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Outcomes and prognostic factors in parotid gland malignancies: A 10-year single center experience

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Abstract

Objectives: To describe a 10-year single center experience with parotid gland malignancies and to determine factors affecting outcomes.

Study Design: Retrospective review.

Methods: The institutional cancer registry was used to identify patients treated surgically for malignancies of the parotid gland between January 2005 and December 2014. Clinical and pathologic data were collected retrospectively from patient charts and analyzed for their association with overall survival (OS) and disease-free survival (DFS).

Results: Two hundred patients were identified. Mean age at surgery was 57.8 years, and mean follow-up time was 52 months. One hundred two patients underwent total parotidectomy, while 77 underwent superficial parotidectomy, and 21 underwent deep lobe resection. Seventy patients (35%) required facial nerve (FN) sacrifice. Acinic cell carcinoma was the most common histologic type (22%), followed by mucoepidermoid carcinoma (21.5%) and adenoid cystic carcinoma (12.5%). Twenty-nine patients (14.5%) experienced recurrences, with mean time to recurrence of 23.6 months (range: 1-82 months). Five- and 10-year OS were 81% and 73%, respectively. Five- and 10-year DFS were 80% and 73%, respectively. In univariate analyses, age > 60, histologic type, positive margins, high grade, T-stage, node positivity,

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perineural invasion, and FN involvement were predictors of OS and DFS. In the multivariate analysis, histology, positive margins, node positivity, and FN involvement were independent predictors of OS and DFS.

Conclusions: Our single-center experience of 200 patients suggests that histology, positive margins, node positivity, and FN involvement are independently associated with outcomes in parotid malignancies.

Level of Evidence: 4

KEYWORDS

acinic cell carcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, parotid carcinoma, parotid gland, salivary glands

1 | INTRODUCTION

Neoplasms of the salivary glands comprise a diverse group of at least 20 histologically distinct disease entities and frequently pose diagnostic and management challenges.[1] This may be further complicated by histologic diversity within the same surgical specimen and co-occurrence with benign entities (eg, carcinoma ex pleomorphic adenoma).[2] Together, salivary gland neoplasms account for approximately 6% of all head and neck neoplasms,[3] with an annual incidence of 0.5 to 2.0 per 100 000 in the general population.[4] Approximately 80% of these tumors involve the parotid gland. An estimated 20% to 25% are malignant in nature, with mucoepidermoid carcinoma described as the most common histology. There are differences in incidence between males and females, with mucoepidermoid carcinomas more common in males and acinic cell and adenoid cystic carcinomas found more commonly among females.[5]

Surgical resection is the primary treatment for salivary malignancy. Prognosis varies widely by histologic subtype, with survival ranging from 95% to 100% for polymorphous low-grade adenocarcinoma[6] to 23% to 50% in cases of high-grade mucoepidermoid carcinoma.[7,8] A variety of factors have been evaluated for prognostic significance, including histological subtype, tumor grade and stage, cervical lymphadenopathy, facial nerve (FN) involvement, perineural invasion (PNI), and positive surgical margins.[9-12] Molecular markers have also been discovered that are associated with prognosis and survival,[13,14] but none are widely used in clinical practice. In addition, detailed single institution reviews of parotid malignancies over a substantial time period remain limited. We therefore sought to utilize our own experience to provide insight into demographics and clinical features of parotid gland malignancies over a 10-year period, and thereby determine clinical and pathologic factors affecting survival and recurrence.

2 | MATERIALS AND METHODS

This study was reviewed by the Massachusetts Eye and Ear Infirmary (MEEI) institutional review board and deemed to be of minimal risk. The institutional cancer registry was used to identify all patients who underwent surgery for primary malignancy of the parotid gland at MEEI, a tertiary referral center in Boston, Massachusetts, between January 2005 and December 2014. Patient charts were reviewed, and relevant demographic, clinical, and pathologic data were recorded.

Overall survival (OS) was defined as the time elapsed between the date of surgery and the date of last documented communication with the patient. Disease-free survival (DFS) was calculated as the time elapsed between the date of surgery and the date of last documented note from an oncologic provider (surgeon, medical oncologist, or radiation oncologist). For patients who had a documented recurrence, DFS was calculated as the time elapsed between the date of surgery and the date of documented recurrence.

For survival analyses, all patients were assumed to be censored unless documented as deceased (for analyses of OS) or having a recurrence (for analyses of DFS). For Cox proportional hazards models, all predictor variables were simplified to binary values as follows: age classified as >60 or ≤60, T-stage classified as low (T1 or T2) or high (T3 or T4), N-stage classified as negative (N0) or positive (N1, N2, or N3), overall stage classified as early (stage I or II) or advanced (stage III or IV), grade classified as low (grade 1) or high (grade 2 or 3), and margin status classified as negative or positive (microscopically or grossly positive). JMP-Pro version 13 (SAS) was used to generate Kaplan-Meier survival curves and for univariate and multivariate Cox proportional hazards models.

3 | RESULTS

Two hundred patients (104 men, 96 women, with average age of 57.8 years [range: 10-96 years]) were treated surgically for primary malignancies of the parotid gland at MEEI between January 2005 and December 2014. The most common histologies were acinic cell carcinoma (N = 44), mucoepidermoid carcinoma (N = 43), adenoid cystic carcinoma (N = 25), salivary duct carcinoma (N = 18), and carcinoma ex pleomorphic adenoma (N = 15). See Table 1 for a summary of histologic subtypes. For Kaplan-Meier curves and Cox proportional hazards models, all histologic types other than these top five were grouped under the category “Other Histologies.”

TABLE 1 Summary of histologic types

Histology	N	%
Acinic cell carcinoma	44	22
Mucoepidermoid carcinoma	43	21.5
Adenoid cystic carcinoma	25	12.5
Salivary duct carcinoma	18	9
Carcinoma ex pleomorphic adenoma	15	7.5
Squamous cell carcinoma	14	7
Adenocarcinoma NOS	5	2.5
Cystadenocarcinoma	5	2.5
Epithelial-myoepithelial carcinoma	4	2
Basal cell adenocarcinoma	3	1.5
Lymphoepithelial carcinoma	3	1.5
Mammary analog secretory carcinoma	3	1.5
Neuroendocrine carcinoma	3	1.5
Basaloid carcinoma	2	1
Carcinoma NOS	2	1
Merkel cell carcinoma	2	1
Myoepithelial carcinoma	2	1
Adenocarcinoma, ductal type	1	0.5
Adenosquamous carcinoma	1	0.5
Clear cell carcinoma	1	0.5
Myofibroblastic sarcoma	1	0.5
Rhabdomyosarcoma	1	0.5
Sebaceous adenocarcinoma	1	0.5
Spindle cell carcinoma	1	0.5
Total	**200**	**100**

Abbreviation: NOS, not otherwise specified.

3.1 | Treatment regimens

Of 200 patients, 77 (33.5%) underwent superficial parotidectomy, 21 (10.5%) underwent deep lobe resection, 14 (7%) underwent subtotal parotidectomy, and 88 (44%) underwent total parotidectomy. Seventy patients (35%) underwent sacrifice of one or more branches of the FN. Seventy-four patients (37%) underwent cervical lymphadenectomy. Seventy-seven patients (38.5%) underwent surgery alone, while the remainder received adjuvant therapy, with 81 (41%) receiving adjuvant radiation therapy (XRT) alone, 2 (1%) receiving adjuvant chemotherapy alone, and 39 (19.5%) receiving adjuvant chemotherapy and XRT.

3.2 | Pathologic characteristics

Patient charts were retrospectively reviewed for data regarding AJCC tumor-node-metastasis (TNM) staging, margin status, grade, FN involvement, PNI, lymphovascular invasion (LVI), and extracapsular extension (ECE). Patients were distributed across all T stages, including Tis (n = 6, 3%), T1 (n = 66, 33%), T2 (n = 51, 25.5%), T3 (n = 31, 15.5%), and T4 (n = 46, 23%). One hundred fifty-seven patients (78.5%) were N0, with 31 being pN0 and 126 being cN0. The remainder were N1 (n = 15, 7.5%), N2 (n = 27, 13.5%), and N3 (n = 1, 0.5%). Histologic grade was determined at the time of original pathologic diagnosis and was classified as low grade (grade 1) or high grade (grade 2 or 3). Grade 2 tumors were classified as high grade to keep approximately equal numbers of high and low grade tumors. Grade reporting was incomplete, with 82 patients (41%) having no grade reported. All 18 cases of salivary duct carcinoma were high grade, and of the remaining cases, 55 (27.5% of total) were high grade, while 45 (22.5% of total) were low grade. FN involvement was seen in 44 patients (22%), PNI in 51 (25.5%), LVI in 26 (13%), and ECE in 5 (2.5% overall, 10% of node-positive). Sixty-eight patients (34%) had microscopic or grossly positive margins, while 132 (66%) had negative margins. Associations between histologic type and clinicopathologic features are shown in Table 2.

3.3 | Follow-up and recurrence

Mean follow-up time was 4.1 years, and 36 patients (18%) were documented as deceased over the follow-up period. There were 29 documented recurrences (14.5% of cases), with a mean time to recurrence of 23.6 months. Distant recurrence (18/29 cases, 62%) was more common than local (11/29 cases, 38%) or regional (1/29 cases, 3%) recurrence, with the most common sites for metastasis being the lung (14/18 cases), brain, bone, mediastinum, liver, and peritoneum. Cases of local recurrence were found in the parotid bed (5/11 cases), temporal bone, external auditory canal, and infratemporal fossa. One patient experienced both local and regional recurrence, while one patient experienced both local recurrence and distant metastasis. Four of 11 patients with local recurrence underwent salvage surgery.

3.4 | Survival analysis

Total OS (Figure 1A) was 87%, 81%, and 73%, while total DFS (Figure 1B) was 84%, 80%, and 73% at 2 years, 5 years, and 10 years, respectively. There was a significant impact of histology on OS and DFS, with salivary duct carcinoma and other histologies having the poorest OS and DFS at 2 and 5 years and adenoid cystic carcinoma, with a significant number of late recurrences and late deaths, having the poorest OS and DFS at 10 years (P = .0016 and .0012 for OS and DFS, respectively). Accordingly, adenoid cystic carcinoma had a significantly higher average time to recurrence than all other histologic types (3.92 vs 1.29 years, P = .0017).

3.5 | Predictors of survival

In the univariate Cox proportional hazards model (n = 200 unless otherwise specified), predictors of OS and DFS included age > 60 (hazard ratio, HR [OS] = 4.1, P = .0001; HR [DFS] = 3.5, P < .0001), "other"

TABLE 2 Breakdown of histopathologic characteristics by tumor histology

	Acinic cell	Mucoepidermoid	Adenoid cystic	Salivary duct	Carcinoma ex pleo	Other histology	*P* value (chi-square)
PNI							
No	42 (95)	39 (91)	12 (48)	5 (28)	13 (87)	38 (69)	<.0001
Yes	2 (5)	4 (9)	13 (52)	13 (72)	2 (13)	17 (31)	
N stage							
N0	40 (91)	38 (88)	22 (88)	6 (33)	12 (80)	39 (71)	<.0001
N+	4 (9)	5 (12)	3 (12)	12 (67)	3 (20)	16 (29)	
Grade							
Low	3 (43)	28 (65)	10 (59)	0 (0)	0 (0)	3 (10)	<.0001
High	4 (57)	15 (35)	7 (41)	18 (100)	2 (100)	28 (90)	
Margin							
Neg	34 (77)	33 (77)	6 (24)	10 (56)	12 (80)	37 (67)	.0001
Pos	10 (23)	10 (23)	19 (76)	8 (44)	3 (20)	18 (33)	
LVI							
No	42 (96)	42 (98)	25 (100)	10 (56)	12 (80)	43 (78)	<.0001
Yes	2 (4)	1 (2)	0 (0)	8 (44)	3 (20)	12 (22)	
Stage							
Early	36 (82)	30 (70)	12 (48)	3 (17)	9 (60)	17 (31)	<.0001
Adv	8 (18)	13 (30)	13 (52)	15 (83)	6 (40)	38 (69)	
Total N	44	43	25	18	15	55	

Note: There were significant associations of tumor histology with all histopathologic characteristics. Percentages are shown in parentheses.
Abbreviations: Adv, advanced; LVI, lymphovascular invasion; Neg, negative; Pleo, pleomorphic; PNI, perineural invasion; Pos, positive.

histology (HR [OS] = 3.2, P = .0008; HR [DFS] = 3.0, P = .0004), positive margins (HR [OS] = 3.0, P = .001; HR [DFS] = 3.3, P < .0001), high grade (n = 118; HR [OS] > 100, P < .0001; HR [DFS] > 100, P < .0001*), advanced T-stage (HR [OS] = 4.5, P < .0001; HR [DFS] = 5.2, P < .0001), node positivity (HR [OS] = 3.8, P = .0002, HR [DFS] = 4.0, P < .0001), PNI (HR [OS] = 3.8, P < .0001; HR [DFS] = 3.8, P < .0001), and FN involvement (HR [OS] = 4.7, P < .0001; HR [DFS] = 4.8, P < .0001). ECE (n = 50, HR [OS] = 2.9, P = .21; HR [DFS] = 4.3, P < .05) was associated with DFS but not OS, and LVI (HR [OS] = 1.6, P = .42; HR [DFS] = 2.1, P = .06) was not associated with either outcome measure.

All predictors that showed significance in the univariate model were tested in the multivariate model, except for grade which was incompletely reported and PNI, which was redundant with FN involvement. In the multivariate model, histology "other," positive margins, node positivity, and FN involvement were found to be significant predictors of OS and DFS, and age > 60 showed a trend in this direction (Table 3). Kaplan-Meier survival curves for OS and DFS stratified by margin status, node positivity, and FN involvement are shown in Figure 2.

4 | DISCUSSION

Here, we report on 200 consecutive cases of parotid malignancies at our institution over a 10-year period. We found that histologic subtype, positive margins, node positivity, and FN involvement were all independent predictors of poor prognosis.

Our total OS and DFS are consistent with prior reports in the literature of good prognosis with surgically treated disease.[6,12,15-20] In a report on 2062 patients with parotid carcinomas from the Swedish cancer registry, the 10 year survival was 71.6% and the figure did not change significantly from 1960 to 1995.[12] Consistent with prior studies, we found a significant impact of histologic subtype on OS and DFS. At 2 and 5 years, salivary ductal carcinoma had the poorest OS of 77% and 68%, respectively, consistent with prior reports of poor survival in patients with this malignancy but higher than previously quoted rates of only 20% to 35%.[21] At 10 years, adenoid cystic carcinoma had the poorest OS at 53%, consistent with a propensity for late recurrence, PNI, and distant metastasis. Prior reports of 5-year survival ranged from 35% to 70%.[22,23] Acinic cell and mucoepidermoid carcinomas had the best OS at 2, 5, and 10 years. It is notable that in our study, survival was defined by last known communication, which may underestimate potential survival since loss to follow-up or transfer of care to alternate providers with incomplete communication is common in a tertiary referral center.

In our cohort, the recurrence rate was 14.5% and the mean time to recurrence was 2 years, consistent with reported recurrence rates of 18.4% to 24.1%.[15,17,18] In our cohort, distant metastasis, which was most common in salivary ductal carcinoma (6/18 cases, 33%), was more common than locoregional recurrence, consistent with prior studies.[15,18] Salivary ductal carcinomas had the highest rates of early recurrence, while adenoid cystic carcinoma had the longest time to recurrence (3.29 years) and the greatest rate for recurrence by 10 years, with an overall recurrence rate of 24%. This propensity for

recurrence at 10 years with good DFS at 2 and 5 years underscores the importance of continued surveillance of patients with adenoid cystic carcinoma well beyond the 5-year time point, which is generally considered to be curative for other malignancies. Biologically, this late recurrence has been attributed to an initial period of relative growth quiescence, followed by aggressive transformation manifested by sudden rapid growth, local invasiveness, and distant metastatic spread.[23] To our knowledge, the molecular correlates of such an aggressive transformation have not been demonstrated and warrant further investigation in an effort to guide therapies targeting these lesions.

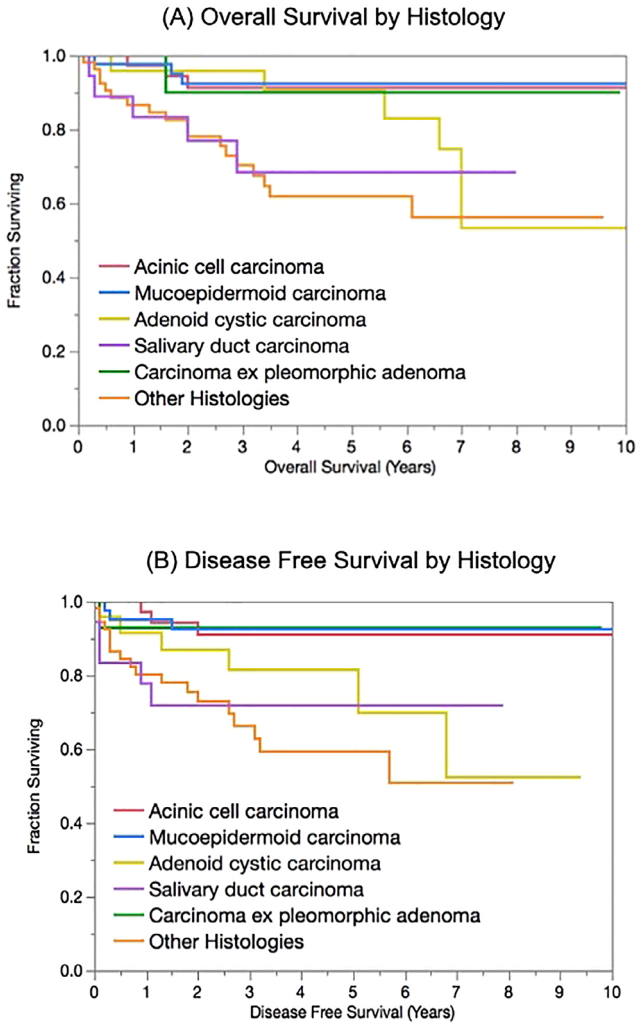

FIGURE 1 Kaplan-Meier curves of A, overall survival and B, disease-free survival by histologic type show a highly significant impact of histology on survival

Several factors were noted to impact survival rates. OS and DFS were significantly impacted by FN involvement (Figure 2E,F) and N-stage (Figure 2C,D), and age > 60 showed a trend (Table 3). Many other studies have similarly demonstrated that older age at presentation is associated with worse survival outcomes,[15,17] perhaps reflecting the more aggressive nature of late-presenting disease, as well as the fact that older individuals are likely to have more comorbidities, poorer functional status, or weakened immunity.[6,17,19] FN involvement, which was seen in 44 patients (22%) in our cohort, has previously been demonstrated to be independently associated with survival outcomes,[17,19] though it remains unclear whether this represents a manifestation of more locally aggressive tumors with skip lesions that are difficult to completely resect or a propensity for distant metastasis, as is seen in adenoid cystic carcinoma, which is most classically associated with perineural spread.

Nodal involvement was associated with significant reduction in survival. Consistent with prior studies,[17,19] 5-year OS and DFS, which were 56% and 46%, respectively, in node-positive patients and 88% and 83%, respectively, in node-negative patients (Figure 2C,D). The overall rate of node positivity was 21.5%, which is similar to previous reports of 18% to 28%.[16,17,24] However, in our cohort, this was significantly associated with intrinsic factors related to the disease entity, as less than 20% of acinic cell, mucoepidermoid, and adenoid cystic carcinomas demonstrated node positivity, while 66% of salivary ductal carcinomas had nodal metastasis at the time of presentation. These findings suggest that patients with salivary ductal carcinomas should uniformly receive cervical lymphadenectomy at the time of primary tumor removal, while those with other histologic types may be considered on an individualized basis depending on other clinical and pathologic features of the primary tumor.

T-stage, tumor grade, and margin status were also found to be associated OS and DFS in the univariate analysis, with margin status not surprisingly retaining significance on multivariate analysis (Table 3, Figure 2A,B). Due to incomplete reporting, tumor grade was removed

TABLE 3 Multivariate Cox proportional hazards model for predictors of OS and DFS

Predictor	HR (OS) [95% CI]	*P* value	HR (DFS) [95% CI]	*P* value
Age > 60	2.17 [0.99-5.27]	.05	1.81 [0.93-3.76]	.08
Histology "Other"	3.23 [1.54-6.81]	.002	3.08 [1.59-5.99]	.001
Positive margin	2.05 [1.01-4.25]	<.05	2.29 [1.21-4.38]	.01
T stage (1/2 vs 3/4)	1.52 [0.66-3.67]	.33	1.83 [0.87-4.02]	.11
N stage (N0 vs N+)	2.05 [1.02-4.06]	.04	1.98 [1.06-3.68]	.03
FN involvement	2.62 [1.17-5.80]	.02	2.32 [1.15-4.66]	.02

Note: Although it was significant in the univariate model, grade was eliminated from the multivariate model due to incomplete reporting.

Abbreviations: CI, confidence interval; DFS, disease-free survival; FN, facial nerve; HR, hazard ratio; OS, overall survival.

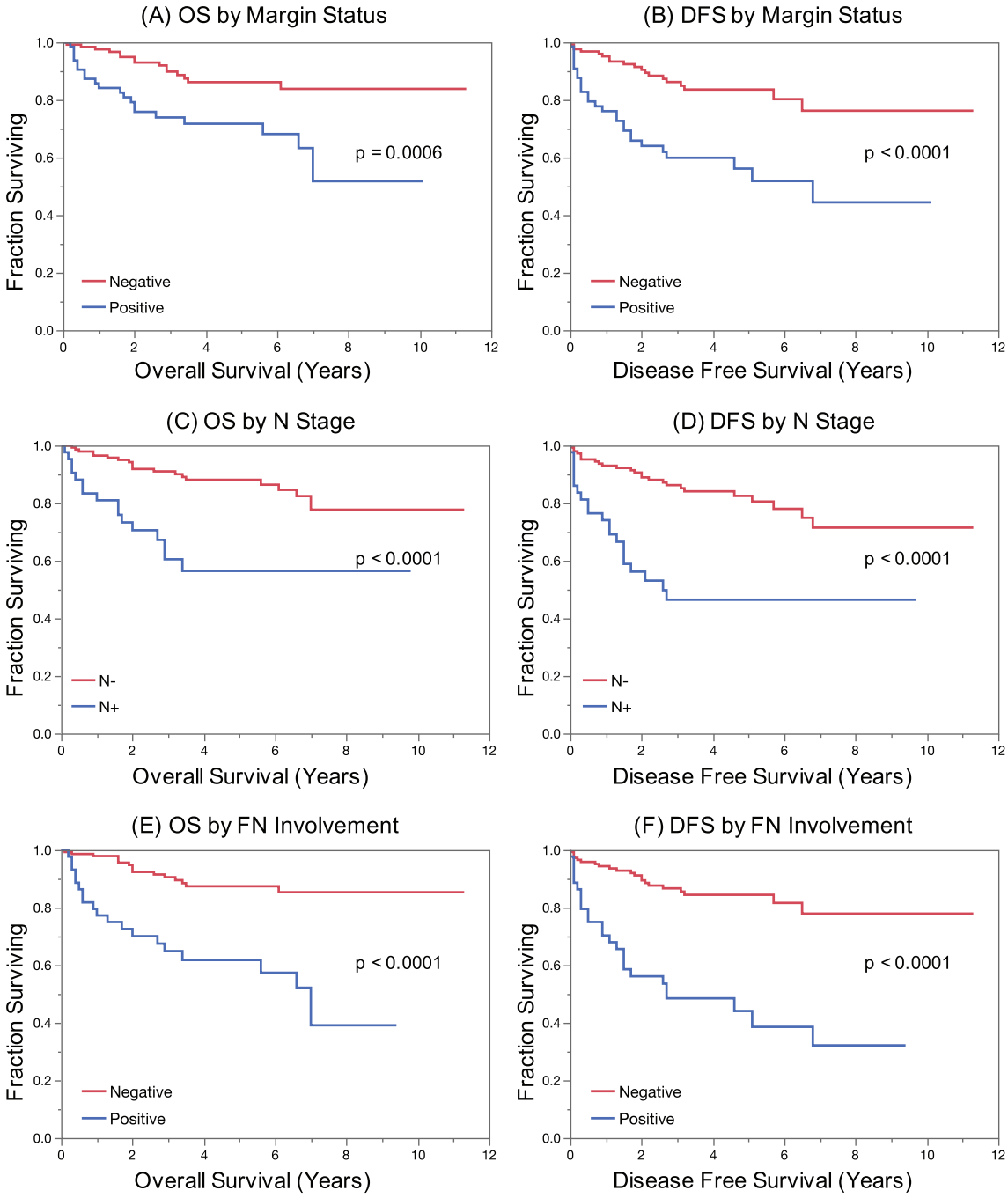

FIGURE 2 Kaplan-Meier curves of overall survival and disease-free survival by A and B, margin status, C and D, N stage, and E and F, facial nerve involvement show highly significant impacts of each of these variables on survival

from the multivariate analysis, though we anticipate that it remains a significant factor in determining prognosis. In mucoepidermoid and acinic cell carcinomas, for example, prior studies have shown 5-year OS to be as high as 100% in low-grade tumors, decreasing to 50% for higher grade tumors.[25,26] At minimum, we conclude that more uniform reporting and additional study of the prognostic impact of tumor grade in salivary gland malignancies is warranted. T-stage lost significance in the multivariate analysis, and we hypothesize that this finding suggests that other clinicopathologic measures better captured the biologic impact of larger tumors.

Limitations of our study include its retrospective nature, reliance on the documentation in the electronic medical record, and approximation of survival by last known communication with the patient. We recognize that this approach to determining survival may underestimate true survival, given lack of follow-up, or transfer of care from a tertiary referral center to alternate providers with no documented communication. We also acknowledge that it may be biased by provider determined need for follow-up and may particularly affect stratification by histology. However, our results of survival, both overall and stratified by histology, are consistent with prior reports in the

literature, thus supporting the validity of our data. The diverse group of histopathologic subtypes makes it challenging to comment upon how the specific histologic subtype may affect long-term outcomes, particularly for less common malignancies. Moreover, we recognize that classification of parotid malignancies has evolved in the past decade, leading to potential underreporting of secretory carcinomas and insufficient classification of carcinoma ex pleomorphic adenomas. In addition, incomplete reporting limited our comment on the impact of tumor grade and highlight the importance of histopathologic assessment of this metric, as it is likely that grade does have an impact on outcomes. However, we hope that our relatively large, single institution cohort of parotid malignancies can contribute to an understanding of the relative demographics and differences in prognosis of the variety of salivary gland malignancies commonly treated by the head and neck surgeon.

5 | CONCLUSIONS

We report outcomes on 200 consecutive patients with malignancies of the parotid gland managed surgically at a single institution. In our cohort, we found that histologic subtype, N-stage, and FN involvement were independent predictors of both OS and DFS. Tumors such as salivary ductal carcinoma were associated with early recurrence, whereas adenoid cystic carcinoma was associated with late recurrence.

CONFLICT OF INTEREST

The authors have no financial disclosures or conflict of interest.

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ENDNOTE

*HR > 100 in this case represents the infinite solution resulting from the fact that there were no events in the low-grade group, thus making this a highly significant effect.

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