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Diagnostic Accuracy and Safety of Endoscopic – Guided Office-Based Biopsies for Laryngeal and Pharyngeal Lesions at St. Luke's Medical Center

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ABSTRACT

Objective: To determine the sensitivity, specificity, positive predictive value, negative predictive value and safety of endoscopic guided office-based biopsies (OBB) in diagnosing laryngeal and pharyngeal neoplasms at the St. Luke's Medical Center in Quezon City and Global City.

Methods:

Design: Diagnostic Accuracy Study

Setting: Two Tertiary Private Training Hospitals

Participants: Records of patients with pharyngeal and laryngeal lesions who underwent endoscopic-guided OBB were included in the study describing safety. Only patients with subsequent operative biopsies were included in assessing diagnostic accuracy.

Results: Thirty-six (36) patients were included: 28 (77.78%) males and 8 (22.22%) females, with median age of 61.5 (IQR 52-73 years). Nearly half (16/36; 44.44%) of the office-based biopsies yielded malignant histopathology results, 19.44% had high grade dysplasia while 36.11% had benign findings. Of 10 patients with operative biopsy for definitive diagnosis, 8 were correctly diagnosed with carcinoma while one had a change in diagnosis from benign to malignant. Office-based biopsy was well tolerated and had no complications reported. Overall, the sensitivity of OBB in predicting malignancy was 88.89%, specificity was 100%, positive predictive value was 100%, and negative predictive value was 50%.

Conclusion: Office-based biopsy is an accurate, reliable and safe modality for screening suspicious pharyngeal and laryngeal neoplasms, and may be part of routine screening during initial endoscopy among selected patients with suspicious pharyngeal and laryngeal neoplasms. Further investigation and larger population studies may provide more robust insights on effectiveness and safety of office-based biopsy in diagnosis of pharyngeal and laryngeal neoplasms.

Keywords: *head and neck neoplasms; flexible endoscopic biopsy; office-based biopsy; malignancy*

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According to the Cancer Care Registry Philippines (CaRe Ph), cancer is the 3rd most common cause of death in the Philippines.[1] Primary head and neck malignancies ranked second among the most diagnosed cancers in the Philippines in 2020, mostly detected during the 5th and 6th decade of life.[1] Malignancies of the pharyngeal and laryngeal region had a prevalence of 0.26-1.01 and 3.76 per 100,000, respectively.[1] Detection of these malignancies may pose a challenge, usually presenting in the advanced stages, as they may have an indolent course and nonspecific symptoms in early stages.

Early diagnosis and initiation of treatment is essential for better prognosis and patient survival.[2] While operative biopsy has traditionally been the gold standard for diagnosis, newer technologies such as office-based endoscopy offer the ability to perform diagnostic and therapeutic procedures, including office-based biopsies, under local anesthesia. The emergence of endoscopy systems incorporating working ports have facilitated performing several diagnostic and therapeutic procedures under local and regional anesthesia including office-based biopsies (OBB).

This study aimed to determine the sensitivity, specificity, positive predictive value, negative predictive value and safety of endoscopic guided office-based biopsies (OBB) in diagnosing laryngeal and pharyngeal neoplasms at the St. Luke's Medical Center in Quezon City and Global City.

METHODS

With St. Luke's Medical Center Institutional Ethics Review Committee approval (RPC-046-02-23), records of patients who underwent endoscopic guided office-based biopsies were gathered from the Voice, Swallowing and Sinus Center (VSSC) of St. Luke's Medical Center Quezon City and St. Luke's Medical Center Global City from January 2018 to December 2022 for suspicious oropharyngeal, hypopharyngeal and laryngeal lesions, were considered for inclusion. Inclusion criteria were: (1) available official endoscopy report with note of presence/absence of adverse events; (2) suspected lesion was identified at the level of the oropharynx, hypopharynx and larynx (leukoplakia, erythroplakia, fungating, and/or nonspecific mucosal lesions); (3) office-based biopsy was done using a flexible biopsy forceps (Radial Jaw TM, Boston Scientific); (4) an electronic copy of histopathologic results was available thru the St. Luke's Medical Center Healthcare Database System; and (5) with or without operative biopsy reports.

In both institutions, patients were previously screened by ear, nose, and throat (ENT) specialists to undergo office-based biopsies using these same criteria: (1) no significant comorbidities including uncontrolled hypertension or diabetes mellitus; (2) not on blood thinners; (3) oriented and cooperative; and (4) consents to undergo office-based procedure; otherwise, they were excluded.

All records fulfilling these criteria were reviewed by both investigators. Patient records were anonymized during data gathering. Demographic data collected included the age, sex, location of lesion, OBB histopathologic result, and operative biopsy results if available. Data was transcribed and collated using Microsoft® Excel version 1808, Microsoft Office Professional Plus 2019 (Microsoft Corp., Redmond, WA, USA).

All suspicious lesions had been previously biopsied under endoscopic guidance using local anesthesia. Prior to biopsy, topical nasal anesthesia was administered in the nasal cavity using cotton pledgets soaked with 10% lidocaine spray (Xylocaine 10mg Spray, 50 mL bottle, Astra Zeneca) and 0.05% oxymetazoline hydrochloride (ClariClear® nasal spray, Bayer Philippines, Taguig City) solution or 5% lidocaine with 0.5% phenylephrine hydrochloride (Co-Phenylcaine Forte nasal spray, Mayne Pharma International Pty Ltd., SA, Australia); and topical laryngeal anesthesia was administered using 5mL 2% lidocaine hydrochloride (Xylocaine 2%, 100 mg in 5 ml vials, Astra Zeneca) instilled into the working channel/port of the endoscope. Using a flexible rhinolaryngovideoscope with a 2.0mm inner diameter working channel (VISERA ENF-VT, Olympus), the laryngeal or pharyngeal region was visualized. All suspicious lesions were biopsied by a Board-Certified Otolaryngologist using a single use flexible biopsy forceps with a 1.8mm jaw diameter (Radial Jaw® 4 Pulmonary Standard Capacity, 100cm working length, Boston Scientific, Costa Rica) passed through the working channel of the endoscope. More than 1 specimen was typically obtained thru multiple passes for tissue adequacy.

The reference standard was operative biopsy, defined as repeat tissue biopsy obtained by suspension laryngoscopy under general anesthesia usually after inconclusive OBB results, and considered as definitive diagnoses. The outcome of safety in performing OBB was determined using complication rates. Complications during and immediately after the OBB procedure were noted, including bleeding, dyspnea, laryngospasm and epistaxis. The outcome of diagnostic accuracy was based on parameters including sensitivity, specificity, positive predictive value and negative predictive value. The OBB results were defined as true positive or true negative when these results were consistent with the operative biopsy results obtained in the operating theatre. The OBB samples obtained that did not proceed with an operative biopsy were described thru prevalence.

Data Analysis

Demographic data were presented as frequencies and percentages for categorical data and median with interquartile range for continuous data. Safety outcomes were described using frequencies and percentages. The OBB diagnosis interval was calculated as time in days from the OBB procedure to OBB histopathologic results using frequencies. Definitive diagnosis interval was calculated as time in days from the OBB procedure to definitive diagnosis (operative biopsy) using frequencies. Accuracy of OBB was evaluated with conventional 2×2 contingency table analysis considering operative biopsy (OPB) as the gold standard, calculating the absolute numbers of true positive (TP), true negative (TN), false positive (FP), and false negative (FN). The TP was defined as presence of malignancy in both OBB and OPB diagnosis. The TN was defined as absence of malignancy in both OBB and OPB diagnosis. The FP was defined as the presence of malignancy in OBB but absence of malignancy in OPB diagnosis. The FN was defined as absence of malignancy in OBB but presence of malignancy in OPB diagnosis. Accuracy parameters were calculated using Microsoft® Excel version 1808, Microsoft Office Professional Plus 2019 (Microsoft Corp., Redmond, WA, USA).

RESULTS

Thirty-six (36) patients underwent OBBs at the Voice, Swallowing and Sinus Center (VSSC) of St. Luke's Medical Center Quezon City and St. Luke's Medical Center Global City from January 2018 to December 2022 for suspicious oropharyngeal, hypopharyngeal and laryngeal lesions. Of the 36, 28 (77.78%) were male and 8 (22.22%) were female with a ratio of 7:2. Their ages ranged from 35 to 82 years (median, 61.5 years; IQR: 52 – 73 years). The most common primary site was at the glottis (41.67%) followed by the hypopharynx (22.22%). Lesions biopsied ranged from benign nodular lesions to suspicious ulcerating and fungating lesions. Samples varied from 1mm x 1mm to 10mm x 10mm in size, taken with at least 1 pass. All samples successfully yielded diagnostic histopathologic results. Nearly half (16/36, 44.44%) of the office-based biopsy yielded malignant histopathology results; 19.44% had high grade dysplasia, while 36.11% had benign findings. *(Figure 1)* No complications were recorded during and after each procedure. Of the 15 OBB-diagnosed squamous cell carcinoma, 4 (26.67%) patients proceeded with definitive surgery within 5 to 14 days.

Out of the 36 OBB patients, 10 proceeded with operative biopsy. *(Table 1)* Among these, eight were correctly diagnosed as malignant, while one had a change in diagnosis from benign to lymphoma (base of tongue), and one maintained the diagnosis of high grade dysplasia for both OBB and operative biopsy. Two out of the 3 high-grade dysplasia had a diagnosis of squamous cell carcinoma after operative biopsy. The OBB diagnosis interval and definitive diagnosis interval had a mean of 3.83 days and 16.2 days, respectively. Overall, the sensitivity of OBB in predicting malignancy was calculated to be 88.89%, specificity was 100%, positive predictive value of 100%, and negative predictive value of 50%. *(Table 2)*

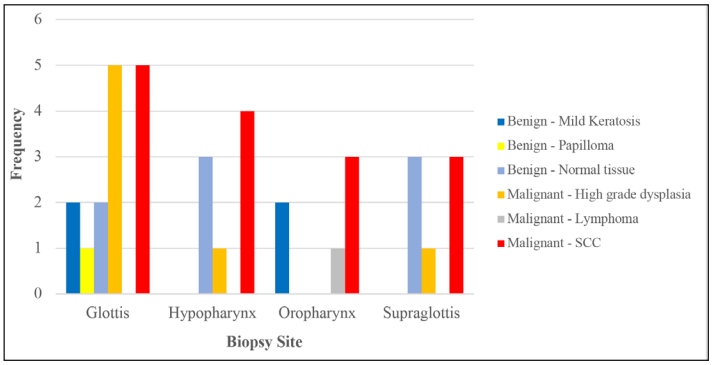

Figure 1. OBB Histopathologic Results Across Biopsy Sites
OBB= office-based biopsy; SCC = squamous cell carcinoma

Table 1. Diagnostic Concordance: Office-based Biopsy and Operative Biopsy

Specimen No.	Site of lesion	OBB Result	OPB Result
1	Glottis	Squamous papilloma	Squamous papilloma
2	Glottis	Squamous cell carcinoma	Squamous cell carcinoma
3	Supraglottis	Squamous cell carcinoma	Squamous cell carcinoma
4	Glottis	Squamous cell carcinoma	Squamous cell carcinoma
5	Glottis	High grade dysplasia	Squamous cell carcinoma
6	Glottis	Squamous cell carcinoma	Squamous cell carcinoma
7	Oropharynx	Mild keratosis	Lymphoma
8	Glottis	High grade dysplasia	Squamous cell carcinoma
9	Glottis	Squamous cell carcinoma	Squamous cell carcinoma
10	Glottis	High grade dysplasia	High grade dysplasia

OBB= office-based biopsy; OPB = operative biopsy

Table 2. 2×2 Diagnostic Table

	OPB malignant	OPB benign	
OBB malignant	8 (TP)	0 (FP)	Positive Predictive Value (PPV) = TP/(TP+FP) = 100%
OBB benign	1 (FN)	1 (TN)	Negative Predictive Value (NPV) = TN/(FN+TN) = 50%
	Sensitivity (Sn) = TP/(TP+TN) = 88.89%	Specificity (Sp) = TN/(TN+FP) = 100%	Accuracy = (TP+TN)/ (TP+FP+FN+TN) = 90%

OBB = Office-based biopsy; OPB = Operative biopsy; PPPV = Positive Predictive Value; NPV = Negative Predictive Value; Sn = Sensitivity; Sp = Specificity; TP = True positive; FP = False positive; FN = False negative; TN = True negative

DISCUSSION

Our study described the outcomes of office-based biopsies as a diagnostic tool for laryngeal and pharyngeal neoplasms. We observed that office-based biopsies (OBB) exhibited a high accuracy rate of 90% and a remarkably high specificity and positive predictive value of 100% in diagnosing malignant and pre-malignant pharyngeal and laryngeal lesions. This indicates those diagnosed with malignancy thru OBB have a high probability of indeed having true malignancy. The low negative predictive value of 50% may indicate the need to undergo an operative biopsy, especially for lesions with suspicious features. Similarly, previous research by Cha, *et al.* reported a sensitivity of 78.2%, and a specificity of 100% for OBB in diagnosing malignancies.[3] Negative results from initial OBB were typically followed by repeat OBB or an operative biopsy.[3-5]

A key factor influencing the accuracy achieved in our study may be the acquisition of multiple representative biopsy samples during OBB, with a minimum of 2 passes. This conjectural observation is supported by Schimberg, *et al.* who found that obtaining at least 2 or 3 representative biopsy samples per procedure was necessary to achieve accuracies of 78% and 93%, respectively, for carcinoma in situ and squamous cell carcinoma.[6] They suggested that a smaller specimen size obtained with smaller flexible biopsy forceps (1.8mm) may contribute to the need for multiple biopsies compared to conventional rigid biopsy forceps used during operative biopsies. Conversely, the 2022 systemic review by Owusu-Ayim, *et al.* found no significant difference between several variables including method of approach, forceps size, additional lighting system (narrow band imaging) nor operator experience.[7] In the same review, they observed a median sensitivity of 73% and specificity of 96.7% for office-based biopsies for laryngopharyngeal lesions, with false-positive rate of 1.08% and false-negative rate of 13.6%.[7]

In our institution, fiberoptic flexible nasopharyngolaryngoscopy has become part of routine screening in patients presenting with symptoms suspicious for laryngopharyngeal neoplasms. With office-based endoscopic biopsies gaining global attention, streamlining operative planning and acquisition of representative biopsies during initial transnasal endoscopy demonstrates its clinical significance. The OBB diagnosis interval at 3.83 days is relatively short, benefiting both the patient and the clinician, facilitating timely clinical decision post-OBB regarding definitive surgery or treatment. This is evidenced by the four patients who proceeded with definitive surgeries following a malignant OBB diagnosis. On the contrary, the definitive diagnosis interval of 16.2 days in our study may be influenced by several factors, including complexity of case or patients' comorbidities precluding medical preoperative clearances prior to operative biopsy. Patients with considerable comorbidities who undergo OBB also avoid systematic risks of undergoing general anesthesia and further delays due to diagnostic clearances prior to operative biopsies. This advancement has also been associated with significantly low complication rates. In a cohort study conducted by Cohen *et al.* involving 390 patients, a 1% complication rate was documented, with epistaxis being the most common complication (n=2).[5] As in our study, office-based biopsy for laryngeal and pharyngeal lesions was well-tolerated with no recorded complications. This may be due to our patient selection criteria and growing experience of the clinicians performing the OBB in our center. Several authors have also consistently concluded that OBB is safe, well-tolerated, and exhibits excellent sensitivity and specificity.[4,5,8,9] Their findings suggest OBB may serve as a viable option to shorten interval of diagnostics to treatment with a minimal to no complications reported. [4,5,8,9] It is important to note that patient selection and factors such as patient tolerability and the level of experience in performing OBB likely played a significant role in the success of the sampling procedure and the minimization of complications. This was also evident in the study of Schutte *et al.,* where they experienced expansion of their inclusion criteria as their experience grew, reflecting an increasing proportion of patients undergoing flexible endoscopic biopsies in their center.[6] They had no complications even though use of anticoagulants were continued for patients undergoing OBB. The same observation was made by Wallenstein *et al.,* where anticoagulant use was reported in 29.9% of 201 patients with no development of bleeding.[10] They reported one patient with a large bilateral glottic tumor who was observed with strong pharyngeal reflex and vigorous coughing post procedure, later developing subglottic edema needing tracheostomy temporarily. Authors therefore concluded that a patient with a compromised airway to be considered an absolute contraindication for OBB.[10] Our study, in agreement with findings of several authors, shows that a successful in-office biopsy can be achieved with the following factors: a well-informed and cooperative patient, exophytic tumors, good local anesthesia technique, and obtaining at least 2 representative tissue samples.[6,11]

Our study is subject to several limitations. Firstly, the COVID-19 pandemic posed a significant constraint as aerosol-generating procedures, including office-based biopsies, were discouraged during the study period. As a result, the number of procedures performed and the ability to ensure adequate follow-up for surgical planning were compromised. The relatively small number of patients who proceeded with operative biopsy may overestimate accuracy of office-based biopsy. Additionally, the retrospective nature of our study relied heavily on previous medical records and endoscopy results, which may have introduced potential biases or missing data. We acknowledge the need

for further prospective studies with larger populations to generate more robust and accurate results. Such studies could provide valuable insights and enhance our understanding of the benefits and limitations of office-based biopsies in this clinical context.

In conclusion, office-based biopsy is an accurate, reliable and safe modality for screening suspicious pharyngeal and laryngeal neoplasms, and may be part of routine screening during initial endoscopy among selected patients with suspicious pharyngeal and laryngeal neoplasms. Combining a high clinical index of suspicion and careful patient selection support the utilization of office-based biopsies for the diagnosis of suspicious pharyngeal and laryngeal lesions for timely clinical decisions, and may improve patient outcome.

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