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Radical resection and reconstruction in patients with adenoid cystic carcinoma in the minor salivary glands of the palate

Wei-liang Chen^{1*†}, Yan Wang^{2†}, Bin Zhou³, Juan-kun Liao⁴ and Rui Chen⁵

Abstract

Background: This study evaluated the clinical outcomes of the patients with adenoid cystic carcinoma (ACC) of the minor salivary glands of the palate.

Methods: Forty-four patients with stage I–II disease and 14 patients with stage III–IV disease underwent radical excision and reconstruction with a facial-submental artery island flap (FSAIF) and titanium mesh plus a free anterolateral thigh flap (ALTF) and radiotherapy respectively. Patients with stage III–IV disease subsequently received cobalt Co 60 adjuvant radiotherapy. Ki-67 expression was determined semiquantitatively in 52 patients with ACC by based on the cytoplasm staining intensity and percentage of positively stained tumor cells.

Results: The median (range) follow-up was 32.9 (14–58) months. Forty-one (71.7%) patients survived without disease recurrence. Nine patients (15.5%) survived with recurrent tumors (four with local recurrence, three with regional recurrence requiring salvage surgery, and two with distant metastasis); among these patients, five had overlapping recurrence. Eight patients (13.8%) died of regional, distant, or multiorgan metastasis (range: 22–42 months). The overall median (95% CI) survival time was 32.5 (25.0–39.5) months, and the median (95% CI) progression-free survival time was 32.9 (28.5–36.9) months. Rates of survival and recurrence differed significantly between patients with low- and high-grade tumors, patients with clinical stage I–II disease and those with stage III–IV disease, patients with and without lymph node metastasis, patients who underwent radical excision with versus without radiotherapy, and patients with low and high Ki-67 expression.

Conclusion: Radical resection and reconstruction with FSAIF is suitable methods for the the treatment of stage I–II ACC of the minor salivary glands of the palate. Stage III–IV tumors require radical resection, reconstruction with titanium mesh and free ALTF, and radiotherapy.

Keywords: Adenoid cystic carcinoma, Minor salivary gland, Palate, Flap, Ki-67 expression, Surgical procedures

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Introduction

Approximately 41.5% of all salivary gland tumors are minor salivary gland neoplasms, and almost 60% of tumors arising from the minor salivary glands are malignant [1, 2]. The palate is the most common site for intraoral minor salivary gland carcinomas [3, 4], and adenoid cystic carcinoma (ACC) is the most common histologic type [5]. ACC is a malignant tumor composed of ductal cells and abluminal modified myoepithelial basaloid cells showing various microscopic patterns [6]. The growth patterns are categorized as *cribriform*, *tubular*, and *solid*. A mixture of these patterns usually occurs within a single tumor, but the foci of cribriform tumors can usually be found even when another type predominates [7]. Although slow growing, ACC is a life-threatening malignant tumor owing to its high risk of recurrence; of the rate of tumor-related death within 30 years after primary treatment is high [8]. However, little research has been performed on the surgical outcomes of patients with ACC originating from the minor salivary glands of the palate. Here, we evaluated the outcomes of patients with ACC of the minor salivary glands of the palate who underwent radical excision and flap reconstruction.

Patients and methods

This retrospective observational study was conducted from January 2011 through December 2019 at the Department of Oral and Maxillofacial Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China. The 58 patients with ACC of the minor salivary glands of the palate enrolled in the study had primary tumors. We collected data on age, sex, size of tumor, histologic diagnosis, classifications for tumors, treatment, rates of survival and recurrence. Diagnostic imaging of the primary lesion was performed using three-dimensional computed tomography (3D-CT) and magnetic resonance imaging (MRI). Age groups are classified according to the cut-off age of the “elderly” recommended by the WHO [9]; The histologic diagnosis was confirmed according to the 2017 WHO classifications for salivary gland tumors [10]; The clinical stages were classified according to the American Joint Committee on Cancer’s *Cancer Staging Manual* (8th edition) [11]; The defects of maxilla and midface were classified by Brown classification [12]; All submandibular lymph nodes were checked during FSAIF elevation and details of the surgery were provided by Chen et al. [13]; All intraoperative proximal margin frozen section (FS) specimens were classified as R0 (FS analysis showed negative surgical margins) or R1 (FS analysis showed positive surgical margins after previous identification of positive margins and additional resection). Ki-67 expression was determined semiquantitatively based on the cytoplasm

staining intensity and percentage of positively stained tumor cells [14]. The exclusion criteria were cachexia, congestive cardiac failure, severe chronic obstructive pulmonary disease, and/or lack of follow-up data.

Statistical analyses

Statistical analyses were performed IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA). Overall survival (OS) and progression-free survival (PFS) were estimated with Kaplan–Meier curves. The chi-square test was used to analyze the data, as appropriate. A *P*-value of ≤ 0.05 was considered significant. The Institutional Review Board of Sun Yat-sen University approved this study.

Results

A total of 58 patients with ACC of the minor salivary glands of the palate were identified who had flap reconstruction following radical resection at the Department of Oral and Maxillofacial Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University (Guangzhou, Guangdong, China). Of the 58 patients, 28 were male and 30 were female. Patient age ranged from 20 to 80 years (median \pm standard deviation, 49.2 ± 9.8 years). We classified patients into ≤ 60 years ($n = 47$) and > 60 years ($n = 11$) age groups according to the cut-off age for “elderly” recommended by the World Health Organization (WHO) [9]. All patients exhibited slow-growing, painless swelling of the palate that began several months prior. Tumors were classified according to size, i.e., as ≤ 2 cm ($n = 9$) or > 2 cm ($n = 49$). In all cases, histologic diagnosis was confirmed according to the 2017 WHO classifications for salivary gland tumors [10]. ACC tumors were histopathologically classified as grade I–III. Grade I tumors showed a tubular and cribriform pattern without solid components ($n = 14$) (Fig. 1); grade II tumors were cribriform with $< 30\%$ solid components ($n = 18$); and grade III tumors had $\geq 30\%$ solid components ($n = 24$) (Fig. 2). Tumors with an area of histologic transformation were classified as *transformed* ($n = 3$).

Perineural invasion, bone invasion, and lymph node metastasis—which were defined as the presence of ACC cells in the nerve fiber (Fig. 3), maxillary bone (Fig. 4), and lymph nodes of the neck (Fig. 5) on histological examination—were noted in 48 (82.8%), 52 (89.7%), and 3 (5.2%) patients, respectively. According to the classifications of the American Joint Committee on Cancer’s *Cancer Staging Manual* (8th edition) [11], 9 (15.5%), 35 (60.3%), 11 (19.0%), and 3 patients (5.2%) had clinical stage I–IV disease, respectively.

Forty-four patients with stage I–II disease underwent radical excision, including subtotal maxillectomy (intraoral approach) and ipsilateral selective neck dissection. According to the Brown classification for maxillary

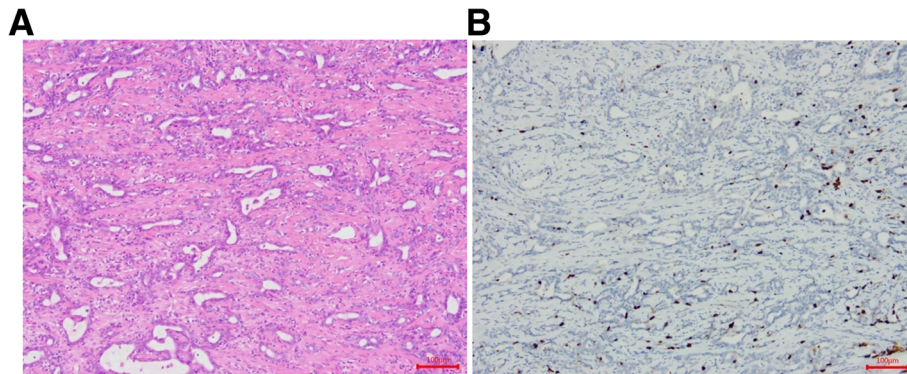


Fig. 1 Grade I tumors showing only a tubular and cribriform pattern without solid components. Solid-type adenoid cystic carcinoma (ACC) with elements of the cribriform and tubular types (hematoxylin and eosin staining) (A). Immunohistochemical staining for Ki-67 in ACC showing 10% positive cells (B)

and midface defects [12], 44 patients had class II maxillary defects (requiring subtotal maxillectomy not involving the orbital floor or adnexa) that were reconstructed with a facial-submental artery island flap (FSAIF) based on the distal facial pedicle (Fig. 6). Fourteen patients with stage III and IV disease underwent radical excision, including total maxillectomy (via the Weber–Ferguson approach) with preservation of the orbital contents, and ipsilateral selective neck dissection. Class III maxillary defects (requiring total maxillectomy and loss of orbital support) were reconstructed with titanium mesh and a free anterolateral thigh flap (ALTF) (Fig. 7).

All submandibular lymph nodes were checked during flap elevation and confirmed as pathologically negative before we harvested the FSAIF. Details of the surgery were provided in a 2008 report [13]. All intraoperative proximal margin frozen section (FS) specimens were classified as R0 (FS analysis showed negative surgical margins) or R1 (FS analysis showed positive surgical margins after previous identification of positive margins and additional resection). Resection status was R0 in 56

patients (96.6%) and R1 in 2 (3.4%). Fourteen patients with stage III and IV were treated with surgical excision followed by cobalt Co 60 adjuvant radiotherapy for the primary tumor site, and the interval between surgery and radiotherapy was 30 days. In total, 60 Gy was administered over 30 days with a conventional dose of 2 Gy fractions/day.

We used immunohistochemistry to analyze Ki-67 expression in paraffin-embedded specimens obtained from 52 patients with ACC. Ki-67 expression was determined semiquantitatively based on the cytoplasm staining intensity and percentage of positively stained tumor cells [14]. Staining intensity was scored as 0, indicating no staining or weak staining; 1, moderate staining; or 2, strong staining. The percentage of immunoreactive tumor cells was scored as 0, representing < 10% positivity (Fig. 1B); 1, 10–50%; or 2, > 50% (Fig. 2B). The overall Ki-67 expression score thus ranged from 0 to 4, i.e., the sum of the points for the percentage of positively stained cells and staining intensity. For statistical analysis, patients were divided into two groups: those with scores of

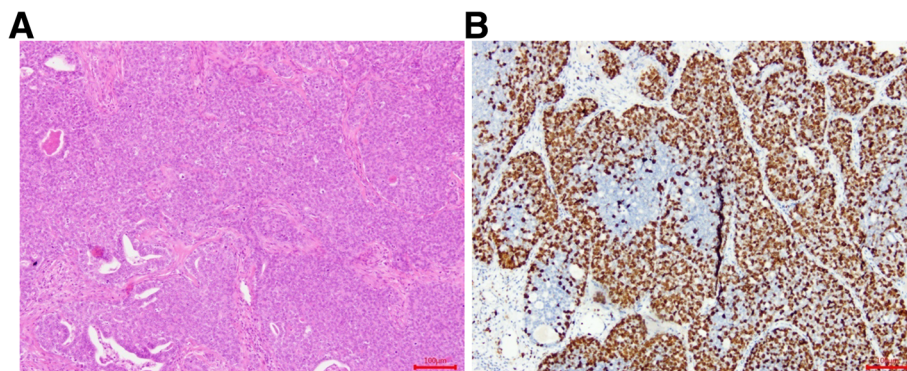


Fig. 2 Grade III tumors showing 60% solid components (hematoxylin and eosin staining) (A). Immunohistochemical staining for Ki-67 in adenoid cystic carcinoma cells, the staining intensity is strong, showing 60% positive cells (B)

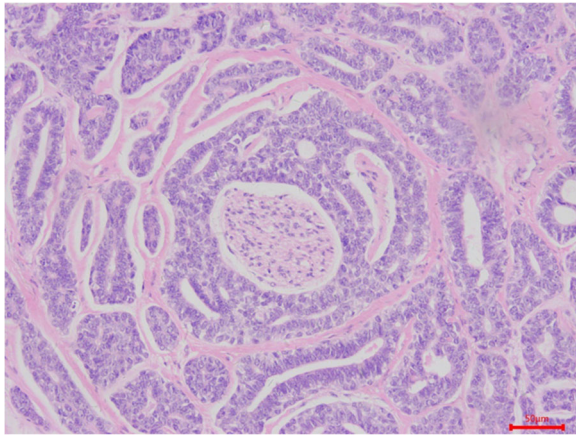


Fig. 3 Histologic section showing perineural invasion by ACC cells (hematoxylin and eosin staining)

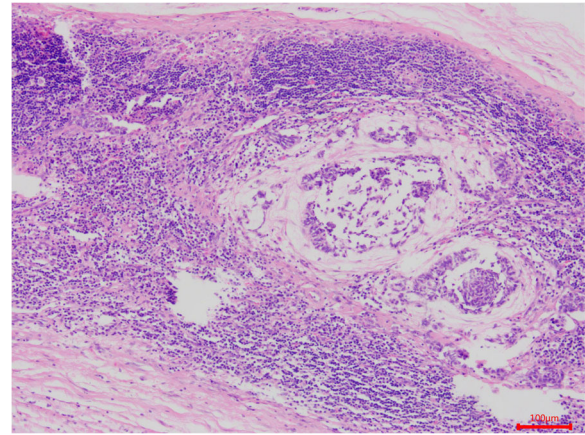


Fig. 5 Histologic section showing lymph node metastasis by ACC cells (hematoxylin and eosin staining)

0–2 were considered to have low Ki-67 expression, and those with scores of 3–4 were considered to have high expression [8]. Ki-67 expression was low in 40 patients (76.9%) and high in 12 patients (23.1%). However, high Ki-67 expression was identified in 3 of 28 patients (10.7%) with low-grade tumors and 9 of 24 patients (37.5%) with high-grade tumors. Table 1 summarizes the demographic and clinical characteristics of the patients with palatal ACC.

All patients underwent radical excision with wide safety margins of normal tissues and successful reconstruction of palate defects with a FSAIF or ALTF. No local or general complications developed. The median (range) follow-up duration was 32.9 (14–58) months. Forty-one (71.7%) patients survived without evidence of disease recurrence. Nine patients (15.5%) survived with recurrent tumors (including four with local recurrence

[maxilla], three with regional recurrence [skull base] who underwent salvage surgery [Fig. 8], and two with distant metastasis [lungs]); among these patients, five had overlapping recurrence. Eight (13.8%) patients died of distant (two patients with brain metastasis and three with lung metastasis), or multiorgan metastasis (three with metastasis in the lungs and liver) between 22 and 42 months. The median (95% CI) OS was 32.5 (25.0–39.5) months, and the median (95% CI) PFS was 32.9 (28.5–36.9) months (Fig. 9).

Sex, age, tumor site, perineural invasion, bone invasion, and surgical margin status were not associated with survival or recurrence ($P > 0.05$). However, survival and recurrence rates differed according to histopathologic grade (i.e., between the low- and high-grade tumor groups) and TNM stage (i.e., between the stage I–II and stage III–IV disease groups) ($P < 0.001$). In addition, survival and recurrence rates differed according to lymph node metastasis (i.e., between those with and without metastasis), treatment (i.e., between those who received radical excision with versus without radiotherapy), and Ki-67 expression (i.e., between those with low and high expression) ($P < 0.05$). Patient outcomes are summarized in Table 1.

Discussion

Radical excision with wide safety margins in combination with postoperative radiotherapy is the preferred treatment of ACC in the head and neck region. In this study, all intraoperative proximal margin FS specimens had negative surgical margins, and radical surgical excision was successful. Moreover, adjuvant radiotherapy with a total dose of 60 Gy was administered to the patients with stage III–IV disease. The median follow-up duration was 32.9 months, 71.7% of patients survived without evidence of disease recurrence, 15.5% survived

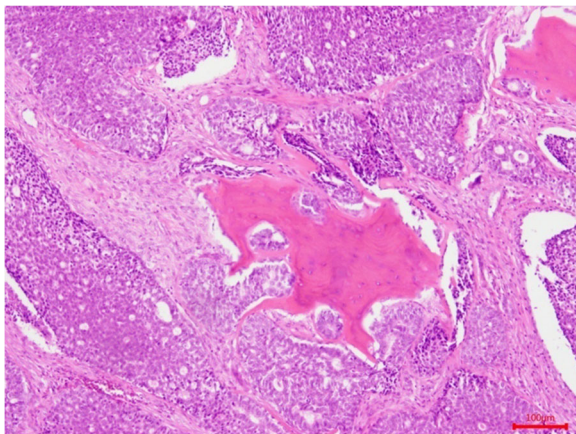
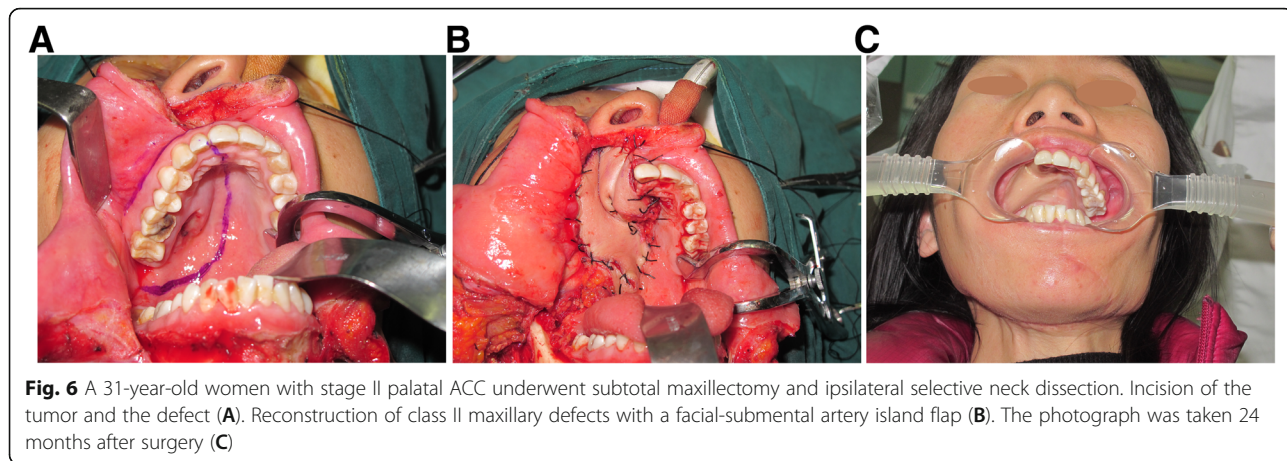


Fig. 4 Histologic section showing bone invasion by ACC cells (hematoxylin and eosin staining)



with recurrent tumors, and 13.8% died of regional, distant, or multiorgan metastasis. The median OS was 32.5 months, and the median PFS was 32.9 months. All patients died of local (brain), distant (lung), or multiorgan metastasis (lung and liver).

ACC of the minor salivary glands of the palate is a life-threatening malignant tumor due to its high risk of

recurrence and multiorgan metastasis. The characteristic biologic features of ACC include local recurrence, perineural spread, and late distant metastasis. Local control of the disease is difficult because of these features, even in patients with clinically clear surgical resection margins. Our study showed that the cervical lymph node metastasis rate of ACC was very low, and only 5.2% was

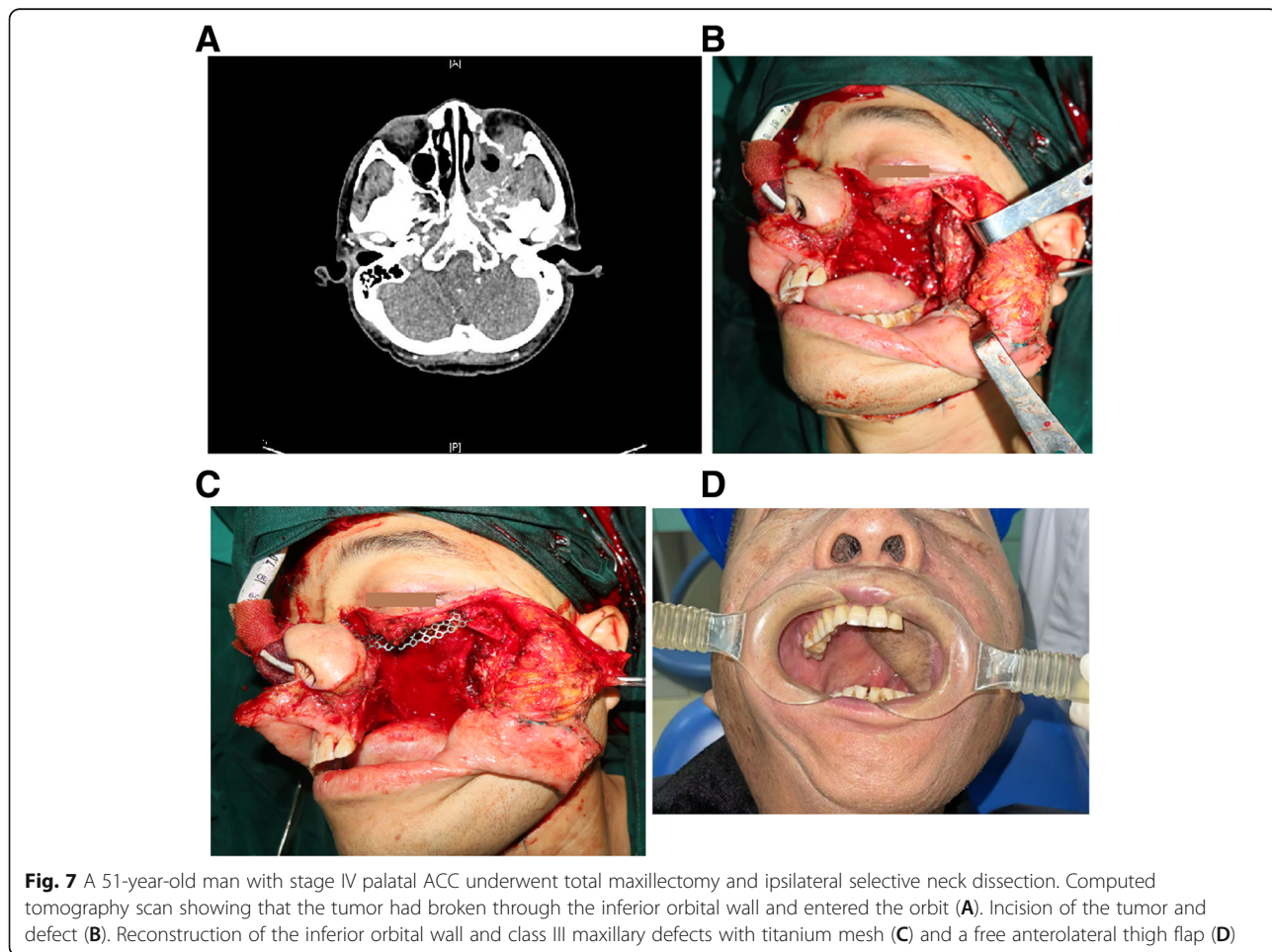


Table 1 Demographic characteristics, clinical characteristics and outcomes of 58 patients with palatal adenoid cystic carcinoma

Parameter	No. Of cases (%)	Survival without disease (%)	Survival with recurrence (%)	Death (%)	P-value
Sex					0.683
Male	28 (48.3)	19/28 (67.9)	4/28 (14.2)	5/28 (17.9)	
Female	30 (51.7)	22/30 (73.3)	5/30 (16.7)	3/30 (10.0)	
Age (y)					0.665
≤ 60 years	47 (81.0)	32/47 (68.1)	8/47 (17.0)	7/47 (14.9)	
> 60 years	11 (19.0)	9/11 (81.8)	1/11 (9.1)	1/11 (9.1)	
Tumor size (cm)					0.109
≤ 2 cm	9 (15.5)	9/9 (100.0)	0/9 (0.0)	0/9 (0.0)	
> 2 cm	49 (84.5)	32/49 (65.3)	9/49 (18.4)	8/49 (16.3)	
Histopathologic grade					0.0001
Low grade (I + II)	(14 + 18) (55.2)	30/32 (90.6)	0/32 (0.0)	2/32 (6.3)	
High grade (III + transformed)	(23 + 3) (44.8)	11/26 (42.3)	9/26 (34.6)	6/26 (23.1)	
Perineural invasion					0.281
Absent	10 (17.2)	9/10 (90.0)	1/10 (10.0)	0/10 (0.0)	
Present	48 (82.8)	32/48 (66.6)	8/48 (16.7)	8/48 (16.7)	
Bone invasion					0.250
Absent	6 (10.3)	6/6 (100.0)	0/6 (0.0)	0/6 (100.0)	
Present	52 (89.7)	35/52 (67.3)	9/52 (17.3)	8/52 (15.4)	
Lymph node metastasis					0.015
Absent	55 (94.8)	41/55 (74.6)	7/55 (12.7)	7/55 (12.7)	
Present	3 (5.2)	0/3 (0.0)	2/3 (66.7)	1/3 (33.3)	
TNM stage					0.0001
Early (I + II)	(9 + 35) (75.9)	39/44 (88.7)	2/44 (4.5)	3 /44 (6.8)	
Advanced (III + IV)	(11 + 3) (24.1)	2/14 (14.3)	7/14 (50.0)	5/14 (35.7)	
Treatment					0.004
Radical excision	44 (75.9)	36/44 (81.8)	4/44 (9.1)	4/44 (9.1)	
Radical excision with radiotherapy	14 (24.1)	5/14 (35.7)	5/14 (35.7)	4/14 (28.6)	
Surgical margin					0.081
R0	56 (96.6)	41/56 (73.2)	8/56	7/56	
R1	2 (3.4)	0/2 (0.0)	(14.3) 1/2 (50.0)	(12.5) 1/2 (50.0)	
Ki-67 expression^a					0.003
Low	40 (76.9)	31/40 (77.5)	5/40 (12.5)	4/40 (10.0)	
High	12 (23.1)	3/12 (25.0)	4/12 (33.3)	5/12 (41.7)	

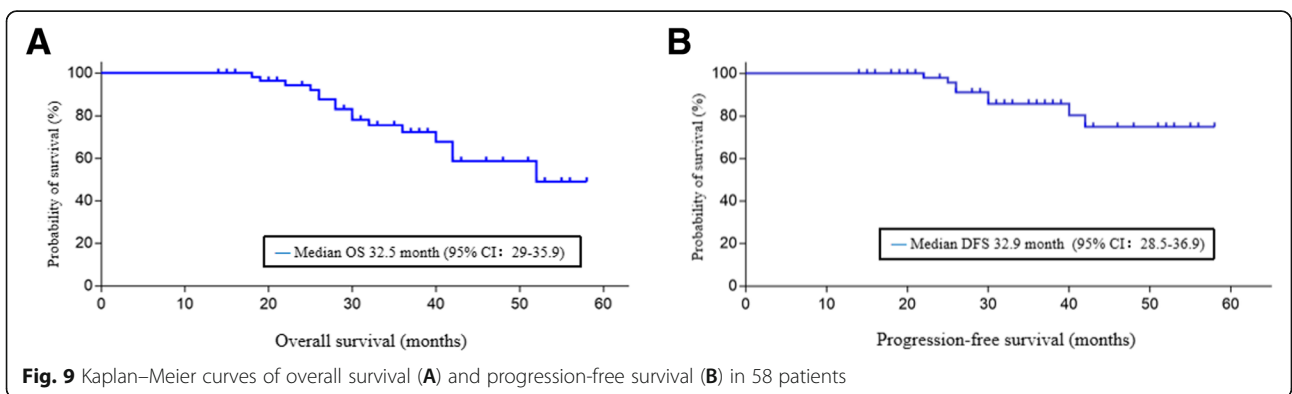
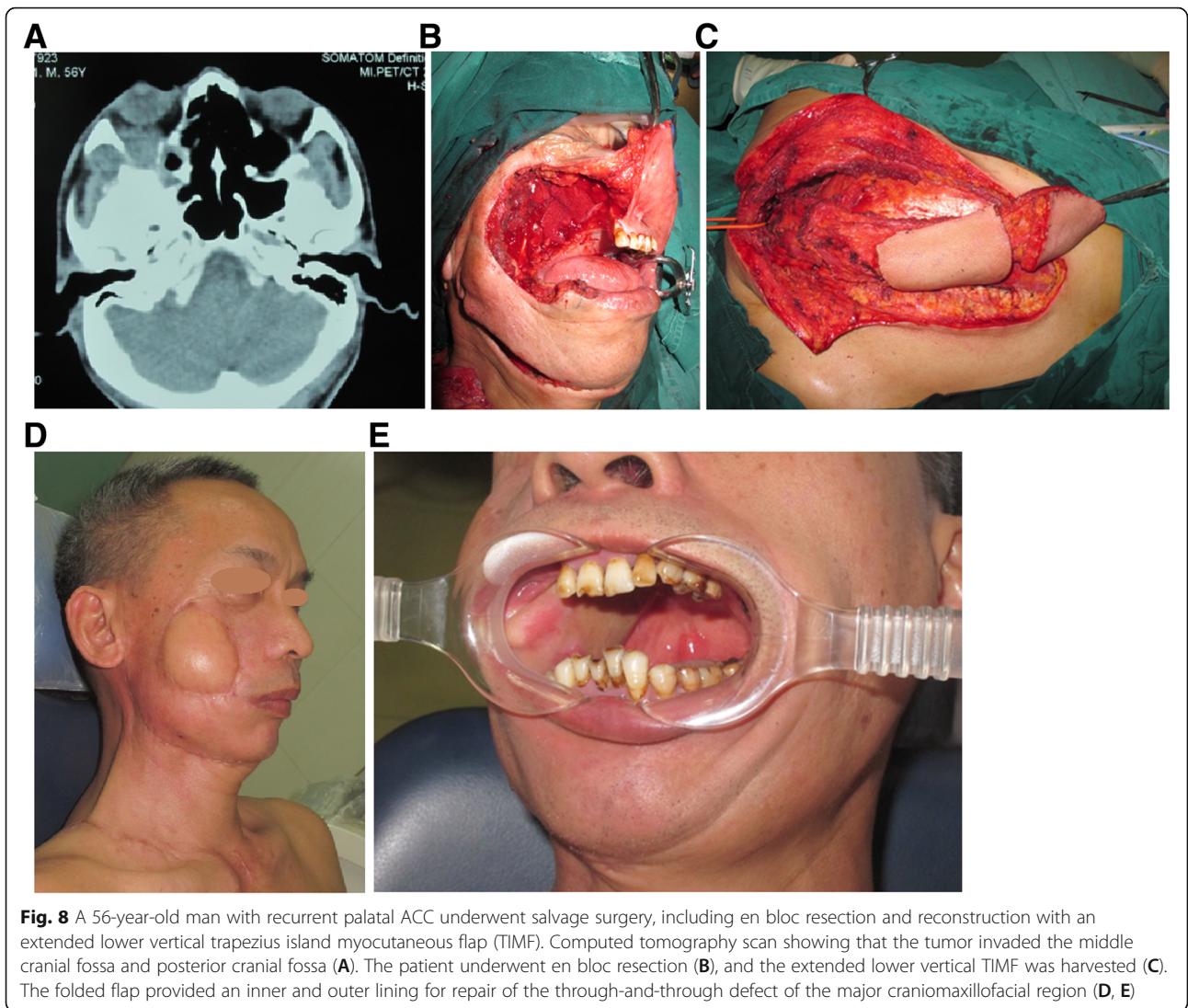
^aDetermined in paraffin-embedded specimens obtained from 52 patients

confirmed. It is suggested that the rationality of selective lymph node dissection needs further study.

Spread via the blood to distant sites, particularly the lungs, usually occurs when the primary tumor has been inadequately treated [15]. In this study, that are more linked to the intrinsic malignancy of the tumor [16]. According to our statistical analysis, the rate of survival without disease was significantly higher in patients with low-grade tumor (90.6%) and stage I–II disease (75.9%) than in patients with high-grade tumor (42.3%) and stage III–IV disease (24.1%). The rates of survival with

disease recurrence and death were significantly higher in patients with high-grade tumor (34.6 and 23.1%, respectively) and stage III–IV disease (50.0 and 35.7%) than in patients with low-grade tumor (0 and 6.3%) and stage I–II disease (4.5 and 6.8%) ($P = 0.0001$).

Although radiotherapy is an important adjuvant treatment [17] and we treated 14 patients with stage III–IV disease with surgical excision followed by adjuvant radiotherapy, and the rate of survival without disease was significantly lower among patients who underwent radical excision with radiotherapy (81.8%) than among



those who underwent only radical excision (35.7%). Obviously, patients with histopathologic grade I–II tumors or stage I–II disease, but without metastatic tumors, had a better prognosis than those with stage III–IV disease, grade III transformed tumors, or metastatic tumors. In a previous study, patients who received primary treatment with curative intent, mainly surgery, for early stage ACC in the minor salivary glands had a favorable prognosis [18]. Moratin et al. recommend surgical therapy for patients with ACC of the minor salivary glands, including elective neck dissection and microvascular reconstruction, to optimize the planning of adjuvant therapy [19].

Importantly, stage III–IV disease, grade III and transformed tumors, and metastatic tumors indicate advanced disease that warrants aggressive treatment (i.e., local or regional recurrence requires salvage surgery). Early initiation of cyclophosphamide, doxorubicin, and cisplatin chemotherapy may help control metastatic ACC [20]. Chemotherapy can be used to treat patients with brain, lung, or multiorgan metastasis, but such treatment failed in our patients. ACC is an indolent, slow-growing tumor but commonly metastasizes to the lungs and bones. Perineural invasion and bone invasion were noted in 82.8 and 89.7% of patients, respectively; these features can cause local or regional recurrence, hematogenous metastasis, and adverse reactions to radiotherapy or chemotherapy.

Ki-67 expression was significantly higher in the high- than low-grade tumor specimens in this study ($P < 0.05$). Ki-67 may be a subtype-specific marker of ACC in the minor salivary glands of the palate, and a possible prognostic biomarker for tumor progression.

Radical resection with safety margins is the mainstay of treatment for malignant tumors; however, reconstruction of the palate after tumor ablation can be challenging. ACC of the minor salivary glands can be treated radically with surgery, but reconstruction of the defect is rarely reported [14, 21, 22].

The FSAIF has a lower complication incidence when compared to the radial forearm free flap, while maintaining speech and swallowing function [23], and associated with less operative time, shorter hospitalization, fewer perioperative complications, and potentially similar disease recurrence rates compared to free tissue transfer for the reconstruction of oral cavity defects [24]. FSAIF is a reliable and safe method for reconstruction of Brown class II maxillary defects after cancer ablation [25]. However, the best outcomes for Brown class III maxillary defects are achieved with titanium mesh and a free ALTF, which provides good functional and esthetic outcomes after maxillectomy [26].

ACC is a life-threatening malignant tumor owing to its high risk of recurrence; of the rate of tumor-related death within 30 years after primary treatment is high [27]. In this study, the median follow-up of 30 months

seems short for a disease like ACC that tends to recur after several years. It is necessary for these patients to continue follow-up.

Conclusions

We believe that the surgical margins of the specimen must be negative, and the patient may require radiotherapy depending on tumor site, stage, and histologic grade. Radical resection is the best treatment for ACC in the minor salivary glands of the palate. Radical resection and reconstruction with FSAIF is suitable methods for the treatment of stage I–II ACC of the minor salivary glands of the palate; radical resection and reconstruction with titanium mesh and free ALTF in combination with radiotherapy is an appropriate treatment for stage III–IV tumors. Patients with local or regional recurrence should undergo salvage surgery and adjuvant radiotherapy. Immunohistochemical analysis of Ki-67 expression may provide additional prognostic information.

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None.

Authors' contributions

Wei-liang Chen conceived the study, oversaw the design of the study, oversaw all clinical and technical aspects of the study, helped analyze the data, provided guidance in the initial draft of the manuscript, and edited and approved the final version of the manuscript in its current form. Yan Wang helped design the study, collected patient data, analyzed the results, wrote the initial draft of the manuscript, and edited and approved the final version of the manuscript in its current form. Bin Zhou assisted in study design, collected patient data, and edited and approved the final version of the manuscript in its current form. Juan-kun Liao and Rui Chen assisted in study design, collected patient data, and edited and approved the final version of the manuscript in its current form. All authors read and approved the final manuscript.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the university's Institutional Review Board (Authorization No. 3–669).

Consent for publication

Informed written consent was obtained from each participant involved in the study.

Competing interests

The authors declare that they have no competing interests.

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