In-office cup biopsy and laryngeal cytology versus operating room biopsy for the diagnosis of pharyngolaryngeal tumors: Efficacy and cost-effectiveness

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ABSTRACT: *Background.* In-office biopsy is an effective technique to diagnose the nature of pharyngolaryngeal lesions.

Methods. We selected patients with pharyngolaryngeal lesions suspicious for malignancy. For in-office biopsy procedures, laryngeal cytology and direct laryngoscopy biopsy were performed, and diagnostic parameters and costs were estimated.

Results. Eighty-eight patients were selected for this study. For laryngeal cytology, sensitivity was 70.3% (95% confidence interval [CI] = 59.9% to 80.7%), specificity 100% with a positive predictive value of 100% and a negative predictive value of 50% (95% CI = 35.2% to 64.8%). In-office biopsy sensitivity was 81% (95% CI = 72.6% to 89.3%), specificity 100% with a positive predictive value of 100% and a negative predictive value of 20% (95% CI = 2.5% to 37.5%). At our hospital, the use of in-office biopsies as a first approach for diagnosis saves $50,140.80 U.S. per annum.

Conclusion. In-office biopsy is a more affordable technique that enables histologic diagnosis of pharyngolaryngeal lesions in a large percentage of patients. © 2014 Wiley Periodicals, Inc. *Head Neck* **37:** 1483–1487, 2015

KEY WORDS: ambulatory surgical procedures, biopsy, cytology, head and neck neoplasms, cost-benefit analysis

INTRODUCTION

The topographic and histological diagnosis of head and neck cancer is of great importance in the subsequent planning of the treatment. Knowing the exact location of the tumor allows indicating or discarding laryngeal preservation techniques. The histological diagnosis is essential for confirming the diagnosis, suggesting a treatment, discarding other causes of laryngeal involvement, as well as obtaining samples for viral and genetic analysis that allow obtaining data about prognosis and therapeutic targeting of these tumors.

The "gold standard" for histological and topographical diagnosis of head and neck cancer is direct laryngoscopy with biopsy. The procedure is performed in the operating theater with the patient under general anesthesia, which carries a nonnegligible anesthetic risk in similar procedures,[1] high costs, and a variable waiting period between the time when laryngeal neoplasm was suspected, the procedure was performed, and the results of the biopsy were obtained.

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In recent years, in-office endoscopic nasopharyngolaryngoscopy has been known to provide highly reliable topographic data of the extension of tumors. This approach also allows obtaining biopsies using cup miniforceps (in-office biopsies), and brushing samples for laryngeal cytology. The procedure, which is performed in the office with the patient under local anesthesia, is well tolerated,[2] and, as we have experienced, several of our patients prefer it in order to avoid general anesthesia.[3] The cost of the office procedure is lower than the direct laryngoscopy biopsy,[4] and resembles other endoscopic procedures, which can be performed in the office, such as transnasal esophagoscopy.[5]

In recent years, we believe that the emergence of new technologies, such as fiberscope with a chip on the tip linked to a high-definition camera, has increased the diagnostic accuracy of the procedures performed in the office, although no published data exists to support this hypothesis. The association of high definition fibroscopy with new methodologies, such as narrow band imaging, will undoubtedly increase the accuracy of the topographic diagnosis of injuries, leading to better therapeutic indications and a better clinical practice.

In our center, we have performed in-office biopsies for more than a decade, as a complementary method to the direct laryngoscopy biopsy in topographic and histological diagnosis of pharyngolaryngeal lesions (Figure 1). The purpose of this study was to evaluate the histologic

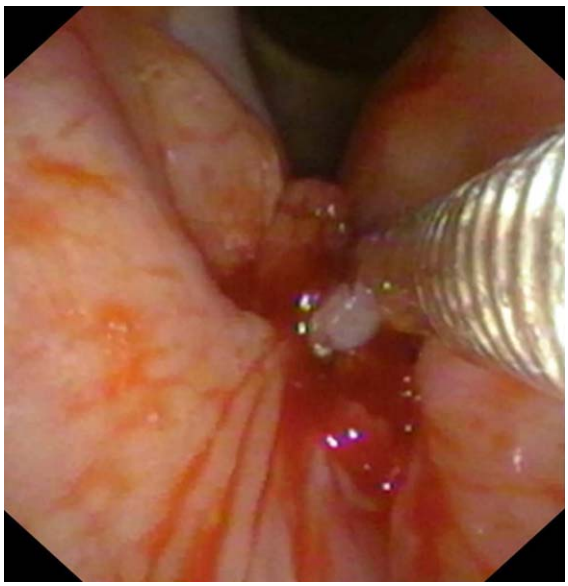

FIGURE 1. Microbiopsy with forceps. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

diagnostic accuracy and costs of in-office procedures (in-office biopsy and laryngeal cytology) versus the "gold standard" (direct laryngoscopy biopsy) in a selected cohort of patients with a suspected tumor in this location.

MATERIALS AND METHODS

We performed 2 study periods. The first one, which was prospective and blinded, took place between April 2008 and December 2011. The second one, which was prospective and unblinded, was carried out between January and November 2012. We selected all patients over 18 years of age that were seen in-office with suspected malignant pharyngolaryngeal tumor at any location. All patients were informed and given the possibility to participate in the study, and those who accepted signed the correspondent consent form. The ethics committee of our hospital had previously approved the study and methodology.

Patients in the first group underwent in-office biopsy and laryngeal cytology over the suspected lesion. At the same time, they were programmed to a direct laryngoscopy biopsy that was performed without knowing the result of the in-office biopsy and laryngeal cytology. The second group of patients underwent in-office biopsy and did not have a laryngeal cytology. Direct laryngoscopy biopsy was scheduled only if the results of the in-office biopsy had been negative for malignancy.

Laryngeal cytology and in-office biopsy were performed using a naso-fiberscope with working channel (K. Storz, model 11001 KL) for microforceps of 1.8 mm in diameter (K. Storz, model 11001 UD). In order to obtain 3 cytology samples from the suspected area in each patient, disposable microbrushes were used (Olympus, model BC-202D-3010). The procedures were performed after placing nasal wicks with 2% lidocaine, oropharyngeal spraying, and by direct instillation in the area through the working channel of the fiberscope. The direct laryngoscopy biopsy was performed using the standard technique with the patient under general anesthesia and biopsies were done using forceps with variable thicknesses. All procedures were performed by authors R.S., R.B., I.C., or by senior residents under the direct supervision of the previously mentioned authors. Biopsies performed both in the office and in the operating room were reviewed by a single pathologist who had previously been informed of the study. A.B. reviewed the totality of laryngeal cytology smears.

Statistical analysis

We conducted a descriptive of the sample by means of absolute and relative frequencies for categorical variables, and mean and range in those numeric variables. In order to evaluate the diagnostic validity of the in-office biopsy and laryngeal cytology versus the "gold standard" (direct laryngoscopy biopsy), we created the corresponding contingency tables and obtained sensitivity, specificity, positive and negative predictive values, likelihood ratios, and accuracy. This approach was conducted for the entire sample and for patients in both study groups, as previously defined.

RESULTS

A total of 88 patients agreed to participate in the study, 76 in the first group and 12 in the second. Of the total sample, 92% ($n = 81$) were men and 8% ($n = 7$) were women, with an average age of 65 years (range = 39–85 years). Histology was squamous cell carcinoma in 100% of cases, with 3.4% ($n = 3$) of the oropharynx (tongue base), 37.5% ($n = 33$) of supraglottis, 29.5% ($n = 26$) glottis, and 29.5% ($n = 26$) of hypopharynx. We did not encounter any instance in which an in-office biopsy could not be performed because of poor patient tolerance, nor did we have airway or other critical concerns during the exploration in any of the cases. In all direct laryngoscopy biopsy procedures, as in in-office biopsy, a biopsy or laryngeal cytology was underwent until we considered it enough for histological analysis, which were analyzed without any problem by our pathologists who had previously been informed of the study.

In the first group of patients, the sensitivity of the in-office biopsy was 81.1% (72.2%; 95% confidence interval [CI] = 95% to 90%), specificity was 100% with a positive predictive value of 100% and a negative predictive value of 12.5% (95% CI = −3.7% to 28.7%). There were no false positives for the in-office biopsy, and the false negative rate was 18.4% (14 of 76). The negative likelihood ratio (LR–) was 0.19 (95% CI = 0.12–0.30). The positive likelihood ratio (LR+) could not be calculated because there were no false-positives and a specificity of 100%. The in-office biopsy diagnostic accuracy was 81.6%. For laryngeal cytology, the sensitivity was 70.3% (95% CI = 59.9% to 80.7%); specificity was 100% with a positive predictive value of 100% and a negative predictive value of 50% (95% CI = 35.2% to 64.8%). The LR– was 0.3 (95% CI = 0.21–0.42). The diagnostic accuracy of the laryngeal cytology was 71.1%. There were no false-

positives and false-negatives were 28.9% of the cases (22 of 76; Table 1).

Once we analyzed the first group of patients, having seen that the laryngeal cytology diagnostic variables did not contribute to increasing diagnostic accuracy when associated with in-office biopsy, and the in-office biopsy had no false-positives, we decided to continue the study without performing laryngeal cytology and requesting direct laryngoscopy biopsy only in cases in which the in-office biopsy was negative. Facing the absence of false-positives in cases of positive in-office biopsy, we assumed a positive direct laryngoscopy biopsy in in-office biopsy positive cases for malignancy. When pooling patients of the first and second groups, the sensitivity of the in-office biopsy was 81% (95% CI = 72.6% to 89.3%), specificity of 100% with a positive predictive value of 100% and a negative predictive value of 20% (95% CI = 2.5% to 37.5%), and a diagnostic accuracy of 81.8%. The LR– was 0.19 (95% CI = 0.12–0.30). The false-negative rate of the in-office biopsy was 18.2% (16 of 88; Table 2).

Assuming no in-office biopsy false-positives, we performed an estimate of the savings in the case of performing an in-office biopsy as the first diagnostic tool in all cases, leaving the direct laryngoscopy biopsy for cases in which the in-office biopsy was negative.

In our center, we normally perform between 45 and 55 direct laryngoscopy biopsy annually, when suspecting malignancy in pharyngolaryngeal exploration, with a cost of $1253.52 U.S. per direct laryngoscopy biopsy ($130.83 U.S. preoperative examinations and a pre-anesthesiology visit; $1112.81 U.S. surgery and related costs; and $9.86 U.S. specimen biopsy). The total cost for these procedures is $62,676.00 U.S. per year. The estimated cost per in-office biopsy is $65.44 U.S. ($45.73 U.S. medical supplies; $19.72 U.S. biopsy ± cytology). For both procedures, we did not take into account the cost of professional training, with a learning curve and a cost derived from it being difficult to estimate. Assuming the in-office biopsy diagnostic sensitivity in our sample was 81%, thus, performing an in-office biopsy as the first diagnostic approach and leaving aside the direct laryngoscopy biopsy for negative cases or where the sample was unsatisfactory, could represent savings of $50,140.80 U.S. per annum. This amounts to 80% of the costs that would have represented performing a direct laryngoscopy biopsy in all patients with a suspected pharyngolaryngeal tumor.

TABLE 1. Diagnostic accuracy between laryngeal cytology versus direct laryngoscopy biopsy and in-office biopsy versus direct laryngoscopy biopsy in the first group studied.

Diagnostic test	Value, % (95% CI)
Laryngeal cytology (first group) vs direct laryngoscopy biopsy	
Sensitivity	70.3 (59.9–80.7)
Specificity	100 (100–100)
PPV	100 (100–100)
NPV	50 (35.2–64.8)
LR+	-
LR–	0.30 (0.21–0.42)
Precision	71.1
In-office biopsy (first group) vs direct laryngoscopy biopsy	
Sensitivity	81.1 (72.2–90)
Specificity	100 (100–100)
PPV	100 (100–100)
NPV	12.5 (−3.7 to 28.7)
LR+	-
LR–	0.19 (0.12–0.30)
Precision	81.6

Abbreviations: 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR–, likelihood ratio negative.

TABLE 2. Diagnostic accuracy between in-office biopsy versus direct laryngoscopy biopsy.

Diagnostic test	Value, % (95% CI)
In-office biopsy (first and second group) vs direct laryngoscopy biopsy	
Sensitivity	81 (72.6–89.3)
Specificity	100 (100–100)
PPV	100 (100–100)
NPV	20 (2.5–37.5)
LR+	-
LR–	0.19 (0.12–0.30)
Precision	81.8

Abbreviations: 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR+, likelihood ratio positive; LR–, likelihood ratio negative.

DISCUSSION

In recent years, there has been a growing interest in in-office procedures.[6] The improvements of technology and endoscopy imagery make these techniques an attractive alternative at a lower cost and similar efficacy to standard diagnostic techniques. In the field of gastroenterology, transnasal esophagoscopy has increased in popularity, reporting correlation rates to conventional endoscopy close to 100%, with a lower cost and great satisfaction of the patients.[7] For topographical and histological diagnosis of pharyngolaryngeal lesions, the use of in-office endoscopic techniques represents a saving of explorations and biopsies in the operating room.[4,8]

However, it is important to take into account that laryngeal sensitivity is variable among patients, as well as being difficult to evaluate objectively,[9,10] which may hinder the realization of a good exploration. In general, endoscopic procedures are well tolerated with a success rate over 90%, however, when there are difficulties in exploration, such as gag reflex or pre-examination anxiety, success rates of these are below 70%.[3]

The way to prevent these exploration drawbacks, or derivatives of excessive laryngeal sensitivity, is the application of local anesthetic on the area, which is a well described and validated procedure.[2,11–13] This approach allows for a satisfactory exploration and, if done habitually, can prevent patients from suffering anxiety attacks derived from a bad experience of a previous endoscopic examination in the office. This approach is also popular among patients, as it decreases their anxiety and allows for both exploring and handling in a safer and more satisfying manner.

After managing the factors that can influence an unsatisfactory endoscopic nasopharyngolaryngoscopy exploration

in a patient with a suspected pharyngolaryngeal lesion, we can aim for the same objectives as with a direct laryngoscopy biopsy, that is to clearly delimitate the tumor, as well as to perform an in-office biopsy ± laryngeal cytology of the suspicious lesion.

The in-office biopsy procedure has been performed for years, yet there is scarce literature confirming its usefulness as a first approximation of the histological diagnosis of these patients. In-office biopsy has great advantages, such as the possibility of quickly obtaining a biopsy without waiting for surgery, reducing the patient's anxiety as the result is available in a shorter period of time, lower costs, as well as the possibility to carry out the procedure immediately once the patient is seen in the office, even during the first visit. The drawback is the learning curve, the need to defer the procedure if taking anticoagulants, and, if negative, the possibility of having to wait for a longer time for direct laryngoscopy biopsy, because a negative in-office biopsy would not rule out the completion of this procedure.

Bastian et al,[8] in a 1989 study, assessed the diagnostic usefulness of direct and indirect videolaryngoscopy in topographic diagnosis of pharyngolaryngeal tumors, finding a great similarity to direct laryngoscopy, being worse in locations closer to the hypopharynx. Bastian et al,[8] also performed oropharyngeal biopsies, obtaining similar results to those in the operating theater. Cohen and Fliss[14] and Cohen et al[15] published 2 articles about the in-office biopsy efficacy as a previous tool to direct laryngoscopy biopsy in the histological diagnosis of pharyngolaryngeal lesions. In the first study,[14] they established that the in-office biopsy was enough for the diagnosis of malignant lesions in 57% of instances, and in the second study[15] in 69.2% of cases. In the latter study, they reported a false-negative rate of 33% with 1 false-positive case (1.1%). Naidu et al,[4] in a small pool of patients, found that the in-office biopsy was enough for pharyngolaryngeal lesion diagnosis in 64% of cases, at a significantly lower cost than that obtained in case of making direct laryngoscopy biopsy as a first approximation.

The great variability in test sensitivity may be due to the sampling. Microbiopsy is a milimetric sample, which seems to have a higher performance in exophytic lesions and lower in submucosal lesions or injuries in difficult locations.[4] However, we believe that it is possible to obtain a valid sampling in a high percentage of cases after a training period.

Our series reports an efficacy of in-office biopsies over 80% for the diagnosis of malignant pharyngolaryngeal tumors, without reporting false-positives. Despite a high specificity, the negative predictive value and LR– of the sample are low, which supports not setting aside invasive examinations, such as direct laryngoscopy biopsy if clinical suspicion persists in spite of a negative in-office biopsy. It is important to remember that the predictive values are altered by the prevalence of the disease, being more useful for clinical practice than the use of the LR when comparing the results between different studies. In our study, LR+ was not possible to obtain because of the absence of false-positives in both groups.

The usefulness of laryngeal cytology is highly variable and depends on a large percentage of cytological techniques. We halted performing laryngeal cytology because we believe that, in our series, it did not contribute at all for the prompt diagnosis of these patients, as results presented above have shown.

The assessment of the costs of medical procedures is of great interest. In our center, we estimate a saving of more than $50,000 U.S. a year using the strategy of making an in-office biopsy to continue with the "gold standard" if necessary. Despite being a good diagnostic strategy at a lower cost, we must not forget our medical criteria in guiding these patients. In instances where a specialist is not sure of the results obtained through in-office biopsy and wants to perform a direct laryngoscopy biopsy, we believe the specialist must be true to her "medical instinct." These situations could emerge even if the in-office biopsy results are negative, perhaps because the sample has been difficult to obtain, or because the lesion is submucosal and the specialist is not satisfied with it, or simply because the endoscopic topographic exploration was not adequate.

Direct laryngoscopy biopsy remains the "gold standard" for obtaining both final histology and exploration. Direct laryngoscopy biopsy allows instrumental palpation and microscopic examination of areas that sometimes are difficult to visualize endoscopically.

CONCLUSIONS

In-office biopsy is an efficient technique, and cheaper than direct laryngoscopy biopsy, in histological diagnosis of patients with suspected pharyngolaryngeal tumors. In our series, laryngeal cytology performed simultaneously provided no additional value to the histological diagnosis of lesions. We suggest in-office biopsy as an initial diagnostic methodology for pharyngolaryngeal tumors, leaving direct laryngoscopy biopsy for negative cases or cases in which the specialist believes will likely obtain negative results, or in which direct laryngoscopy biopsy is preferred because of the tumor location.

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