Systematic Review

THE TUBARIAL GLANDS: KEY ANATOMICAL FEATURES AND CLINICAL SIGNIFICANCE

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ABSTRACT

Medical technological advancements have revealed previously unknown anatomical features in the nasal cavity known as tubarial glands. However, many questions remain unanswered concerning these glands. Through this systematic review, we sought to analyze the tubarial glands, including their major discovery, anatomical and histological features, and clinical significance. Articles were identified according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, with data collected from Scopus, ScienceDirect, SpringerLink, and PubMed until September 2024. Medical Subject Headings (MeSH) were utilized with various terminology: "tubarial gland*", "tubarial salivary gland*", and "radiotherapy". The inclusion criteria were: (1) resources categorized as original research reports, case reports, case studies, letters to the editor, brief communications, commentaries, editorials, and news; (2) publications with accessible full text; and (3) articles providing information on the tubarial glands. The exclusion criteria were: (1) papers categorized as systematic reviews, meta-analyses, or bibliometric analyses; and (2) articles not published in English. The identification yielded 37 resources from around the world, including 19 original research reports (51.3%), 3 case reports (8.1%), 6 letters to the editor (16.2%), 2 brief communications (5.4%), 7 commentaries (18.9%), 1 editorial (2.7%), and 1 news article (2.7%). The research subjects comprised 1 healthy patient (2.7%) out of 26 subjects, 12 prostate cancer patients (32.4%) out of 612 subjects, 3 head and neck cancer patients (8.1%) out of 38 subjects, 1 nasopharyngeal carcinoma patient (2.7%) out of 240 subjects, 1 Sjögren's syndrome patient (2.7%) out of 29 subjects, 1 patient with oncocytic papillary cystadenoma (2.7%), and 20 patients with other conditions (54.0%). This systematic review suggests that the newly discovered glands exhibit similar morphological, histological, and physiological properties to salivary glands and may have a function in the lubrication and maintenance of the upper airway.

Keywords: Tubarial glands; prostate-specific membrane ligand positron emission tomography (PSMA PET) scans; neglected disease; disease burden; health risk

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Highlights:

1. This article presents a detailed investigation of the potential of new organs, beginning with their genesis, the scientific structure of their anatomy and histology, as well as the probable clinical symptoms they induced or derived from them simultaneously.
2. This study enhances knowledge on the tubarial glands, potentially guiding future research and clinical practice through anatomical and histological features while also incorporating relevant material into academic medical education.

INTRODUCTION

Recent developments in medical technology, notably in imaging and treatment, have identified previously unknown anatomical structures in the human body. A notable discovery was the identification of the tubarial glands, a pair of salivary glands located within the nasopharynx. These glands were recently discovered by positron emission tomography (PET) imaging utilizing prostate-specific membrane ligand (PSMA) (Valstar et al. 2021a). This discovery has attracted extensive interest in oncology, particularly in the treatment of head and neck tumors. Prior to the discovery of the tubarial glands, three primary pairs of salivary glands have been well-known and studied: the parotid, submandibular, and sublingual glands. These glands contribute significantly to saliva production, digestion, and general oral health. Radiation therapy's impact on the salivary glands, particularly in patients with head and neck cancer, has been a major subject of concern because it can have serious side effects, including xerostomia (dry mouth) and difficulties in swallowing (Ellsworth et al. 2021).

The tubarial glands, due to their strategic location and potential significance in salivary secretion, may play an essential role in treating the adverse effects of radiation therapy (Dave 2020). Earlier research has indicated that limiting radiation exposure to these glands may lessen the likelihood of difficulty swallowing among individuals following radiation treatment. However, many concerns remain unsolved regarding the function of the tubarial glands, their accurate depiction in imaging, and the effect of radiation exposure on these glands (Pushpa et al. 2021).

The objective of this article was to provide a comprehensive review of the tubarial glands, including their discovery, anatomical and histological features, and clinical significance. This study was intended to offer an improved understanding of the tubarial glands, guide future research and clinical practice, and establish a foundation for incorporating pertinent information into academic medical education.

MATERIALS AND METHODS

This systematic review was recorded in the International Prospective Register of Systematic Reviews (PROSPERO), under registration No. CRD42023487083. The article identification and screening protocols were designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. All publications included in this systematic review were indexed in Scopus, the Emerging Sources Citation Index (ESCI), and/or PubMed Central (PMC). The Risk-of-Bias Visualization (robvis) tool (https://www.riskofbias.info/welcome/robvis-visualization-tool) was utilized to produce high-quality figures that summarize the risk-of-bias assessment of the included articles, which was performed as a part of this systematic review (McGuinness 2019). The data were gathered from Scopus, ScienceDirect, SpringerLink, and PubMed until September 2024. The search terms were determined according to Medical Subject Headings (MeSH) to identify related articles regardless of the authors' varying terminology or spellings. This selection led to the following search terms: "tubarial gland", "tubarial salivary gland", and "radiotherapy". The inclusion criteria used comprised: (1) publications classified as original research reports, case reports, case studies, letters to the editor, brief communications, commentaries, editorials, and news; (2) articles with available full text; and (3) articles containing information pertinent to the tubarial glands. The exclusion criteria for this systematic review were: (1) publications identified as systematic reviews, meta-analyses, or bibliometric analyses; and (2) papers published in languages other than English.

Five investigators worked independently to conduct the search and retrieve the articles, while four investigators chose and reviewed the retrieved studies. Afterwards, the investigators examined the article list and data extractions for duplicate articles. The full texts of relevant publications were then assessed for eligibility through the risk of bias assessment for inclusion in this systematic review. The final decision regarding the inclusion of the studies was determined by consensus among all investigators. The data were initially examined using the problem, intervention, comparison, and outcome (PICO) approach to describe general characteristics of the selected studies, with the following details: (1) problem: the discovery of tubarial glands; (2) intervention: radiotherapy; (3) comparison: not applicable (N/A); and (4) outcome: the emergence of the tubarial glands. Subsequently, the included articles were thoroughly evaluated in relation to the major discovery (MD), anatomical and histological features (AHF), and clinical significance (CS) of the tubarial glands.

RESULTS

A total of 143 studies were retrieved from the literature search across several databases. Upon initial scrutiny by screening the titles, 35 duplicates were removed, while 11 publications were eliminated due to thematic irrelevance. During the additional assessment, 24 papers were excluded since they did not meet the established inclusion criteria. A total of 19 papers were not retrieved due to limited access. The eligibility of the articles was assessed according to the availability of the required information, leading to the exclusion of 17 articles that contained irrelevant content. As a result, this systematic review included a total of 37 studies. The stages of review and study selection in accordance with the PRISMA guidelines are illustrated in Figure 1.

The final articles selected from the screening and identification processes originated from various countries worldwide. The distribution of the studies included 19 original research reports (51.3%), 3 case reports (8.1%), 6 letters to the editor (16.2%), 2 brief communications (5.4%), 7 commentaries (18.9%), 1 editorial (2.7%), and 1 news article (2.7%). According to the research subjects, the studies involved 1 healthy patient (2.7%) from a total of 26 subjects, 12 prostate cancer patients (32.4%) from a total of 612 subjects, 3 head and neck cancer patients (8.1%) from a total of 38 subjects, 1 nasopharyngeal carcinoma patient (2.7%) from a total of 240 subjects, 1 Sjögren's syndrome patient (2.7%) from a total of 29 subjects, 1 oncocytic papillary cystadenoma patient (2.7%), and 20 patients with various other conditions (54.0%). Almost every article provided relevant information from their findings. The general findings of the 37 included studies are presented in Table 1.

Almost all of the selected articles revealed the major discovery of tubarial glands, attributed to the application of radiation in a prostate-specific membrane ligand positron emission tomography scan (PSMA PET scan). The selected articles presented information regarding the anatomical position of the tubarial glands, including their location between the parotid glands, with the inferior section plainly apparent Sample et al. (2024), with the bilateral structures posterior to the nasopharynx (Dave 2020, Glantschnig et al. 2024, Sample et al. 2024) and proximal to the eustachian tube (Ebrahim et al. 2024), draping over the torus tubarius (Mentis & Chrousos 2021, Pringle et al. 2023, Kumar et al. 2024) and the posterolateral pharyngeal recess (Singh & Reddy 2021, Thakar et al. 2021, Nagahata et al. 2022, Alvarez-Lozada et al. 2024). Figure 2 depicts the anatomical position of the tubarial glands.

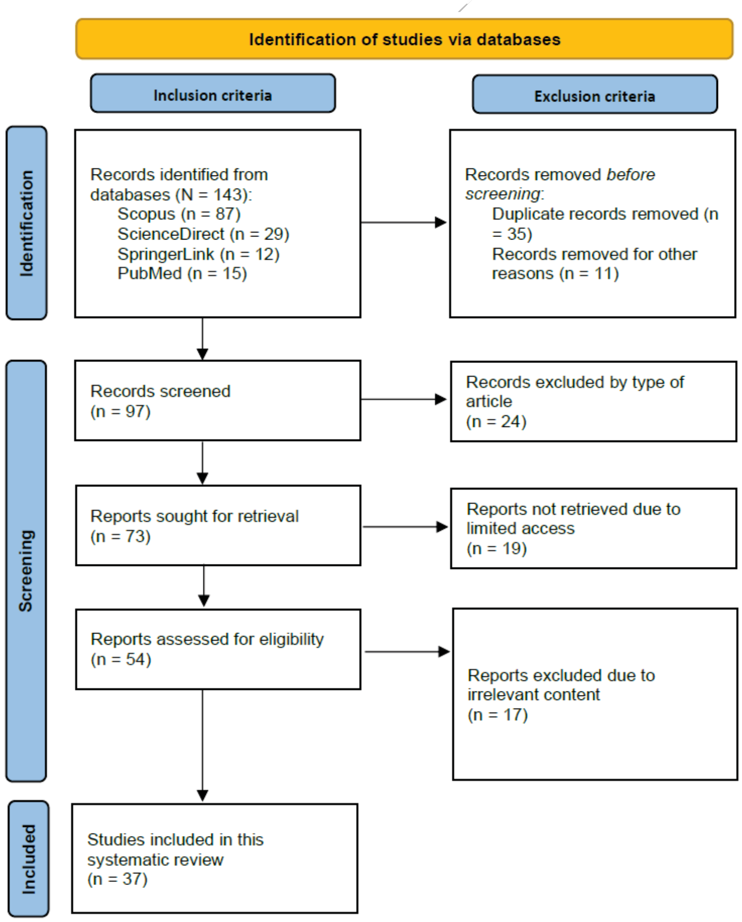

Figure 1. PRISMA flowchart for the screening and identification processes.

Table 1. General findings of the included studies.

No.	Authors	Subjects (n)	Types of studies	Overall findings
1.	Guerreiro et al. (2024)	H (26)	Original research	MD: Repeatability of multiple quantitative magnetic resonance imaging (qMRI) techniques across a broad selection of organs at risk in the head and neck region AHF: The tubarial glands exhibited the lowest size relative to the other salivary glands, measuring 25±0.6 cc. CS: Radiation-induced damage to the salivary glands and swallowing muscles of HNC patients led to late toxicities, such as xerostomia and dysphagia, which severely impaired the patients' quality of life.
2.	Sample et al. (2024a)	PC (30)	Original research	MD: The tubarial glands were discovered while performing PSMA PET scans. CS: Differences in therapeutic doses between regions with large PSMA PET uptake might lead to differences in xerostomia incidence rates and salivary output measurements.
3.	Sample et al. (2022)	PC (30)	Original research	AHF: The inferior aspect of the tubarial glands was visible between the parotid glands.
4.	Glantschnig et al. (2024)	PC (1)	Case report	MD: The tubarial glands were non-invasively visualized by a SUVmax of 7.44. AHF: The tubarial glands had a bilateral structure located posteriorly in the nasopharynx, with ligand uptake similar to that of major salivary glands. CS: Salivary glands were found to be interesting since the toxicity of radioligand therapy using Lu-PSMA ligands may result in dose-limiting xerostomia.
5.	Sample et al. (2024a)	PC (30)	Original research	MD: The tubarial glands were discovered with considerations of whether the uptake in non-prostate tissues was mediated by the expression of PSMA in these tissues or if the PSMA ligand uptake was a result of other physiological mechanisms. AHF: The tubarial glands were bilateral salivary glands in the posterior nasopharynx. CS: Xerostomia led to significant reductions in self-assessed quality-of-life scores, largely due to radiation exposure in salivary glands during radiotherapy.
6.	Ebrahim et al. (2024)	PC (8)	Original research	MD: The anatomical location was clinically accessible through nasal endoscopy only. AHF: The tubarial glands were a collection of salivary glands located within the nasopharynx, proximal to the eustachian tube. The glands were identified as a set of predominantly mucinous glands located around the torus tubarius within the nasopharynx. The mean measurements were 5.7x105±3.4x105 μm^2 for the largest lobule area and 3.2x103±1.3x103 μm^2 for the mucinous acini area, while the mean number of mucinous acini was 82.0±30.4. The histological image, obtained from hematoxylin and eosin (HE) staining at 100X magnification, showed that these glands contained densely packed clusters of predominantly mucinous acini surrounded by loose connective tissue. The glandular tissue comprised a duct, serous acini, and mucinous acini. CS: The tubarial glands led to complications such as xerostomia (dry mouth) and dysphagia (difficulty eating due

No.	Authors	Subjects (n)	Types of studies	Overall findings
				to issues with mastication and swallowing).
7.	Ling et al. (2024)	PC (100)	Original research	MD: The tubarial glands were identified as a "new" organ at risk for radiation burden. This demonstrated an effect on the development of xerostomia after external beam radiotherapy (EBRT) or PSMA-targeted radionuclide therapy (RNT). AHF: Median SUVmean=2 (IQR=1.6–2.4), median SUVmax=4.2 (IQR=3.2–4.8), median TO-PSMA=10.6 (IQR=8.6–14.5). CS: The development of xerostomia was affected by external beam radiotherapy (EBRT) or PSMA-targeted radionuclide therapy (RNT).
8.	Kumar et al. (2024)	PC (1)	Case report	MD: Incidental tracer uptake in the tubarial glands of a metastatic carcinoma prostate patient was observed on ^{68}Ga-PSMA PET/CT and subsequently on ^{17}7Lu PSMA-617 post-therapy. AHF: The tubarial glands were bilateral macroscopic glands in the posterior nasopharynx, draping over the torus tubarius and facilitating the lubrication of the nasopharynx and oropharynx. CS: The tubarial salivary glands might be involved in a variety of clinical disorders, e.g., IgG4-related disease, Sjögren's syndrome, and malignancies.
9.	Alvarez-Lozada et al. (2024)	PC (202)	Original research	MD: The tubarial glands were externally validated according to initial observations on their location, size, and ligand uptake using ^{68}Ga-PSMA-11 PET/CT. AHF: The tubarial glands were a pair of mucosal glands located in the nasopharynx, near the torus tubarius and the posterolateral pharyngeal recess. CS: The findings highlighted the importance of tubarial glands as an organ at risk in radiotherapy planning due to the risk of toxicity.
10.	Grootelaar et al. (2023)	SS (29)	Original research	MD: ^{18}F-FDG PET/CT scans detected inflammatory conditions of the salivary glands. AHF: The tubarial glands were located in the nasopharynx and resembled palatal salivary glands most closely. The visual uptake (0-3) for Sjögren's syndrome patients was 2 (1-3), for giant cell arteritis patients was 1 (0-2), and for non-autoimmune patients was 1 (0-2). For visual uptake of ≥2, there were 29 Sjögren's syndrome patients (72.5%), 19 giant cell arteritis patients (47.5%), and 14 non-autoimmune patients (35%). The SUVmax/bloodpool was 1.54 (1.36-1.96) for Sjögren's syndrome patients, 1.23 (1.06-1.48) for giant cell arteritis patients, and 1.20 (0.87-1.40) for non-autoimmune patients. CS: ^{18}F-FDG PET/CT uptake could detect inflammatory conditions in the salivary glands.
11.	Pringle et al. (2023)	PC (1)	Original research	MD: The tubarial glands were examined using the PET/CT imaging modality. AHF: The tubarial glands exhibited structures surrounding the torus tubarius cartilage in the nasopharynx. HE staining revealed their location and gross histological appearance, as well as the positioning of the torus tubarius cartilage. The tubarial glands were cushioned by connective tissue and fat, and they contained cells that expressed

No.	Authors	Subjects (n)	Types of studies	Overall findings
				proteins indicative of mucous acinar cells as well as potential myoepithelial and seromucous acinar cells. The acinar-like clusters of the tubarial glands consisted of mucous-type acinar cells (AQP5+, ADRB1+, MUC5B+, alcian blue+) and two potential cell types surrounding them, predominantly myoepithelial cells (ADRB1+ and KRT14+) and seromucous acinar cells (ADRB1+, PIP+, PRH2+). CS: Radiotherapy targeting the tubarial glands resulted in an increased risk of hyposalivation and dysphagia toxicity, as evaluated in a large clinical cohort of patients undergoing radiotherapy for head and neck cancer.
12.	Zhao et al. (2023)	NC (240)	Original research	CS: The tubarial glands played a role in xerostomia, with the severity of injury to each gland affecting xerostomia degree and recovery.
13.	De Felice et al. (2022)	HNC (12)	Original research	CS: The development of xerostomia in patients undergoing chemoradiation therapy for head and neck squamous cell carcinoma manifested a complicated anatomical distribution.
14.	Li et al. (2022)	N/A	Commentary	AHF: The histological examination revealed a predominance of mucous acini with partial serous acini, suggesting that the glands had features of a mixed gland. CS: The tubarial glands secreted mucin that kept the mucosal surface moist, thus preventing heat-induced desiccation from respiration and aiding in the physiological functioning of the Eustachian tube. Adequate planning could prevent the development of side effects, such as nasopharyngeal dryness and dysphagia.
15.	Nishida et al. (2022)	PC (55)	Original research	AHF: The tubarial glands were histopathologically classified as seromucinous glands. CS: The tubarial glands were found to express PMSA, rendering them at risk to radiation. Several tiny salivary glands had been discovered in the nasopharynx. However, owing to malignant poisoning, new organs emerged.
16.	North et al. (2022)	N/A	Commentary	CS: Adenoid cystic carcinoma might arise from the newly classified tubarial glands and then lead to inferior or apical orbital adenoid cystic carcinoma via direct extension.
17.	Nagahata et al. (2022)	IRD	Original research	MD: The tubarial glands were detected using PSMA PET/CT. AHF: The tubarial glands were identified as newly refocused glandular tissues near the tori tubarius in the posterolateral nasopharyngeal walls. CS: The clinical significance of tubarial glands pertained to the relation between high-dose radiotherapy in the region of these glands and associated toxicities, such as xerostomia and dysphagia.
18.	Kalshetty et al. (2021)	PC (50)	Original research	MD: PSMA-labeled radioligands for PET/CT imaging in prostate carcinoma patients significantly transformed disease management. The recent implementation of PSMA-targeted radionuclide therapy for patients with castration-resistant prostatic carcinoma created new prospects for the theranostic pair in both diagnosis and treatment.

No.	Authors	Subjects (n)	Types of studies	Overall findings
				AHF: The SUVmean and SUVmax for normal organs were determined to be 2.7±1.97 and 5.3±1.41.
19.	Pushpa et al. (2021)	N/A	Brief communication	AHF: The stained tissue showed predominantly mucous glands with macroscopic ducts opening onto the dorsolateral wall of the nasopharynx. The cells exhibited nearly 100% cytoplasmic expression of PSMA, with a preference towards the luminal side, and PSMA-ligand uptake similar to the mucous acini of minor salivary glands present in the palate. They lacked amylase expression, indicating the meager count of serous acini, comparable to that of sublingual glands.
20.	Mentis & Chrousos (2021)	N/A	Brief communication	AHF: The tubarial glands were located between the throat and the nasal cavity, notably the torus tubarius. CS: Radiotherapy targeting the pharyngeal area of these glands led to xerostomia and dysphagia, suggesting a major functional role of the recently identified organs and a potential for averting these symptoms by excluding this region from radiation exposure.
21.	Hasny et al. (2021)	OPC (1)	Case report	MD: Contrast-enhanced computed tomography (CECT) of the paranasal sinus was performed in an outpatient setting. CS: Tubarial oncocytic papillary cystadenoma might present as slow-growing, painless tumors or a compressive sequela and could typically be identified only when accompanied by otologic sequelae or nasal symptoms, such as epistaxis.
22.	Singh & Reddy (2021)	N/A	Editorial	MD: PSMA PET/CT scans were performed on the head and neck region. The radioactive tracer used in this technique not only bound to the cells of prostate glands but also exhibited strong binding with PSMA in the cells of salivary glands. AHF: The secretions from these glands were poured onto the dorsolateral wall of the nasopharynx, thereby lubricating and moistening the upper part of the throat located behind the nose (nasopharynx) and behind the mouth (oropharynx). CS: The sparing of these glands during radiotherapy for head and neck cancer patients might alleviate common post-therapy symptoms, such as dryness of the mouth (xerostomia) and difficulty swallowing (dysphagia).
23.	Matsusaka et al. (2021)	SPECT (12)	Original research	MD: The visual analysis showed no significant [^{99m}Tc] pertechnetate uptake in the tori tubarius.
24.	Mudry & Jackler (2021)	N/A	Letter to the editor	MD: In 1981, glandular elements were identified around the nasopharyngeal end of the Eustachian tube, exhibiting the same appearance as minor salivary glands in the oral cavity. In 1866, "throat glands" were identified in the rear wall of the pharynx. In the opposite of the choanae, a little powerful but continuous region formed, while further downward, they became sparse and very small. The strongest glands in the upper part of the pharynx measured no more than 2 mm in diameter, whereas those in the lower pharynx measured 0.3 mm in diameter. In 1878 and subsequently in 1889, they were described as a network of glands around the tubal orifice.

No.	Authors	Subjects (n)	Types of studies	Overall findings
25.	Schumann (2021)	N/A	Commentary	MD: In 1927, the salivary glands were depicted in the human nasopharynx. These mucous glands were extensively developed around the pharyngeal recess. Moreover, these glands formed a distinct continuous layer in the submucous layer of the pharynx. The macroscopically visible openings of the excretory ducts were also noted.
26.	Valstar et al. (2021)	N/A	Commentary	MD: The existence of the tubarial salivary glands was not proved for three reasons: (1) PSMA PET/CT failed to prove the existence of the salivary glands; (2) histological analysis did not confirm the existence of the salivary glands; (3) it was considered anatomically incorrect to assert that these organs represented newly discovered salivary glands.
27.	Thakar et al. (2021)	JNA (1)	Commentary	MD: PSMA uptake was observed in the major salivary glands and lacrimal glands, including the tubarial salivary glands. AHF: The tubarial salivary glands were present in the dorsolateral pharyngeal wall around the Eustachian tube. CS: The presence of tubarial glands might lead to the development of malignant and benign tumors originating from salivary glands, similar to other sites.
28.	Iwanaga et al. (2021)	N/A	Letter to the editor	MD: the existence of the tubarial salivary glands is not proven for three reasons. First, PSMA PET/CT does not prove existence of a salivary gland. Second, histology does not prove existence of a salivary gland. Finally, it is anatomically incorrect to say this represents a newly discovered salivary gland.
29.	Nascimento et al. (2021)	N/A	Letter to the editor	MD: The glands were identified as clusters in the mucosa of the auditory tube and regions adjacent to the tubarius torus, with the presence of acinar, intraepithelial, and lymphatic glands.
30.	Narayan et al. (2021)	N/A	Letter to the editor	MD: The tubarial glands, a potential organ, require further evidence. The findings did not reveal the specified sources of blood supply, lymphatic drainage, and innervations for these glands independent from the resident tissue.
31.	Cohen Goldemberg et al. (2021)	N/A	Commentary	MD: The PET/CT physiological distribution of PSMA-ligand in the salivary glands and seromucous glands of the head and neck indicated that the tubarial seromucous glands did not exhibit a significant uptake.
32.	Ellsworth et al. (2021)	N/A	Commentary	MD: The near-complete exclusion of women from the functional imaging analysis that identified the "tubarial glands" precluded the determination of potential sexual dimorphism in these newly identified salivary glands, hence challenging the generalizability of the findings.

No.	Authors	Subjects (n)	Types of studies	Overall findings
33.	Bikker & Vissink (2021)	N/A	Letter to the editor	MD: Damage was identified in the structures lubricating the nasopharyngeal and oropharyngeal mucosa. The so-called tubarial salivary glands might play an important role in this lubricating process. This could be deduced from the observation that a reduced cumulative radiation dose to these glands correlated with fewer swallowing problems.
34.	Valstar et al. (2021b)	PC (100)	Original research	MD: Projections of PSMA PET/CT. CS: The radiotherapy dose administered to the tubarial glands resulted in xerostomia and dysphagia, along with toxicity effects due to the dose received by the parotid glands.
35.	Dave (2020)	N/A	News	MD: The visualization of salivary glands was achieved using PET/CT with radio-labeled ligands for PSMA. AHF: All patients exhibited identical PSMA-positive areas bilaterally in their posterior nasopharynx. Moreover, two human cadaver dissections were performed, and the area of interest was analyzed histologically.
36.	Aral et al. (2024)	HNC (-)	Original research	MD: Radiotherapy was performed on patients with head and neck cancer. CS: A significant correlation was found between tubarial gland doses and acute dysphagia during the radiotherapy. Tubarial glands value (TGs-V) of 25% showed higher significance compared to other values.
37.	Sample et al. (2022)	PC (30)	Original research	MD: Piflufolastat F-18 (^{18}F-DCFPyL) PSMA PET and radiotherapy treatment planning with CT imaging for a small cohort of prostate cancer patients. CS: The tubarial glands in the optimization of head and neck radiotherapy demonstrated the potential to improve patient outcomes with minimal effort.

Legends: H=healthy; PC=prostate cancer; SS=Sjögren's syndrome; NC=nasopharyngeal carcinoma; HNC=head and neck cancer; IgG4=immunoglobulin G4; IRD=IgG4-related disease; OPC=oncocytic papillary cystadenoma; JNA=juvenile nasopharyngeal angiofibroma; SPECT=single photon emission computed tomography; PET=positron emission tomography; CT=computed tomography; PSMA=prostate-specific membrane antigen; SUVmax=maximum standardized uptake value; SUVmean=mean standardized uptake value; IQR=interquartile range; TO-PSMA=Target Operated-Photon Emission Computed Tomography; AQP5+=Aquaporin 5; ADRB1+=Beta-1 Adrenergic Receptor; MUC5B+=Mucin 5B; KRT14+=Keratin 14; PIP+=Prolactin-inducible Protein; PRH2+=Proline Rich Protein HaeIII Subfamily 2; N/A=not applicable; MD=major discovery; AHF=anatomical and histological features; CS=clinical significance. The SPECT scans were conducted using [^{99m}Tc]-pertechnetate, fluorodeoxyglucose F 18 ([^{18}F]-FDG), or [^{11}C]-methionine radiotracer. The PET/CT scans were performed using [^{68}Ga] Ga-PSMA-11 radiotracer.

According to the histological features, the collected data pertaining to salivary glands Grootelaar et al. (2023), Glantschnig et al. (2024) mostly consisted of mucinous/mucosal/mucous acinar glands with partially serous acini (seromucinous) (Pushpa et al. 2021, Nishida et al. 2022, Li et al. 2022, Alvarez-Lozada et al. 2024), cushioned by connective tissue and fat (Pringle et al. 2023, Ebrahim et al. 2024). The verdicts regarding size were clearly presented, indicating the smallest size relative to the other salivary glands, measuring 25±0.6 cc (Guerreiro et al. 2024), with a mean largest lobule area of $5.7 \times 10^5 \pm 3.4 \times 10^5$ μm^2, a mean mucinous acini area of $3.2 \times 10^3 \pm 1.3 \times 10^3$ μm^2, and a mean mucinous acini number of 82.0±30.4 (Ebrahim et al. 2024). The median of the mean standardized uptake values (SUVmean) was 2, with an interquartile range (IQR) of 1.6–2.4. The median of the maximum standardized uptake values (SUVmax) was 4.2, with an IQR of 3.2–4.8. Meanwhile, the median TO-PSMA was 10.6, with an IQR of 8.6–14.5 (Ling et al. 2024). The histological features of the tubarial glands can be seen in Figure 3.

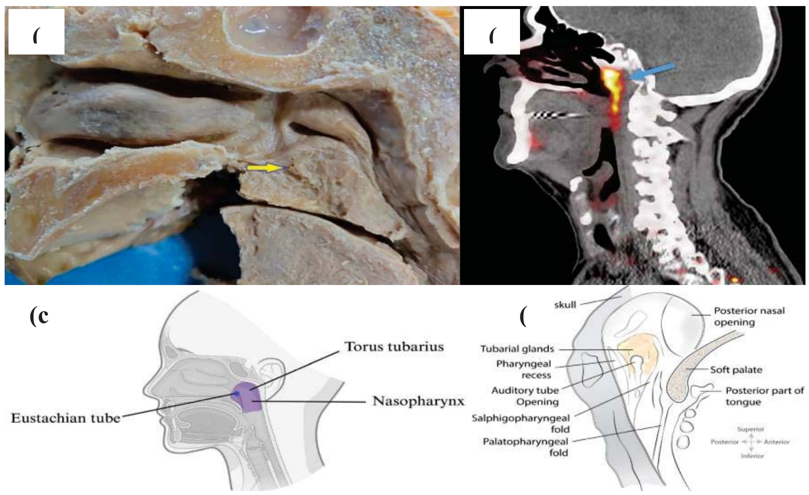

Figure 2. Anatomical locations of the tubarial glands: (a) torus tubarius (yellow arrow) located on the posterolateral nasopharyngeal wall of a human cadaver (Li et al. 2022); (b) tubarial glands projected as yellow speckle (blue arrow) on grayscale CT (PSMA/PET scan) (Valstar et al. 2021b); (c) anatomical area of the tubarial glands (Ebrahim et al., 2024); (d) proposed site of the new salivary glands (Pushpa et al. 2021).

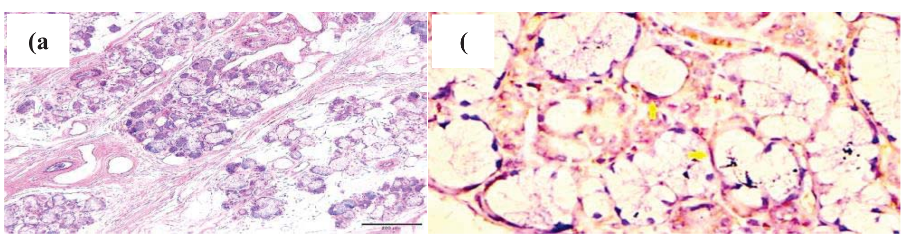

Figure 3. Histological features of the tubarial glands: (a) hematoxylin and eosin (HE) staining results indicative of seromucous glands (100X magnification) (Li et al. 2022); (b) yellow arrow indicative of diffuse basal positivity for myoepithelial cells (cluster of differentiation 100, 40X magnification) (Pushpa et al. 2021).

The aforementioned clinical importance indicated that the effects of radiation during cancer therapy are the primary cause of the formation of this organ. Radiation-induced damage to the salivary glands and swallowing muscles in the head and neck might cause late toxicities, such as xerostomia (dry mouth) and dysphagia (eating difficulty due to issues with mastication and swallowing) (Sample et al. 2024a, Guerreiro et al. 2024, Ebrahim et al. 2024). Differences in treatment doses among cohorts with high PSMA PET uptake might affect the incidence rates of xerostomia (Singh & Reddy 2021, Sample et al. 2022) The toxicity associated with radioligand treatment using Lu-PSMA ligands might result in dose-limiting xerostomia (Nagahata et al. 2022, Glantschnig et al. 2024).

Xerostomia developed as a toxic effect following external beam radiation (EBRT) or PSMA-targeted radionuclide treatment (RNT) due to the dose administered to the parotid glands (Valstar et al. 2021b, Ling et al. 2024). This condition potentially created organs at risk (OARs) as a result of the exposure (Alvarez-Lozada et al. 2024). The ^{18}F-FDG-PET/CT uptake in inflammatory salivary gland ailments provided evidence for this condition (Grootelaar et al. 2023). The tubarial glands exhibited a role in xerostomia, as radiotherapy targeting these glands increased the risk of hyposalivation and dysphagia toxicity, complicating this anatomical distribution (De Felice et al. 2022, Zhao et al. 2023, Pringle et al. 2023). There was a substantial association between tubarial gland dosages and acute dysphagia during radiation (Aral et al. 2024).

The tubarial glands were found to secrete mucin, which maintained the moisture of the mucosal surface, reducing heat-induced desiccation from respiration and supporting the physiological functioning of the Eustachian tube (Li et al. 2022). The expression of PSMA in the tubarial glands indicated the presence of malignant poisoning (Nishida et al. 2022). Tubarial oncocytic papillary cystadenoma was characterized by the presence of slow-growing, painless tumors or their compressive sequelae (Hasny et al. 2021). The tubarial glands might potentially result in malignant or benign cancers in salivary glands located in identical regions (Thakar et al. 2021).

DISCUSSION

The tubarial glands pose two intriguing issues to discuss: (1) the appropriateness of labeling them as an organ and (2) whether their entity has existed since the beginning of the embryological process or if they emerge as a result of radiation exposure. The recent discovery of the tubarial glands has caused heated controversy within the medical and scientific communities. Their previously unknown structures, discovered in 2020 by a group of Dutch researchers, are located in the rear of the nasal cavity, nestled in the throat's nasopharynx (Valstar et al. 2021b). While their discovery was a watershed moment in human anatomy, one basic question remains unheeded: Are the tubarial glands genuinely an organ, a specialized tissue, or something completely different? The tubarial glands were discovered during research employing PSMA PET-CT scans, a cutting-edge imaging method commonly used to identify prostate cancer (Kumar et al. 2024, Sample et al. 2024a, 2024b, Ling et al. 2024). Researchers discovered two symmetrical structures in the nasopharynx that had not previously been described in anatomy textbooks (Alvarez-Lozada et al. 2024, Sample et al. 2024a, Ebrahim et al. 2024). These structures were revealed to share similar features with salivary glands, prompting the hypothesis that they constitute a previously unknown salivary gland (Grootelaar et al. 2023, Pringle et al. 2023). The tubarial glands are anatomically characterized by the presence of ducts and a tissue network similar to those of salivary glands present in other areas of the body, such as the parotid or submandibular glands (Li et al. 2022, Pringle et al. 2023). They appear to help lubricate the throat and upper airways, akin to the role of other salivary glands in saliva production for digesting. However, their position and size differ from ordinary salivary glands (De Felice et al. 2022, Zhao et al. 2023). They are relatively tiny and located deep in the nasopharynx, complicating their classification alongside bigger, more established organs. This raises a fundamental question: Should they be considered a full-fledged organ or simply a collection of specialized tissue?

For anything to be classified as an organ, it must satisfy certain requirements, such as possessing distinct anatomical traits and performing a unique, crucial role in the body. While the tubarial glands are anatomically unique, they have yet to be proved to serve a vital, solitary role required for life. Although they assist in lubricating the upper airways and facilitating easier swallowing, their role may be regarded as supplemental rather than essential. This debate is compelling on whether the tubarial glands are genuinely a new organ, given that they only improve an existing function rather than providing a new one (Iwanaga et al. 2021). On the other hand, it is conceivable that the tubarial glands are specialized tissues within the larger salivary system. The tubarial glands, similar to other tissues in the human body that support larger, more complex systems, may be a previously unnoticed but non-vital addition to the network of glands helping in secretion and lubrication (Narayan et al. 2021, Schumann 2021). The tubarial glands, regardless of being classified as an organ or merely tissue, have clinical significance that cannot be ignored (Mudry & Jackler 2021). The revelation has reinvigorated interest in head and neck cancer therapies, notably radiation therapy. If the tubarial glands are involved in keeping the upper airways moist, they may need to be preserved during radiation treatments to prevent damage that can impair a patient's ability to swallow or airway function (Cohen Goldemberg et al. 2021, Nascimento et al. 2021).

The findings discussed in this study might have substantial ramifications for illnesses affecting the salivary glands, including autoimmune disorders such as Sjögren's syndrome, which impair glandular function and cause dry mouth among other symptoms (Mentis & Chrousos 2021, Grootelaar et al. 2023). Further research may reveal that the tubarial glands have a more important role in these illnesses than previously acknowledged. The classification of tubarial glands as either an organ or a tissue remains contentious. This challenges conventional conceptions of an organ and underlines the complexities of human anatomy, demonstrating how the most modern technology can discover previously unknown components of our biology (Nagahata et al. 2022, North et al. 2022). As research progresses, the tubarial glands may either change our knowledge of organs or remain an anatomical curiosity.

The second topic of discussion is the presence of the tubarial glands, which might have originated during embryogenesis or arisen as a clinical manifestation of radiation exposure. One explanation holds that the tubarial glands have existed from early embryological development but have gone unnoticed until recently. Human salivary glands, similar to other organs, develop throughout the early stages of embryonic growth via a process known as branching morphogenesis (Pushpa et al. 2021). This process produces the major salivary glands (parotid, submandibular, and sublingual), while numerous minor glands are found throughout the mouth and throat. If the tubarial glands developed from the same embryological process, they might represent a previously unknown component of the salivary gland network. Because the tubarial glands are located so deep in the nasopharyngeal area, they might easily be overlooked in anatomical investigations or misidentified as part of another structure (Singh & Reddy 2021, Hasny et al. 2021).

There is a discussion on the tubarial glands developed as a result of radiation exposure, particularly in those receiving irradiation for head and neck tumors. Radiotherapy is known to harm salivary glands, resulting in problems such as dry mouth (xerostomia) (Dave 2020, Aral et al. 2024). This raises an intriguing question: Is it possible that the tubarial glands originated or underwent alterations because of radiation-induced cellular responses? Radiation can stimulate tissue regeneration, resulting in structural alterations or the development of new tissue (Cohen Goldemberg et al. 2021, Yazdani et al. 2024). If this idea is correct, the tubarial glands may not be embryonic glands at all, but rather tissues that develop in response to stress or radiation exposure (Bikker & Vissink 2021). They may represent a type of tissue adaptation or a compensating mechanism created by the organism in response to glandular injury. However, this idea raises further challenges. If the tubarial glands are a result of radiation, why do they appear symmetrically in those who have not had such treatments? Furthermore, these glands exhibit structural similarities to known salivary glands, indicating that they may represent a normal feature of human anatomy rather than a product of an external trigger.

The evidence supporting the embryological origin of the tubarial glands appears to be stronger at this point, considering their anatomical similarities to other salivary glands and their presence in healthy persons who have not undergone radiation therapy (Narayan et al. 2021, Thakar et al. 2021). It seems more plausible that these glands have always been present in human anatomy but were only recently discovered due to advances in imaging technologies. If the tubarial glands form through the same processes as other salivary glands, their function and location would most likely serve a specialized role in regulating the moisture balance of the nasopharynx (Schumann 2021). The idea that the development of the tubular glands is radiation-induced, while intriguing, is poorly established. Radiation treatment is known to harm salivary tissues rather than regenerate fresh, functional glands (Kalshetty et al. 2021, Matsusaka et al. 2021). While radiation can cause cellular alterations, it does not appear to be the major source of a symmetrical gland-like structure that resembles normal salivary tissue.

There are significant clinical consequences in understanding the exact origins of the tubarial glands. If the tubarial glands are an embryological entity, it is critical to understand their role in proper salivary function and to protect them during medical treatments, such as radiation therapy. Damage to these glands during cancer therapies can lead to numerous issues, including trouble swallowing or persistent dry throat. Therefore, their preservation may improve patient outcomes (Sample et al. 2022). On the other hand, if further research establishes a link between these glands and radiation exposure, it may yield new insights into tissue responses to radiation, perhaps leading to improved therapeutic techniques for lowering side effects in patients receiving radiotherapy (Ellsworth et al. 2021).

For the time being, it is evident that the tubarial glands warrant additional investigations because of their potential medicinal relevance and the need to reexamine long-held assumptions regarding the anatomy of the human body. The tubarial glands, whether classified as an organ or a specialized tissue, demonstrate that human anatomy retains undiscovered mysteries. While the tubarial glands have opened new avenues of anatomical and medical research, their genesis remains largely unexplored. Current data suggest that the glands demonstrate an embryological origin, implying that they have always been integral to human anatomy yet overlooked by prior investigations (Bikker & Vissink 2021). It is worth investigating whether environmental variables, such as radiation, may influence the development or function of these glands. The discovery of the tubarial glands, whether integral to human salivary structure or an adaptive reaction, serves as a reminder that further research is still required to elucidate other aspects of the human body that remain uncovered. Further studies are anticipated to reveal new insights into the real origins and function of the tubarial glands, which may influence the treatment of associated medical disorders in the future.

Strength and limitations

This systematic evaluation of the tubarial glands may offer a thorough understanding of the new anatomical discovery by combining current data. However, given the novelty of the topic and limitations in available data, the results of this systematic review should be interpreted cautiously, acknowledging the need for further research to clarify and expand our understanding of this contentious entity.

CONCLUSION

This systematic review focuses on the recent discovery of the tubarial glands facilitated by sophisticated imaging techniques, such as prostate-specific membrane ligand positron emission tomography/computed tomography (PSMA PET/CT) scans. The recently discovered glands in the nasopharynx share morphological, histological, and physiological characteristics with salivary glands, suggesting their potential involvement in the lubrication and maintenance of the upper airway. Additional studies are necessary to properly understand the developmental origins and potential therapeutic ramifications of the tubarial glands, as well as their classification as either a major or minor component of the salivary system. Nonetheless, the discovery of the tubarial glands marks a substantial advancement in our understanding of human anatomy, histology, and physiology, with implications for both diagnosis and therapy in medicine.

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Author contribution

All authors contributed to the conception and design, collection and assembly of the data, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article. DMNA, JEM, BB, S, and ASW independently conducted the literature search and retrieved the articles. WNS, DAS, DSP, and SND examined the relevant publications and conducted data extractions to identify duplicates. Subsequently, DMNA, JEM, BB, and ASW assessed the retrieved articles for eligibility, conducted the risk of bias assessment, and determined their inclusion in this systematic review. All authors reached consensus on the final decision for the inclusion of the studies.

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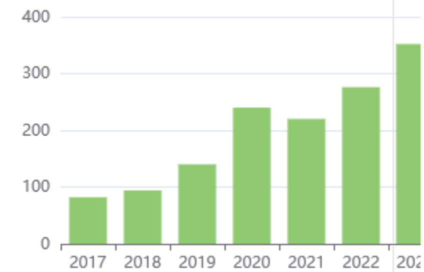

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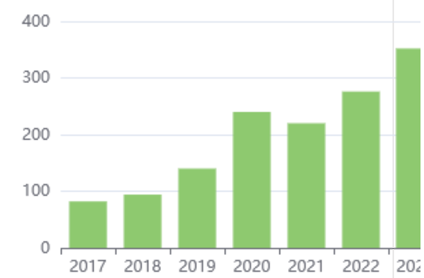

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