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Letter to the Editor

Further comments on the tubarial glands

Dear Editor,

We read with interest the original article by Valstar et al. entitled "The tubarial salivary glands: A potential new organ at risk for radiotherapy" [1], the comments by several colleagues [2–10], and a summarized reply by the authors of the original article [11]. We have performed related studies on the tubarial gland that may shed more light on this subject, and we are pleased to participate in the discussion on this issue.

Specimen harvest and histological study

The head of one human cadaver (male, 83 years old, case number: 2018106), fixed in 10% formalin, was provided by the Department of Anatomy of Peking University School of Basic Medicine. Gross examination revealed that the torus tubarius is located on the posterolateral nasopharyngeal wall (Fig. 1) and has a smooth mucosal membrane. In front of the torus tubarius is the inferior turbinate. The upper and rear parts continue with the soft tissues of the skull base and the posterior pharyngeal wall, and the lower part is connected with soft tissues such as the tensor veli palatini muscle. We harvested the entire torus tubarius for use as the specimen.

Histological examination with hematoxylin–eosin (HE) staining showed that the columnar epithelium coated the mucous membrane. Further, conglomerated glandular tissues could be seen at the submucosa under a lower-power microscope (Fig. 2). The glands were mostly composed of mucous acini with a few serous or mixed acini. The ducts were interspersed in the mesenchyma of the gland (Fig. 3).

Histochemical and immunohistochemical studies

Combined staining with Alcian blue (AB) and periodic acid Schiff (PAS) showed that most of the acinar cells were positive for AB, especially the cell cytoplasm, with peripheral staining of PAS observed in some acinar cells (Fig. 4). These staining observations indicated that acinar cells are mostly composed of acidic glycosaminoglycan, with some amount of neutral glycosaminoglycan also present. Immunohistochemical staining showed most acini were positive for anti-smooth muscle actin (SMA) antibody. The staining was located in the periphery of the acini; this indicates that myoepithelial cells play a role in the composition of the acini (Fig. 5).

Comments on several interesting issues

Is the tubarial gland a salivary gland?

There are several perspectives on this question. Many colleagues have advocated that it is too early to call this gland a salivary gland. One of the main reasons is that there is no evidence for myoepithelial cells in this gland. However, in our study, immunohistochemical staining demonstrated that the acini were positive for anti-SMA antibody, which is one of the most common markers of myoepithelial cells. Further, combined histochemical staining with AB and PAS showed that the acinar cells were majorly composed of acidic glycosaminoglycan. These similarities in the histo/histochemical/immunohistochemical characteristics of salivary glands and the tubarial gland might be proof that the tubarial gland is a salivary gland. Histological examination indicated a predominance of mucous acini with partial serous acini. Hence, this gland exhibits features of a mixed gland and could be called a tubarial seromucous gland.

Is the tubarial gland a major salivary gland similar to the sublingual gland?

In their original article, Valstar et al. reported that "when compared to the known major salivary glands, the tubarial glands had the most similarities with the sublingual glands based on the predominant mucous acini, similar PSMA-ligand uptake, and the presence of multiple draining ducts" [1]. The main differences between the tubarial gland and the sublingual gland are their size, shape, and ductal system. The sublingual gland is long and appears like a strip: length, 2.5–3 cm; width, 0.8–1.2 cm; thickness, 1.5–2 cm (Fig. 6). Typically, there is a main duct connecting to Wharton's duct of the submandibular gland (Fig. 7) or directly opening at the sublingual caruncle. In contrast, in the tubarial gland, there is only one layer of glandular tissue underneath the mucous membrane of the torus tubarius that does not have a distinctive shape or a main duct. In fact, its features are similar to those of the minor salivary glands present at the lip, buccal mucosa, and palate. Therefore, it would be more appropriate to classify the tubarial gland as a minor salivary gland. Further, according to its location, the term tubarial gland would be appropriate.

Is the tubarial gland an organ?

The question of whether the tubarial gland is an organ is under debate. An organ typically consists of more than one kind of tissue, has a definite shape and structure, and performs specific functions [1]. Additionally, Narayan et al. pointed out that organs with salivary gland, such as the parotid gland, submandibular gland, and sublingual gland, should be grossly dissectable and separable [3]. However, macroscopic and histologic examinations conducted in our study indicate that the tubarial gland is a relatively sparsely aggregated gland that is not dissectable. Therefore, the tubarial gland does not meet the characteristics of a major salivary gland. With regard to this argument, Valstar et al. explained that "an organ at risk (OAR) is a radiotherapy term and does not only con-

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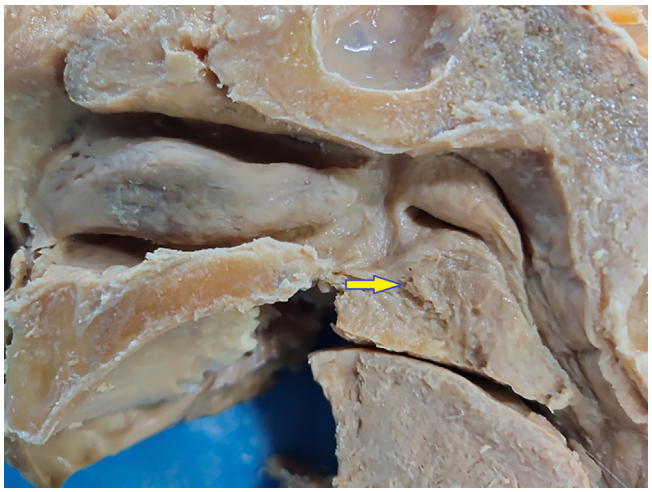

Fig. 1. Location of the torus tubarius (arrow) on the posterolateral nasopharyngeal wall in a human cadaver specimen.

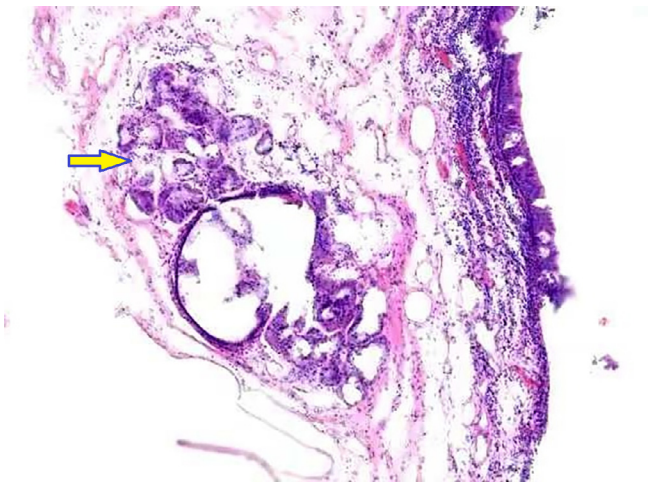

Fig. 2. Conglomerated glandular tissues (arrow) distributed at the submucosal level (HE, 40×).

cern organs, but also comprises all tissues near the clinical target volume that can get damaged by radiation." [11] It seems that the term of "organ at risk" has a special definition different from the conventional definition of organ.

The role of the tubarial gland and its clinical relevance

As a minor salivary gland located in the nasopharyngeal area, the tubarial gland secretes mucin, which keeps the mucosal surface moist, thus preventing heat-induced desiccation caused by the breathing of air and helping in the maintenance of the physiological functioning of the Eustachian tube [3]. Hence, it is important to protect the tubarial gland from radiation-induced damage during the planning of head and neck radiotherapy [9]. Adequate planning could prevent the development of side effects such as nasopharyngeal dryness and, possibly, dysphagia. With regard to the prevention of xerostomia, secretion of three major salivary glands accounts for more than 90% of whole saliva, while the secretion of minor salivary gland accounts for only less than 10% [12]. Therefore, the contribution of the tubarial gland for prevention of

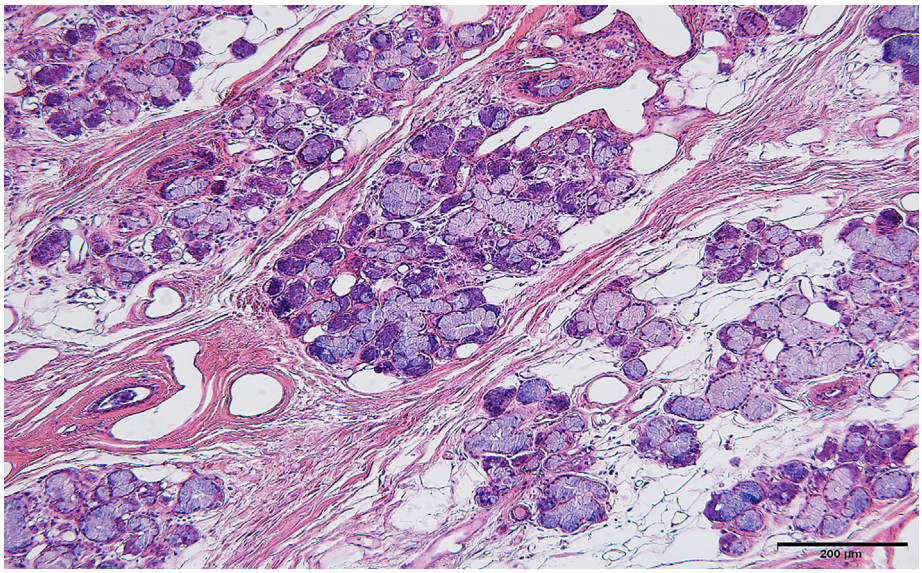

Fig. 3. Histological staining results indicative of a mixed gland with a predominance of mucous acini (HE, 100×).

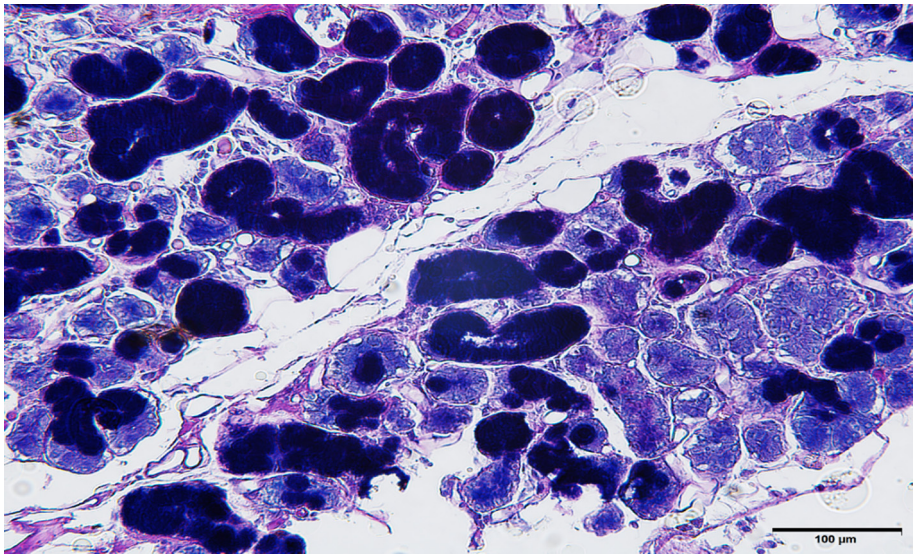

Fig. 4. AB/PAS staining showed a positive reaction (AB/PAS, 200×).

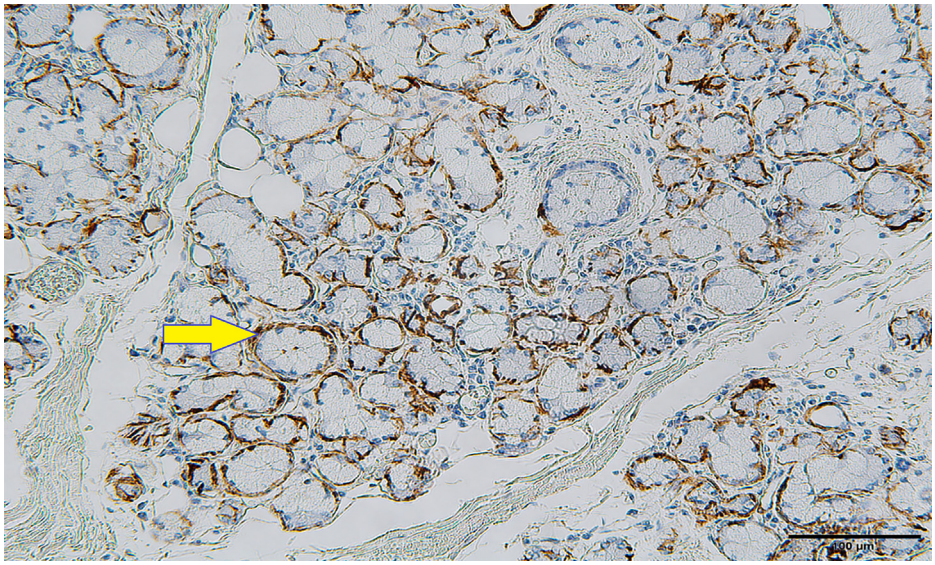

Fig. 5. Immunohistochemical staining for the anti-SMA antibody showing positive staining in most acinar cells (arrow) (200×).

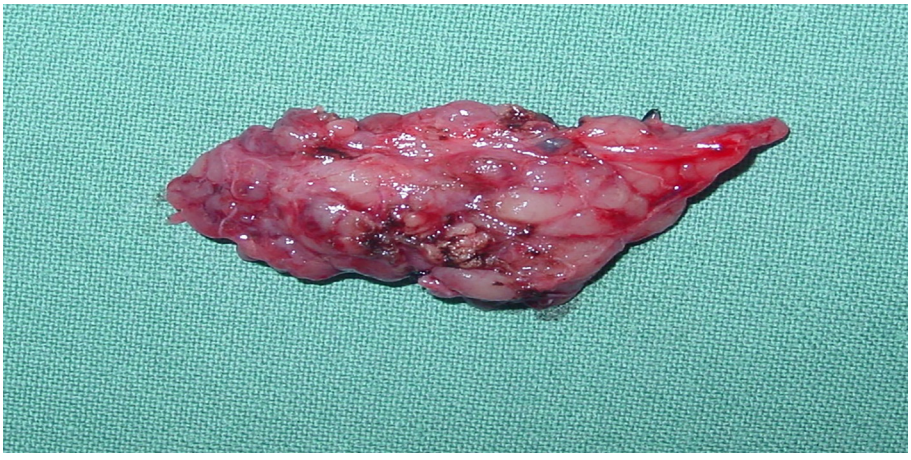

Fig. 6. A postoperative specimen of the sublingual gland in the form of a long strip.

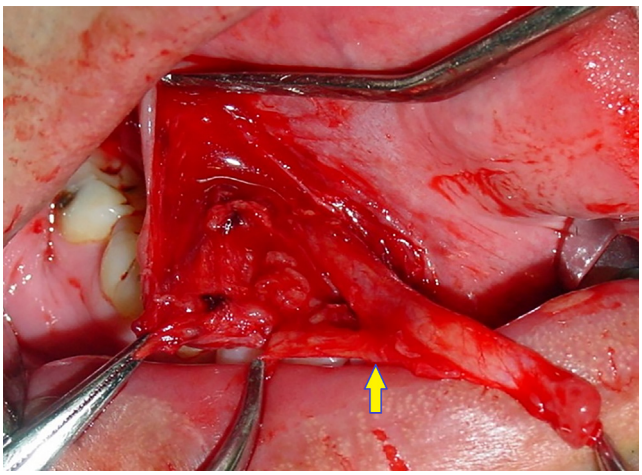

Fig. 7. A photo taken during submandibular gland transplantation for the treatment of severe dry eye showing the connection between the main duct of the sublingual gland (arrow) and Wharton's duct of the submandibular gland.

radiation-induced xerostomia is limited because it secretes very low amounts of saliva.

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