Diagnostic Accuracy Study

Medicine®

OPEN

# Clinical and pathological analysis of 10 cases of salivary gland epithelial–myoepithelial carcinoma

Feng Wang, MD, Bowen Li, MD, Yufan Wang, PhD, Yuehong Shen, PhD*, Hongyu Yang, PhD*

**Abstract**

Epithelial–myoepithelial carcinoma (EMC) is a rare neoplasm of the salivary glands. The aim of this study is to review and evaluate clinicopathological features and treatment of EMC of salivary gland for better sensitivity and specificity of the diagnosis.

The clinical and pathological data of the 10 salivary gland EMC cases from 2008 to 2017 were analyzed.

Six cases of EMC were diagnosed to be originated from parotid gland and 4 cases were from the minor salivary gland including palate, tongue, and oropharynx. Seven cases were performed radical surgery and 3 cases had radiotherapy postoperation, 2 cases had a local recurrence. The follow-up period was 4 to 104 months and the survival rate was 100%. Histopathology showed the tumors had a dominant prototypical biphasic tubular structure consisting of inner, cuboidal ductal cells and an outer layer of clear, myoepithelial cells, which grew infiltratively. The immunohistochemistry (IHC) showed the marker proteins CK, S-100, CD117, and Calponin were strongly positive in most EMC.

EMC is a rare and low-grade malignant tumor with good overall survival but relatively high tendency for local recurrence. Surgery is the priority choice for EMC therapy. Complete surgical excision and negative margins are necessary for good prognosis. Imaging techniques should be used to assess the neck dissection and it is unclear whether adjuvant radiotherapy is beneficial. To ensure the sensitivity and specificity of the EMC diagnosis, we should perform both pathological and IHC analysis.

**Abbreviations:** EMC = epithelial–myoepithelial carcinoma, IHC = immunohistochemistry.

**Keywords:** clinicopathological features, epithelial–myoepithelial carcinoma, salivary gland, sensitivity and specificity

## 1. Introduction

Epithelial–myoepithelial carcinoma (EMC) is a rare, low-grade malignant tumor that occurs in salivary glands. It is composed of 2 cell types that typically form double-layered duct-like structures with expansive borders and lacking a true capsule. In salivary gland tumors, the incidence of EMC accounts for about 1%, most of which occur in the parotid gland, and a small proportion occur in the submandibular gland and small salivary gland. [1] It presents a painless lump with slow growth, but poorly differentiated cells may show increased growth resulting in pain and nerve paralysis. It often occurs in female and more than 70% of people who get sick are over 50 years old. EMC was first reported by Donath in 1972, and only over 300 cases have been reported so far. The domestic and foreign literatures are mostly case reports. Due to the invasive growth, the tumor with postoperative recurrence and lymph node metastasis are common. Recently, reports on the trend of high-level transformation of low-grade salivary tumors are increasing and the prognosis is obviously poor, so the clinicopathological characteristics and treatment of EMC patients have been controversial.[2,3] This article retrospectively analyzed 10 EMC patients in our hospital, and discussed the clinicopathological characteristics and treatment options of EMC in conjunction with relevant literatures.

## 2. Methods

### 2.1. Clinical information

Patient meeting the following standards was selected as the research object: tumor was originated from salivary gland; pathological section was examined by 2 individual pathologists. The clinical and pathological data of 10 research objects with salivary gland EMC from January 2008 to June 2017 in our hospital were analyzed. Informed consent was obtained from all patients in accordance with the ethical guidelines of Peking University (Protocol No. 37923/2-3-2012). This study was approved by Ethics Committee of Peking University Health Science Center (IRB00001053-08043).

Editor: Jianxun Ding.

This study was supported by the National Natural Science Foundation of Guangdong Province (2019A1515011911), the Basic Research Program of the Shenzhen Innovation Council of China (grant nos. JCYJ20180228175511141, JCYJ20170306161518559, and SZBC2017023), and the Sanming Project of Medicine in Shenzhen (SZSM 201512036, Oral and Maxillofacial Surgery Team, Professor Yu Guangyan, Stomatology Hospital Peking University) to the Department of Oral and Maxillofacial Surgery, Peking University Shenzhen Hospital, Shenzhen, Guangdong, China.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Department of Oral and Maxillofacial Surgery, Peking University Shenzhen Hospital, Shenzhen, Guangdong Province, China.

* Correspondence: Yuehong Shen, Hongyu Yang, Department of Oral and Maxillofacial Surgery, Peking University Shenzhen Hospital, Shenzhen 518036, Guangdong, China
(e-mails: yuehongshen@hotmail.com, hyyang192@hotmail.com).



How to cite this article: Wang F, Li B, Wang Y, Shen Y, Yang H. Clinical and pathological analysis of 10 cases of salivary gland epithelial–myoepithelial carcinoma. Medicine 2020;99:41(e22671).

Received: 10 March 2020 / Received in final form: 11 June 2020 / Accepted: 10 September 2020

http://dx.doi.org/10.1097/MD.0000000000022671

**Table 1**

**Clinicopathological characteristics of 10 cases with EMC of salivary gland.**

| Gender/age | Location | TNM | Treatment | Radiation | Follow-up |
|---|---|---|---|---|---|
| Male/46 | Right tongue base | T2N0M0 | Expanded resection | Yes | 9 yr tumor-free |
| Female/29 | Left palate | T1N0M0 | Resection | No | 7 yr tumor-free |
| Female/77 | Left parotid gland | T1N0M0 | Expanded resection | No | 4 yr tumor-free |
| Male/26 | Right parotid gland | T1N0M0 | Resection | No | 4 yr tumor-free |
| Female/58 | Left parotid gland | T4N0M0 | Expanded resection<br>Partial patella Resection<br>Partial masseterectomy | Yes | Recurrence; no tumor after multiple surgeries; Survive for 4 yr. |
| Female/27 | Right parotid gland | T1N0M0 | Resection | No | 4 yr tumor-free |
| Female/41 | Left oropharynx | T2N0M0 | Expanded resection | No | 4 yr tumor-free |
| Male/52 | Right palate | T1N0M0 | Expanded resection | Yes | 2 yr tumor-free |
| Female/33 | Right parotid gland | T1N0M0 | Whole parotid resection | No | Recur 10 mo after surgery without continuing surgery. |
| Female/87 | Left parotid gland | T2N0M0 | Resection | No | 4 mo tumor-free |

### 2.2. Pathological specimen

All 10 specimens were surgical dissections, fixed with 10% neutral formalin buffer, embedded in paraffin, sectioned, performed with hematoxylin and eosin and immunohistochemical (IHC) staining referred to the typical standards.

### 2.3. Follow-up and prognosis evaluation

The follow-up period of the 10 patients was starting from the day of patient's initial treatment (including out-of-hospital treatment).

## 3. Results

### 3.1. Clinical information

The 10 patients included 3 men and 7 women, with a male-to-female ratio of 3: 7. The youngest patient was 26 years old, while the oldest was 87 years old. The median age was 43.5. It was confirmed that 6 tumors originated from the large salivary gland (parotid gland) and 4 tumors originated from the small salivary gland (2 in the palate, 1 in the oropharynx, and 1 in the base of the tongue). Patients with tumors in the parotid gland were usually asymptomatic, however, of whom 2 patients were accompanied with pain and discomfort at the time of initial diagnosis. All 10 patients underwent surgical treatment, 4 patients had tumor resection only, 6 patients underwent enlarged tumor resection, including 1 whole parotid gland resection, 1 partial sacral bone and partial masseter resection, and 3 patients underwent radiation therapy. Two of the 10 patients had a local recurrence, of whom 1 had multiple recurrences and 1 had survived to date without lymph node metastasis. Clinicopathological characteristics of 10 cases with EMC of salivary gland were summarized in Tables 1 and 2. The follow-up period of 10 patients was 4 to 104 months, and the median was 48 months. The survival rate was 100%.

### 3.2. Pathological analysis

The pathological results of 10 EMC patients were characterized by typical biphasic structures. A single layer of cubic glandular epithelial cells was seen in the center, and cytoplasmic hyaline epithelial cells were seen in the periphery. The tumor showed invasive growth (Fig. 1). All specimens from 10 patients were conducted with IHC staining. The results showed that the glandular epithelial markers was positive, such as CD117 (9/10, Fig. 2A), and the surrounding layer was positive for myoepithelial markers, including P63 (7/10, Fig. 2B), S-100 (9/10, Fig. 2C), SMA (6/10, Fig. 2D), and Calponin (10/10, Fig. 2E). Ki67 is a typical proliferation marker for the evaluation of cell proliferation and growth and is widely used in pathological investigation. In addition, it can predict tumor progression and is significantly higher expressed in malignant cells.[4] Among the 6 Ki-67 positive specimens, the Ki-67 signal was increased up to 30% in 3 cases and diffusely distributed in the other 3 cases.

## 4. Discussion

EMC is a rare low-grade malignancy that usually occurs in the salivary glands. It was not until 1991 that the WHO defined EMC as an independent salivary gland tumor. Usually, tumors are invasive and can invade nerves, blood vessels, and bones, but EMC have a lower mortality rate. Statistical analysis of the

**Table 2**

**Clinicopathological characteristics of 10 cases with EMC of salivary gland.**

| Parameter | Numbers of patients |
|---|---|
| Total case | 10 |
| Gender | |
| Male | 3 |
| Female | 7 |
| Age (yr) | |
| <50 | 6 |
| ≥50 | 4 |
| Location | |
| Parotid gland | 7 |
| Palate | 2 |
| Oropharynx | 1 |
| TMN stage | |
| I–II | 9 |
| III–IV | 1 |
| Radiation | |
| Yes | 7 |
| No | 3 |
| Recurrence | |
| Yes | 2 |
| No | 8 |

EMC = epithelial–myoepithelial carcinoma.

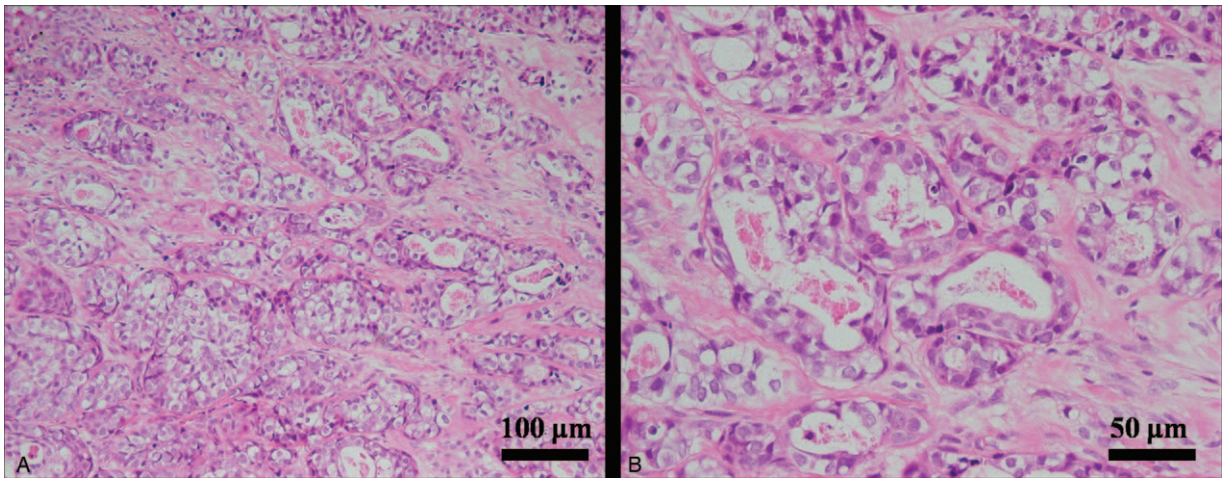


**Figure 1.** The EMC of salivary gland was mainly composed of inner layer epithelial cells and an outer clear myoepithelial cell layer. H&E staining; magnification, ×100 (A) and ×200 (B), respectively. EMC = epithelial–myoepithelial carcinoma, H&E = hematoxylin and eosin.

prognosis of 246 EMC patients based on the foreign literatures showed that when the postoperative follow-up period reached to 60 and 120 months, the patients' survival rates were 91.3% and 90.2%, respectively.[1] The survival rate of the patients in this article is 100%, which reflects the postoperative survival of EMC patients is outstanding. Since our follow-up period is short and there are only 2 patients followed up for more than 60 months, the survival rate is higher than that reported in the literatures. EMC occurs predominantly in elderly women. The average age of onset is about 60 years old. The most common region of EMC is the parotid gland, and the second most common regions are submandibular gland and the small salivary gland. In the small salivary gland, the palate is the most common region where tumors occur which can also be found in the maxillary sinus, Oropharynx, tongue base, etc.[2] The results in this article were basically consistent with previous reports, but the age of onset tend was younger.

The confirmative diagnosis of EMC depends on the results of histopathology and immunohistochemistry. Tumors are usually 0.5 to 20 cm and are lobulated or nodular, occasionally accompanied with bleeding, necrosis, or cystic transformations. Under the light microscope, the typical EMC morphology is a double-layered tubular structure, composed of glandular epithelium and myoepithelial cells in different proportions, that is, the inner layer is a single layer of cubic sacral epithelial cells, and the outer layer is composed of transparent myoepithelial cells. The cells are polygonal, the cytoplasm is characteristically transparent, and the nucleus are vacuole-like-shaped.[5,6] Recently, there have been more and more reports on rare morphological subtypes of EMC, such as eosinophilic type, translucent type, sebaceous cell type, apocrine secretion type, and high-grade transformative type.[6] Most of tumors from the patients in this group had a typical double-layer duct-like structure, but in 1 patient case, spindle cells were arranged in bundles, and the cell density was high, closely related to the classic EMC area. It is considered that EMC has a high incidence of malignant spindle cell tumor level conversion in this patient. In IHC staining, cytokeratin7, CAM5.2, and MNF116 are commonly used to label inner glandular epithelial cells, while the outer myoepithelial cell markers are S-100, SMA, P63, and Actin.[7,8] Seethala et al[2] reported that the specificity and sensitivity of P63 were excellent for labeling myoepithelial epithelium, and the positive rate was up to 100%. Some new myoepithelial markers, like Vimentin and Calponin, have been proved to be of good sensitivity and specificity for salivary tumor myoepithelial cells, facilitating to confirm the diagnosis and reflect the prognosis conditions of patients.[9,10] The cases in this article showed that Calponin was a sensitive marker in tumor which was positive in 10 patients. SMA and P63 were relatively less sensitive than Calponin. Therefore, Calponin is of great significance for the diagnosis of EMC. Since EMC has no characteristic clinical manifestation, pathological morphology and immunohistochemistry are the reliable methods for EMC diagnosis and differential diagnosis. Referring to the pathological morphology, it is crucial to distinguish EMC from primary salivary gland tumors, such as clear cell carcinoma, myoepithelial tumor, eosinophiloma, adenoid cystic carcinoma, and mucoepidermoid carcinoma.[11] Combining Pathological morphology with a variety of specific immunohistochemical markers is beneficial for diagnosing EMC, such as glandular epithelial markers CK, EMA, CD117, and myoepithelial markers P63, SMA, Calponin, S-100, GFAP, and Actin, etc.

Although EMC is a low-grade malignant tumor, the recurrence rate is high, the local recurrence rate can reach about 40%, and the lymph node metastasis rate and distant metastasis rate are 20% and 10%, respectively.[12] Seethala et al reported that 61 patients with EMC had a local recurrence rate of 36.3%, a distant metastasis rate of 5.2%, and a 5-year survival rate of 93.5%.[6] Therefore, to improve the quality of life of patients, surgery is the preferred method for treating EMC. Considering the susceptibility of tumors to recurrence and ensuring physical functions, the scope of tumor resection should be expanded as much as possible in the initial surgery to ensure a sufficient margin of safety. The necessity of performing lymph node dissection remains controversial.[13]

In our study, no cervical lymph node dissection was performed in patients, and 6 patients underwent expanded tumor resection of whom 2 had local recurrences and 1 had multiple recurrences. The recurrence rate was 20%, lower than that reported in the previous literatures. Therefore, it is hypothesized that higher

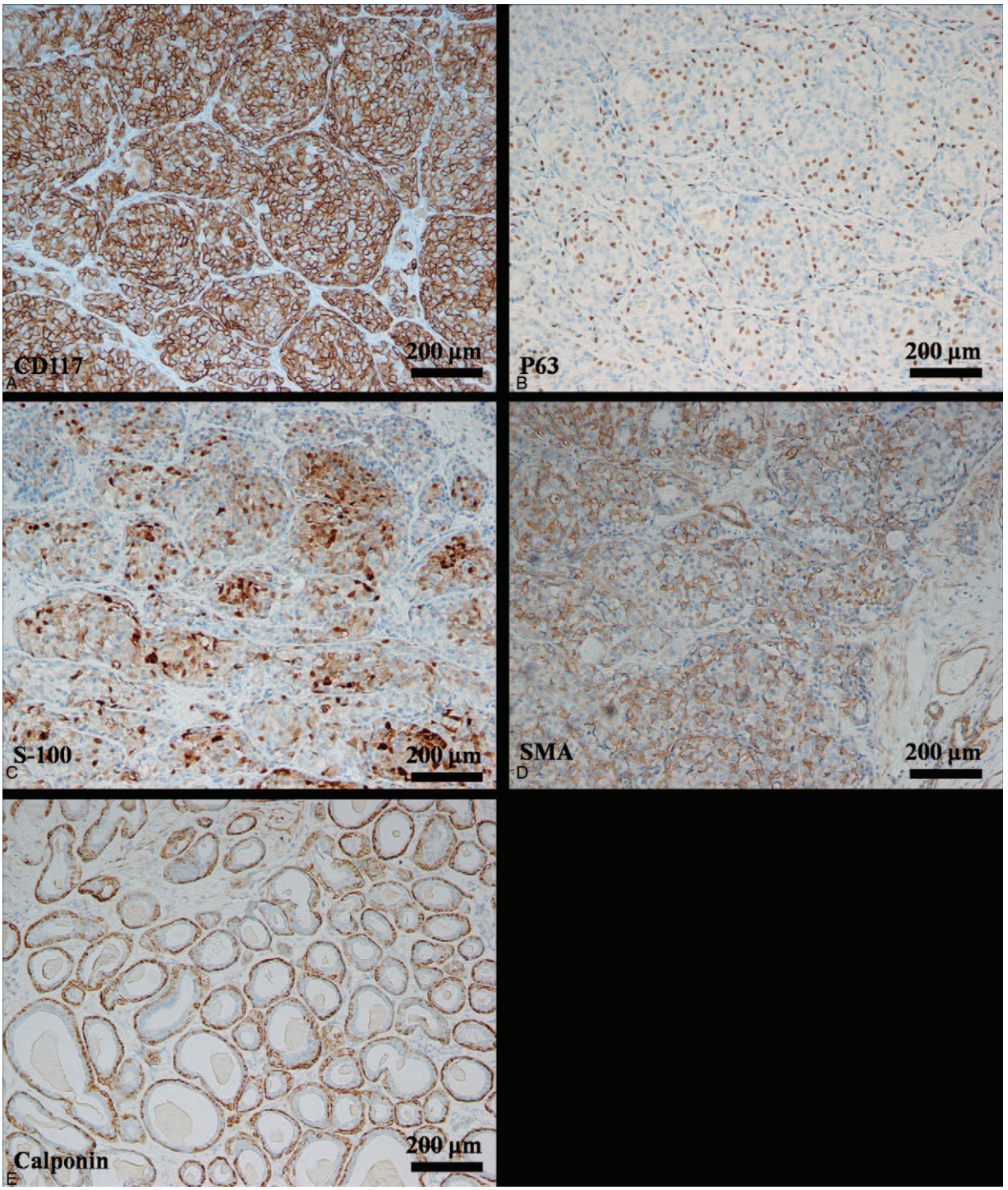


**Figure 2.** The CD117 was positive in the epithelial cells (A), P63 was positive in the myoepithelial cells (B), S-100 was positive in the myoepithelial cells (C), SMA was positive in the myoepithelial cells (D), Calponin was positive in the duct myoepithelial cells (E). (Magnification, ×200).

recurrence rate is closely related to the scope of the initial surgical resection. Routine neck magnetic resonance imaging should be performed to determine whether there is lymphadenopathy. If there is an enlarged lymph node, cervical lymphadenectomy should be performed, which, otherwise, is unnecessary. It is unclear whether adjuvant radiotherapy after EMC surgery can improve the prognosis of patients. Generally, while the safety margin is difficult to ensure when performing the surgical resection of the lesion, postoperative adjuvant radiotherapy can help reduce the local recurrence risk.[14] Peters et al[15] achieved good results by radiotherapy for EMC at the base region of the tongue. However, after reviewing 246 EMC patients, Vazquez et al[1] found that the 10-year survival rate of patients only treated with surgery was 93.2%, and the 10-year survival rate of patients

treated with surgery and radiation therapy was 87.6%. There was no statistical significance with $P = .4832$.[1] After comparing the cumulative 5-year recurrence-free survival rate of the 2 groups of patients with surgery only and surgery combined with radiotherapy, Ni et al also thought that radiotherapy did not significantly improve the prognosis of patients. In all cases, 1/3 case recurred when treated with postoperative radiotherapy, and 1/7 case relapsed treated with surgery only. The recurrence rate of patients was not significantly decreased even after radiotherapy. Therefore, the reporters said that the effectiveness of postoperative adjuvant radiotherapy was still worth discussing.

In summary, EMC is a rare low-grade malignant tumor of salivary glands. Due to the lack of clinical manifestations of EMC, pathological and immunohistochemical results are beneficial to clearly diagnose the tumor. Considering the high recurrence rate of EMC, we believe that the extent of tumor resection and the determination of the operation safety margin during the initial operation are the keys to reduce tumor recurrence and improve the prognosis of patients. Whether cervical lymph node dissection should be performed needs to be evaluated by preoperative imaging.

## Author contributions

**Conceptualization:** Hongyu Yang.
**Data curation:** Feng Wang, Bowen Li, Yu-fan Wang.
**Methodology:** Feng Wang.
**Supervision:** Hongyu Yang.
**Writing – original draft:** Feng Wang.
**Writing – review & editing:** Yuehong Shen, Hongyu Yang.

## References

[1] Vazquez A, Patel TD, D'Aguillo CM, et al. Epithelial-myoepithelial carcinoma of the salivary glands: an analysis of 246 cases. Otolaryngol Head Neck Surg 2015;153:569–74.
[2] Seethala RR, Barnes EL, Hunt JL. Epithelial-myoepithelial carcinoma: a review of the clinicopathologic spectrum and immunophenotypic characteristics in 61 tumors of the salivary glands and upper aerodigestive tract. Am J Surg Pathol 2007;31:44–57.
[3] Seethala RR, Hunt JL, Baloch ZW, et al. Adenoid cystic carcinoma with high-grade transformation: a report of 11 cases and a review of the literature. Am J Surg Pathol 2007;31:1683–94.
[4] Yang C, Zhang J, Ding M, et al. Ki67 targeted strategies for cancer therapy. Clin Transl Oncol 2018;20:570–5.
[5] Kumai Y, Ogata N, Yumoto E. Epithelial-myoepithelial carcinoma in the base of the tongue: a case report. Am J Otolaryngol 2006;27:58–60.
[6] Dimitrijevic MV, Tomanovic NR, Jesic SD, et al. Epithelial-myoepithelial carcinoma—review of clinicopathological and immunohistochemical features. Arch Iran Med 2015;18:218–22.
[7] van Tongeren J, Creytens DH, Meulemans EV, et al. Synchronous bilateral epithelial-myoepithelial carcinoma of the parotid gland: case report and review of the literature. Eur Arch Otorhinolaryngol 2009;266:1495–500.
[8] Konoglou M, Cheva A, Zarogoulidis P, et al. Epithelial-myoepithelial carcinoma of the trachea—a rare entity case report. J Thorac Dis 2014;6 (suppl 1):S194–9.
[9] Hornick JL, Fletcher CD. Myoepithelial tumors of soft tissue: a clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. J Thorac Dis 2003;27:1183–96.
[10] Naggar A, Batsakis JG, Luna MA, et al. DNA content and proliferative activity of myoepitheliomas. J Laryngol Otol 1989;103:1192–7.
[11] Zhou LX, Wang YL, Yao HT. Clinicopathological analysis of epithelial-myoepithelial carcinoma of the salivary gland. J Chinese Oncol 2012;18:629–31.
[12] Chen F, Yang SD, Zhang WF, et al. Epithelial-myoepithelial carcinoma with high-grade transformation: a clinicopathologic study of a case and literature review. J Clin Stomatol 2014;30:414–6.
[13] Ni S, Zhu YM, Wang J, et al. Epithelial-myoepithelial carcinoma of salivary glands, report of 23 cases. Chinese Arch Otolaryngol Head Neck Surg 2015;22:563–5.
[14] Deere H, Hore I, McDermott N, et al. Epithelial-myoepithelial carcinoma of the parotid gland: a case report and review of the cytological and histological features. J Laryngol Otol 2001;115:434–6.
[15] Peters P, Repanos C, Earnshaw J, et al. Epithelial-myoepithelial carcinoma of the tongue base: a case for the case-report and review of the literature. Head Neck Oncol 2010;2:1–7.