Reliability of a Transnasal Flexible Fiberoptic In-Office Laryngeal Biopsy

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**Objective:** To compare pathologic results obtained via in-office TFL with those of subsequent direct laryngoscopy to assess the accuracy of TFL as a diagnostic tool.

**Setting:** Tertiary reference medical center.

**Participants:** One-hundred two patients with suspicious laryngeal lesions.

**Intervention:** All patients underwent in-office biopsies.

**Main Outcome Measures:** All patients with malignant lesions were referred to appropriate services for treatment, and those with a diagnosis of a benign lesion or carcinoma in situ were referred for direct laryngoscopy for definitive diagnosis. The results of the pathologic testing on specimens from in-office and direct laryngoscopy were compared.

**Results:** Adequate tissue for diagnostic purposes was obtained in 96 of 102 in-office TFL biopsies (94.1%). The biopsy results revealed invasive carcinoma in 34 patients (35.4%), carcinoma in situ in 17 patients (17.7%), and benign lesions in 45 patients (46.9%). All patients with benign lesions and carcinoma in situ were referred for biopsy of samples obtained using direct laryngoscopy, to which 57 patients agreed. The final pathologic results identified from the biopsies on direct laryngoscopy revealed that there was an underestimation of the TFL results in 30 of 91 patients (false-negative rate, 33.0%) and an overestimation in 1 patient (false-positive rate, 1.1%). The sensitivity of TFL biopsy compared with that of direct laryngoscopy biopsy was 69.2% and the specificity was 96.1%.

**Conclusions and Relevance:** Transnasal fiberoptic laryngoscopy yielded low sensitivity in assessing suspicious lesions of the larynx. These results may indicate that direct laryngoscopy represents the definitive pathologic diagnostic procedure whenever the pathologic results of an in-office TFL procedure are interpreted as benign or as carcinoma in situ.

This method is convenient and expeditious for obtaining a biopsy specimen and can theoretically replace direct laryngoscopy performed with general anesthesia for the purpose of obtaining tissue for histologic examination in selected cases. Publications on in-office laryngeal biopsy have concurred that this procedure is safe, feasible, and easy to perform. The accuracy of in-office biopsy via TFL, however, has not been established. The aim of this study was to examine this issue.

METHODS

All patients who were examined in the outpatient clinic of Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, and underwent in-office biopsies for suspicious lesions of the larynx between May 1, 2006, and December 31, 2009, were recruited and provided written informed consent for participation. Patients with discrete, suspicious-appearing lesions were eligible for inclusion. Suspicious lesions included leukoplakia, erythroplakia, ulceration, a cauliflower appearance, and a lesion on an immobile vocal cord, thus excluding patients with benign-appearing lesions such as polyps, nodules, Reinke space edema, and findings compatible with chronic laryngitis due to reflux. Patients with suspicious lesions were referred for TFL biopsy to determine whether the lesion was malignant or benign.

The diagnosis of invasive carcinoma using a biopsy specimen obtained through TFL was considered equivalent to that obtained through direct laryngoscopy biopsy. However, all patients with benign lesions or carcinoma in situ (CIS) were referred for subsequent direct laryngoscopy for definitive diagnosis. Findings of CIS were added to those of invasive carcinoma when sensitivity and specificity measurements were calculated. Pathologic results of the specimens from both procedures were compared.

All relevant demographic and clinical data were retrieved for analysis. The study was approved by the ethics committee of the institution, and all suitable patients signed an informed consent form before undergoing the procedure.

BIOPSY TECHNIQUE

In our biopsy procedure, the endoscope (FNL10RP3; KayPentax or ENT 2000; Vision Sciences) is connected proximally to a camera and monitor (KayPentax Digital Video Stroboscopy System; KayPentax). The soft palate is locally anesthetized with lidocaine hydrochloride spray, 10%, and the nasal cavity is anesthetized with tetracaine, 2%, mixed with oxymetazoline hydrochloride, 0.05%. The endoscope is covered with a disposable plastic sheath that has a working channel (EndoSheath slide-on; Vision Sciences). After insertion of the endoscope, 2 mL of lidocaine, 2%, is injected through the working channel. A 2-mm-diameter biopsy forceps is inserted through the working channel (laryngeal biopsy forceps; Medtronic). In some cases more than 1 specimen was collected to evaluate different parts of the lesion. The tissue is collected in a designated pathology plastic cup containing normal saline solution. The patient remains in the clinic for observation for 30 minutes after undergoing the procedure.

STATISTICAL ANALYSIS

Data on the agreement between in-office biopsy results and the direct laryngoscopy findings were evaluated using the Cohen \( \kappa \) index of agreement. The McNemar test of symmetry assessed whether one of the 2 methods had higher sensitivity to detect CIS or invasive carcinoma. All instances in which there was agreement between the 2 methods were compared with discordant cases using the \( \chi^2 \) test. Data were analyzed using commercial software (SAS for Windows, version 9.1.3; SAS Institute, Inc.).

A total of 102 patients underwent in-office biopsies for suspicious-appearing lesions in the larynx during the study period. The group included 83 men and 19 women (median age, 69 years; range, 30-89 years). The most common presenting symptom was dysphonia (68 patients [66.7%]). Other symptoms included dysphagia, chronic cough, throat discomfort, and dyspnea. Fifty-nine patients (57.8%) had additional comorbidities including ischemic heart disease, chronic renal failure, chronic lung disease, and history of cerebrovascular accident. Sixty-two patients (60.8%) were smokers.

Adequate amounts of tissue for pathologic studies were obtained in 96 of 102 patients (94.1%) who underwent in-office TFL biopsies. The other 6 patients were referred for further evaluation of the lesions using direct laryngoscopy, and their data were excluded from the final statistical analysis (in all of these cases an inadequate amount of tissue was the result of the patients’ intolerance of the procedure).

Forty-five of 96 patients (46.9%) had benign lesions, and all were referred for direct laryngoscopy for subsequent evaluation. Thirty-four patients (35.4%) received a diagnosis of invasive carcinoma, and all were referred directly for definitive treatment (radiotherapy, combined chemotherapy and radiotherapy, and/or surgery) after completing their staging workup.

Seventeen of 96 patients (17.7%) received a diagnosis of CIS; all were referred for direct laryngoscopy to confirm the diagnosis, although only 12 patients agreed to do so. All 5 patients who refused to undergo direct laryngoscopy were referred to the oncology unit, and their data were excluded from final statistical analysis. Therefore, the data of 91 patients were included for statistical analysis.

A total of 57 patients (62.6%) underwent direct laryngoscopy following TFL: 45 patients with biopsy specimens showing a benign lesion underwent direct laryngoscopy for subsequent evaluation. Of these, the benign result was confirmed in 25 patients (55.6%), 16 patients (35.6%) received a diagnosis of invasive carcinoma, and 4 patients (8.9%) were identified as having CIS (Table 1).

Twelve patients with a finding of CIS underwent direct laryngoscopy for subsequent evaluation of the lesions. Of these, biopsies performed in the operating room revealed 10 cases of invasive carcinoma, 1 case of CIS, and 1 case of a benign lesion.

The final results of the biopsies performed on samples from direct laryngoscopy revealed that there was an underestimation of the TFL results in 30 of 91 patients (false-negative, 33.0%) and an overestimation in 1 patient (false-positive, 1.1%); however, this patient underwent direct laryngoscopy 3 months later because of persistent disease, and examination of that biopsy specimen revealed invasive carcinoma.
Table 1. Accuracy of Transnasal Flexible Fiberoptic Laryngoscopy

<table>
<thead>
<tr>
<th>TFL/DL Finding</th>
<th>Benign</th>
<th>Carcinoma In Situ</th>
<th>Squamous Cell Carcinoma</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>25</td>
<td>4</td>
<td>16</td>
<td>45 (49.5)</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>1</td>
<td>1</td>
<td>10</td>
<td>12 (13.2)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>0</td>
<td>0</td>
<td>34^b</td>
<td>34 (37.4)</td>
</tr>
<tr>
<td>Total, No. (%)</td>
<td>26 (28.6)</td>
<td>5 (5.5)</td>
<td>60 (65.9)</td>
<td>91 (100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: DL, direct laryngoscopy; TFL, transnasal fiberoptic laryngoscopy.  
^a The boldface type indicates a discrepancy in the TFL and DL pathologic results.  
^b Invasive carcinoma was considered as conclusive pathologic results equal to DL results.

Table 2. Sensitivity and Specificity of Transnasal Fiberoptic Laryngoscopy

<table>
<thead>
<tr>
<th>TFL/DL Finding</th>
<th>Benign</th>
<th>Carcinoma In Situ/ Squamous Cell Carcinoma</th>
<th>Total, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>25</td>
<td>20</td>
<td>45 (49.5)</td>
</tr>
<tr>
<td>Carcinoma in situ/squamous cell carcinoma</td>
<td>1</td>
<td>45</td>
<td>46 (50.5)</td>
</tr>
<tr>
<td>Total, No. (%)</td>
<td>26 (28.6)</td>
<td>65 (71.4)</td>
<td>91 (100.0)</td>
</tr>
</tbody>
</table>

Abbreviations: DL, direct laryngoscopy; TFL, transnasal fiberoptic laryngoscopy.  
^a The sensitivity was 69.2% and the specificity was 96.1%.

The Cohen κ index for agreement was calculated to evaluate agreement between the 2 laryngoscopy methods, accounting for possible random agreement. The value (κ = 0.38) indicated fair agreement between them. The McNemar test for symmetry was applied to determine whether the number of biopsies resulting in a diagnosis of a malignant lesion by direct laryngoscopy was significantly larger than the number identified by TFL alone. The McNemar test yielded a highly significant result (P < .001), thus indicating that direct laryngoscopy was more diagnostic for laryngeal lesions than was TFL alone.

To calculate the sensitivity and specificity of TFL in the diagnosis of malignant laryngeal lesions, we divided our biopsy results into 2 groups: (1) benign lesion and (2) invasive carcinoma and CIS lesion. The sensitivity of TFL biopsies compared with that of direct laryngoscopy biopsies was 69.2% and the specificity was 96.1% (Table 2).

The demographic and clinical variables of the group of 60 patients for whom agreement was achieved between the 2 methods were compared with those of the remainder of the patients (n = 31). There was a higher rate of smoking in the nonagreement group compared with the agreement group (28 patients [90.3%] vs 27 [45.8%], P < .001), as well as a higher rate of dysphonia (27 patients [87.1%] vs 31 [51.7%], P = .001). There were no other significant differences between the groups.

Complications of in-office TFL were limited to postprocedure aspiration in 1 patient (without serious consequences) and self-limited epistaxis in 2 patients.

Since its introduction more than 150 years ago, laryngoscopy has undergone numerous changes in clinical application. Laryngoscopy had started as an indirect procedure with the manipulation of a laryngeal mirror performed with an awake patient and progressed to direct laryngoscopy with an operating microscope and the patient under general anesthesia. The latter afforded the operating laryngologist obvious advantages, such as bimanual dexterity, superior precision, and the relative ease of examining an anesthetized patient. Today, office-based procedures using new technologies, such as indirect flexible laryngoscopy, are becoming popular once again, offering a simple and cost-effective alternative to the traditional direct laryngoscopy procedures, especially for patients who are not candidates for general anesthesia or laryngeal suspension.

The unanswered question is whether TFL yields accurate final results of pathologic testing. According to our statistical analysis, the specificity of TFL in diagnosing invasive carcinoma is excellent, but the sensitivity of diagnosing a suspicious lesion as being CIS or invasive carcinoma is only 69.2%. These results may indicate that direct laryngoscopy represents the definitive diagnostic procedure whenever the tissue sample obtained in an office TFL procedure is interpreted as being a benign lesion or CIS. This conclusion refutes the findings of several recent studies, although the comparison is not direct because most of these studies focused on suspect lesions of the upper aerodigestive tract and mainly on the esophagus and hypopharynx. Postma et al reported 100% accuracy of transnasal esophagoscopy in 17 patients with lesions of the upper aerodigestive tract. All 17 masses were presumptively suspected to be malignant and were later inspected and verified as being malignant through panendoscopy with biopsy. The results of transnasal esophagoscopy and panendoscopy with biopsy specimens were identical. One factor that may explain the differing findings from our study is that esophageal biopsy speci-
mens obtained using transnasal esophagoscopy are easier to achieve than are those from the larynx because of the gag and cough reflexes. Thus, inadequate sample sizes and “off-base” specimens may bias results. Price et al14 reviewed the findings on 18 patients who underwent transnasal flexible laryngo-esophagoscopy either for localization of a primary cancer or investigation of the upper aerodigestive tract (12 cases of laryngeal lesions). Those authors expressed concern that the size of the acquired biopsy specimen might result in underestimation of the depth of invasion. In one of their cases, the biopsy result was suggestive of invasion but was not diagnostic, and the diagnosis of 3 other cases was benign lesions. Transnasal flexible laryngo-esophagoscopy was not compared with direct laryngoscopy in cases with results indicating benign lesions. Wang et al15 evaluated the efficacy of transnasal esophagogastroduodenoscopy performed without sedation in the diagnosis of esophageal lesions and reported an 11.1% rate of inaccurate diagnosis among 27 patients with hypopharyngeal cancer. The conclusions of these studies12-15 were drawn from results derived from much smaller cohorts than the one reported herein and were not compared with the conclusions of other studies: this may explain the higher accuracy described in previous reports.

It is our impression that pathologists are reluctant to conclude that cancer is present in laryngeal biopsy specimens from small tissue samples. This notion is supported in a novel series by Sarioglu et al16 in which laryngeal preneoplastic lesions were evaluated by 14 pathologists using the World Health Organization, Ljubljana, and squamous intraepithelial neoplasia classification systems.17-23 All 42 laryngeal biopsy specimens were labeled as squamous hyperplasia; mild, moderate, or severe dysplasia; CIS; or invasive carcinoma. Sarioglu et al concluded that there was a significant difference between the participants in all 3 classification systems, and they questioned intraobserver accuracy. The lack of willingness on the part of pathologists to commit to a final diagnosis of CIS/invasive carcinoma on the basis of small fragments of tissue obtained via TFL is also apparent in our 6 patients who were ultimately referred for direct laryngoscopy because of an insufficient amount of tissue in the specimen.

An inherent error in laryngeal biopsies on final pathologic evaluation is the diagnosis of CIS on the basis of the basement membrane remaining microscopically intact. This diagnosis, often sampling only the “tip of the iceberg,” may overlook other parts of the vocal fold that otherwise may contain microinvasive carcinoma or even invasive carcinoma. This might partially explain the low sensitivity in the TFL group when small and unrepresentative material is initially diagnosed as CIS and later diagnosed as invasive carcinoma on direct laryngoscopy biopsies.

There was a higher rate of smoking in the nonagreement group compared with the agreement group as well as a higher rate of dysphonia. This might be the result of the presence of Reinke space edema, which can partially obscure small pathologic lesions and interfere with obtaining an adequate tissue sample for biopsy.

We used fiberoptic equipment to achieve the laryngeal view in this study. Perhaps with improved in-office evaluation using newer distal chip endoscopes and different lighting algorithms (eg, narrow-band imaging), we would be able to improve our diagnostic accuracy.

In conclusion, the low sensitivity rate for diagnosing suspicious lesions of the larynx using TFL with biopsy raises serious doubts about its clinical value. As such, it is recommended that all patients with a suspicious lesion diagnosed by TFL biopsy as being benign or CIS should undergo direct laryngoscopy for verification of the findings.

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REFERENCES