

Distant metastasis is a critical mode of failure for patients with localized major salivary gland tumors treated with surgery and radiation

Moses Tam · Nadeem Riaz · Lucas Resende Salgado · Daniel E. Spratt · Evangelia Katsoulakis · Alan Ho · Luc G. T. Morris · Richard Wong · Suzanne Wolden · Shyam Rao · Nancy Lee

Received: 2 April 2013 / Accepted: 25 June 2013 / Published online: 10 July 2013
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Abstract

Objectives Excellent local–regional control can be achieved for major salivary gland tumors treated with surgery and postoperative radiotherapy. We evaluated the cumulative incidence and predictors of distant metastasis in high-risk major salivary gland tumors.

Methods Between 1990 and 2011, 200 patients with major salivary gland tumors received postoperative radiotherapy at our center. The patients' median age was 60 years. Patients had primary tumors of the parotid gland (84 %), submandibular (16 %), and one sublingual gland. Among the patients, 34 % had T3–T4 tumors, 32 % had nodal involvement. Other high-risk features included close/positive margins and high-grade tumors. The median RT dose was 63 Gy.

Results With a median follow-up of 50 months, the 5-year local control and regional control were 88 and 94 %, respectively. The 5-year freedom from distant metastasis was 73 %. The median overall survival was 14.6 years corresponding to a 5- and 10-year overall survival of 77 and 59 %, respectively. T category and nodal involvement were independent predictors of distant metastasis. Nodal involvement was also an independent predictor of overall survival.

Conclusions Distant relapse was the predominant mode of failure despite excellent local–regional control in high-risk major salivary gland tumors. Both advanced T category and nodal involvement were independent predictors of distant metastasis. More effective systemic therapy is needed to combat distant relapse.

Keywords Major salivary gland tumors · Distant metastasis · Systemic therapy · Radiation therapy · Parotid gland

Introduction

Malignant major salivary gland tumors are rare and account for about 5 % of all head and neck cancers. These tumors demonstrate a wide histologic diversity and may arise from the parotid, submandibular, and sublingual glands [1]. The most common malignant histology of the parotid gland is mucoepidermoid carcinoma but other common histologies include adenoid cystic carcinoma, adenocarcinoma, and acinic cell carcinoma [1]. Major salivary gland tumors are managed primarily by surgical excision; however, many retrospective studies have demonstrated improved locoregional control with postoperative radiation in patients with high-risk disease features including T3–T4 disease, nodal involvement, or high-grade histologies [2–5].

Limited literature is available regarding rates of distant metastasis for high-risk major salivary gland tumors that receive modern day treatment of postoperative radiotherapy. Noh et al. reported a distant metastasis rate of 22.7 % in a study of 94 patients with major salivary tumors treated with and without postoperative radiation therapy after a median follow-up of 49 months [6]. It is unclear whether the relatively high rate of distant metastasis may be related to the poor local control (LC) of 78.2 % observed in surgery group alone [6]. However, excellent LC may not have an impact on distant metastasis-free survival (DMFS) as suggested by one study. Mendenhall

Moses Tam and Nadeem Riaz contributed equally to this study.

M. Tam · N. Riaz · L. R. Salgado · D. E. Spratt · E. Katsoulakis · S. Wolden · S. Rao · N. Lee (✉)
Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
e-mail: leen2@mskcc.org

A. Ho
Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

L. G. T. Morris · R. Wong
Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

et al. reported a 10-year DMFS of 67 % in a study that included both major and minor salivary gland tumors treated with postoperative radiation therapy despite a 10-year LC of 90 % [7].

The purpose of this paper is to examine the cumulative incidence of distant metastasis and predictors of distant metastasis in a large cohort of patients with high-risk major salivary gland tumors who have been treated with postoperative radiation therapy.

Methods

Between May 1990 to February 2011, 200 consecutive patients with histologically confirmed major salivary gland carcinomas were treated with surgery followed by postoperative radiation therapy at Memorial Sloan-Kettering Cancer Center. Patients were excluded from this analysis if they had prior head and neck radiation therapy, received radiation therapy at an outside institution, had gross disease following surgery, or had distant metastasis on initial diagnostic work up.

Pretreatment evaluation typically included a complete history/physical examination, complete blood counts, liver function tests, chest X-ray, dental evaluation, as well as magnetic resonance imaging and/or computed tomography (CT) scans of the head and neck region. Bone scans, CT scans of the chest and abdomen, and positron emission tomography scans were obtained for patients before the start of treatment as indicated. Tumors of the major salivary glands were staged according to the latest *AJCC Cancer Staging Manual* at the time of diagnosis.

Treatment of primary tumor

All patients were initially treated with definitive surgery. The type of procedure was dependent on the location and extent of disease, majority of which were parotidectomies and submandibular gland resections. One hundred forty six (73 %) patients had close/positive margins, which may be expected given the goal of facial nerve preservation in parotidectomies. A close margin was determined based on histologic type and the invasive pattern of the tumor since no standard definition of a close margin exists for salivary gland tumors. Sixty three (32 %) patients presented with nodal metastases and 72 (36 %) patients received a neck dissection. Postoperative radiation therapy was delivered to the primary site using techniques available at the time of treatment. Median time between surgery and the beginning of radiation was 49 days. Patients were treated with external beam radiation therapy using intensity-modulated radiotherapy (IMRT), three-dimensional conformal radiotherapy (3DCRT), or with conventional therapy which consisted of either wedge pair or photon–electron techniques. Patients were immobilized in the supine position with thermoplastic head/neck mask ± shoulder mask to ensure

daily reproducibility of treatments. Patients treated with intensity-modulated radiotherapy had target volumes outlined slice by slice at 3-mm intervals on treatment planning CT images. Typically, positive margins received a higher a prescribed dose of 66 Gy compared with negative margins which received 60 or 63 Gy; however, actual practices depended on the radiation oncologist. The median dose of radiation was 63 Gy. Patients with major salivary gland tumors with a high risk for neck involvement (e.g., advanced T category, neck involvement, and certain histologies) typically received ipsilateral neck radiation treatment regardless of whether neck dissection was performed or if the patient was pN0.

Chemotherapy

Chemotherapy was used in selected patients at the discretion of the treating physicians. Twenty (10 %) patients received the chemotherapy concurrently with radiation treatment. Among the 20 patients given concurrent chemotherapy, 14 (93 %) of the 15 patients with known histologic grade were high grade. Eleven (58 %) of the 19 patients with known T category had either T3 or T4 disease. Twelve (63 %) of the 19 patients with known nodal status had positive nodal disease. Eleven (55 %) patients had positive margins and seven (35 %) patients had close margins. Sixteen (89 %) of the 18 patients with known extracapsular extension status were positive for extracapsular extension (ECE).

Single-agent cisplatin was used in 14 patients. Nine patients received cisplatin every 3 weeks while five patients received cisplatin weekly. Additionally, 18 (90 %) of these patients received IMRT while the remaining two patients received 3DCRT.

Follow-up

After treatment completion, patients were typically evaluated every 2–3 months for the first 2 years and every 4–6 months over the following 3 years and then yearly thereafter. At each follow-up visit, a physical examination was performed, including fiber optic endoscopy if indicated. Imaging using CT, MRI, or positron emission tomography (PET) scan was performed if there was a suspicion of recurrence. Patients treated more recently received PET scans 3–4 months after radiotherapy. Toxicities were documented according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical analysis

Two- and 5-year probabilities of LC, regional control (RC), freedom from distant metastasis, and overall survival (OS) were calculated according to the Kaplan–Meier method. Univariate and multivariate analyses were performed using log-rank and Cox regression methods, respectively. Time to event was calculated from the first day of radiation treatment. Local

control, regional control, and freedom from distant metastasis were defined as the absence of disease in the primary treatment region, the local lymph nodes, and a distant metastatic site, respectively. The following predictors were analyzed as prognostic variables: histology, T category, N stage, margin status, and subsite location. Advanced T category is defined as T3–T4 disease. Additional information on tumor grade, ECE, and perineural invasion were not reported given incomplete and inconsistent pathology reporting as many of these patients received surgery at outside institutions.

Results

Patient characteristics are listed in Table 1. Of the 200 patients included in the analysis, the primary tumor subsite location was parotid in 84 % and submandibular gland in 16 %. One patient had a tumor of the sublingual gland.

Local control and regional control

The 2- and 5-year LC were 91 and 88 %, respectively. Local failure occurred in 20 (10 %) patients (Fig. 1a). Local failures (80 %) typically occurred within 2 years of the start of therapy (range, 1.7–53.3 months). Univariate analysis showed nodal involvement predicted for local failure ($p=0.045$). Univariate analysis did not find advanced T category, margin status, histology, and subsite location to be predictive of local failure.

The 2- and 5-year RC were 96 and 94 %, respectively (Fig. 1b). Regional failure occurred in 11 (6 %) patients. Regional failures (73 %) mostly occurred within 2 years of the start of therapy. Univariate analysis was not performed given the low incidence of regional failures.

Distant metastasis

Freedom from distant metastasis at 2 and 5 years were 84 and 73 %, respectively (Fig. 2). Forty-eight patients showed evidence of metastatic disease during the follow-up period. Among these patients, 77 % of distant metastasis occurred within 3 years of the start of therapy. Only four patients failed after 5 years. Seven (15 %) patients initially received concurrent chemotherapy treatment.

Univariate analysis showed that advanced T category ($p=0.004$), nodal involvement ($p<0.001$), and histology ($p<0.001$) were predictive of distant metastasis (Fig. 2a, b). Patients who presented with T3–T4 tumors had a 61.8 % 5-year freedom from distant metastasis compared to a 78.6 % for T1–T2 tumors ($p=0.004$). Similarly, node positive patients experienced a 5-year freedom from distant metastasis of 53.8 % compared to 81.0 % for node negative patients ($p<0.001$). Histologic types associated with a better 2-year freedom from distant metastasis were acinic cell carcinoma

Table 1 Patient characteristics and univariate analysis for distant metastasis

Clinical feature	Number of patients	Percentage of patients	<i>p</i> value
Gender			
Male	104	52	
Female	96	48	
Age			
Median	60		
Range	6–89		
Race			
White	156	78	
Black	9	5	
Other	35	18	
Site			0.186
Parotid	167	84	
Submandibular	32	16	
Sublingual	1	1	
Histology			<0.001
Acinic cell	29	15	
Mucoepidermoid	52	25	
Adenoid cystic	31	16	
Myoepithelial	21	11	
Adenocarcinoma	45	23	
Poorly differentiated carcinoma	4	2	
Salivary ductal carcinoma	18	9	
T Category			0.004
T1	61	31	
T2	66	33	
T3	37	19	
T4	29	15	
N Stage			<0.001
0	129	65	
1	27	14	
2	36	18	
Margins			0.72
Negative	41	21	
Close	53	27	
Positive	93	47	
RT Treatment			
2D/3DCRT	101	51	
IMRT	99	50	

Significant *p* values bolded

CRT conformal radiotherapy, *IMRT* intensity-modulated radiotherapy

(96 %), mucoepidermoid carcinoma (86.3 %), adenoid cystic carcinoma (95.2 %), and myoepithelial carcinoma (83.3 %), while poorly differentiated carcinoma (50.0 %) and salivary ductal carcinoma (53.2 %) were associated with a worse

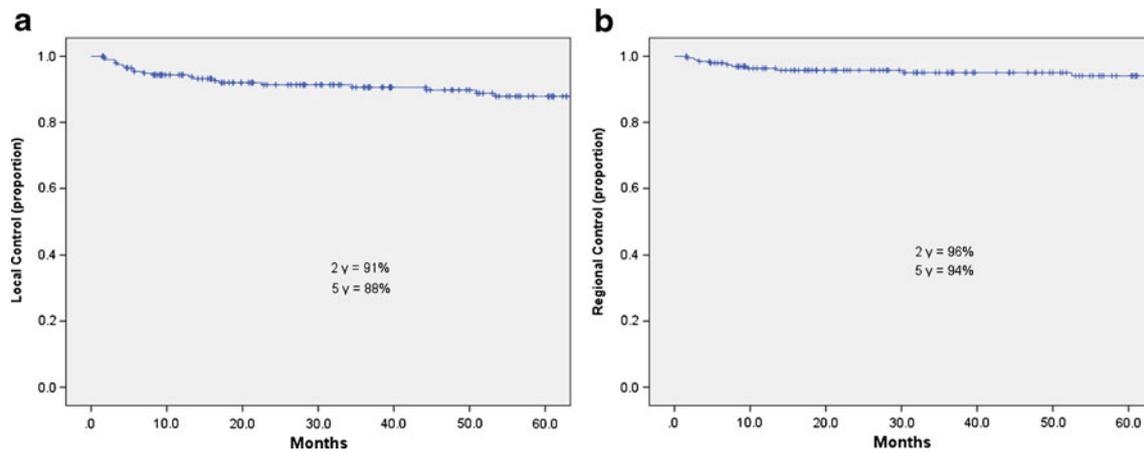


Fig. 1 **a** Local control and **b** regional control

freedom from distant metastasis. Univariate analysis also found local failure to be predictive of distant metastasis ($p < 0.001$). No significant association was found between distant metastasis and margin status or subsite location. However, margin status was not available or unclear in 5 % of patients. Multivariate analysis confirmed that advanced T category (hazard ratio (HR)=2.822, 95 % confidence interval (CI)=1.15–3.69, $p=0.015$) and nodal involvement (HR=2.060, 95 % CI=1.57–5.01, $p=0.001$) were predictive of distant metastasis (Fig. 3).

Overall survival

Median follow-up for surviving patients was 49.8 months (mean, 62.0 months; range, 1.6–220) (Fig. 4). Fifty seven patients died during the follow-up period. The median OS was 14.6 years corresponding to a 5- and 10-year OS of 76.6 and 59.0 %, respectively.

Univariate analysis found advanced T category ($p=0.016$), nodal status ($p < 0.001$), and histology ($p < 0.001$) to be predictive of OS. Patients who presented with T3–T4 tumors had a 68.7 % 5-

year OS compared to 81.5 % 5-year OS for T1–T2 tumors ($p=0.016$). Similarly, node positive patients experienced a 56.6 % 5-year OS compared to 87.2 % 5-year OS for node negative patients ($p < 0.001$). The histologic type that predicted better OS was acinic cell carcinoma ($n=29$), while poorly differentiated carcinoma ($n=4$) and salivary ductal carcinoma ($n=18$) predicted worse OS. Local failure also predicted decreased overall survival on univariate analysis ($p < 0.001$). Univariate analysis found no significant association between OS and margin status or subsite location. Multivariate analysis confirmed that nodal involvement (HR=3.735, 95 % CI=2.128–6.555, $p < 0.001$) was predictive of OS.

Acute toxicity

Acute and late toxicities were obtained by retrospective review of patient's medical records and scored according to CTCAE v4.0. Acute toxicity data were available for 197 patients. The remaining three patients either did not have immediate follow-up or had incomplete records regarding acute toxicities. The most common toxicities were skin reactions, occurring in 164 (82 %) patients and mucositis occurring in 155 (67 %) patients. Other common acute toxicities included xerostomia (51 %), fatigue (31 %), and dysphagia (25 %). Trismus occurred in 14 (7 %) patients, but there was no grade 3 or 4 toxicity in this regard. Otagia was observed in eight (4 %) patients but none were higher than grade 1. Of note, a few of these symptoms may be due to the adjuvant chemotherapy treatment that some of these patients received. Specifically, follow-up notes for two patients indicated that nausea, fatigue, and otalgia may be attributed to adjuvant chemotherapy treatment. No patients experienced grade 4 acute toxicities.

Late toxicity

Late toxicity data was available for 176 patients. No patients experienced grade 4 late toxicities. The most common toxicity

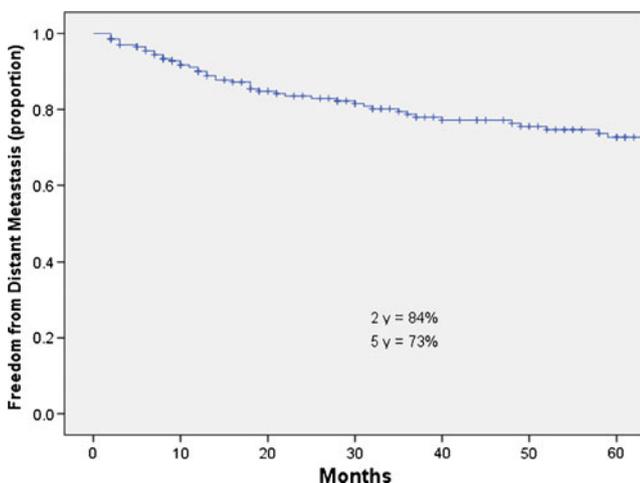


Fig. 2 Freedom from distant metastasis

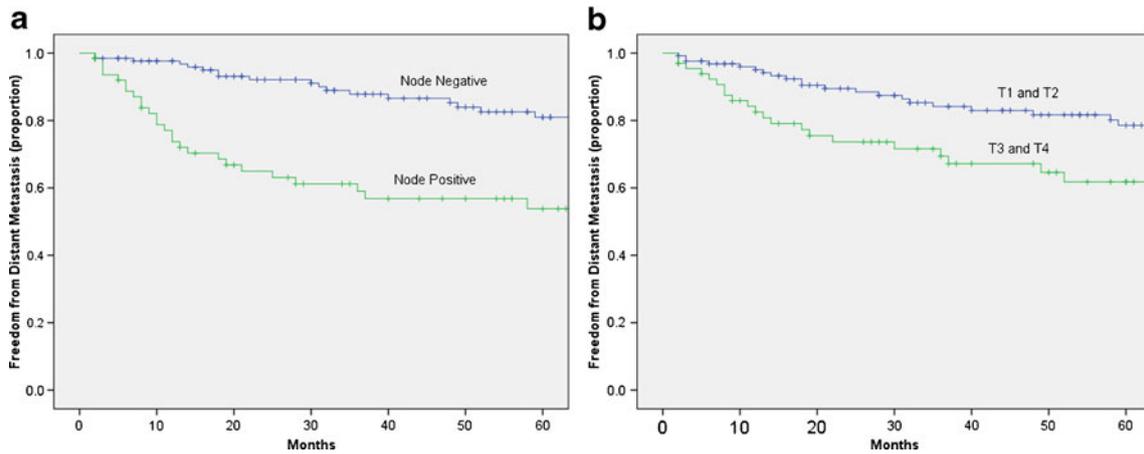


Fig. 3 Predictors of distant metastasis: **a** Nodal status and **b** T category

was xerostomia, which occurred in 97 (54 %) patients. Among those with known grades, majority (98 %) had grades 1 or 2 xerostomia. Hearing loss was the second most common late toxicity, affecting 34 (19 %) patients. Hearing loss in the majority of patients was determined from physician follow-up notes and not properly graded according to CTCAE criteria. The few patients with proper grading had grades 1–3 hearing impairments. Four cases of hearing loss resolved. Treatment with or without IMRT was not predictive of hearing loss. Three patients required PEG placement, one of whom received chemoradiation. Radiation necrosis, neuropathy, and headaches were rare, and no patient experienced grade 2 or higher toxicity. Radiation necrosis occurred in three (1 %) patients. No patients experienced blindness or grade 4 late toxicities.

Discussion

With a 5-year OS of 77 % and a 5-year LC of 88 %, the treatment outcomes we reported are consistent with outcomes

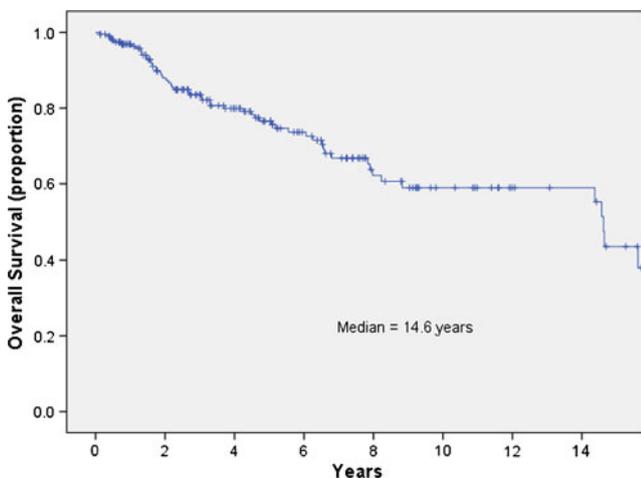


Fig. 4 Overall survival

reported at other institutions (Table 2) [2, 7, 8]. The excellent 5-year RC of 94 % is also similar to outcomes of other institutions but could not be directly compared [2, 7]. Positive nodal status was predictive of local failure which suggests a difference in biology or aggressiveness of the tumor, especially in regards with salivary gland tumors which are very heterogeneous in histology. However, predictors of regional failure could not be properly evaluated statistically given the overall excellent regional control rates. Node positive disease and T3–T4 disease did not appear to predict for regional failure and therefore suggests that radiation therapy is effective in neutralizing microscopic residual disease. Toxicity with modern radiotherapy is also minimal and therefore suggests radiation therapy is indicated for patients at high risk of local failure.

The effect of postoperative radiation therapy on improving local control and local–regional control may also show benefits on overall survival. Recently, Mahmood et al. looked at 2,170 patients in the Surveillance, Epidemiology, and End Results registry with high-grade and/or locally advanced nonmetastatic tumors of the major salivary glands [5]. Using multivariate analysis, the study found a survival benefit on the group of patients who received adjuvant radiation therapy when compared to those who received surgery alone.

Despite the excellent rates of local–regional control, the 5-year freedom from distant metastasis was 73 % and 5-year OS was 77.1 %. The predominant mode of failure as distant metastasis highlights the need for effective systemic therapies. The effect of postoperative concurrent chemotherapy on outcomes could not be evaluated from our study given the low number of patients who received adjuvant concurrent chemotherapy.

Our results showed that both advanced T category and nodal status were independent predictors of distant metastasis. Histologic type was also predictive of distant metastasis but could not be assessed using multivariate analysis given the low incidence of distant metastasis within each histologic group. Similarly, Mendenhall et al. showed that overall stage independently predicted DMFS in a study of the major and

Table 2 Published series on major salivary gland tumors

	Author	Year	No. of patients w/ postoperative RT	Major salivary (%)	Local control (y)	Freedom from DM (y)	OS (y)
	Garden	1997	166	100	92 (5)		60 (10)
	Terhaard	2005	386	73	94 (5)		
<i>RT</i> radiation therapy, <i>y</i> number of years, <i>DM</i> distant metastasis, <i>OS</i> overall survival	Mendenhall	2005	160	53	90 (10)	67 (10) ^a	48 (10)
	Feinstein	2011	74	80	76 (5)		55 (5)
	MSKCC	2013	200	100	92 (5)	73 (5)	59 (10)

^a Reported as DMFS

minor salivary gland carcinomas [7]. In addition, Terhaard et al. also found that T and N stage were the most important independent factors for developing distant metastasis [9]. Overall, studies have shown that advanced T category, nodal involvement, and histology are important prognostic factors for major salivary gland carcinomas [2, 7, 10]. Other poor prognostic factors reported include extracapsular extension, positive margins, skin invasion, perineural invasion, and sub-mandibular site [4, 5, 8, 11]. Many of these prognostic factors were not evaluated in our study given the incomplete reporting of these features in the pathology reports.

Studies have shown that the addition of concurrent chemotherapy has improved local–regional control in squamous cell carcinoma of the head and neck [12, 13]. The activity of systemic chemotherapy alone for recurrent and/or metastatic salivary gland tumors is relatively modest, dependent upon tumor histology and overall understudied [14–16]. For example, single-agent paclitaxel yielded partial responses in 8 out of 30 evaluable patients with non-adenoid cystic carcinomas but failed to produce a response in 13 evaluable patients with adenoid cystic carcinomas [14].

Nevertheless, there is very limited data on the role of postoperative concurrent chemotherapy in high-risk major salivary gland tumors. In a recent retrospective matched case-control study of 24 patients, Tanvetyanon et al. found that while progression-free survival was not significantly different, 3-year overall survival favored the postoperative chemoradiation group compared to the radiation alone [17]. There was also a hint of improved progression-free survival in the chemoradiation group ($p=0.14$). Among those receiving chemotherapy, eight (67 %) patients received single-agent cisplatin, three (25 %) patients received carboplatin, and one (8 %) patient received cisplatin with fluorouracil. Another study on 78 patients with major salivary gland tumors found concurrent chemotherapy to be an independent predictor of longer disease-free survival ($p=0.05$) [11]. A few studies have examined the role of postoperative concurrent chemotherapy in major and minor salivary gland tumors. These small studies hinted at a pattern of failure in major and minor salivary gland tumors occurring as distant metastasis despite excellent local–regional control with use of postoperative concurrent chemotherapy [18, 19].

Currently, we anticipate the results of Radiation Therapy Oncology Group (RTOG) 1008, which is a randomized phase II study of postoperative chemoradiation versus radiation alone in high-risk malignant salivary gland tumors. RTOG 1008 includes patients with T3/T4 stage or nodal involvement, which were both found to be significant predictors of poor freedom from distant metastasis in our study. RTOG 1008 also includes close (≤ 1 mm) and positive surgical margins which our study did not find to be predictive of distant metastasis; however, margin status was not available for all our patients. The phase II study includes only the following histologic subtypes: intermediate and high-grade adenocarcinoma, intermediate and high-grade mucoepithelioid carcinoma, salivary duct carcinoma, and high-grade acinic cell carcinoma or high-grade adenoid cystic carcinoma. Our study found that salivary ductal carcinoma predicted worse freedom from distant metastasis. However, grading of the other histologic types was not available on retrospective chart review and therefore could not be properly assessed.

Targeted therapy may also be important to further improve outcomes in major salivary gland tumors. These tumors are composed of a wide array of histologic types with likely distinct biologic drivers that may infer susceptibility to targeted agents. So far, there has been limited success using this approach. Therapies targeting c-kit (imatinib), HER2/neu and epidermal growth factor receptor (EGFR) (lapatinib), and EGFR alone (cetuximab) [20] have been evaluated with generally disappointing results.

Conclusion

Distant relapse was the predominant mode of failure despite excellent local and regional control rates in this large cohort of patients with major salivary gland tumors treated with postoperative radiation therapy. Both advanced T category and nodal involvement were independent predictors of distant metastasis. Our data suggests more effective systemic therapy is needed to combat distant relapse.

Conflict of interest Moses Tam, Nadeem Riaz, Lucase Resende Salgado, Daniel E. Spratt, Evangelia Katsoulakis, Alan Ho, Luc G. T. Morris, Richard Wong, Suzanne Wolden, Shyam Rao, and Nancy Lee declare that they have no conflict of interest.

Ethical statement This article does not contain any studies with humans subjected and performed by any of the authors. Institutional Review Board approval was obtained for this study.

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