Journal of Cancer Research and Clinical Oncology (2019) 145:1055–1062
https://doi.org/10.1007/s00432-019-02876-5

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Lymph node ratio predictive of recurrence, distant metastasis, and survival in submandibular gland carcinoma patients

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Received: 22 January 2019 / Accepted: 22 February 2019 / Published online: 26 February 2019

Abstract

Purpose Submandibular gland (SMG) carcinoma has an unfavorable clinical course and a low survival rate. Specific tumor and nodal findings might help predict posttreatment recurrence and survival in SMG carcinoma patients. This study evaluated factors predictive of posttreatment recurrence and survival in SMG carcinoma patients.

Methods This study enrolled 99 consecutive patients with previously untreated SMG carcinoma. All patients underwent tumor and metastatic lymph node resection along with or without radiation/chemo-radiation. The predictive clinical and pathological factors for disease-free survival (DFS), distant metastasis–free survival (DMFS), disease-specific survival (DSS), and overall survival (OS) were determined using univariate and multivariate Cox proportional hazards regression analyses.

Results The median tumor size was 2.7 cm and 53 patients (53.5%) had high-grade tumors. The rates of initial nodal and distant metastasis at initial presentation or follow-up were 45.5% and 42.4%, respectively. The actuarial 5-year DFS, DMFS, DSS, and OS rates were 46.4%, 55.9%, 61.5%, and 59.7%, respectively. The independent factors associated with poor DFS, DMFS, DSS, and OS outcomes (all $p < 0.05$) were T3–T4 classification and lymph node ratio. A histological high-grade tumor was an independent prognostic factor predictive of poor DMFS, DSS, and OS outcomes (all $p < 0.05$).

Conclusions A high rate of distant site failure is associated with SMG carcinoma, resulting in a poor survival rate. Lymph node ratio might help predict recurrence, distant metastasis, and death due to SMG carcinoma.

Keywords Submandibular gland carcinoma · Prognostic factors · Survival · Lymph node · Metastasis

Introduction

Salivary gland cancer is a rare type of cancer and accounts for < 0.5% of all cases of malignancy and 3–5% of all head and neck cancers (Pinkston and Cole 1999; Speight and Barrett 2002; Suh and Cho 2016). Salivary gland cancer originates in the parotid, submandibular, and sublingual major salivary glands and in other minor salivary glands in the head and neck. The World Health Organization (WHO) recognizes diverse pathologies and 22 histological subtypes of salivary gland cancer, each with a different metastatic potential and clinical course (Thompson 2006; El-Naggar et al. 2017).

Regional and distant site metastasis of salivary gland cancer is an important poor prognostic indicator posttreatment (Ali et al. 2014). Additionally, salivary gland cancer metastasizes more to distant sites than other head and neck cancers, with an occurrence rate of ~ 20% (Ali et al. 2015). Approximately 80% of all salivary gland cancers originate in the parotid gland, whereas only 5–15% originate in the submandibular gland (SMG) (Thompson 2006; El-Naggar et al. 2017). SMG and sublingual gland carcinomas show a high propensity for metastasis: SMG (20–25%) and sublingual gland (> 90%) (Pinkston and Cole 1999; Aro et al. 2018b).

Surgery remains the main treatment strategy for all salivary gland cancers. Radiotherapy is considered a postoperative adjuvant treatment strategy for reducing locoregional disease recurrence without survival gain from combined chemotherapy (Noh et al. 2010; Amini et al. 2016).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00432-019-02876-5) contains supplementary material, which is available to authorized users.

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However, SMG carcinoma has a high propensity for regional and distant site metastases; hence, survival is poor (Roh et al. 2008). Therefore, further identification of prognostic factors as well as development of new treatment strategies is required.

The tumor node metastasis (TNM) staging system proposed by the American Joint Committee on Cancer (AJCC) has changed considerably, particularly with regard to nodal classification including extranodal extension for increased discrimination of survival outcomes in salivary gland cancer patients (Lydiatt et al. 2017). The evaluation of prognostic factors for SMG carcinoma is relatively difficult because of its rarity and various histological subtypes. Therefore, herein, we hypothesized that variables related to metastatic lymph nodes (LNs) influence posttreatment recurrence and survival in SMG carcinoma patients. Therefore, we evaluated prognostic factors predictive of recurrence, distant metastasis, and survival in a relatively large SMG carcinoma cohort.

Materials and methods

Patients

We used electronic medical records to find SMG carcinoma patients at our hospital between January 1990 and December 2015. Only patients who underwent surgery for previously untreated SMG carcinoma were included in the study. Patients with a history of previous treatment or recurrent SMG carcinoma, those who underwent palliative treatment alone without surgical extirpation of locoregional disease, and/or those with early loss < 2 years after surgery were excluded. Therefore, the final number of patients included in the study was 99. The tumors were staged according to AJCC's TNM staging system (7th edn.). The study was reviewed and approved by the institutional review board of our hospital, and informed consent from all patients was waived.

All 99 patients underwent tumor and metastatic node resection along with or without radiation/chemo-radiation. On the basis of tumor pathology and grade, surgery involved wide resection of locoregional disease and neck dissection for the removal of LNs clinically involved in or at high risk of occult metastasis. Neck dissection involved cervical I–III (cN0) or I–V levels (cN+). In four patients with clinical evidence of contralateral neck metastasis, ipsi- and contralateral neck dissections were simultaneously performed. Patients with adverse pathological findings (e.g., nodal metastasis, involved margin, high-grade pathology, and perineural or lymphovascular invasion ['National Comprehensive Cancer Network (NCCN)]. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version I. 2018; Fort Washington, PA, 2018.') underwent postoperative external beam or intensity-modulated median 64 Gy (range 45–72 Gy) radiotherapy in a daily fraction of 1.8–2.0 Gy five times a week. Median time elapsed from the date of surgery to the first date of irradiation was 42 days (range 29–68 days). Additionally, patients with lung-disseminated diseases underwent cisplatin-based chemotherapy.

All patients were followed up at an outpatient clinic every 1–3 months in year 1, 2–4 months in year 2, 6 months in years 3–5, and annually thereafter (Denaro et al. 2016). Any suspicion of locoregional disease recurrence on examination and imaging was confirmed by biopsy. Distant site recurrence was confirmed by biopsy or, if biopsy was not available, serial follow-up imaging.

Variables

The following patient demographic data were collected: age (> 60 years), sex, smoking status (> 20 pack-years), alcohol use (≥ 1 drink/day), and Charlson comorbidity index (≥ 1). Other data such as pathological tumor size (≤ 2, 2.1–4, > 4 cm), histological grade (G1/G2/G3: well/moderate/high grade), extraparenchymal extension, perineural invasion, lymphovascular invasion, surgical margins involved, and radiotherapy were also included. T and N classifications and overall TNM stages were noted, in addition to the pathological findings of LNs: presence of metastasis, number of positive LNs, lymph node ratio (LNR) (i.e., number of positive LNs divided by number of harvested LNs) (Hong et al. 2015; Suzuki et al. 2015; Denaro and Merlano 2018; Zheng et al. 2018) and extranodal extension (ENE).

Statistical analysis

Herein, continuous variables were expressed as median and range, and categorical variables were expressed in numbers and percentages. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of recurrence at any site, and distant metastasis–free survival (DMFS) was defined as the time from the date of surgery to either the date of recurrence at a distant site or the date of the last visit. Disease-specific survival (DSS) was defined as the time from the date of surgery to the date of death due to SMG carcinoma, and overall survival (OS) was defined as the time from the date of surgery to either the date of death due to any cause or the date of the last visit. The cutoff values of the optimal number of positive LNs or the LNR were determined using receiver operating characteristic (ROC) curve analysis and estimates of the area under the curve (AUC) for OS events (Heagerty et al. 2000). Univariate Cox proportional hazards regression analysis was performed to evaluate the prognostic factors associated with survival. Multivariate models of Cox proportional hazard regression were adjusted for clinical and pathological variables with p values of < 0.1 in univariate analyses. Multivariate Cox proportional hazards regression analysis was performed using backward stepwise selection with all the clinically significant variables. Kaplan–Meier and log-rank tests were used to determine survival and statistical significance, respectively. $p < 0.05$ was considered to be statistically significant. All the statistical tests were two-tailed tests. Statistical analyses were performed using SPSS version 24.0 (IBM, Chicago, IL, USA).

Results

Patient characteristics

Of the 99 patients in this study, 60 were men (60.6%) and 39 were women (39.4%). Their median age was 55 years (range 11–82 years). Table 1 summarizes the patients' clinical and pathological data. The median tumor size was 2.7 cm (range 0.5–11.5 cm), and 53 patients (53.5%) had high-grade tumors. The most frequent cancers were adenoid cystic carcinomas ($n = 29$, or 29.3%), followed by salivary duct carcinomas ($n = 22$, or 22.2%), carcinoma ex pleomorphic adenoma (CXPA; $n = 16$, or 16.2%), mucoepidermoid carcinomas ($n = 11$, or 11.1%), and other types of cancers (see Supplementary Table S1).

We found extraparenchymal extension in 67 patients (67.7%), perineural invasion in 50 patients (50.5%), lymphovascular invasion in 35 patients (35.4%), and surgical margins involved in 34 patients (34.3%). The tumor stages were T3–T4 in 39 patients (39.4%), N+ (positive LNs) in 45 patients (45.5%), and ENEs in 24 patients (24.0%). Median (range) numbers of excised LNs and positive LNs were 22 (3–127) and 0 (0–68), respectively. Median LNR was 0 (range 0–1.00). Of the 99 patients, 69 (70%) underwent postoperative radiotherapy (PORT) and 10 (10%) underwent concomitant chemotherapy. Of the 29 patients with adenoid cystic carcinomas, 5 with initial lung metastasis underwent complete resection of locoregional disease, followed by radiotherapy and systemic chemotherapy. These patients with initial M1 were excluded in the analyses of DFS and DMFS.

The median follow-up period of the surviving patients was 65 months (range 24–269 months). At the last follow-up, 39 patients (39.4%) were alive and disease free, 40 (40.4%) died due to SMG carcinoma, 8 (8.1%) died due to other causes, and 12 (12.1%) were alive with SMG carcinoma. During follow-up, we found recurrence in 56 patients (56.6%): 13 (13.1%) in primary sites, 9 (9.1%) in regional sites, and 42 (42.4%) in distant sites, with overlap of recurrent sites in some patients. The 5-year DFS, DMFS, DSS, and OS rates were 46.4%, 55.9%, 61.5%, and 59.7%, respectively.

Table 1 Patient characteristics ($n = 99$)

Variable	n (%)
Age (years), median (range)	55 (11–82)
Sex, men	60 (60.6)
Smoking, > 20 pack-years	31 (31.3)
Alcohol, ≥ 1 drink/day	39 (39.4)
Charlson comorbidity index, ≥1	31 (31.3)
Size of tumor (cm), median (range)	2.7 (0.5–11.5)
Histological grade, G1/G2/G3	25/21/53 (25.3/21.2/53.5)
Extraparenchymal extension	67 (67.7)
Perineural invasion	50 (50.5)
Lymphovascular invasion	35 (35.4)
Surgical margin, involved	34 (34.3)
T category, T3–T4	39 (39.4)
No. of positive LNs, median (range)	0 (0–68)
LN ratio	0 (0–1.00)
Follow-up duration, median (range)	65 (24–269)
5-year DFS, % (SE)	46.4 (5.3)
5-year DMFS, % (SE)	55.9 (5.6)
5-year DSS, % (SE)	61.5 (5.2)
5-year OS, % (SE)	59.7 (5.2)

Variables are expressed as numbers (percentages), unless otherwise indicated

DFS disease-free survival, *DMFS* distant metastasis–free survival, *DSS* disease-specific survival, *G1/G2/G3* well/moderate/high grade, *LN* lymph node, *N+* positive lymph node (at initial presentation), *OS* overall survival, *SE* standard error

Factors predictive of recurrence, distant metastasis, and survival

The cutoff values of the number of positive LNs and the LNR were set at 4 and 0.15, respectively, with AUC values of 0.75 (range 0.65–0.85) and 0.78 (range 0.68–0.88), respectively (both $p < 0.001$). Univariate Cox proportional hazards regression analysis showed significant association of tumor size (> 4 cm), histological grade (G3), extraparenchymal extension, lymphovascular invasion, surgical margins involved, T3–T4 classification, N + stage, overall III–IV stages, number of positive LNs (≥ 4), LNR, and ENEs with all the DFS, DMFS, DSS, and OS outcomes (all $p < 0.05$) (see Table 2). Age (> 60 years) was a significant factor predictive of OS outcomes ($p = 0.042$).

Multivariate Cox proportional hazards regression analysis showed that T3–T4 classification and LNR (> 0.15) are independent factors associated with poor DFS, DMFS, DSS, and OS outcomes (all $p < 0.05$) (see Table 3). Histological grade (G3) was also found to be an independent factor predictive of poor DMFS, DSS, and OS outcomes (all $p < 0.05$). Figure 1 shows the representative curves of DFS and DSS based on different categorical values of the histological grade, T classification, and LNR.

Table 2 Univariate Cox proportional hazards regression analysis of factors of recurrence, distant metastasis, and survival

Variable	DFS		DMFS		DSS		OS	
	HR (95% CI)	p^a	HR (95% CI)	p^a	HR (95% CI)	p^a	HR (95% CI)	p^a
Age, > 60/≤60 years	1.53 (0.88–2.64)	0.131	1.75 (0.94–3.27)	0.079	1.48 (0.78–2.80)	0.230	1.83 (1.02–3.27)	0.042
Sex, male/female	1.06 (0.62–1.82)	0.825	1.24 (0.66–2.34)	0.500	1.08 (0.57–2.06)	0.820	1.14 (0.63–2.05)	0.673
Smoking, > 20/≤20 pack-years	1.29 (0.73–2.28)	0.392	1.36 (0.70–2.62)	0.363	1.29 (0.65–2.53)	0.468	1.55 (0.83–2.91)	0.171
Alcohol, ≥ 1/0 drink/day	1.02 (0.59–1.75)	0.941	1.14 (0.60–2.16)	0.682	1.04 (0.54–2.00)	0.901	1.04 (0.57–1.91)	0.891
Charlson comorbidity index, ≥ 1/0	1.29 (0.74–2.23)	0.366	1.04 (0.54–2.00)	0.916	1.12 (0.57–2.17)	0.746	1.22 (0.67–2.24)	0.517
Tumor size, ≤ 2 cm	1		1		1		1	
2.1–4 cm	1.10 (0.56–2.14)	0.789	1.56 (0.69–3.51)	0.283	1.10 (0.46–2.60)	0.832	1.18 (0.55–2.54)	0.668
>4 cm	3.11 (1.51–6.43)	0.002	3.31 (1.34–8.19)	0.010	3.75 (1.60–8.81)	0.002	3.39 (1.54–7.43)	0.002
Histological grade, G1	1		1		1		1	
G2	1.41 (0.56–3.59)	0.468	2.95 (0.78–11.17)	0.110	0.99 (0.22–4.43)	0.832	0.49 (0.13–1.86)	0.295
G3	4.28 (1.96–9.35)	< 0.001	9.47 (2.85–31.49)	< 0.001	6.91 (2.41–19.84)	< 0.001	4.51 (2.05–9.92)	< 0.001
Extraparenchymal extension, yes/no	2.17 (1.16–4.05)	0.015	2.78 (1.28–6.03)	0.009	3.07 (1.28–7.35)	0.012	2.80 (1.30–6.00)	0.008
Perineural invasion, yes/no	1.54 (0.91–2.63)	0.111	2.65 (1.35–5.18)	0.004	1.76 (0.93–3.33)	0.084	1.50 (0.84–2.67)	0.169
Lymphovascular invasion, yes/no	2.31 (1.36–3.94)	0.002	2.59 (1.40–4.79)	0.002	3.79 (1.99–7.22)	< 0.001	3.17 (1.77–5.66)	< 0.001
Surgical margin, involved/no	2.35 (1.38–4.03)	0.002	2.93 (1.58–5.43)	0.001	3.08 (1.63–5.81)	0.001	2.38 (1.34–4.22)	0.003
T classification, T1	1		1		1		1	
T2	1.23 (0.56–2.72)	0.608	1.74 (0.63–4.79)	0.284	1.21 (0.42–3.50)	0.731	1.25 (0.51–3.06)	0.621
T3	3.05 (1.36–6.81)	0.007	3.99 (1.42–11.18)	0.009	3.23 (1.17–8.94)	0.024	2.68 (1.10–6.56)	0.031
T4	5.17 (2.01–13.35)	0.001	8.11 (2.59–25.38)	< 0.001	7.38 (2.37–22.96)	0.001	6.34 (2.24–17.98)	0.001
N classification, N0	1		1		1		1	
N1	2.68 (1.08–6.65)	0.034	3.48 (1.24–9.74)	0.018	4.06 (1.45–14.59)	0.009	3.08 (1.03–9.22)	0.044
N2	3.60 (2.03–6.41)	< 0.001	4.70 (2.37–9.31)	< 0.001	5.23 (2.53–10.83)	< 0.001	4.07 (217–7.63)	< 0.001
Overall TNM stage, I	1		1		1		1	
II	1.11 (0.33–3.80)	0.865	1.59 (0.31–8.20)	0.580	1.89 (0.20–18.20)	0.584	1.24 (0.31–4.96)	0.766
III	3.79 (1.23–11.68)	0.020	4.65 (0.98–22.01)	0.052	7.77 (0.97–62.28)	0.054	3.03 (0.82–11.24)	0.097
IVA	5.62 (1.95–16.23)	0.001	9.29 (2.16–39.94)	0.003	15.20 (2.04–113.12)	0.008	6.27 (1.87–21.00)	0.003
IVC	–		–		20.04 (2.23–180.45)	0.008	8.37 (1.84–38.09)	0.006
No. of positive LNs, 0	1		1		1		1	
1–3	2.08 (0.95–4.53)	0.066	2.46 (0.99–6.09)	0.052	2.93 (1.09–7.90)	0.034	2.04 (0.80–5.20)	0.134
≥4	3.95 (2.18–7.16)	< 0.001	5.13 (2.56–10.28)	< 0.001	5.41 (2.62–11.19)	< 0.001	4.48 (2.36–8.50)	< 0.001
LN ratio, > 0.15/≤0.15	3.87 (2.24–6.70)	< 0.001	4.43 (2.36–8.34)	< 0.001	6.27 (3.21–12.23)	< 0.001	5.46 (2.98–9.98)	< 0.001
Extranodal extension, yes/no	3.22 (1.80–5.78)	< 0.001	3.91 (2.01–7.59)	< 0.001	3.73 (1.92–7.23)	< 0.001	3.55 (1.89–6.68)	< 0.001
PORT, yes/no	1.24 (0.66–2.31)	0.510	1.96 (0.86–4.45)	0.107	1.38 (0.67–2.84)	0.380	1.45 (0.75–2.80)	0.268

CI confidence interval, *DFS* disease-free survival, *DMFS* distant metastasis–free survival, *DSS* disease-specific survival, *HR* hazard ratio, *TNM* tumor node metastasis, *LN* lymph node, *OS* overall survival, *PORT* postoperative radiotherapy

[a]Univariate Cox proportional hazards regression analysis

Discussion

Salivary gland cancers originate mostly in the parotid gland. SMG carcinoma is a rare disease, accounting for only 20 of 1403 (1.4%) patients with salivary gland cancers reported in a single center in the United Kingdom (Renehan et al. 1996). SMG carcinoma is also accounting for only 1.4–11% of salivary gland cancers and 30–54% of SMG tumors are malignant (Renehan et al. 1996; Barnes 2005; Thompson 2006; El-Naggar et al. 2017). A few retrospective studies

Table 3 Multivariate Cox proportional hazards regression analysis of factors of recurrence, distant metastasis, and survival

Variable	DFS		DMFS		DSS		OS	
	HR (95% CI)	p^a	HR (95% CI)	p^a	HR (95% CI)	p^a	HR (95% CI)	p^a
Histological grade, G3/G1–G2	1.96 (0.94–4.08)	0.071	3.29 (1.35–8.02)	0.009	3.30 (1.18–9.24)	0.023	3.02 (1.27–7.22)	0.013
T classification, T3–T4/ T1–T2	2.75 (1.48–5.12)	0.001	2.37 (1.12–5.00)	0.024	2.96 (1.34–7.80)	0.008	2.68 (1.34–5.36)	0.005
LN ratio, > 0.15/≤0.15	2.91 (1.44–5.87)	0.003	3.09 (1.41–6.76)	0.005	3.98 (1.50–7.06)	0.003	3.50 (1.64–7.49)	0.001

CI confidence interval, *DFS* disease-free survival, *DMFS* distant metastasis–free survival, *DSS* disease-specific survival, *HR* hazard ratio, *LN* lymph node, *OS* overall survival

[a]Multivariate Cox proportional hazards regression analysis was performed using backward stepwise selection with the variables of $p < 0.1$ on univariate results

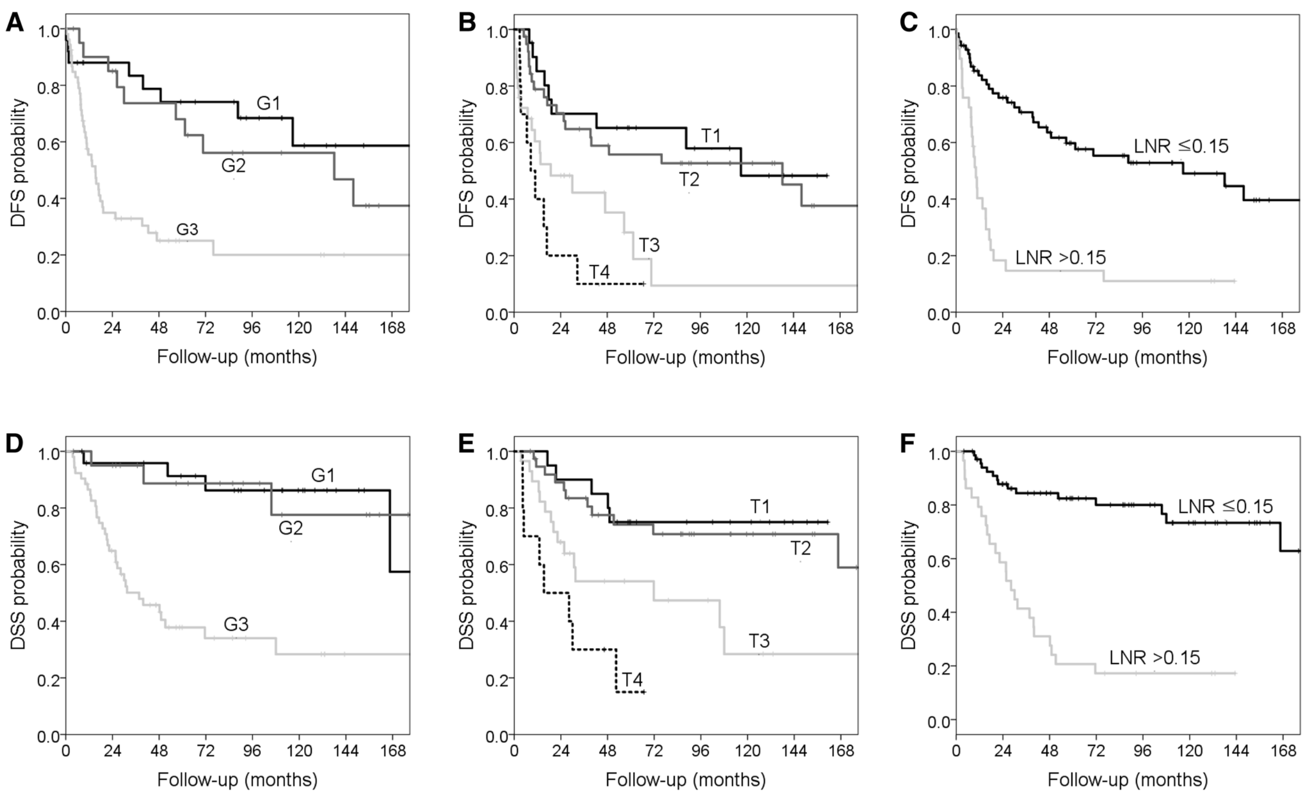

Fig. 1 Kaplan–Meier curves estimating the DFS (**a**–**c**) and DSS (**d**–**f**) of salivary gland cancer patients on the basis of histological grade (**a, d**), T classifications (**b, e**), and LNR (**c, f**). Log-rank test; $p < 0.001$. *DFS* disease-free survival, *DSS* disease-specific survival, *LNR* lymph node ratio

have reported 25–83 SMG carcinoma patients who underwent radical surgery with adjuvant therapy. The largest series of 370 cases of SMG carcinoma were reported from the Surveillance, Epidemiology and End Results (SEER) database between 1988 and 1998 (Bhattacharyya 2004). Supplementary Table S2 summarizes all the series reporting carcinomas originating in the SMG. As can be seen from the table, adenoid cystic carcinoma is the most common pathology, followed by mucoepidermoid carcinoma and CXPA. High-grade and metastatic carcinomas were reported as 10–91% and 17–40%, respectively. PORT was performed in 51–100% of the reported cases. For a follow-up period of 29–108 months, the 5-year DFS, DSS, and OS rates ranged from 53 to 72%, 61–76%, and 50–77%, respectively. A large proportion of high-grade tumors included salivary duct carcinoma (22%) and poorly differentiated carcinoma (6%) in this study compared with previous reports (Supplementary Table S2). These results might explain the high rates of nodal metastasis at initial presentation (45.5%) and of distant metastasis at initial presentation or follow-up (42.4%), resulting in relatively lower survival outcomes than in previous reports.

Several studies have reported prognostic factors for SMG carcinoma in terms of predicting posttreatment recurrence, distant metastasis, and survival. The earliest study identified tumor stage and perineural invasion as factors for DFS and DSS and age and nodal metastasis as factors for OS (Vander Poorten et al. 1999), showing high rates of late recurrence and lung metastases in adenoid cystic carcinoma (Sykes et al. 1999). Early irradiation is also associated with a low DFS rate (Storey et al. 2001). SEER database analyses showed that pathological types and grade, age, and radiotherapy are associated with OS (Bhattacharyya 2004). A positive resection margin is also reported to be a significant factor predictive of recurrence (Cohen et al. 2004). Our previous study identified T classification and a positive resection margin as factors for locoregional disease control and high-grade carcinoma as a factor for DMFS and DFS (Roh et al. 2008). Perineural invasion and radiotherapy dose were reported to be significant predictors of locoregional disease control, and T classification and overall stage affected DFS outcomes (Mallik et al. 2010). Recent studies have identified independent prognostic factors for survival: high-grade tumor for DMFS outcomes and nodal metastasis (≥ N2) for DMFS and OS outcomes (Yamada et al. 2018); fixed mass, nodal metastasis, and a positive margin for DFS and OS outcomes (Liu et al. 2018); T and N classifications for DFS and OS outcomes; and T classification, perineural invasion, and lymphovascular invasion for DMFS outcomes (Hsieh et al. 2018). This study also identified independent factors for survival: high-grade tumor, T classification, and LNR for DMFS, DSS, and OS outcomes.

Studies have recognized nodal factors as major prognostic indicators of head and neck cancer (Argiris et al. 2008; de Morais et al. 2017; Kim et al. 2018). The survival of head and neck cancer patients can be predicted by AJCC's TNM staging system (Amin MB, Edge SB). The 8th edition of the AJCC staging system includes ENEs for head and neck cancer and salivary gland cancer (Amin MB). Pathological ENEs are staged up to N3b regardless of the size or number of metastatic LNs (Amin MB). The N2–N3 nodal classification depends on the size of nodal positivity for ≥ 2 LNs, not on the metastatic burden. The number of metastatic LNs and the LNR as metastatic burden indicators have been reported as important predictors of disease failure and survival outcomes in head and neck cancer patients (Ebrahimi et al. 2014; Ho et al. 2017). LNR is also reportedly a prognostic indicator in high-grade (Hong et al. 2015) or major salivary gland cancer patients (Suzuki et al. 2015). A recent study has proposed a new nodal staging system, including the number of positive LNs as a quantitative metastatic burden, to improve salivary gland cancer staging (Aro et al. 2018a). The number of positive LNs is also suggested as an important prognostic indicator for DMFS and OS outcomes in salivary duct carcinoma patients (Qian et al. 2018). However, univariate, not multivariate, Cox proportional hazards regression analysis has recognized ENE as a significant predictor of survival (Aro et al. 2018a; Qian et al. 2018). This study also identified the number of positive LNs, LNR, and ENEs as major prognostic indicators of nodal factors for SMG carcinoma, of which LNR was only an independent factor predictive of DFS, DMFS, DSS, and OS outcomes. Further multi-institutional studies of SMG and salivary gland cancers are required to validate these findings.

Herein, PORT appeared to prevent recurrence and death in patients with adverse pathological findings. This finding is supported by studies that have reported that adjuvant radiotherapy is associated with an un-increased risk of locoregional disease recurrence (Jegadeesh et al. 2015) and excellent long-term survival outcomes (Hosni et al. 2016). However, in salivary gland cancer, distant metastasis is the most frequent failure of treatment with or without adjuvant radiotherapy (Roh et al. 2008; Hosni et al. 2016), implying the necessity of systemic therapy in metastatic salivary gland cancer patients. A systematic review has shown only palliative benefits of chemotherapy in adenoid cystic carcinoma patients with progressive, symptomatic disease (Laurie et al. 2011). Few patients with metastatic disease received systemic chemotherapy, the effects of which were not properly assessed. The present study showed the prognostic significance of factors in the largest series of SMG carcinoma cases. Pathological nodal findings, such as LNR, might provide prognostic prediction and the need of adjuvant therapies.

In conclusion, this study showed high rates of initial nodal metastasis (45.5%) and distant metastasis at initial presentation or follow-up (42.4%). LN metastasis and high rates of distant site failure are associated with a poor survival of SMG carcinoma patients. The T classification and LNR are independent factors of all survival outcomes. A high-grade tumor is an independent prognostic factor for DMFS, DSS, and OS outcomes. The number of positive LNs, LNR, and ENEs are significant factors predictive of all survival outcomes. Of the nodal findings, only LNR might help predict recurrence, distant metastasis, and death due to SMG carcinoma.

Funding None reported.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent from all individual participants was waved because of the retrospective nature of this study.

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