Original Article

Treatment outcome and prognostic factors analysis of carcinoma ex pleomorphic adenoma of major salivary glands

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Background: Carcinoma ex pleomorphic adenoma (CXPA) is an uncommon malignant tumor with aggressive behavior but the treatment outcomes and prognostic factors are rarely reported.

Methods: From April 2008 to May 2021, clinical data of 22 patients with pathologically proven CXPA were retrospectively reviewed. Twenty patients received surgery first, followed by adjuvant radiotherapy (n=13), chemoradiotherapy (n=5) and observation (n=2). Definitive chemoradiotherapy without operation was delivered for 2 cases. We analyze treatment outcomes and prognostic factors.

Results: After a median follow-up of 46.5 months (range, 13–128 months), we observed 8 relapses (4 distant metastases alone, and 4 combined distant metastases with locoregional recurrence) and 5 deaths (all due to uncontrolled tumor). The 5-year overall survival (OS), progression-free survival (PFS), locoregional-free survival (LRFS) and distant metastasis-free survival (DMFS) were 71.9%, 65.3%, 78.1%, and 61.4%, respectively. Prognostic factor analyses for all 22 patients found 2 potential predictors—tumor origin and clinical N-stage. Combining both factors revealed that patients with submandibular origin plus clinical positive regional nodes had significantly worse OS (5-year rate, 0% *vs.* 90.0%, P<0.001), PFS (5-year rate, 0% *vs.* 75.7%, P<0.001), LRFS (5-year rate, 0% *vs.* 86.8%, P=0.002), and DMFS (5-year rate, 0% *vs.* 73.5%, P<0.001). Cox univariate analysis confirmed similar findings. Among unfavorable pathological features for 20 patients who received surgery, invasiveness subtype is the only potential factor in predicting PFS (P=0.048) but not significant for OS (P=0.158), LRFS (P=0.185), and DMFS (P=0.071).

Conclusions: Our treatment results of 5-year OS 71.9% and PFS 65.3% for CXPA still have room for improvement. This study identifies three potential prognostic factors—tumor origin, clinical N-stage, and pathological invasiveness subtype.

Keywords: Carcinoma ex pleomorphic adenoma (CXPA); major salivary gland; prognostic factors; treatment outcome

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Introduction

Carcinoma ex pleomorphic adenoma (CXPA) is an uncommon malignant tumor with aggressive behavior. The prevalence of CXPA ranges from approximately 3% to 15% among all malignant salivary gland tumors (1-4). Histologically, CXPA is a carcinoma arising from a primary or recurrent benign pleomorphic adenoma (5). Preoperative diagnosis is challenging, because the residual mixed tumor component may be quite small, and various carcinoma subtypes may be present (6). CXPA with previously treated pleomorphic adenoma was seen in 21% to 25% (1,7). Clinically, it is found frequently arising from the parotid gland, predominantly in the sixth to eighth decades of life and slightly more common in females (5).

The primary treatment of CXPA is surgery, followed by adjuvant radiotherapy for patients with poor prognostic factors (5). The role of chemotherapy is uncertain. The treatment outcomes for CXPA are unsatisfactory, with reported 5-year overall survival (OS) rates between 30% and 76% (1,2,6,8,9). The purpose of this study was to analyze the treatment outcomes and prognostic factors in patients with CXPA arising from the major salivary glands.

Methods

Patients

Inclusion criteria for this retrospective study were (I) pathologically proven CXPA arising from major salivary glands; (II) no distant metastasis at diagnosis; (III) available chart records and image data; (IV) received regular post-treatment follow-up. This study was approved by the Institutional Review Board of Changhua Christian Hospital (No. 210422), and the need for a written informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). From April 2008 to May 2021, 22 eligible patients were enrolled. We reviewed hospital charts, diagnostic imaging studies, operation notes, pathological reports, and radiotherapy/chemotherapy records. There were 14 men and 8 women with a median age of 48.5 years (range, 24–84 years). Sixteen (72.7%) patients arose from the parotid gland and 6 (27.3%) from the submandibular gland. The median duration of symptom onset was about 1 year. Six (27.3%) of our patients had a prior history of benign salivary gland disease. *Table 1* summarizes the patients' characteristics. Clinical staging was defined according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system of major salivary glands. Twelve (54.5%) patients presented with early T-stage (T1 or T2), and 10 (45.5%) advanced T-stage (T3 or T4). Most patients (63.6%) had no enlargement of the regional lymph nodes, while 8 (36.4%) patients had clinical positive regional lymph node metastasis. The overall clinical stage distribution was stage I 9.1% (2/22), stage II 45.5% (10/22), stage III 27.3% (6/22), and stage IV 18.2% (4/22), respectively.

Highlight box

Key findings

- This study identified three potential prognostic factors for carcinoma ex pleomorphic adenoma (CXPA) arising from major salivary glands—tumor origin, clinical N-stage, and pathological invasiveness subtype.

What is known and what is new?

- CXPA is an uncommon malignant tumor with aggressive behavior but the treatment outcomes and prognostic factors are rarely reported. We investigated the clinical presentation and treatment results for 22 CXPA cases in our hospital.

What is the implication, and what should change now?

- Patients with those high-risk clinical characteristics should receive more aggressive treatments.

Treatment

The treatment modality consisted of surgery alone (n=2), surgery plus adjuvant radiotherapy (n=13) or chemoradiotherapy (n=5), and definitive chemoradiotherapy (n=2). Among 20 patients who received surgery, 8 patients (40%) underwent primary tumor resection and regional lymph node dissection and 12 received primary tumor excision only. For patients who received radiotherapy (n=20), the median dose of radiotherapy was 66 Gy (range, 59.4–73.5 Gy) in 33 fractions (range, 30–40 fractions), with median elapsed days of 46.5 days (range, 39–67 days). After primary treatment, 21 (95.45%) of 22 patients achieved complete remission.

Statistical analysis

The endpoints of this study were treatment outcomes and prognostic factors analyses. We used the Kaplan-Meier method to estimate OS, progression-free survival (PFS), locoregional-free survival (LRFS), and distant metastasis-free survival (DMFS). The OS was calculated from the

Table 1 Patient characteristics (n=22)

Characteristics	No. of case (%)
Age (year), median [range]	48.5 [24–84]
Symptom duration (month), median [range]	12.0 [0.7–240]
Gender	
Male	14 (63.6)
Female	8 (36.4)
Alcohol consumption	
Yes	5 (22.7)
No	17 (77.3)
Smoking	
Yes	11 (50.0)
No	11 (50.0)
Betel-nut chewing	
Yes	3 (13.6)
No	19 (86.4)
Prior history of benign salivary gland tumor	
Yes	6 (27.3)
No	16 (72.7)
Tumor origin	
Parotid gland	16 (72.7)
Submandibular gland	6 (27.3)
Clinical T-stage	
T1 or T2	12 (54.5)
T3 or T4	10 (45.5)
Clinical N-stage	
N0	14 (63.6)
N+	8 (36.4)
Primary tumor border (image)	
Well-defined	12 (54.5)
Ill-defined	10 (45.5)
Primary tumor central necrosis (image)	
Yes	16 (72.7)
No	6 (27.3)

first day of curative treatment until the date of death or last follow-up visit. The PFS was calculated from the first day of curative treatment until the first date of disease progression, death or last follow-up visit. The LRFS was measured from the first day of curative treatment until the date of local, regional, both failures or last follow-up visit. The DMFS was measured from the first day of curative treatment until the date of distant metastasis or last follow-up visit. Comparisons of various survival curves were performed using the log-rank test. The univariate Cox proportional hazards model was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Analyzed factors included age, gender, alcohol consumption, smoking, betel-nut chewing, symptom duration, prior history of benign salivary gland tumor, tumor origin, clinical T-stage, clinical N-stage, and image findings (primary tumor border and central necrosis) for all 22 patients. For 20 patients who received surgery, we also analyzed additional pathological features including invasiveness subtype, resection margin, lymphovascular invasion, perineural invasion, extranodal extension. Invasiveness subtype was divided into three categories based on the presence and extent of invasion of the carcinomatous component outside the fibrous capsule, as non-invasive, minimally invasive and invasive subtype. The carcinoma component is confined within the fibrous capsule of the pleomorphic adenoma in non-invasive subtype CXPA. Minimally invasive subtype indicates malignant component of CXPA with <1.5 mm penetration into extracapsular tissue. If the malignant component extends greater than 1.5 mm outside the tumor capsule into adjacent tissue, it is classified as invasive subtype (1). All statistical analyses were performed using SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA). P value of less than 0.05 was considered statistically significant.

Results

Treatment outcome

After a median follow-up of 46.5 months (range, 13–128 months), we observed 8 relapses and 5 deaths. Of 6 relapse diseases who received operation, there were 4 invasive subtype, 1 minimally invasive subtype, and 1 non-invasive subtype. Two people didn't undergo operation thus the status of invasiveness was unknown. The treatment failure pattern showed 4 distant metastases alone, and 4 combined distant metastases with locoregional recurrence. The median time to develop distant metastasis was 18.5 months (range, 8–63 months), and locoregional recurrence 15.5 months (range, 4–36 months). At the time of this writing, 5 patients had died and all due to uncontrolled tumors. The 5-year OS, PFS, LRFS and DMFS of all 22 patients were 71.9%,

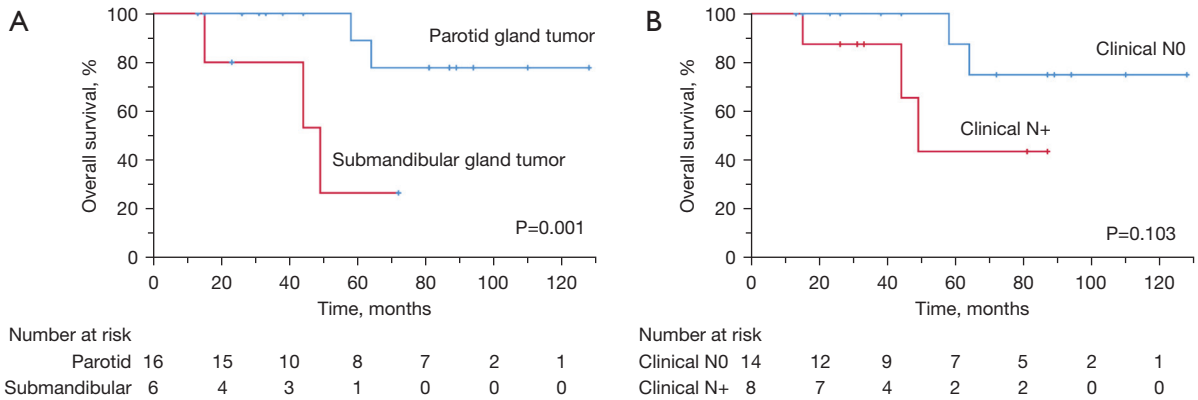

Figure 1 Kaplan-Meier estimates of overall survival according to the tumor origin (A) and clinical N-stage (B).

65.3%, 78.1%, and 61.4%, respectively.

Prognostic factors analyses for all 22 patients

Kaplan-Meier survival curve analyses reveal that tumor origin is the only significant factor in predicting OS. Tumors arising from submandibular gland have a significantly worse OS (5-year rate, 26.7% *vs.* 88.9%, P=0.001) compared with those of parotid gland (*Figure 1A*). Clinical N-stage (positive *vs.* negative) affects OS (P=0.103, *Figure 1B*) but does not reach statistically significant. We combine both factors and re-analyze the data. Patients with submandibular origin and clinical positive regional nodes not only have significantly worse OS (P<0.001, *Figure 2A*), but also PFS (P<0.001, *Figure 2B*), LRFS (P=0.002, *Figure 2C*), and DMFS (P<0.001, *Figure 2D*).

Table 2 shows the results of Cox univariate analyses for OS, PFS, LRFS and DMFS. We found that tumor origin and clinical nodal status were two potential factors in predicting survivals. Tumor arising from the submandibular (*vs.* parotid) gland had significantly worse OS (HR =7.79, 95% CI: 1.25–48.55, P=0.028). Patients presented with clinically regional lymph nodes positive (*vs.* negative) predict worse PFS (P=0.055), LRFS (P=0.081) and DMFS (P=0.064). By grouping these two factors together, we observed that patients with submandibular origin and clinical positive regional nodes had significantly worse PFS (P=0.006), LRFS (P=0.023), and DMFS (P=0.003). The calculated HR, 95% CI and P value for OS cannot be reliably estimated due to a low incidence of one subgroup. We do not do multivariate analysis due to small sample size. In addition, most variables fail to show significant results by univariate analysis.

Prognostic impacts of pathological features for 20 patients who received surgery

Among 20 patients who received surgical resection, 7 (35%) patients were non-invasive CXPA, 6 (30%) patients were minimally invasive CXPA, and 7 (35%) patients were invasive CXPA. Other unfavorable pathological features and its percentage revealed unsafe (involved/close) margin in 50% (10/20), perineural invasion in 25% (5/20), lymphovascular invasion in 15% (3/20), and extranodal extension in 10% (2/20) patients.

Kaplan-Meier survival curve analyses revealed that the invasiveness subtype was a significant predictor for PFS (P=0.026) and DMFS (P=0.046). We also observed a lower OS (P=0.132) and LRFS (P=0.142) for patients with invasive subtype, but the difference does not reach a statistically significant level.

Table 3 illustrated Cox univariate analyses using five pathological features (invasiveness subtype, resection margin, perineural invasion, lymphovascular invasion, and extranodal extension) for 20 patients who received surgery. We found that tumors with invasive subtype (*vs.* minimally invasive/non-invasive subtypes) was the only significant predictor for PFS (P=0.048). Worse but non-significant OS (P=0.158), LRFS (P=0.185), and DMFS (P=0.071) were observed for patients with invasive subtype.

Discussion

CXPA is an uncommon malignancy among head and neck region and reports for treatment outcome of CXPA are relatively rare. It is important for patients diagnosed as CXPA treated by a multidisciplinary team. Patients are diagnosed

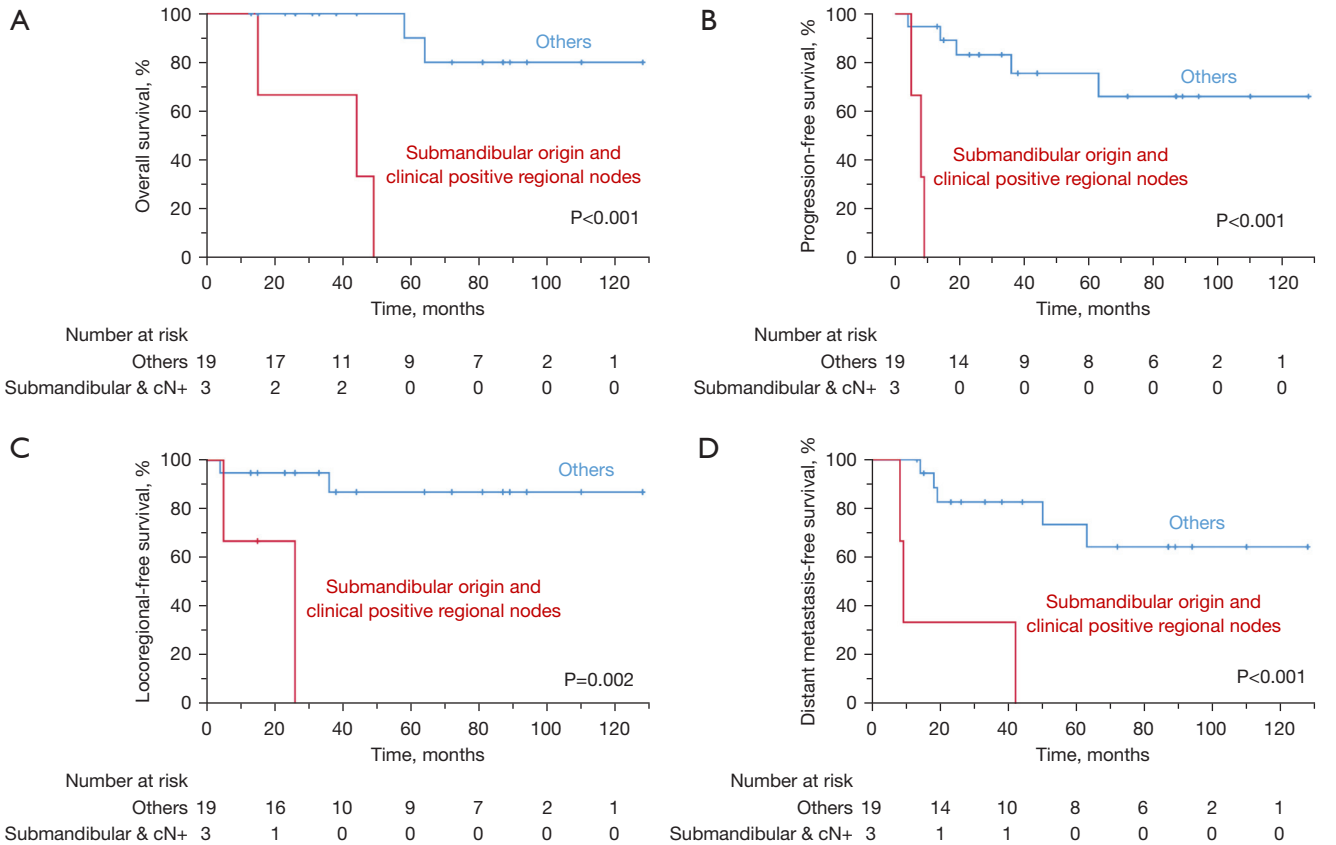

Figure 2 Kaplan-Meier estimates overall survival (A), progression-free survival (B), locoregional-free survival (C), and distant metastasis-free survival (D) between patients with submandibular origin plus clinical positive regional nodes versus the remaining patients.

and staged mostly by head and neck surgeons, and they may undergo operation or definitive chemoradiotherapy depending on the disease status and patients' preference. A good efficacy and functional impact balance must be evaluated and well-explained to the patient (10). After operation, radiation oncologists decide the radiotherapy treatment planning according to the surgical finding and pathologic features reported by the pathologist. Post-operative adjuvant radiotherapy is performed within 6 weeks after surgery when indicated. In locally advanced or metastatic disease, hematology oncologists provide best medication choices for these patients. There may also be a role in stereotactic body radiation therapy (SBRT) for oligometastatic patients (11).

Severe retrospective studies with limited case numbers revealed 5-year rates of 30–76% for OS (1,2,6,8,9) and 37–75% for disease-specific survival (DSS) (1,2,6-9,12). A multi-institutional retrospective study in the northern Japan area with shorter follow-up time reported a 3-year OS 79.9% and PFS 76.8% for 33 patients with CXPA of the parotid gland (13). By using the Surveillance, Epidemiology, and End Results (SEER) database, Gupta *et al.* identified 619 patients of major salivary gland CXPA from 1973 to 2015 and found the 5-year OS of 68.5% and DSS of 80.4% (14). Our results of 5-year OS 71.9% and PFS 65.3% are compatible with the literature.

The reported overall treatment failure rates for CXPA were 33.3–53.0% (6,8,13). Eight of 22 (36.4%) our patients encountered treatment failure. Regarding detailed treatment failure pattern, only a few reports showed the data. In our study, distant metastases account for 36.4% of the patients and outnumber locoregional recurrence rate (18.2%). There were 6 patients in this study presented with early stage (stage I or II) while 16 patients presented with advanced stage (stage III or IV). It may be the reason that distant relapse rate was two-fold compared to locoregional recurrence rate. Two prior studies showed similar failure patterns- more distant failures rather than locoregional recurrences (13,15). Hu *et al.* from Shanghai,

Table 2 Cox univariate analyses of various survivals using clinical factors for all 22 patients

Characteristics	Overall survival			Progression-free survival			Locoregional-free survival			Distant metastasis-free survival		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age												
>50 *vs.* ≤50 years	2.47	0.39 to 15.62	0.337	1.95	0.47 to 8.02	0.357	5.66	0.58 to 55.50	0.137	2.09	0.50 to 8.79	0.314
Symptom duration												
>1 *vs.* ≤1 year	0.69	0.11 to 4.16	0.682	0.59	0.15 to 2.39	0.460	0.20	0.02 to 1.92	0.162	0.46	0.12 to 1.88	0.282
Gender												
Male *vs.* female	0.82	0.14 to 4.93	0.828	1.36	0.34 to 5.51	0.668	1.61	0.23 to 11.41	0.636	1.30	0.32 to 5.28	0.716
Alcohol consumption												
Yes *vs.* no	1.82	0.19 to 17.06	0.602	1.12	0.22 to 5.59	0.890	0.03	0 to 847.15	0.511	1.64	0.32 to 8.28	0.552
Smoking												
Yes *vs.* no	1.79	0.30 to 10.77	0.525	0.50	0.12 to 2.12	0.347	0.31	0.03 to 2.94	0.304	0.72	0.17 to 3.08	0.660
Betel-nut chewing												
Yes *vs.* no	8.49	0.51 to 141.44	0.136	1.02	0.12 to 8.48	0.987	0.04	0 to 20,089.71	0.632	1.47	0.17 to 12.66	0.724
Prior history of benign salivary gland tumor												
Yes *vs.* no	0.63	0.07 to 5.64	0.677	0.68	0.14 to 3.38	0.635	0.03	0 to 381.34	0.469	0.77	0.16 to 3.84	0.752
Tumor origin												
Submandibular *vs.* parotid gland	7.79	1.25 to 48.55	0.028	2.54	0.58 to 11.03	0.215	4.74	0.61 to 37.11	0.138	2.77	0.65 to 11.82	0.169
Clinical T-stage												
T1–2 *vs.* T3–4	0.39	0.04 to 3.51	0.401	1.21	0.30 to 4.89	0.791	0.47	0.05 to 4.55	0.515	1.44	0.36 to 5.85	0.610
Clinical N-stage												
N+ *vs.* N0	4.05	0.66 to 24.78	0.130	4.11	0.97 to 17.39	0.055	7.78	0.78 to 78.01	0.081	3.90	0.92 to 16.47	0.064
Primary tumor border												
Ill-defined *vs.* well-defined	1.86	0.31 to 11.14	0.499	2.15	0.51 to 9.09	0.297	4.60	0.48 to 44.63	0.188	2.03	0.48 to 8.50	0.333
Primary tumor central necrosis												
Yes *vs.* no	35.49	0.01 to 112,720.97	0.386	2.87	0.35 to 23.51	0.325	38.48	0.01 to 265,335.99	0.418	3.30	0.40 to 26.87	0.265

HR, hazard ratio; CI, confidence interval.

Table 3 Cox univariate analyses of various survivals using pathologic features for 20 patients who received surgery

Characteristics	Overall survival			Progression-free survival			Locoregional-free survival			Distant metastasis-free survival		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Invasiveness subgroup												
Invasive *vs.* others	3.66	0.60 to 22.24	0.158	5.63	1.02 to 31.15	0.048	5.24	0.45 to 60.52	0.185	4.80	0.88 to 26.31	0.071
Resection margin												
Involved/close *vs.* free	2.27	0.38 to 13.69	0.371	2.58	0.47 to 14.36	0.278	2.79	0.25 to 31.16	0.406	2.85	0.52 to 15.72	0.229
Lymphovascular invasion												
Yes *vs.* no	1.40	0.16 to 12.63	0.766	1.23	0.14 to 10.56	0.851	2.98	0.26 to 34.01	0.381	1.44	0.17 to 12.39	0.738
Perineural invasion												
Yes *vs.* no	2.25	0.37 to 13.84	0.381	3.02	0.61 to 15.00	0.176	6.11	0.54 to 69.37	0.144	3.47	0.70 to 18.26	0.128
Extranodal extension												
Yes *vs.* no	4.71	0.43 to 52.12	0.206	2.76	0.30 to 25.00	0.367	7.65	0.47 to 123.41	0.152	4.52	0.46 to 44.19	0.194

HR, hazard ratio; CI, confidence interval.

China reported 54 distant metastases (16.2%) and 30 locoregional recurrences (8.9%) among 334 patients who had available follow-up information (15). They defined a subgroup of 174 patients with widely invasive CXPA and observed 53 distant failures (30.6%) and 29 locoregional recurrences (16.8%) (15). There were 8 distant failures (24.2%) and 5 locoregional recurrences (15.2%) among 33 patients in Suzuki *et al.*'s study from Japan (13). In contrast, another two studies found more locoregional recurrences rather than distant metastasis (8,12). Zhao *et al.* studied 51 patients in Zhejiang Cancer Hospital, China, and revealed a 39.2% locoregional recurrent rate and a 27.5% distant metastasis rate of their patients (8). Ye *et al.* investigated 135 patients with frankly invasive CXPA from Beijing, China and showed more than half these cases (73 of 135; 54.1%) developed local recurrences; 25 (18.5%) developed regional metastasis; 21 (15.6%) developed distant metastases (12). In addition, Chen *et al.* collected 63 patients of parotid CXPA from the University of California, San Francisco (UCSF) and reported 20 local recurrences (31.7%), 8 regional recurrences (12.7%), and 27 distant metastases (42.9%) (9). Based on these data, it is still non-conclusive regarding the most frequent site of treatment failure for CXPA.

Many predicting factors of DSS were reported for CXPA. Hu *et al.* reviewed a largest sample size of 361 CXPA patients from a single institute (15). Among them, 334 patients had available follow-up information. They found that age (P<0.001), T-stage (P<0.001), N-stage (P<0.001), invasiveness (P<0.001), histologic grade (P<0.001), proportion of carcinoma (P<0.001), perineural invasion (P<0.001), and vascular invasion (P=0.010) were significant predictors for DSS by Kaplan-Meier analysis (15). Cox univariate analysis revealed the same results (15). In Cox multivariate analysis, T-stage (P=0.002), N-stage (P<0.001) and invasiveness (P=0.002) were significant predictors for DSS (15). A total of 151 patients with CXPA were reviewed by Ye *et al.* from Beijing, China and revealed that T-stage, N-stage, overall clinical stage, invasiveness, and malignant subtype were significant risk factors for DSS (12). Two reports from the SEER database, showed several prognostic factors. Gupta *et al.* enrolled 619 patients of major salivary gland CXPA from 1973 to 2015 and found that high grade, late stage, larger tumor size (≥4 cm), extra-parenchymal extension, multiple positive regional nodes, and initial distant metastasis were poor predictors for DSS by univariate analysis (14). Among these factors, a tumor size ≥4 cm, multiple positive lymph nodes and initial distant metastasis were independent prognostic factors using multivariable analysis (14). Chen *et al.* extracted

278 patients with CXPA arising from parotid gland in the SEER databank [1988–2009] and revealed race, multiple metastatic lymph nodes and initial distant metastasis were independent prognostic factors of DSS (16). Katabi *et al.* reviewed 43 patients with CXPA from the Memorial Sloan-Kettering Cancer Center and illustrated that vascular invasion and initial distant metastases conferred significant worse DSS (P<0.05) (17). Olsen *et al.* investigated 66 patients with CXPA who received primary treatment at Mayo Clinic and found that clinical adenopathy, overall clinical stage, and local extension beyond the gland evaluated by clinical exam were significant predictors for DSS by univariate analysis (6). In a detailed pathologic study from the same institute on the same patients, Lewis *et al.* reported that pathologic T-stage, pathologic N-stage, overall pathologic stage, tumor size, histologic grade, proportion of carcinoma, extent of invasion, and proliferation index of the carcinoma component affected DSS significantly by univariate analysis (18).

Predictors for OS were less frequently reported. In Mayo Clinic's study mentioned above, factors predicting DSS also affected OS, including clinical factors (6) and pathologic factors (18). In UCSF's report, T-stage, N-stage, facial nerve involvement, and the use of postoperative radiation therapy were identified as significant predictors for OS using univariate analysis but only pathologic lymph node metastasis was the independent predictor by multivariate analysis (9). In Zhao *et al.*'s study, factors significantly associated with OS were age, histological grade, invasiveness, T-stage, lymph node involvement, overall clinical stage and perineural invasion (8). Using Cox multivariate analysis, T-stage, lymph node involvement, histological grade and perineural invasion were identified as independent prognostic factors for OS (8).

In our study, Kaplan-Meier survival analyses revealed that tumor origin affected OS significantly (P=0.001) and clinical N-stage had a potential impact on OS (P=0.103). In addition, patients with submandibular origin plus clinical positive regional lymph nodes had significantly worse OS (P<0.001), as well as for PFS (P<0.001), LRFS (P=0.002), and DMFS (P<0.001). Among 20 patients who received surgery, invasiveness (invasive *vs.* minimally invasive/non-invasive subtypes) was a significant predictor for PFS (P=0.026) and DMFS (P=0.046), a lower but non-significant factor in predicting OS (P=0.132) and LRFS (P=0.142).

All patients in this study received novel radiotherapy techniques, with 3D conformal radiotherapy (3D-CRT), intensity modulated radiation therapy (IMRT), image-guided radiotherapy (IGRT) or tomotherapy. The novel radiation technique decreased radiation doses of the organs at risk while preserving locoregional control. Limitations of this study include small patient's number, non-uniform treatment, and retrospective nature, etc.

Recently the application of artificial intelligence has progressed in the clinical medicine field (19). De Felice *et al.* applied machine learning approaches to make decision tree algorithms based on their clinical data to analyze survival outcomes and predict recurrence rate in patients with high-risk salivary gland malignant tumors (19). On the other hand, there were some studies involving the relationship between oral microbiome and cancer oncogenesis. Identifying a microbiome signature may potentially define different classes to predict cancer risk, treatment outcomes and even RT-related oral mucositis based on individual radiosensitivity (20). These novel techniques may help in clinical decision making and prediction of survivals.

Conclusions

Based on our results and above discussion, we conclude that treatment outcomes for CXPA still have much room for improvement (a 33.3–53.0% overall treatment failure rate; 5-year rates of OS, 30–76% and DSS, 37–75%). Most patients fail distantly and how to strengthen the systemic therapy is an urgent need in the future. The most important factors in predicting survivals are invasiveness and N-stage, followed by overall stage, T-stage, and histologic grade. Patients with these poor prognostic factors may need the application of postoperative radiotherapy. Other minor factors such as margin status, perineural invasion and vascular invasion may also be taken into consideration. In addition, accurate diagnosis and aggressive surgical and radiological management of patients presenting with CXPA may increase the survival rates. Due to the small patient number in this study, prospective data or larger number retrospective study is needed to confirm this conclusion.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-23-11/coif). J.C.L. serves as an unpaid editorial board member of *Therapeutic Radiology*

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Changhua Christian Hospital (No. 210422), and individual consent for this retrospective analysis was waived.

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