Carcinoma Ex Pleomorphic Adenoma: Is It a High-Grade Malignancy?

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Purpose: The objective of this study was to investigate the clinicopathologic features of carcinoma ex pleomorphic adenoma (CXPA) and comprehensively improve an understanding of this disease.

Materials and Methods: This retrospective study investigated 151 cases of histologically confirmed CXPA. Disease-specific survival, local recurrence, and regional and distant metastases were analyzed.

Results: Most cases were classed as frankly invasive CXPA (135 of 151). More than half these cases (73 of 135; 54.1%) developed local recurrence; 25 (18.5%) developed cervical metastasis; 21 (15.6%) developed distant metastasis; and 60 patients (55.6%) died during follow-up. In contrast, only 1 patient in the noninvasive CXPA group (n = 10) died after treatment for lung metastasis and 1 patient developed cervical metastasis. Similarly, only 1 patient in the minimally invasive CXPA group (n = 6) died of lung metastasis and the remaining 5 patients had an uneventful recovery after treatment.

Conclusions: Frankly invasive CXPA was a high-grade malignancy with an unfavorable prognosis. Elective neck dissection should be performed in cases of frankly invasive CXPA that originate in the submandibular gland. Patients with minimally invasive and noninvasive CXPA should be followed closely after primary treatment because regional or distant metastasis can occur.

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Benign pleomorphic adenoma is the most common form of salivary neoplasm, accounting for almost 80% of all salivary tumors. Malignant degeneration arising from pleomorphic adenoma often occurs in patients with a prolonged history of untreated or recurrent benign pleomorphic adenoma. A report has suggested that the median onset of pleomorphic adenoma is 10 years of age.[1] According to the World Health Organization (WHO) classification system,[2] there are 3 main categories of malignant pleomorphic adenoma: carcinoma ex pleomorphic adenoma (CXPA), carcinosarcoma, and metastatic benign pleomorphic adenoma. Although cases of CXPA greatly outnumber those for the other 2 subtypes, it is a relatively rare carcinoma. Estimates suggest it accounts for 5 to 15% of salivary malignancies and 3.6% of all salivary tumors.[3-6] These proportions could increase as knowledge of this disease increases. CXPA generally has been recognized as a high-grade carcinoma owing to its potential for regional and distant metastases, resulting in a high rate of mortality.[7,8] However, this categorization might not be conclusive.

CXPA presents with epithelial malignancy mixed with benign pleomorphic adenoma in variable proportions.[9] CXPA can be divided into 3 subtypes based on the extent of the malignancy[2]: noninvasive CXPA if the malignancy is confined by the tumor capsule; minimally invasive CXPA if invasion extends no farther than 1.5 mm beyond the capsule; and frankly invasive CXPA if invasion extends farther than 1.5 mm beyond the capsule.[2] Not all these subtypes are aggressive; minimally invasive and noninvasive forms of CXPA generally behave in a benign manner, with a prolonged and uneventful clinical

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course, especially after standard treatment,[10] whereas frankly invasive CPXA frequently results in disease-related death. Therefore, not all cases of CXPA can be conclusively categorized as a high-grade malignancy.

Despite considerable research into CXPA and data on prognostic factors, including tumor size, grade, proportion of carcinoma, extent of invasion extent, proliferation index, and clinical outcome,[4,5,11] CXPA remains a poorly understood neoplasm. Therefore, the aim of the present study was to analyze retrospectively the clinical and pathologic features and survival outcome of 151 cases of CXPA to improve an understanding of this disease.

Materials and Methods

PATIENT SELECTION AND CHARACTERISTICS

This study was approved by the institutional review board of the Peking University School of Stomatology (Beijing, China). The medical records of all patients treated for malignant pleomorphic adenoma of the salivary gland at the Department of Oral and Maxillofacial Surgery at the Peking University School and Hospital of Stomatology from 1960 through 2015 were retrospectively reviewed, as were available pathologic specimens. Diagnosis was histologically confirmed by an experienced pathologist (Y.G.) and 151 cases of CXPA were selected for this study. Excluded were 10 cases that were previously misdiagnosed (4 were definitively identified as myoepithelial carcinoma, 4 as mucoepidermoid carcinoma, 1 as salivary duct carcinoma, and 1 as carcinosarcoma). Tumor size, TNM staging, type of carcinomatous element, and extent of invasion were recorded. The cases were subclassified as noninvasive (intracapsular), minimally invasive, and frankly invasive CXPA, in accordance with the WHO classification system.[2] Demographic data, treatment, and clinical and prognostic information were obtained from the patients' medical records and follow-up telephone calls. The mean follow-up time was 61 months (range, 6 to 228 months).

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS 20.0 (SPSS, Inc, Chicago, IL). Survival data were compared by the Kaplan-Meier method. Univariate analysis with log-rank test was applied to identify potential prognostic factors. A P value less than .05 was considered statistically significant.

Results

PATIENTS' CLINICOPATHOLOGIC CHARACTERISTICS AND TREATMENT

The 151 patients with CXPA included 80 men (53.0%) and 71 women (47.0%) with a mean age of

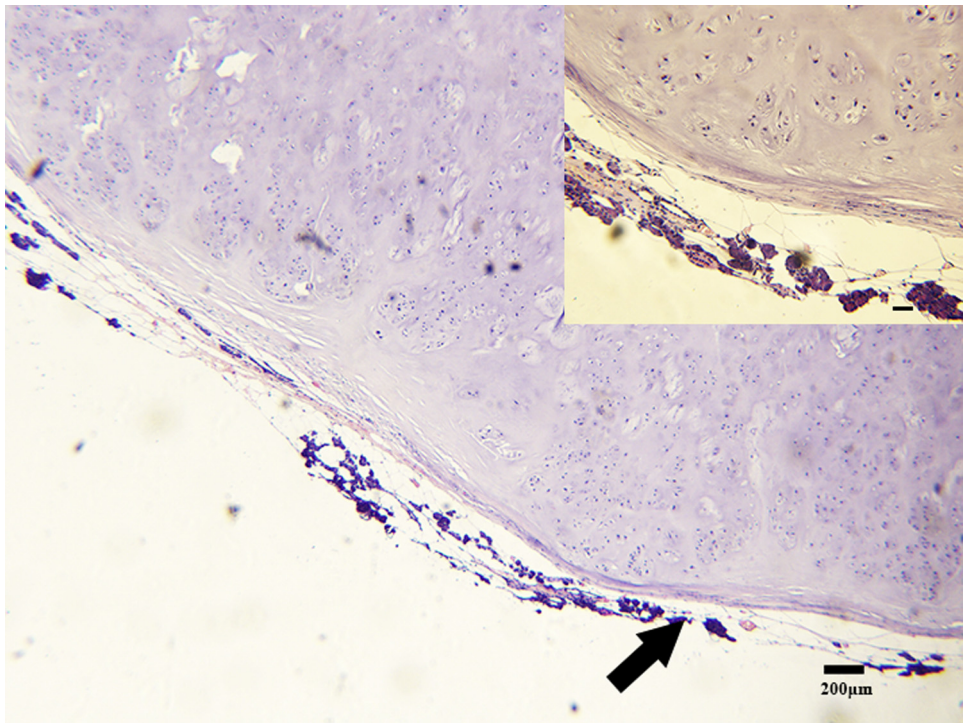

FIGURE 1. Photomicrograph (magnification, ×4) of noninvasive carcinoma ex pleomorphic adenoma with well-circumscribed malignancy (*arrow*). *Inset*, Photomicrograph at higher magnification (×20) showing the well-defined capsule (bar = 50 μm).

Ye et al. CPXA: Is it a High-Grade Malignancy. J Oral Maxillofac Surg 2016.

54 years (range, 14 to 83 years). Ten cases were classed as noninvasive CXPA, 6 as minimally invasive CXPA, and 135 as frankly invasive CXPA (Figs 1-6). Most primary lesions were located in the parotid gland (76 cases; 50.3%), with 39 cases in the palatine gland (25.8%), 19 cases in the submandibular gland (12.6%), and 4 cases in the sublingual gland (2.6%); the remaining 13 cases (8.6%) were located in other minor salivary glands (buccal, lip, and tongue base). In total, 101 patients presented with primary tumors and 50 presented with recurrent tumors. The patients' clinicopathologic data are presented in Table 1.

In descending order of patient numbers, most cases with primary tumors were graded as T2 (50 of 101; 49.5%), T3 (23 of 101; 22.8%), T1 (15 of 101; 14.9%), and T4 (13 of 101; 12.9%). The clinical complaints reported by these patients included local pain (n = 33), facial paralysis (n = 9), and rapid tumor growth (n = 34; Table 1). The mean period of complaint was 68 months (range, 1 to 480 months).

Most patients (97 of 151; 64.2%) underwent surgery alone; 51 of 151 (33.8%) underwent surgery with adjuvant radiotherapy owing to a positive surgical margin or regional metastasis; 1 patient received chemotherapy alone; 1 received palliative radiotherapy alone; and 1 patient declined any treatment (Table 1).

Among those patients treated by surgery, 10 with clinically positive neck metastasis underwent radical neck dissection and were found to have pathologically positive lymph nodes. Another 26 underwent elective neck dissection; of these, 17 had pathologically

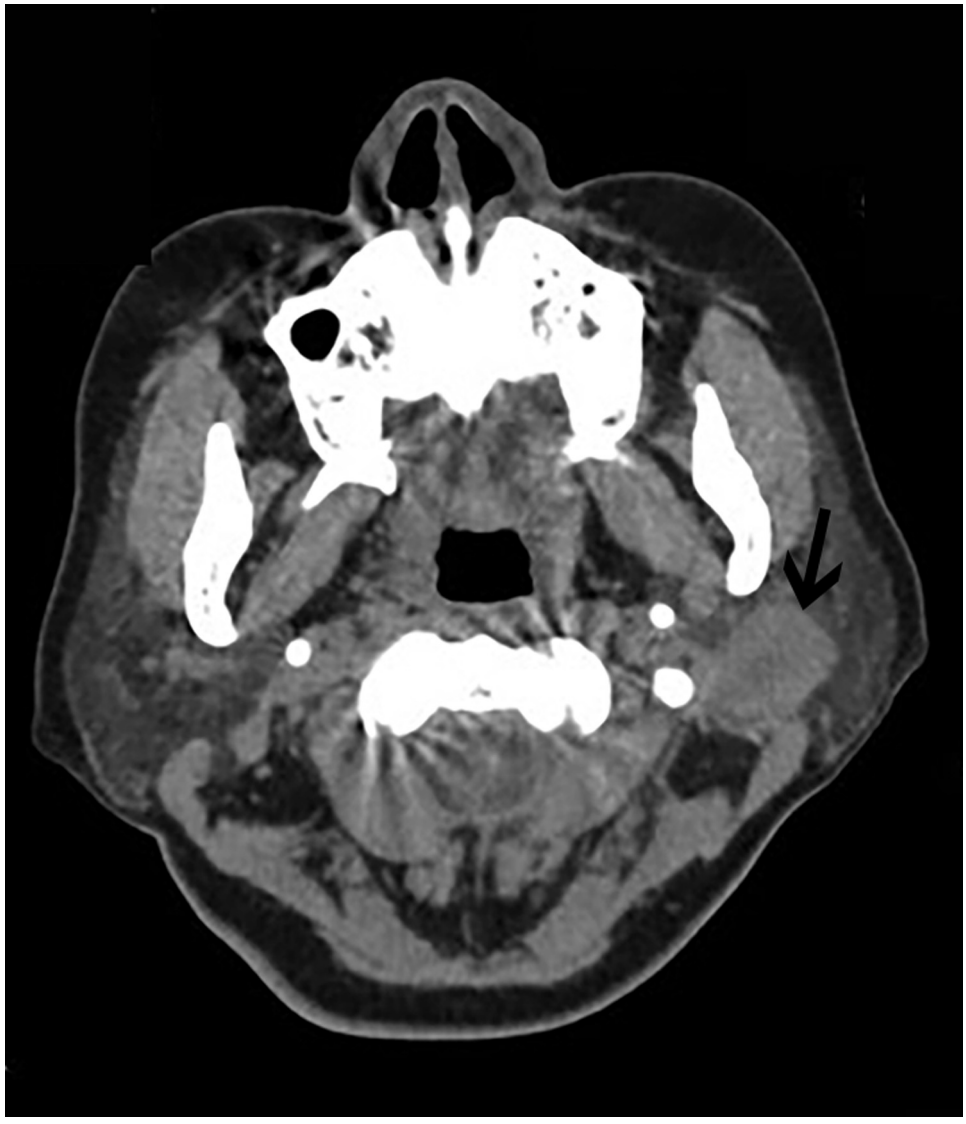

FIGURE 2. Axial computed tomogram of noninvasive carcinoma ex pleomorphic adenoma (*arrow*).

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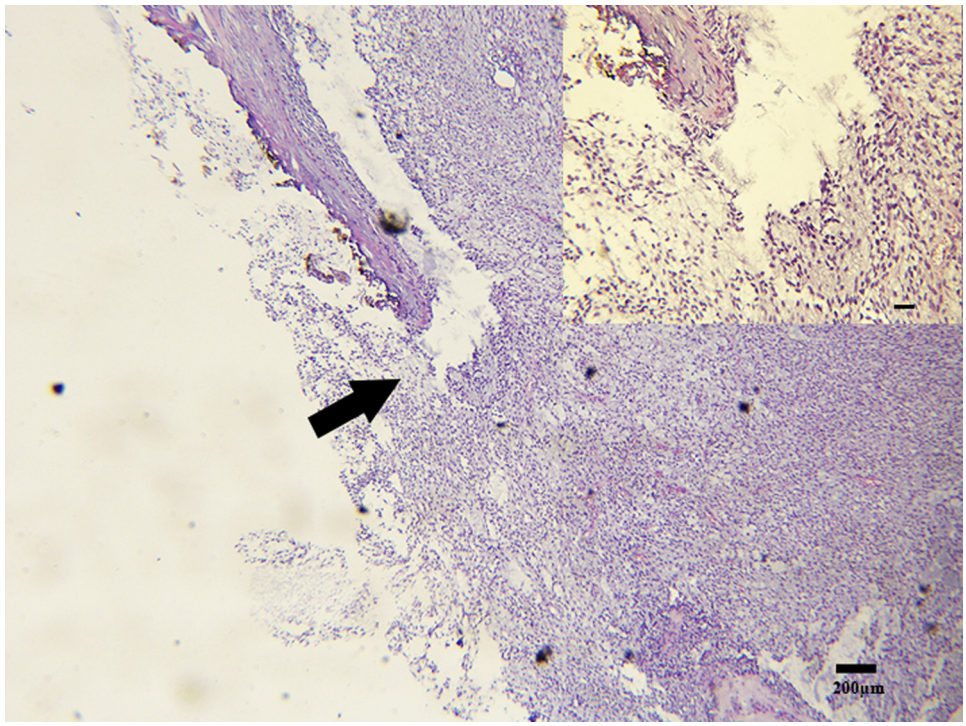

FIGURE 3. Photomicrograph (magnification, ×4) of minimally invasive carcinoma ex pleomorphic adenoma with a malignant component within 1.5 mm beyond the capsule (*arrow*). *Inset*, Photomicrograph at higher magnification (×20; bar = 50 μm).

Ye et al. CPXA: Is it a High-Grade Malignancy. J Oral Maxillofac Surg 2016.

positive lymph nodes. Overall, those patients treated with surgery combined with radiotherapy showed lower local recurrence rates compared with those treated with surgery alone ($P < .01$). However, in cases of T1 and T2 tumors (for all 151 patients), the difference was not significant ($P = .308$).

PATHOLOGIC REVIEW AND MALIGNANCY SUBTYPE

Pathologic slides were available for all 151 patients. These showed that the most common subtype of CXPA was myoepithelial carcinoma (26.5%), followed by adenocarcinoma not otherwise specified (21.9%), mucoepidermoid carcinoma (11.9%), adenoid cystic carcinoma (10%), salivary duct carcinoma (6.6%), basal cell carcinoma (4.6%), squamous cell carcinoma (4%), oncocytic carcinoma (3.3%), papillary cystadenocarcinoma (3.3%), epithelial-myoepithelial carcinoma (2.6%), clear cell carcinoma (2.6%), acinar cell carcinoma (2%), and polymorphous low-grade adenocarcinoma (0.7%).

The 2 main histologic subtypes in the frankly invasive CXPA group were myoepithelial carcinoma and adenocarcinoma not otherwise specified (33 and 28 cases, respectively). Patients with the former subtype had significantly longer 5-year survival rates than those with the latter subtype (60.7% vs 27.6%, respectively; $P < .05$; Table 2).

FRANKLY INVASIVE CXPA

More than half the patients with frankly invasive CXPA developed local recurrence (73 of 135; 54.1%). Distant metastasis occurred in 21 patients (15.6%; 19 in the lung and 2 in the bones) and 25 patients (18.5%) developed cervical metastasis. Sixty patients in this group (44.4%) died of this disease.

The primary neoplasms in patients with cervical metastasis occurred in different locations. The numbers and rates for each primary gland are listed in Table 3. With the exception of other minor salivary glands ($P = .062$), all rates were significant ($P < .05$).

MINIMALLY INVASIVE CXPA

Five of the 6 patients with minimally invasive CXPA had an uneventful recovery after treatment. However, 1 patient developed lung metastasis and died.

NONINVASIVE CXPA

Two of the 10 patients with noninvasive CXPA developed metastasis (1 patient died of lung metastasis and 1 patient developed cervical metastasis, but remained disease free after treatment). None of the other patients developed disease progression during the follow-up time.

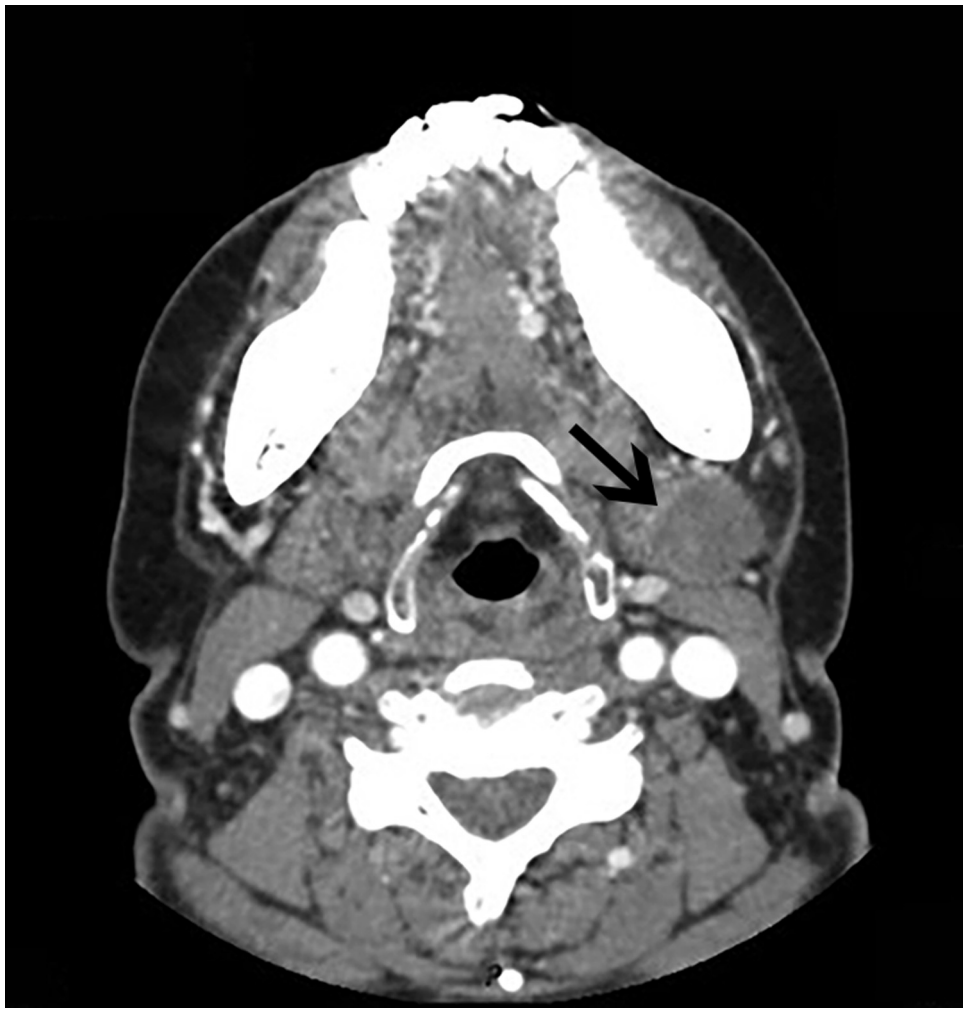

FIGURE 4. Axial computed tomogram of minimally invasive carcinoma ex pleomorphic adenoma (*arrow*).

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PATIENT SURVIVAL

Sixty-two patients (41%) died of this disease during follow-up; however, the disease-specific 5-year survival rate in the study group was 63%. Clinical stage, tumor size, recurrence, regional and distant metastasis, invasiveness, and malignant subtype were identified as significant risk factors for disease-specific survival ($P < .05$ for all comparisons), whereas gender, tumor location, and treatment modality had no influence on survival rates ($P = .226$, $P = .976$, $P = .934$, respectively). Patients with noninvasive or minimally invasive CXPA showed significantly higher survival rates compared with those with frankly invasive CXPA ($P < .05$). Similarly, patients without metastasis had higher survival rates than those with cervical or distant metastasis ($P < .01$). Survival curves, separated by characteristics, are shown in Figures 7 to 12.

Discussion

Despite extensive research, the pathogenesis of CXPA remains poorly understood, in part because of the rarity of this aggressive malignancy. The general consensus is that it derives from pre-existing benign pleomorphic adenoma, with approximately 25% of untreated cases resulting in CXPA.[1,12] Most patients with CXPA present with an uneventful mass for many years before new symptoms, such as sudden growth, facial paralysis, or local pain, occur. This observation is in agreement with the present findings. Gender predominance in CXPA seems to be ambiguous.[12,13] Consistent with previous studies, most primary CXPA tumors were located in the parotid gland, with the submandibular gland, palatine gland, and other minor salivary glands being less involved.[4,6]

Previous investigations of frankly invasive CXPA have reported regional metastasis in 49 to 56% of cases

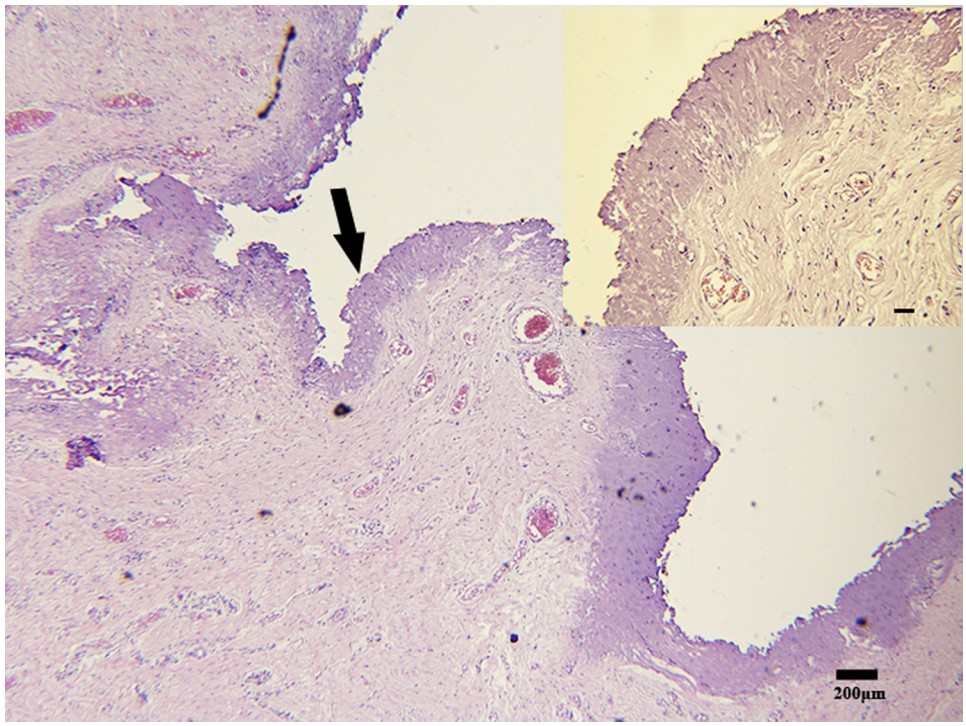

FIGURE 5. Photomicrograph (magnification, ×4) of frankly invasive carcinoma ex pleomorphic adenoma with a poorly defined and infiltrative malignancy (*arrow*). *Inset*, Photomicrograph at higher magnification (×20; bar = 50 μm).

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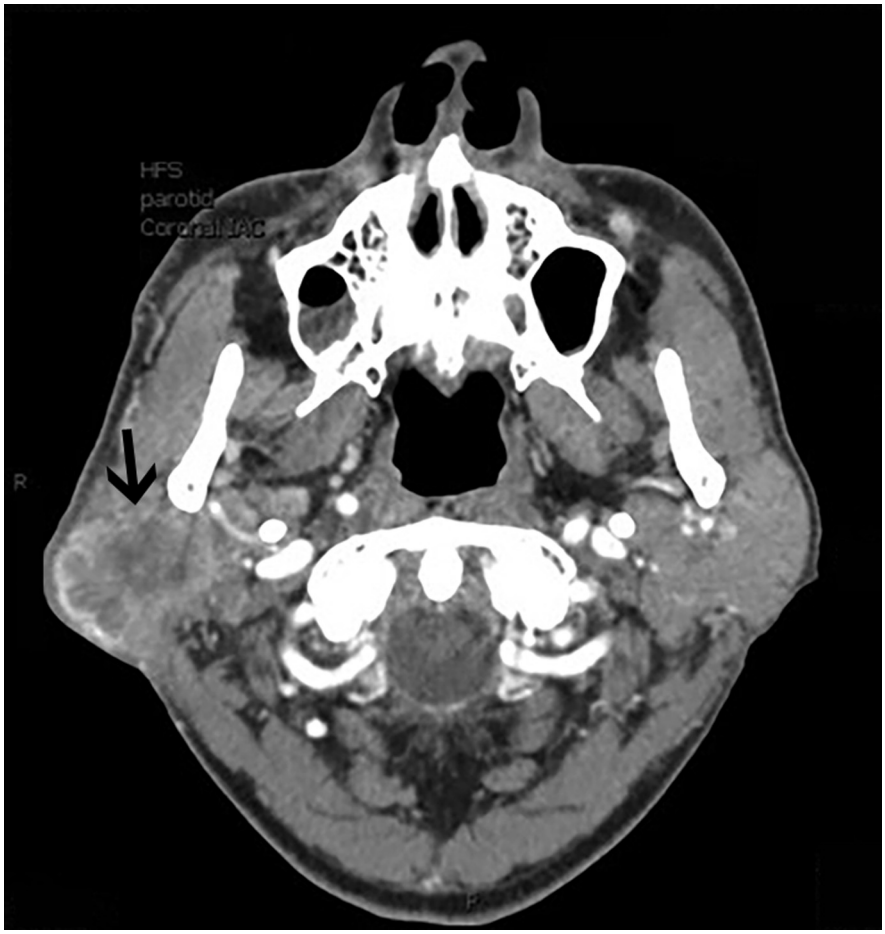

FIGURE 6. Axial computed tomogram of frankly invasive carcinoma ex pleomorphic adenoma (*arrow*).

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Table 1. CLINICOPATHOLOGIC CHARACTERISTICS AND PROGNOSTIC FACTORS OF 151 PATIENTS WITH CXPA

Characteristics	Patients (N = 151), n (%)	Determinate Survival (*P* Value)
Gender		
Men	80 (53.0)	.226
Women	71 (47.0)	
Primary or recurrent		
Primary CXPA	101 (66.9)	.023*
Recurrent CXPA	50 (33.1)	
Tumor size (primary tumor)		
T1-T2	65 (64.4)	.002*
T3-T4	36 (35.6)	
Clinical presentation (primary tumor)		
Local pain	33 (32.7)	.001*
Facial paralysis	9 (8.9)	.003*
Rapid growth	34 (34.7)	.001*
Clinical stage (primary tumor)		
I-II	55 (54.5)	.001*
III-IV	46 (45.5)	
Invasiveness		
Frankly invasive CXPA	135 (89.4)	.035*
Minimally invasive CXPA	6 (4.0)	
Noninvasive CXPA	10 (6.6)	
Treatment modality		
Surgery only	97 (64.2)	.934
Surgery and RT	51 (33.8)	
Chemotherapy only	1 (0.7)	
RT only	1 (0.7)	
No intervention	1 (0.7)	
Cervical metastasis		
Yes	25 (18.5)	.001*
No	126 (81.5)	
Distant metastasis		
Yes	22 (14.5)	.001*
No	129 (85.5)	
Status		
Survived until last follow-up	89 (58.9)	
Died of CXPA	62 (41.1)	

Abbreviations: CXPA, carcinoma ex pleomorphic adenoma; RT, radiotherapy; T, tumor stage of TNM classification system.

* Significant.

Ye et al. CPXA: Is it a High-Grade Malignancy. J Oral Maxillofac Surg 2016.

and distant metastasis in 40 to 44% of cases[11,14]; furthermore, most of these cases originated in major salivary glands. In contrast to these reports, the present rates of cervical metastasis and distant metastasis were 18.8 and 15.8%, respectively. These low rates can be attributable to the large proportion of cases that originated in minor salivary glands (35%) in this study. Very few of these studies

Table 2. COMPARISON OF SURVIVAL RATES BETWEEN PATIENTS WITH FRANKLY INVASIVE CXPA AND THOSE WITH MALIGNANCY SUBTYPES

Histologic Subtype	Cases (n = 135)	5-yr Survival (*P* Value)	Determinate Survival (*P* Value)
AdNOS	28	27.6%	
MC	33	60.7% (.01*†)	.002*‡
MEC	18		
ACC	15		
SDC	8		
BCA	6		
SCC	6		
OCC	4		
Others	17		

Abbreviations: ACC, adenoid cystic carcinoma; AdNOS, adenocarcinoma not otherwise specified; BCA, basal cell adenocarcinoma; MC, myoepithelial carcinoma; MEC, mucoepidermoid carcinoma; OCC, oncocytic carcinoma; SCC, squamous cell carcinoma; SDC, salivary duct carcinoma.

* Significant.

† *P* value versus AdNOS.

‡ Determinate survival analysis for all histologic subtypes.

Ye et al. CPXA: Is it a High-Grade Malignancy. J Oral Maxillofac Surg 2016.

investigated the relation between the rate of cervical metastasis and the location of the primary tumor. In the present analysis, the lowest rate of cervical metastasis involved the palatine gland (5.1%). This was significantly lower than metastases involving the parotid and submandibular glands (19.4 and 33.3%, respectively; $P < .05$). Based on these observations, the authors recommend that elective neck dissection be considered in cases of frankly invasive CXPA that

Table 3. COMPARISONS BETWEEN LOCATION OF THE PRIMARY TUMOR AND RATE OF CERVICAL METASTASIS IN PATIENTS WITH FRANKLY INVASIVE CARCINOMA EX PLEOMORPHIC ADENOMA

	Cases of Cervical Metastasis (n = 25)		
Location of Primary Tumor (n = 135)	Cases Relative to Origin, n	Rate, %	*P* Value
Palatine gland	2/38	5.3	
Parotid gland	12/62	19.4	.021*
Submandibular gland	6/18	33.3	.005*
Sublingual gland	2/4	50.0	.004*
Other minor salivary gland	3/13	23.1	.062

Note: P values are given relative to rates in the palatine gland.

* Significant.

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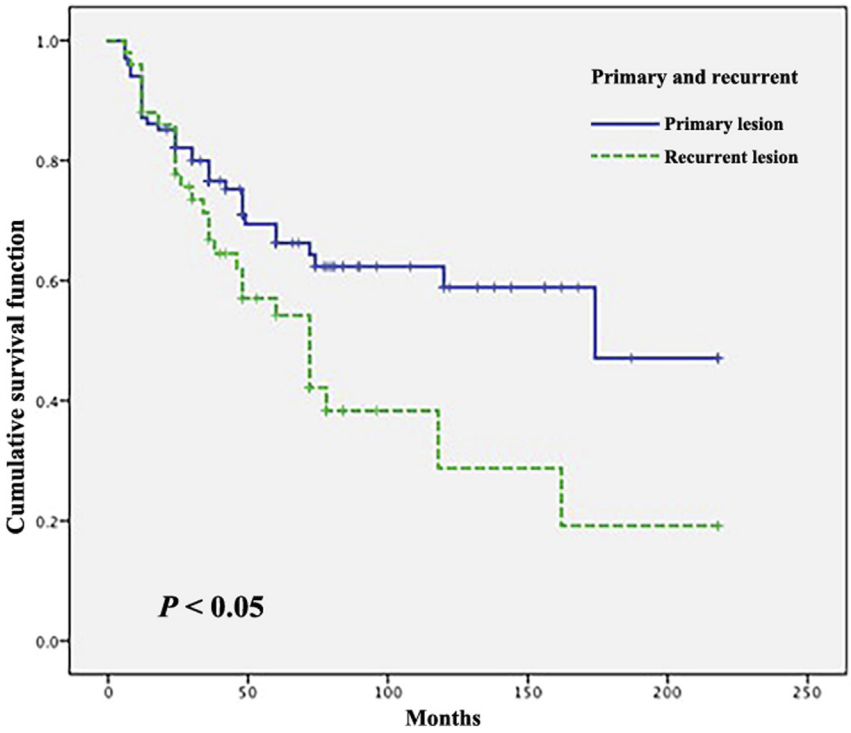

FIGURE 7. Kaplan-Meier curves with log-rank test showing that patients with primary carcinoma ex pleomorphic adenoma survived considerably longer than those with recurrent carcinoma ex pleomorphic adenoma.

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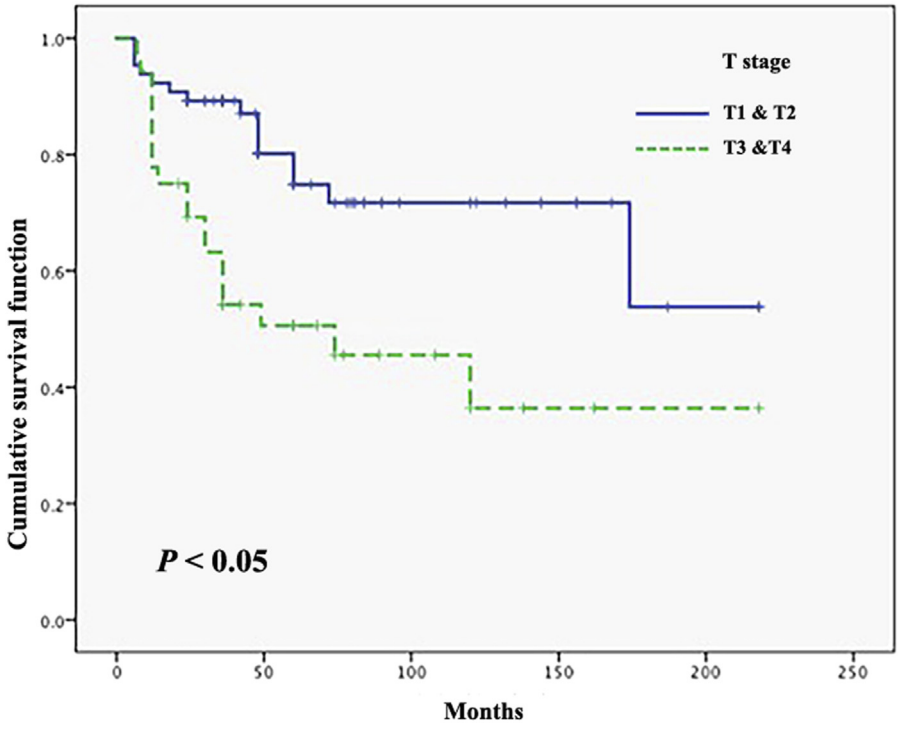

FIGURE 8. Kaplan-Meier curves with log-rank test showing that patients with T1 and T2 carcinoma ex pleomorphic adenoma survived considerably longer than those with T3 and T4 carcinoma ex pleomorphic adenoma.

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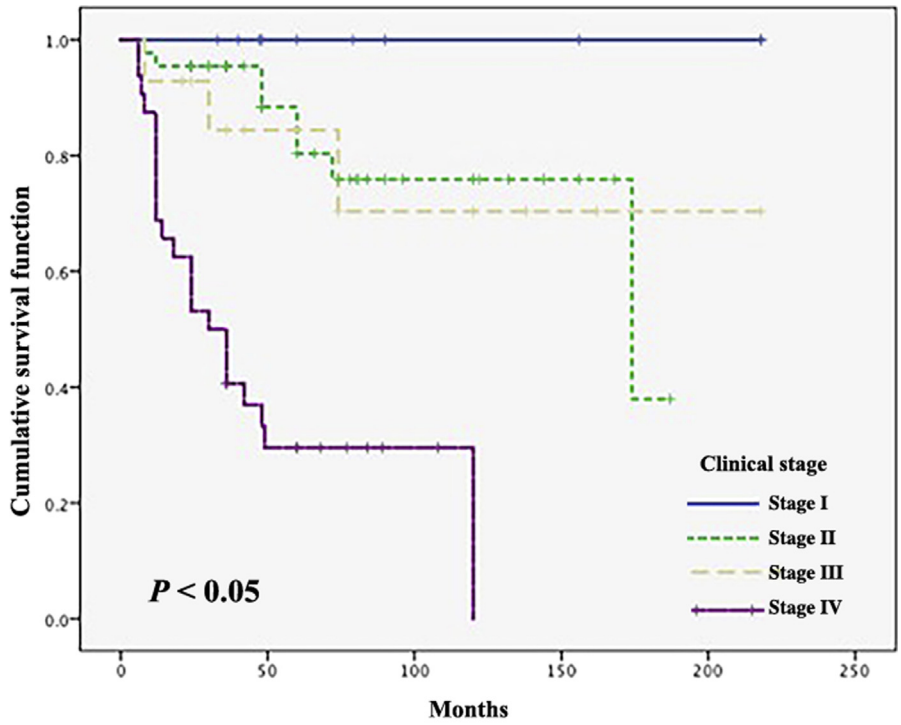

FIGURE 9. Kaplan-Meier curves with log-rank test showing that clinical stage substantially affected the survival rate of patients with carcinoma ex pleomorphic adenoma, with those with an early stage surviving longer than those with an advanced stage.

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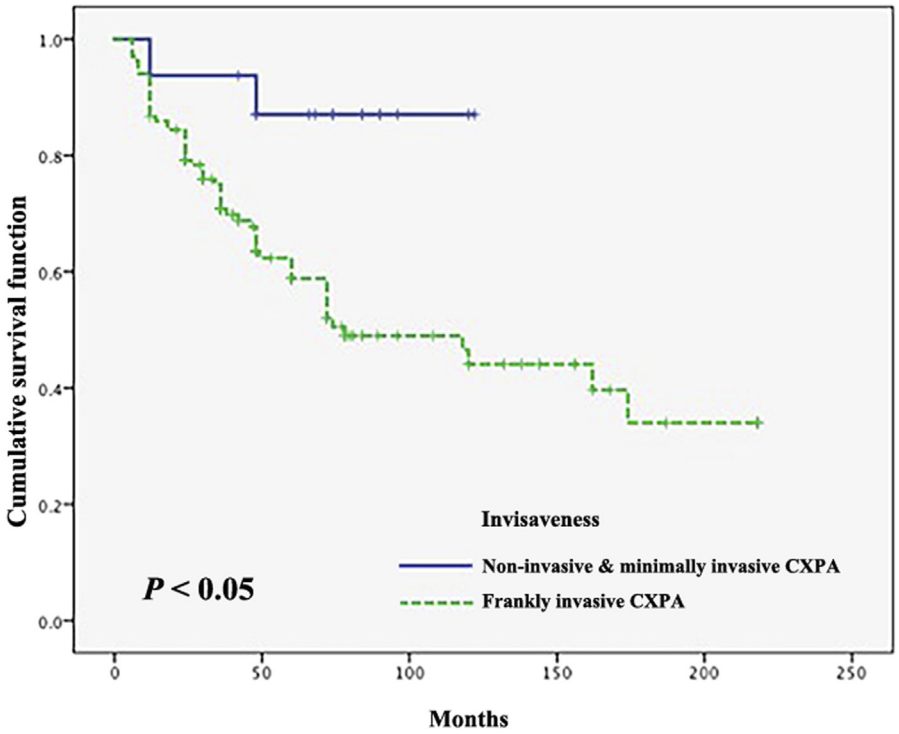

FIGURE 10. Kaplan-Meier curves with log-rank test showing that patients with noninvasive and minimally invasive CXPA survived considerably longer than those with frankly invasive CXPA. CXPA, carcinoma ex pleomorphic adenoma.

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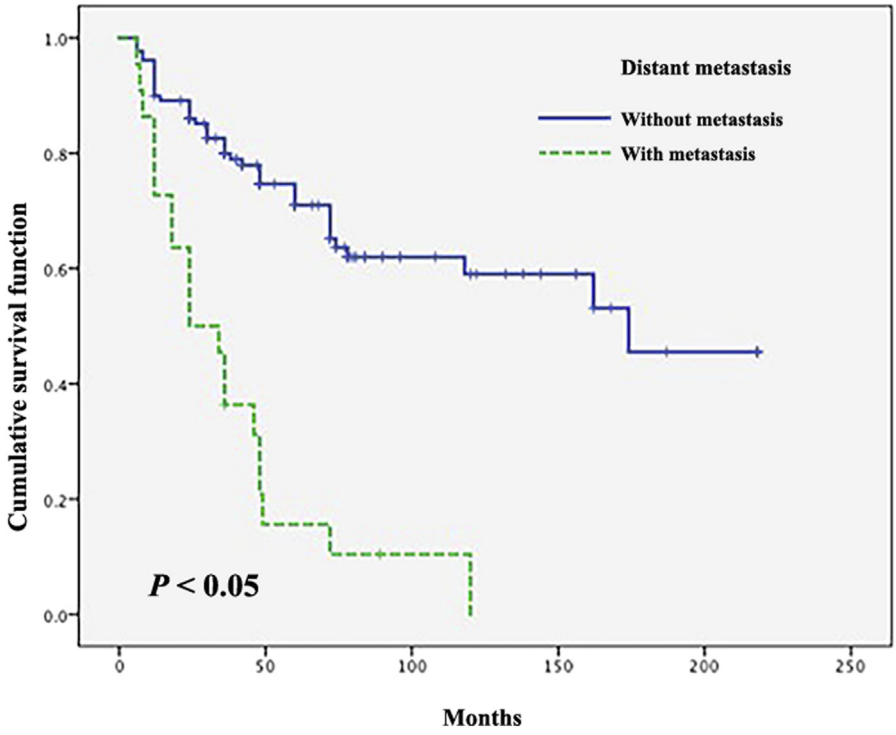

FIGURE 11. Kaplan-Meier curves with log-rank test showing that patients without distant metastasis survived substantially longer than those with distant metastasis.

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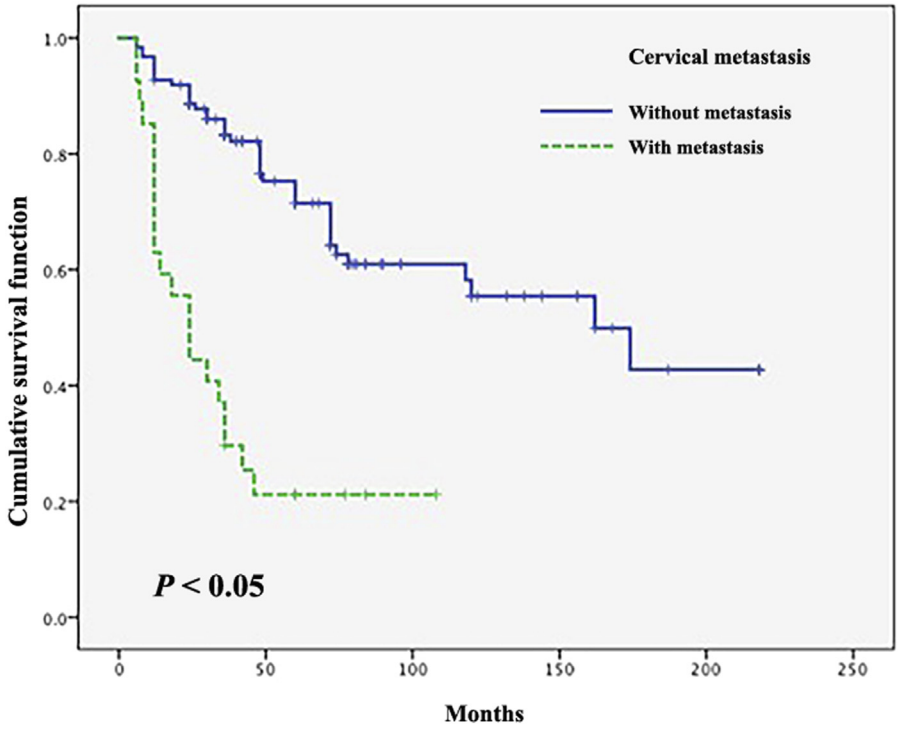

FIGURE 12. Kaplan-Meier curves with log-rank test showoing that patients without cervical metastasis survived considerably longer than those with cervical metastasis.

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originate in the submandibular gland, but this procedure should be used with caution in cases that originate in the parotid gland.

The main histologic subtypes of CXPA identified in this study were myoepithelial carcinoma and adenocarcinoma not otherwise specified, suggesting that CXPA is a high-grade malignancy. This finding was inconsistent with previous reports that found adenocarcinoma not otherwise specified and salivary duct carcinoma to be the most common histologic subtypes.[10,11] In addition, patients with frankly invasive CXPA with a histologic subtype of adenocarcinoma not otherwise specified had substantially lower 5-year survival rates than those with myoepithelial carcinoma, suggesting that adenocarcinoma not otherwise specified might serve as an important prognostic indicator for poor survival in patients with frankly invasive CXPA. In contrast, Lewis et al[11] reported that histologic subtype had no meaningful influence on survival outcome. These discrepancies might be due to the wide spectrum of locations of primary lesions in the present patients.

In general, noninvasive CXPA has been associated with a favorable prognosis.[5,9,11,13,15,16] In agreement with these previous reports, most cases of noninvasive CXPA in this study behaved in a benign manner, with no recurrence or regional or distant metastasis during the follow-up period; 1 patient died of multiple lung metastases after surgical excision of the primary lesion and 1 patient developed cervical metastasis, but remained disease free after treatment. Although 1 study found no cases of recurrence or death in patients with minimally invasive CXPA,[17] others have reported several cases of recurrence and death in patients with intracapsular or minimally invasive CXPA.[18-20]

Various treatment modalities have been proposed for the treatment of CXPA, based on tumor location, surgical margin, lymph node involvement, and pathologic grade. LiVolsi and Perzin[5] recommended performing a wide en bloc surgical excision to achieve a tumor-free margin and a discontinuous radical neck dissection for CXPA arising from the major salivary gland. Olsen and Lewis[14] recommended total parotidectomy to remove the tumor and intraparotid lymph nodes and selected neck dissection and postoperative radiotherapy for high-grade neoplasm to decrease locoregional recurrence. Nouraei et al[18] also recommended surgery combined with radiotherapy to achieve good locoregional disease control. Although different treatment strategies were administered in the present study, including surgery, preoperative chemotherapy, and postoperative adjuvant or palliative radiotherapy, treatment modality had no relevant effect on survival outcome in patients with frankly invasive CXPA. The overall disease-specific 5-year survival rate for all 151 patients in this study was 63%. The significant prognostic factors for survival ($P < .01$) included clinical stage, tumor size, recurrence, regional and distant metastases, invasiveness, and malignant subtype. These factors were consistent with those reported from previous investigations.[2,3,7,8,12]

This study confirmed that frankly invasive CXPA is a high-grade malignancy. The authors believe that timely removal of neoplasms from salivary glands could decrease the incidence of CXPA, and elective neck dissection should be considered in cases of frankly invasive CXPA originating in the submandibular gland. Although noninvasive CXPA was generally associated with a good prognosis, these patients should be followed closely because regional or distant metastasis can occur after primary treatment.

References

1. Beahrs OH, Woolner LB, Kirklin JW, et al: Carcinomatous transformation of mixed tumors of the parotid gland. Arch Surg 75: 605, 1957
2. Gnepp DR, Brandewein-Gensler MS, El-Nagger AK: Carcinoma ex pleomorphic adenoma, *in* Barnes L, Eveson JW, Reichart P, et al (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. Lyon, France, IARC Press, 2005, pp 242–243
3. Foote FW Jr, Frazell EL: Tumors of the major salivary glands. Cancer 6:1065, 1953
4. Spiro RH, Huvos AG, Strong EW: Malignant mixed tumor of salivary origin: A clinicopathologic study of 146 cases. Cancer 39: 388, 1977
5. LiVolsi VA, Perzin KH: Malignant mixed tumors arising in salivary glands. I. Carcinomas arising in benign mixed tumors: A clinicopathologic study. Cancer 39:2209, 1977
6. Gnepp DR: Malignant mixed tumors of the salivary glands: A review. Pathol Annu 28:279, 1993
7. Eneroth CM, Zetterberg A: Malignancy in pleomorphic adenoma. A clinical and microspectrophotometric study. Acta Otolaryngol 77:426, 1974
8. Kashiwagi N, Murakami T, Chikugo T, et al: Carcinoma ex pleomorphic adenoma of the parotid gland. Acta Radiol 53:303, 2012
9. Zbaren P, Zbaren S, Caversaccio MD, et al: Carcinoma ex pleomorphic adenoma: Diagnostic difficulty and outcome. Otolaryngol Head Neck Surg 138:601, 2008
10. Tortoledo ME, Luna MA, Batsakis JG: Carcinomas ex pleomorphic adenoma and malignant mixed tumors. Arch Otolaryngol 110:172, 1984
11. Lewis JE, Olsen KD, Sebo TJ: Carcinoma ex pleomorphic adenoma: Pathologic analysis of 73 cases. Hum Pathol 32:596, 2001
12. Thackray AC, Lucas RB: Tumors of the major salivary glands, *in* Atlas of Tumor Pathology. Fascicle 10, Series 2. Washington, DC, Armed Forces Institute of Pathology, 1979
13. Eveson JW, Cawson RA: Salivary gland tumours. A review of 2410 cases with particular reference to histological types, site, age and sex distribution. J Pathol 146:51, 1985
14. Olsen KD, Lewis JE: Carcinoma ex pleomorphic adenoma: A clinicopathologic review. Head Neck 23:705, 2001
15. Brandwein M, Huvos AG, Dardick I, et al: Noninvasive and minimally invasive carcinoma ex mixed tumor: A clinicopathologic and ploidy study of 12 patients with major salivary tumors of low (or no?) malignant potential. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81:655, 1996
16. Nakamori K, Ohuchi T, Hasegawa T, et al: Carcinoma ex pleomorphic adenoma of the buccal region is composed of salivary duct carcinoma and squamous cell carcinoma components. Int J Oral Maxillofac Surg 38:1116, 2009
17. Mariano FV, Noronha AL, Gondak RO, et al: Carcinoma ex pleomorphic adenoma in a Brazilian population: Clinico-

pathological analysis of 38 cases. Int J Oral Maxillofac Surg 42: 685, 2013
18. Nouraei SAR, Hope KL, Kelly CG, et al: Carcinoma ex benign pleomorphic adenoma of the parotid gland. Plast Reconstr Surg 116:1206, 2005
19. Weissferdt A, Langman G: An intracapsular carcinoma ex pleomorphic adenoma with lung metastases composed exclusively of benign elements: Histological evidence of a continuum between metastasizing pleomorphic adenoma and carcinoma ex pleomorphic adenoma. Pathol Res Pract 206:480, 2010
20. Katabi N, Gomez D, Klimstra DS, et al: Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: A clinicopathologic study of 43 cases. Hum Pathol 41:927, 2010