

SDC is most frequently seen in men aged 50 or older [4,6,16,18,19] and is one of the more rare malignant salivary tumors. In one series of all salivary gland cancers during a 5-year period in Finland, it was estimated that 4–6% were SDC [20]. A review of the SEER Medicare Database found that SDC comprised 1.8% of all major salivary gland cancers included in the database [19].

Histopathologic features

Though described as early as 1968, SDC was only recognized as a distinct tumor type by the World Health Organization in 1991 [21]. Prior to this time, SDC was not frequently diagnosed, possibly due to limited awareness of its existence as a separate histologic entity. Studies on the histopathologic features of this tumor have helped considerably to distinguish it from other salivary malignancies, and as a result SDC may be less rare than originally thought. SDC specimens show high-grade apocrine/ductal morphology [22]. Specimens commonly demonstrate papillary-cribriform growth patterns, with areas of pleomorphism and necrosis [21]. Papillary/micropapillary, sarcomatoid, mucinous, oncocytic, and basaloid morphologic variants have been described but are rare [6,22,23]. Another variant with a low grade histologic pattern and relatively indolent growth has also been described [24,25], which is often mistaken for low-grade acinic cell carcinoma or mammary analog secretory carcinoma [25]. The detection of androgen receptors, expressed in the vast majority of SDC tumors, can be critical in distinguishing SDC from other tumor types [21,22,26].

Interestingly, a high proportion of SDC tumors are found within a benign pleomorphic adenoma; SDC tumors that are also classified as carcinoma ex pleomorphic adenoma may be frequent, with studies reporting evidence of prior pleomorphic adenoma in 20–70% of SDCs [7,11,27,28]. An encapsulated, in situ form of SDC has also been

* Corresponding author at: National Institute on Deafness and Other Communication Disorders, National Institutes of Health, 10 Center Drive, Room 7N240B, Bethesda, MD 20892, United States.
E-mail addresses: Nschmit4@jhmi.edu, Nicole.schmitt@nih.gov (N.C. Schmitt).

http://dx.doi.org/10.1016/j.oraloncology.2017.09.008
Received 20 June 2017; Received in revised form 16 August 2017; Accepted 12 September 2017

Table 1
Survival and patterns of failure in SDC across studies. Only studies with at least 10 patients were included in the above table.

Study	Sample size[a]	Median duration of follow-up, months	DFS	OS[b]	Site(s) of failure
Lewis et al. [16]	n = 26			Mean: 36 months	Local: 35% Distant: 62%
Guzzo et al. [9]	n = 26	36 (mean)		2 year: 42% 5 year: 12%	Local: 12% Regional: 27% Distant: 46%
Hosal et al. [10]	n = 15	34 (mean)		43%	Local: 21% Distant: 43%
Jaehne et al. [4]	n = 50	96		Average:[c] 56 months	Local: 48% Regional: 8% Distant: 48%
Williams et al. [40]	n = 59	30		2 year: 62% 5 year: 20%	
Roh et al. [47]	n = 21			5 year: 44%	
Ko et al. [64]	n = 30	37	3 year: 39%	3 year: 47%	Local: 40% Regional: 27% Distant: 50%
Kim et al. [5]	n = 35	43	5 year: 47%	5 year: 55%	Local: 16% Regional: 26% Distant: 38%
Piao et al. [31]	n = 35			5 year: 14%	
Salovaara et al. [45]	n = 25		2 year: 79% 5 year: 56%	2 year: 66% 5 year: 41%	Locoregional: 12% Distant: 24%
Shinoto et al. [32]	n = 25		5 year: 45%	5 year: 47%	Local: 28% Regional: 16% Distant: 32%
Jayaprakash et al. [19]	SEER database; n = 228			10 year: 42% Median: 79 months	
Kim et al. [14]	n = 15	38		4 year: 93%	Local: 13% Distant: 47%
Ku et al. [61]	n = 48	48		Median: 76 months	Locoregional: 17%
Roh et al. [46]	n = 56	71		5 year: 42% Median: 48 months	Local: 13% Regional: 16% Distant: 63%
Han et al. [15]	n = 28	63	3 year: 38%	3 year: 78%	Locoregional: 29% Distant: 50%
Huang et al. [18]	n = 11			2 year: 75%	
Masubuchi et al. [33]	n = 32	22	2 year: 51%	2 year: 73%	
Nakashima et al. [34]	n = 26	26	3 year: 54%	3 year: 48%	
Breinholt et al. [2]	Danish national database; n = 34	29		2 year: 58% 5 year: 32% 10 year: 27%	Locoregional: 42% Distant: 52%
Gilbert et al. [7]	n = 75	55	Median: 32 months	Median: 37 months	
Johnston et al. [11]	n = 54	68		5 year: 43%	Local: 17% Regional: 18% Distant: 52%
Luk et al. [6]	n = 23	26	5 year: 36%		
Mifsud et al. [12]	n = 17	37	3 year: 63% Median: 49 months		Distant: 65%
Otsuka et al. [35] and Kawatika et al. [37]	Multi-institutional; n = 141	36	3 year: 38%	3 year: 71%	Local: 9% Regional: 13% Distant: 39%

Abbreviations: DFS: disease free survival; OS: overall survival; SDC: salivary duct carcinoma; SEER: Surveillance, Epidemiology, and End Result
[a] All studies were single institution studies, unless otherwise specified
[b] If a time point is not specified, then survival at last follow-up is displayed.
[c] It was not specified in the study whether the average was mean or median.

described, characterized by lack of capsular invasion. This in situ variant, usually occurring within a pleomorphic adenoma, is often less aggressive than typical cases of SDC [23,26,29]. Griffith and colleagues characterized 117 cases of SDC ex pleomorphic adenoma and found that while most were widely invasive with aggressive clinical behavior and poor survival, the five patients who had intracapsular SDC ex pleomorphic adenoma had a more indolent course with no disease progression [30].

Many patients present with advanced T stage (i.e. T3 or T4), with figures ranging from 35-74% [2,4–7,9,11,12,14,15,18,22,31–38]. Two separate National Cancer Data Base (NCDB) studies, each with over 400 patients, found that 40–42% of patients presented with advanced T stage [36,38]. However, analyses of multi-institutional data in Japan revealed an advanced T stage incidence of 65–66% [35,37].

The risk of pathologic N+ disease ranges from 47 to 83% in the literature [2,4–10,12,14–16,18,19,22,31–40]. However, analyses using national databases or multiple institutions described an N+ incidence of 47–56% [2,19,35–38]. In a National Cancer Data Base (NCDB) analysis of 22,653 patients with parotid malignancies, the risk of N+ disease and occult nodal disease were 54% and 24%, respectively, for patients with SDC, higher than that seen for any other parotid gland pathologies (mean for all parotid malignancies: 24% and 10%, respectively) [36]. Among patients with SDC, tumor size (> 3 cm) and histologic grade have been identified as risk factors for nodal involvement [19,36].

Perineural invasion (PNI) and lymphovascular invasion (LVI) are