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Peer Review File

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Reviewer A

I read the work “Multiple synchronous neoplasms in the ipsilateral parotid gland: Case series” with pleasure. I absolutely agree with the authors' conclusions, that clinicians should be aware of the possibility of multiple synchronous neoplasms in the ipsilateral parotid gland, and that accurate diagnosis and treatment require preoperative imaging tests, clinical examinations, and careful palpation during surgery. In this respect, this publication is very interesting, but according to the "Type of Study", these results qualify as "Case series, low-quality cohort or case-control studies", which means that according to the Grades of Recommendation, they are only "C" level and 4th level according to the Level of Evidence. Undoubtedly, this topic requires further research on larger groups of patients.
In my opinion, it is a well-written research paper, but I have some doubts about the high scientific value of this publication. Unfortunately, I can not recommend this work for publication in Annals of Palliative Medicine.

➔ We have modified the paper to reflect the opinions of other reviewers.

Reviewer B

Comment 1:
Page 3, lines 28-30
“Based on FNAC, 13 cases were diagnosed with Warthin tumor and 1 case with pleomorphic adenoma. The remaining 7 cases were not diagnosed accurately.”
Fine needle aspiration interpretation can be challenging. How did the authors ascertain the correct diagnosis of those 7 cases that were not diagnosed accurately? What were the limitations of FNAC diagnosis in those cases, such as specimen adequacy?

➔ The role of FNAC in the diagnosis of parotid tumor is controversial owing to its diverse morphological pattern and overlapping features between benign and malignant lesions. For the 7 patients who were not accurately diagnosed, the judgment was made based on the physical findings and imaging tests before surgery, and the final diagnosis was made through the final biopsy after surgery.

We have modified the sentence, “Based on FNAC, 13 cases were suspected with Warthin tumor and 1 case with pleomorphic adenoma. The remaining 7 cases were judged to be non-diagnostic.”

Comment 2:
Page 3, lines 38-39
“different histopathologic neoplasms (oncocytic carcinoma and 39 pleomorphic adenomas) in the ipsilateral parotid gland in 1 case”

Carcinoma ex-pleomorphic adenoma (CXPA) is a WHO-defined malignant neoplasm that arises in association with primary or recurrent pleomorphic adenoma (PA). The carcinoma component can be of any salivary gland tumor type, including adenocarcinoma, NOS. Oncocytic adenocarcinoma is a sub-type of adenocarcinoma, NOS. About two-thirds of CXPA displays PLAG1 or HMGA2 rearrangements and/or amplification, markers of pre-existing PA. PLAG1 or HMGA2 rearrangements detected by FISH serve as a marker of pre-existing PA and can assist in diagnosing CXPA. The typical clinical presentation of CXPA is that of a long-standing painless mass with recent rapid progression or of a previous diagnosis of a PA.
One case in your study had pleomorphic adenoma and oncocytic carcinoma in an ipsilateral parotid gland. It is possible that oncocytic carcinoma may represent the carcinoma component of CXPA arising in the association with PA. In that scenario, this patient may have progressed to carcinoma from a pre-existing pleomorphic adenoma rather than having two synchronous primary tumors. Answers to the following questions may help to resolve this issue.

I. For how long had the patient had this mass and was there any rapid growth noted before the diagnostic workup?

➔ A 49-year-old man presented with a right, infra-auricular,painless swelling that had been present for more than three months.

II. Histologically, was PA a discrete nodule or intermixed with carcinoma?

➔ Tumors were present separately from each other. This case has been published as a paper by us in the past. (Reference 9. Lee DH, Choi YD, Yoon TM, Lee JK, Lim SC. Synchronous pleomorphic adenoma and oncocytic carcinoma in the ipsilateral parotid gland. Br J Oral Maxillofac Surg. 2018;56(7):629-631.)

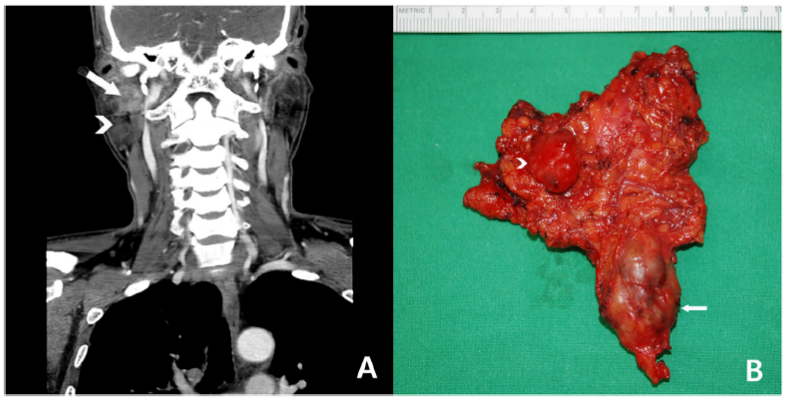

Fig. 1. (A) Computed tomogram of the neck showing two lesions in the right parotid gland. A larger 3.3 × 2.2 cm, irregularly circular, heterogeneously enhanced, focal necrotic mass (arrow) is in the more superior and deeper portion of the right parotid gland, and a smaller 1.7 × 1.5 cm, well-defined, homogeneous, slightly enhanced, mass (arrowhead) is located in the more inferior and superficial portion. (B) The surgical specimen showing two morphologically distinct tumours, the larger one in the deep lobe of the parotid gland (arrow), and the smaller one in the superficial lobe (arrowheads).

III. Any immunohistochemistry or FISH studies for PLAG1 or HMGA2 were performed?

➔ No.

IV. Any clinical or radiological suspicion for the metastatic tumor? Any additional immunohistochemical or other ancillary studies were performed to rule out a metastatic tumor?

➔ Through imaging examination, it was diagnosed as oncocytic carcinoma (high-grade, pT2 N0 M0), and CCRT was performed. Immunohistochemical studies (S-100 (+), CK7 (+), P63 (focal,+), CD10 (-), GCDFP15 (-), DOG-1 (-)) were performed. Six years after the operation, the patient is still under follow-up with no metastasis or recurrence.

Comment 3:

According to your study, the most common synchronous tumor was the Warthin tumor. Since there is a strong association between smoking and Warthin tumors, it would be interesting to know if those patients had any smoking history.

➔ We have added the smoking history in Result and Table 1. Fourteen patients (82.4%) had a smoking history.

Reviewer C

The authors provide interesting results pertaining to synchronous ipsilateral parotid neoplasms.

There should be a more extensive discussion of prior research articles published on synchronous ipsilateral parotid neoplasms. A table with a review of the literature would add great value to the paper. This would be good to compare the rate to other published articles. Also the the most common tumors involved in the literature, and if the high male to female ratio is also similar.

➔ We have added the Table 2 (review of the literature).

Please provide histology pictures of a few representative tumors. I would like to know more about the oncocytic carcinoma (histology picture), and pertinent immunostaining (androgen receptor, GATA-3,GCDFP-15). If this tumor is positive for any of those makers it is likely a salivary duct carcinoma and not an oncocytic carcinoma.

➔ This case has been published as a paper by us in the past. (Reference 9. Lee DH, Choi YD, Yoon TM, Lee JK, Lim SC. Synchronous pleomorphic adenoma and oncocytic carcinoma in the ipsilateral parotid gland. Br J Oral Maxillofac Surg. 2018;56(7):629-631.) Immunohistochemical studies (S-100 (+), CK7 (+), P63 (focal,+), CD10 (-), GCDFP15 (-), DOG-1 (-)) were performed.

Multiple grammatical errors, for example:
Page 2 Line 39 - Fix grammar
Page 3 line 10-11 - Fix grammar –

➔ Grammar has been corrected by a professional English proofreading company.

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Multiple synchronous neoplasms in the ipsilateral parotid gland

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