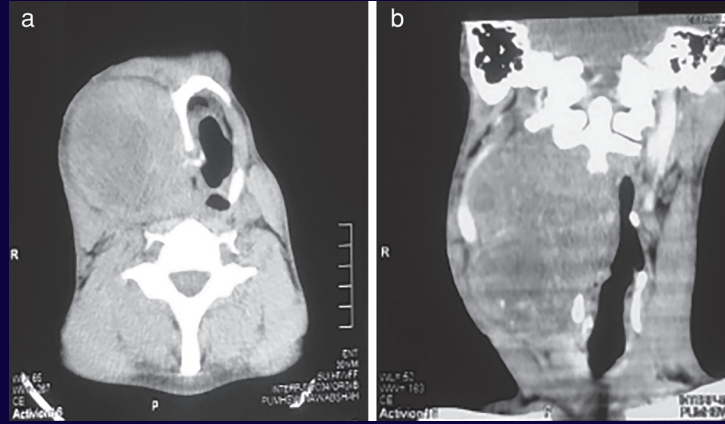


# Turkish Archives of Otorhinology



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# Salvage Endoscopic Nasopharyngectomy for Recurrent Nasopharyngeal Cancer: an Institutional Experience

Original Investigation

✉ Ergin Eroğlu, ✉ A. Erim Pamuk, ✉ Serdar Özer, ✉ Tevfik Metin Önerci

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## Abstract

**Objective:** This study aims to present the surgical and oncological long-term outcomes of patients with locally recurrent nasopharyngeal cancer (NPC) following endoscopic endonasal nasopharyngectomy (EEN).

**Methods:** The medical records of 11 patients who underwent EEN due to recurrent NPC were retrospectively reviewed.

**Results:** The mean age of the patient cohort, consisting of 10 males (90.9%) and one female (9.1%), was 44±13.01 years at the time of initial diagnosis. Seven patients (63.7%) had local recurrence, and four patients (36.3%) had loco-regional recurrence. The mean time to first recurrence from the initial diagnosis was 40.3 months, with a 5-year overall survival (OS) rate of 72.7% and a disease-free survival (DFS) rate of 27.3%. There were no significant differences between the concurrent chemoradiotherapy (CRT) and induction chemotherapy+concurrent CRT treatment groups in terms of DFS and OS as a first-line treatment (p=0.645).

**Conclusion:** EEN is a viable alternative approach for selected cases of locally recurrent NPC, considering the morbidities associated with re-irradiation.

**Keywords:** Nasopharyngeal carcinoma, local neoplasm recurrence, natural orifice endoscopic surgery, salvage therapy, treatment outcome, survival analysis

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## Introduction

Nasopharyngeal cancer (NPC) is a disease with an epidemiological pattern commonly observed in China, Hong Kong, and Southeast Asia (1). According to the World Health Organization's 5<sup>th</sup> edition classification of head and neck cancers, NPC is classified into three subtypes: non-keratinizing squamous cell carcinoma, keratinizing squamous cell carcinoma, and basaloid squamous cell carcinoma (2).

The treatment of NPC involves radiotherapy (RT) alone in early-stage disease, while concurrent chemoradiotherapy (CCRT) is administered in advanced stages (3). Advanced RT techniques such as intensity-modulated radiotherapy (IMRT) have shown 5-year local control rates ranging from 76% to 91% (4, 5).

NPC is an aggressive tumor that often leads to bilateral or multiple neck metastases and the reported rates of local recurrence after initial treatment range from 8.4% to 10.9%



(6-8). Surgical resection, re-irradiation, and chemotherapy are options for the management of recurrent NPC (9). Despite the advancements in IMRT, re-irradiation can result in high morbidity and mortality, including complications such as osteoradionecrosis, trismus, transverse myelitis, brain abscesses, and osteomyelitis. Chemotherapy is generally used as a palliative treatment in advanced cases (9).

Salvage nasopharyngectomy (SNP) has shown better outcomes in terms of 5-year survival rates (40-60%) compared to patients treated with re-irradiation (8-36%) (10). SNP can be applied in recurrent cases of NPC, especially in patients with rT1, rT2, or limited rT3 tumors (11). The success of the surgical procedure is highly correlated with the clinical stage of NPC (12). Various surgical approaches can be used for SNP, including trans-palatal, trans-mandibular, maxillary swing, and infratemporal approaches (13). These surgical approaches are currently less frequently used because of the potential for significant complications and the need for large incisions. The development of endoscopic imaging technology and surgical instruments specifically designed for endoscopic surgery has brought new approaches to this field. Endoscopic endonasal nasopharyngectomy (EEN) offers a solution to the morbidities associated with open approaches (14, 15).

In this study we aimed to present the surgical and oncological long-term outcomes of patients with locally recurrent NPC following EEN.

## Methods

Before starting our study, we obtained approval from the ethical committee of the Hacettepe University Non-Invasive Clinical Research Ethics Committee (decision no.: 2023/09-38, date: 21.02.2023). The medical records of 11 patients who underwent EEN due to recurrent NPC at the Hacettepe University, Department of the Otorhinolaryngology in the years between 2011 and 2019 were retrospectively reviewed. Informed consent was obtained from the patients.

The demographic characteristics of the patients, year of initial diagnosis, first, and if applicable, second recurrence status (local, regional, or distant), and treatments received were noted. Histopathological examination results after EEN and additional treatments administered to the patients were documented. The last follow-up dates were recorded, and survival data were collected by contacting the patients or their relatives via telephone for late survival analysis. The patients were restaged using magnetic resonance and positron emission tomography imaging.

## Statistical Analysis

In the statistical analysis of the study, Kaplan-Meier analysis was utilized to obtain both overall survival (OS) and disease-free survival (DFS) rates.

## Results

Of the 11 patients included in the study, 10 (90.9%) were male and one (9.1%) was female. The mean age at the initial diagnosis was  $44 \pm 13.01$  years. The minimum follow-up time was 42 months (median 82, min 42-max 242 months). CCRT alone was administered to four (36.4%) patients as the initial treatment, while induction chemotherapy (IC) followed by CCRT (IC+CCRT) was administered to seven (63.6%) patients. The mean time to first recurrence from the initial diagnosis was 40.3 months. Seven patients (63.7%) had local recurrence, whereas four patients (36.3%) had loco-regional recurrence. When the patients were restaged, five patients were rT2N0M0, three patients were rT3N1M0, one patient was rT1N0M0, one patient was rT4N0M0, and one patient was rT3N2M0. All patients with recurrent neck disease underwent salvage neck dissection. In cases with rT3 involvement, skull base involvement was observed, and resection was performed until reaching healthy bone. In the single case with rT4 involvement, resection, and duraplasty were performed due to dural involvement.

Preoperative biopsies were obtained from all patients who underwent nasopharyngectomy, confirming the presence of recurrence pathologically. According to the multidisciplinary tumor board's decisions, four (36.4%) patients received re-irradiation (three patients received stereotactic radiosurgery), three (37.2%) patients received additional CCRT, and four (36.4%) patients did not receive any additional treatment (Table 1).

The five-year DFS rate for our patients with NPC was 27.3%, with the latest recurrence observed in the 96<sup>th</sup> month (Figure 1). The OS rates were 72.7% at five years and 53% at 10 years (Figure 1). Mortality was observed in three patients with rT1N0M0, one patient with rT2N0M0, one patient with rT3N0M0, one patient with rT3N2M0, and one patient with rT4N0M0. When comparing the groups that received IC+CCRT or CCRT alone after the initial diagnosis, no statistically significant difference was found in terms of OS ( $p=0.645$ ). The 5-year OS rate was 75% in the group receiving concurrent treatment, whereas it was 71.4% in the IC+CCRT group (Figure 2). Finally, when comparing the 5-year DFS rates between these two treatment groups, the concurrent treatment group had a rate of 50%, while the IC+CCRT group had a rate of 14.3%, but the difference was not statistically significant ( $p=0.123$ ). None of the patients underwent surgery more than once, and there were no major complications.

## Discussion

Although NPC is a radiosensitive malignancy, local or regional recurrence remains a significant cause of treatment failure (16). Various treatment modalities, including re-

irradiation and surgery, are preferred for recurrent disease. In addition to these two treatments, with the advancement of medical technology, proton therapy, targeted therapies, and immunotherapies can also be applied (17). To the best of our knowledge, our study is the first to be reported from Turkey regarding salvage endoscopic nasopharyngectomy.

Patients with NPC require close monitoring during the first five years following the primary treatment. Studies have reported local recurrence rates of 60-65% within the first three years, increasing to 80% within the first five years (18, 19). While in our study, the mean time between the initial

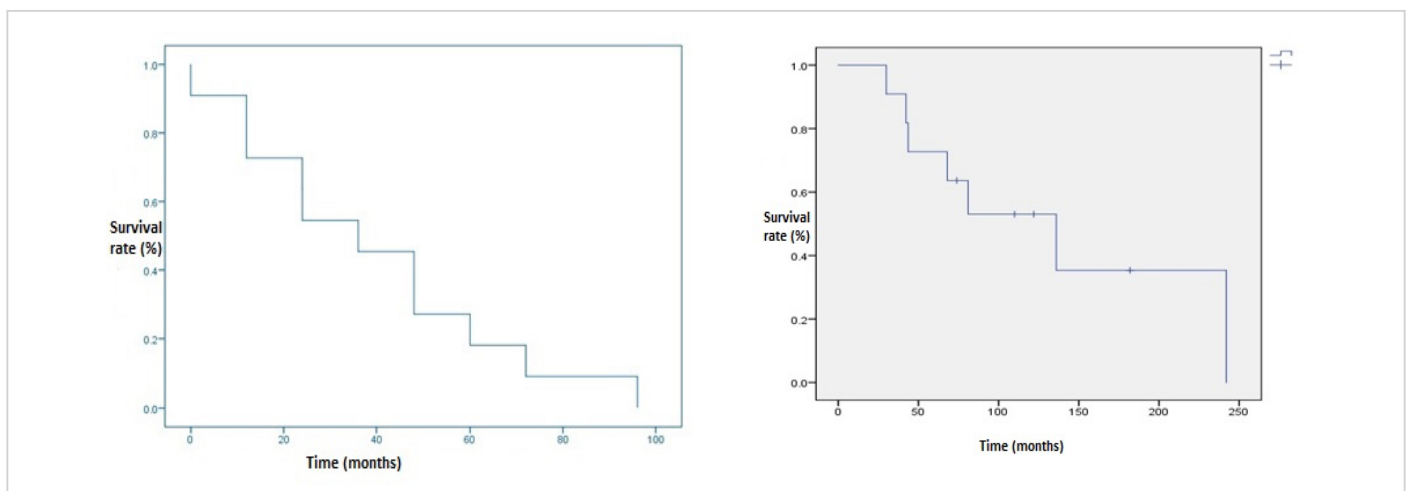
treatment and first recurrence was 40.3 months, Wong et al. (20) reported this time as 30 months. Another study found a mean time of 33 months between the primary disease and local recurrence (21). In our study, local recurrence was observed in three patients as the first recurrence, while regional and distant metastasis was observed in seven (63.6%) and one (9.1%) patients, respectively.

Re-irradiation has been used in the treatment of local recurrence, either with external RT or stereotactic radiosurgery. However, it can lead to serious morbidities, including complications such as osteoradionecrosis, cranial

**Table 1.** Distribution of patients' demographic characteristics and oncological data

Features	Frequency (%), n=11
Age at the first diagnosis (mean±SD, years)	44±13.01
<b>Gender</b>	
Male	10 (90.9)
Female	1 (9.1)
<b>The first treatment</b>	
Concurrent CRT	4 (36.4)
Induction CT + concurrent CRT	7 (63.6)
Time to relapse (mean±SD months)	40.3±6.1
<b>Re-staging</b>	
rT1N0M0	5 (45.4)
rT2N0M0	1 (9.1)
rT3N1M0	3 (27.2)
rT3N2M0	1 (9.1)
rT4N0M0	1 (9.1)
<b>Adjuvant treatment after nasopharyngectomy</b>	
Re-irritation	3 (27.2)
Concurrent CRT	4 (36.4)
None	4 (36.4)

SD: Standard deviation, CRT: Concurrent chemoradiotherapy, CT: Chemotherapy



**Figure 1.** Kaplan-Meier curves of the 5-year a) disease-free survival (27.3%) and b) overall survival (72.7%) rates



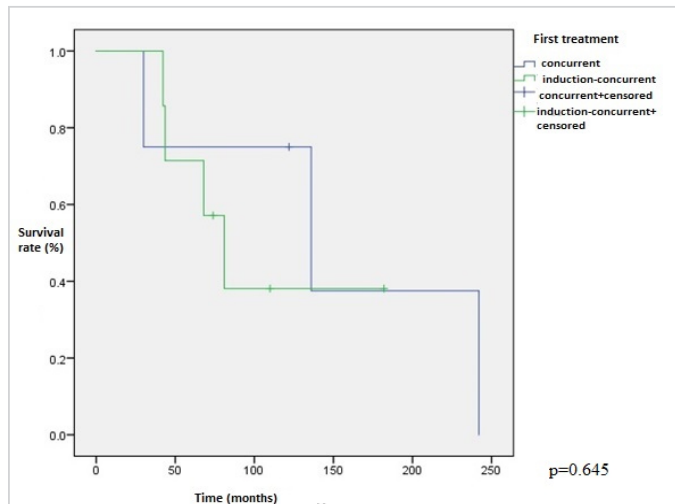
nerve neuropathies, brain abscesses, and mortality. Although there were no complications in our patient cohort, surgery-associated morbidities should always be kept in mind. Success rates are lower in advanced-stage recurrent tumors (rT3, rT4) (6). With the development of advanced RT techniques, reports have started to emerge regarding better outcomes with fewer complications. Studies on patients with rT3 and rT4 tumors reported OS rates of 35-36% and 19-30.2% for 5-year periods, respectively (22-24).

In our study, the OS rate at five years was 72.3%, and at 10 years, it was 53%. The 5-year OS rates in cases where nasopharyngectomy was performed as the treatment for local recurrence of NPC vary between 39% and 75.1% in the literature (18, 20, 21, 25, 26). Wong et al. (27) reported a 2-year OS rate of 66.7% following EEN, while Peng et al. (28) reported a rate of 66.3% (Table 2). The 5-year DFS rate in our study was 27.3%, slightly lower than the literature (Table 2). In the study conducted by Li et al. (29), the 3-year OS rate was reported as 55.2%, and the DFS rate as 29.4%. Furthermore, factors such as low body mass index, advanced

age, stage rT+, tumor necrosis, and invasion of the internal carotid artery by the tumor were identified as predictors of poorer OS. Additionally, low body mass index and stage rT4 were associated with worse DFS outcomes. Endoscopic nasopharyngectomy, like all endoscopic surgeries, is a procedure that requires advancement along the learning curve. As experience in the anatomy of this head region increases, even advanced-stage surgeries are becoming feasible. Initially, it is advisable to start this surgery with cases that do not extend to the posterior cranial fossa dura and do not cross laterally beyond both carotid arteries. Recurrence of NPCs particularly limited to the nasopharynx without widespread involvement at the skull base can be more suitable for SNP instead of IMRT.

Endoscopic endonasal surgery is a less complicated surgical approach compared to open procedures. In a study by Salom et al. (21), open nasal and endoscopic surgery approaches were compared, and moderate to severe complications were found to be more frequent in open surgeries. We did not encounter any significant complications in our patient series. The main disadvantage of EEN is the inability to clearly evaluate the surgical margins. As a result, some patients require adjuvant treatment after surgery. In our study, adjuvant treatment was administered to seven (63.6%) patients after surgery. In a study by Peng et al. (28), additional treatment was given to 19 (33.9%) patients.

In their randomized, controlled trial, one of the largest studies in the literature, Liu et al. (30) compared IMRT (71 of the 100 patients received cisplatin-based chemotherapy) and SNP. Three-year OS, DFS, and locoregional recurrence-free survival rates were significantly higher in the SNP group. However, 5-year OS and DFS rates did not reach statistical significance despite being better in the SNP group compared to the IMRT group. In our study, seven (63.6%) patients received IC+CCRT, while four (36.4%) patients received CCRT. The OS rates were 75% and 50%, and DFS rates were 50% and 14.3% in these groups, respectively, with no statistically significant difference.



**Figure 2.** Comparison of overall survival rates between concurrent chemoradiotherapy (CCRT) and induction chemotherapy+CCRT groups (75% vs 71.4%, respectively) (p=0.645)

**Table 2.** Overall and disease-free survival rates from various studies in the literature

	Number of cases	5-year overall survival rate (%)	5-year disease-free survival rate (%)
Salom et al. (21)	8	75	-
Castelnuovo et al. (25)	27	75.1	58.1
Wong et al. (20)	15	50	25
Liu et al. (18)	91	38.3	30.2
Sun et al. (26)	71	39	39.9
Wong et al. (27)	15	66.7 (2- years)	40 (2- years)
Peng et al. (28)	56	48.6	42.6
Liu et al. (30)	100	73.8	59
Li et al. (29)	120	55.2 (3-years)	55.2 (3-years)

The limitations of our study include its retrospective nature and a relatively small patient population. Furthermore, we lack sufficient long-term information on the duration of medical treatment and drug doses. The presence of patients with recurrent neck disease and those receiving additional treatment has also contributed to the heterogeneity of the patient group. Finally, the uneven distribution of patient T stages hindered our ability to present stage-specific survival rates.

## Conclusion

Our study highlighted that EEN is a viable alternative approach for selected cases of locally recurrent NPC, considering the morbidities associated with re-irradiation. Although the results of OS and DFS support the use of the EEN approach, randomized controlled studies with long-term follow-up and larger patient populations are needed. With the advancements in endoscopic imaging systems and surgical instruments, it is expected that better results will be reported in this field in the future.

**Ethics Committee Approval:** Before starting our study, we obtained approval from the ethical committee of the Hacettepe University Non-Invasive Clinical Research Ethics Committee (decision no.: 2023/09-38, date: 21.02.2023).

**Informed Consent:** Informed consent was obtained from the patients.

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## Main Points

- Considering the morbidities associated with re-irradiation, endoscopic endonasal nasopharyngectomy is a good alternative treatment option for locally recurrent nasopharyngeal cancer (NPC).
- Recurrence of NPCs, particularly those limited to the nasopharynx without crossing laterally beyond both carotid arteries, can be more suitable for salvage nasopharyngectomy.
- With the advancement of endoscopic surgical techniques in the future, 5-year overall and disease-free survival rates may improve.

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# Evaluating the Performance of ChatGPT, Gemini, and Bing Compared with Resident Surgeons in the Otorhinolaryngology In-service Training Examination

Original Investigation

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## Abstract

**Objective:** Large language models (LLMs) are used in various fields for their ability to produce human-like text. They are particularly useful in medical education, aiding clinical management skills and exam preparation for residents. To evaluate and compare the performance of ChatGPT (GPT-4), Gemini, and Bing with each other and with otorhinolaryngology residents in answering in-service training exam questions and provide insights into the usefulness of these models in medical education and healthcare.

**Methods:** Eight otorhinolaryngology in-service training exams were used for comparison. 316 questions were prepared from the Resident Training Textbook of the Turkish Society of Otorhinolaryngology Head and Neck Surgery. These questions were presented to the three artificial intelligence models. The exam results were evaluated to determine the accuracy of both models and residents.

**Results:** GPT-4 achieved the highest accuracy among the LLMs at 54.75% (GPT-4 vs. Gemini  $p=0.002$ , GPT-4 vs. Bing  $p<0.001$ ), followed by Gemini at 40.50% and Bing at 37.00% (Gemini vs. Bing  $p=0.327$ ). However, senior residents outperformed all LLMs and other residents with an accuracy rate of 75.5% ( $p<0.001$ ). The LLMs could only compete with junior residents. GPT-4 and Gemini performed similarly to juniors, whose accuracy level was 46.90% ( $p=0.058$  and  $p=0.120$ , respectively). However, juniors still outperformed Bing ( $p=0.019$ ).

**Conclusion:** The LLMs currently have limitations in achieving the same medical accuracy as senior and mid-level residents. However, they outperform in specific subspecialties, indicating the potential usefulness in certain medical fields.

**Keywords:** Artificial intelligence, ChatGPT, otorhinolaryngology, otorhinolaryngology in-service examination, resident education

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## Introduction

The emergence of artificial intelligence (AI) has drawn a lot of attention towards large language models (LLMs), a member of natural language processing tools. These models are highly proficient in processing and generating text resembling human speech. They are created using advanced deep-learning techniques and

comprehensive datasets from the internet (1).

LLMs are sophisticated AI systems designed to understand, interpret, and generate human language in a meaningful and contextually relevant way. They can identify patterns, comprehend context, and link various pieces of information, abilities that make them capable of



providing insightful responses and advice on a vast range of subjects (2).

These models, including OpenAI's ChatGPT, Google's Gemini, and Microsoft's Bing, are trained using machine learning, where they learn to predict and generate text based on the patterns they observe in the training data. This allows them to perform language-related tasks like translation, summarization, and question-answering (3).

A variety of studies have explored the effectiveness of LLMs in some exams. Specific research has been conducted on other professions, such as the University of Minnesota Law School, the Bar Exam, the Wharton Master of Business Administration, and accounting exams, even without fine-tuning the pre-trained model (4-7). In the medical field, some studies have assessed the performance of ChatGPT in the United States Medical Licensing Examination (8, 9). Further, some studies compared the performance of different LLMs in various exams like Ophthalmic Knowledge Assessment Program and Neurosurgery Oral Board (10, 11).

Some studies in the field of otorhinolaryngology explored the effectiveness of ChatGPT. One study examined the success rate of ChatGPT and found that it could pass the Royal College of Physicians and Surgeons of Canada Otorhinolaryngology Board Exam (12). Another study explored the usefulness of ChatGPT in the board preparation process by examining quiz skills in various otolaryngologic subspecialties (13).

This study aimed to evaluate the performance of LLMs, namely ChatGPT, Gemini, Bing, and resident surgeons, in the otorhinolaryngology in-service examination (ORLITE). The study also intended to compare the accuracy of each model in various otorhinolaryngology topics. We believe that exploring the potential effectiveness of AI in medical education can assist medical students and potentially improve their exam performances.

## Methods

### Study Design

This cross-sectional observational study compared the responses of LLMs, namely, ChatGPT, Google Gemini, Microsoft Bing, and the otorhinolaryngology residents in ORLITE. The study did not require ethics committee approval as it relied solely on the question database of the university clinic, which was derived from publicly available online medical textbooks.

### Development and Implementation of the ORLITE

ORLITE is an exam designed to assess the periodic competencies of residents specializing in otorhinolaryngology at a tertiary-level university hospital. The questions for the ORLITE are based on the Resident Training Textbook, which

is available on the Turkish Society of Otorhinolaryngology-Head and Neck Surgery website (<https://www.kbb.org.tr>). The exam content is created collaboratively by five experienced and board-certified faculty members, ensuring a consensus-driven approach to the exam content. It is conducted four times in a single academic year, and each consists of 40 questions, including multiple-choice, multiple-select, free-response, and image-based questions. These questions include topics in general otorhinolaryngology, otology/neurotology, rhinology, head and neck surgery, and laryngology. They are prepared in the Turkish language. Each correct answer is rewarded with 2.5 points, with no negative marks for incorrect choices. Residents are given 40 minutes to complete the exam.

### Selection of the Questions and Querying Process

Three-hundred-and-twenty questions retrieved from eight ORLITE sessions applied over the last two academic years, 2021-2022 and 2022-2023, were reviewed. Four of these questions were excluded due to incomprehensible image-based content, leaving 316 multiple-choice, multiple-selection, short-answer, and image-based questions to be presented to different LLMs separately. The querying process was conducted from February 15 to February 18, 2024, by an otorhinolaryngology specialist using the website of each model. Each question was asked individually, and the page was refreshed each time to prevent the relevant LLM from establishing connections with previous questions and forming memory. Before each question, the models were prompted with the following message: "Hello, you are a physician currently undergoing training in otorhinolaryngology. You will be answering questions related to the resident training exam conducted at the otorhinolaryngology department of the university clinic. You are only required to indicate the correct option. Are you ready?" The generated responses were marked as correct versus incorrect and recorded.

### Description of LLMs and the Resident Surgeons

During the study, various chatbots capable of producing human-like responses were tested. The chatbots used in the study included the subscription-based, paid version ChatGPT, an upgraded version of ChatGPT 3.5 developed by OpenAI and released in March 2023. In addition, the Gemini, a product of Google DeepMind introduced in December 2023, and Bing Chat, which is reported to utilize ChatGPT architecture and was made available to Edge users by Microsoft in February 2023, were also employed. The 22 human participants of the study were resident surgeons who had studied in a department of the otorhinolaryngology clinic of the university hospital in the years indicated. They were divided into three groups based on their five-year specialization training periods: the first 1.5 years as junior (3<sup>rd</sup> resident), the following two years as mid-level (2<sup>nd</sup> resident), and the final 1.5 years as senior (1<sup>st</sup> resident).

There were 7 junior residents, 10 mid-level residents, and 5 senior residents in their respective groups. The success of their exams was then categorized in terms of points.

### Statistical Analysis

Statistical analyses were performed to evaluate the overall success rate for each chatbot model and resident, which were calculated as the percentage of correct answers. Independent sample t-tests were applied to compare the accuracy values of chatbots and residents. Descriptive statistics such as mean and standard deviation were preferred to evaluate the performance of each exam. A significance level of  $\alpha=0.05$  was set. Statistical data analysis was performed using IBM SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.) Statistical Software package.

## Results

### Evaluation of the Performance of LLMs versus Residents in the ORLITE

In the ORLITE, ChatGPT outperformed Gemini and Bing with an accuracy of 54.75%, establishing itself as the leading model ( $p=0.002$  and  $p<0.001$ , respectively). Gemini and Bing achieved similar accuracies of 40.50% and 37.00%, respectively, with a non-significant difference ( $p=0.327$ ). These results highlight the exceptional comprehension and logical reasoning abilities of ChatGPT compared to other models.

The results revealed that senior residents had the highest accuracy rate of 75.50%, outperforming all LLMs and other residents ( $p<0.001$ ). Mid-level residents showed superior results with an accuracy of 63.45% compared to Gemini ( $p<0.001$ ) and Bing ( $p<0.001$ ), though ChatGPT approached their performance levels ( $p=0.013$ ). LLMs were found to be competitive only with junior residents. Junior residents achieved a success rate of 46.90%, outperforming Gemini and Bing ( $p=0.019$ ), but could not pass ChatGPT. However, the differences in performance between junior residents and ChatGPT and between junior residents and Gemini were not statistically significant ( $p=0.058$  and  $p=0.120$ , respectively). Gemini and Bing showed the lowest accuracy scores among them all. Table 1 summarizes, and Figure 1 illustrates, the performance of LLMs compared to residents.

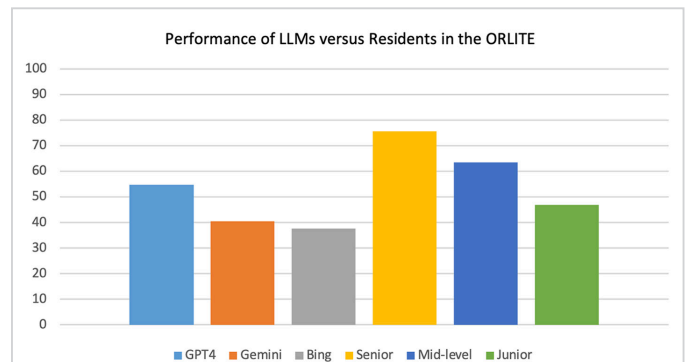
T-tests were used to analyze the accuracy differences between the LLMs among themselves and when compared with residents. Statistically, the significance level is considered as  $p<0.05$ .

### Comparison of the Accuracy Rates of LLMs and Residents in ORLITE Per Examination

We analyzed the accuracies of eight ORLITE exams and recorded the results. The standard deviations for each model and residents were as follows: ChatGPT (7.60%), Gemini (7.30%), Bing (7.00%), senior resident (5.80%), mid-level resident (3.80%), and junior resident (7.90%). The results were more consistent among senior and mid-level residents. Figure 2 illustrates the performance of LLMs and residents per the ORLITE exam.

### Investigation of the Accuracies of LLMs in Subspecialties of Otorhinolaryngology

We evaluated the performance of LLMs across various subspecialties within otorhinolaryngology, including general Ear Nose Throat (ENT), otology, rhinology, laryngology, and head and neck surgery. ChatGPT demonstrated the highest accuracy across most subspecialties, with notable performance in head and neck and rhinology, achieving accuracy rates of 59.40% and 55.60%, respectively. Gemini, on the other hand, showed consistent but more moderate success, with its highest accuracy, same as ChatGPT in head and neck and rhinology at 42.20% and 42.90%, respectively. While generally lower in all subspecialties than ChatGPT and Gemini, Bing was competitive in laryngology, where it



**Figure 1.** Performance of LLMs in comparison with residents  
LLM: Large language model

**Table 1.** Comparative accuracy and statistical significance of LLMs and residents

	Accuracy (%)	ChatGPT p-value	Gemini p-value	Bing p-value
ChatGPT	54.75	-	0.002	<0.001
Gemini	40.50	<0.001	-	0.327
Bing	37.00	<0.001	0.327	-
1 <sup>st</sup> Resident	75.50	<0.001	<0.001	<0.001
2 <sup>nd</sup> Resident	63.45	0.013	<0.001	<0.001
3 <sup>rd</sup> Resident	46.90	0.058	0.120	0.019

T-tests were used to analyze the accuracy differences between the LLMs and residents. Statistically, the significance level is considered as  $p<0.05$

LLM: Large language model

nearly matched ChatGPT with an accuracy rate of 48.10%. Figure 3 demonstrates the accuracy rates of each model in different otorhinolaryngology fields.

Examples of ORLITE questions and corresponding responses provided by ChatGPT, Gemini, and Bing, are presented in Table 2.

### Discussion

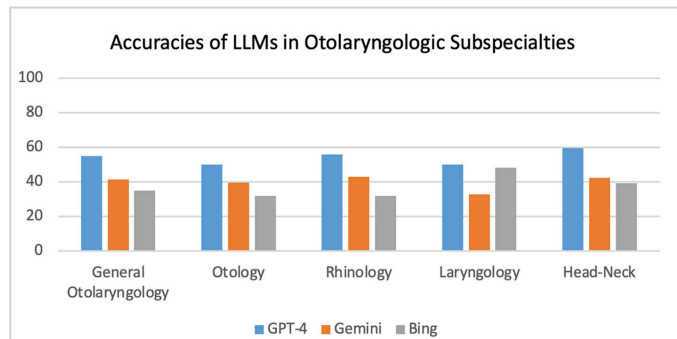
Three AI models were used in the study: OpenAI ChatGPT Plus (ChatGPT), Google Gemini, and Microsoft Bing. ChatGPT can be accessed through a subscription option, while the others are free to access on their website. It is worth noting that Bing prefers the ChatGPT infrastructure model, but Gemini works with a different type called Palm2 (14, 15). This study is the first of its kind to evaluate the performance of AI models in otorhinolaryngology exams and to compare them with humans specializing in the field.

In previous literature, there have been inconsistent results in studies comparing the performance of different LLMs

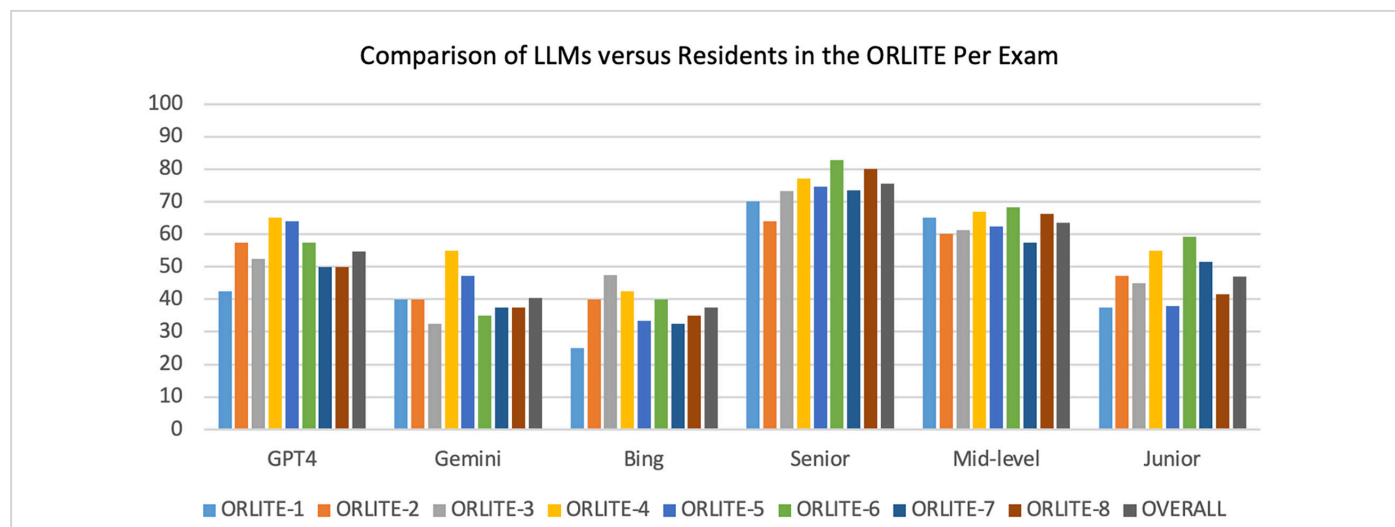
in various medical fields. For instance, one study on neurosurgery oral board exam preparation question bank concluded that ChatGPT was more effective than Gemini in responding to advanced knowledge queries, and another study on answering frequently asked questions about lung cancer found that ChatGPT was more accurate than Google Gemini (11, 16). However, a study on the Royal College of Ophthalmologists fellowship exams presented a contrasting perspective. It showed that Bing Chat outperformed other AI systems, including the lowest-ranked ChatGPT (17).

Previously, there have been studies examining the performance of ChatGPT in otorhinolaryngology and with various methodologies. Kuşcu et al. (18) conducted a study on the performance of ChatGPT in answering frequently asked questions about head and neck cancers. The results showed that the model had a high success rate, with 86.4% of responses being comprehensive and correct. Radulesco et al. (19) investigated the ability of ChatGPT to diagnose rhinological clinical cases accurately. They achieved a 62.5% correct or plausible response rate, and the stability of responses was moderate to high.

The performance of an LLM is mainly influenced by the model’s architecture, the amount of diverse training data, the duration of training, and the allocation of resources. To improve the effectiveness of the model, it is crucial to optimize techniques and fine-tune hyperparameters during training. In fields like medicine, where knowledge bases are rapidly evolving, up-to-date and relevant training data are vital. Customization through additional training for specific tasks or sectors can help optimize performance. Additionally, the linguistic and cultural diversity of the training data affects the model's effectiveness across different languages and cultural contexts (20).



**Figure 3.** Accuracies of LLMs in subspecialties of otorhinolaryngology  
LLM: Large language model



**Figure 2.** Comparison of LLMs versus residents in the ORLITE Per Exam  
LLM: Large language model, ORLITE: Otorhinolaryngology in-service exam

**Table 2.** Examples of ORLITE questions and corresponding answers provided by the three LLMs

Question	Specialty	ChatGPT 	Gemini 	Bing 
How long does it take for T lymphocytes involved in wound healing to reach their peak? a) 6 hours b) 24 hours c) 2 days <b>d) 7 days</b> e) 14 days	General ENT	<b>d) 7 days.</b> T lymphocytes, which play a role in the immune response during wound healing, typically peak activity around 7 days after injury. This is part of the proliferative phase of wound healing, where immune cells are active in clearing infection, promoting tissue growth, and supporting the repair process.	<b>d) 7 days.</b> T lymphocytes infiltrate the wound site gradually, not immediately after injury. Their numbers increase throughout the inflammatory phase and peak around 7 days after wounding.	<b>d) 7 days.</b> In the healing of wounds, the peak production time of duty T lymphocytes is between the 5 <sup>th</sup> and 7 <sup>th</sup> days. In this period, the inflammation stage in the healing process usually concludes, and the proliferation phase begins right after.
Which of the following is not a complication associated with the drainage of an abscess in the head and neck area? a) Aspiration b) Cranial nerve injury c) Bleeding from major arteries and veins <b>d) Jugular vein thrombosis</b> e) Sepsis	General ENT	<b>d) Jugular vein thrombosis.</b> This specific condition is generally not a direct complication of abscess drainage but can occur as a complication of infections in the neck, such as Lemierre's syndrome, which is different from the direct mechanical or procedural complications of draining an abscess.	<b>a) Aspiration.</b> Aspiration is the intended outcome of draining an abscess. It involves using a needle or surgical incision to remove the pus, the infected material within the abscess.	<b>a) Aspiration.</b> The option not related to the complications of head and neck abscess drainage is aspiration.
In stapes surgery, ideally, how many millimeters should the piston be inserted into the vestibule? a) 0.10 mm <b>b) 0.25 mm</b> c) 0.50 mm d) 0.75 mm e) 1.00 mm	Otology	<b>c) 0.50 mm.</b> This measurement is considered optimal to ensure the piston engages effectively with the inner ear structures without extending too far, which could potentially damage the sensitive structures within the inner ear, such as the cochlea.	<b>c) 0.50 mm.</b> This depth helps to balance several factors: Avoiding dislocation of the prosthesis from sudden pressure changes (e.g., sneezing). Maintaining proximity to the inner ear structures for optimal sound transmission. Surgeons aim for this depth to achieve a successful stapedotomy outcome.	<b>b) 0.25 mm.</b> There are different opinions regarding the ideal protrusion length of the piston into the vestibule in stapes surgery. However, many studies suggest that the piston should not protrude more than 0.25 mm into the vestibule.
Which of the following is considered a good prognostic factor in the prognosis of sudden hearing loss? a) Being over 60 years old <b>b) Hearing loss predominantly affects low frequencies</b> c) Hearing loss present for more than 3 months d) Accompanying vertigo e) Hearing loss having a flat configuration	Otology	<b>b) Hearing loss predominantly affects low frequencies.</b> Patients with sudden hearing loss that primarily affects low frequencies tend to have better recovery rates compared to those whose hearing loss affects all frequencies or predominantly the high frequencies. This is possible because damage limited to the low frequencies may indicate a less extensive injury to the cochlea.	<b>e) Hearing loss having a flat configuration.</b> A flat audiogram indicates a sensorineural hearing loss that affects all frequencies more or less equally. This suggests a more widespread issue potentially affecting the inner ear fluids or blood flow, which may respond better to treatment compared to a specific frequency loss.	<b>b) Hearing loss predominantly affects low frequencies.</b> The flat configuration of hearing loss (i.e., similar loss across all frequencies) is generally considered less favorable for recovery compared to low-frequency or high-frequency predominant hearing loss. So, b) Hearing loss predominantly affecting low frequencies might be a better prognostic factor



**Table 2.** Continued

Question	Specialty	ChatGPT 	Gemini 	Bing 
<p>In a patient with nasal polyps, asthma, aspirin intolerance, and daily rhinitis symptoms, which treatment would you prefer initially?</p> <p><b>a) Intranasal corticosteroids</b></p> <p>b) Systemic corticosteroids</p> <p>c) Antibiotics</p> <p>d) Leukotriene antagonists</p> <p>e) Antifungals</p>	Rhinology	<p><b>d) Leukotriene antagonists.</b></p> <p>For a patient with nasal polyps, asthma, aspirin intolerance, and daily rhinitis symptoms—a combination often referred to as Samter’s triad or aspirin-exacerbated respiratory disease (AERD)—the initial preferred treatment would be Leukotriene antagonists. They are particularly effective in this group because they target the pathway involved in both asthma and nasal polyp growth that is exacerbated by aspirin intolerance. This treatment helps reduce inflammation and may improve nasal and asthma symptoms.</p>	<p><b>a) Intranasal corticosteroids.</b></p> <p>The patient’s symptoms point towards a condition called AERD, also known as Samter’s triad. This involves nasal polyps, asthma, and aspirin intolerance.</p> <p>Intranasal corticosteroids are the mainstay of treatment for AERD because they effectively reduce inflammation in the nasal passages, improving rhinitis symptoms and potentially reducing polyp size.</p>	<p><b>a) Intranasal corticosteroids.</b></p> <p>Samter’s Triad, also known as AERD, is a chronic condition characterized by the following three components: Asthma, sinus inflammation with recurring nasal polyps, and sensitivity to aspirin and other non-steroidal anti-inflammatory drugs. Intranasal corticosteroids are a reasonable choice for managing sinus inflammation and nasal polyps as initial treatment strategy.</p>
<p>In paranasal sinus neoplasias, which lesion is identified by the bending forward of the posterior wall of the maxillary sinus, known as the Holman-Miller sign in imaging?</p> <p>a) Osteoma</p> <p>b) Ameloblastoma</p> <p><b>c) Angiofibroma</b></p> <p>d) Papilloma</p> <p>e) Thornwaldt cyst</p>	Rhinology	<p><b>c) Angiofibroma.</b></p> <p>This sign is particularly associated with juvenile nasopharyngeal angiofibroma (JNA), which is a benign but locally aggressive vascular tumor that predominantly affects adolescent males. The Holman-Miller sign indicates the anterior bowing of the posterior wall of the maxillary sinus due to tumor pressure or growth in the nasopharynx and pterygopalatine fossa.</p>	<p><b>c) Angiofibroma.</b></p> <p>The Holman-Miller sign is a characteristic finding associated with JNA, a type of benign vascular tumor that frequently arises in the nasopharynx and can extend into the maxillary sinus. The expanding tumor mass causes the posterior wall of the maxillary sinus to bulge forward on imaging studies like lateral skull X-rays or cross-sectional scans.</p>	<p><b>c) Angiofibroma.</b></p> <p>The Holman-Miller sign, also referred to as the antral sign, is associated with JNA. It manifests as the anterior bowing of the posterior wall of the maxillary antrum on imaging studies.</p>
<p>According to the European Laryngological Society (ELS) classification of supraglottic laryngectomy, what type is the endolaryngeal surgery that involves the removal of the epiglottis, preepiglottic space, and one ventricular band?</p> <p>a) Type I</p> <p>b) Type IIa</p> <p>c) Type IIb</p> <p>d) Type IIIa</p> <p><b>e) Type IIIb</b></p>	Laryngology	<p><b>c) Type IIb.</b></p> <p>The ELS classification of supraglottic laryngectomy categorizes different types of endolaryngeal surgery based on the extent of tissue removal. In this case, the surgery described involves the removal of the epiglottis, preepiglottic space, and one ventricular band. The correct answer would be Type IIb.</p>	<p><b>e) Type IIIb.</b></p> <p>Considering the removal of the epiglottis, pre-epiglottic space, and one ventricular band, Type IIIb best aligns with the ELS classification the correct answer should be Type IIIb.</p>	<p><b>e) Type IIIb.</b></p> <p>The ELS has proposed a classification system for different types of endoscopic supraglottic partial laryngectomies. The surgery involving removal of the epiglottis, preepiglottic space, and one ventricular band corresponds to Type IIIb in the ELS classification.</p>

**Table 2.** Continued

Question	Specialty	ChatGPT 	Gemini 	Bing 
<p>Which of the following vocal cord vibration modes is the most efficient and commonly used in daily life?</p> <p>a) Glottal fry <b>b) Modal register</b> c) Falsetto d) Resonance e) Articulation</p>	Laryngology	<p><b>b) Modal register.</b></p> <p>This is the normal vocal register used in daily conversation. It involves the vibration of the vocal folds in a regular and relatively relaxed manner, producing most of the sounds used in speech.</p>	<p><b>b) Modal register.</b></p> <p>Modal register refers to the normal speaking voice. It produces clear and efficient sound by allowing the vocal cords to vibrate fully at their fundamental frequency. This vibration pattern uses the least amount of energy to create a strong, audible voice.</p>	<p><b>b) Modal register.</b></p> <p>Modal register is the normal speaking voice that we use for everyday communication. In this mode, the vocal folds vibrate regularly, producing clear and resonant sounds.</p>
<p>Which specific lymphoma of the head and neck region is more commonly associated with Epstein-Barr virus (EBV)?</p> <p>a) Waldeyer's ring lymphoma <b>b) Sinonasal lymphoma</b> c) Salivary gland lymphoma d) Thyroid lymphoma e) Laryngeal lymphoma</p>	Head & Neck	<p><b>b) Sinonasal lymphoma.</b></p> <p>Lymphoma of the head and neck region commonly associated with EBV typically occurs in the nasal cavities (sinonasal). EBV has been associated with various types of lymphomas, such as Burkitt lymphoma, but sinonasal lymphoma in the head and neck region is more distinctly linked with EBV.</p>	<p><b>a) Waldeyer's ring lymphoma.</b></p> <p>EBV is strongly linked to Burkitt's lymphoma, a type of aggressive B-cell non-Hodgkin lymphoma. Waldeyer's ring, located in the upper pharynx behind the nose and above the tonsils, is a frequent site for Burkitt's lymphoma development, especially in children and young adults. While EBV can be associated with other lymphomas in the head and neck region, the connection is strongest with Burkitt's lymphoma arising in Waldeyer's ring.</p>	<p><b>b) Sinonasal lymphoma.</b></p> <p>EBV-associated lymphomas are a diverse group of lymphoproliferative disorders linked to EBV infection. Given the options provided, the lymphoma most commonly associated with EBV in the head and neck region is sinonasal lymphoma. Sinonasal lymphomas often exhibit angiocentric and natural killer cell features, and EBV infection is implicated in their pathogenesis.</p>
<p>Which of the following characteristics affect the choice of treatment in toxic solitary nodule?</p> <p>I. thyroid-stimulating hormone (TSH) level II. Nodule size III. Response to antithyroid treatment IV. Pregnancy or lactation V. Presence of compressive symptoms</p> <p>a) I, II, IV, V b) I, III, IV, V <b>c) II, III, IV, V</b> d) I, II, III, IV e) I, II, III, V</p>	Head & Neck	<p><b>c) II, III, IV, V.</b></p> <p>The choice of treatment in toxic solitary nodules is influenced by factors such as TSH levels (I), nodule size (II), response to antithyroid treatment (III), and the presence of compressive symptoms (V). These factors help determine whether medical management, radioactive iodine therapy, or surgical intervention is most appropriate for managing the condition.</p>	<p><b>c) II, III, IV, V.</b></p> <p>The choice of treatment for a toxic solitary nodule is influenced by several factors: nodule size, response to antithyroid treatment, pregnancy or lactation, and presence of compressive symptoms. A toxic nodule, by definition, suppresses TSH, so the absolute TSH level is not a major factor in choosing treatment.</p>	<p><b>b) I, III, IV, V.</b></p> <p>The choice of treatment for a toxic solitary nodule (also known as a toxic adenoma) depends on several factors. The correct answer is I, III, IV, V. These factors play a role in determining the most appropriate treatment for toxic solitary nodules. Remember that individual patient characteristics and preferences also influence treatment decisions.</p>

ENT;

LLMs are known to perform differently in various languages, which is often linked to the amount and quality of training data available. Since a considerable amount of online content is in English, LLMs in English usually have better comprehension capabilities and access to a broader knowledge base. A technical report released on GPT4 revealed that GPT3.5 and PaLM perform 70.1% and 69.3% accuracy in massive multitask language understanding studies, respectively, whereas GPT4 shows 85.5% in English (21). It has been found that Turkish has a similarity rate of 80%, closely matching Italian at 84.1%, German at 83.7%, and Korean at 77%. However, the success rate drops for Nepali to 72.2%, Thai to 71.8%, and Telugu to 62% (22).

Furthermore, the complexity of a language's structure, its grammatical rules, and cultural factors can influence the model's performance (23). Languages with more complex grammatical features, such as gender, case, and tense, may pose greater challenges for LLMs. Nonetheless, technological advancements and the increasing use of multilingual models have significantly improved performance in other languages. This progress can make language models more universally applicable, providing better services to users in different languages.

As the world advances in every manner, educational models continuously evolve from traditional to more technology-based styles (23). Residents in various specialty areas and students in medicine can benefit from using LLMs to enhance their learning and clinical experiences. LLMs are advanced repositories of medical knowledge that provide instant access to a wide range of medical literature and research, making it easier to learn and make decisions based on evidence. They provide personalized education by offering responses tailored to specific queries, allowing residents and students to explore complex medical scenarios. LLMs also aid in developing differential diagnoses by providing conditions based on existing symptoms, which can help with clinical reasoning and decision-making processes (24).

In addition to their primary functions, these models can be used to interpret medical data such as laboratory results and radiographic images. The models can help medical professionals make more informed decisions by providing contextual information and potential implications. LLMs can also be used for language translation in medical contexts. This is particularly useful in understanding medical texts in various languages, promoting a more global medical perspective. LLMs also offer the potential for simulation-based learning, where residents and students can engage in virtual patient scenarios to enhance their diagnostic and therapeutic skills in a safe environment (25).

There are a few limitations to this study that are worth noting. Firstly, we only examined three of the most commonly used LLMs today: ChatGPT, Gemini, and Bing. While

these models are widely available, many others could also be included in more comprehensive studies to further our knowledge in this field. Secondly, one potential limitation is that the reproducibility of the chatbots' responses varied with each query. This is something to keep in mind when interpreting the results. Thirdly, the questions used in the study were based on a specific textbook formatted according to the universal medical literature by the Turkish Society of Otorhinolaryngology Head and Neck surgery. It is important to consider that different question formats based on various database sources may produce different outcomes. Lastly, it is worth noting that the questions were designed to comply with the International Test Commission guidelines (26). However, minor discrepancies may occur since they were prepared by a joint commission of five faculty members.

## Conclusion

Our study suggests that LLMs currently have limitations in achieving the same medical accuracy as senior resident surgeons. However, that the performance of ChatGPT is comparable to that of mid-level residents-and they excel in specific subspecialties-indicates the potential usefulness in certain medical fields. Meanwhile, Gemini and Bing show promise as valuable resources for education and the initial stages of clinical support, as their accuracy levels are similar to junior surgeons. Nevertheless, the performance of these models varies across different subspecialties, highlighting the need for the development and application of tailored LLMs to meet the requirements of each field.

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**Ethics Committee Approval:** The study did not require ethics committee approval as it relied solely on the question database of the university clinic, which was derived from publicly available online medical textbooks.

**Informed Consent:** The study did not require patient consent as it was based entirely on the university clinic's database of questions obtained from publicly available online medical textbooks.

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### Main Points

- Technology and artificial intelligence are becoming ever-increasingly popular and being integrated into our lives. Artificial intelligence products known as Large Language Models (LLMs), such as chatbots, generate human-like responses and problem-solving skills. Their abilities to solve exam questions such as USMLE, Bar, and MBA have been investigated.
- Although examined in cardiology, ophthalmology, orthopedics, obstetrics, gynecology, and otorhinolaryngology, the comparison of the success of LLMs and human counterparts has not yet been investigated.
- In this study, the performance of LLMs in exams applied for resident training at a University Clinic was compared among themselves and with residents at three levels of seniority, using the Turkish Otorhinolaryngology Head and Neck Society Assistant Training Basic Textbook as reference.
- ChatGPT was more successful than other LLMs in total and across all subspecialties of otorhinolaryngology. Bing showed close success to ChatGPT in the field of laryngology. The senior residents was the most successful, while ChatGPT approached the performance of the mid-level residents. ChatGPT and Gemini achieved results similar to those of the junior residents.
- LLMs are far from senior residents' levels of knowledge, skills, and experience under current conditions. However, they can be preferred for their supportive features in the early years of resident training.

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# Investigation of Acoustic Voice Characteristics of Individuals Diagnosed with Muscle Tension Dysphonia

## Original Investigation

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## Abstract

**Objective:** Muscle tension dysphonia (MTD) is a functional voice condition that causes irregular and imbalanced laryngeal and paralaryngeal muscle activation. Our study aimed to examine the acoustic characteristics of patients with MTD and reveal the differences between genders.

**Methods:** The study retrospectively reviewed the acoustic examination findings from the files of patients diagnosed with MTD during evaluations in the laryngology outpatient clinic at a tertiary reference hospital between 2015 and 2022. The parameters assessed in prolonged vowel phonation analysis were fundamental frequency (F0), jitter, shimmer, noise-to-harmonic-to-ratio, and soft phonation index; in the counting task analysis, they were intensity, frequency, and semitone. Gender differences in acoustic measurements obtained during prolonged vowel phonation and counting tasks were also examined.

**Results:** The study included 80 individuals diagnosed with MTD. Although all parameters in the acoustic analysis of /a/ phonation were increased, differences were statistically significant only in the F0 and jitter parameters between females and males ( $p \leq 0.05$ ). In the analysis of the counting task, the mean and minimum F0 parameters were significantly higher in females than in males ( $p = 0.000$ ). The mean dB level was decreased, particularly in the counting task, but the results for the intensity parameter did not differ significantly between genders ( $p > 0.05$ ).

**Conclusion:** The values in the acoustic voice analysis parameters of patients with MTD were determined. These acoustic parameters are thought to guide the clinician in evaluating voice and determining voice therapy goals for MTD patients.

**Keywords:** Dysphonia, acoustic analysis, muscle tension, voice disorder, voice quality, laryngology

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## Introduction

Primary muscle tension dysphonia (MTD) is a condition associated with excessive, atypical, or abnormal laryngeal activities that happen during phonation without an evident psychological or neurological

cause or any organic pathology in the vocal folds (1). Primary MTD is more common in women and constitutes 40% of the dysphonic patients presenting to outpatient clinics (2). The precise cause of abnormal muscle activity in primary



MTD remains unknown. However, it could be associated with the following factors: a) psychological and/or personality factors, b) excessive vocal demands that lead to technical misuse of the vocal mechanism, c) acquired adaptations after upper respiratory tract infections, and d) increased pharyngolaryngeal tone resulting from laryngopharyngeal reflux (3). Individuals with MTD can exhibit variability in the severity of dysphonia, affecting aspects such as the intensity, quality, pitch, resonance, flexibility, and endurance of the voice (4).

MTD patients need to be evaluated in many aspects, such as case history, laryngoscopic examination, auditory-perceptual evaluation, acoustic and aerodynamic analysis, and voice-related musculoskeletal system (5,6). Physical examination usually reveals an increase in extrinsic laryngeal muscle tone. The larynx is located high in the neck, and the thyrohyoid distance is narrowed. During speech, the supraclavicular fossae are tense and prominent (3). On laryngeal examination, various glottic and supraglottic contraction patterns are associated with primary MTD. Laryngeal findings commonly reported in the literature are anterior-posterior compression in the vocal folds, medial compression in the ventricular folds, inadequate glottic closure, and posterior glottic opening (6). There are no specific mucosal changes in primary MTD (7).

Acoustic voice analysis is a computer-based, repeatable, objective, quantitative, and non-invasive method for evaluating voice quality. Using this method, the acoustic characteristics of a normal, artistic, or pathological voice can be detected and analyzed (8). Continuous vowel phonation is utilized more commonly in research than speaking and reading tasks as vocal folds contain richer vibration patterns and can be acquired rapidly and readily (9). Therefore, acoustic parameters such as fundamental frequency (F0), jitter, shimmer, and noise-harmonic ratio (NHR) are commonly examined to evaluate vocal function (10,11). In clinical practice, there are still some aspects that need to be improved, such as following standardized recording, analysis, and reporting protocols; improving the understanding of the relationship between perceptual and instrumental acoustic results; accounting for common variables related to speech and language, such as speech sound pressure level (SPL) and F0, phonetic context, and differences in content; and availability of a much larger database to understand the normal variability within and between individuals with and without dysphonia, depending on age and gender (12). Patients with MTD have also reported abnormalities in acoustic parameters due to hyperfunctional behavior (10). In studies conducted on MTD, it is seen that acoustic voice analyses are mostly performed during vowel phonation. We deemed vowel production and speech activities in MTD essential to enhance comprehension of the voice alterations exhibited by this dysphonic group and expand the database.

Acoustic voice analysis of patients with MTD during different tasks is a crucial tool, particularly in voice clinics, for supporting the diagnosis, developing a patient-specific treatment plan to document the efficacy of treatment, and providing an objective estimate of pathological changes in patients' voice function.

Our study aimed to examine the acoustic voice parameters that can characterize patients with MTD, to create acoustic measurement reference values for subsequent studies, to define acoustic measurement values that can distinguish these patients from other types of voice disorders, and to examine the change in the determined values between gender groups.

## Methods

This study used a descriptive method to analyze the acoustic voice characteristics of individuals diagnosed with MTD.

### The Study Group

The files of patients who presented to the Otolaryngology Department of the University of Health Sciences Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital between January 2015 and August 2022 and were diagnosed with MTD because of their evaluation in the voice center due to voice disorders were retrospectively examined. We obtained Ankara Etlik City Hospital No. 1 Clinical Research Ethics Committee before starting the study (decision no.: AEŞH-EK1-2023-145, date: 12.07.2023). Videolaryngoscopic examination and acoustic analysis findings were reviewed from the patients' files. The inclusion criteria for the study were: a) aged over 18 years; b) a diagnosis of primary MTD based on videolaryngoscopic examination, anamnesis, acoustic and auditory-perceptual analyses; and c) absence of any underlying organic or neurogenic disorder that could cause a voice disorder. Data from 80 patients who met the study criteria were reviewed. The review results indicated that the study excluded patients with organic or neurogenic disorders.

### Assessment Tools

In our clinic, all patients who are diagnosed with voice disorders undergo routine objective and subjective voice evaluations, including evaluations using anamnesis, laryngeal examination, Grade, Roughness, Breathiness, Asthenia, Strain (GRBAS), self-assessment instruments, and acoustic and aerodynamic measurements. Patients' anamnesis forms and self-reports are stored physically, and voice samples are stored digitally using the Computerized Speech Lab Multi-Dimensional Voice Program (MDVP) and the real-time pitch (KAYPENTAX:PENTAX Medical Company, USA) program. The analysis of acoustic data from patients diagnosed with MTD constituted the only focus of our research.

In videolaryngoscopic examination, a rigid endoscope with Kay Pentax RLS 9100 B equipment (Key Elemetrics, Lincoln Park,

New Jersey, USA) was used to record the images and voices of the patients. Videolaryngoscopic examination was performed by two experienced laryngologists.

Acoustic voice analysis was performed using the MDVP and real-time pitch programs (Kay Elementrics Group Computerized Speech Lab-CSL, Model 4500). The recordings were made in a quiet room using a Shure brand microphone (Shure SM48-LC model). The microphone was placed approximately 10 cm away from the mouth at a 45-degree angle. MDVP was used for the acoustic voice analysis of the /a/sound, and the real-time pitch program was used for the analysis of the counting task (counting 1-10). For MDVP measurement, the patient was asked to produce /a/ phonation at a comfortable and normal intensity for five seconds, and then the first and last parts of the recordings were cut and the three seconds in the middle of the phonation interval were analyzed. Among the measurement parameters, F0, jitter (%), shimmer (%), NHR, and soft phonation index (SPI) were recorded numerically. In the real-time pitch program, participants were asked to count from one to 10 in a comfortable tone, and the recordings were analyzed. Intensity, frequency, and semitone parameters were examined in the analysis measurements.

### Statistical Analysis

The data from the study were analyzed using the Statistical Package for Social Sciences (SPSS) Version 26.0 (IBM SPSS Statistics for Windows. Armonk, NY, USA). Before analysis, the data was evaluated with the Kolmogorov-Smirnov test to

check whether the data conformed to a normal distribution. Test results were used for analysis of normally distributed data [F0, SPI, maximum (max.) dB, mean dB, minimum (min.) hz, max. hz, average hz, range hz, periodicity, semitone range) using a t-test for independent samples; the Mann-Whitney U test was used for analyzing the data that did not show normal distribution (jitter, shimmer, NHR, min. dB, range dB). The results of the score values for the dimensions were reported by descriptive statistical analysis.

### Results

A total of 80 individuals with a MTD diagnosis were included in the study. Of these, 33.8% (n=27) were male, and 66.2% (n=53) were female. Descriptive statistical results of acoustic analysis findings in the /a/ vowel and counting tasks (1-10) according to gender are shown in Table 1.

Table 2 reveals a significant gender difference in the F0 scores of individuals diagnosed with MTD ( $t=-5.337$ ;  $p=0.000$ ). Accordingly, the average F0 scores of females and males were 224.24 and 156.08 hz, respectively. It is seen that there is no difference in SPI values in terms of gender ( $t=0.690$ ;  $p=0.492$ ).

When Table 3 is examined, it is seen that the shimmer and NHR scores of individuals diagnosed with MTD do not differ significantly between genders ( $z=-0.366$ ;  $p=0.714$ ;  $z=-0.031$ ;  $p=0.976$ ). It was observed that the jitter scores of individuals diagnosed with MTD differed significantly between the genders ( $z=-2.203$ ;  $p=0.028$ ). Accordingly, it can be said that

**Table 1.** Descriptive statistical results of acoustic analysis findings by gender

Parameters	Group	N	Min.	Max.	Mean	SD
F0	Male	27	96.149	214.905	156.080	34.102
	Female	53	83.523	386.787	224.248	61.607
	Total	80	83.523	386.787	201.241	62.715
Jitter	Male	27	0.277	6.887	1.738	1.817
	Female	53	0.349	20.015	2.942	3.500
	Total	80	0.277	20.015	2.536	3.079
Shimmer	Male	27	1.997	21.731	6.367	4.198
	Female	53	0.139	35.022	6.503	5.611
	Total	80	0.139	35.022	6.457	5.151
NHR	Male	27	0.112	0.583	0.186	0.114
	Female	53	0.099	2.287	0.240	0.338
	Total	80	0.099	2.287	0.222	0.283
SPI	Male	27	1.096	31.802	13.210	6.808
	Female	53	0.157	34.050	12.106	6.740
	Total	80	0.157	34.050	12.479	6.740
Min. dB	Male	27	35.000	39.420	36.318	1.061
	Female	53	26.920	43.460	36.598	2.484
	Total	80	26.920	43.460	36.503	2.110



**Table 1.** Continued

Parameters	Group	N	Min.	Max.	Mean	SD
Max. dB	Male	27	37.290	74.400	62.473	7.053
	Female	53	44.030	74.670	61.533	6.263
	Total	80	37.290	74.670	61.850	6.511
Mean dB	Male	27	37.050	66.150	53.142	5.945
	Female	53	38.900	62.630	53.770	5.564
	Total	80	37.050	66.150	53.558	5.665
Range dB	Male	27	0.470	35.060	26.172	6.965
	Female	53	7.960	39.470	24.726	6.043
	Total	80	0.470	39.470	25.214	6.362
Min. hz	Male	27	76.430	142.680	96.097	16.788
	Female	53	70.100	225.960	128.895	42.705
	Total	80	70.100	225.960	117.826	39.201
Max. hz	Male	27	81.070	393.880	297.799	77.237
	Female	53	151.860	392.250	316.703	55.153
	Total	80	81.070	393.880	310.323	63.612
Mean hz	Male	27	79.330	263.220	151.803	41.008
	Female	53	122.550	337.290	216.344	45.968
	Total	80	79.330	337.290	194.562	53.735
Range hz	Male	27	3.370	309.000	197.258	80.585
	Female	53	52.470	306.540	187.726	73.492
	Total	80	3.370	309.000	190.943	75.584
Periodicity	Male	27	0.320	6.240	2.389	1.415
	Female	53	-0.080	9.790	2.912	2.087
	Total	80	-0.080	9.790	2.736	1.894
Semitone Range	Male	27	1.000	26.000	18.962	5.761
	Female	53	4.000	29.000	16.264	6.886
	Total	80	1.000	29.000	17.175	6.617

F0: Fundamental frequency, NHR: Noise to harmonic ratio, SPI: Soft phonation index, Min.: Minimum, Max.: Maximum, SD: Standard deviation

**Table 2.** T-test results for the comparison of F0 and SPI scores of individuals diagnosed with MTD according to gender

Variable	Group	N	Mean	SD	t	p
F0	Male	27	156.08	34.10	-5.337	<b>0.000</b>
	Female	53	224.24	61.60		
SPI	Male	27	13.21	6.80	0.690	0.492
	Female	53	12.10	6.74		

p<0.005. F0: Fundamental frequency, NHR: Noise to harmonic ratio, SPI: Soft phonation index, SD: Standard deviation, MTD: Muscle tension dysphonia

the female jitter scores (mean=44.60) are significantly higher than the male scores (mean=32.44).

When Table 4 is examined, it is seen that the maximum dB, mean dB, maximum hz, range hz, periodicity, and semitone range scores of individuals with MTD did not differ significantly between the genders (t=608; p=0.545; t=-0.467; p=0.642; t=-1.262; p=0.211; t=0.531; p=0.597; t=-1.171; p=0.245; t=1.747; p=0.085). It is seen that the mean and minimum hz scores of individuals with MTD differed significantly between the

genders (t=-6.151; t=-3.833; p=0.000). Accordingly, female mean hz scores (mean=216.34) were significantly higher than male scores (mean=151.80), and female minimum hz scores (mean=128.89) were significantly higher than male scores (mean=96.09).

Table 5 shows that the minimum and range dB scores of individuals with MTD did not differ significantly between the genders (z=-0.198; p=0.843; z=-1.526; p=0.127).

**Table 3.** Mann-Whitney U test results for comparison of jitter, shimmer, and NHR scores of individuals diagnosed with MTD according to gender

Variable	Group	N	Rank average	U	Z	p
Jitter	Male	27	32.48	499.000	-2.203	<b>0.028</b>
	Female	53	44.58			
Shimmer	Male	27	41.83	679.500	-0.366	0.714
	Female	53	39.82			
NHR	Male	27	40.61	712.500	-0.031	0.976
	Female	53	40.44			

p<0.005 NHR: Noise to harmonic ratio, U and Z: Statistical values in Mann-Whitney U test

**Table 4.** T-test results for comparison of scores obtained from acoustic analysis findings in the counting task of individuals with MTD according to gender

Variable	Group	N	Mean	SD	t	p
Max. dB	Male	27	62.47	7.05	0.608	0.545
	Female	53	61.53	6.26		
Mean dB	Male	27	53.14	5.94	-0.467	0.642
	Female	53	53.77	5.56		
Min. hz	Male	27	96.09	16.78	-3.833	<b>0.000</b>
	Female	53	128.89	42.70		
Max. hz	Male	27	297.79	77.23	-1.262	0.211
	Female	53	316.70	55.15		
Mean hz	Male	27	151.80	41.00	-6.151	<b>0.000</b>
	Female	53	216.34	45.96		
Range hz	Male	27	197.25	80.58	0.531	0.597
	Female	53	187.72	73.49		
Periodicity	Male	27	2.38	1.41	-1.171	0.245
	Female	53	2.91	2.08		
Semitone Range	Male	27	18.96	5.76	1.747	0.085
	Female	53	16.26	6.88		

p<0.005 MTD: Muscle tension dysphonia, Min.: Minimum, Max.: Maximum, SD: Standard Deviation

**Table 5.** Mann-Whitney U test results for comparison of scores obtained from acoustic analysis findings in the counting task of individuals with MTD according to gender

Variable	Group	N	Rank average	U	Z	p
Min. dB	Male	27	41.22	696.000	-0.198	0.843
	Female	53	40.13			
Range dB	Male	27	46.06	565.500	-1.526	0.127
	Female	53	37.67			

MTD: Muscle tension dysphonia, Min.: Minimum, p<0.005, U and Z: Statistical values in Mann-Whitney U test

## Discussion

Acoustic voice analysis is a beneficial technique for detecting voice disorders that can be identified by measuring various acoustic parameters. A series of voice parameters are acquired by recording and analyzing a voice signal. This method enables the identification of voice disorders by comparing voice parameters acquired from individuals with healthy voices and those with dysphonic voices (13). In our study, the acoustic voice

analysis parameters of patients with MTD were reviewed, and the changes in acoustic parameters related to MTD were noted.

MTD is a prevalent problem observed in women of middle age and younger. Due to the imbalance between synergist and antagonist muscles, this vocal issue disrupts the position of the vocal folds and induces tension in the remaining portion of the vocal tract. Numerous factors, such as possible psychological or personality traits, could contribute to this tension in muscle

activity (14). In our study, 66.2 percent of participants with MTD were women. According to Ali et al. (14), 43 of the 72 patients diagnosed with MTD were women. According to another study, 64% of female participants had MTD (15). The high number of female participants in our research and other studies supports the idea that MTD is more common in females.

Symptoms such as varying degrees of tense or effortful voice quality, hoarseness, glottal fry, breathiness, abnormal pitch, voice breaks, voice fatigue (16), odynophonia, vocal tract, and neck discomfort occur in primary MTD (15). A correct diagnosis of MTD is essential. A proper diagnosis depends on first recognizing auditory-perceptual traits and then rigorously eliminating other structural or neurological diseases with comparable voice characteristics. Therefore, knowing the endoscopic, acoustic, and aerodynamic features facilitates the accuracy of the diagnosis (1,17). Furthermore, the therapy for these patients can include techniques aimed at specific aspects of voice production. Furthermore, there is a lack of outcome statistics on specific therapy elements meant to alter voice production toward maximum function (18). Thus, objective evidence is required to expose both diagnosis and therapeutic efficacy. Vocal hyperactive behaviors in MTD cause abnormalities in the voice's perceptual and acoustic parameters (10). These patients may exhibit distinctive behavioral alterations during voice production, such as glottal muscle tension or glottal attack. As a result, acoustic analyses serve as a valuable instrument for assessing these modifications (19). In studies on the acoustic properties of voice, acoustic parameters such as F0, first formant frequency, jitter, shimmer, and NHR have been commonly used (20).

F0 represents the number of cycles generated by the vocal folds per second and indicates the first harmonic of the voice (2). Pitch is strongly perceptually related to F0. F0 varies significantly between males and females, primarily because of anatomical distinctions. In addition to having a longer vocal tract than females, males also have thicker, more prominent vocal folds. As a result, they generate a lower F0 by vibrating at approximately half the frequency of females during phonation (21). The average F0 in females is 180-230 hz; in males, it is 100-150 hz (22). Bengisu et al. (23) reported the mean F0 of female patients with primary MTD as 222.95 hz.

In another study, the mean cepstral peak prominence (CPP) F0 of patients with MTD was 207.6±20.2 hz (24). In our study, the F0 mean of the isolated vowel sound in the acoustic analysis was 224.2 hz, with a minimum of 83.5 hz and a maximum of 386.7 hz in females, while the F0 mean in males was 156.0 hz, with a minimum of 96.1 hz and a maximum of 214.9 hz. Furthermore, the counting task yielded similar results for these values in both males and females. According to the findings obtained in our study, the F0s of males and females were found to be within a range that defines their gender. However, it is worth noting

that although the F0 averages of females and males were within their respective voice ranges, the minimum and maximum F0 values varied. Increased F0 in patients with MTD is associated with increased tension. It has also been reported that the tension in the vocal folds increases in these patients due to excessive contraction in the laryngeal muscle. Generally, stiffness and excessive tension of the intrinsic and extrinsic muscles of the larynx, as well as the high vertical position of the larynx in the neck, cause the formation of a high-pitched voice quality (25). Studies indicate that F0 is a crucially perceived acoustic quality of dysphonic voice (10). Even if the average F0 values of MTD patients reflect their gender, knowing the differences in F0 values (minimum and maximum hz values) in some patients will guide the clinician in evaluating the voice and planning appropriate voice therapy approaches.

Perturbation measurements such as jitter and shimmer parameters reveal short-term variations in the intensity and fundamental frequency between cycles. From cycle to cycle, the frequency and intensity of a healthy voice show some variation. On the other hand, excessive variability indicates unhealthy vocal fold function. Effective differentiation between healthy and pathological voices has been demonstrated using perturbation measurements (11). Jitter was measured at 1.319 and shimmer at 0.779 in 20 female participants diagnosed with MTD (23). De Oliveira Lemos et al. (26) found jitter to be 0.46 and shimmer to be 4.58 in individuals with MTD. Jitter and shimmer measurements in our study revealed that the associated values for females were 2.94 and 6.50, whereas, for males, these values were 1.73 and 6.36, respectively. Jitter values in females are significantly higher than in males. Although there is no difference in terms of gender, shimmer values are seen to be relatively higher than the studies conducted in the literature. The higher these parameters were in our study, the higher the effect on voice quality. This situation is thought to cause irregularities in the vibration of the vocal folds due to increased tension in individuals with MTD (20). This resulted in the observation that both frequency and intensity parameters were impacted. The literature reports the mean NHR value for individuals with MTD to be 0.105 and the average SPI value 29.80 (23). Ten individuals with MTD were evaluated by Mathieson et al. (27) regarding NHR and SPI values in connected speech and vowel phonation. The researchers determined that the NHR value for vowel production was 0.121, and the SPI value was 29.86. In connected speech, the NHR value was 0.250, and the SPI value was 28.36. The NHR value determined in our study was 0.222, while the mean SPI value was 12.47. It is important to note that the maximum mean SPI value among all participants was 34.0. This finding shows that the vocal folds in patients with MTD do not close entirely due to muscle tension during phonation. Knowing the SPI value will assist the clinician in both the evaluation and treatment phases (before and after treatment) in determining appropriate voice therapy techniques.

Acoustic analysis has revealed a reduced intensity in patients with MTD due to the tension in the phonatory mechanism (28). A study conducted at a voice center in New York reported that, in a comparison of the group with primary MTD and the group without MTD, SPL (dB) during vocalization was one of the critical parameters affected and explained 65% of the variance between the variables [airflow during vocalization, SPL (dB), mean air pressure, peak F0, CPP mean vowel (dB)] (15). Another study conducted with individuals with MTD stated the average vocal intensity as 66.95 dB SPL (28). Altman et al. (29) reported that 86% of patients with MTD complained about excessive use of voice or the need to use loud sounds in daily activities. A study reported that as voice intensity increased, acoustic perturbation parameters improved, in other words, jitter, shimmer, and NHR decreased (30). In our study, all participants' mean minimum, maximum, and mean intensity levels during the counting task were 36.5 dB, 61.8 dB, and 53.5 dB, respectively. The low mean maximum intensity level especially shows us that the vocal intensity decreases in patients due to the tension in the phonatory mechanism.

Further studies examining the acoustic parameters of healthy individuals may provide more detailed information about the deviation in the voice characteristics of individuals with MTD. It is also known that MTD involves components such as stress and anxiety that can significantly affect voice production. Our study did not address psychological aspects that could affect acoustic sound characteristics. Future studies incorporating psychological assessments may further elucidate the interplay between physiological and psychological factors in MTD patients. Addressing these limitations in subsequent studies will increase the robustness and applicability of the findings, ultimately advancing the field of voice disorders and improving clinical practice.

In our study, we investigated the acoustic voice parameter values of individuals diagnosed with MTD during vowel and counting tasks. In the vowel phonation analysis, the average F0 value was 224 hz (min.-max.: 83 hz-386 hz) in females and 156 hz (min.-max.: 96 hz - 214 hz) in males. Likewise, F0 values were similar in the counting task. Although the F0 averages of males and females were within the range of their respective genders, the minimum and maximum F0 values differed. The average jitter, shimmer, NHR, and SPI values of all MTD patients were 2.53, 6.45, 0.222, and 12.47, respectively. The average intensity in the counting task was found to be 53.5 dB (min.-max.: 36.5-61.8 dB).

In our study, we studied a larger sample group diagnosed with MTD compared to studies in the literature. We believe that gender-specific differences in acoustic voice characteristics provide valuable information about the nature of MTD. This study will constitute an important reference value for future studies, especially for patients with MTD. Moreover, we believe that when determining targets and treatment plans for patients

with MTD, appropriate intervention plans should be prepared by considering the individual acoustic values caused by the tension in the phonatory mechanism.

**Ethics Committee Approval:** We obtained Ankara Etlik City Hospital No. 1 Clinical Research Ethics Committee before starting the study (decision no.:AEŞH-EK-2023-145, date: 12.07.2023).

**Informed Consent:** The study retrospectively reviewed the acoustic examination findings from the files of patients diagnosed with MTD during evaluations in the laryngology outpatient clinic at a tertiary reference hospital between 2015 and 2022

### Authorship Contributions

Concept: E.B., E.A., D.S., E.Ç.T., Design: E.B., E.A., D.S., Data Collection and/or Processing: E.B., E.A., D.S., E.Ç.T., Analysis and/or Interpretation: E.B., E.A., E.Ç.T., Literature Search: E.B., D.S., Writing: E.B., D.S., E.Ç.T.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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### Main Points

- Muscle tension dysphonia (MTD) affects the voice quality of patients.
- We established reference values for the acoustic voice parameters of patients with MTD.
- Acoustic parameters must be considered in the voice evaluation and intervention of MTD patients.

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# Management of Disseminated Rhinosporidiosis: Experience From a Single Tertiary Institution

Original Investigation

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## Abstract

**Objective:** This study aims to present a series of patients with disseminated rhinosporidiosis with diagnostic and therapeutic features.

**Methods:** A retrospective study was conducted in a tertiary health care centre in South India from 2007 to 2020 with disseminated rhinosporidiosis. Twelve patients with multiple sites of involvement like the nose, nasopharynx, oropharynx, larynx, lacrimal sac and skin were included in the study. All patients underwent surgical excision, followed by peroral dapsone for one year.

**Results:** The age group was around 30-55 years, with male predominance (11:1). Pond bathing history was present in 50% (n=6). The most common site of lesion was the nose (100%), oropharynx (83.3%), skin (75%), larynx (50%) and less commonly, nasopharynx (41.6%) and lacrimal sac (25%). One patient underwent surgery four times (8.3%), followed by thrice and twice by five (41.6%) and six (50%) patients, respectively. On two years of follow-up, two patients (16.6%) had a recurrence in the nose and larynx whereas eight patients (66.6%) had no recurrence and two patients (16.6%) were lost to follow-up.

**Conclusion:** This original article highlights the rare occurrence of disseminated rhinosporidiosis, the possibility of which should be kept in mind, mainly when two or more sites are involved. The most significant number of disseminated rhinosporidiosis cases in the literature is reported here. Dissemination with the cutaneous and multisite disease is rarely reported and poses difficulty in management. Early diagnosis and intervention prevent the dissemination of spores into various parts of the body.

**Keywords:** Rhinosporidiosis, disseminated infections, cutaneous manifestations, nasopharyngeal diseases, disease management, tertiary care centers, otolaryngology

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## Introduction

Rhinosporidiosis is one of the differential diagnoses for nasal mass with epistaxis. It is a chronic granulomatous disease that is endemic in South India. Malbran first identified the causative organism, but Guellermo Seeber described its structure and named it *Rhinosporidium seeberi* (1).

It mainly involves mucosal surfaces of the nose, nasopharynx, and oropharynx (70–75%), followed by the eye (15%), skin, or disseminated areas. The floor of the nose and inferior turbinate are the most common sites of involvement; the lesions may appear elsewhere too. Three or more sites involved in the disease is labeled as disseminated rhinosporidiosis. The organism enters the body via traumatized epithelium followed by the formation of microcysts and its local replication. This is associated with localized immune response and host cell hyperplasia. No host immunity against the organism has been noted. Dissemination to other sites may be due to autoinoculation, hematogenous or lymphatic spread (2). Satellite lesions are seen adjacent to the lesions because of autoinoculation. The diagnosis is based on strong clinical suspicion whereas histopathology confirms the diagnosis. This retrospective study highlighted the largest number of disseminated rhinosporidiosis cases reported in the literature. Additionally, it described cases of dissemination involving cutaneous and multisite disease, and detailed how we managed patients with disseminated rhinosporidiosis.

## Methods

From retrospective data collection, 127 patients had isolated rhinosporidial lesions. Being a tertiary hospital, disseminated cases were referred to our center. This was a retrospective study of twelve patients treated for disseminated rhinosporidiosis at our institution from 2007 to 2020. The age groups of patients in the study were 30–55 years and predominantly males (male: female 11:1). Informed consent and ethical committee approval were obtained. The patients were presented with varied symptoms (Table 1). On examination, almost all patients (n=100%) noted a pink polypoidal lesion in the nasal cavity and

oropharynx (Figure 1). Diagnostic nasal endoscopy was done in all patients showing a pinkish polypoidal, friable mass with yellow spots that bled on touch. One patient (n=8.3%) had left medial canthal swelling associated with epiphora (Figure 2). The visual acuity and extraocular movements were normal. There was a regurgitation of fluid from the puncta after giving pressure over the swelling, indicating lacrimal sac disease. Around six patients (n=50%) presented with either hoarseness or breathing difficulty. The larynx showed polypoidal lesions on direct laryngoscopy involving true cords at the anterior commissure without compromising the airway (Figure 3). Cutaneous lesions (n=75%) showed warty papules or nodules with crusting, bleeding, and whitish spots on the surface (Figure 4). One of the patients presented with nasal obstruction, multiple cutaneous papules over the face, chest, abdomen, and back and calf swelling (Figure 5). Blood investigations were normal, and serology reports (HIV, HbsAg and HCV) were negative. All patients underwent surgical excision and electro-desiccation of the base of the lesion under general anesthesia. The patients with airway involvement were managed using spontaneous anesthetic techniques and surgical procedures. In patients with laryngo-tracheal lesions, excision with microlaryngeal surgery (MLS) was performed. Histopathological examination showed numerous sporocysts in various stages of maturation with surrounding vessels, suggestive of *Rhinosporidium seeberi* (Figure 6). Peroral dapsone (100 mg/day) was given for one year for all disseminated rhinosporidiosis patients after surgery. All patients were followed up for two years.

## Results

This is a retrospective study of disseminated rhinosporidiosis from 2007 to 2020. Twelve cases were diagnosed with disseminated rhinosporidiosis over this period (Table 2). The findings and patient characteristics are summarized in Table 2. There were eleven male patients and one female patient. The history of taking baths in ponds was present in 50%. One patient underwent surgery four times (8.3%), followed by thrice and twice by five (41.6%) and six (50%) patients, respectively. On two years of follow-ups, two patients (16.6%) had a recurrence in the nose and larynx whereas eight patients (66.6%) had no recurrence and two patients (16.6%) were lost to follow-up.

## Discussion

Rhinosporidiosis was first described in Argentina (3). The causative organism, *Rhinosporidium seeberi*, is a cryptic microbe. Still, it belongs to the human pathogen, Mesomycetozoa, which includes Dermocystidium, Rosette agent, Ichthyophonous and Psorosperminum clade parasite, depending upon its phylogenetic analysis of the *18sRNA* gene (4). *Cyanobacterium Microcystis aeruginosa* had been reported as the causative agent for rhinosporidiosis (5).

**Table 1.** Patient symptoms

Symptoms	% of patients (n=12)
Nasal obstruction	100 (12)
Snoring and mouth breathing	91.6 (11)
Epistaxis	100 (12)
Hoarseness or breathing difficulty	50 (6)
Watering of eyes	25 (3)
Skin lesions	75 (9)
Eye swelling	8.3 (1)
Calf swelling	8.3 (1)



**Figure 1.** Shows a pink polypoidal lesion in the nose and oropharynx

**Table 2.** Presentation and outcome of 12 cases with their presentation and outcome

S. no	Age/sex	Sites of lesion	Pond bathing	Number of procedures	Outcome
1	30/M	Nose, nasopharynx, oropharynx, larynx, skin	No	3	No recurrence
2	43/M	Nose, nasopharynx, oropharynx, larynx	No	4	No recurrence
3	64/M	Nose, oropharynx, lacrimal sac, skin	Yes	2	No recurrence
4	45/F	Nose, oropharynx, larynx, trachea	Yes	3	Recurrence in larynx
5	37/M	Nose, oropharynx, skin	Yes	3	Lost to follow-up
6	47/M	Nose, oropharynx, lacrimal sac, skin	No	3	No recurrence
7	39/M	Nose, nasopharynx, oropharynx, larynx, skin	No	3	No recurrence
8	34/M	Nose, oropharynx, larynx, skin	No	2	No recurrence
9	46/M	Nose, nasopharynx, oropharynx, skin	No	2	No recurrence
10	39/M	Nose, oropharynx, larynx	Yes	2	Recurrence in nose
11	53/M	Nose, lacrimal sac, skin	Yes	2	Lost to follow-up
12	30/M	Nose, nasopharynx, skin, calf swelling	Yes	2	No recurrence

M: Male, F: Female

Rhinosporidiosis is endemic in South India, Sri Lanka and Africa. The endemicity is high temperature and humidity, favouring the development of spores. It spreads through contaminated water and soil and enters the body via minor abrasions. Our patients had a history of pond bathing contaminated with spores (6). It most commonly affects men more than women. It enters the body as trophozoite (6–8 μm), develops into immature and mature sporangia, and is released as free electron-dense bodies.

Manifestations of the disease can be nasal, ocular, cutaneous, and disseminated (1,7). Autoinoculation, hematogenous, and lymphatic spread are the routes of spread of spores. The nose and pharynx is the most common site of inoculation via minor abrasions (trans epithelial infection) over the mucosal surfaces (8). Kirkpatrick (9) published the first case of lacrimal sac rhinosporidiosis in 1912. Ocular rhinosporidiosis occurs because of the spread of infection through the nasolacrimal duct. Mishra et al. (3) reported a lacrimal sac rhinosporidiosis who underwent

dacryocystorhinostomy followed by peroral dapsone 100 mg once a day for one year.

Out of 127 patients with rhinosporidiosis, 12 patients had disseminated disease at the time of presentation. Studies discussing disseminated cases were quite low. Our disseminated cases were mostly from endemic areas. The chance of recurrence increases proportionately with inadequate removal, bleeding, surgical techniques, and injury to nearby tissues. The dissemination could be because of surgical techniques used in the previous surgeries and endemic factors. Recurrence rates following surgical and medical therapy are quoted in the literature as 5–63%. This indicates the risk of dissemination of spores into the submucosa during surgery. The host factors and endemicity also contribute to dissemination and recurrence.

The clinical symptoms include nasal obstruction and epistaxis (nasal); epiphora and swelling (ocular); snoring, mouth breathing, and dysphagia (pharyngeal); stridor,



hemoptysis, and voice change (laryngeal). Cutaneous rhinosporidiosis results in satellite lesions, generalized cutaneous (hematogenous) or primary cutaneous lesions (autoinoculation). All 11 patients (n=100%) had a nasal obstruction. Daharwal et al. (10) reported a rare case of laryngeal rhinosporidiosis who underwent MLS excision. Usage of CO<sub>2</sub> or KTP laser aids in the complete excision of the lesion by providing proper visualization with better clearance margins, causing minimal trauma, reducing intra-operative bleeding, decreasing the chance of recurrence due to less contamination with spores, eliminating direct contact with the lesion, and ensuring good postoperative voice quality (11).

Ali et al. (12) reported a case with nasopharyngeal rhinosporidiosis extending to the oropharynx, whose main complaint was something stuck in the throat like a foreign body. The patient underwent an excisional biopsy and was disease-free after surgery (12,13). Clinical examination reveals a pinkish polypoidal mass studded with yellow spots, with typical strawberry-like regions that are friable and bleeds on touch. Nasopharyngeal polyps often have a variegated appearance and are multi-lobed (12,13). Prasad et al. (14) reported a case of disseminated cutaneous rhinosporidiosis

with nasal and pharyngeal lesions who underwent surgical excision and became disease free after one year of peroral dapsone use.

Computed tomography (CT) and magnetic resonance imaging have a limited role in the diagnosis but help in the preoperative extent of the disease and surgical excision planning. CT dacrocystography helps in identifying lacrimal sac involvement (15).

Histopathological examination confirms the diagnosis of rhinosporidiosis (16). It has characteristic features of numerous sporocysts at various stages of development and the stromal and cellular reaction of the host as well. The absence of Splendore-Hoeppli (antibody-mediated) eosinophilic deposit around rhinosporidial bodies differentiates it from other mycelial infections because these patients have high antibody titres (16).

The differential diagnoses include coccidiomycosis, warts and verrucous tuberculosis, pyogenic granuloma, hemangioma, condyloma acuminata, and lacrimal sac tumour or mucocele (1,13). The standard treatment is surgical excision of the lesion and electrocautery at the base. The laser can also be used to excise lesions with less chance of recurrence. Multiple site involvement requires single or multiple surgeries. The site involved first should be operated first because the epicentre will be at that site. Multiple site involvement requires surgery addressing the inferior site to the superior site to prevent contamination with spores to other sites and for better visualization without bleeding from the superior site. Localised disease usually will be cleared by surgery. But disseminated cases presents with recurrence more often and our patients also underwent multiple surgeries for disease clearance. Powered



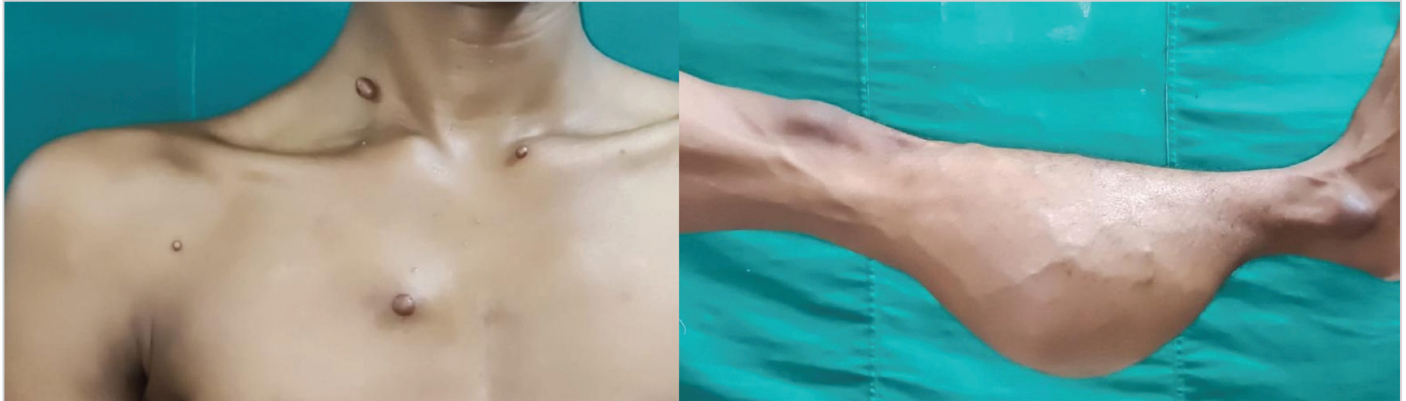
**Figure 2.** Shows left medial canthal swelling



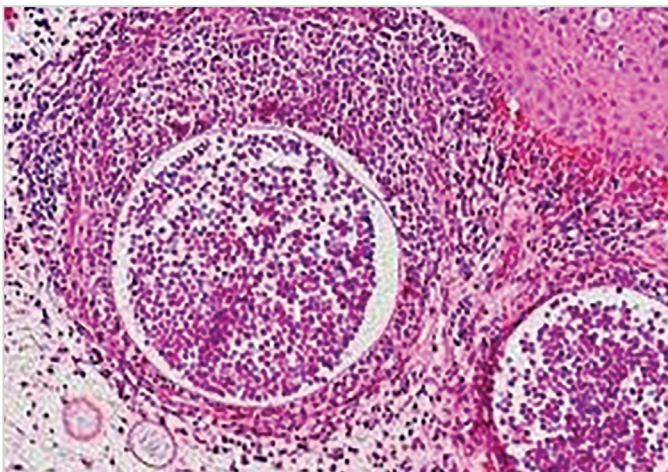
**Figure 3.** Shows cutaneous lesions



**Figure 4.** Shows a lesion at the anterior commissure on direct laryngoscopy



**Figure 5.** Shows multiple cutaneous lesions and calf swelling



**Figure 6.** H&E stain of specimen (x400 magnification) showing hyperplastic epithelium with numerous sporangia in different stages of development and there is a surrounding dense, mixed inflammatory infiltrates

H&E: Hematoxylin and eosin

instruments like coblation and harmonic scalpel are useful in preventing dissemination of spores during surgery and thereby recurrence. These instrument help in the complete removal and keep the surrounding tissues intact without any injury (17).

Spontaneous regression of the lesions is rare. Since the organism could not be propagated *in vitro*, the sensitivity of testing of the drugs is not possible (2). Anti-fungal drugs like amphotericin B, ketoconazole, and dapsone and antibiotics like ciprofloxacin were tried, but dapsone is proven more effective. Cycloserine, an anti-tubercular drug can also be used. Dapsone (diaminodiphenyl sulfone) appears to arrest the maturation of spores and induce stromal fibrosis by accelerating degenerative responses (18). Our patients also responded well to peroral dapsone, which was given for one year. Eight patients (66.6%) had no recurrences on two years follow-up, whereas two patients (16.6%) had a recurrence in

the nose and larynx. None of the patients had been tried only with medical therapy. All of our patients either localised or disseminated underwent surgery. But disseminated cases only were given peroral dapsone for one year. Localised cases were kept under regular follow-up and recurrence rates were less. Long-course usage of dapsone may be helpful in disseminated rhinosporidiosis. But prolonged usage of dapsone results in methemoglobinemia and hemolytic anaemia. These side effects are most commonly seen in patients with glucose-6-phosphate dehydrogenase deficiency (18). But none of our patients ever experienced these complications. Multi-drug therapy can be used in disseminated rhinosporidiosis. This will help in reducing the size of visceral and subcutaneous lesions and the disappearance of friable lesions. The disease's recurrence rate is high because of incomplete removal, reinfection and lack of oral medications. Disseminated cases requires multiple revision surgeries and regular follow-up (17,18).

## Conclusion

This original article described how the disseminated rhinosporidiosis cases were managed successfully without affecting the quality of life-avoiding a bath in stagnant water or ponds, proper hygiene, and early diagnosis and treatment to help prevent dissemination or autoinoculation of spores.

**Informed Consent:** Obtained from the patients for participation.

## Authorship Contributions

Surgical and Medical Practices: K.R., S.T., A.A., L.K.P., S.K.S., Concept: K.R., Design: K.R., S.T., A.A., L.K.P., S.K.S., Data Collection and/or Processing: K.R., S.T., A.K., B.H.S., R.K., Analysis and/or Interpretation: S.T., A.A., L.K.P., S.K.S., Literature Search: S.T., Writing: S.T., A.K., R.K.

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### Main Points

- Disseminated rhinosporidiosis is a mucocutaneous chronic granulomatous disease.
- The causative organism is an aquatic protistan parasite, *Rhinosporidium seeberi*, that belongs to the class Mesomycetozoa.
- Stagnant water contaminated with spores is the source of infection.
- Dissemination occurs through autoinoculation, hematogenous or lymphatic spread.
- This organism could not be grown in culture media. So, antimicrobial or anti-fungal therapy is ineffective.
- Dissemination with the cutaneous and multisite involvement is rarely reported and poses difficulty in management because it requires multiple surgeries, long term medical therapy and regular follow-up.

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# Angiosarcoma Arising in a Vagal Schwannoma - Report and Literature Review

## Case Report

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## Abstract

Schwannoma and angiosarcoma are rare occurrences. Angiosarcoma's occurrence in a preexisting schwannoma is a very rare event with only fifteen cases reported in the literature. We report the sixteenth case of angiosarcoma arising in a schwannoma, a 30-year-old male patient with a long-standing (15 years) history of right neck lump. The lump measured around 10x7 cm at the time of presentation and all cranial nerves were intact. We performed a fiberoptic laryngoscopy and a computed tomography scan of the head and neck with contrast. Our provisional diagnosis was a parapharyngeal space neoplasm, most likely a salivary gland malignancy. The tumor was excised surgically. On histopathology it contained two distinct tissue architectures representing a schwannoma and epithelioid angiosarcoma, also confirmed on immunohistochemistry. Literature review of these limited cases implicates a poor prognosis of the disease. The pathogenesis is uncertain, but the theories put forward suggest chronic vascular stasis or vascular endothelial proliferation as possible etiologies. The main takeaway of our report is to consider the potential of malignancy in long standing cases of schwannomas. Prompt surgical treatment should be offered, and the patient and their family be counselled for postoperative adjuvant treatment for better prognosis.

**Keywords:** Angiosarcoma, schwannoma, malignant peripheral nerve sheath tumors, neck, surgery, immunohistochemistry, case report

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## Introduction

Schwannomas are slow growing, painless benign peripheral nerve tumors with a distinct morphology on microscopy. It is extremely rare for schwannomas to undergo malignant transformation. Among these, malignant peripheral nerve sheath tumors (MPNSTs) are the most common variety with angiosarcoma being the least common (1). Peripheral nerve sheath tumors are more commonly

associated with neurofibromatosis type 1 (2, 3).

The majority of MPNST cases and all cases of angiosarcoma arising in schwannoma have an epithelioid morphology (4). There still is no explanation for this finding. Throughout the literature so far, only fifteen cases have been reported. To the best of our knowledge, this is the sixteenth such case and the seventh case arising in a vagal nerve schwannoma.



## Case Presentation

A 30-year-old male patient was referred to our ENT outpatient department with a long-standing (15 years) history of a right neck lump. It was insidious in onset with gradual progression. He started experiencing a change in voice (hot potato voice) about eight years back. One year later, he started experiencing dysphagia. Examination showed a huge right-sided neck mass approximately 10x7 cm. A scar mark was seen on the most prominent part of the lump due to an incisional biopsy attempted at another center, which was inconclusive. Fiberoptic laryngoscopy showed a bulge in the nasopharynx, but the gag reflex and bilateral vocal cord mobility were normal. All cranial nerves were normal on examination. Computed tomography (CT) scan (Figure 1) showed a soft tissue density mass measuring 8.0x8.5 cm extending from the skull base to the level of cervical vertebrae C5, causing partial luminal narrowing of the airway and lateral displacement of the carotid sheath. We considered various parapharyngeal space tumors in differential diagnosis based on the findings.

A surgical excision was performed, and the mass was removed in toto. Perioperatively the mass was well encapsulated (Figure 2), displacing contents of the carotid sheath laterally but was not adherent to any surrounding structures. Postoperatively, the patient had an uneventful recovery.

On gross histopathological examination, the tumor measured 11.5x9x6 cm with the overlying skin ellipse measuring 9x3 cm. It was well-circumscribed, reddish, hemorrhagic, and friable. On microscopic examination two distinct different components were seen. Several sections of the tumor revealed necrotic tissue exhibiting spindle cell lesion arranged in sheets with wavy and hyperchromatic

nuclei (Figure 3). These cells stained positive with S-100 on immunohistochemistry (IHC) (Figure 4). Verocay bodies, diagnostic for schwannoma were also seen.

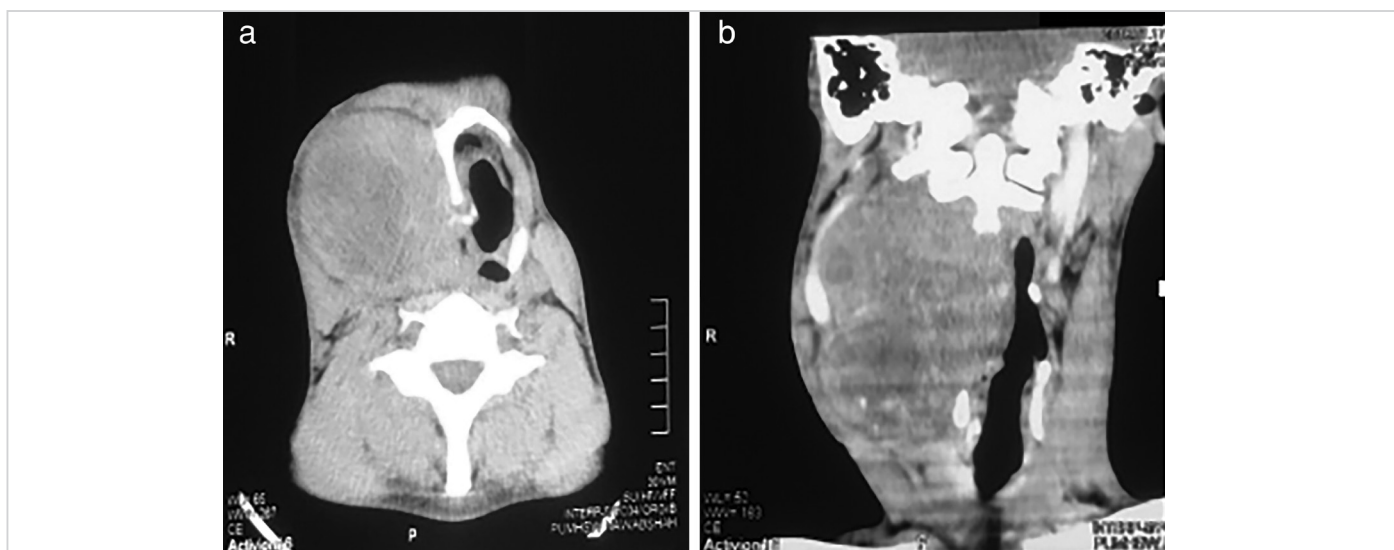
The second component exhibited polygonal cells that had a moderate amount of eosinophilic cytoplasm with round to oval, hyperchromatic nuclei with mitotic figures raising the suspicion of a vascular tumor (Figure 3). IHC on epithelioid cells showed high proliferative activity (Ki-67 >10%), positive CD-31, and erythroblast transformation specific related gene (ERG)-which are markers for vascular tissue-however, negative CD-34, P63, S-100 and Cytokeratin 5/6. Hence, the diagnosis of epithelioid angiosarcoma arising in a schwannoma was made.

Based on the diagnosis, postoperative positron emission tomography/CT scan was advised to plan the patient for adjuvant concurrent chemoradiotherapy. Despite repeated efforts to contact the patient and his family, he was lost to follow up.

Written consent was taken from the patient after histopathology report was finalized to report this case.

## Discussion

Schwannomas are benign peripheral nerve sheath tumors. Approximately 25-45% occur in the head and neck region with parapharyngeal space being the most common site extracranially involving the vagus, the glossopharyngeal and phrenic nerves more commonly (5). These are slow growing tumors with evidence of degeneration in long standing cases. Malignant transformation is a rare occurrence and should be documented as a case report. The dominant presenting feature in these patients is a painless mass with hot potato voice in only one patient.



**Figure 1.** Computed tomography scan showing a large, heterogeneous mass with intact surrounding fat planes. a) Axial image at the level of hyoid bone, b) coronal image

The histogenesis of angiosarcoma arising in a schwannoma remains indistinct. Since the epithelioid component also stains positively for S-100, it is hypothesized to arise from the malignant transformation of differentiated neoplastic Schwann cells (6). Various theories have been put forward to explain its origins. Chronic vascular stasis in longstanding cases of schwannoma was proposed as a means of pathogenesis of angiosarcoma by Rückert et al. (7). On the other hand, Trassard et al. (8) found Weibel-Palade bodies in the cytoplasm of epithelioid cells by means of electron microscopy. They suggested that these could have arisen from pre-existing vascular tissue in schwannoma. The presence of

vascular endothelial growth factor in Schwann cells on IHC has been implicated in another study (3).

Since 1996 when the first case was described by Trassard et al. (8), only 15 patients of angiosarcoma in a schwannoma have been reported. None of these had an association with NF 1 or 2. Among these, six were reported in the neck, making it the most common site. All of these originated on the right side of neck except one and all arose in vagus nerve except one from phrenic nerve. The mean age is 55 years, the size of the tumor ranges from 2.5 to 11 cm with median at 6 cm. Interestingly, in our case, the patient belonged to a younger age group with a larger tumor size at 11.5 cm in comparison to other reported patients (Table 1).

Differential diagnosis in our patient would include epithelioid MPNST and epithelioid malignant change (9). The presence of high proliferative activity as indicated by the Ki-67 index, is common in these tumors as is the presence of S-100 positivity. But the positive staining of CD-31 and ERG delineates the angiosarcoma on IHC.

The available literature on angiosarcoma arising in a schwannoma indicates poor prognosis due to rapid local growth, high rate of recurrence and early distant metastasis. Of the reported cases, three patients developed local recurrence, four developed distant metastasis and two patients died of the disease. The recognized causes of poorer outcomes are large tumor size, capsular penetration and incomplete resection (10). Understandably, there is no large

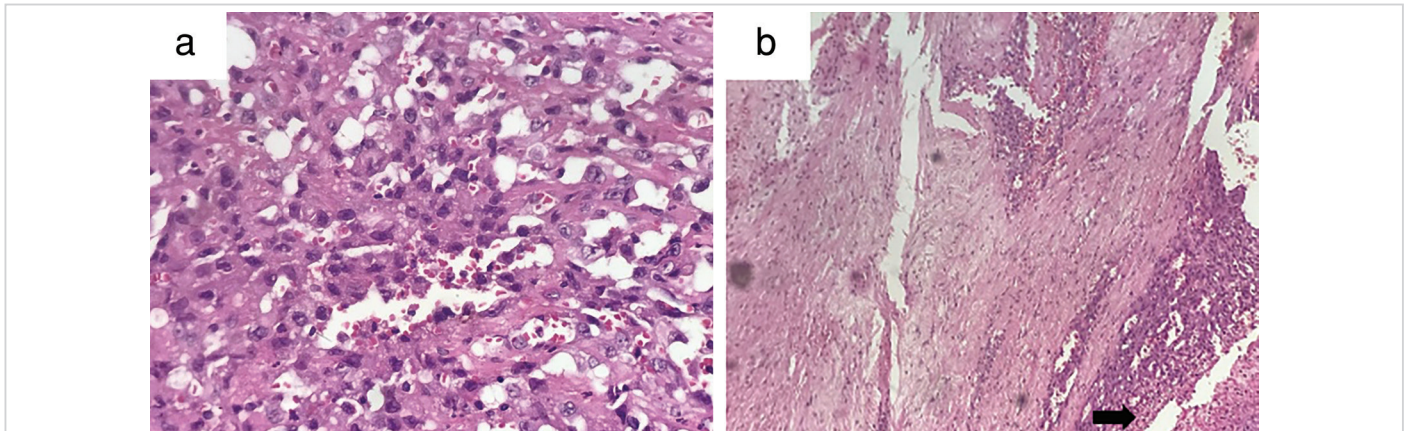


Figure 2. Tumor specimen postoperatively with overlying skin

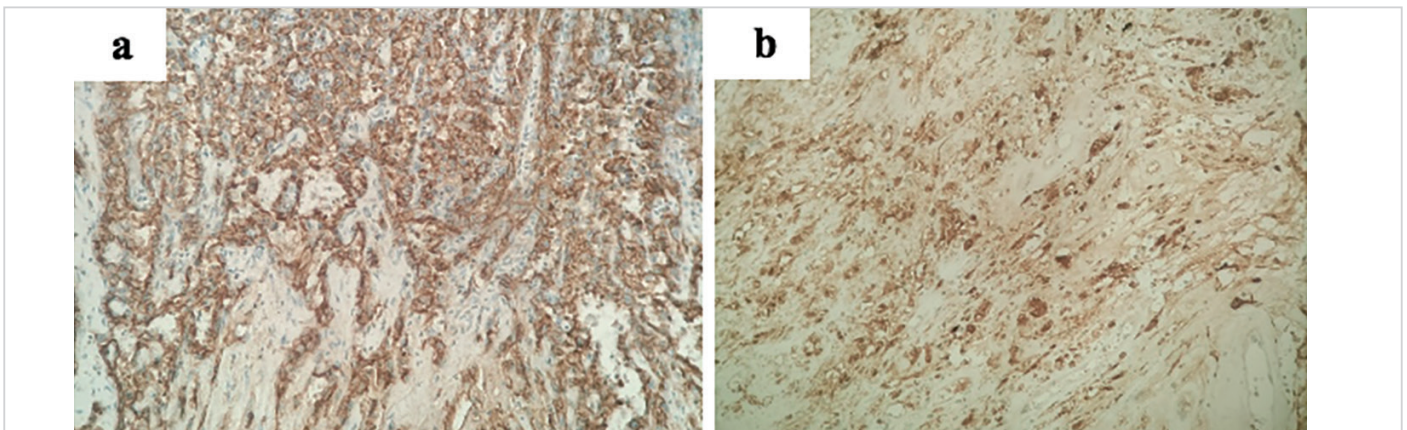
Table 1. Reported cases of angiosarcoma in a schwannoma

Sr No.	Case	Age (years)	Sex	Size (cm)	Site	Presentation	Treatment	Outcome
1	Mentzel and Katenkamp (3)	73	F	5x4.5x4	Rt. neck vagus nerve	Long standing mass	Surgery	NED at 43 months
2	Mentzel and Katenkamp (3)	63	M	4x3x2	Rt. neck vagus nerve	Bulge in oropharynx, long standing mass	Surgery + RT	Death with disease at 5 months
3	Rückert et al. (7)	50	M	4.5x3.5x3.5	Rt. neck vagus nerve	Neck mass for six months	Surgery	NED at 27 months
4	McMenamin and Fletcher (9)	74	F	5.5x4.5x4	Rt. neck vagus nerve	Neck mass for 30 years	Surgery	NED at 6 months
5	McMenamin and Fletcher (9)	17	F	6	Rt. neck phrenic nerve	Dyspnea on exertion for one year, swelling right neck for two weeks	Surgery + RT + CH	Death with distant metastasis at 14 months
6	Li et al. (10)	55	M	6x5x5	Lt. neck vagus nerve	Left neck mass for more than four years	Surgery	NED at 32 months
7	Mahajan et al. (1)	41	M	11x6.5x3.5	Lt. neck vagus nerve	Left neck mass for 12 years	Surgery + CH	Death with distant metastasis at 4 months
8	Current study	30	M	11.5x9x6	Rt. neck vagus nerve	Right neck mass for 15 years, change in voice for eight years, dysphagia for seven years	Surgery	Lost to follow up at 3 months

M: Male, F: Female, N/A: Information Not available, Rt.: Right, Lt.: Left, CH: Chemotherapy, RT: Radiotherapy, NED: No evidence of disease



**Figure 3.** Hematoxylin and Eosin staining. Epithelioid angiosarcoma cells arranged in nest with marked vascularity. Cells are polygonal with moderate eosinophilic cytoplasm and round to oval nuclei (a) 40x. Spindle-shaped schwannoma cells lesion arranged in sheets, nuclei are wavy and hyperchromatic with Verocay body formation. Arrow indicates vascular lesion (b) 20x



**Figure 4.** IHC. a) CD-31 was positive in endothelial cells, b) Cytoplasmic and nuclear components show S-100 positivity in Schwann cells  
IHC: Immunohistochemistry

scale study to compare the various modes of treatment, but the most advocated approach is wide local excision followed by postoperative radiation +/- chemotherapy (7, 9).

Epithelioid angiosarcoma is a rare neoplasm with an unknown pathogenesis and a very poor prognosis. A painless lump causing dysphagia is the usual presentation in the neck. It is characterized by sheets of epithelioid endothelial cells that can imitate several epithelioid malignancies. Histopathological examination with IHC remains the gold standard of diagnosis. Early and complete surgical excision of the primary tumor is imperative. Adjuvant radiation therapy and chemotherapy may also contribute to prolonging survival. Patient and family should be counselled regarding the aggressive nature of the disease to ensure regular follow ups postoperatively.

**Informed Consent:** Written consent was taken from the patient after histopathology report was finalized to report this case.

#### Authorship Contributions

Surgical and Medical Practices: Z.A.S., I.A.M.K., Concept: Z.A.S., I.A.M.K., P.N., Design: Z.A.S., P.N., H.A., Data Collection and/or Processing: Z.A.S., A.D., P.N., H.A., Analysis and/or Interpretation: Z.A.S., I.A.M.K., A.D., P.N., Literature Search: Z.A.S., A.D., H.A., Writing: Z.A.S., A.D., P.N., H.A.

**Conflict of Interest:** There is no conflict of interest to disclose.

**Financial Disclosure:** The authors declared that this study has received no financial support.

### Main Points

- Vagal schwannomas are rare entities and management is often delayed due to non-peculiar symptoms.
- Angiosarcomas are also rare vascular tumors and are seldom associated with vagal schwannomas; to date, only 15 cases have been reported in the literature.
- Surgical management is the mainstay of treatment along with adjuvant concurrent chemoradiotherapy.
- Long term outcomes indicate poor prognosis due to rapid local growth, high rate of recurrence and early distant metastasis.

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# IgG4-Related Disease Involving the Ear: A Case Report

## Case Report

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## Abstract

IgG4-related disease is a chronic inflammatory disease with widespread clinical presentation. It mimics various malignant, infectious, and inflammatory conditions, leading to confusion in diagnosis and management. Otological manifestations, though relatively rare, can lead to significant complications.

A 45-year-old male with a recent history of ventilation tube placement in the right ear presented with a sensation of imbalance associated with profound hearing loss. He was managed in line of acute otitis media with labyrinthitis with steroids and antibiotics and removal of the ventilation tube. He returned in one week and presented with right-sided lower motor neuron-type facial paresis. Computed tomography images of the temporal bone showed a soft tissue density lesion in the right middle ear cavity extending to the mastoid antrum. He underwent a right cortical mastoidectomy with decompression of the facial nerve. Histopathology and immunohistochemistry of granulation tissues from the middle ear and the mastoid revealed evidence suggestive of probable IgG4 disease.

IgG4-related disease is a relatively new entity, and its pathogenesis has not been properly understood. IgG4 subclass has been involved in this disease resulting in fibro-inflammatory conditions leading to tumor-like masses or fibrosis of the affected organs. Treatment includes glucocorticoids and immunosuppressant medications.

**Keywords:** IgG4 related, chronic inflammation, facial nerve palsy, vertigo

## Introduction

IgG4-related disease presents with widespread unspecific symptomatology. It is an immune-mediated chronic inflammatory process and mimics various malignant, infectious, and inflammatory conditions (1). This leads to a diagnostic dilemma and inadequate management of the condition. In otolaryngology, salivary and lacrimal gland involvement is more common. The condition has favorable outcomes if treatment is initiated early. Recurrences are common and delay in treatment can lead to severe multi-

organic complications (2). Otological manifestations, though relatively rare, can also lead to significant complications.

## Case Presentation

A 45-year-old male with no chronic illnesses presented with a history of sensation of imbalance for four days. He had a history of ventilation tube insertion in his right ear one month before. On examination, the tympanic membrane was dull on the right side and the ventilation tube was in-situ. The audiogram revealed profound sensorineural-type hearing loss

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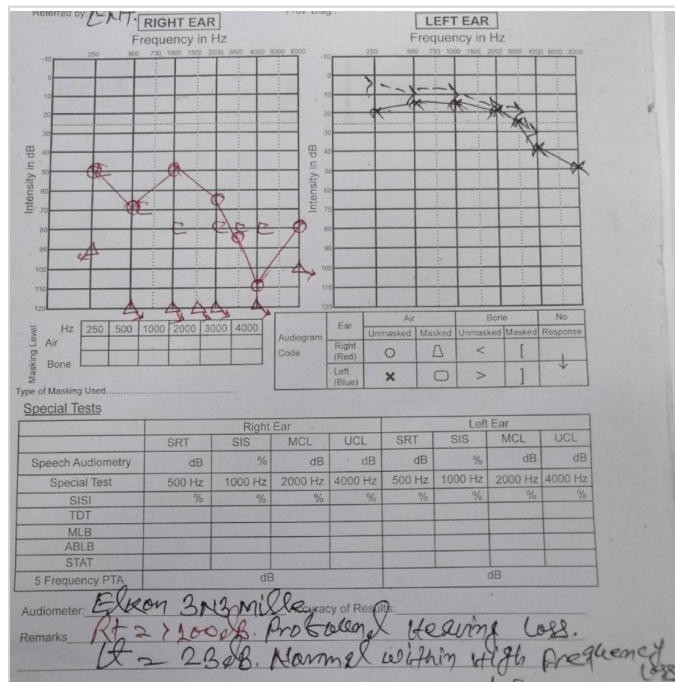
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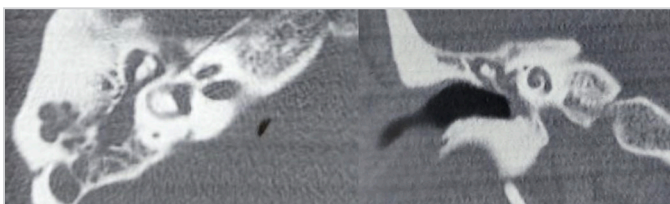


on the right side (Figure 1). Magnetic resonance imaging of the brain revealed normal findings. Systemic examination and investigations were done to rule out other conditions. He was admitted with intravenous antibiotics and steroids in line of labyrinthitis. His ventilation tube was removed. The sensation of imbalance gradually improved and was discharged after one week of hospital stay.

He presented again one week later with a right-side lower motor neuron-type facial paresis (House-Brackmann Grade III) (3). He was admitted with intravenous antibiotics and steroids. Computed tomography images of the temporal bone showed a soft tissue density lesion in the right middle ear cavity extending to the mastoid antrum (Figure 2). He underwent a right cortical mastoidectomy with decompression of the facial nerve. The surgery revealed granulation tissues in the middle ear and mastoid cavity. The tympanic and mastoid segments of the facial nerve were traced and found intact. The dural plate, the sinus plate, and the dome of the lateral semicircular canal were intact. The ossicles were intact and mobile. Granulation tissue was sent for histopathological



**Figure 1.** Audiogram of the patient showing profound sensorineural hearing loss in right side



**Figure 2.** Axial and coronal computed tomography scan of the patient showing soft tissue density lesion in the middle ear, the aditus and the mastoid antrum

examination. Gene Xpert of the tissue specimen came out to be negative. Right middle ear granulation tissue biopsy reports revealed keratinizing stratified squamous epithelium bony tissue and fibrocartilaginous tissue fragments showing abundant lymphoplasmacytic infiltration without evidence of granuloma, obliterative phlebitis and malignancy (Figure 3).

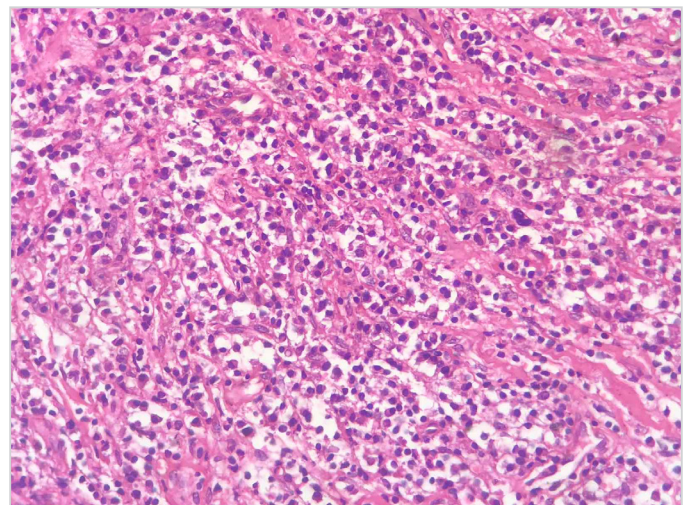
Immunohistochemistry showed 50/hpf plasma cells with IgG4 expression and 80/hpf plasma cells with IgG expression. The IgG4/IgG ratio was 62.5%. Diagnosis as probable IgG4 disease was done. He was started on oral steroids and methotrexate along with rituximab injection after consultation with a rheumatologist. After six months of diagnosis and initiation of treatment, his facial paralysis has gradually been recovered and there is no sensation of vertigo. The condition of hearing loss is static.

Systemic screening was done after the disease was diagnosed and no other focus was seen.

An informed consent form was signed by the patient to publish this case.

## Discussion

Facial paralysis usually occurs due to Bell's palsy or a traumatic temporal bone fracture. Radiographic evidence of penetrating injury to the nerve, as in open full-thickness incision in trauma-induced paralysis, is an indication for surgical exploration, decompression, and repair with primary neuroorrhaphy or grafting, depending on the situation. Apart from this, the treatment of a facial nerve palsy secondary to trauma is similar to that of Bell's palsy. Surgical intervention is considered in patients with Bell's palsy or traumatic facial nerve palsy who have complete paralysis within 14 days of onset, show more than 90% degeneration on electroneurography testing, and have no electromyographical



**Figure 3.** Microscopic image of tissue showing dense inflammatory infiltrates and fibrosis (Hematoxylin and Eosin, 40x)

activity (4). In our center, however, mastoid and tympanic segment decompression is performed on all patients who undergo mastoid exploration due to facial paralysis, regardless of the degree of paralysis. Therefore, in the presented case, the first mastoid exploration and subsequent decompression of the tympanic and mastoid segments of the facial nerve were performed.

IgG4-related disease was first described with involvement of the pancreas more than two decades ago. Since then, it has been practically reported in almost all organs in the head and neck.

The first otological involvement was described in 2010 and since then mastoid has been the most frequent location to be involved in the ear (5).

Below 5% of the total IgG antibody is said to be of IgG4 type in healthy individuals. IgG4 response is initiated after prolonged and recurrent exposure to antigens. One distinctive feature of the IgG4 antibody is its capacity for a half-antibody exchange reaction, whereby the IgG4 antibody readily creates disulfide bonds within the hinge region of its heavy chains. Dissociation of non-covalent bonds allows the chains to separate and randomly recombine leading to the formation of asymmetric antibodies with two different antigen-binding sites. Consequently, the resulting bispecific IgG4 molecules are incapable of cross-linking antigens, thereby forfeiting their ability to generate immune complexes. Also, unlike other IgG subclasses, its amino-acid difference leads to an ineffective complement activation pathway (6).

Pathogenesis of IgG4-related disease has not been clearly understood. But as the name suggests, the IgG4 subclass has been involved in this disease resulting in fibro-inflammatory condition leading to tumor like masses or fibrosis of affected organs. It has been proposed that a collective effect of cytotoxic T lymphocytes and IgG4 antibody causes inflammation leading to fibrotic phase in which pro-fibrotic cytokines are secreted. Resultant activated fibroblasts deposit extracellular matrix, giving rise to dense stratal reaction which is responsible for distorting tissue architecture. This distortion can lead to organ dysfunction and may also culminate in organ failure (7).

Revised comprehensive diagnostic criteria for IgG4-related disease is based on clinical/radiological component, serological evaluation, and pathological assessment (8).

Clinical/radiological criteria: presence of diffuse or localized swelling in one or more organs  
Serological criteria: serum IgG4 levels greater than 135 mg/dL.

Pathological criteria: presence of at least two of following three criteria:

a. Dense infiltration of lymphocyte and plasma cells combined with fibrosis,

b. Ratio of IgG4-positive plasma cells to IgG-positive cells greater than 40% with more than 10 IgG4-positive plasma cells per high power field,

c. Presence of characteristic tissue fibrosis, especially storiform fibrosis or obliterative phlebitis.

Definitive diagnosis consists when all clinical/radiological, serological and pathological criteria are met. Positive pathological criteria along with clinical/radiological features are classified as probable IgG4-related disease. Positive serological criteria along with clinical/radiological features are classified as possible IgG4 disease.

In the management of active, untreated cases, glucocorticoids serve as the primary choice for inducing remission in all patients. Combination of glucocorticoids with steroid-sparing immunosuppressive agents such as methotrexate, azathioprine, 6-mercaptopurine, mycophenolate, tacrolimus and cyclophosphamide may be required right from the onset of treatment. This approach is chosen because glucocorticoid monotherapy may prove ineffective in controlling the disease and long-term glucocorticoids carry a significant risk of adverse effects. After a successful course of induction therapy, some patients may derive benefits from ongoing maintenance therapy with low dose glucocorticoids or steroid sparing agents (9). Induction of remission is usually done over 2-3 months and maintenance of therapy may take 6-12 months (10). Administering rituximab every 6 months as part of a maintenance therapy regimen has proven to be effective in preventing IgG4-related disease relapse (11).

IgG4-related disease is a relatively new entity, and its pathogenesis has not been properly understood. It can mimic common conditions and a high degree of suspicion is required for identification of the disease. Diagnosis is important as it has favorable prognosis if treatment is initiated early. Recurrences are common and delay in management may lead to severe complications. Adequate awareness is necessary regarding the disease condition among healthcare workers.

**Informed Consent:** An informed consent form was signed by the patient to publish this case.

#### Authorship Contributions

Surgical and Medical Practices: R.B.P., Concept: K.D., Design: U.A., Data Collection and/or Processing: U.A., Analysis and/or Interpretation: K.D., Literature Search: U.A., Writing: U.A.

**Conflict of Interest:** There is no conflict of interest to disclose.

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### Main Points

- IgG4-related disease presents with widespread unspecific symptomatology.
- It can mimic various malignant, infectious, and inflammatory conditions leading to confusion in diagnosis and management.
- Diagnosis is based on clinical features, radiology, serology, and histopathology.
- Treatment includes glucocorticoids and steroid-sparing immunosuppressive agents.
- Recurrences are common and delays in management can lead to severe complications.

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