Clinicopathological Factors are Predictors of Distant Metastases From Salivary Gland Carcinoma After Surgery Combined With ^{125}I Internal Brachytherapy

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Purpose: Distant metastasis (DM) indicates a poor outcome from cancer treatment. The present study estimated the incidence of DM and identified risk factors associated with development of DM in patients with salivary gland carcinoma that achieved locoregional control after surgery combined with ^{125}I internal brachytherapy.

Materials and Methods: A retrospective cohort study was performed using consecutive patients treated with surgery combined with ^{125}I internal brachytherapy at the Peking University School and Hospital of Stomatology. Variables that might be associated with DM, including clinical, treatment characteristics, pathologic findings, and time to DM were recorded. Kaplan-Meier was performed to estimate incidence of DM, and Cox proportional hazard model was used to identify factors associated with DM.

Results: Data from 156 patients were obtained for statistical analysis. The DM was observed in 16 of 156 with rate being 10.3%. The median interval from diagnosis of primary tumor to DM was 30.0 months. The 3-, 5-, 10-year overall survival rates were 97.0, 94.6, 85.2%, respectively, for patients without DM compared with 60.9, 52.2, 26.1%, respectively, for those with DM ($P < .001$). Univariate analysis revealed that the factors that significantly influenced DM were primary tumor site ($P = .012$) and histologic grade ($P = .001$). Multivariate Cox proportional hazard model indicated that histologic grade was the most important risk factor for predicting the risk of DM ($P = .005$; hazard ratio: 2.79; 95% confidence interval: 1.36 to 5.72).

Conclusions: Histologic grade was the major risk factor that significantly influenced DM in patients with salivary gland carcinoma that achieved locoregional control. Patients with high-grade tumors should be under close evaluation for DM.

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Salivary gland carcinoma compromises nearly 1 to 3% of all head and neck tumors and 7% of epithelial cancers.[1-3] An improved locoregional control of salivary gland carcinoma has been achieved with the introduction of radiotherapy and adjuvant chemotherapy.[4,5] However, the overall survival rate has not significantly improved. The main factor accounting for low overall survival is the appearance of distant metastasis (DM),[6] and some DM develops in patients who have already achieved locoregional control. As per the literature, the DM rate varies extensively in clinical studies, ranging between 13 and 26%.[7-9] The possible risk factors of DM have been evaluated, including histologic type, locoregional control, primary site, younger age, advanced stage, and metastatic lymph nodes.[10-13]

However, previous studies of the possible risk factors have been heterogeneous, with patients receiving different forms of treatment. ^{125}I internal brachytherapy is a feasible, safe treatment for salivary gland carcinoma, and few studies mention DM of salivary gland carcinoma after treatment with ^{125}I internal brachytherapy.[4,5] Hence, the purpose of the present study was to evaluate the frequency of DM and clinical-histologic risk factors in the development of DM in patients with salivary gland carcinoma that have achieved locoregional control after treatment with surgery combined with ^{125}I internal brachytherapy. The present study identified risk factors associated with DM using univariate and multivariate analyses. We hypothesized that histologic grade was the major risk factor that significantly influenced DM in patients with salivary gland carcinoma that achieved locoregional control after surgery combined with ^{125}I internal brachytherapy.

Materials and Methods

SUBJECTS

A retrospective study was conducted to evaluate the incidence of DM and to identify risk factors associated with development of DM in patients with salivary gland carcinoma that achieved locoregional control after surgery combined with ^{125}I internal brachytherapy at the Peking University School and Hospital of Stomatology from October 2006 to March 2015. The inclusion criteria were as follows: *1)* patient follow-up conducted for a minimum of 2 years or until death and *2)* patient achieved locoregional control after surgery combined with ^{125}I internal brachytherapy. The exclusion criteria were as follows: *1)* a history of malignancy in other sites; *2)* presented with pulmonary metastases before ^{125}I seed implantation; and *3)* prior radiotherapy or chemotherapy. Informed consent was obtained from each patient, and the institutional ethics committee approved the study.

Predictor variables were documented that may be associated with DM, including age, gender, primary site, T stage, histologic grade, and surgical margin. Margins with invasive tumor or carcinoma in situ were considered involved. Invasive tumors that were within 5 mm of the surgical margin were labeled close. Uninvolved tumors with surgical margins greater than 5 mm were labeled clear. The outcome variable was considered the time to DM, and the interval time between the diagnosis of the primary tumor and initial DM diagnosis was considered the time to DM.

SURGICAL TREATMENT AND ^{125}I SEED IMPLANTATION

All patients underwent surgery with the purpose of extended resection, but selected patients had positive or close margins because of tumor nature or vital structures involved in the tumor, such as a facial nerve or main artery. The brachytherapy treatment plan for all patients was designed using a computerized treatment planning system (RT-RSI; Beijing Atom and High Technique Industries Inc., Beijing, China) based on computerized tomography (CT) images. The planning target volume was defined as a 10- to 15-mm extension of the preoperative gross tumor volume and the postoperative bed on the basis of CT scans in combination with imaging of the target area by intraoperative photography. ^{125}I seed implantation (Model 6711; Beijing Atom and High Technique Industries; energy level, 27.4–31.4 KeV; t1/2, 59.4 days) was performed in all patients postoperatively with a median interval of 14 days after wound healing, which had been achieved as per the treatment plan. Radioactivity was between 18.5 and 33.3 MBq (0.7 to 0.8 mCi) per seed, and seed distribution was determined from CT scans in combination with the target area, as recorded by intraoperative photographs. The space between seeds (center to center) was maintained at 10 mm. Following the implantation plan, seeds were placed in the target volume. The matched peripheral dose was 80 to 120 Gy and was adjusted as per previous treatments and adjacent structures. The dose was prescribed as the matched peripheral dose that encompassed the planning target volume.

FOLLOW-UP AND EVALUATION OF DM

The initial day of surgery was considered the start of patient observation. All patients included were followed for a minimum of 2 years or until death, which ranged from 1 to 135 months (median was 56 months). Patients who died because of DM less than 2 years after primary therapy were included. The DM diagnosis was confirmed by histopathological examination or by radiological examinations, such as CT scan of the thorax, bone scanning, abdominal

ultrasound scanning, brain scans, and positron emission tomography-CT, if the initial tests were abnormal or if the patient showed symptoms. When DM occurred, we recorded the interval between initial DM diagnosis and the diagnosis of the primary tumor, the location, and survival after diagnosis of DM.

STATISTICAL METHODS

Statistical analysis was performed using IBM SPSS Statistics, version 19.0, software (IBM Corp, Armonk, NY, USA). A *P* value less than 0.05 was considered statistically significant. Survival analysis was calculated by the Kaplan-Meier method. The differences between DM-free survival (DMFS) and clinicopathological factors were analyzed using the logrank test for univariate analysis. Multivariate analyses were then performed by a Cox proportional hazards model, including all significant variables in the univariate analysis (those with a *P* value of < 0.2) to identify independent predictive factors and hazard ratios for DM.

Results

DEMOGRAPHICS

The present retrospective study included 156 patients (63 men and 93 women; mean age was 43.3 years with range of 6 to 77 years). A total of 117 patients exhibited tumors of the major salivary glands and 39 had tumors in the minor salivary glands. Salient features of the 156 patients are described in Table 1.

Table 1. CLINICAL AND HISTOLOGIC CHARACTERISTICS OF PATIENTS (N = 156)

Characteristics	No. of Patients (%)
Age (yr)	
<60	127 (81.4)
≥60	29 (18.6)
Gender	
Male	63 (40.4)
Female	93 (59.6)
Primary site	
Parotid gland	91 (58.3)
Submandibular gland	11 (7.1)
Sublingual gland	17 (10.9)
Minor salivary gland	37 (23.7)
T stage	
T1	39 (25.0)
T2	94 (60.3)
T3	16 (10.3)
T4	7 (4.4)
Histologic grade	
Low	70 (44.9)
Intermediate	69 (44.2)
High	17 (10.9)
Surgical margin	
Clear	111 (71.2)
Close	30 (19.2)
Involved	15 (9.6)
Distant metastasis	
Yes	16 (10.3)
No	140 (89.7)

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DM RATE AND LOCATION

Sixteen (10.3%) patients presented with DM during a follow-up examination. DM was present predominantly in the lung (15 of 16 [93.8%]), either alone (11 patients) or contemporaneously with other sites (4 patients), and the most common histologic type involved was adenoid cystic carcinoma (5 cases [31.3%]). The liver was the second most frequent site, followed by bone.

DM PERIOD AND POST-DM SURVIVAL TIME

DM developed between 8 and 120 months after diagnosis of the primary tumor. The median interval from diagnosis of primary tumor to DM was 30.0 months (mean 42.1 months). Nearly 69% of the patients included in our study developed DM within 3 years after the diagnosis of the primary tumor. However, 31% of patients presented with DM between 3 and 10 years after the diagnosis of the primary tumor.

At the time of last follow-up, 8 of the 16 patients with DM had died; the median survival time was 8 months (range 1 to 18 months, mean 8.4 months), and nearly 86% of patients died within 12 months. The 3-, 5-, and 10-year overall survival rates were 97.0, 94.6, and 85.2%, respectively, for the 140 patients without DM compared with 60.9, 52.2, and 26.1%, respectively, for the 16 patients with DM. As shown in Figure 1, the survival rate was much lower for patients with DM (*P* < .001).

UNIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH DMFS

As displayed in Table 2, no significant difference was found in DMFS rates by age, gender, stage, or surgical margin. DMFS was significantly associated with primary tumor site (*P* = .012) and histopathological grade (*P* = .001). Primary tumors that were located in sublingual glands and demonstrated high histopathological grade were high-risk factors associated with DM.

MULTIVARIATE ANALYSIS OF RISK FACTORS ASSOCIATED WITH DM

A Cox proportional hazards multivariate analysis was carried out with the potential prognostic value of the univariate analysis. Only 1 factor remained significant, which was histopathological grade. On the

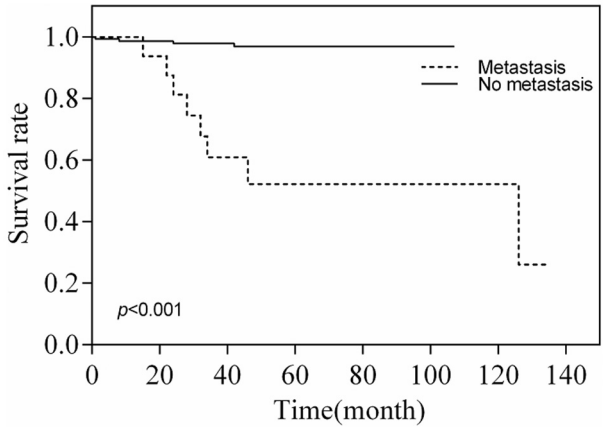

FIGURE 1. The overall survival was lower in patients with distant metastasis than in patients without metastasis ($P < .001$).

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contrary, the primary tumor site was excluded from this model. The hazard ratio and 95% confidence interval for histopathological grade were 2.79 and 1.36 to 5.72, respectively ($P = .005$) (Table 3). Three-year DMFS rates for the different histopathological grades were as follows: 98.6% for low grade, 92.0% for intermediate grade, and 69.7% for high grade. Kaplan-Meier curves for DMSF by histopathological grade are shown in Figure 2.

Discussion

DM is the emergence of secondary tumors at distant sites from a primary tumor.[14] The true incidence of DM in salivary gland cancers remains uncertain, in the literature, it varies widely from 20 to 50%.[15] Several factors account for this wide range, including histologic type, locoregional control, primary site, younger age, advanced stage, and metastatic lymph nodes.[10-13] However, previous studies of the possible risk factors of DM have been heterogeneous, with patients receiving different forms of treatment. In the present study, we aimed to evaluate the rate and clinical-histologic risk factors in the development of DM in patients with salivary gland carcinoma that achieved locoregional control after treatment with surgery combined with ^{125}I internal brachytherapy. The present findings showed that the DM rate was 10.3% and that

Table 2. UNIVARIATE ANALYSIS OF POTENTIAL FACTORS ASSOCIATED WITH DM

Variable	DMFS at 3 yr	HR (95% CI)	*P*
Age (yr)		1.32 (0.41 to 4.25)	0.814
<60	93.1%		
≥60	89.3%		
Gender		0.35 (0.12 to 1.02)	0.177
Male	85.9%		
Female	96.7%		
Primary tumor site		0.95 (0.62 to 1.44)	0.012
Parotid gland	94.4%		
Submandibular gland	81.8%		
Sublingual gland	72.9%		
Minor salivary gland	96.0%		
T stage		1.44 (0.77 to 2.69)	0.827
T1	94.4%		
T2	91.9%		
T3	93.3%		
T4	85.7%		
Histologic grade		3.23 (1.50 to 6.96)	0.001
Low	98.6%		
Intermediate	92.0%		
High	69.7%		
Surgical margin		1.34 (0.68 to 2.62)	0.82
Clear	92.3%		
Close	95.7%		
Involved	86.7%		

Note: Survival analysis was calculated by the Kaplan-Meier method. The differences between distant metastasis-free survival and clinicopathological factors were analyzed using the log-rank test for univariate analysis.

Abbreviations: 95% CI, 95% confidence interval; DM, distant metastasis; DMFS, distant metastasis–free survival; HR, hazard ratio.

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Table 3. MULTIVARIATE COX ANALYSES OF POSSIBLE RISK FACTORS ASSOCIATED WITH DM

Variable	Score	HR (95% CI)	*P*
Age (yr)			
<60	0	1	
≥60	1	1.16 (0.32 to 4.19)	0.822
Gender			
Male	0	1	
Female	1	2.82 (0.80 to 9.93)	0.106
Primary tumor site			
PG	0	1	
SMG	1	1.13 (0.11 to 11.86)	0.919
SLG	2	4.12 (0.31 to 54.54)	0.282
MSG	3	5.28 (0.50 to 55.85)	0.167
T stage			
T1	0	1	
T2	1	1.54 (0.13 to 17.73)	0.731
T3	2	1.28 (0.14 to 11.70)	0.828
T4	3	2.87 (0.26 to 31.24)	0.386
Histologic grade			
Low	0	1	
IM	1	2.02 (1.26 to 4.62)	0.013
High	2	2.79 (1.36 to 5.72)	0.005
Surgical margin			
Clear	0	1	
Close	1	0.74 (0.10 to 5.73)	0.774
Involved	2	0.69 (0.10 to 6.35)	0.742

Note: Multivariate analyses were performed by a Cox proportional hazards model.

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; IM, intermediate; MSG, minor salivary gland; PG, parotid gland; SLG, sublingual gland; SMG, submandibular gland.

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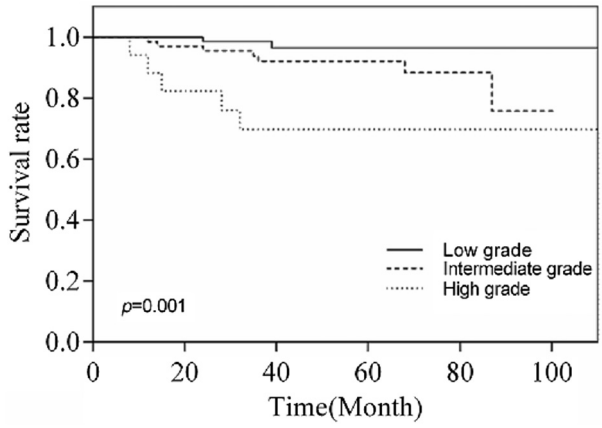

FIGURE 2. Kaplan-Meier survival curves for distant metastasis-free survival by histologic grade (*P* = .001).

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histologic grade was a major risk factor that significantly influenced DM. Thus, our hypothesis that histologic grade was a major risk factor was confirmed.

In the present study, DM was located predominantly in the lung (93.8%), either alone or occurring with other sites. The liver was the second most frequent site, followed by bone. Nearly 69% of DM developed in the first 3 years after diagnosis of the primary tumor, and 31% of patients developed DM from 3 to 10 years. The median interval was 30.0 months, which is longer than squamous cell carcinoma, with an average interval between 9 and 15.3 months.[16,17] Once DM occurred, the chances of a cure were slim, with a median survival of 8 months. Eighty-six percent of patients with DM were dead within 1 year. The 10-year survival rate was only 26.1% in the DM group compared with 85.2% in the no-DM group. Our results agreed with those of previously reported studies in the literature.[15,18] Therefore, a routine chest radiograph is necessary for each patient when other special examinations are suggested, such as a CT scan of the thorax, bone scan, bronchoscopy with sputum cytology, brain scan, abdominal ultrasound, positron emission tomography-CT, and serum liver function tests.[15] Moreover, each patient should be clinically assessed and followed at least once a year for life.[19] Until now, the treatment for DM was not ideal, depending on the clinical manifestation. DM can be managed with watchful waiting, local therapies, such as surgery and radiation, or systemic therapy, such as induction chemotherapy.[20-23] It is incumbent on surgeons to further understand the interactions between the secondary organ microenvironments and tumor cells, which may guide cancer metastasis-targeted therapy.[24] In addition, greater efforts should be made to prevent the occurrence of DM.[16]

Previous studies have found an association between the location of primary tumors and DM, in addition to locoregional control. Marianoet al[13] reported that tumors located in the submandibular gland (42%) had a greater risk of DM than tumors in the parotid (20%) and sublingual glands (17%). Schwentner et al.[18] found that the likelihood of developing DM was associated with tumors located in pharyngeal, posterior tongue, and submandibular gland. In addition, Gao et al[25] showed that submandibular gland tumors had a higher rate of distant metastases. Furthermore, patients with submandibular gland neoplasms displayed the worst prognosis.[26,27] In the present study, location of the tumor was an important predictor of DM using a univariate analysis, and tumors located in the sublingual gland demonstrated a higher DM rate because sublingual gland tumors are usually high-grade.[28]

Histologic type is a significant prognostic factor in the development of DM.[11] High-grade tumors, such as undifferentiated carcinoma, adenoid cystic carcinoma,

salivary duct carcinoma, high-grade mucoepidermoid carcinoma, adenocarcinoma not otherwise specified, squamous cell carcinoma, and carcinoma expleomorphic adenoma, are more likely to metastasize than low-grade tumors.[15,18,19] Renehan et al.[29] demonstrated that the occurrence of DM was associated with histologic type of the neoplasm (low 2%, intermediate 44%, and high 36%; $P < .001$). In the univariate and multivariate analysis, we found a relationship between histologic type and DM; therefore, high-grade salivary gland tumors should be under close surveillance and treated aggressively, such as with surgery and irradiation.

Some investigators have shown a close correlation between positive surgical margin and DM.[30,31] However, we failed to find such a correlation in the present study. The conventional treatment of malignant parotid gland tumors with an involved facial nerve is extensive excision of the tumor, sacrificing the nerve. However, it would bring disastrous injury to patients, both physiologically and psychologically, resulting in distortion of commissure, difficulty in raising the eyebrow, and closing the eye.[32] In our study, we preserved the facial nerve with postoperative ^{125}I seed brachytherapy, although the surgical margin was positive, a good locoregional control and facial nerve function was achieved. Therefore, patients with an involved facial nerve, especially those with special requirements and occupations, should consider a limited surgery with preservation of the facial nerve and postoperative ^{125}I seed brachytherapy.[5]

The present retrospective study focused on patients with salivary gland carcinoma that achieved locoregional control after surgery combined with ^{125}I internal brachytherapy, which differed from previous studies that reported patients receiving different forms of treatment. However, our study had some limitations. The present study showed that patients with high-grade tumors were at high risk for developing DM. However, other parameters, such as lymphatic and/or vascular invasion, epidermal growth factor receptor expression, ezrin, HER2, p53, and Ki-67 expression, might act as other risk factors and are currently under investigation.[33,34] A more acute risk assessment may be achieved by combining these factors, and patients with high-risk tumors should be included in future clinical trials.

Findings from the present study showed that the DM rate was 10.3% in patients with salivary gland carcinoma that had achieved locoregional control after treatment with surgery combined with ^{125}I internal brachytherapy. Histologic grade was the major risk factor that significantly influenced DM, and patients with high-grade tumors should be under extensive evaluation for DM and considered for systemic therapy.

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