Received: 6 February 2019 | Revised: 10 May 2019 | Accepted: 4 June 2019

DOI: 10.1002/hed.25843

ORIGINAL ARTICLE

WILEY

A nomogram to estimate the risk of developing distant metastases in parotid cancer

Luca Giovanni Locatello MD[1] | Angelo Cannavicci MD[1] | Chiara Bruno MD[1] | Giandomenico Maggiore MD[1] | Vincenzo Napoleone MSc[2] | Oreste Gallo MD[1]

[1]Department of Otolaryngology - Head and Neck Surgery, Careggi University Hospital, Florence, Italy

[2]Biodigita, Institute for Biostatistical Analysis, Florence, Italy

Correspondence
Luca Giovanni Locatello, Department of Otolaryngology - Head and Neck Surgery, Careggi University Hospital, Florence - Largo Brambilla, 3 - 50134 Firenze, Italy.
Email: locatello.lucagiovanni@gmail.com

Abstract

Background: Parotid cancer (PC) is a heterogeneous group of malignant tumors whose management mainly focuses on locoregional control. However, distant metastases (DM) can represent the most common cause of treatment failure. We have defined the predictors and developed a model that can predict a single patient's risk to develop DM.

Methods: We have analyzed our institutional database of 259 patients with PC and use it to develop a nomogram. C-index and calibration curves were used to assess performance of our model.

Results: DM appeared in 18.9% of patients. Age, cT, pN, perineural invasion, and adenoid cystic carcinoma were significantly associated with distant failure.

Conclusions: We here present the first model to identify patients with PC at high risk of DM. Such tool can be of great value in managing these rare cancers in terms of a more precise prognosis and follow-up while waiting for better systemic therapies to come in the future.

KEYWORDS

head and neck cancer, metastases, nomogram, parotid cancer, risk factors

1 | INTRODUCTION

Parotid cancer (PC) represents a wide array of rare and biologically different malignant tumors.[1,2] Recent epidemiological data show the crude incidence of primary malignant salivary tumors to be 0.9 per 100 000 and almost 80% of them to arise in the parotid gland.[3] Despite recent new insights, molecular carcinogenesis of PC remains at present poorly understood.[4,5] It is thus very hard to develop prevention strategies because no clear etiologies are known, although a recent and well-conducted study has suggested former and current smoker status to be a significant risk factor for PC.[5] Mortality has not changed in the last decades with a 5-year overall survival (OS) of about 60%.[3-5] It is currently established that PC management is chiefly surgical with adjuvant radiation therapy (RT) in most cases.[6] It is crucial for surgery to be performed in a high-volume facility in order to obtain a margin-free resection because it has been recently highlighted how this have a tremendous impact on prognosis.[7] At present, while the optimal management of locoregional disease and facial nerve has reached a large consensus in the literature, we continue to suffer the lack of effective systemic therapy.[8,9]

Distant metastases (DM) can occur on average in 20%-30% of patients (range, 0%-61.5%) and, according to some authors, it is the most common cause for treatment failure.[10-12] Interestingly, their appearance seems unrelated to locoregional control and this poses many issues as far as the global management strategy of PC patients is concerned.[10,12,13] Once diagnosed, prognosis is generally poor and combination chemotherapy (CHT) regimens offer low response rates and duration.[10,12] The risk of DM is known to be associated with several factors such as histologic type, grade, and so forth.[13] To the best of our knowledge, no specific tool exist in the literature that can help head and neck surgeons to predict the risk of DM. Thus, we have updated and analyzed data from our institution to create a model and its

nomogram so that more tailored decisions can be made in planning PC therapy.

2 | PATIENTS AND METHODS

2.1 | Criteria for selecting patients and predictors

We have collected all patients who received surgery for primary PC at the Division of Otorhinolaryngology of the University of Florence, updating our existing data set from 1980 up to 2018.[13] For each patient, after the Institutional Review Board approval, the following data were extracted from medical records: age at diagnosis, sex, date and type of surgery (superficial vs total vs radical parotidectomy), clinical and pathological tumor and nodal stage reclassified whenever possible according to the VIII edition of the TNM system (American Joint Committee on Cancer-Union Internationale Contre le Cancer, 2018),[14] type of neck dissection (none, selective, radical/modified radical), presence of facial nerve paresis/paralysis, presence of skin involvement, and adjuvant therapy performed (RT or CHT). At our institution, all cases had at least ultrasound scans of the salivary glands and the neck and a fine needle aspiration/biopsy before surgery. Only in the last 10 years, gadolinium-enhanced MRI of the head and neck was additionally requested as a staging procedure. Chest x-ray was always obtained before surgery and no other diagnostic techniques were performed unless specific signs or symptoms were evident. Clinical involvement before surgery or intraoperative evidence of facial nerve infiltration was our criteria for performing radical parotidectomy. Follow-up consisted of scheduled clinical and radiological evaluation with the head, neck, and chest CT depending on cases. In the postoperative period, further evaluation such as the liver, brain, or bone imaging was requested only when a clinical suspicion was apparent.

2.2 | Statistical methods

We have adapted our previously implemented model to the present series and we refer the interested readers to that paper for more detailed explanation.[15] Briefly, potential factors predictive of DM were initially searched for by univariate analysis using logistic regression. Then, multivariate analysis was performed for all patients and then separately for each histotypes, incorporating every single covariate at the $P < .1$ level and using multinomial logistic regression model. We chose to determine unadjusted odds ratios with 95% confidence intervals (CIs) by the likelihood ratio and Wald test. We have built the model for all PC by including covariates that exhibited a significant association with the event at the $P < .1$ level at the univariate and at the $P < .2$ level at the multivariate analysis using the backward stepwise elimination method. Multicollinearity was corrected by Akaike information criterion. Concordance was assessed by calculating the C-index and the receiver operating characteristic (ROC) curve which corresponds to C-index in case of binary categorical covariate.[16] Calibration accuracy was assessed grouping into deciles the probability of developing DM and finally represented by a calibration plot.[16,17] Standard statistics were implemented for the descriptive part and OS analysis was conducted using the Kaplan-Meier method. OS was defined as the time elapsing from the month of surgery to death or last follow-up visit. All tests conducted were 2-tailed, and $P < .05$ was considered statistically significant. Overall, missing values represented 4.61% of the data and we have decided to exclude them from the calculations without applying any correction technique because of their low proportion. Columns regarding histological grade and surgical margins were the most heavily affected by missing data.

All statistical analyses were performed using the open source statistical environment R, build 3.5.1 (10-02-2018, The R Foundation for Statistical Computing, available at www.r-project.org) with "rms," "modelgood," and "pROC" additional packages.

3 | RESULTS

A descriptive analysis of the cohort of 259 patients is presented in Table 1. Our population had a mean age of 58 years (range, 10-87; median, 61) and mean follow-up time was 66.58 months ranging from 2 to 221. For patients who were alive at the end of follow-up time, mean follow-up was 77.68 months with a median of 74 months. In almost the totality of cases, patients underwent total parotidectomy (with or without facial nerve sacrifice) and the majority of them (62.6%) received at least I-III or I-IV elective ipsilateral neck dissection. From an histopathologic point of view, 166 (64.3%) patients with PC were considered to be high grade. Facial nerve paralysis was present in 47 out of the 61 cT4 patients (77%) whereas skin infiltration was evident in 13 of them (21.3%). After elective neck dissection, 26 patients deemed to be clinically node negative showed occult nodal metastasis (12.2%) which was a criterion for adjuvant RT. Another one was represented by positive resection margins which were found in 37 cases (14.3%). Overall, postoperative RT was administered in 156 (60.2%) whereas only 20 patients received concomitant RT-CHT. We had 55 (21.2%) local and 27 regional recurrences (10.4%). Mean time to the appearance of local recurrence was 23 months; for neck recurrence, it was 20 months. When OS is considered, Kaplan-Meier curve is shown in Figure 1. In the present work, the OS at 3, 5, and 10 years are 75.9%, 65.4%, and 54.1%, respectively.

Forty-nine patients out of 259 (18.9%) eventually developed DM during the period of observation. There were 29 males (59%) and 20 females (41%, $P = .11$) in this group with a mean

TABLE 1 General and surgical descriptive features of the study population (total no. = 259)

	Characteristics	No. (%)
Sex	Male	151 (58.3)
	Female	108 (41.7)
T classification	cT1	49 (18.9)
	cT2	104 (40.2)
	cT3	45 (17.3)
	cT4	61 (23.6)
N status	cN0	213 (82.2)
	cN1	18 (6.9)
	cN2	26 (10.1)
	cN3	2 (0.8)
Stage	I	47 (18.1)
	II	91 (35.1)
	III	48 (18.5)
	IV	73 (28.2)
Type of surgical resection	Superficial parotidectomy	19 (7.3)
	Total parotidectomy (with preservation of facial nerve)	162 (62.6)
	Radical parotidectomy (with sacrifice of facial nerve)	78 (30.1)
Neck management	No dissection	28 (10.8)
	Selective neck dissection (levels I-IV)	162 (62.6)
	(Modified) Radical neck dissection	69 (26.6)

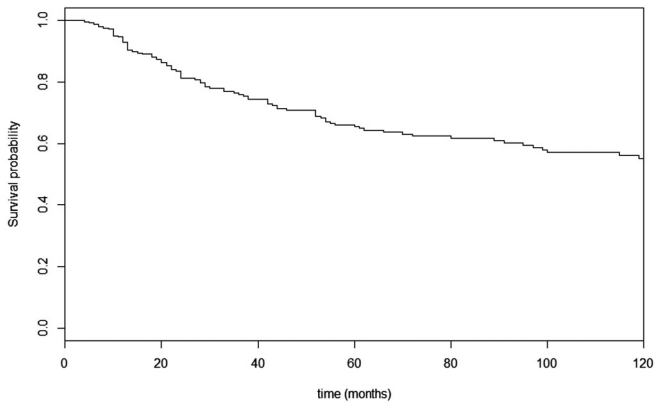

FIGURE 1 Overall survival curve according to Kaplan-Meier method with 10 years of follow-up in our population

age of 53.9 years (range, 11-78). In Table 2, all histotypes included in the present series and tumor specific proportion of DM are shown. In the present series, mucoepidermoid carcinoma (MEC), acinic cell carcinoma, and adenoid cystic carcinoma (ACC) were the most represented types of PC. The latter

TABLE 2 Histologic types and proportion of distant metastases (DM) in the study population

Histotype	No. of cases (%)	No. of DM (%)
Mucoepidermoid carcinoma	56 (21.6)	6 (10.7)
Adenoid cystic carcinoma	47 (18.1)	15 (31.9)
Acinic cell carcinoma	39 (15.1)	5 (12.8)
Carcinoma ex pleomorphic adenoma	30 (11.6)	3 (10)
Adenocarcinoma, NOS	32 (12.4)	7 (21.8)
Salivary duct carcinoma	17 (6.6)	5 (29.4)
Epithelial-myoepithelial carcinoma	14 (5.4)	2 (14.2)
Squamous cell carcinoma	12 (4.6)	1 (8.3)
Basal cell adenocarcinoma	6 (2.3)	2 (33.3)
Undifferentiated carcinoma	5 (1.9)	3 (60)
Clear cell carcinoma	1 (0.4)	0 (0)
Total	259 (100)	49 (18.9)

showed a particularly high rate of DM with almost one out of three patients affected. Patients with DM had more often high grade tumors (81.6% vs 59.52%, $P = .004$) and more often perineural invasion (PNI) was found at pathological examination (38.7% vs 16.1%, $P = .001$). On the other hand, no significant differences were spotted in terms of higher cT proportion (53% in cM1 vs 61.9% in cM0 cohort, $P = .06$) or positive surgical margins (16.3% vs 13.8%, $P = .65$) between the two groups. A very intriguing result is that neither local nor regional recurrence was associated with DM growth. Among the 49 patients with DM, 12 (24.4%) had also local relapses and 6 (12.4%) showed regional failure. In other words, 31 of 49 (63.2%) patients in the present series developed DM despite locoregional control was obtained thanks to surgery/RT.

Mean time to DM appearance was 52.32 months with a range of 0-142 months. When only ACC is considered, DM became apparent about 7 years after surgery on average (84.6 months). Regarding site of DM, the lungs (33, 67.3%) were mostly affected followed by the skeletal bones (7, 14.3%), brain (2, 5.1%), and multiple sites (6, 12.24%). Among the 95 (36.6%) patients who died during the follow-up, excluding two of them whose death was unrelated to PC, we notice how 49 of 93 (52.6%) patients had DM as the main or subsidiary cause of death. We have then investigated whether the time to DM appearance could affect oncologic outcomes. Taking into account all histotypes, survival curves (Figure 2) suggest early DM portends a significantly poorer prognosis when cutoff is set at 1 year (log-rank test, $P = .03$). For other cutoffs, differences were not significant but trend was always in favor of late onset DM (log-rank test for 24 months, $P = .21$; for 36 months, $P = .24$; for 60 months, $P = .67$). When only ACC is considered, again a higher OS was found in case of late-appearing

DM but differences did not reach significance (log-rank test for 12 months, $P = .83$; for 24 months, $P = .91$; for 36 months, $P = .92$; for 60 months, $P = .91$).

We have then performed univariate (Table 3) and multivariate analyses (Table 4) in order to identify the strongest predicting factors of DM. Afterward, by choosing among the aforementioned covariates, we built a general model and its user-friendly representation (Figure 3) to estimate the risk of developing DM. Figure 4 shows instead the strength of our nomogram in predicting the DM expressed by calibration plot and ROC curve. Its C-index was 71.5% and we can see how the model loses some power (ie, calibration is lower) when DM predicted risk exceeds 50% (Figure 4). We eventually tried to develop some histology-specific models for the most represented types in our series. Unfortunately, not MEC or ACC cases were sufficient to develop such model because of too low statistical power to build a nomogram.

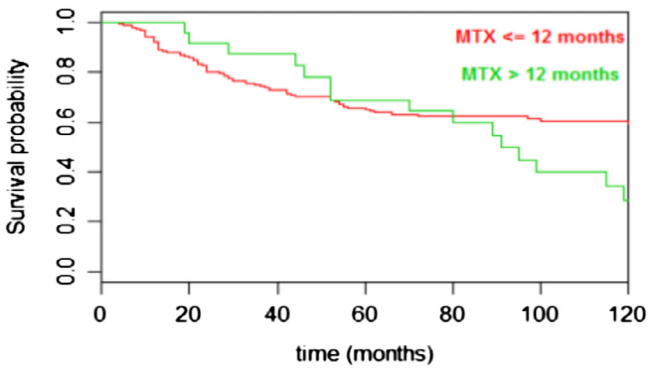

FIGURE 2 Overall survival curve for all histotypes according to time to appearance of distant metastases (DM) and with cutoff time at 12 months. MTX stands for "metastases." Log-rank test, $P = .03$ [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In the literature, incidence of DM in salivary gland malignant tumors is estimated to be around 20%-30%.[18,19] Even in

TABLE 4 Factors predictive of developing distant metastases (DM) in parotid malignancies at multivariate analysis and that have been incorporated into the graphical model

Covariates	Beta (SE)	ORCI 95% (Wald)	*P* value
Age	.018 (0.010)	0.982* 0.963-1.002	.06
cT	.275 (0.166)	1.317* 0.951-1.823	.09
pN+	.715 (0.373)	2.044* 0.984-4.246	.06
PNI	.838 (0.399)	2.312** 1.058-5.053	.04
ACC vs other histology	.706 (0.422)	2.026* 0.886-4.633	.09

Abbreviations: ACC, adenoid cystic carcinoma; CI, confidence interval; OR, odds ratio.
*$P < .1$; **$P < .05$.

TABLE 3 Univariate analysis of all factors considered to be predictors of developing distant metastases

Covariates	OR	*P* value	Covariates (cont.)	OR	*P* value
Sex	1.046	.89	Skin infiltration	1.985	.27
Age	0.988	.15	PNI	3.260***	.001
cT	1.416**	.02	Adjuvant RT	4.234***	.000
cN	1.205	.20	Adjuvant CHT	3.220**	.02
cN0 vs cN+	2.225**	.03	Local recurrence	1.260	.54
pT	1.546***	.004	Regional recurrence	1.256	.64
pN	1.323*	.02	Mucoepidermoid carcinoma	0.447*	.08
pN0 vs pN+	1.323*	.02	Adenoid cystic carcinoma	2.454**	.01
Occult N	1.326	.57	Salivary duct carcinoma	1.875	.26
Stage	1.424**	.02	Carcinoma ex pleomorphic adenoma	0.442	.19
Facial nerve paralysis	3.624***	.000	Acinic cell carcinoma	0.588	.29
Grade	2.928***	.007	Epithelial-myoepithelial carcinoma	0.770	.74
Type of resection (superficial vs total parotidectomy)	0.408***	.001	Squamous cell carcinoma	0.377	.36
Resection margins	1.204	.67	Basal cell adenocarcinoma	2.191	.37

Note: Occult N refers to a clinically N0 patients who shows node metastases at final pathological report.
Abbreviations: CHT, chemotherapy; OR, odds ratio; PNI, perineural invasion; RT, radiation therapy.
*$P < .1$; **$P < .05$; ***$P < .01$.

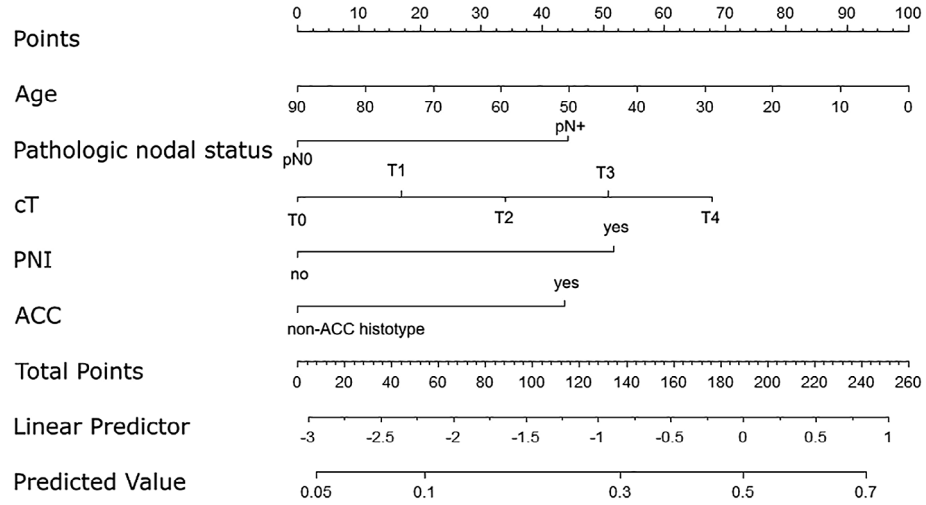

FIGURE 3 A nomogram to predict the risk of developing distant metastases (DM) from a primary parotid gland malignant tumor. Each factor (age, pathologic nodal status etc.) must be vertically referred to the "Points" line and the sum of points for each variable is then calculated for the single patient. At the bottom, total points correspond, by vertical downward projection, to the estimated overall probability of developing DM. As a practical example, a 55-year-old man with a mucoepidermoid carcinoma causing facial nerve paralysis and which turns out to have PNI and occult neck disease at final pathologic report has got a very high probability (210 points, nearly 60%) of developing DM. On the other hand, a small capsulated cT1 acinic cell carcinoma with no regional metastases or PNI in a 70-year-old woman has a negligible risk of DM (40 point, less than 10%). C-index for the model is 0.715. ACC, adenoid cystic carcinoma; cT, clinical T classification according to TNM VIII ed.; PNI, perineural invasion

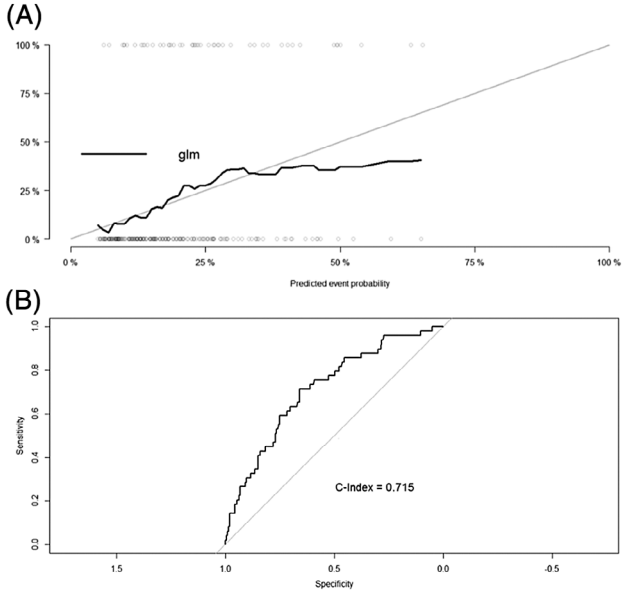

FIGURE 4 Measures of accuracy of the nomogram for the prediction of developing distant metastases (DM). A, Calibration plot for DM risk model. It shows ideal (straight line) correspondence between models predicted (plotted in the x axis) and actual observed DM development in our series (plotted in the y axis). glm, generalized linear model. B, Receiver operating characteristic curve with C-index

our series, one in five cases of PC eventually developed DM and this risk depends upon numerous variables which have been variously investigated in the last decades.[11-13,19] In the present paper, we have confirmed the prediction value of some of them and proposed a practical instrument to estimate individual's chance to develop disseminated disease.

Clinical and pathological factors, such as tumor grade, margin status, PNI, or age, have proven to be more useful to predict prognosis than the sheer clinical or pathological stage.[16] About 20 years ago, individualized prognostic scores for PC had already been developed by Vander Poorten et al.[20] Such prognostic tool has also been subsequently applied to several cohorts, proving the overall validity of this classification.[21-24] Nevertheless, the TNM system for major salivary gland cancer, even in its latest edition, does not take into account the aforementioned variables.[14]

In this regard, nomograms could help to easily consider important prognostic factors beyond the mere T and N classification. The Memorial Sloan Kettering Cancer Center has recently developed and externally validated three nomograms to predict overall cancer-specific survival and recurrence (therein defined as local, regional, and distant) for major salivary glands cancer.[25] Remarkably, their latter model was quite similar to ours in terms of covariates included.[25] In 2015, the same group had presented their data on 301 salivary cancers of the head and neck and they also found cT, pN, and PNI as significant predictors of DM.[26] In their cohort, 266 (88%) were primary parotid lesions and their reported incidence of DM for salivary duct and adenocarcinoma was comparable to ours whereas for ACC it was lower.[26]

In the last years, we have found other three large published series of PC that need to be discussed.[27-29] The first is a data set

of 165 patients from India that identifies nodal disease as the most important risk factor affecting survival.[27] Of note, they declared a mean and median follow-up time of 43.5 and 38 months which explains the only 14 cases (8.4%) of DM reported.[27] The second is a multi-institutional study from Japan considering 195 surgically treated PC cases.[28] Authors identified only pathological nodal positivity as a risk factor for a lower DM-free survival in multivariate analysis.[28] They also found an occult nodal disease in only 12 of 195 (6.1%) patients which is the half compared to our findings; anyway, these figures can be better interpreted in light of an elective neck dissection percentage of 33.7% vs the 62.6% in the present work. Finally, a report from Princess Margaret Cancer Center of 215 patients with PC confirmed the predictive role of nodal positivity in DM development and suggested lymphovascular invasion to be an additional factor.[29] They report a DM rate of 13.4% whereas 5- and 10-year OS were higher than ours and this could be explained by their far lower proportion of ACC in the data set (9.3% vs 18.1%).[29]

The independence of locoregional control from distant failure for PC had been already suggested many years ago and the present paper represents an update from two previous works conducted at our institution.[13,30] By using our model, it is possible to estimate a personalized risk of developing DM and this could help surgeons both to identify which patients would benefit from an aggressive treatment strategy (ie, once locoregional control is achieved, it would become extremely unlikely to die of distant relapse) and to select which patients need a more intense (and costly) follow-up strategy. For instance, it is known that positron emission tomography (PET) imaging has an excellent sensitivity (92%) and a good specificity (82%) for staging and restaging PC.[31] A retrospective work has shown PET/CT to be the deciding exam between curative or palliative intent in 14.5% of patients with PC.[32] In addition, some specific PET parameters have been recently shown to predict DM-free and disease-specific survival.[33,34] Thus, in face of no clear guideline indication about whether and when to perform PET imaging in PC cases, a more precise estimate of the individual's risk could become the basis of a more rational and cost-effective choice.[35]

In terms of therapeutic management, when confronted with the over 20 primary malignant tumors described in the latest WHO classification, it is currently accepted that response to CHT is histotype-specific.[36,37] Platinum-based polychemotherapy is superior to monotherapy against ACC whereas paclitaxel or gemcitabine are active against adenocarcinoma or MEC.[36,38] However, oncological results of conventional regimens remain disappointing and the same is true for newer cytotoxic drugs.[36] In addition, given the relative indolent nature of most metastatic lesions, most oncologists agree to initiate CHT only in face of symptomatic or rapidly progressing disease.[36] Regarding targeted drugs and biomarker-driven CHT, figures are slightly better. In particular, anti-HER2 drugs or androgen-deprivation therapy in disseminated salivary duct carcinomas have demonstrated complete or partial responses even for several years with negligible toxicity compared to combination CHT.[36,39,40]

Nowadays, salvage surgery for DM maintains a niche indication and metastasectomy remains so far the only local effective therapy for ACC disseminated to the lungs.[6,41] A recent study has clarified that the advantage in terms of prognosis exists only when complete resection is performed (regardless of the number and the site of lung lesions) and the time to appearance of DM after primary resection is >36 months.[41] In our series, we have shown a similar trend in terms of late-onset DM but, for ACC cases only, we could not find a significant difference (log-rank test for 36 months, $P = .92$).

There are three major limitations of the present study: first, the impossibility of creating a histology-specific nomogram for DM. Although these tools would have indeed more clinical significance for the head and neck surgeon, yet only few centers could have the statistical power to reach significance and future collaborative efforts seem to be the only way to solve this issue.[42] Two good examples are the works published not long ago by Ganly et al and by Xu and coworkers.[43,44] In the former, authors present several nomograms for overall and cancer-specific survival and recurrence-free probability from a multi-institutional series of 438 ACC cases of major and minor salivary glands including sinonasal disease.[43] The latter work illustrates a Chinese cohort of 75 MEC of the hard and soft palate (all of which had neither regional nor distant disease preoperatively) and a MEC-specific/site-specific prediction model is proposed.[44]

Another problem comes from the prognostic factors analyzed in ours and other published nomograms which might be somehow considered "coarse" in today's scientific setting. New findings of several molecular markers are being published every year and it seems imperative to rapidly translate them into clinical practice thus refining our prediction tools.[45,46] For instance, ACC's indolent behavior is explained by its scarce genetic instability whereas salivary duct carcinomas are characterized by a high mutation rate and the expression of androgen receptor.[45] Therefore, this latter type of PC has an aggressive clinical course yet promising trials are being conducted using androgen-deprivation therapy.[36] Even more recently, it has been demonstrated how programmed death-1 ligand-1 (PD-L1) expression can significantly predict outcomes and the risk of developing DM.[46] This opens new perspectives given the upcoming role of anti-PD1 drugs in squamous and non-squamous carcinomas of head and neck, including PC.[46,47] In this regard, the aforementioned nomogram for MEC of the minor salivary glands has the great merit of including into the model the expression of stem cell markers CD44, CD133, SOX2, and Nanog as negative prognostic factors.[44] A paper has just suggested the expression of cancer testis antigen MAGE-A4 to be associated with a low risk of DM in a large series of salivary gland cancer from Zurich.[48]

However, identification of such biological predictors is still at beginning and future studies are eagerly anticipated. The last point is that, as other published models, ours is to be validated in other external cohort in order to gain generalizability.[17]

5 | CONCLUSION

This is the first nomogram predictive of DM in patients with PC. Today, despite no successful treatment strategies are available to manage distant failure of PC, we believe the creation of such model could represent a crucial point to assess follow-up, prognosis and, in the near future, a more effective systemic targeted treatment. In order to enhance its value, future integration with molecular oncology and international multicenter studies are needed so that a true tailored approach can be applied to these rare and complex group of head and neck cancers.

CONFLICT OF INTEREST

All authors declare they have nothing to disclose.

AUTHOR CONTRIBUTIONS

L.G.L., A.C., C.B. performed data curation, formal analysis, investigation, methodology, validation, visualization, and writing of original draft. G.M. handled the project administration, resources, supervision, and review, and editing. V.N. performed formal analysis, methodology, software, validation, and visualization. O.G. performed conceptualization, data curation, project administration, resources, supervision, and review, and editing.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Luca Giovanni Locatello https://orcid.org/0000-0002-1879-5580
Angelo Cannavicci https://orcid.org/0000-0002-9537-2549
Chiara Bruno https://orcid.org/0000-0002-2506-4452

REFERENCES

1. Salivary Gland Cancer Treatment (Adult) (PDQ®). PDQ Cancer Information Summaries [Internet]. May 3, 2018. Bethesda, MD: National Cancer Institute.
2. Seethala RR, Stenman G. Update from the 4th edition of the World Health Organization classification of head and neck tumours: tumors of the salivary gland. *Head Neck Pathol*. 2017;11(1):55-67.
3. de Ridder M, Balm AJ, Smeele LE, Wouters MW, van Dijk BA. An epidemiological evaluation of salivary gland cancer in the Netherlands (1989–2010). *Cancer Epidemiol*. 2015;39(1):14-20.
4. Gallo O, Franchi A, Bianchi S, Boddi V, Giannelli E, Alajmo E. p53 oncoprotein expression in parotid gland carcinoma is associated with clinical outcome. *Cancer*. 1995;75(8):2037-2044.
5. Sawabe M, Ito H, Takahara T, et al. Heterogeneous impact of smoking on major salivary gland cancer according to histopathological subtype: a case-control study. *Cancer*. 2018;124(1):118-124.
6. Thielker J, Grosheva M, Ihrler S, Wittig A, Guntinas-Lichius OG. Contemporary management of benign and malignant parotid tumors. *Front Surg*. 2018;5:39.
7. Morse E, Fujiwara RJ, Judson B, Prasad ML, Mehra S. Positive surgical margins in parotid malignancies: institutional variation and survival association. *Laryngoscope*. 2019;129:129-137.
8. Lombardi D, McGurk M, Van der Poorten V, et al. Surgical treatment of salivary malignant tumors. *Oral Oncol*. 2017;65:102-113.
9. Guntinas-Lichius O, Silver CE, Thielker J, et al. Management of the facial nerve in parotid cancer: preservation or resection and reconstruction. *Eur Arch Otorhinolaryngol*. 2018;275:2615-2626.
10. Lewis AG, Tong T, Maghami E. Diagnosis and management of malignant salivary gland tumors of the parotid gland. *Otolaryngol Clin North Am*. 2016;49(2):343-380.
11. Renehan AG, Gleave EN, Slevin NJ, McGurk M. Clinicopathological and treatment-related factors influencing survival in parotid cancer. *Br J Cancer*. 1999;80(8):1296-1300.
12. Schwentner I, Obrist P, Thumfart W, Sprinzl G. Distant metastasis of parotid gland tumors. *Acta Otolaryngol*. 2006;126(4):340-345.
13. Gallo O, Franchi A, Bottai GV, Fini-Storchi I, Tesi G, Boddi V. Risk factors for distant metastases from carcinoma of the parotid gland. *Cancer*. 1997;80(5):844-851.
14. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
15. Gallo O, Locatello LG, Larotonda G, Napoleone V, Cannavicci A. Nomograms for prediction of postoperative complications in open partial laryngeal surgery. *J Surg Oncol*. 2018;118:1050-1057.
16. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol*. 2008;26(8):1364-1370.
17. Tham T, Machado R, Herman SW, Kraus D, Costantino P, Roche A. Personalized prognostication in head and neck cancer: a systematic review of nomograms according to the AJCC precision medicine core (PMC) criteria. *Head Neck*. 2019;1-12.
18. Franchi A, Gallo O. Distant metastases and management. In: Bradley PJ, Guntinas-Lichius O, eds. *Salivary Gland Disorders and Diseases: Diagnosis and Management* chapter 34. Stuttgart, Germany: Thieme; 2011:341-349.
19. Bradley PJ. Distant metastases from salivary glands cancer. *ORL*. 2001;63(4):233-242.
20. Vander Poorten VL, Balm AJ, Hilgers FJ, et al. The development of a prognostic score for patients with parotid carcinoma. *Cancer*. 1999;85(9):2057-2067.

21. Vander Poorten VL, Hart AA, van der Laan BF, et al. Prognostic index for patients with parotid carcinoma: external validation using the nationwide 1985–1994 Dutch Head and Neck Oncology Cooperative Group database. *Cancer*. 2003;97(6):1453-1463.
22. Paderno A, Tomasoni M, Mattavelli D, Battocchio S, Lombardi D, Nicolai P. Primary parotid carcinoma: analysis of risk factors and validation of a prognostic index. *Eur Arch Otorhinolaryngol*. 2018;12:1-3.
23. Takahama A Jr, Sanabria A, Melo Benevides G, Paes de Almeida O, Paulo Kowalski L. Comparison of two prognostic scores for patients with parotid carcinoma. *Head Neck*. 2009;31(9):1188-1195.
24. Lu CH, Liu CT, Chang PH, et al. Validation and comparison of the 7th edition of the American Joint Committee on Cancer staging system and other prognostic models to predict relapse-free survival in Asian patients with parotid cancer. *J Cancer*. 2016;7(13):1833-1841.
25. Hay A, Migliacci J, Zanoni DK, et al. Validation of nomograms for overall survival, cancer-specific survival, and recurrence in carcinoma of the major salivary glands. *Head Neck*. 2018;40(5):1008-1015.
26. Ali S, Bryant R, Palmer FL, et al. Distant metastases in patients with carcinoma of the major salivary glands. *Ann Surg Oncol*. 2015;22(12):4014-4019.
27. Chakrabarti S, Nair D, Malik A, et al. Prognostic factors in parotid cancers: clinicopathological and treatment factors influencing outcomes. *Indian J Cancer*. 2018;55(1):98.
28. Honda K, Tanaka S, Shinohara S, et al. Survival in patients with parotid gland carcinoma–results of a multi-center study. *Am J Otolaryngol*. 2018;39(1):65-70.
29. Erovic BM, Shah MD, Bruch G, et al. Outcome analysis of 215 patients with parotid gland tumors: a retrospective cohort analysis. *J Otolaryngol Head Neck Surg*. 2015;44(1):43.
30. Mannelli G, Cecconi L, Fasolati M, Santoro R, Franchi A, Gallo O. Parotid adenoid cystic carcinoma: retrospective single institute analysis. *Am J Otolaryngol*. 2017;38(4):394-400.
31. Sharma P, Jain TK, Singh H, et al. Utility of 18F-FDG PET-CT in staging and restaging of patients with malignant salivary gland tumours: a single-institutional experience. *Nucl Med Commun*. 2013;34(3):211-219.
32. Razfar A, Heron DE, Branstetter BF IV, Seethala RR, Ferris RL. Positron emission tomography-computed tomography adds to the management of salivary gland malignancies. *Laryngoscope*. 2010;120(4):734-738.
33. Lim WS, Oh JS, Roh JL, et al. Prediction of distant metastasis and survival in adenoid cystic carcinoma using quantitative 18F-FDG PET/CT measurements. *Oral Oncol*. 2018;77:98-104.
34. Lee SH, Roh JL, Kim JS, et al. Detection of distant metastasis and prognostic prediction of recurrent salivary gland carcinomas using 18F-FDG PET/CT. *Oral Dis*. 2018;24:940-947.
35. Colevas AD, Yom SS, Pfister DG, et al. NCCN Guidelines Insights: Head and Neck Cancers, version 1.2018. *J Natl Compr Cancer Netw*. 2018;16(5):479-490.
36. Alfieri S, Granata R, Bergamini C, et al. Systemic therapy in metastatic salivary gland carcinomas: a pathology-driven paradigm? *Oral Oncol*. 2017;66:58-63.
37. El-Naggar AK, ed. *WHO Classification of Head and Neck Tumours*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.
38. Schvartsman G, Pinto NA, Bell D, Ferrarotto R. Salivary gland tumors: molecular characterization and therapeutic advances for metastatic disease. *Head Neck*. 2019;41(1):239-247.
39. D'heygere E, Meulemans J, Vander Poorten V. Salivary duct carcinoma. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26(2):142-151.
40. van Boxtel W, Locati LD, van Engen-van Grunsven AC, et al. Adjuvant androgen deprivation therapy for poor-risk, androgen receptor–positive salivary duct carcinoma. *Eur J Cancer*. 2019;110:62-70.
41. Girelli L, Locati L, Galeone C, et al. Lung metastasectomy in adenoid cystic cancer: is it worth it? *Oral Oncol*. 2017;65:114-118.
42. Hu YH, Li W, Zhang CY, et al. Prognostic nomogram for disease-specific survival of carcinoma ex pleomorphic adenoma of the salivary gland. *Head Neck*. 2017;39(12):2416-2424.
43. Ganly I, Amit M, Kou L, et al. Nomograms for predicting survival and recurrence in patients with adenoid cystic carcinoma. An international collaborative study. *Eur J Cancer*. 2015;51(18):2768-2776.
44. Xu W, Wang Y, Qi X, et al. Prognostic factors of palatal mucoepidermoid carcinoma: a retrospective analysis based on a double-center study. *Sci Rep*. 2017;7:43907.
45. Son E, Panwar A, Mosher CH, Lydiatt D. Cancers of the major salivary gland. *J Oncol Pract*. 2018;14:99-108.
46. Suzuki C, Kiyota N, Imamura Y, et al. P1-008 efficacy and safety of nivolumab for previously treated non-squamous cell carcinoma of the head and neck. *Ann Oncol*. 2018;29(Suppl_7):mdy375.
47. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Eng J Med*. 2016;375(19):1856-1867.
48. Vital D, Ikenberg K, Moch H, Roessle M, Huber GF. The expression of the cancer testis antigen MAGE A4: a favorable prognostic biomarker in salivary gland carcinomas related to low tumor grading. *Laryngoscope Investig Otolaryngol*. 2018;3:182-190.

How to cite this article: Locatello LG, Cannavicci A, Bruno C, Maggiore G, Napoleone V, Gallo O. A nomogram to estimate the risk of developing distant metastases in parotid cancer. *Head & Neck*. 2019;41:3309–3316. https://doi.org/10.1002/hed.25843