

Trans-oral versus trans-nasal approach in office-based laryngeal biopsy; a cohort-selection cross-sectional diagnostic accuracy study.

Ahmed Refaat¹ and Ahmed Negm²

¹Ain Shams University Faculty of Medicine

²Misr University for Science and Technology College of Medicine

August 14, 2020

Abstract

Objective: The aim of this study is to explore the accuracy of two different approaches; trans-oral versus trans-nasal office-based laryngeal biopsy. **Methods:** The study was a cohort-selection cross-sectional study that included all patients aged 18 years or more with suspicious lesions of the larynx or the oropharynx who came to the outpatient clinic [removed for blind peer review], due to different reasons during the period of March 2017 and March 2020. Full evaluation was done using Flexible naso-endoscope with distal chip. Patients with suspicious lesions were referred for office-based-based biopsy; either trans-nasal biopsy or trans-oral biopsy; to determine whether the lesion was malignant or benign. Then, all patients were referred for subsequent direct laryngoscopy for definitive diagnosis. Both groups were compared for all demographic variables as well as clinic-pathologic variables and for diagnostic accuracy. **Results:** The overall sample was 60 cases; 30 in each group. Both groups are comparable with regard the age and gender (p-values > 0.05). The majority in both groups are smokers (83.3 & 76.7%). The most frequent cause of referral for biopsy was suspicious laryngeal mass in both groups; mentioned in 80.0% of both groups (p-value 0.736). The number of biopsies obtained was significantly higher in the trans-oral group (3.7 ± 1.0) than in the trans-nasal group (3.1 ± 0.9), (p-value = 0.013). Both approaches were tolerated by all patients with few limited aspiration or epistaxis. The trans-oral approach has a higher Chohen kappa index (0.79) than the trans-nasal approach (0.14). Also, it has got higher diagnostic accuracy (93.3%) than the trans-nasal approach (50.0%). The sensitivity of trans-oral approach biopsies compared with that of direct laryngoscopy biopsies was 95.8% and the specificity was 83.3%. On the other hand, the sensitivity of trans-nasal approach biopsies compared with that of direct laryngoscopy biopsies was 26.3% and the specificity was 90.9%. **Conclusion:** The trans-oral approach to obtain a biopsy from the upper aero-digestive tract has better diagnostic accuracy than the trans-nasal approach. When combined with trans-nasal visualization and transcriothyroid anesthesia. **Succinct Keypoints:** Trans-nasal approach; trans-oral approach; office-based laryngeal biopsy; sensitivity; specificity; diagnostic accuracy

Trans-oral versus trans-nasal approach in office-based laryngeal biopsy; a cohort-selection cross-sectional diagnostic accuracy study.

Keypoints:

1. Office base laryngeal biopsy has been increasingly spreading around the world.
2. Benefits from office based procedures including time saving and avoidance of general anesthesia and saving of hospital cost.
3. Short description of the setting and tools and approaches used in office based biopsy.
4. Short description of the types of local anesthesia used.
5. Transoral approach in obtaining biopsy has a higher sensitivity and specificity.

Abstract

Objective: The aim of this study is to explore the accuracy of two different approaches; trans-oral versus trans-nasal office-based laryngeal biopsy.

Design: cohort-selection cross-sectional study.

Setting: outpatient clinic of Phoniatrics [removed for blind peer review]

Participants: The study was a that included all patients aged 18 years or more with suspicious lesions of the larynx or the oropharynx who are eligible for biopsy who came to the outpatient clinic, due to different reasons during the period of March 2017 and March 2020.

Main outcome measures: Patients with suspicious lesions were referred for office-based-based biopsy; either trans-nasal biopsy or trans-oral biopsy. Then, all patients were referred for subsequent direct laryngoscopy for definitive diagnosis.

Results: The overall sample was 60 cases; 30 in each group. The majority in both groups are smokers. The most frequent cause of referral for biopsy was suspicious laryngeal mass. The number of biopsies obtained was significantly higher in the trans-oral group. Both approaches were tolerated by all patients with few limited aspiration or epistaxis.

The sensitivity of trans-oral approach compared with that of direct laryngoscopy was 95.8% and the specificity was 83.3%. On the other hand, the sensitivity of trans-nasal approach compared with that of direct laryngoscopy was 26.3% and the specificity was 90.9%.

Conclusion: The trans-oral approach to obtain a biopsy from the upper aero-digestive tract has better diagnostic accuracy than the trans-nasal approach. When combined with trans-nasal visualization and trans-cricothyroid anesthesia.

Keywords: Trans-nasal approach; trans-oral approach; office-based laryngeal biopsy; sensitivity; specificity; diagnostic accuracy.

Introduction

Cancer is still the most disastrous disease in the world. The fifth most common cancer is that of head and neck cancer, with more than 500 thousands newly diagnosed cases every year with the laryngopharynx as one of the most frequent sites. It is considered the second most prevalent malignancy of the head and neck. Moreover, squamous cell carcinoma (SCC) of the larynx continues to be the commonest cancer of the head and neck in many countries. Also, cancer of the oropharynx has been on the rise. [1-3]

The milestone in diagnosis is the tissue diagnosis by obtaining a biopsy for histopathological examination which is a crucial step that must be completed before any treatment. Traditionally, laryngopharyngeal biopsies have been obtained in the operating room under general anesthesia. [4-5]

The advent of the technology of the flexible fiber-optic and the distal chip scope allow these procedures to be performed in awake, non-sedated patients under local anesthesia in an office-based setting. Office-based biopsies are performed in clinic examination suite. This suite consists of an examination chair and a video tower with photo-documentation capability. No cardiopulmonary monitoring is performed during the procedure; however, the patient's vital signs are collected before the visit. [4-5]

A flexible trans-nasal laryngoscope with instrumental channel is used to obtain the biopsy through the biopsy forceps passing through the channel of the laryngoscope. Alternatively, a trans-oral approach may be used. [4-5]

Obtaining the biopsy in the office rather than in the operating theatre has several advantages as there is no need for general anesthesia with all its subsequent risks. Also, many patients have bad general health conditions that add to the risk of general anesthesia especially in old age, cardiac patients and many other conditions. [6]

There is little written on office-based biopsy of the oropharynx and the larynx. Thus, the rationale intended for this current study was to explore the accuracy of two different approaches; trans-oral versus trans-nasal office-based laryngeal biopsy.

Methods

The current study was a cross-sectional diagnostic accuracy study that included all patients aged 18 years or more with suspicious lesions of the larynx or the oropharynx who are eligible for biopsy who came to the outpatient clinic of [removed for blind peer review] due to different reasons during the period of March 2017 and March 2020.

The objective of the study as well as the steps of the procedures was explained plainly to the study participants. All participants included in the study have provided an informed consent. The Ethical Review Board has approved this study.

Suspicious lesions were a lesion on an immobile vocal fold, ulcer, leukoplakia or erythroplakia, a mass with cauliflower appearance. Exclusion criteria were: age less than 18 years, refusal to participate, patients with benign-appearing lesions such as polyps, nodules, Reinke space edema, and chronic laryngitis due to GERD.

Patients with suspicious lesions were referred for office-based-based biopsy; either trans-nasal biopsy or trans-oral biopsy; to determine whether the lesion was malignant or benign. Then, all patients were referred for subsequent direct laryngoscopy for definitive diagnosis. Findings of carcinoma in situ (CIS) were added to those of invasive carcinoma when sensitivity and specificity measurements were calculated. Histopathologic results of the specimens from both approaches were compared to the results of direct laryngoscopy biopsy.

Procedural approach

1] Biopsies via trans-oral approach

Trans-oral biopsies was with a long 22 cm. curved biopsy forceps (Figure 1) after appropriate topical anesthesia of the oral cavity, nasal cavity and larynx. The larynx is viewed with a flexible scope (Henke Sass Wolf, Distal chip flexible endoscope, Germany) held by assistant while the surgeon holds the patient's tongue and directs the biopsy forceps through the oral cavity (figure 2). Alternatively, the larynx can be views with a rigid laryngoscope 70 degree (6 mm, Henke Sass Wolf, Germany). The patient holds on to his/her tongue while the surgeon directs the scope and biopsy forceps.

2] Biopsies via trans-nasal approach

The other technique for biopsies involves using a flexible endoscope (*RZ flexible endoscope with instrumental (internal) side channel, 4.2 mm, Germany*) with a working channel through which a small flexible biopsy forceps can be passed (figure 3). After topical anesthesia to the nose and larynx, the scope is advanced to a position with the lesion in view and a 1.8-mm flexible cup biopsy forceps is passed through the working channel by an assistant until visible 1 to 2 cm beyond the tip of the scope. The forceps are then opened and the scope is advanced until the forceps come into contact with the lesion. The forceps are then closed and removed from the scope. The scope can be left in place and multiple biopsies can be taken.

Statistical analysis

The patients were grouped into two groups randomly; one using trans-nasal approach and the other using the trans-oral approach. Both groups were compared for all demographic variables as well as clinic-pathologic variables.

The primary outcome of this study is to compare the diagnostic accuracy of both trans-oral and trans-nasal approaches of taking a biopsy. The secondary outcome variables were the safety, tolerance and how easy is each approach. Also, evaluation of visualization approaches and methods of anesthesia were among the secondary outcome variables.

Recorded data were coded, entered, cleaned, and analyzed using the statistical package for social sciences, version 25.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square (χ^2) test of significance was used in order to compare proportions between two qualitative parameters, and the student t-test was used for the numerical parametric data. The confidence level was set to 95% and the margin of error accepted

was set to 5%. So, the p-value was considered significant if < 0.05 . The Cohen kappa index for agreement was calculated to evaluate agreement between methods of biopsies. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of the two different approaches of office-based based biopsy were calculated.

Results

Ninety-nine patients were invited to participate in the study; 35 refused to participate, 14 were ineligible; thus, 60 enrolled to the study signed a consent form and randomized into two groups: 30 trans-nasal group and 30 trans-oral group.

Demographic and clinic-pathologic characteristics of both groups

Both groups, trans-oral and trans-nasal groups are comparable with regard the age and gender. The mean age was 63.8 ± 11.8 and 63.9 ± 11.8 years in the trans-oral group and trans-nasal group, respectively (p-value = 1.000). The males are more than females in both groups; 86.7% & 90.0% in the trans-oral group and trans-nasal group, respectively (p-value = 0.688) (Table 1).

The majority of patients in both groups are smokers; 83.3% and 76.7% in the trans-oral group and trans-nasal group, respectively (p-value = 0.519).

The main complaint in both groups was dysphonia; 80.0% and 80.0% in the trans-oral group and trans-nasal group, respectively (p-value = 0.475). The most frequent cause of referral for biopsy was suspicious laryngeal mass in both groups; mentioned in 80.0% of both groups (p-value 0.736). Other causes were post cricoid mass, pharyngeal mass and vallecular lymph node, as shown in Table 1.

The most frequent approach for visualization in both groups was the trans-nasal; used in 29 (96.7%) of cases in both groups, (p-value = 1.000). In addition, the methods of anesthesia were comparable between groups, with the trans-cricothyroid injection of xylocaine as the most frequent method in both groups; used in 63.3% and 56.7% in the trans-oral group and trans-nasal group, respectively (p-value = 0.835).

The time needed for the procedures was less in the trans-oral group (7.9 ± 1.6 minutes) than in the trans-nasal group (9.3 ± 3.6), (p-value = 0.051). However, the number of biopsies obtained was significantly higher in the trans-oral group (3.7 ± 1.0) than in the trans-nasal group (3.1 ± 0.9), (p-value = 0.013).

Size of obtained biopsies were comparable between both groups (p-value = 0.574). The most frequent size was 0.5 mg obtained from 19 (63.3%) & 17 (56.7%) via the trans-oral and the trans-nasal approaches, respectively (Table 1).

Results of histopathological examination were squamous cell carcinoma in 80.0% and 20.0% of the trans-oral group and trans-nasal group, respectively (p-value < 0.001). Other results were inflammatory cells, dysplasia and papilloma seen in (3.3%, 13.3% & 3.3%) and (56.7%, 13.3% & 10.0%) of the trans-oral group and trans-nasal group, respectively (Table 1).

Tolerance, safety and post-procedure complications

Complications of the trans-nasal approach were limited to post-procedure aspiration in one patient (without significant consequences) and self-limited epistaxis in another patient. While in the trans-oral approach one patient suffered post-procedure aspiration (without significant consequences). Both approaches were safe. Both approaches were tolerated by all patients.

Diagnostic accuracy of both approaches

The Cohen kappa index for agreement was calculated to evaluate agreement between the trans-oral approach and direct laryngoscopy methods, accounting for possible random agreement. The value ($k = 0.79$) indicated fair agreement between them. Also, the Cohen kappa index for agreement was calculated to evaluate agreement between the trans-nasal approach and direct laryngoscopy methods, accounting for possible random agreement. The value ($k = 0.14$) indicated low agreement between them.

To calculate the sensitivity and specificity of the trans-oral approach and the trans-nasal approach in the diagnosis of malignant laryngeal lesions, we divided the biopsy results into two groups: (1) benign lesions or inflammatory condition and (2) invasive carcinoma.

The sensitivity of trans-oral approach biopsies compared with that of direct laryngoscopy biopsies was 95.8% and the specificity was 83.3%, with a diagnostic accuracy of 93.3%.

The sensitivity of trans-nasal approach biopsies compared with that of direct laryngoscopy biopsies was 26.3% and the specificity was 90.9%, with a diagnostic accuracy of 50.0% (Table 2).

Discussion

Without doubt taking a biopsy via direct laryngoscopy in an operating room under general anesthesia is the gold standard for diagnosis of malignancy of the upper aero-digestive tract. However, with the improvement of the technology of endoscopy, that enabled surgeons to search for the use of office-based procedures via trans-oral or trans-nasal approaches for taking these biopsies without the need for general anesthesia and an operating room. [7]

This current cross-sectional study aimed to compare the diagnostic accuracy of trans-oral and trans-nasal office-based laryngeal biopsies against the direct laryngeal biopsies in operating room. The Cohen kappa index for agreement was calculated to evaluate agreement between each diagnostic approach the gold standard approach. The results of this study showed that the trans-oral approach has a higher Chohen kappa index (0.79) than the trans-nasal approach (0.14). Also, it has got higher diagnostic accuracy (93.3%) than the trans-nasal approach (50.0%).

The sensitivity of trans-oral approach biopsies compared with that of direct laryngoscopy biopsies was 95.8% compared to 26.3% sensitivity of trans-nasal approach. On the other hand, the specificity was 83.3% & 90.9% for trans-oral and trans-nasal approaches, respectively. Both approaches were tolerated by all patients with very few post-procedural complications.

According to *Cohen et al. (2013 & 2014)* the specificity of trans-nasal-laryngoscope in diagnosing invasive carcinoma is excellent (96% & 96.6%), but the sensitivity of diagnosing a suspicious lesion as being carcinoma in situ or invasive carcinoma is only 69.2% & 70.6% sensitivity. In retrospective analysis, some studies reported somewhat different results as 60% sensitivity and 87% specificity. [8-11]

In a retrospective analysis of consecutive 581 cases, office-based biopsies via trans-nasal approach for laryngeal lesions were evaluated by Cha et al. (2016) and the results showed sensitivity of 78.2% and a specificity of 100.0%. However, and unlike our study, not all the cases have a confirmatory direct operating room laryngeal biopsy which is the gold standard. [12]

The higher diagnostic accuracy and sensitivity of the trans-oral approach in the results of our study is in accordance with the study of *Hassan et al. (2018)* which showed a 100% sensitivity and 75.6% specificity. [13]

Healing after office-based superficial laryngeal biopsies generally takes places very quickly and voice rest is not typically required after the procedure [14]. Our study showed very few post-procedural complications in both approaches as well as good tolerance of patients which is in agreement with other studies. [4, 6, 15]

However, it was reported by *Shah and Johns (2013)* that the trans-oral approach can be difficult to perform and is not well tolerated by some patients. On the other hand, Trans-nasal is generally better tolerated by most patients. [14]

In the current study the number of biopsies obtained was significantly higher in the trans-oral group than in the trans-nasal group. Also, the time needed for the procedure was insignificantly less in the trans-oral group than in the trans-nasal group. The sizes of obtained biopsies were comparable between groups.

Trans-nasal is often not advisable, as false-negative results are possible because of the small size of the biopsy forceps [14]. However, in exophytic lesion it was easier to biopsy than in ulcerative lesions; also,

tumors whose surface was perpendicular to the endoscope were easier to biopsy than tangential tumors. [16]

From our experience, as regard the visualization, the trans-nasal approach is more applicable and easy for the patients but need assistance; however, the trans-oral approach may increase the gag reflex but does not need assistance. Also, we found that the trans-oral approach was better than the trans-nasal approach as regard the number of obtained biopsies.

Finally, we found that the combination of trans-nasal visualization, trans-oral approach of obtaining the biopsy and the transcricothyroid anesthesia was the best one in our practice.

Conclusion:

The trans-oral approach to obtain a biopsy from the upper aero-digestive tract has better diagnostic accuracy than the trans-nasal approach. When combined with trans-nasal visualization and transcricothyroid anesthesia, it gives a better yield with an easy procedure.

Table 1: Demographic data and patients' characteristics

	Trans-oral approach N = 30	Trans-nasal approach N = 30	P
Gender n (%)			
Male	26 (86.7)	27 (90.0)	0.688
Female	4 (13.3)	3 (10.0)	
Age in years, mean (SD)	63.8 (11.8)	63.9 (11.8)	1.000
Main complaint n (%)			
Dysphonia	24 (80.0)	24 (80.0)	0.475
Dysphagia	3 (10.0)	5 (16.7)	
Dysphagia and otalgia	2 (6.7)	0 (0.0)	
Nasal bleeding	1 (3.3)	1 (3.3)	
Smoker n (%)	25 (83.3)	23 (76.7)	0.519
Cause of referral for biopsy n (%)			
Laryngeal mass	25 (83.3)	24 (80.0)	0.736
Post cricoid mass	1 (3.3)	3 (10.0)	
Pharyngeal mass	3 (10.0)	2 (6.6)	
Vallecular lymph node	1 (3.3)	1 (3.3)	
Visualization n (%)			
Trans-nasal	29 (96.7)	29 (96.7)	1.000
Trans-oral	1 (3.3)	1 (3.3)	
Anesthesia n (%)			
Trans-cricothyroid injection of xylocaine	19 (63.3)	17 (56.7)	0.835
Oral Xylocaine spray anesthesia through long straw	7 (23.3)	9 (30.0)	
Trans-nasal injection through instrumental channel	4 (13.3)	4 (13.3)	
Time of office-based biopsy in minutes, mean (SD)	7.9 (1.6)	9.3 (3.6)	0.051
Number of obtained biopsies, mean (SD)	3.7 (1.0)	3.1 (0.9)	0.013
Size of obtained biopsies n (%)			
0.4	1 (3.3)	3 (10.0)	0.574
0.5	19 (63.3)	17 (56.7)	
1.0	10 (33.3)	10 (33.3)	
Results of histopathological examination n (%)			
Inflammatory cells (no malignancy)	1 (3.3)	17 (56.7)	< 0.001
Squamous cell carcinoma	24 (80.0)	6 (20.0)	
Dysplasia (not malignant)	4 (13.3)	4 (13.3)	
Papilloma (no malignancy)	1 (3.3)	3 (10.0)	

Table 2: Evaluation of diagnostic accuracy

	Trans-oral approach
Histopathologic results of the second biopsy through direct laryngoscopy under general anesthesia n (%)	
Squamous cell carcinoma	24 (80.0)
Inflammatory cells	1 (3.3)
Dysplasia	4 (13.3)
Papilloma	1 (3.3)
Diagnostic test results	
True positive	23 (76.7)
True negative	5 (16.7)
False negative	1 (3.3)
False positive	1 (3.3)
Sensitivity	95.8%
Specificity	83.3%
Positive predictive value (PPV)	95.8%
Negative predictive value (NPV)	83.3%
Diagnostic accuracy	93.3%

References

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2017;3:524-48. doi:10.1001/jamaoncol.2016.5688
2. American Cancer Society. Cancer Facts and Figures, 2007. Atlanta, GA:American Cancer Society; 2007.
3. Simard EP, Torre LA, Jemal A. International trends in head and neck cancer incidence rates: differences by country, sex and anatomic site. *Oral Oncol* 2014;50:387-403. doi: 10.1016/j.oraloncology.2014.01.016. Epub 2014.
4. Naidu H, Noordzij JP, Samim A, Jalisi S, Grillone GA. Comparison of efficacy, safety, and cost-effectiveness of in-office cup forceps biopsies versus operating room biopsies for laryngopharyngeal tumors. *J Voice* 2012;26: 604-606.
5. Verma SP. Office-based laryngopharyngeal biopsy. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2012 Sep 1;23(3):203-5.
6. Lippert D, Hoffman MR, Dang P, McCulloch TM, Hartig GK, Dailey SH. In-office biopsy of upper airway lesions: safety, tolerance, and effect on time to treatment. *Laryngoscope*. 2015;125(4):919-923. doi:10.1002/lary.25007
7. Sunil P. Office-based laryngopharyngeal biopsy, *Operative Techniques in Otolaryngology*. 2012; 23(3): 203-205
8. Cohen JT, Safadi A, Fliss DM, Gil Z, Horowitz G. Reliability of a transnasal flexible fiberoptic in-office laryngeal biopsy. *JAMA Otolaryngol Head Neck Surg*. 2013;139:341e345.
9. Cohen JT, Benyamini L. Transnasal Flexible Fiberoptic in-office Laryngeal Biopsies-Our Experience with 117 Patients with Suspicious Lesions. *Rambam Maimonides Med J*. 2014;5(2):e0011. Published 2014 Apr 28. doi:10.5041/RMMJ.10145
10. Richards AL, Sugumaran M, Aviv JE, Woo P, Altman KW. The utility of office-based biopsy for laryngopharyngeal lesions: comparison with surgical evaluation. *Laryngoscope*. 2015;125(4):909-912.

doi:10.1002/lary.25005

11. Zalvan CH, Brown DJ, Oiseth SJ, Roark RM. Comparison of trans-nasal laryngoscopic office based biopsy of laryngopharyngeal lesions with traditional operative biopsy. *Eur Arch Otorhinolaryngol*. 2013 Sep 1;270(9):2509–13. Available from: <https://doi.org/10.1007/s00405-013-2507-z>
12. Cha W, Yoon B-W, Jang JY, Lee JC, Lee BJ, Wang S-G, et al. Office-based biopsies for laryngeal lesions: Analysis of consecutive 581 cases. *The Laryngoscope*. 2016;126(11):2513–9. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/lary.25930>
13. Hassan N, Usman R, Yousuf M, Ahmad A, Hirani I. Transoral flexible laryngoscope biopsy: Safety and accuracy. *World Journal of Otorhinolaryngology - Head and Neck Surgery*. 2018 Nov 1;5.
14. Shah M and Johns M. Office-based laryngeal procedures. *Otolaryngological Clinics of North America*. 2013; 46: 75–84.
15. Wellenstein DJ, de Witt JK, Schutte HW, Honings J, van den Hoogen FJA, Marres HAM, et al. Safety of flexible endoscopic biopsy of the pharynx and larynx under topical anesthesia. *Eur Arch Otorhinolaryngol*. 2017 Sep 1;274(9):3471–6. Available from: <https://doi.org/10.1007/s00405-017-4647-z>
16. Harini N, Noordzij J, Arang S, Scharukh J and Gregory A. Comparison of efficacy, safety, and cost-effectiveness of in-office cup forcep biopsies versus operating room biopsies for laryngopharyngeal tumors. *Journal of Voice*. 2011; 26(5): 604-606.

Figures and tables

Figure 1: Transoral long curved forceps

Figure 2: Transoral biopsy

Figure 3: Flexible endoscope with instrumental channel with the forceps in place.



