

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/apm-22-1475>

### Reviewer Comments

Dear Author,

Your article focuses on the surgical management of pharyngocutaneous fistula, a severe complication that can occur after head and neck reconstruction and concurrent chemoradiotherapy. You conducted a retrospective review of 17 patients who developed this complication between 2017 and 2021 at your hospital and developed an algorithmic approach for surgical management based on your clinical experience. You found that there currently needs to be more consensus and practical protocols regarding the surgical timing and specific procedures for managing pharyngocutaneous fistula in the current literature. However, you guide different conservative and surgical approaches to adopt depending on the fistula's acute, subacute, or chronic stage. You highlight the importance of timely and appropriate interventions for this complication to achieve complete remission of the fistula. In addition, your article adds to the current literature by guiding surgical management based on your clinical experience.

This well-written manuscript adds value to managing these "complicated" patient cases. However, some vital information is missing:

1) with how many Gy (irradiation dose were the patients irradiated)?

Reply: Thank you for pointing out the radiation therapy factors. All head and neck malignancy patients followed the NCCN guidelines for specific cancer treatment dose, and received a total dose ranging from 60-70 Gy. We have mentioned this in the discussion part. As standard radiotherapy suggested, the general dose given is in 2 Gray (Gy) fractions per day, 5 days per week for a total of 60 to 70 Gy (Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet*. 2000;355(9208):949-955.). However, it is important to note that radiation dose does not necessary translate to higher incidence of complications as fistula. Other studies focusing on esophageal fistula has already demonstrated that radiation dose may not increase

the complication incidence (Hu B, Jia F, Zhou H, et al. Risk Factors Associated with Esophageal Fistula after Radiotherapy for Esophageal Squamous Cell Carcinoma. *J Cancer*. 2020;11(12):3693-3700. Published 2020 Mar 31.). This information was thus not the major concern for the pharyngocutaneous fistula patients in this study.

2) is there any further information about potential factors influencing wound healing?

Reply: Thank you for mentioning the importance of potential risk factors of wound healing. However, the common risk factors of developing pharyngocutaneous fistula has been well established, including systemic reviews and meta-analysis results, and those articles were referenced in our reference list 5-8. Therefore, these factors were discussed in our discussion paragraphs with direct suggestions of precautions and management approaches incorporated into our algorithm instead of detailing individual factors for their potential impacts. Since this is a study focusing on the “surgical treatment and approach” instead of the etiology and risk factors of fistula formation, the potential factors to wound healing were less of the main interest for the audience of this article trying to search for possible “solutions” to this complication.

3) Regarding the action scheme: isn't it also crucial to address the wound conditions and defect size? Please give the reader a more concrete recommendation for action (such as in the article mentioned below).

Reply: Thank you for the valuable comments. We appreciated the idea of wound condition being critical to wound healing and development of fistula. As we also mentioned in our article and study design, this is the main reason why we categorized the stages of fistula wound into acute, subacute, and chronic ones. The wound condition differs as they enter different wound stages in terms of duration and phases, and exhibit various biomolecular characteristics that should be treated under different approaches. However, in our experience, the defect size is not related to developing “fistula”, as pharyngocutaneous fistula is a problematic “tract” opening to the inner digestive tract. The outer skin defect size does not necessarily mean the wound is challenging for treatment. As long as they are not connected to the inner digestive tracts, they could be easily treated with negative pressure wound therapy or skin grafting. Fistula formation, however, often has a

small hole on the outer skin only, yet the constant secretion of saliva and digestive juice from the tract will significantly prevent the wound from healing. This is the basic difference between fistula and other general wounds that should be addressed in the surgical management and dressing care of such patients.

4) Please provide more detailed information about the wound conditions and the extension of the fistula.

I have attached a paper to the review elaborating on these aspects very neatly. However, colleagues are also dealing with this topic. Therefore, this paper should also be addressed in the discussion:

Koch M, et al. Analysis of surgical treatment strategy and outcome factors in persistent tracheoesophageal fistula: a critical analysis of own cases and review of the literature. *Eur Rev Med Pharmacol Sci.* 2022 Jan;26(1):257-269.

Reply: Thank you for mentioning an also valuable article discussing the surgical treatment of fistula. It is however important to note that the subject this article was discussing differs greatly to our study, as “pharyngocutaneous fistula” connects the digestive tract to the outer skin instead of the connection of respiratory tracts to digestive tracts in “tracheoesophageal fistula”. The management concepts thus differ greatly as tracheoesophageal fistula focused on treatment for symptoms of choking, coughing, and frequent lung infections due to food residuals dropping into the respiratory tract (which is why it is related to defect size) and often treated with stenting or patching (also related to defect size as well); yet pharyngocutaneous fistula focuses on the digestive juice irritation and inflammation that prevents the epithelization to seal the wound properly. The management approach and surgical interventions should be completely different as they attempt to solve problems stemming from different etiology. Therefore, we do not find the article suitable for inclusion in our reference, though it also addresses important findings in other issues of common post-surgical and -radiation therapy complications in oropharyngeal cancers.