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RESEARCH ARTICLE
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Online Attention to Cochlear Implant Research: Altmetric and Bibliometric Analysis

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ABSTRACT

Objective: Assessing the quality of scientific publications accurately and objectively is critical. This study analyzes the most cited articles on cochlear implants using altmetrics (alternative metrics) and traditional metrics.
Materials and Methods: A basic search was conducted in the Web of Science database using the term "cochlear implant." The analysis included the year of publication, years since publication, number of citations, and average number of citations per year for each publication. Additionally, the impact factor (IF), 5-year IF, Q category of the journals, and altmetric scores (ASs) were evaluated.
Results: ASs showed significant correlations with the number of citations, IF, 5-year IF, and publication year. Notably, open-access articles constituted 68% of the total. However, no significant differences were observed between open-access and nonopen-access articles concerning citations (p=0.489) or ASs (p=0.735), respectively.
Conclusion: Although altmetrics are currently viewed as complementary to traditional metrics, it exhibits potential for increased importance over time.
Keywords: Audiology, cochlear implants, bibliometrics, social media, altmetric

INTRODUCTION

Accurately and objectively assessing the quality of scientific papers is important. It assists researchers in selecting appropriate journals for publication, supports organizations in allocating funds, promotion, and faculty appointment decisions and furnishes healthcare practitioners with reliability ratings to improve patient care. Bibliometric quality indicators employ mathematical approaches to analyze and measure the impact of articles, journals, and other academic publications (1). Traditionally, article- and journal-level metrics, such as citation counts and impact factor (IF), have served as primary tools for evaluating research dissemination. However, altmetrics (alternative metrics) have emerged as unconventional means to assess the visibility and short-term social engagement of publications, complementing traditional bibliometric assessments that primarily gauge long-term impact (2).

The Altmetric Attention Score (AS), inaugurated in 2010, has swiftly gained prominence as a tool for assessing article impact (3, 4). The score reflects the frequency with which a publication is "mentioned" across various media platforms, including social media (e.g., Facebook and Twitter), newspapers, encyclopedias (e.g., Wikipedia), public policy papers, online reference managers (e.g., Mendeley and Connotea), multimedia sites (e.g., YouTube), and patents (4). Altmetrics captures audience engagements with research outputs beyond traditional citation metrics, including the complete area of interaction that clinical and scientific communities have with articles, presentations, and book chapters (5). Unlike traditional bibliometrics, altmetrics broaden the scope to include engagement from nonacademic audiences, such as patients and other interested individuals, thereby offering a more comprehensive evaluation of impact (5).

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There is a growing expectation for scientists to extend their research communication beyond academic platforms (6). Presently, social media significantly influence individual's choices regarding health services and specialists. Many individuals turn to social media platforms for information concerning health conditions (7). A survey conducted in 2021 found that 11% of Americans utilized social media for health-related information (8). Furthermore, 25% of American social media users reported that information obtained on these platforms influenced their future healthcare decisions, with 32% expressing high or very high confidence in health information disseminated through social media (9). Consequently, experts should consider the methods and frequency with which their research is communicated via social media channels.

Cochlear implants (CIs) have long been a captivating and pertinent subject within the fields of audiology and otology. However, to the best of our knowledge, there is no literature examining traditional metrics and altmetrics concerning CIs. Therefore, the objective of this study is to analyze the top 100 most cited articles on CIs in terms of altmetrics and traditional metrics.

MATERIAL and METHODS

The core collection databases of the Web of Science were accessed, and the keyword "cochlear implant" was input into the basic search section. Publications falling within the publication years 2011 and 2021 were selected. Articles were then ranked based on their citation count, from highest to lowest. This study focused on the top 100 most cited publications on CIs (see supplemental appendix for a list of articles; accessed on April 1, 2022). Inclusion criteria for this study included various subtopics related to CIs, including auditory performance, speech perception, music perception, localization, auditory memory and attention, neuroplasticity, electrophysiology, electrode properties and/or mapping parameters, language development and outcomes, cognitive, emotional, and social development, histopathology, etiology, epidemiology, depression and quality of life, auditory rehabilitation, genetics, and modeling. Topics unrelated to CIs and audiology, such as CI surgery and medical treatment options, were excluded. The evaluated parameters for each publication included the title, publication years, number of years since publication (NYP), number of citations, and average citations per year (ACY). Additionally, the IF for 2019, the 5-year IF, and the Q category of the journals in which the papers were published were examined. Information regarding article access type, study type, Scimago Journal and Country Rank category, and study population was also analyzed. ASs for the articles were obtained using the bookmark "Altmetric it!" Clicking on this bookmark presents users with a color representing the article's AS, visually indicating the types and frequency of attention garnered (Figure 1).

Statistical Analysis

Statistical analyses were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA). Initially, visual methods (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests) were used to assess the normality of the variables. Given that the numerical data did not exhibit a normal distribution according to the Shapiro–Wilk test, descriptive statistics including the median and the 25%–75% interquartile range (IQR) were utilized. Categorical data are presented as numbers or percentages. Spearman's rank correlation analysis was performed to explore the relationships among AS, number of citations, ACY, IF, 5-year IF, year of publication, and NYP. The Mann–Whitney U test was used to compare the number of citations and AS between articles categorized as open access and those that were not. Additionally, the Mann–Whitney U test was used to assess differences in ASs across publication years. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 illustrates the correlations among AS, citation number, ACY, IF, 5-year IF, publication year, and NYP. Significant correlations were observed between AS and all variables except ACY and NYP. Moreover, significant correlations were found between the number of citations and AS, IF, and 5-year IF. ACY correlated with IF, 5-year IF, publication year, and NYP. Additionally, significant correlations were observed between IF and AS, citation number, ACY, 5-year IF, and publication year.

Table 1: Correlation between traditional metrics and altmetrics

	AS	Time cited	ACY	IF	5 year IF	Publication year	NYP
AS	1	**0.256***	0.018	**0.320***	**0.328***	**0.264***	0.104
Time cited	**0.256***	1	0.004	**0.304***	**0.308***	0.109	−0.018
ACY	−0.165	0.004	1	**0.370***	**0.288***	**0.583***	**0.583***
IF	**0.320***	**0.304***	**0.288***	1	**0.975***	0.096	−0.110
5 year IF	**0.328***	**0.308***	**0.288***	**0.902***	1	0.112	−0.083
Publication year	**0.264***	0.109	**0.583***	0.096	0.112	1	**−0.996***
NYP	0.104	−0.018	**0.583***	−0.110	−0.083	**−0.996***	1

The values above the diagonal consisting of 1 value extending from the top left to the bottom right represent the "r" value, and the values below represent the "p" value. ACY: Average citation per year, AS: Altmetric score, IF: Impact Factor, NYP: Number of years since publication. *Statistically significant.

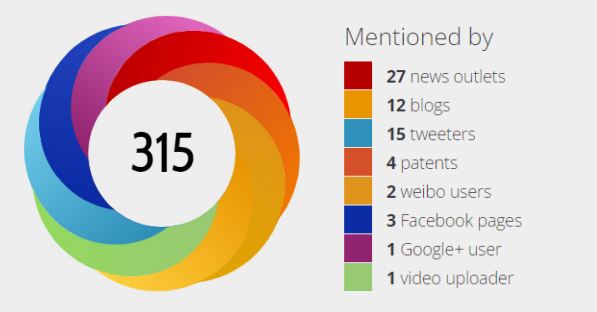

Figure 1: Altmetric donut

Similarly, 5-year IF significantly correlated with AS, citation number, ACY, and IF. Furthermore, publication year significantly correlated with AS, ACY, and NYP, whereas NYP correlated with ACY and publication year.

A Web of Science search yielded 11,680 articles on CIs published between 2011 and 2021. Among the top 100 articles, the number of citations ranged from 73 to 455. The median citation number was 91 (IQR: 80.0–113.0), whereas the median AS was 4 (IQR: 1–10). The article titled "Close-Field Electroporation Gene Delivery Using the Cochlear Implant Electrode Array Enhances the Bionic Ear" by Pinyon et al., published in Science Translational Medicine in 2014, boasted the highest AS (316) with 90 citations. Conversely, the article titled "Factors Affecting Open-Set Word Recognition in Adults with CIs" by Holden et al., published in Ear and Hearing in 2013 amassed the most citations (455) with an AS of 4.

Among the top 100 articles, the article and study types were evaluated, 74 were original research articles, and 26 were reviews. Table 2 displays the ASs and citation numbers of the top 100 articles by study type.

A total of 44 journals contributed to the publication of articles on CIs. Among them, Ear and Hearing and Otology & Neurotology had the most relevant publications, with 13 articles in the top 100, and had the highest IFs (3.57 and 2.311, respectively). According to the Scimago Journal and Country Rank category, there were 46 journals in Q1, 25 in Q2, 28 in Q3, and 1 in Q4. In Q1, the median AS was 5 (IQR: 1–21), and the median number of citations was 97.50 (IQR: 84–129.25). In Q2, Q3, and Q4, the median ASs were 3 (IQR: 2.0–7.0), 3 (1.0–5.75), and 0 (IQR: 0), respectively, and the median citations were 84 (IQR: 77.50–106.50), 89.50 (IQR: 78.25–101.0), and 88.0 (IQR: 88.0–88.0), respectively.

Among the top 100 articles, 12 were published in 2011, 19 in 2012, 28 in 2013, 21 in 2014, 8 in 2015, 8 in 2016, and 4 in 2017. No articles were published after 2017. Regarding publication years, 2014 had the article with the highest AS (316), while 2013 had the article with the highest number of citations (455) (Table 3). The median ASs of the publications before and after 2014 were 44.75 and 58.77, respectively. The difference in ASs before and after 2014 was statistically significant (p=0.017).

Open-access articles constituted 68% of the total. The median AS of open-access articles was 3 (IQR: 1–13.50), while for nonopen-access articles, it was 4.5 (IQR: 1–7.75). Similarly, the median number of citations for open-access articles was 90 (IQR: 80.25–107.75), compared to 96.5 (IQR: 79.25–130.75) for nonopen-access articles. However, no significant differences were found between open-access and nonopen-access articles regarding citations (p=0.489) or ASs (p=0.735).

Subtopics within the top 100 articles were analyzed, revealing 38 articles falling under the category of "auditory and music perception," making it the most prevalent subtopic. Following this, "electrode and/or implant properties" emerged as the next most common subtopic. Table 4 illustrates the ASs and citations of the top 100 articles organized by subtopics.

Furthermore, study populations were categorized into four groups: pediatric patients, adults, geriatric patients, and others (including animal experiments, medical devices,

Table 2: Altmetric scores and citation numbers of top 100 articles, ranked according to the study types

Study type	Number of articles	Altmetrics scores	Citations
All article	100	4 (1–10)	91 (80–113)
Original scientific paper	74	3 (1–6)	90 (80–109)
Prospective	17	6 (1–16)	106 (86–106)
Descriptive	10	4 (1–2)	79 (74–142)
Case-control	10	5 (0-NA)	105 (88-NA)
Cohort study	10	6 (0-NA)	80 (72-NA)
Retrospective	9	5 (3–26)	87 (77–133)
Cross-sectional	6	25 (16-NA)	106 (91-NA)
Animal study	6	4 (0.50–12)	134 (103.75–242.25)
Experimental	4	79.50 (79-NA)	5 (1-NA)
Methodological	2	27 (14–27)	110.50 (88-NA)
Review and meta-analysis	26	7 (3–20)	103 (79–122)

Median (25%-75% interquartile range) were used, NA: Not applicable.

Table 3: Altmetric scores and citation numbers of top 100 articles, ranked according to published years

Published years of articles	Number of articles	Altmetrics scores	Citations
2011	12	1 (0–3)	78 (76–83)
2012	19	4 (2–10)	88 (79–112)
2013	28	3 (1–8)	101 (86–123)
2014	21	4 (3–34)	94 (84–109)
2015	8	4 (2–11)	96 (79–128)
2016	8	8 (3–13)	87 (79–104)
2017	4	4 (3–13)	96 (83–104)
2018	NA	NA	NA
2019	NA	NA	NA
2020	NA	NA	NA
2021	NA	NA	NA

Median (25%–75% interquartile range) was used, NA: Not applicable

Table 4: Altmetric scores and number of citations of top 100 articles, ranked according to the study subtopics

Study subtopics	Number of articles	Altmetrics scores	Citations
Auditory and music perception	38	4 (1–16.25)	91.50 (77.75–123)
Electrode and implant properties	19	4 (1–10)	91 (84–109)
Neuroplasticity and electrophysiology	8	4.50 (1–47.75)	100 (86–119.75)
Cognitive functions, emotional and behavioral development	7	3 (2–5)	84 (74–130)
Histopathology, etiology, epidemiology, and anatomy	7	3 (0–8)	81 (78–121)
Language outcomes	6	13.50 (1-NA)	114.50 (108-NA)
Depression and quality of life	6	3.50 (0–6.75)	86.50 (78.25–148)
Genetics and modeling	4	4 (1.25–12)	113 (87.25–114)
Auditory outcomes	3	1.50 (1-NA)	79.50 (75-NA)
Auditory rehabilitation	2	81 (4-NA)	95.50 (85-NA)

Median (25%–75% interquartile range) was used, NA: Not applicable.

histopathological, cellular, etc.). Among these, 33 studies exclusively involved pediatric patients, 32 focused on adults, and 6 targeted geriatric patients. Additionally, 11 studies involved pediatric, adult, and geriatric populations, whereas 18 involved other populations. Median citation numbers for studies involving pediatric, adult, and geriatric populations were 85 (IQR: 80–107), 96 (IQR: 80–125), and 85 (IQR: 80–87), respectively. Median ASs for studies involving pediatric, adult, and geriatric populations were 4 (IQR: 1–14), 4 (IQR: 2–6), and 6 (IQR: 1–11), respectively. Interestingly, the category of "other populations" exhibited a median citation number of 305 and a median AS of 20.

DISCUSSION

This study investigated the relationship between AS and traditional bibliometrics in the CI literature. To our knowledge, this analysis stands as the only exploration of this relationship within this specialty. Our findings showed an overall correlation between traditional bibliometrics and the innovative AS, shedding light on their interplay. Notably, a correlation was observed between the number of citations and journal IF, an anticipated outcome considering IF's reliance on citation counts for its calculation.

Maggio et al. conducted a study examining the relationship between altmetrics and traditional dissemination metrics in health professions education, noting a positive association between certain altmetric outcomes and citations (10). Additionally, they found that public accessibility positively influenced article access. While significant correlations between traditional metrics and altmetrics have been observed in various fields such as urology, plastic surgery, and pediatric surgery, some scholars argue against using AS as a direct substitute for traditional metrics in evaluating scientific literature impact (2, 11, 12). This standpoint may be influenced by several factors. Notably, AS values are subject to constant fluctuations over time, as highlighted by Collins et al. (1). Furthermore, AS does not include all online platforms, leaving gaps in online attention assessment. Moreover, disparities in online attention between scientific and lay communities remain poorly understood. Differential

levels of interest exhibited by these communities toward various article types may influence correlation outcomes. Consequently, online attention may yield favorable and detrimental effects. While contentious papers might not significantly impact the scientific community, they could increase public interest, consequently elevating AS. Articles accumulating numerous citations typically exert substantial influence within the scientific community by advancing knowledge, influencing practice changes, and often serving as foundational work for further research endeavors (13).

In this study, older articles did not accrue more citations, whereas more recent publications exhibited higher ASs. This observation was likely rooted in the assumption that older articles had more time for dissemination. However, numerous factors influence citation frequency beyond publication age. One such factor is the topical interest level; articles addressing less popular topics initially tend to gain fewer citations. As interest in a given topic grows over time, newer articles may attract more citations, potentially rendering older articles outdated. This phenomenon arises from the immediate measurability of online attention compared with the gradual accumulation of citations. Furthermore, articles published after 2014 demonstrated a higher median AS compared with those published before 2014, underscoring the increasing use of social media among academics, scientists, and healthcare professionals for disseminating scientific content (14). DeAtkine et al. examined the social media presence of otolaryngology residency programs and noted substantial growth in social media utilization in 2020 compared with previous years (15). This trend implies that scientific communities leverage social media platforms to engage with the public and potential patients, which holds significance for medical practitioners, researchers, and publishers. Additionally, social media platforms serve as effective marketing tools. Moreover, research indicates that incorporating infographics alongside article links enhances social media presence and amplifies article impact (16). Among the rampant dissemination of false information online, social media platforms play crucial roles in disseminating accurate medical information and fostering constructive dialogue (17, 18).

Open-access articles are readily accessible to all readers, leading to the expectation of increased readership and citation frequency (19, 20). Antelman et al. found that open-access publications across various fields, such as philosophy, political science, engineering, and mathematics, exhibited higher citation rates than nonopen-access articles (19). Similarly, Silva et al., in a study of 4,022 sports science articles, observed a stronger correlation between AS and citation numbers than between AS and IF or open-access status (21). However, contrary to these expectations, our study revealed that open-access status did not significantly impact AS or citation numbers. Patel et al. also reported similar findings, indicating no discernible differences in ASs between open-access and nonopen-access articles (22). These findings suggest that while open access may enhance visibility within the academic community, it did not necessarily translate to increased media attention (22).

Regarding CI subtopics, our analysis identified auditory and music perception, electrode and/or implant properties, neuroplasticity, and electrophysiological studies as the most prevalent themes among the top 100 articles. However, studies on neuroplasticity, genetics, in vivo animal testing, bioinformatics, and computational models were more likely to be published and cited in journals with higher IFs. This inclination could be attributed to the innovative findings yielded by studies employing molecular methodologies, potentially leading to treatments with significant clinical implications, thereby increasing the likelihood of publication in high-ranking journals (23, 24).

Despite our findings indicating a correlation between IF and certain aspects of article visibility, it is crucial to acknowledge that our study did not aim to equate IF with the quality of individual articles. The IF has deviated from its original purpose of gauging the journal's influence and no longer serves as an accurate measure of the scientific merit of each article (25). Indeed, a high IF rating may not necessarily correlate with the number of citations received by published papers (26). It is widely recognized that a small fraction of highly influential papers that contribute disproportionately to a journal's citations may primarily drive its high IF (27, 28). Consequently, rather than relying solely on bibliometric indicators, the quality and impact of any study should be evaluated based on its scientific and/or societal significance (29).

Furthermore, it is important to interpret the findings of this study cautiously. First, our study's scope was confined to original research articles and systematic reviews categorized under CI, potentially excluding broader ENT, audiology, or multidisciplinary journals. In addition, certain audiology subtopics, such as surgery, were not included in our analysis, possibly resulting in the omission of certain frequently cited articles. Therefore, it is conceivable that certain influential articles within the media and scientific community were overlooked. However, our study design reduced the impact of inherent biases in IF calculations on research endpoints by focusing solely on audiology papers (30). Notably, IF calculations are susceptible to manipulation, particularly through the inclusion of noncitable items such as editorials and commentaries, which may inflate the total citation count but are not factored into the baseline of IF calculation (31, 32).

In this study, correlations between AS and traditional metrics were observed, highlighting the growing significance of media in science communication and the encouragement of media coverage for scientific articles. As altmetrics gain popularity, they complement traditional citation-based metrics, reflecting a broader spectrum of research impact. Bibliometrics, which lies at the core of scientific research data analysis, is widely accepted as a valid and reliable method for research evaluation, offering advantages such as quantifying scholarly output (13). However, it lacks indicators of different types of research output, limiting its scope in comprehensively evaluating influence. While bibliometric indicators are viewed as objective and transparent, appropriate statistical methods must be

employed due to their numerical nature and highly skewed distributions (5). One notable limitation is the time required to acquire bibliometric data, with reliable impact estimation typically taking 3 years after publication (13). Altmetrics have emerged as a solution to this challenge, offering early impact data (33) and addressing the lack of systematic procedures for identifying and evaluating societal impact (34). These metrics, available immediately after publication or presentation, serve as early indicators of potential long-term influence, capturing societal effects beyond the academic community. Altmetrics also offers the advantage of quantifying information beyond standard outputs such as conference presentations and gray literature, including diverse outputs such as YouTube videos (34). However, challenges remain in utilizing altmetrics in decision-making processes (33, 34) and ethical considerations, such as the potential introduction of bias through Twitter bots, must be addressed (34).

Documenting the scientific and clinical impact of research is increasingly vital across disciplines, including audiology. Alternative impact metrics supplement bibliometrics, reflecting further research influence (5). With metric methodologies evolving in the modern technological era, researchers should familiarize themselves with new bibliometrics and other metrics necessary for submission to employers or institutions (5).

Methodological considerations/limitations

Methodological considerations and limitations are inherent in this study. First, its retrospective nature presents a limitation, as current trends may diverge from those observed during data collection. In addition, the findings may not be generalizable to articles in other specialties or those published outside the study period. The selection of time frames could have influenced the results, and controlling for these variables could have enhanced the reliability of AS estimation. Furthermore, while altmetrics are effective at detecting early impacts, the analysis only included the top 100 most cited papers. Consequently, the inability to access AS data for papers published after 2017 represents another limitation in terms of revealing early impacts. Nevertheless, newer publications exhibited higher ASs, indicating a potential trend worth exploring further.

CONCLUSION

This study marks the first analysis of ASs among the 100 most cited articles in the field of CI. The predominant subtopics among the most cited articles pertained to factors influencing speech perception in adults, whereas the article with the highest AS focused on genetics. Original research articles comprised the majority (74%) of the analyzed articles, with systematic reviews and meta-analyses accounting for the remaining 26%. Notably, open-access articles constituted 68% of the total. While articles categorized in Q1 journals exhibited higher citation numbers and ASs, those in Q2, Q3, and Q4 displayed similar metrics. The study revealed significant correlations between traditional metrics and altmetrics, indicating that more frequently cited publications were associated with higher ASs. This underscores the complementary nature of altmetrics to traditional metrics, with their importance anticipated to increase over time.

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RESEARCH ARTICLE
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Is Gentamicin-Induced Ototoxicity Reversible with Delayed Administration of Nigella Sativa Oil? An Experimental Study

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ABSTRACT

Objective: Gentamicin (GM) is a potent antibiotic but is known to cause irreversible ototoxic effects. Nigella sativa oil (NSO) can offer protective prophylaxis against ototoxicity when administered prior to GM treatment. This study aims to assess the impact of delayed NSO administration on GM-induced ototoxicity using the auditory brainstem response (ABR) test.

Material and Methods: Adult male Sprague-Dawley rats were randomly divided into three groups, each consisting of six animals. All groups received intraperitoneal (i.p.) GM (120 mg/kg i.p.) for a duration of 10 days. The first two groups were given 0.3 ml/kg/day NSO for five days, while the third group received 0.9% saline for the same duration. Group 1 involves the early administration of NSO (NSOE) 10 days after starting GM, Group 2 involves the late administration of NSO (NSOL) 25 days after starting GM, and Group 3 is the saline (control) group. Hearing thresholds were recorded for both ears prior to treatment initiation and again 30 days after the start of treatment.

Results: Two rats expired and were excluded from the study. A total of 64 ABR test results were obtained. No difference was found between the pre- and post-treatment ABR values in Groups 1 and 2. However, a significant increase in ABR thresholds was observed only in Group 3. A significant difference was found in post-treatment hearing thresholds ($p<0.001$) between Group 3 and the other two groups.

Conclusion: The results suggest the delayed administration of NSO within a period of 30 days, whether earlier or later, to be able to effectively reverse the GM-induced ototoxic effects.

Keywords: Gentamicin, nigella sativa oil, ototoxicity, auditory brainstem response test

INTRODUCTION

Aminoglycosides (AG) are highly effective antibiotics utilized in the treatment of serious infections (1, 2). Nonetheless, they are well-established to possess ototoxic properties, with the risk of ototoxicity escalating with higher dosages, more frequent administration, and prolonged treatment durations (3, 4).

Nigella sativa (NS) is an annual flowering plant with a significant historical background in traditional medicine (5). The oil has been traditionally used to support respiratory, stomach, and intestinal health (6). Thymoquinone and other active constituents of NS have recently been found to have numerous potential therapeutic properties. NS is commonly used as a natural remedy for various illnesses and conditions, including asthma, diabetes, hypertension, cough, bronchitis, inflammation, eczema, headache, dizziness, influenza, and fever (7). Previous research has demonstrated that, when used together or as a preventative measure with ototoxic drugs, NSO offers protection against ototoxicity. However, the efficacy of NSO in reversing the ototoxic effects after treatment with GM has not been assessed (3, 8, 9). This study plans to evaluate the effect of administering nigella sativa oil (NSO) up to 30 days after starting gentamicin (GM) treatment on GM-induced ototoxicity using the auditory brainstem response (ABR) test.

MATERIALS and METHODS

The study was carried out using male Sprague-Dawley rats weighing between 300-400 g that had been bred at the Bursa Uludağ University Experimental Animal Breeding and Research Unit. The surgical interventions were approved by the Bursa Uludağ University Ethical Committee on Animal Research (Date: October 5, 2022, No: 2022-10/07). The study was planned taking into account the Guide for the Care and Use of Laboratory Animals. The animals were placed in secure cages

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with unrestricted access to food and water. The study evaluated the ABR thresholds in all rats and included 18 rats with normal hearing thresholds. The rats were divided into three groups, each consisting of six animals.

Group 1: GM+NSOE (Early administration starting on day 10 after the first GM dose)

Group 2: GM+NSOL (Late administration starting on day 25 after the first GM dose)

Group 3: GM+Saline (Control group; saline started on day 25 after the first GM dose)

All three groups were administered GM at a dose of 120 mg/kg intraperitoneally (i.p.) for a duration of 10 days. Groups 1 and 2 received NSO (0.3 ml/kg/day i.p.) for 5 days in the early and late stages, respectively. Group 3 was given saline (0.3 ml/kg/day i.p.) and served as the control group. Adequate and appropriate doses were determined based on the results from the previous study (9).

ABR tests were performed before starting the GM treatment and again 30 days post-start of GM treatment on both ears of the rats while under general anesthesia with sevoflurane using the Interacoustics Eclipse EP15 device. A total of 64 test results were obtained from 16 rats. ABR results were compared statistically among the groups. Clicks were delivered using an in-ear headphone. A total of 2,000 responses to repetitive stimuli were recorded and averaged at a frequency of 31.1 Hz. These responses were then analyzed within a duration of 18 milliseconds. ABR thresholds were determined by positioning the active needle electrode on the vertex of the head, while placing the reference needle electrodes on both sides of the mastoid region. The ground needle electrode was inserted subcutaneously into the sacral region (Figure 1). The minimum level of intensity required to observe Wave V was determined as the threshold for the ABR.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics (ver. 28.0; IBM, USA). All variables were presented as Mean±SD. The Wilcoxon signed-rank test was used to compare within-group parameters and one-way analysis of variance (ANOVA) test to compare the variables among the groups, where $p<0.05$ is considered statistically significant.

RESULTS

Two rats (one in Group 1, one in Group 3) were excluded from the study due to death before completion of the experiment. The ABR tests were conducted before the initiation of the GM treatment and on day 30 after treatment had commenced. A total of 64 test results were obtained, comprising 32 measurements for both the right and left ears of the rats. Table 1 presents the average values of the hearing thresholds before and after treatment as determined by the ABR results.

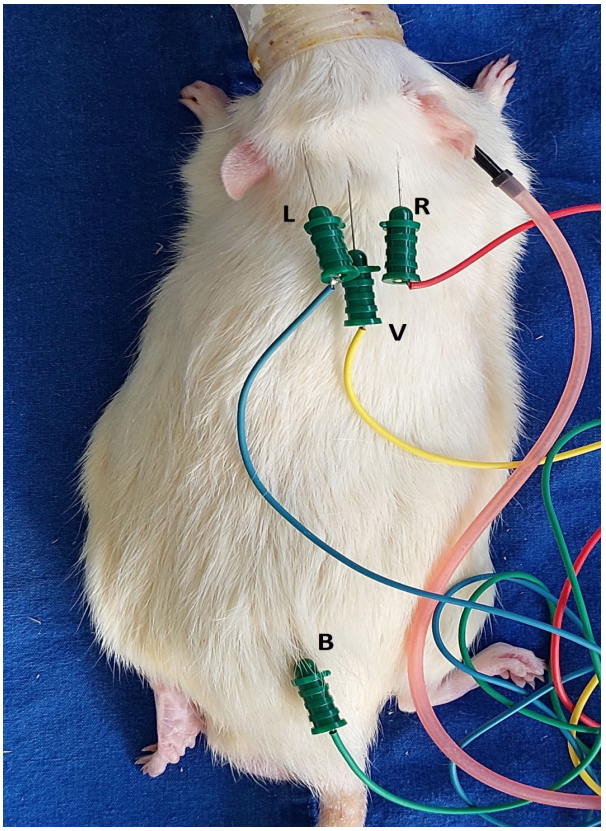

Figure 1: Sevoflurane anesthesia was given in order to perform the ABR test. ABR thresholds were obtained by placing the active needle electrode in the vertex (V), the reference needle electrodes bilaterally in the mastoid region (L and R), and the ground needle electrode in the back region subcutaneously (B).

The mean ABR measurements pre- and post-treatment were compared. No difference was found between the pre- and post-treatment ABR values for Groups 1 and 2. However, a significant increase in ABR threshold was observed only in Group 3 ($p=0.038$). When comparing the pre-treatment measurements alone, no significant difference was observed among the groups ($p=0.316$), while a significant difference became evident in terms of the post-treatment values ($p<0.001$). Figures 2 and 3 illustrate examples from the pre- and post-treatment ABR recordings.

DISCUSSION

Ototoxicity is a frequently reported adverse drug reaction, and its impact on hearing loss greatly affects quality of life (10). In a survey conducted on children, notable developmental differences were present between those with hearing loss and those with normal hearing. Children affected by ototoxicity have also been revealed to experience lower quality of life in terms of communication skills, independence, and emotional development (11).

Drug-induced ototoxicity may occur during or after drug therapy (12). Patients who complain of hearing loss are referred to an

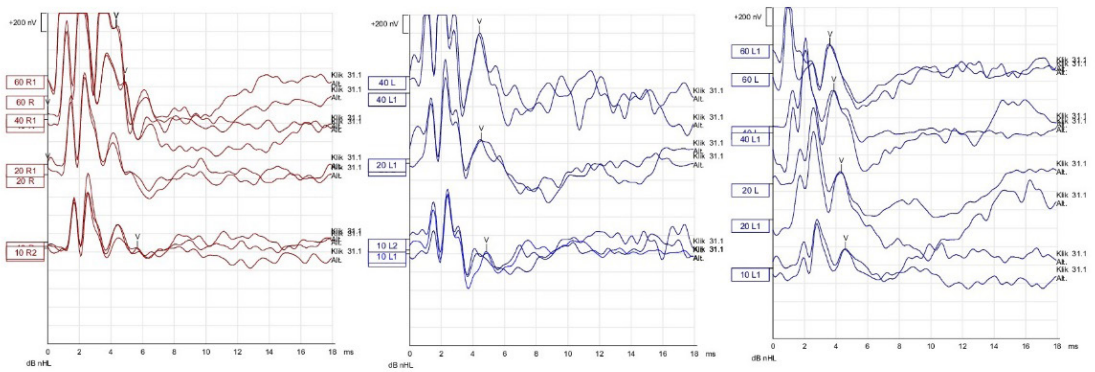

Figure 2: Examples of the pre-treatment ABR test results for the rats from Groups 1, 2, and 3.

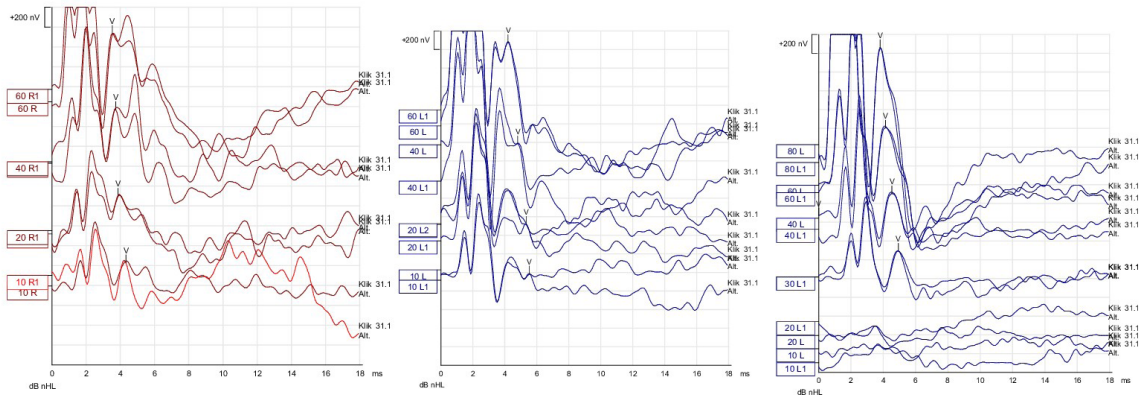

Figure 3: Examples of the post-treatment ABR test results for the rats from Groups 1, 2, and 3.

otorhinolaryngology department. However, the irreversible nature of the toxic effects presents challenges for physicians in terms of providing appropriate treatment. Rizk et al.'s review study reported 194 drugs to be able to cause ototoxicity when administered systemically. According to their findings, the most common class of medication was antimicrobials, followed by psychotropics (13). Ototoxic drugs can affect the inner ear through various mechanisms (14). The ototoxic effects of AG are reported to typically be bilateral and permanent (3, 15). These drugs target the outer hair cells at the basal turn of the cochlea and are hypothesized to enter the hair cells and marginal cells of the stria vascularis, thereby inhibiting mitochondrial protein synthesis via ribosomal binding. This process also induces the formation of ferric cations that produce reactive oxygen species (ROS) (12, 16). The risk of AG-induced ototoxicity has been reported to increase with the mutation of the gene encoding the mitochondrial 12s rRNA (17).

Table 1: Mean hearing levels for all groups (dB) ± SD: Pre and post-treatment results

Group No.	Group Name	Pre-treatment ABR Hearing Threshold (dB, mean)	Post-treatment ABR Hearing Threshold (dB, mean)	p
1	GM+NSOE	10	10	1
2	GM+NSOL	10.83±2.88	10.3±2.88	1
3	GM+Saline	12±4.22	19±7.38	**0.038**

ABR: Auditory brainstem response test; dB: Decibel; GM: Gentamicin; NSO: Nigella sativa oil; NSOE: Early NSO started on day 10 after first GM dose; NSOL: Late NSO started on day 25 after the first GM dose

Currently, no universally recognized agent is found to be utilized in clinical practice for treating GM-induced ototoxicity (3). Antioxidants have protective properties against prooxidant ROS and have been demonstrated to be able to sometimes have prooxidant effects on their own (7). However, *in vitro* tests have shown NSO, which possesses antioxidant properties, to not act as a prooxidant (18, 19). The present study has discovered the ABR test results of the rats that had been given NSO after GM administration to be identical to those obtained before GM administration. One month after GM administration, the hearing thresholds of the rats not administered NSO was observed to be significantly lower than those of rats treated with NSO.

Nigella sativa (NS) possesses a range of biological effects, including anti-inflammatory, anti-hyperlipidemic, anticancer, antioxidant, antidiabetic, and wound healing properties (6, 20, 21). Limited studies have examined the efficacy of NSO in reversing drug-induced hepatotoxicity. Jaswal et al. treated rats with antituberculosis drugs for 8 weeks (3 days/week), followed by NS for 8 weeks (3 days/week) and reported NS to exhibit excellent hepatoprotective abilities and to reverse hepatotoxic effects (22). Similarly, Hassan et al. suggested thymoquinone to be able to reverse the oxidative stress damage produced by atorvastatin in the rat liver, proposing its use in reversing hepatic injury (23).

Previous research has shown NSO to provide protection against ototoxicity when used concomitantly or prophylactically with ototoxic drugs (3, 8, 9). Sagit et al.'s experimental study conducted with rats demonstrated histopathologically that GM-caused ototoxicity was reduced when high doses of thymoquinone were administered simultaneously with GM (8). In another study, Edizer et al. reported the simultaneous administration of intratympanic NSO and GM in rats for 3 weeks to partially alleviate the ototoxic effect caused by GM (3). The previous study utilizing dose titration determined the optimal prophylactic dose of NSO to prevent ototoxicity (9). However, the effectiveness of NSO administration in reversing late-detected ototoxic effects after GM treatment has not been previously evaluated. The objective of the current study has been to examine whether delayed administration of NSO is able to effectively mitigate permanent hearing loss in GM-induced ototoxicity, and the findings have revealed administering 0.3 ml/kg/day NSO for 5 days within 30 days of the start of GM treatment to effectively reverse GM-induced ototoxicity and to completely restore hearing function. The study proposes the short-term administration of appropriate doses of NSO in the later period after starting the use of ototoxic drugs to be able to provide otoprotective benefits.

Recognizing the limitations of the current study is imperative. Firstly, the reversibility of the toxic effects was not confirmed through cochlear histopathological studies. Additionally, the current study only assessed the effectiveness of NSO in reversing ototoxic effects within the first month. Future investigations should evaluate the retrospective benefits of NSO application during later periods.

CONCLUSION

The study has demonstrated the administration of 0.3 ml/kg/day NSO at any time within 30 days of initiating GM treatment to be able to effectively reverse ototoxic effects. Further research is necessary to assess the possibility of reversing ototoxic effects through NSO administration beyond the initial 30-day period. The ability of NSO to reverse ototoxic effects offers hope for the management of late-onset drug-induced ototoxicity.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Bursa Uludağ University Ethical Committee on Animal Research (Approval No. 2022-10/07 dated October 5, 2022).

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- B.T., G.T.; Data Acquisition- B.T., G.T.; Data Analysis/Interpretation- B.T., G.T.; Drafting Manuscript- B.T., G.T.; Critical Revision of Manuscript- B.T., G.T.; Final Approval and Accountability- B.T., G.T.; Material or Technical Support- B.T., G.T.; Supervision- B.T., G.T.

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

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RESEARCH ARTICLE
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Texture Analysis of Thyroid Nodules Using Computed Tomography: Is it a Viable Method for Objective Assessment of Thyroid Nodules?

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ABSTRACT

Objective: Computed aided detection (CAD) systems can be developed to help radiologists in the accurate interpretation of computed tomography (CT) images. The recently popularised texture analysis method allows for qualitative and quantitative evaluation by analysing the grey-level distribution and relationships within an image. We aimed to compare the ratios of texture analysis data in the differentiation of benign-malignant nodules with the proportions of radiologists in the distinction between benign and malignant nodules and to compare the results.
Materials and Methods: Retrospectively, the data of 80 patients who underwent thyroidectomy and had contrast-enhanced neck CT preoperatively were analysed. Two radiologists, experienced in head and neck radiology, blinded to the patients' data evaluated neck CT images. Manual marking was performed and scanned to take tissue sections from the nodule area in transverse contrast-enhanced CT images, and the size of the nodule in the contralateral normal thyroid parenchyma was almost equal.
Results: The computed tomography texture analysis (CTTA) model achieved the highest sensitivity of 81.4%, followed by the first radiologist at 51.2% and the second radiologist at 55.8%. Additionally, the CTTA model achieved the highest accuracy at 61.3%, followed by the first radiologist at 41.3% and second radiologist at 47.5%. On average, the CTTA model performed significantly better than the two radiologists, especially with regard to sensitivity.
Conclusion: The CTTA model was superior to both radiologists in differentiating between benign and malignant thyroid nodules. Medical experts can benefit from CTTA-based solutions to extend their understanding of thyroid nodules in their routine practise.
Keywords: Texture analysis, thyroid cancer, computer-aided diagnosis, thyroid nodules

INTRODUCTION

Thyroid carcinomas account for 2,5% of all cancers and 95% of all endocrine tumours (1). Most thyroid carcinomas are differentiated tumours with a slow progression (2). Although ultrasound examination reveals thyroid nodules in up to 70% of adults, only <7% of these nodules are diagnosed as malignant (3). To avoid unnecessary surgical interventions, the differential diagnosis of malignant or benign nodules should be performed precisely. Fine needle aspiration biopsy (FNAB) and noninvasive imaging techniques are the basic approaches and equipment that enable us to differentiate between malignant and benign nodules. Ultrasonography (USG) is an accurate and efficient diagnostic tool for the detection of thyroid nodules and differentiation between malignant and benign nodules (4). Due to its high specificity and sensitivity, noninvasiveness, and low cost, USG is the first test requested when a patient presents with suspicion of a thyroid nodule. The characteristics of thyroid nodules on USG, such as hypoechogenicity, irregular margins, solid component, microcalcifications, and taller-than-wide shape, can show a significant relationship with malignant nodules (4). For many thyroid nodules, USG and FNAB are quite effective and sufficient for decision making. There are a substantial number of patients with no obvious suspicion of malignancy on thyroid USG and whose FNAB was reported as undeterminate cytology (Bethesda 3 or 4). It is known that

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Follicular Thyroid Cancer (FTC) and Follicular-variant of Papillary Thyroid Cancer (FVPTC) display relatively benign sonographic features in contrast to conventional variants of papillary thyroid carcinoma (5, 6). In this group of patients, in addition to USG and FNAB, other imaging modalities may impact the decision-making process.

Computed Tomography (CT) is not initially used to evaluate thyroid nodules; however, it provides valuable information in some circumstances, such as retrosternal goitres, malignant tumours with extrathyroidal extension, or lymph node metastasis, and also in the follow-up of thyroid cancer, especially in cases of suspected structural disease recurrence (7, 8). In clinical practise, radiologists visually inspect a large number of CT images, and some subtle CT features, like calcification, could be missed during visual inspection. In a retrospective study by Saaedan et al., it was reported that 48% of patients with intrathyroidal calcification were diagnosed with thyroid carcinoma by histopathology, and increased rates of thyroid cancer and lymph node metastasis were observed in patients with calcified nodules (9). Computed aided detection (CAD) systems can be developed to help radiologists in the accurate interpretation of CT images.

The recently popularised texture analysis method allows for qualitative and quantitative evaluation by analysing the grey-level distribution and relationships within an image. Because of the possible heterogeneous structure of the tumour tissue, the texture analysis procedure can give varying results. Typically, medical images contain an extensive amount of tissue information. For instance, CT or MR images cannot provide microscopic details that can be visually evaluated; however, histological changes caused by certain diseases may cause tissue changes that can be quantified on CT and MR images. In other words, while the information obtained from CT or MR images is limited regarding the nature of the tissue, the quantitative data obtained from texture analysis has increased our understanding of histological changes and possible diseases (10).

The objective of our study was to investigate the differences in tissue analysis parameters obtained from CT images between malignant and benign nodules and to evaluate the potential clinical utility of these differences in distinguishing between malignant and benign nodules. In addition, we aimed to compare the ratios of texture analysis data in the differentiation of benign-malignant nodules with the proportions of radiologists in the distinction between benign and malignant nodules and to compare the results obtained with those found in the literature.

MATERIALS and METHODS

Patients

The Marmara University Faculty of Medicine Ethics Committee for Clinical Research approved the study on June 18, 2021, with the number 09.2021.396. Informed consent was not obtained from patients because of the retrospective design of the study. Retrospectively, the data of 525 patients who underwent thyroidectomy surgery between January 2012 and April 2021 were analysed through the hospital automation system. Neck CT was performed in 150 of these 525 patients for any reason (retrosternal extension, suspicion of extrathyroidal invasion or lymphatic spread in malignant cases, and any suspected neck pathology independent of the thyroid), and in 80 of them, images that were demarcation of the borders of the nodules apparent and contrast-enhanced were included in the study (Figure 1).

Computed tomography acquisition and image review

Contrast-enhanced neck CT scans of the patients were performed in the supine position, the neck in the extended position as much as possible, the scanning range from the oropharynx to the supraclavicular region, with the Philips Brilliance ICT 256 device with intravenous contrast, with the technical parameters specified. The tube potential is 100-120kVp, tube current is 200 mAs, cross-section gap is 3.75 mm, section thickness is 3 mm, field of view (FOV) values are 250 mm, and pitch is 0.1. In CT scans, 80-100 ml of nonionic iodinated contrast material (Omnipaque 300, 300 mg I/mL; Amersham Health, Cork, Ireland) was administered via the antecubital vein in an amount of 1.2 mL/kg and at a rate of 2-3 mL/s. The scan delay was 40-50 seconds.

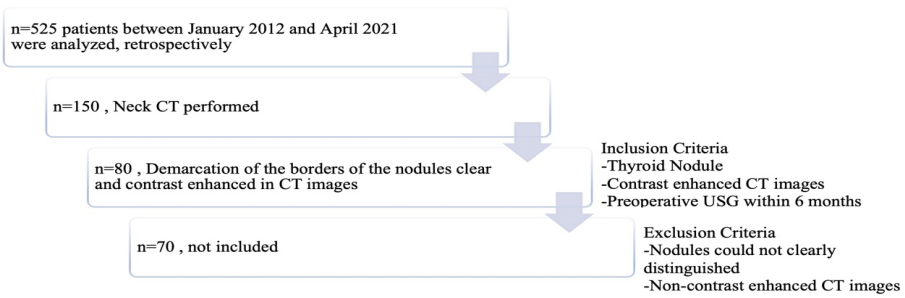

Figure 1: Patient selection flowchart following the application of inclusion and exclusion criteria.

Computed tomography texture analysis (CTTA)

Two radiologists, experienced in head and neck radiology, blinded to the patients' clinical information, preoperative examinations, or postoperative histopathological diagnoses evaluated neck CT images. The most prominent and suspicious nodule on USG was found and determined on contrast-enhanced neck CT of the patients. Manual marking was performed and scanned to take tissue sections from the nodule area in transverse contrast-enhanced CT images, and the size of the nodule was almost equal to that of the contralateral normal thyroid parenchyma (Figure 2). Sections and markings were made in the same way for each patient. A total of 160 (80 nodule area, 80 contralateral nodule-free area) images were obtained. Texture analysis measurements were made from pictures taken separately from both sides (with and without nodules). Texture analysis and histogram evaluations were performed using the MaZda programme (MaZda 4.60, The Technical University of Lodz, Institute of Electronics, Poland). To evaluate tissue properties, 21 parameters were examined, including the Hounsfield Unit (HU) value.

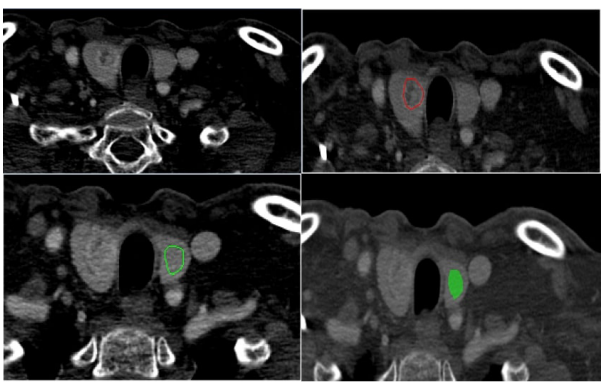

Figure 2: Manuel marking of the nodule and nodule-free area.

The following four stages were carried out in the study:

1-Based on the postoperative thyroid histopathology results, patients were divided into benign and malignant groups. A comparison was made between the preoperative USG findings and texture analysis measurements obtained from the nodule location.

2-Tissue analysis measurements taken from the nodule area were compared between the two groups.

3- The texture analysis measurements obtained from the nodule area of patients in the benign and malignant groups and those obtained from the contralateral nodule-free site (with normal thyroid parenchyma) were compared.

4-To investigate the views of clinical experts in radiology regarding the prediction of thyroid nodules as benign or malignant and compare texture analysis data with the results.

Statistical analysis

SPSS 22 (IBM SPSS Corp., Armonk, NY, USA) programme was used in the analysis of the data. Data are presented as numbers, percentages, mean, standard deviation, and median. The Kolmogorov–Smirnov test was used for the normality test. Parametric analyses were preferred in the study of normally distributed data, and non-parametric analyses were preferred in non-normally distributed data analysis. The analysis used the Mann–Whitney U, Kruskal–Wallis, and Spearman correlation tests. A value of $p<0.05$ was considered statistically significant.

RESULTS

Table 1 presents the demographic details of the patients and the preoperative USG features of the thyroid nodules.

Table 1: Demographics of patients and preoperative USG characteristics of thyroid nodules

	Bening n=37	Malignant n=43
Mean Age 52.00±17.05 (min=11-max=78). 32.5% (n:26) **male** / 67.5% (n:54) **female**		
Number of patients (n = 80)	37 (46.25%)	43 (53.75%)
Extent of the Surgery		
Total thyroidectomy	32 (40%)	43 (53.75%)
Lobeisthmectomy	5 (6.25%)	0
Neck dissection	0	16 (20%)
Preoperative USG Findings		
Calcification (n = 26) (32.5%)	8 (10%)	18 (22.5%)
Microcalcification (n = 14)	0	14
Echogenicity		
Hypoechoic (n=39) (48.8%)	10 (12.5%)	29 (36.25%)
Isoechoic (n=13) (16.3%)	6	7
Hyperechoic (n=2) (2.5%)	2	0
No evaluation (n=26) (32.4%)		
Solid/Cystic Characteristic		
Solid (n=39) (48.8%)	14 (17.5%)	25 (35%)
Cystic (n=11) (13.8%)	9 (11.25%)	2 (2.5%)
Mixed (n=8) (10%)	2 (2.5%)	6 (7.5%)
No evaluation (n=22) (27.4%)		

The percentages in parentheses are calculated based on the total number of patients (n=80).

Comparative analysis of preoperative USG and CTTA measurements

This study revealed a statistically significant disparity in the correlation (Correlat) values obtained from CTTA measurements based on calcification within the tissue. Notably, individuals with calcification exhibited a higher correlation (Correlat) value, as shown in Table 2.

Upon comparing CT measurements based on the solid and cystic structure of the nodule, a statistically significant difference was observed in the mean (Mean), kurtosis (Kurtosis), histogram panels (Perc01, Perc10, Perc50, Perc90, Perc99), and HU values (Table 3). The post hoc analysis of the measurements revealed

Table 2: Comparison of CT texture analysis based on the presence or absence/not evaluated of calcification in USG

	CALCIFICATION						
	Present			Absence/Not evaluated			
	X	SD	Median	X	SD	Median	p
Mean	1134.14	38.02	1134.29	1122.35	40.31	1123.19	0.312
Variance	1618.70	1764.36	954.89	2341.99	6171.39	1116.42	0.801
Skewness	-0.11	2.34	0.01	0.25	2.38	0.05	0.825
Kurtosis	8.27	36.00	0.14	10.15	33.10	0.07	0.865
Perc01	1064.85	44.70	1063.00	1048.30	43.39	1044.50	0.237
Perc 10	1091.88	41.36	1085.50	1078.61	41.18	1074.50	0.358
Perc50	1133.58	37.71	1134.50	1120.72	40.30	1121.50	0.256
Perc90	1175.31	44.43	1173.00	1166.56	50.57	1161.00	0.281
Perc99	1226.19	96.63	1206.00	1221.83	145.07	1186.50	0.369
AngScMom	0.00	0.00	0.00	0.00	0.00	0.00	0.438
Contrast	77.88	37.42	74.56	99.46	45.82	91.41	0.057
Correlat	**0.61**	**0.18**	**0.66**	**0.51**	**0.20**	**0.49**	**0.027**
SumOfSqs	100.41	14.33	105.43	99.73	17.35	105.70	0.988
InvDfMom	0.18	0.07	0.16	0.16	0.06	0.14	0.082
SumAverg	64.14	1.24	64.33	64.13	1.18	64.32	0.662
Sum Varnc	323.78	59.30	333.70	299.46	63.71	299.96	0.106
SumEntrp	1.79	0.08	1.81	1.78	0.11	1.82	0.922
Entropy	2.75	0.25	2.83	2.77	0.28	2.85	0.569
DifVarnc	31.25	13.35	30.28	38.11	16.44	41.55	0.089
DifEntrp	1.19	0.12	1.22	1.24	0.13	1.26	0.082
HU	117.33	39.74	114.58	108.27	39.04	107.72	0.337

P values that are statistically significant and their related row are highlighted in bold. X: Mean value, SD: Standard deviation; HU: Hounsfield Unit

Table 3: Comparison of CT texture analysis based on solid or cystic characteristics as observed by ultrasound

	SOLID-CYSTIC												
	Solid			Cystic			Solid+Cystic			No evaluation			
	X	SD	Median	X	SD	Median	X	SD	Median	X	SD	Media	p
Mean	**1140.94**	**31.26**	**1135.00**	**1106.85**	**38.87**	**1126.15**	**1144.80**	**47.43**	**1147.58**	**1102.92**	**37.43**	**1102.58**	**0.002**
Variance	2697.24	7187.58	1104.28	1296.69	784.73	897.26	3317.95	3163.37	2123.69	1025.21	615.18	938.14	0.523
Skewness	-0.34	2.72	-0.02	0.65	1.57	0.39	2.27	3.35	1.48	-0.06	0.48	0.03	0.054
Kurtosis	14.21	43.36	0.17	5.23	14.82	-0.16	18.96	43.29	3.38	-0.02	0.52	-0.17	0.016
Perc01	**1065.51**	**40.68**	**1064.00**	**1033.36**	**52.59**	**1030.00**	**1072.63**	**33.05**	**1064.00**	**1035.95**	**41.74**	**1026.50**	**0.013**
Perc10	**1096.36**	**35.80**	**1096.00**	**1063.91**	**47.04**	**1074.00**	**1099.25**	**39.83**	**1093.50**	**1062.68**	**38.83**	**1056.00**	**0.006**
Perc50	**1139.03**	**31.63**	**1136.00**	**1106.64**	**39.93**	**1125.00**	**1139.13**	**48.72**	**1139.50**	**1103.82**	**38.48**	**1102.00**	**0.006**
Perc90	**1186.10**	**46.21**	**1188.00**	**1149.55**	**35.12**	**1147.00**	**1190.13**	**57.94**	**1200.00**	**1142.18**	**40.41**	**1146.50**	**0.002**
Perc99	**1242.72**	**158.90**	**1207.00**	**1190.82**	**38.07**	**1186.00**	**1319.38**	**155.37**	**1319.00**	**1170.00**	**45.56**	**1171.50**	**0.006**
AngScMom	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.273
Contrast	88.74	37.92	83.30	81.49	42.53	61.81	92.75	54.09	100.84	104.39	51.74	117.03	0.540
Correlat	0.56	0.18	0.60	0.58	0.22	0.70	0.50	0.19	0.49	0.51	0.24	0.47	0.728
SumOfSqs	98.94	17.07	105.37	99.85	14.40	102.87	87.72	27.85	95.90	106.24	4.42	108.53	0.093
InvDfMom	0.17	0.06	0.15	0.17	0.04	0.16	0.22	0.12	0.16	0.15	0.05	0.12	0.293

SumAverg	64.32	1.24	64.45	63.95	1.04	64.30	63.75	1.47	64.03	64.03	1.10	64.32	0.598
SumVame	307.02	61.44	320.48	317.92	73.83	349.54	258.13	74.91	282.27	320.59	49.62	313.46	0.167
SumEntrp	1.78	0.11	1.83	1.79	0.10	1.83	1.72	0.12	1.73	1.81	0.06	1.82	0.133
Entropy	2.75	0.29	2.83	2.76	0.24	2.82	2.65	0.31	2.58	2.84	0.24	2.90	0.405
DifVarne	34.64	13.83	31.38	32.33	17.12	28.01	39.85	17.54	43.09	38.42	17.98	42.86	0.631
DifEntrp	1.21	0.13	1.23	1.21	0.10	1.18	1.18	0.21	1.24	1.26	0.13	1.30	0.354
HU	**127.61**	**32.30**	**137.05**	**98.07**	**33.52**	**107.31**	**121.32**	**47.93**	**120.42**	**85.05**	**35.51**	**82.59**	**<0.001**

P values that are statistically significant and their related row are highlighted in bold. X: Mean value; SD: Standard deviation; HU: Hounsfield Unit

Table 4: Ratio of CT texture analysis values obtained from nodule- and nodule-free regions in both benign and malignant groups.

	DIAGNOSIS						
	Benign			Malign			
	X	SD	Median	X	SD	Median	p
Mean ratio	0.96	0.05	0.96	0.94	0.04	0.94	0.085
Variance ratio	15.52	26.53	3.15	6.78	8.88	4.17	0.253
Skewness ratio	-7.84	74.40	0.19	-0.26	16.23	0.18	0.769
Kurtozis ratio	-138.13	872.55	-0.93	-5.90	54.19	0.03	0.058
perc01 ratio	0.93	0.05	0.92	0.92	0.05	0.92	0.572
perc10 ratio	0.94	0.05	0.93	0.93	0.05	0.93	0.466
perc50 ratio	0.95	0.05	0.96	0.94	0.04	0.94	0.144
perc90 ratio	**0.98**	**0.06**	**0.99**	**0.95**	**0.04**	**0.96**	**0.044**
perc99 ratio	**1.03**	**0.15**	**1.00**	**0.97**	**0.04**	**0.96**	**0.042**
AngScMom ratio	**1.03**	**0.94**	**0.67**	**0.63**	**0.44**	**0.50**	**0.022**
Contrast ratio	0.74	0.58	0.58	1.04	1.36	0.68	0.377
correlate ratio	8.54	38.46	1.74	2.45	1.90	1.80	0.904
SumOfSqs_ratio	0.95	0.21	0.98	1.28	1.62	0.99	0.566
InvDfMom ratio	1.60	0.81	1.37	1.38	0.60	1.28	0.347
SumAverg_ratio	0.99	0.02	1.00	0.99	0.03	0.99	0.889
SumVarnc ratio	1.12	0.31	1.09	1.49	1.82	1.12	0.612
SumEntrp_ratio	1.03	0.09	1.03	1.07	0.09	1.06	0.052
Entropy ratio	**1.08**	**0.14**	**1.08**	**1.15**	**0.13**	**1.15**	**0.023**
DifVarne ratio	0.81	0.57	0.72	1.12	1.44	0.77	0.599
DifEntrp ratio	0.92	0.12	0.93	0.97	0.17	0.96	0.185

P values that are statistically significant and their related row highlighted in bold
X: Mean value; SD: Standard deviation

that the statistical disparity was attributable to the solid and unevaluated groups.

Comparative analysis of postoperative histopathology and CTTA measurements

The study involved categorising patients into two distinct groups based on the nature of their condition: benign and malignant. CTTA values obtained from nodule sections of both groups were compared. No statistically significant difference was observed when comparing CTTA measurements between benign and malignant nodules.

The logistic regression model established the significance of incorporating texture analysis measurements of the CT section where the nodule is situated in estimating nodules' benign-malignant risk (p=0.021). The model's dependent variable pertains to the pathology result of the nodule, specifically whether it is benign or malignant. The model's independent variables consist of CTTA values obtained from the nodule region. The model's accuracy rate is 61.3%. The independent variables account for 19.2% of the variability observed in the dependent variable. The Forward LR method was employed as the primary modelling technique. The utilisation of Histogram

percentage-99% (Perc99) and HU measurements substantially contributes to the model. The study revealed that an elevation in the Perc99 measurement by 0.006 units results in a 1.006-fold decrease in the likelihood of malignancy. Conversely, an increase in the HU measurement by 0.023 units results in a 1.024-fold increase in the risk of malignancy.

Comparative analysis of CTTA measurements of nodule and nodule-free areas

Table 4 compares the ratios of CTTA values obtained from the thyroid nodule and CTTA analysis measurements taken from the side opposite to the nodule (nodule-free part) of the same patient. The histogram percentage of 90% (perc90), histogram percentage of 99% (perc99), and AngScMom (uniformity) rates were significantly higher in the malignant group, whereas the entropy rates were considerably higher in the benign group. The ratios were calculated as nodule area measurements and contralateral nodule-free area measurements.

Comparison between CTTA and radiologist

Two radiologists, who were blinded to the final histopathology of the patients, performed differential diagnoses using the CT images of the cohort. Their ability to detect malignant cases compared with CTTA model-based diagnosis was measured. The CTTA model demonstrated a sensitivity of 81.4% and specificity of 37.8%. In comparison, the first radiologist achieved a sensitivity of 51.2% and a specificity of 29.7%, whereas the second radiologist achieved a sensitivity of 55.8% and a specificity of 37.8%. Additionally, the CTTA model achieved the highest accuracy at 61.3%, followed by the first radiologist at 41.3% and second radiologist at 47.5%. On average, the CTTA model performed significantly better than the two radiologists, especially with regard to sensitivity.

DISCUSSION

Thyroid nodules are prevalent in more than half of the adult patients undergoing thyroid imaging. Research indicates that approximately 7% of these nodules have been identified as malignant (11). In cases where benign nodules do not result in thyroid dysfunction, respond to antithyroid treatment, and do not cause functional disorders due to compression of the surrounding structures, follow-up is typically deemed adequate. However, surgery is generally considered unavoidable action for malignant nodules. Early detection of thyroid nodules is crucial for effective management and minimising unwarranted morbidity.

USG is a key diagnostic modality in the primary assessment of thyroid nodules because of its cost-effectiveness and utility. In addition to USG, CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) are valuable diagnostic modalities. CT is particularly advantageous in diagnosing retrosternal goitres and suspected extracapsular spread in cases of malignancy. CT is a notable modality for identifying incidental thyroid nodules. Variations are discernible in the interpretation of these nodules. In contrast to USG, experts lack agreement regarding the potential for malignancy associated with the nodule characteristics identified on CT scans.

Texture analysis can offer qualitative and quantitative evaluation by scrutinising the dispersion and interdependence of grey levels within images. The potential heterogeneity of tumour tissue structure may lead to varying outcomes in the texture analysis approach. The subtypic of renal cell carcinoma, differentiation of portal vein thrombus between malignant-benign groups, differentiation of high- and low-grade intraductal papillary mucinous neoplasms of the pancreas, differentiation of intestinal polyps from neoplastic-nonneoplastic, and differentiation of benign-malignant lung nodules have yielded significant results through texture analysis, as reported in the literature (10). Although there is an increasing number of studies on texture analysis, research specifically focussed on texture analysis of thyroid nodules or malignancies is sparse.

To date, numerous research endeavours have been conducted to assess the efficacy of CT imaging in diagnosing thyroid nodules. The evaluation of thyroid nodules was conducted by Li et al. through the utilisation of dual-energy (dual phase) CT images, as reported in their study (12). A notable dissimilarity was observed between benign and malignant thyroid nodules in terms of their iodine concentration, HU values, and adequate atomic numbers (12). Yoon et al. conducted a retrospective analysis of thyroid nodules incidentally detected on neck CT scans and identified characteristics that indicate malignant potential (13). The authors contended that the presence of calcification at the periphery of the nodule, a high ratio of anterior-posterior diameter to transverse diameter (AP/T ratio), and a mean attenuation value measured in HU exceeding 130 were indicative of an elevated likelihood of the nodule Benign malignant. The authors contended that the risk of malignancy in incidental thyroid nodules identified on CT scans, as determined by the same study, was relatively low at 9.4%. Therefore, they concluded that there is no requirement for supplementary assessment with USG without any malignancy-suggestive features. Lee et al. conducted a study on 259 patients, and their findings were consistent with those of Yoon et al. The study found that small nodules with low mean attenuation values and homogeneous characteristics were frequently benign (14). Our study concluded that a significant proportion of patients (69.2%) with calcification on preoperative USG had malignancy. The identification of calcification through CT imaging, coupled with the characterisation of such calcification, the detection of irregularities in the margin of the thyroid nodule, and the observation of a heterogeneous structure within the nodule indicate a higher likelihood of malignancy (12-14). Given this information, as the number of research utilising CTTA models in thyroid nodules continues to rise, it is important to provide supplementary parameters to augment the features acquired from USG to differentiate between benign and malignant nodules.

In this study, texture analysis was conducted using first- and second-degree statistics, and 21 distinct features were

evaluated. Initially, the preoperative USG results, which included the identification of calcification, solid-cystic structure, and echogenicity assessment, were compared with the texture analysis data acquired from the CT section. Our study revealed that nodules with calcification exhibited higher correlation values, indicating a significant pixel correlation with the adjacent tissue. This finding was interpreted as a potential indicator of malignancy because a higher correlation value may suggest a greater likelihood of malignancy. In addition, the predominance of solid or cystic components of the nodule was compared with the data obtained from texture analysis. A statistically significant difference was observed in the mean, kurtosis, and histogram percentage measurements between solid and cystic nodules. Specifically, the measurements of Perc01, Perc10, Perc50, Perc90, and Perc99 showed significant differences. No statistically significant discrepancy was observed between the echogenicity observation assessed through USG and the texture analysis information. Studies have been conducted in the literature on USG-based texture analysis to quantify radiologists' subjective comments regarding thyroid USG examination (15). Jung et al. conducted research to differentiate benign (K-TIRADS 2) and suspicious (K-TIRADS 3, 4, 5) nodules on chest CT by CTTA (16). The model incorporating MPP, kurtosis, and skewness with a medium philtre using the single most extensive cross-section analysis correctly predicted the suspicious nodules with high sensitivity and specificity (84.4% and 81.0%, respectively). In our study, we conducted CT-based texture analysis without computer-assisted filtering programmes and compared the resulting parameters with preoperative USG findings. Due to the lack of comparable conclusions in the existing literature, it is impossible to draw a comparative analysis. Nevertheless, the texture analysis parameters acquired during our study regarding the differentiation of calcification present-absent and solid-cystic are noteworthy (15).

The research's second phase involved comparing postoperative thyroid histopathology and texture analysis data, which yielded no statistically significant differences. The usability of texture analysis data as a diagnostic test was assessed by examining the results of the ROC curve analysis. The findings indicated that the areas under the curve were not statistically significant, concluding that this method is inappropriate for distinguishing between benign and malignant conditions. After conducting a logistic regression analysis, the accuracy rate of the model was determined to be 61.3%. The study revealed that the Perc99 (Histogram percentage-99%) and HU measurements substantially contributed to the model. The data indicate that an increase of 0.006 units in the Perc99 metric is associated with a 1.006-fold reduction in the probability of malignancy. Furthermore, an increase in the HU measurement by 0.023 units led to a 1.024-fold increase in the risk of malignancy. The correlation between the elevation of HU and the heightened probability of malignancy is consistent with previous findings in the literature (12, 13).

In the third stage of the research, a comparison was made between the texture analysis data obtained from the section extracted from the nodule and the texture analysis data obtained from the section extracted from the nodule-free side, which refers to the relatively intact thyroid tissue. Upon comparing the data of nodule tissue and nodule-free tissue in each patient, it was observed that the malignant group exhibited higher rates of Perc90 (Histogram percent-90%), Perc99 (Histogram percent-99%), and AngScMom (Angular second moment- angular second moment, uniformity). In contrast, the benign group demonstrated a significantly higher entropy value. The measure of uniformity, also known as the angular second moment, pertains to the evenness of the distribution of intensity levels in an image; on the other hand, entropy characterises the degree of randomness and irregularity in pixel density. In our study, the observed high degree of uniformity within the malignant group and elevated entropy within the benign group may indicate that benign nodules exhibit more significant heterogeneity than malignant nodules compared with normal thyroid tissue. However, it is advisable to conduct a comprehensive assessment of the texture analysis information rather than relying solely on individual interpretations. A study similar to the one led by Liu et al. involved CT-based texture analysis and a support vector machine (SVM) to examine thyroid nodules. The researchers evaluated the programme's efficacy following filtering through a computer-assisted programme to enhance the sensitivity and specificity of the acquired data (17). As a result, it was found that in multiple punctate calcifications in the nodule, the mean intensity, standard deviation, and entropy increased while the uniformity decreased. The study also revealed that the accuracy of thyroid cancer prediction was 0.8673 after utilising a computer-aided programme to philtre texture analysis data. However, the accuracy rate of our model was low (0.613) in differentiating benign-malignant nodules in various patients; this could be attributed to the lack of use of a computer-aided filtering programme in the study. Peng et al. conducted a study that extracted first-order statistical features and used SVM to identify normal thyroid tissues and nodules based on CT images (18). The study revealed notable dissimilarities in entropy, uniformity, standard deviation, and skewness measurements in the nodule area compared with healthy thyroid tissue, which can be attributed to the heterogeneous composition of the nodule tissue. Our study differs from Peng et al. 's study in that it involves the use of images that depict the thyroid nodule, followed by the application of a texture analysis method after manual marking and aimed to investigate potential disparities in the differentiation of benign and malignant nodules using texture analysis techniques, as opposed to the system that distinguishes the existing nodule from the surrounding normal thyroid tissue.

To the best of our knowledge, although there are comparative analyses between the texture analysis of USG images and the subjective analysis of radiologists (19, 20), no study has been conducted to compare the classification of thyroid nodules using CT texture analysis and subjective assessment by radiologists. In our study, compared with the first and second radiologists, the CTTA model was superior at differentiating between benign and malignant thyroid nodules. CTTA will not

replace radiologists in the upcoming years. However, medical experts can still benefit from CTTA-based solutions to extend their understanding of thyroid nodules in their routine practise.

This study is subject to certain limitations. First, radiologists must outline the ROIs on the CT slices manually. Our prospective efforts include implementing automated segmentation techniques for the thyroid region of interest (ROI) to enhance operational effectiveness. Other limitations include the small number of patients and computer-assisted filtering programmes not being used to analyse texture analysis data. Evaluating CT sections from more patients is necessary to standardise the current method. Other limitations of the study are that the study was retrospective, not all features were reported on USG (54 patients (67.5%) who were not assessed for calcification on USG, 26 patients (32.5%) who were not evaluated for echogenicity, and 22 patients (27.5%) whose solid-cystic distinction was not considered), and the same radiologist did not evaluate USG.

CONCLUSION

When evaluating thyroid nodules, quantitative data can be obtained via texture analysis. Although texture analysis cannot substitute for USG, it produces promising results in providing further information in thyroid nodule assessment. Other multicenter prospective trials, including larger cohorts of patients, should corroborate these findings.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Marmara University (Date: 18.06.2021, No: 09.2021.396).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Ö.T.K., S.İ.; Data Acquisition- S.İ., B.K.; Data Analysis/Interpretation- Ö.T.K., S.İ.; Drafting Manuscript- Ö.T.K., B.K.; Critical Revision of Manuscript- S.İ., A.C.Y.; Final Approval and Accountability- A.C.Y., S.İ.; Material or Technical Support – B.K., A.C.Y.; Supervision- A.C.Y.

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Bilateral Abductor Vocal Fold Paralysis; Outcomes of Surgical Management in Adult Yemeni Patients

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ABSTRACT

Objective: Bilateral vocal fold paralysis is characterised by complete or partial immobilisation of the vocal folds, resulting in narrowing of the airway at the glottic level and breathing difficulty. This study aimed to evaluate the outcomes of surgical treatments for bilateral vocal cord paralysis, focussing on airway patency, voice quality, and associated complications.

Materials and Methods: A prospective study was conducted on 25 female patients, aged 20–50 years, who presented to our department between June 2016 and May 2021 with a diagnosis of bilateral vocal cord paralysis. All patients underwent posterior cordotomy or partial arytenoidectomy.

Results: Following surgery, significant improvement was observed in breathing, and voice quality improved to an acceptable level over a 2-month period. The applied surgical procedures demonstrated satisfactory outcomes in terms of breathing and voice functions.

Conclusion: The findings of this study suggest that posterior cordotomy and partial arytenoidectomy are effective surgical interventions for treating bilateral abductor vocal fold paralysis. These procedures resulted in improved airway patency and acceptable voice quality, thereby providing satisfactory outcomes for patients.

Keywords: Posterior cordotomy, Bilateral vocal fold paralysis, Arytenoidectomy, Bilateral abductor palsy, outcomes, Yemen

INTRODUCTION

Bilateral abductor paralysis can cause respiratory distress. Causes of this condition include neck surgery, particularly thyroid procedures, prolonged intubation, trauma, neurological disorders, and malignancies (1). The most common cause, accounting for 90% of cases, is peripheral laryngeal paralysis resulting from damage to the vagus nerve or recurrent laryngeal nerve (RLN). Accurate diagnosis requires awake laryngeal endoscopy, and comprehensive airway endoscopy under general anaesthesia is recommended to rule out other airway-related pathologies (2). Evaluation and treatment of bilateral vocal fold paralysis present significant challenges due to critical airway involvement and the complexity of selecting an appropriate treatment plan.

In acute airway emergencies, tracheostomy is typically performed, providing an effective airway and voice. However, many patients prefer to avoid the long-term burden of living with a neck tube (3). Tracheotomy offers the advantage of restoring the airway without altering laryngeal anatomy while allowing for potential spontaneous recovery of vocal fold function, which occurs in 33-65% of cases (4, 5). To prevent lifelong tracheostomy dependency, various endoscopic and external methods have been introduced (6). Historically, tracheostomy was the only management option for bilateral vocal cord paralysis to get rid of respiratory dyspnoea until 1922 (7). In subsequent years, surgical techniques were developed to improve the airway. Extra laryngeal arytenoidectomy was suggested by King in 1939 (8). Woodman introduced external arytenoidectomy in 1946 as the preferred method for patients with challenging endoscopic exposure (9). Endoscopic arytenoidectomy was introduced in 1948, as reported by Thornell (10).

In 1989, Dennis and Kashima invented one of the most effective procedures: endoscopic laser posterior cordotomy. This entails cutting the vocal fold transversely directly in front of the vocal process, excising a tiny piece of the false cord, and extending tissue resection laterally until it reaches the

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thyroid cartilage's inner perichondrium (11). Crumley in 1993 proposed endoscopic medial arytenoidectomy to preserve the phonatory structure where a resection of the medial part of the arytaenoid body is performed and the other aspects of the cartilage are preserved (12).

Laryngeal reinnervation and functional electrical stimulation show promise for treating bilateral vocal fold palsy, but research in these areas is limited, especially in children (13). The results of laryngeal pacing, which demonstrated improvements in spirometric parameters without compromising voice quality and swallowing, were reported in 2016 by Mueller et al. (14, 15). Surgeons have also proposed and adapted various minimally invasive endoscopic procedures for the management of abductor palsy. Apart from reinnervation, all surgical procedures cause breathiness in the voice. The choice of surgical method depends on achieving a balance between phonation and maintaining a clear airway (6). Post-operative oedema, infection, scar formation, granuloma, and arytaenoid perichondritis due to cartilage exposure are reported complications (16).

An internet search was performed using the key words (arytenoidectomy, posterior cordotomy, bilateral vocal cord paralysis with Yemen). No results have been found for previous studies on these topics in our country. Our objective was to evaluate abductor paralysis surgical management in adult Yemeni patients, focussing on airway patency, voice quality, and associated complications.

MATERIALS and METHODS

This prospective study was conducted at the AL-Thawrah Teaching Hospital in Sana'a, Yemen, from June 2016 to May 2021. After Ethical approval was obtained from our department, all patients presenting with a diagnosis of bilateral paralysis of the vocal cord and signed written informed consent were enrolled in this study. All patients had a minimum of a 12-month interval between diagnosis and inclusion in the study. Full medical history and was examined to determine the underlying cause of paralysis. Flexible laryngoscopic examinations were performed to evaluate the mobility of vocal folds, rule out airway masses, and monitor patients during follow-up visits. Preoperative data, postoperative complications, and patient progress were meticulously recorded and documented using Microsoft Excel. Data was analysed using SPSS (IBM SPSS Corp., Armonk, NY, USA) 26.0 for Windows where $p<0.05$ is considered significant.

Surgical technique

Under general anaesthesia, using a cuffed endotracheal tube (size 5.5mm), suspension laryngoscopy was performed to expose the glottis. The surgical procedure was performed using either microlaryngoscopy or videolaryngoscopy. A saline-soaked cotton piece was delicately placed beneath the vocal cord to cover the tube cuff.

Using electrocautery, all patients underwent unilateral posterior cordotomy or partial cordoarytenoidectomy. A C-shaped wedge (diameter 3.5–4 mm) was carefully removed from one vocal fold at its posterior end. Starting from the free border anterior to the vocal process, the excision was extended 4 mm laterally over the false vocal fold (Figure 1). This procedure created an approximately 6-mm opening in the posterior part of the glottis. Anti-reflux medications were prescribed for a duration of 8 weeks following the surgery, and patients were advised to be in voice rest for 10 days postoperatively. Follow-up assessments were conducted for a minimum of 1 year for all patients.

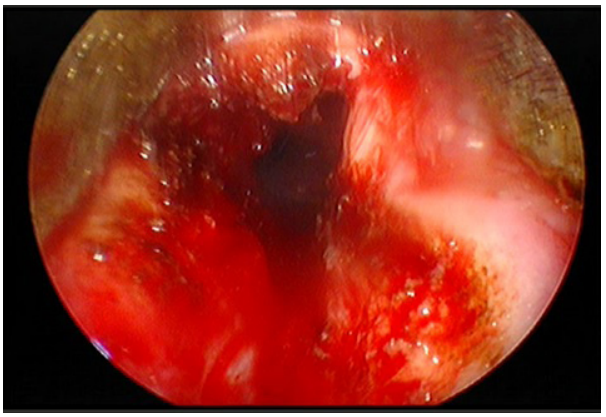

Figure 1: Right vocal fold posterior cordotomy -1

RESULTS

In this study, 25 female patients with bilateral abductor vocal fold paralysis were enrolled. Their ages ranged between 25 and 50 years. All patients were post-thyroidectomy and presented with difficulty in breathing and stridor on exertion. Moreover, two patients presented with a tracheostomy tube in situ, but adhesion between vocal folds at the membranous part was observed in one patient (Figure 2). This patient was decannulate after 3 weeks with no recurrence of adhesion. Postoperative aspiration occurred in 5 (20%) patients for 4 weeks, especially in cases that underwent partial cordoarytenoidectomy. There was a decrease in voice for 10 -12 weeks then improved gradually to an acceptable level, with improvement in breathing in all

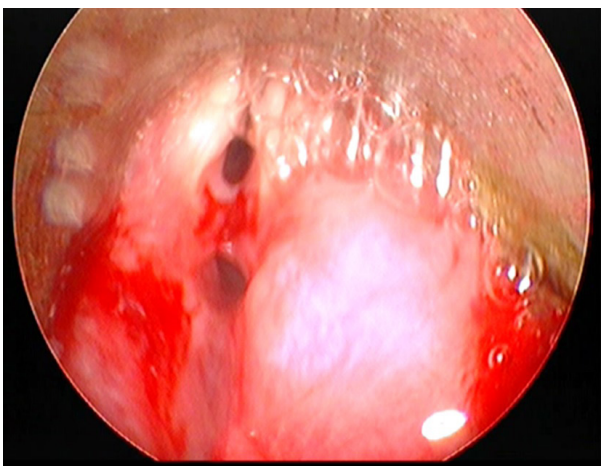

Figure 2: Adhesions between the vocal fold -1

patients. Only two patients complained of inspiratory dyspnoea postoperatively and required reoperation (partial cordo-arytenoidectomy) after 6 months.

DISCUSSION

Natural laryngeal function rarely recovers spontaneously after paralysis of both recurrent laryngeal nerves. Consequently, various approaches to surgically overcome glottic narrowing were coined and are being used when spontaneous recovery is not anticipated. The primary objective of treating bilateral palsy is to secure the patient's airway and restore smooth breathing. However, it is also crucial to restore additional functions of the larynx, including phonation and swallowing, to ensure a good quality of life (17). Effortless breathing was achieved in all our patients as the primary outcome of the surgical interventions and smooth swallowing and acceptable phonatory function.

With the advent of endoscopic surgery and the use of CO2 lasers in laryngeal surgery, advancements were made. The advantages of these techniques include accurate targeting, decreased intraoperative oedema and precise haemostasis. However, these procedures do have some disadvantages, as they may result in granulation tissue formation, voice worsening, adhesions, aspiration, dysphagia, and inflammation of the cricoid cartilage's perichondrium (18). To our knowledge, CO2 laser is not available in Yemen, neither in private nor in governmental health facilities.

Tracheotomy used to be the prevailing procedure for establishing a secure airway for patients with bilateral vocal fold paralysis, particularly in cases of glottic obstruction (3). The vocal fold and arytaenoid abduction are two examples of anatomical components that may be realigned or removed during glottic expansion treatments. The reversibility of laterofixation and its limited influence on swallowing and speaking abilities make laterofixation a viable alternative to tracheostomy. Nevertheless, tracheotomy is not favoured by most patients because of the existence of an opening with a tube in the neck, the necessity for long-term care, and the resultant reduction in quality of life (19). In this context, two of our patients presented with a tracheostomy tube in situ which was used as the first-line management. Moreover, tracheostomy can be performed by neck surgeons other than otolaryngologists.

In our study, 25 female patients aged between 25 and 50 years who had undergone thyroidectomy with no evidence of other causes were managed during the study period. Thyroid surgery represents the only cause of paralysis in our patients, which could be attributed to the prevalence of this operation. This is comparable with the findings of Vajpayee et al. (6), where total thyroidectomy was the most frequent cause, but prolonged intubation was second in their study.

Among our patients, two presented with tracheostomy tubes, which were successfully removed 2 weeks after the operation, resulting in satisfactory breathing. This aligns with the findings of Bizakis et al. (20), who reported decannulation in (100%) of his patients, as well as Boslely et al. (21). We also observed no difference in outcomes between partial arytenoidectomy and posterior cordotomy procedures, which is consistent with previous research (6).

In order to maximise laryngeal airway while preserving voice quality, both procedures (posterior cordotomy and medial arytenoidectomy) were implemented for management of bilateral abductor palsy patients (21). These procedures preserve the vocal cord's vibrating segment, which helps to minimise alterations in voice quality; however, if the vocal cord's vibrating portion is damaged, it can result in a hoarse and breathy voice and a deterioration in overall voice quality (19). In our study, there was a decrease in voice for 10–12 weeks before gradually improving to an acceptable level. This was aided by voice rest and voice therapy during the recovery period.

We selected cases for posterior cordotomy and partial arytenoidectomy after at least 12 months had passed since the diagnosis of bilateral abductor paralysis. Some studies suggest waiting for 12 months to allow for the resolution of the underlying neurological cause (6), whereas others suggest waiting only 6 months after the diagnosis (17).

Airway narrowing can result from complications such as scar formation and granuloma development, which can occur after medial arytenoidectomy and posterior cordotomy surgeries. One or more revision procedures are usually necessary in such circumstances (1). This was the situation with two of our patients who complained of inspiratory dyspnoea; a revision partial cordo-arytenoidectomy was performed after 6 months and was successful.

Although surgical intervention is commonly indicated, it is also essential to manage inflammatory and infectious conditions that may contribute to paralysis. Corticosteroids have demonstrated effectiveness in conditions such as sarcoidosis, polychondritis, and Wegner's granuloma. In children, spontaneous resolution of symptoms occurs in over 50% of cases within the first 12 months (22). Therefore, before considering invasive surgical interventions that could affect phonation and swallowing, this aspect should be carefully considered. In adults, prognosis is highly dependent on the underlying cause. However, if a patient is experiencing increased work of breathing or significant stridor, surgical intervention to improve the airway becomes necessary, even if spontaneous recovery is anticipated (23).

It is important to acknowledge the limitations of our study, including the absence of a control group to compare outcomes with alternative treatment modalities such as laser therapy and the relatively small number of cases.

CONCLUSION

The results of the current study contribute to the existing body of evidence on surgical interventions for BVFP, demonstrating the potential benefits of posterior cordotomy and partial cordoarytenoidectomy in improving respiratory and phonatory outcomes. The management of bilateral vocal fold paralysis

must be highly individualised, and the treatment approach may vary depending on the specific needs and goals of each patient.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Sana'a University (Date: 10.05.20216).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.O.M., N.Y.AO.; Data Acquisition- A.O.M., N.Y.AO.; Data Analysis/ Interpretation- A.O.M., N.Y.AO.; Drafting Manuscript- A.O.M., N.Y.AO.; Critical Revision of Manuscript- A.O.M., N.Y.AO.; Final Approval and Accountability- A.O.M., N.Y.AO.; Material or Technical Support - A.O.M., N.Y.AO.; Supervision- A.O.M., N.Y.AO.

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

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Evaluation of Voice in Patients with Antineutrophil Cytoplasmic Antibody Associated Vasculitides*

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ABSTRACT

Objective: Antineutrophil cytoplasmic antibody-associated vasculitides (AAV) can affect the upper and lower respiratory tract. Evaluation of voice quality was aimed at patients with AAV in this paper.
Materials and Methods: In this study, AAV-diagnosed patients and their age-gender-compatible healthy counterparts were enrolled. Participants with histories of airway surgery, smoking, laryngopharyngeal reflux symptoms, allergy, active nose, throat, and larynx infection were excluded. After the otolaryngologic examination, Voice Handicap Index-10 (VHI) scores, maximum phonation times (MPT), auditory-perceptual analysis of voice (GRBAS score), and acoustic analysis were performed. The MPT, VHI, GRBAS, F0, jitter, shimmer, and harmonic-to-noise ratio (HNR) values of both groups were compared statistically. Parameters were evaluated using the PRAAT software.
Results: There were 30 subjects in each group (16 women and 14 men). The mean ages were 51.1 and 51.5 years in the patient and control groups. Significant differences were found between the two groups regarding median VHI scores, MPT, and GRBAS scores ($p<0.05$). While median VHI and GRBAS scores were higher in the vasculitis group, median MPT was shorter.
Conclusion: Voice quality may disturb patients with AAV, especially in terms of VHI, MPT, and GRBAS scores.
Keywords: PRAAT, voice analysis, GRBAS score, jitter, shimmer

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitides (AAV) are systemic diseases that can affect various organs, especially the upper respiratory tract, lungs, and kidneys. Microscopic polyangiitis (mPAN), eosinophilic granulomatosis with polyangiitis (EGPA), and granulomatosis with polyangiitis (GPA) are the three main forms of this group of diseases. Their main characteristic histopathology is necrotising granulomatous inflammation that most often involves the respiratory tract. It is assumed that granulomatosis lesions during respiratory infection or other inflammatory conditions prepare neutrophils for a prompt by AAV in the airway mucosa (1).

For phonation, we must be able to adduct our vocal folds, establish subglottic pressure, and vibrate the vocal folds. An organised stimulation from the bilateral recurrent laryngeal nerve provides movement in the vocal folds medio-inferiorly owing to the contraction of the adductor intrinsic muscles and movement of the arytaenoid cartilages in normal phonation. Symmetric adduction of the vocal folds is maintained in this manner. When the subglottic pressure that forms expires from the lungs reaches a particular brink, the air runs away from the glottis, and vocal folds vibrate. A condition that interferes with any of this physiology may produce a change in voice quality. Neurogenic disorders cause dysphonia by affecting the abduction and adduction of vocal folds at appropriate times. It is necessary to have sufficient breath support to achieve the

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phonatory threshold pressure. It may be deficient in pulmonary disorders. Mucosal lesions of the airway distort vibration and, therefore, also cause dysphonia (2). AAV can disturb voice quality, influencing the lungs and upper airway mucosa, and cause small vessel vasculitis such as vasonervorum of the recurrent laryngeal nerve.

The aim of this study was to evaluate the voice quality of patients with AAV by comparing them with healthy subjects.

MATERIALS and METHODS

The study was planned as a case–control study performed between April 2022 and December 2022 in a university hospital. After ethical committee approval (Erciyes University, Ethical Committee of Clinical Research. Date: 27.07.2022, No: 2022/534); patients with AAV and over 18 years old who the rheumatology department followed were invited to the study. An informed consent form was obtained from all participants. Patients with histories of airway surgery, smoking, laryngopharyngeal reflux symptom index scores in local language of more than 13, allergy, active nose, throat, and larynx infection were excluded (3). Then, patients were taken to a soundproofed room to cheque their speech; their maximal phonation times (MPT) were recorded with the /a/ vowel. It was repeated three times, and the maximum values were selected.

For self-perceptual analysis, a valid and safe voice handicap index (VHI-10) survey in the local language was performed on patients (4). The VHI survey consisted of 10 questions with scores between 0 and 4 according to symptom severity (0 = never, 1 = almost never, 2 = sometimes, 3 = almost always, and 4 = always).

Patients were requested to read a phonetically balanced sentence at an undisturbed range and sound and recorded. Subjects' voices were recorded using a microphone (Shure SM-58; Shure Inc., Niles, IL, USA) with a standard soundboard (Sound Blaster Live Value, Creative Technology Ltd., Jurong East, Singapore). These records were used to estimate for auditory perceptual analysis. A well-known scale was made with five aspects: grade, roughness, breathiness, asthenia, and strain (GRBAS). GRBAS scales were rated by an experienced otolaryngologist blind to the groups of subjects. Each aspect had 4 points (0 = normal, 1 = mild, 2 = moderate, 3 = severe disorder in voice).

Voice analysis: Analysis was done using the same ambience with /a/ vowel. These recordings were made at a steady mouth-to-microphone distance (15 cm). Before recording to obtain maximum steady phonation; subjects were instructed to maintain /a/ vowels at an undisturbed range and sound of noise three times. The vowel /a/ articulated with a calm voice was recorded for five seconds and digitalised in all patients for evaluation.

Age- and gender-compatible subjects admitted to the hospital, except for those with voice complaints, were included in the study as the control group. All procedures, and VHI and GRBAS evaluation and voice recording, were performed. The exclusion criteria were implemented again. Neither patients nor healthy subjects were voice professionals.

Specialised PRAAT software, which is a valuable interface for voice analysis, was used (5). The voice analysis results of patients [basic frequency (F0), jitter %, shimmer %, and harmonic-to-noise ratio (HNR) values for the /a/ vowel) were evaluated with the control group. Patients and age-gender compatible subjects were statistically compared regarding MPT, VHI scores, GRBAS scores, and voice analysis.

Statistical analysis

SPSS (version 24.0; IBM, New York, USA) software was used for the analyses. A Shapiro-Wilk test was used to evaluate the normality of the data distribution. Normally distributed data are presented as the mean ± standard deviation (SD). When data measures were not normally distributed, they were presented as medians (25-75 percentiles), and the Mann -Whitney U test was used for the analysis. A p-value of 0.05 was considered statistically significant.

RESULTS

There were 30 people in each group (16 women and 14 men). The mean ages were 51.1±2.7 and 51.5±2.8 in the patient and control groups, respectively. The patient and control groups were similar to age and gender ($p>0.05$).

Laryngeal examination: There was no pathology in the laryngoscopy in both groups.

MPT scores: Median MPT values of the patient group were shorter (19 to 23.5 sec, respectively) than healthy controls, and this difference was significant statistically ($p<0.05$).

VHI scores: Median VHI scores were higher than the control group's (2.5 to 0, respectively), and the difference was significant statistically ($p<0.05$).

GRBAS scores: While median GRBAS scores were higher in the patient group [2 (0-4)], it was 0 [0-0.25)] in control group. The difference was significant statistically ($p<0.05$).

Voice quality: Despite being statistically insignificant, median F0 and median HNR values were lower in patients (177.5 to 180.5 Hz and 14.44 to 16.64, respectively). In contrast, median jitter and median shimmer values (1.39 to 1.2 and 10.64 to 9.34, respectively) were higher in the patient group. These differences were not statistically significant ($p>0.05$). Comparison of groups were given in Table 1.

Patient subgroups showed no significant difference according to their autoantibody type (myeloperoxidase/proteinase 3). In addition, there were no significant differences between the vasculitis subtypes (EGPA / GPA and mPAN).

Table 1: Comparisons of groups in terms of variables statistically

	ANCA + Group (n:30)	Control Group (n:30)	p
Women	16	16	1
Age	51.1±2.7	51.5±2.8	0.86
	Variable [Median (25%-75%]		
MPT (sec)	19 (15-25)	23.5 (18.75-28)	**0.012**
VHI	2.5 (0-9.75)	0 (0-1.25)	**0.02**
GRBAS Score	2 (0-4)	0 (0-0.25)	**0.00**
F0	177.5 (138.75-221)	180.5 (119.75-215.75)	0.53
Jitter %	1.39 (0.85-2.83)	1.2 (0.6-1.72)	0.196
Shimmer %	10.64 (9.2-16.37)	9.34 (7.05-14.51)	0.179
HNR	14.44 (11.64-18.41)	16.76 (14.69-19.47)	0.104

VHI: Voice Handicap Index; MPT: Maximum Phonation Time; GRBAS: Grade, Roughness, Breathiness, Astheny, and Strain; F0: Fundamental Frequency; HNR: Harmonic to Noise Ratio

DISCUSSION

Because AAV influences the lung and upper respiratory tract, this involvement can affect voice quality. We designed a study to evaluate voice quality in patients with AAV by comparing age- and gender-compatible healthy controls. There were significant differences in the median MPT, VHI, and GRBAS scores. In addition, the median F0 and HNR values were lower in patients than in the control group. The median jitter and shimmer values were higher in the patient group. Voice quality parameters were worse in the patient group.

AAV is a group of diseases characterised by inflammation of blood vessels, endothelial injury, and tissue damage. The vessels affected by AAV are typically capillaries, arterioles, and venules. Small arteries and veins may also be involved. AAV represents one of several types of autoimmune vasculitis. Although GPA and MPA can involve small blood vessels in any organ or tissue, they commonly affect the upper and lower respiratory tract and kidneys. Prevalence rates have been reported as 300–421 per million people in recent studies, a rise presumably elucidated by advances in survival and better case definition. Necrotising or granulomatous inflammation can affect the ear, nose, and throat tract. Therefore, the patient experiences chronic rhinitis, sinusitis, or laryngitis symptoms. In a similar manner, pulmonary haemorrhage that presents as cough, haemoptysis and shortness of breath may develop (6).

Dejonckere et al. recommended performing a comprehensive voice assessment, laryngeal imaging, self-assessment, auditory-perceptual impression, and aerodynamic and acoustic analyses (7). This study attempted to comply with these parameters.

MPT is accepted as an aerodynamic assessment that evaluates glottal adequacy by assessing the pulmonary reservoir's capability and the larynx's myoelastic forces (8). Healthy lung function and air flow velocity are necessary to sustain balanced phonation. When the MPT duration is weak, it means that the breathing volume is difficult or that the glottal resistance is too low, which might cause a distortion in voice quality (9, 10). The median MPT was shorter in the patient group in this study, which suggests that AAV can distort voice quality by affecting the upper respiratory tract and lungs.

VHI is a scale to evaluate voice from the patient's perspective and is a widely used survey for voice self-assessment. VHI scores range from 0 to 4 according to symptom severity (0 = never, 1 = almost never, 2 = sometimes, 3 = almost constantly, and 4 = always). The higher the score, the worse the voice quality. A valid and reliable form of VHI-10 in the local language was applied in this study (4). The median VHI score was higher in the patient group.

The clinicians perspective is as important as that of the patients for voice assessment. Because auditory-perceptual voice analysis is affected by multiple factors such as experience, profession, and rating stimuli, GRBAS scores have been developed to standardise voice assessment (11). The higher the score, the worse the voice quality. The median GRBAS score was significantly higher in the patient group, indicating that AAV may disrupt voice quality.

Jitter and shimmer are other acoustic parameters related to voice perturbation. Shimmer shows disarrays in the mucosal oscillating wave, obvious as high transient versatility in either vocal signal width. If this irregularity is related to the vocal signal, it is called jitter, which is higher in dysphonic subjects (12). Jiang et al. reported that the jitter percentage in adult patients' voices with vocal folds' polyps and nodules was significantly higher than that in normal subjects (13). Despite statistical insignificance, jitter and shimmer were higher in the patient group in the present study.

There are harmonic and aperiodic (noise) components of the speech signal. The HNR parameter indicates the ratio of the harmonic and noise fragments. Pathologies in the vocal folds switch the phonation course because the vibration types during the opening and closing phases of the vocal cords are unsteady

(14). HNR measures the amount of correlative noise. The lower the HNR, the more noise there is in the voice. Laryngeal diseases may lead to ineffective adduction of the vocal folds and therefore boost the quantity of random noise in the vocal note. If a laryngeal problem causes more air to escape during vibration, this creates turbulent noise; the more significant the proportion of noise, the lower the HNR (15). The median HNR was lower in the patient group in this study.

Gurbuzler et al. studied the voice quality of patients with Behçet's disease and healthy controls (16). They reported that Behçet's disease impaired voice quality. F0, jitter, shimmer, and HNR values were used in their study. They also evaluated the subjects' MPT and VHI scores. They found significant differences in MPT and shimmer. MPT was higher in healthy subjects than in the patients in their study. We found comparable results in terms of MPT in this study. Although they found no difference between the VHI scores, the median VHI score was higher in the patient group than in the control group in our study.

Castro et al. reported a study evaluating voice parameters in patients with rheumatoid arthritis (17). They did not compare the patients with any control. They reported that patients with RA had 70% dysphonia and high VHI scores. Laryngeal examination, VHI, perceptual analysis, F0, jitter, shimmer, and HNR were used parameters in their study, as in this paper.

De Macedo et al. evaluated voice in patients with systemic lupus erythematosus (SLE) and found that voice quality was worse in the patient group than in healthy subjects (18).

Ali and Figueiredo reported a patient with hoarseness and giant cell arteritis. They emphasised that this symptom could be overlooked in such patients and should be considered (19). Sünter et al. reported that F0 was lower in patients with ankylosing spondylitis (20). Rheumatologic disease can disturb voice quality.

Phonation is one of the most complex processes in the human body. It requires a good lung function for the reservoir first. Bilateral symmetric neuromuscular function that provides vocal fold mobility is another necessity for a sound voice. Despite the normal laryngeal view endoscopically, these structures may be affected by AAV, chronic inflammation in other words. There were significant differences in the MPT, VHI, and GRBAS score results in the present study. MPT was related to lung function rather than the larynx. VHI and GRBAS scores were subjective parameters. Because of this, laryngeal endoscopy may have viewed normal.

To the best of our knowledge, no study has evaluated voice quality in patients with AAV. Considering the incidence of AAV, the sample size can be assumed to be acceptable.

CONCLUSION

In short, patients and physicians should be aware of the possibility of voice disorders in AAV, and voice therapy may be advised to the patients. AAV may disturb voice quality in terms of aerodynamic aspects, voice handicap index, and auditory-perceptual analysis. Broader studies can be established on this issue.

Ethics Committee Approval: This study was approved by the Ethics Committee of the Erciyes University (Date: 27.07.2022, No: 2022/534).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Characteristics of Patients with Craniopharyngioma and Long-Term Outcomes of Treatment

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ABSTRACT

Objective: Craniopharyngioma (CP) is benign, but its treatment is challenging because of its occurrence in a critical area. Hypothalamic-pituitary dysfunction (HPD) is an important complication that is related to tumour itself or to therapy. This study identified the long-term outcomes of CPs.
Material and Methods: Records of 44 patients with CPs followed up at the Istanbul Faculty of Medicine were retrospectively reviewed.
Results: The mean age of 34 patients (M/F: 19/15) at diagnosis was 24±13.3 years. The most common symptoms were headache (60.3%) and visual impairment (45.5%). The tumour was localised in suprasellar region in 76.6%, in sellar-suprasellar in 16.7%, and in the sellar region in 6.7% of the patients. The mean tumour diameter was 32.7±10.4 mm (n: 19). Surgery was the first line of treatment in all patients except one, and 13 patients underwent more than one operation. Ten patients received radiotherapy. The median duration of follow-up was 6.5 years. Anterior pituitary dysfunction was observed in all patients: hypocortisolism in 88.2%, hypothyroidism in 97%, hypogonadism in 88.2%, growth hormone deficiency in 68.2%, and prolactin deficiency in 20.6% of the patients. Diabetes insipidus occurred in 97% of the patients. Recurrence developed in 2 patients (after 5-6 years). At the end of all treatments, 15 patients had residual disease.
Conclusion: The curative treatment of CP is surgery. HPD is associated with increased mortality and morbidity and decreased quality of life. It is essential to protect the hipothalamo-pituitary axis and to choose the best treatment option for each patient.
Keywords: Craniopharyngioma, hormone, pituitary, hormone deficiency, hypothalamus

INTRODUCTION

Craniopharyngiomas (CPs) are rare and benign epithelial tumours arising along the craniopharyngeal duct and located in the sella turcica or suprasellar area near vital structures like the hypothalamus, hypophysis, optic chiasm, third ventricle, cranial nerves, and major blood vessels. CPs constitute 2-5% of all primary intracranial neoplasms (1). The age-adjusted incidence of CP is 0.19 /100,000 persons in the United States (2). There are two histological subtypes, adamantinomatous (ACP) and papillary (PCP), which also differ in pathogenesis and age distribution. BRAF V600E mutations are detected in up to 95% of the PCP subtypes, and they are typically solid tumours. In contrast, CTNNB1 (encoding β-catenin) mutations are found in up to 96% of ACP subtypes, and these are predominantly cystic tumours (3, 4).

CPs occur equally in males and females and exhibit a bimodal age distribution with the highest incidence rate in children aged 5-15 years and older adults aged 50-74 years (5). CPs are slow-growing tumours, therefore the diagnosis is often delayed. It is diagnosed when the patient develops symptoms due to compression or damage to adjacent structures. Clinical manifestations include headache, visual impairment, endocrine deficiencies, psychiatric disturbances, slowed cognition, nausea, vomiting, and lethargy (6). Although they are benign tumours, their surgical treatment is challenging because they have aggressive behaviour and tend to infiltrate adjacent

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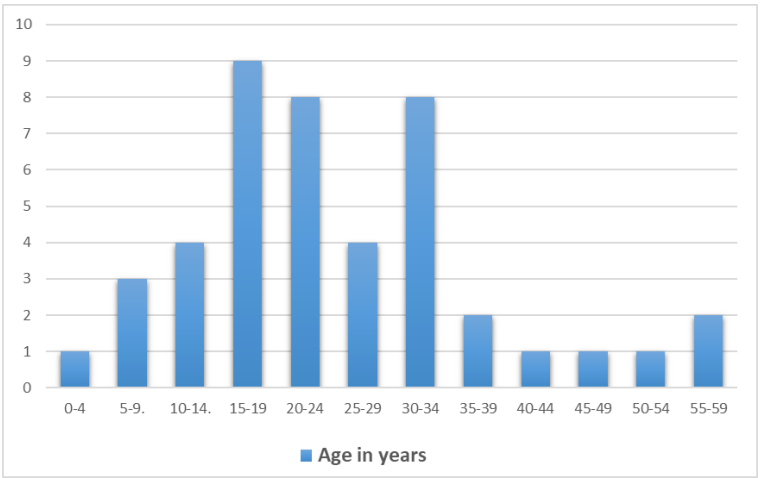

Figure 1: Age distribution of patients with craniopharyngioma

structures. Damage to these critical adjacent structures leads to increased mortality and morbidity (7).

Surgery is the primary treatment, but treatment strategies are controversial. Total gross resection (GTR) is associated with better overall and progression-free survival than subtotal resection alone. Nevertheless, subtotal resection followed by adjuvant radiotherapy (RT) results in similar rates of tumour control as GTR, particularly in tumours with hypothalamic involvement, and is associated with a decreased risk of central diabetes insipidus (DI) (8-11). Surgical complications include bleeding, CSF leakage, infection, and injury to critical structures. Radiation-specific complications include atherosclerosis and vascular anomalies. In addition, endocrine abnormalities can be intensified after treatment due to injury to the hypothalamus and pituitary gland. Isolated hypothyroidism, hypogonadism, adrenal insufficiency, growth hormone deficiency, or panhypopituitarism may develop after therapy because of damage to the pituitary gland. Hypothalamic damage may lead to disturbed hunger-satiety and thirst feelings, disturbances of circadian rhythm and temperature regulation, obesity, type 2 diabetes mellitus, nonalcoholic fatty liver disease, hypopituitarism, and central DI.

In this study, we aimed to evaluate the clinical features, presence and type of pituitary-hypothalamic dysfunction (HPD), and long-term treatment outcomes of patients with CP.

MATERIALS and METHODS

This study was designed retrospectively, and patients diagnosed with CP who were followed up in the Department of Endocrinology and Metabolic Diseases of İstanbul Faculty of Medicine between 1980 and 2023 were included. Clinical characteristics, laboratory results, treatment modalities, state of hypothalamic-pituitary axis function, and treatment outcomes were obtained from the patients' medical records. For detailed examination, patients with a follow-up period of at least 1 year were included in the study.

The study protocol was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (Date: 08.09.2023- No: 18). Informed consent was not obtained from the patients because of the nature of the retrospective study.

Statistical analysis

Statistical analyses were performed using the SPSS (IBM SPSS Corp., Armonk, NY, USA) software (version 21.0). Categorical variables are presented as frequency and percentage of occurrence, whereas numerical variables are presented as median, mean, and standard deviation (SD). The Mann-Whitney U test and Student's t-test were performed to compare the groups (non-parametric and parametric data, respectively). Cross-group comparison for categorical variables was obtained using Chi-square/Fisher tests. A "p" value of <0.05 was considered statistically significant.

RESULTS

A retrospective review of the patients' medical records revealed 44 patients with CP. The mean age at diagnosis of CP was 24.4±12 years (range, 2 to 57). The distribution according to age at diagnosis is shown in Figure 1. There were 19 females (43.2%) and 25 males (56.8%), and the male to female ratio were 1.3/1. After excluding 10 patients because of a short follow-up period or lack of follow-up data, 34 CP patients constituted the study group. The mean age at diagnosis of these patients was 24±13.3 years. There were 13 patients under the age of 18 years and 21 patients over the age of 18 years at the time of diagnosis. There were 15 females (44%) and 19 males (56%).

The most common symptoms at presentation were headache and visual impairment, which occurred in 60.6% and 45.5% of patients, respectively. The other symptoms were nausea and vomiting (21.2%), polyuria-polydipsia (12%), seizure (9%), growth retardation (4 /13), delayed puberty (1/13), menstrual irregularities in women, or loss of libido (8/21). Fourteen patients had deficiency of anterior pituitary hormones: hypogonadism in 9 patients, hypocortisolemia in 4 patients, hypothyroidism in 2 patients, and growth hormone deficiency in 2 patients. In 30 patients, data about the localisation of the

CP was available and tumour was localised at the suprasellar region in 23 patients (76.6%), at sellar-suprasellar region in 5 patients (16.7%), and in the sella in 2 patients (6.7%). Data about tumour diameter was available in 19 patients, and the mean diameter was 32.7±10.4 mm (range, 18-60). Only 1 patient had a papillary subtype of tumour.

Surgery was the first line of treatment in all patients except one patient with cystic CP who was treated with endocavitary radioisotopes before surgery. A residual tumour was present in 50% of patients (17/34) after initial surgical treatment. Three of them were re-operated and the tumour was removed completely. In 3 patients, the tumour could not be removed

Table 1: Characteristics of patients, treatment modalities, response to therapy, and presence of hypothalamic-pituitary dysfunction

Patients	Sex	Age at diagnosis	Diameter of tm (mm)	Localisation	No. of surgeries	RT	Presence of residual disease after therapy	Presence of HPD No. of deficient hormone*	Presence of DI
Case 1	M	13	40	Suprasellar	1	+	+	4	+
Case 2	F	12	30	Suprasellar	1	-	-	3	+
Case 3	M	15	60	Suprasellar	3	+	+	3	+
Case 4	M	26	25	Suprasellar	1	-	-	3	+
Case 5	F	30	40	Suprasellar	2	-	-	3	+
Case 6	M	15	NA	NA	1	-	-	5	+
Case 7	M	26	NA	NA	1	+	+	3	+
Case 8	M	24	25	Suprasellar	2	+	+	4	+
Case 9	M	16	NA	Suprasellar	1	-	-	4	+
Case 10	M	38	18	Sellar-Suprasellar	1	-	+	3	+
Case 11	F	30	35	Suprasellar	1	-	-	2	+
Case 12	M	23	40	Suprasellar	4	+	+	5	+
Case 13	M	21	22	Suprasellar	1	-	+	4	+
Case 14	F	34	27	Suprasellar	1	+	-	2	+
Case 15	F	6	NA	NA	1	-	-	1	+
Case 16	F	16	NA	Sellar-Suprasellar	1	-	-	4	+
Case 17	F	57	NA	Suprasellar	1	-	-	2	+
Case 18	F	20	21	Sellar-Suprasellar	2	-	+	4	+
Case 19	F	35	NA	Sellar	2	-	+	2	+
Case 20	M	31	32	Suprasellar	3	+	+	3	+
Case 21	F	15	NA	Suprasellar	2	-	-	2	-
Case 22	M	23	NA	Suprasellar	1	-	-	3	+
Case 23	M	11	25	Suprasellar	1	-	+	4	+
Case 24	F	8	NA	Suprasellar	1	-	-	4	+
Case 25	M	52	NA	Suprasellar	1	-	-	3	+
Case 26	F	5	NA	Suprasellar	3	-	+	4	+
Case 27	M	27	43	Sellar-Suprasellar	3	-	-	5	+
Case 28	M	2	44	Sellar-Suprasellar	4	+	+	5	+
Case 29	F	45	30	Suprasellar	1	-	+	3	+
Case 30	F	42	25	Suprasellar	1	+	-	2	+
Case 31	M	33	NA	NA	2	-	-	5	+
Case 32	M	33	NA	Sellar	1	-	-	3	+
Case 33	F	10	NA	Suprasellar	2	+	+	2	+
Case 34	M	22	39	Suprasellar	1	-	-	5	+

*Anterior pituitary hormones, NA: Not available; Tm: Tumour; No. of surgery: Number of surgery; RT: Radiotherapy; HPD: Hypothalamic-pituitary dysfunction; DI: Diabetes insipidus

completely despite multiple surgeries (total 2 operations in 2 patients, 3 in one patient). Four of the 17 patients with residual tumours were followed up, including a patient who had previously received intracavitary radioisotope therapy. Two patients received only RT. Five of the 17 patients with residual tumours underwent both surgeries plus RT after surgery. CSF leakage developed in 2 patients, haematoma in 2 patients, worsening of vision in 2 patients, and subdural fluid collection in 1 patient. A total of 10 patients received RT, with stereotactic radiosurgery being used in 3 of them (cyber-knife in 2 patients, gamma-knife in 1 patient).

removed after the first operation, 2 patients developed recurrence (after 5 years in 1 patient, and after 6 years in the other). Details are summarised in Table 1.

When the patients were evaluated in terms of disease or treatment-related anterior pituitary dysfunction, five hormone deficiencies developed in six patients, four hormone deficiencies in nine patients, three hormone deficiencies in 11 patients, two hormone deficiencies in seven patients, and one hormone deficiency in one patient. DI occurred in all patients except one. Four of these patients were diagnosed with

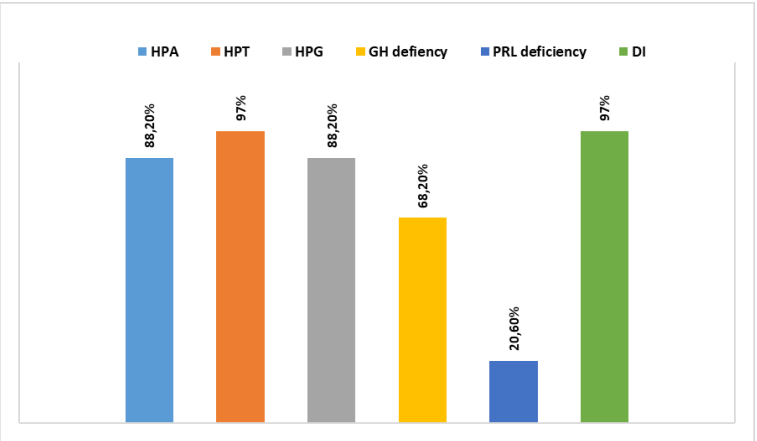

Figure 2: Proportion of patients according to the pattern of hypothalamic-pituitary dysfunction

HPA: Hypothalamic-pituitary-adrenal; HPT: Hypothalamic-pituitary-thyroid; HPG: Hypothalamic-pituitary-gonad; GH: Growth hormone; PRL: Prolactin; DI: Diabetes insipidus

Table 2: Factors influencing hypothalamic-pituitary dysfunction

	All patients n=34	Patients with no. of hormone deficiency** >2 (n=26)	Patients with no. of hormone deficiency** ≤2 (n=8)	p
Age at diagnosis (years) mean±SD	24±13.3	22.6±11.8	28.6±17.3	0.379
Male gender % (n)	55.9 (19)	73.1 (19)	0	**<0.001**
Tumour diameter (mm) at presentation(n=19) mean±SD	32.7±10.4	33.4±11.1 n=16	29±5.3 n=3	0.329
Duration of follow-up (months) Median (IQR)	78 (36-174)*	84 (35-164)*	67 (38.5-208.5)*	0.984
RT % (n)	30.3 (10)	26.9 (7)	37.5 (3)	0.646
Multiple operations % (n)	38.2 (13)	38.5 (10)	37.5 (3)	1.000
Presence of the residue % (n)	44.1 (15)	46.2 (12)	37.5 (3)	1.000

*Median values were used because the data did not comply with the normal distribution. ** anterior pituitary hormone

The mean duration of follow-up from the first surgery to the last visit was 9.75±8.75 years (median 6.5 years; range, one to 34). Among the 17 patients whose tumours were completely

DI at presentation. Details are summarised in Figure 2. The development of more than two hormone deficiencies was not associated with age at diagnosis, tumour size, follow-up time,

number of surgeries, or RT. In contrast, it was associated with male gender (Table 2).

Growth hormone replacement was used in 6 patients (in 5 patients during childhood). One adult patient with no residual tumour had been using growth hormone for 8 years. Eight patients had increased appetite and weight gain after the operation, two of whom developed obesity. Two patients had behavioural disturbances. Diabetes mellitus developed in 8 patients, 5 of whom also had hyperlipidaemia.

DISCUSSION

In this study, the characteristics of patients with CP followed in our centre, their management strategies, the course of their disease, long-term outcomes, and pituitary dysfunction during the follow-up of patients were reviewed.

The incidence of CP is equal in males and females. Bunin et al. reported that the incidence is lowest between the ages of 15 and 34 years, the period defined as late adolescence and early adulthood. A slight male predominance (M/F: 1.2/1) was observed in our study, and in contrast to the study of Bunin et al, the majority of our patients (29/44) were diagnosed between 15 and 34 years of age, and the distribution of age was not bimodal in our patient group (5). The most common symptoms at the presentation of CP are headache and visual impairment. Visual disturbances were observed in 62% of the patients and headache in 43% of the patients in the study of Frič R et al. Tumour location was the suprasellar region in 92% of the patients, the third ventricle and infundibulum in 7% of the patients, and the intrasellar region in 1% of the patients in the study mentioned above. Similarly, the most common symptoms at presentation were headache (60.6%) and visual impairment (45.5%). In addition, the most common location of the tumour was the suprasellar region (suprasellar: 76.6%; sellar-suprasellar: 16.7%) in our patients. However, sellar location was more frequent (6.7% vs 1%) in our study (12). A study that included a total of 666 adult patients with CP reported that 30.3% of the CPs were ACP, 14.1% were PCP, and 55.6% of CPs were reported as histological subtype not otherwise specified (13). In our study, 29.4% of CPs were APC, 3% were PCP, and in the remaining 67.6% of the patients, the subtype was not specified.

Total resection of the tumour is curative for CPs. However, it may not be possible because of the critical location because severe damage to surrounding vital structures increases long-term mortality and morbidity and decreases the quality of life. Therefore, patients may need to undergo reoperation and/or receive RT for residue tumours after the first surgery (8). Damage to the hypothalamic-pituitary region due to surgery or RT or caused by the tumour itself may result with hypothalamic-pituitary dysfunction. It has been reported that the incidence of long-term endocrine hormone deficiencies were significantly increased after the second surgery and/or RT intervention (14, 15).

In addition, Poretti et al. stated that large tumours in the hypothalamic area, young age at diagnosis, and multiple operations for the treatment of recurrent disease were associated with poor functional outcomes (16). In our study, 13 patients (38.2%) underwent multiple operations. The number of surgical procedures was 2 in 7 patients, 3 in 4 patients, and 4 in 2 patients. Panhypopituitarism developed in 6 patients, of whom 4 underwent multiple surgical treatments and 2 of these 4 patients also received RT.

DI was observed in 12% of our patients at presentation. DI was reported in 15% of CP patients at presentation in the literature, which is similar to our finding (17). Although 4 patients had DI preoperatively, almost all patients developed DI postoperatively (29/33). In the study of Frič et al., it was reported that DI developed in 56% of patients and hypopituitarism developed in 74% of patients (panhypopituitarism in 59%, partial hypopituitarism in 15%: growth hormone deficiency in 8%, hypothyroidism in 3% and hypogonadism in 3%) postoperatively (12). Guo et al. demonstrated that suprasellar origin and growth, older age at presentation, transcranial surgery, partial resection or recurrence/progression of the tumour, and ACP type were associated with increased risk of hypothalamic-pituitary dysfunction in patients after surgery. In their study, preoperative and postoperative HPD was observed in 77.5% and 96.9% of the patients, respectively, whereas preoperative and postoperative DI was reported in 24% and 60.1% of the patients, respectively (18). Compared with both studies mentioned above, HPD was observed more frequently after treatment in our study.

In the study of Kiliç et al, it was stated that 3 of the 45 patients (6.6%) whose tumour was resected totally in their first surgery developed recurrence during 15—34 months of their follow-up. In our study, the recurrence rate was similar (2/34, 5.9%), but the time to recurrence was longer (5-6 years) (19). Caldarelli et al. reported that 9 of the 49 patients with CP developed recurrence or regrowth of residue (“true” recurrences in 3 patients), and the overall recurrence rate was nearly 19%, and “true” recurrences were observed between 4 and 6 years after the operation (20).

The limitations of our study include the lack of detailed information about surgical procedures, CP subtype results, and tumour size at diagnosis in all patients. Therefore, we could not assess the effect of surgical methods, tumour size, and subtype on the development of endocrine dysfunction.

CONCLUSION

CPs arise in critical locations and can be life-threatening. Surgery is a curative treatment option, but during surgery, preserving the stalk and hypothalamus is crucial for long-term outcomes, including mortality, morbidity, and quality of life. Targeted therapy options in PCP harbouring BRAF-V600E mutations and advances in surgical and radiotherapy techniques will provide better long-term outcomes for patients.

Ethics Committee Approval: This study was approved by the Ethics Committee of the İstanbul University, İstanbul Faculty of Medicine (Date: 08.09.2023- No: 18).

Informed Consent: Informed consent was not obtained from the patients because of the nature of the retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- H.H., G.B.O., G.Y.Y., N.G., A.K.U., O.S.S., D.D., B.B., R.M.; Data Acquisition- H.H., G.B.O., G.Y.Y., N.G., A.K.U., O.S.S.; Data Analysis/Interpretation- H.H., G.B.O., O.S.S.; Drafting Manuscript- H.H., G.B.O., G.Y.Y., N.G., A.K.U., O.S.S., D.D., B.B., R.M.; Critical Revision of Manuscript- H.H., G.B.O., O.S.S.; Final Approval and Accountability- H.H., G.B.O., G.Y.Y., N.G., A.K.U., O.S.S., D.D., B.B., R.M.; Material or Technical Support- H.H., G.B.O., G.Y.Y., N.G., A.K.U., O.S.S., D.D., B.B., R.M.; Supervision- G.Y.Y., N.G., A.K.U., O.S.S.

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CASE REPORT
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Plasma Cell Neoplasms of Paranasal Sinuses: Two Case Reports

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ABSTRACT

Sinonasal system malignancies are rare, constituting only 1% of all malignancies and less than 5% of head and neck malignancies. The common form of plasma cell dyscrasias is called multiple myeloma (MM), and the localized forms are called solitary bone plasmacytoma and extramedullary plasmacytoma (EMP). EMP constitutes 3-4% of malignant plasma cell dyscrasias and 1% of all head and neck tumors. 90% of EMP cases occur in the head and neck region, because the nasal and paranasal sinus regions are rich in plasma cells at around 75%. This study aims to present two different cases of plasma cell tumors presenting in the paranasal region. Based on the imaging studies, the first case is seen to have been diagnosed as MM due to bone marrow involvement and to have received systemic chemotherapy treatment, whereas the second case is seen to have undergone endoscopic total excision of the lesion due to the absence of systemic involvement. In the first case, MM was considered to have gone into remission in the sixth month after chemotherapy; however, the patient died one year after diagnosis. In the second case, no recurrence was detected during the fifth year postoperative follow-up. As a result, patients who show sinonasal symptoms should be examined in detail.

Keywords: Extramedullary plasmacytoma, paranasal sinuses surgery, multiple myeloma

INTRODUCTION

Sinonasal system malignancies are rare, constituting only 1% of all malignancies and less than 5% of head and neck malignancies (1). The common form of plasma cell dyscrasias is known as multiple myeloma (MM), with the localized forms being solitary bone plasmacytoma and extramedullary plasmacytoma (EMP). EMP constitutes 3-4% of malignant plasma cell dyscrasias and 1% of all head and neck tumors (2, 3). The median age at diagnosis is 55-60 years, with approximately two-thirds of patients being male (4). 90% of EMP cases occur in the head and neck region (5), due to the nasal and paranasal sinus regions being rich in plasma cells at around 75% (6, 7). The study aims to present two different cases of plasma cell tumors presenting in the paranasal region that required different treatment and had different prognoses.

CASE PRESENTATIONS

Case 1

A 72-year-old female patient presented to the clinic with a complaint of a headache that had been occurring behind her left eye for the last 2 months. The patient had a history of diabetes and hypertension. On physical examination, limitation was seen to be present in the left eye movements, as well as diplopia. Upon endoscopic examination, a mass lesion was observed in the left nasal passage filling the middle meatus. The patient's complete blood count, biochemical parameters, kidney function tests and coagulation test values were normal. Paranasal computed tomography (CT) revealed a mass filling the left nasal passage, eroding the anterior wall of the sphenoid sinus and the anterior skull base (Figure 1). In magnetic resonance imaging (MRI), a solid mass lesion measuring

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Figure 1: In the preoperative paranasal CT scan along the coronal plane without contrast, soft tissue is seen in the superior part of the nasal cavity filling the anterior part of the sphenoid sinus and extending superiorly anteriorly to the base of the cranial fossa, largely filling the nasal cavity and extending into the intra-orbital space on the left.tympanic segment of the facial canal

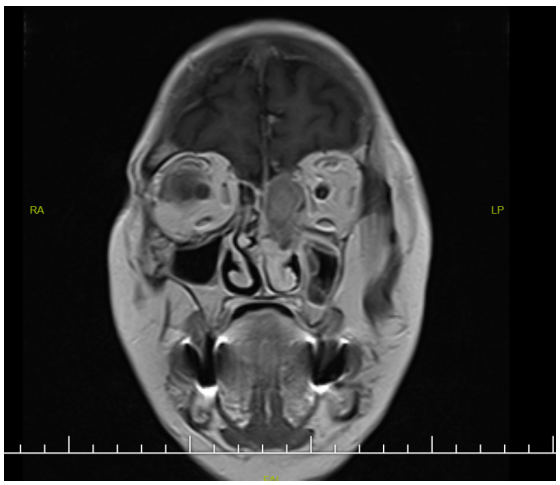

Figure 2: This orbital T1-weighted MR imaging scan of the coronal view shows a solid mass lesion measuring approximately 50x33x28 mm, with minimal compression in the medial rectus muscle, narrowing the optic canal; it is indistinguishable from the medial and inferior parts of the bilateral cavernous sinus

50x33x28 mm was observed, compressing the optic nerve and appearing hyperintense in the contrast-enhanced series (Figure 2). A written informed consent form was obtained from the patient.

Multiple biopsies were taken under general anesthesia from the polypoid mass extending to the anterior and posterior ethmoid cells. The pathology result was reported as EMP. In the positron emission tomography, fludeoxyglucose (FDG) uptake was detected in the medullary region of the left iliac wing, in addition to the mass in the paranasal region. The patient was referred to the hematology department for diagnosis. A bone marrow biopsy was taken and reported as plasma cell myeloma, after which chemotherapy treatment was planned. The orbital MRI and CT performed at six months after treatment showed the lesion to have regressed (Figures 3 and 4).

The patient presented with poor general condition 12 months after the end of her treatment. A brain MRI showed widespread parenchymal and leptomeningeal contrast enhancement and edema in the bilateral cerebellar and cerebral hemispheres. This was thought to possibly be a result of leptomeningeal involvement due to MM. Chemotherapy treatment could not be given to the patient due to her poor overall health. Despite all interventions, the patient died due to cardiopulmonary arrest while following up in the intensive care unit.

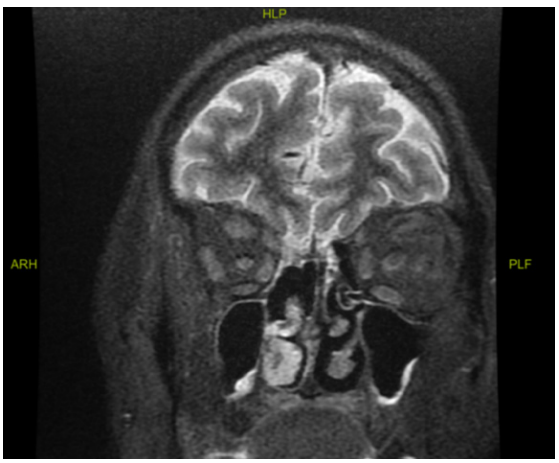

Figure 3: Regression of the existing lesion from the previous imaging studies in the orbital T1-weighted MR imaging scan from the coronal view, six months post-chemotherapy

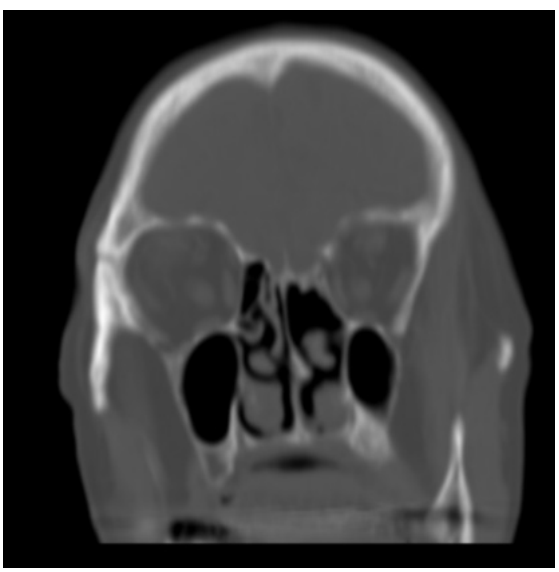

Figure 4: A paranasal CT of the coronal view in the sixth month after chemotherapy showing regression of the existing lesion in the previous imaging studies

Case 2

A 35-year-old male patient was admitted to the clinic with complaints of nasal congestion and nosebleeds for the last 3 months. In the endoscopic examination, a polypoid mass was observed starting from the nasal vestibule and extending posteriorly. He had no history of any chronic diseases. The patient's complete blood count, biochemical parameters, kidney function tests, and coagulation values were normal. In the paranasal CT, a mass was observed in the nasal cavity that had destroyed the anterior wall of the sphenoid sinus, ethmoid cells, skull base, and left orbital medial wall. In the MRI, a 41X33 mm mass with a mild to moderately contrast-enhancing was observed in the left nasal cavity expanding toward the left maxillary sinus in the medial nasal cavity, inferomedial of the orbital and anterior skull base (Figures 5 and 6). Written informed consent form was obtained from the patient.

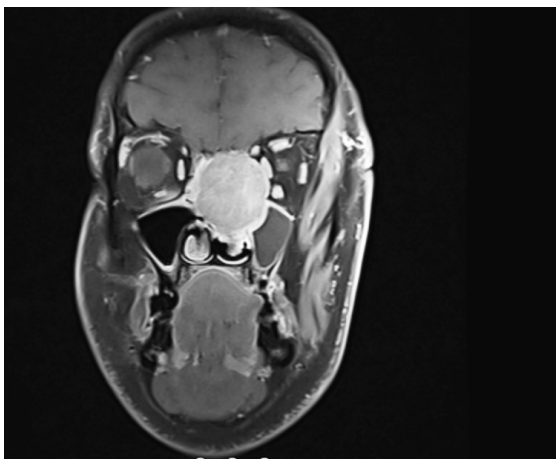

Figure 5: This paranasal T1-weighted MR imaging scan from the coronal view shows a contrasting lesion 41X33 mm in size in the left nasal cavity expanding towards the left maxillary sinus , inferomedial of the orbital and anterior skull base

Figure 6: A paranasal T1-weighted MR imaging scan of the sagittal view showing a contrasting lesion 41X33 mm in size in the left nasal cavity expanding toward the anterior skull base

The patient underwent endoscopic excision of the mass under general anesthesia. The frozen section obtained during the operation was reported as a plasma cell tumor, and the lesion was completely excised endoscopically with blunt and sharp dissection from the surrounding structures. A defect was observed at the skull base, but no finding was present

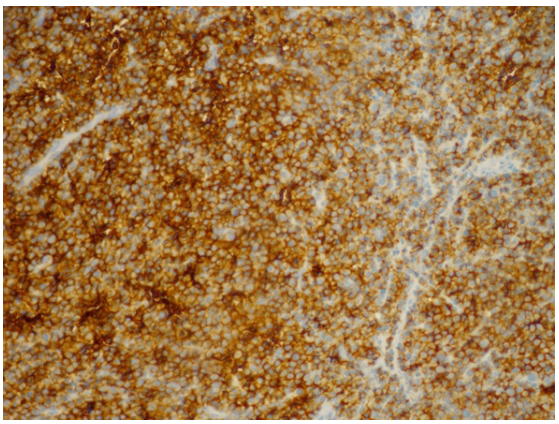

Figure 7: All cells were stained with CD38 (Immunohistochemistry; x20 obj)

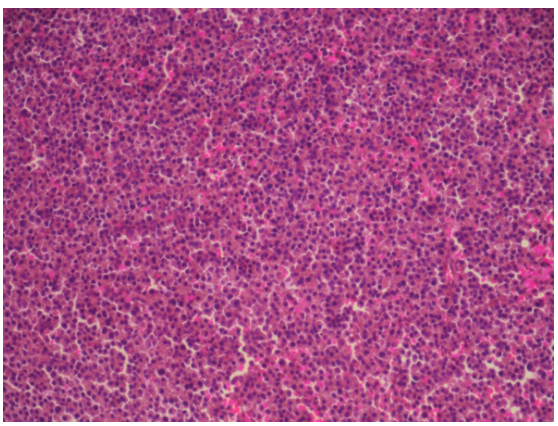

Figure 8: Neoplastic plasma cells (H&E; x20 obj)

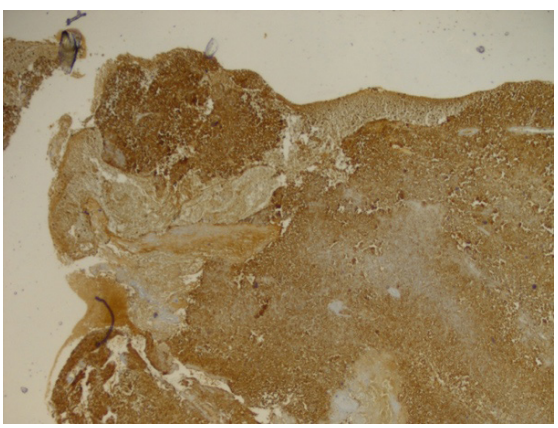

Figure 9: Positive staining with lambda (Immunohistochemistry; x4 obj)

suggestive of dural invasion, and the operation was terminated without repair due to the diameter of the defect being less than 1 cm. The pathology result was reported as a completely resected plasma cell neoplasia showing lambda clonality (Figures 7-9).

In the lumbar spine MRI, no lesion was detected, and the bone marrow biopsy results showed hypercellular bone marrow, thus ruling out any systemic involvement. No recurrence was detected in the endoscopic examination, blood tests, or MRI in five years of follow-ups.

DISCUSSION

EMP can remain localized or develop into systemic MM after a latent period. EMP has a better prognosis than MM and can be treated surgically (8). EMP progresses as a locally invasive tumor, but 5-20% of cases may present with cervical lymph node metastasis at diagnosis (9). The symptoms due to tumoral mass include nasal congestion, facial swelling, pain, and nose bleeding (10). The diagnosis of EMP is made by lesion biopsy and pathological examination of clonal plasma cell populations, with a lack of clonal plasma cells in the bone marrow and involvement in the spine and pelvis (11). The overall 10-year survival rate in EMP cases has been reported to be 70% (12), with 11-30% of cases able to progress to MM within 10 years (13).

Various surgical methods are found in the treatment of EMP; however, radiotherapy is considered as a preferred treatment method due to the tumor's radiosensitivity. İn recent studies, the combination of radiation therapy (RT) and surgical excision has shown better results for the long-term follow-up periods. In a case study examining seven cases, the authors performed RT in the first postoperative month. At the time of analyzing these data 5 patients were alive and two have died of their disease. A single patient, presenting local relapse at 6 months, one patient progressed to multiple myeloma (14). Sasaki et al. showed patients who receive any combination of RT and surgery to have significantly improved survival rates compared to patients receiving RT or surgery alone (15). The present study's first case had been referred to systemic treatment because she had been diagnosed with MM. In The second case, only surgical treatment was applied after the presence of a systemic disease had been excluded. Due to no tumor being found within the surgical margins, radiotherapy treatment was not given afterwards.

CONCLUSION

Because the symptoms in the early stages of paranasal sinus tumors are subtle and the findings may mimic chronic sinusitis, proper diagnosis may be delayed. All patients with symptoms of sinonasal neoplasia should undergo detailed endoscopic examination.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study - H.A., D.M.M.; Data Acquisition- M.M.; Data Analysis/Interpretation- G.A., D.Ö.; Drafting Manuscript- H.A., D.M.M., G.A.; Critical Revision of Manuscript- M.M., D.Ö.; Final Approval and Accountability- H.A., D.Ö., M.M., G.A., D.M.M.

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

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The Turkish Journal of Ear Nose and Throat (Tr-ENT) aims to contribute to the literature by publishing high quality original articles, case clinical reports, surgical techniques and invited reviews focusing on key subjects and contemporary developments in the field. The scope of the journal includes otology, neurootology, rhinology, head and neck, general ORL, facial plastic surgery and laryngology. The journal welcomes articles from other disciplines as well, provided that these are related to the major subject area. The target audience of the journal consists of academicians, researchers, professionals, students, related professional and academic bodies and institutions.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

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POLICIES

Publication Policy

The journal is committed to upholding the highest standards of publication ethics and pays regard to Principles of Transparency and Best Practice in Scholarly Publishing published by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME) on https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

The subjects covered in the manuscripts submitted to the Journal for publication must be in accordance with the aim and scope of the Journal. Only those manuscripts approved by every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Changing the name of an author (omission, addition or order) in papers submitted to the Journal requires written permission of all declared authors.

Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors. All manuscripts not in accordance with the accepted ethical standards will be removed from the publication. This also contains any possible malpractice discovered after the publication.

Plagiarism

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. If plagiarism/self-plagiarism will be found authors will be informed. Editors may resubmit manuscript for similarity check at any peer-review or

production stage if required. High similarity scores may lead to rejection of a manuscript before and even after acceptance. Depending on the type of article and the percentage of similarity score taken from each article, the overall similarity score is generally expected to be less than 15 or 20%.

Double Blind Peer-Review
After plagiarism check, the eligible ones are evaluated by the editors-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope. The editor provides a fair double-blind peer review of the submitted articles and hands over the papers matching the formal rules to at least two national/international referees for evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

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ETHICS

Publication Ethics and Malpractice Statement
The Turkish Journal of Ear Nose and Throat (Tr-ENT) is committed to upholding the highest standards of publication ethics and pays regard to Principles of Transparency and Best Practice in Scholarly Publishing published by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME) on https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing

All parties involved in the publishing process (Editors, Reviewers, Authors and Publishers) are expected to agree on the following ethical principles.

All submissions must be original, unpublished (including as full text in conference proceedings), and not under the review of any other publication synchronously. Authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

Each manuscript is reviewed by at least two referees under double-blind peer review process. Plagiarism, duplication, fraud authorship/denied authorship, research/data fabrication, salami slicing/salami publication, breaching of copyrights, prevailing conflict of interest are unethical behaviors.

All manuscripts not in accordance with the accepted ethical standards will be removed from the publication. This also contains any possible malpractice discovered after the publication.

Research Ethics
The journal adheres to the highest standards in research ethics and follows the principles of international research ethics as defined below. The authors are responsible for the compliance of the manuscripts with the ethical rules.

- Principles of integrity, quality and transparency should be sustained in designing the research, reviewing the design and conducting the research.
- The research team and participants should be fully informed about the aim, methods, possible uses and requirements of the research and risks of participation in research.
- The confidentiality of the information provided by the research participants and the confidentiality of the respondents should be ensured. The research should be designed to protect the autonomy and dignity of the participants.
- Research participants should participate in the research voluntarily, not under any coercion.
- Any possible harm to participants must be avoided. The research should be planned in such a way that the participants are not at risk.
- The independence of research must be clear; and any conflict of interest or must be disclosed.
- In experimental studies with human subjects, written informed consent of the participants who decide to participate in the research must be obtained. In the case of children and those under wardship or with confirmed insanity, legal custodian's assent must be obtained.
- If the study is to be carried out in any institution or organization, approval must be obtained from this institution or organization.
- In studies with human subject, it must be noted in the method's section of the manuscript that the informed consent of the participants and ethics committee approval from the institution where the study has been conducted have been obtained.

Ethics Committee Approval and Informed Consent

The Turkish Journal of Ear Nose and Throat (Tr-ENT) takes as principle to comply with the ethical standards of World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects revised in 2003 and WMA Statement on Animal Use in Biomedical Research revised in 2016.

An approval of research protocols by the Ethics Committee in accordance with international standards mentioned above is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, the name of the ethics committee, and the ethics committee approval number should also be stated in the Materials and Methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, signed releases of the patient or of their legal representative should be enclosed.

Author's Responsibilities

It is authors' responsibility to ensure that the article is in accordance with scientific and ethical standards and rules. And authors must ensure that submitted work is original. They must certify that the manuscript has not previously been published elsewhere or is not currently being considered for publication elsewhere, in any language. Applicable copyright laws and conventions must be followed. Copyright material (e.g. tables, figures or extensive quotations) must be reproduced only with appropriate permission and acknowledgement. Any work or words of other authors, contributors, or sources must be appropriately credited and referenced.

All the authors of a submitted manuscript must have direct scientific and academic contribution to the manuscript. The author(s) of the original research articles is defined as a person who is significantly involved in "conceptualization and design of the study", "collecting the data", "analyzing the data", "writing the manuscript", "reviewing the manuscript with a critical perspective" and "planning/conducting the study of the manuscript and/or revising it". Fund raising, data collection or supervision of the research group are not sufficient roles to be accepted as an author. The author(s) must meet all these criteria described above. The order of names in the author list of an article must be a co-decision and it must be indicated in the Copyright Agreement Form. The individuals who do not meet the authorship criteria but contributed to the study must take place in the acknowledgement section. Individuals providing technical support, assisting writing, providing a general support, providing material or financial support are examples to be indicated in acknowledgement section.

All authors must disclose all issues concerning financial relationship, conflict of interest, and competing interest that may potentially influence the results of the research or scientific judgment.

When an author discovers a significant error or inaccuracy in his/her own published paper, it is the author's obligation to promptly cooperate with the Editor to provide retractions or corrections of mistakes.

Responsibility for the Editor and Reviewers

Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, sexual orientation, citizenship, religious belief or political philosophy of the authors. He/She provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

Editor-in-Chief is responsible for the contents and overall quality of the publication. He/She must publish errata pages or make corrections when needed.

Editor-in-Chief does not allow any conflicts of interest between the authors, editors and reviewers. Only he has the full authority to assign a reviewer and is responsible for final decision for publication of the manuscripts in the Journal.

Reviewers must have no conflict of interest with respect to the research, the authors and/or the research funders. Their judgments must be objective.

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees must be ensured. In particular situations, the editor may share the review of one reviewer with other reviewers to clarify a particular point.

PEER REVIEW

Peer Review Policies

Only those manuscripts approved by its every individual author and that were not published before in or sent to another journal, are accepted for evaluation.

Submitted manuscripts that pass preliminary control are scanned for plagiarism using iThenticate software. After plagiarism check, the eligible ones are evaluated by editor-in-chief for their originality, methodology, the importance of the subject covered and compliance with the journal scope.

The editor hands over the papers matching the formal rules to at least two national/international referees for double-blind peer review evaluation and gives green light for publication upon modification by the authors in accordance with the referees' claims.

Responsibility for the Editor and Reviewers

Editor-in-Chief evaluates manuscripts for their scientific content without regard to ethnic origin, gender, citizenship, religious belief or political philosophy of the authors. Editor-in-Chief provides a fair double-blind peer review of the submitted articles for publication and ensures that all the information related to submitted manuscripts is kept as confidential before publishing.

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- Does the manuscript contain new and significant information?
- Does the abstract clearly and accurately describe the content of the manuscript?
- Is the problem significant and concisely stated?
- Are the methods described comprehensively?
- Are the interpretations and consclusions justified by the results?
- Is adequate references made to other Works in the field?
- Is the language acceptable?

Reviewers must ensure that all the information related to submitted manuscripts is kept as confidential and must report to the editor if they are aware of copyright infringement and plagiarism on the author's side.

A reviewer who feels unqualified to review the topic of a manuscript or knows that its prompt review will be impossible should notify the editor and excuse himself from the review process.

The editor informs the reviewers that the manuscripts are confidential information and that this is a privileged interaction. The reviewers and editorial board cannot discuss the manuscripts with other persons. The anonymity of the referees is important.

Manuscript Organization and Submission

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Author(s) are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at https://dergipark.org.tr/tr/journal/3565/submission/step/manuscript/new Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Author(s) are required to submit the following documents together with the manuscript and must ensure that the abstract and keywords are in line with the standards explained in below.

- **Copyright Agreement Form**
- **Author Form and ICMJE Potential Conflict of Interest Disclosure Form**
- **Ethics Committee Approval**
- **Cover Letter to the Editor**
- **Title Page**: A separate title page should be submitted with all submissions and this page should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, academic degree(s) and ORCID ID(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: Abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Materials and Methods, Results, and Conclusion). Abstracts of Case Reports and Reviews should be unstructured. Abstracts should be 200-250 words.

Keywords: Each submission must be accompanied by a minimum of 3 to a maximum of 6 keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (http://www.nlm.nih.gov/mesh/MBrowser.html) .

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Method, Results, Discussion, and Conclusion subheadings..

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Invited Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends
Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: “Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)”

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

Revisions
When submitting a revised version of a paper, the author must submit a detailed “Response to the reviewers” that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer’s comment, followed by the author’s reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over. Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal’s webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within two days of their receipt of the proof. The latest status of the submitted manuscripts and other information about the journal can be accessed at http://tr-ent.com. The editorial and publication processes of the journal are conducted in accordance with the guidelines of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice). An ORCID ID is required for all authors during the submission of the manuscript. The ID is available at http://orcid.org with free of charge.

Reference Style and Examples
Authors are responsible for supply complete and correct references. References should be numbered according to the order used in the text. Numbers should be given in brackets and placed at the end of the sentence. Examples are given below on the use of references. Reference end note style Vancouver

Periodicals: Author(s) Last Name initial(s) name of author(s) (if there are six or fewer authors, all authors should be written; if the number of authors are seven or more, only the first six of the authors should be written and the rest as “et al”). The title of the article, the abbreviated name of the journal according to the Index Medicus, Year; Volume (Issue): The first and last page numbers.

Example: Robson A, Greene J, Ansari N, Kim B. Eccrine porocarcinoma (malignant eccrine poroma): a clinicopathologic study of 69 cases. The American Journal of Surgical Pathology 2001;25:710-20. Books: Surname of the author(s) initial name(s) of author(s). The name of the book. The edition number. Place of publication: Publisher, Publication year.

Book chapters: The author (s) surname of the chapter initial (s) letter of the name. Section title. In: Surname of editor (s) initial (s) letter of first name (s) ed / eds. The name of the book. Edition number. Place of publication: Publisher, year of publication: The first and last page numbers of the chapter. Web address: If a "web" address is used as the reference address, the web address date should be given in brackets with the address. The DOI (Digital Object Identifier) number must be provided, when a web access article used in the text as a reference.

Example: AB Author, CD Author. Title of document. Retrieved from http://Web address (Accession date: aa/bb/2016).

Congress papers:
Thesis: Maden KL. Experimental investigation of the ..... Master Thesis, Health Science Institute of Ankara University, Ankara, 2005.

SUBMISSION CHECKLIST

- Cover letter to the editor
  - The category of the manuscript
  - Confirming that "the paper is not under consideration for publication in another journal".
  - Including disclosure of any commercial or financial involvement.
  - Confirming that the statistical design of the research article is reviewed.
  - Confirming that last control for fluent English was done.
  - Confirming that journal policies detailed in Information for Authors have been reviewed.
  - Confirming that the references cited in the text and listed in the references section are in line with NLM.
- Copyright Agreement Form
- Author Form
- Permission of previous published material if used in the present manuscript
- Acknowledgement of the study "in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.
- Statement that informed consent was obtained after the procedure(s) had been fully explained. Indicating whether the institutional and national guide for the care and use of laboratory animals was followed as in "Guide for the Care and Use of Laboratory Animals".
- Title page
  - The category of the manuscript
  - The title of the manuscript
  - Short title (running head)
  - All authors' names and affiliations (institution, faculty/department, city, country), e-mail addresses
  - Corresponding author's email address, full postal address, telephone and fax number
  - ORCIDs of all authors.
- Main Manuscript Document
  - The title of the manuscript
  - Abstract 200-250 words
  - Key words: 3 - 6 words
  - Main article sections
  - References
  - Acknowledgement (if exists)
  - All tables, illustrations (figures) (including title, description, footnotes)

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