Utility of Blind Forceps Biopsy of the Main Carina and Upper-Lobe Carina in Patients With Non-small Cell Lung Cancer*

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Background and objective: Preoperative detection of non-small cell lung cancer (NSCLC) metastasis to the main carina and upper-lobe carina can alter the operative approach, preclude further staging procedures, and save many patients from thoracotomy. This study assessed whether bronchoscopic forceps biopsy of the normal-appearing main carina and upper-lobe carina (blind biopsy) ipsilateral to the primary NSCLC lesion improved the accuracy of cancer staging and helped guide the management of these patients.

Patients and methods: A prospective study of 52 patients was carried out at the SSK Süreyyapasa Center for Chest Disease and Cardiotoracic Surgery. Over a 6-month period, we bronchoscopically evaluated 52 consecutive NSCLC patients who were radiologically classified as operable. At least five blind forceps biopsy specimens were obtained from the main carina and/or upper-lobe carina during each patient’s initial fiberoptic bronchoscopic examination. Biopsy specimens were collected from the main carina and upper-lobe carina in 51 and 17 patients, respectively. Initially, all patients were staged and evaluated for operability in standard fashion, without histologic assessment of the blind biopsy specimens. We then restaged the disease and reassessed the patients’ operability in light of the biopsy findings.

Results: Metastasis was histologically diagnosed in seven patients (13.7%) who underwent main carina biopsy and in four patients (23.5%) who underwent upper-lobe carina biopsy. Cancer-positive blind biopsy results changed the status of 25% (6 of 24) of patients from operable to inoperable, and changed the surgical approach in 11.1% (2 of 18) of patients who ultimately did undergo surgery. We found no statistical relationship between metastasis to either carina and tumor type, stage of disease, visibility of the tumor on fiberoptic bronchoscopy, primary tumor location, T status, or N status (p > 0.05).

Conclusions: A blind forceps biopsy of the main carina and upper-lobe carina ipsilateral to the lesion site should be done routinely at initial bronchoscopic examination of all radiologically operable patients with suspected lung cancer. This type of screening can save a significant number of NSCLC patients from inappropriate or unnecessary thoracotomy and further staging procedures with their associated morbidity and risk.

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Key words: blind biopsy; carina; fiberoptic bronchoscopy; lung cancer

Abbreviations: FOB = fiberoptic bronchoscopy; NSCLC = non-small cell lung cancer

Currently, surgical excision is the only way to achieve complete cure in lung cancer, and this is not always possible. Despite the range of available techniques for assessing patients with non-small cell lung cancer (NSCLC), there are still major inconsistencies between preoperative assessment and postoperative staging and survival. In most cases, this is related to undetected local and distant metastases. Research has shown that inappropriate or unnecessary surgery for lung cancer shortens survival and increases the cost of the treatment.

Bronchoscopic examination is important for preoperative evaluation and staging of patients with NSCLC. Bronchoscopy helps guide treatment strat-
egy by allowing the examiner to visualize tumors directly, perform biopsies, and assess for local extension. Routine use of this technique in bronchogenic carcinoma is well established. However, some of the earliest bronchoscopic methods, despite their high yield, have been replaced in time by expensive, time-consuming, and invasive methods.

Bronchoscopic forceps biopsy of the normal-appearing main carina, or “blind biopsy,” was first described by Rabin et al in 1952. Since then, only three similar studies have been performed, and all have confirmed that it reduces the morbidity, mortality, and costs of further invasive testing in many lung cancer patients. Our study is the first to investigate blind forceps biopsy of the upper-lobe carina ipsilateral to the tumor site. The rationale for assessing this site was that microscopically detected tumor involvement at either carina would change the operative approach, or mean that some patients were no longer surgical candidates.

We prospectively investigated the value of blind forceps biopsy of the main carina and upper-lobe carina ipsilateral to the tumor in patients with NSCLC. Our aim was to determine how this screening influenced classical preoperative staging, surgical approach, and surgical candidacy in NSCLC patients who had been classified as radiologically operable.

MATERIALS AND METHODS

The study was carried out between May 1996 and October 1996 at SSK Süreyyapasa Center for Chest Diseases and Cardiothoracic Surgery. The protocol was approved by the ethics committee, and all subjects gave their informed consent. Seventy-five consecutive patients with suspected bronchogenic carcinoma who were classified as radiologically operable (10 female and 65 male patients; mean ± SD age, 59.3 ± 7.8 years) and scheduled for routine fiberoptic bronchoscopy (FOB) were enrolled in the study. Candidacy for radiologic operability, determined prior to bronchoscopy, was based on findings on standard lateral and posteroanterior chest radiographs and thoracic CT. All individuals indeterminately staged as T4, N3, or M1 and required further examination or staging procedures for confirmation were also considered radiologically operable.

At each patient’s initial FOB examination, we collected blind forceps biopsy specimens from the main carina and/or upper-lobe carina ipsilateral to the lesion site (Fig 1). Bronchoscopy (Olympus PF IT30; Olympus; Tokyo, Japan) was done transnasally under local anesthesia. Regarding the blind carinal biopsies, at least five specimens were collected from each carina screened, and separate forceps were used at each of the two different sites to avoid contamination. The examiner made every attempt to obtain biopsy specimens deep enough to include submucosal tissue. The appearance of the carinae at bronchoscopy was recorded as “normal,” “suspicious,” or “gross tumor invasion.” The term suspicious was assigned to carina exhibiting granulation tissue, loss of mucosal sheen, and in cases where the tissue was thickened, swollen, fixed deviated, or had thickened ridges or increased vasculature. Blind biopsy specimens were taken only at the initial FOB and from normal-appearing carinae (Fig 1). Taking biopsy specimens from suspicious or grossly invaded carinae is a standard procedure, and such carinae were routinely sampled at the initial FOB. Positive blind biopsy results were taken into consideration only if there was histopathologic confirmation of tumoral invasion of the tissue.

If histopathologic examination result of the tumor and direct findings on FOB did not dictate further staging procedures unnecessary, abdominal CT, bone scintigraphy, and cranial CT (if
there was any complaint or tumor type was adenocarcinoma) were performed. Mediastinoscopy or mediastinotomy were routinely done in patients with suspicious mediastinal lesions or lymph node abnormalities that might have eliminated them as surgical candidates. Some of the patients underwent additional testing according to symptoms and abnormal findings on detailed physical examination. All patients with NSCLC were classically staged considering the data from these examination methods, and the results of the blind biopsies were not considered here.

Simple spirometric assessment was done at least 3 days after the initial bronchoscopic examination. Patients were cleared for thoracic surgery if their FEV1 was ≥ 80% of predicted, or FEV1 was > 2 L. Patients who did not meet these criteria underwent further testing to determine their predicted postoperative FEV1 or diffusing capacity of the lung for carbon monoxide by using scintigraphic methods described by Markos et al.8 After the classical staging, the operability was decided regarding their clinical and cardiac status (history, physical examination, 12-lead ECG, and echocardiography) and pulmonary function tests described above. At this point, we then reviewed each case in light of the blind biopsy results. Based on the positive histologic findings, some patients were restaged (upstaging), and the final operability was decided according to the last stage and pulmonary function tests that might not suffice because of the apparent need for wider resection in some patients with positive blind biopsy results.

For statistical analysis, we used Fisher's Exact Test and Kolmogorov-Smirnov Test to test for correlation between metastasis to either carina and the parameters of T status, N status, tumor location, tumor type, disease stage, and tumor visibility on FOB. All p values < 0.05 were considered to indicate statistical significance.

Results

There were no complications associated with blind forceps biopsy. Twenty-three patients were excluded for the further evaluation due to gross invasion of the main carina (n = 1), nonmalignant lesion (n = 4), diagnosis of small cell carcinoma (n = 13), and metastasis to lung (n = 5). A total of 52 patients with NSCLC completed the study (Fig 2).

We performed biopsy of the main carina in 51 of the 52 patients. The excluded patient (epidermoid carcinoma) had widening of the main carina. The cancer diagnoses are listed in Table 1. A blind biopsy was performed of the upper-lobe carina in 17 patients; in these patients, the primary tumor was epidermoid carcinoma (n = 11), adenocarcinoma (n = 5), and large cell carcinoma (n = 1). In the remaining 35 patients, the upper-lobe carina was either grossly invaded by tumor (n = 22) or appeared suspicious (n = 13); all of these carinae were routinely subjected to standard biopsies. Histologic examination of the blind biopsy specimens revealed malignancy in the main carina of seven patients (13.7%) and the upper-lobe carina in four patients (23.5%). In all cases with positive blind biopsy findings, the histologic diagnosis matched that of the primary tumor. Statistical analysis revealed no signif-

**Figure 2.** Study group, visibility of tumor via FOB, and results. Twenty-three patients were excluded for further evaluation. Of the 52 patients who completed the study, 1 patient with a suspicious appearance of the main carina was excluded for the blind main carinal biopsy and 35 patients were excluded for the blind upper-lobe carinal biopsy because of gross invasion (n = 22) and suspicious appearance (n = 13) of the upper-lobe carina.
significant relationship between metastasis to either carina and type of tumor ($p > 0.05$). Table 2 lists primary tumor location and carinal biopsy status for all patients. Our analysis also showed no statistical correlation between metastasis to either carina and primary tumor location ($p > 0.05$).

The primary tumor was visualized on FOB in 38 patients. In this group, the main carina biopsies ($n = 38$) and upper-lobe carina biopsies ($n = 9$) showed tumoral invasion in five patients (13.2%) and one patient (11.1%), respectively. In the other 14 patients, the tumor was not directly observed on bronchoscopic examination. In this group, main carina biopsies ($n = 13$) and upper-lobe carina biopsies ($n = 8$) exhibited tumoral invasion in two patients (15.4%) and three patients (37.5%), respectively (Fig 2). The initial fiberoptic bronchoscopic examination led to definitive diagnosis in all the tumors that were directly visible ($n = 38$), but five of the tumors that were not directly observed ($n = 14$) required a second FOB for diagnosis, and two of these five were ultimately diagnosed by transthoracic fine-needle aspiration (Fig 1).

Classical preoperative staging revealed 11 stage I, 6 stage II, 14 stage IIIA, 7 stage IIIIB, and 14 stage IV cases. One of the stage IIIIB patients was the individual who did not undergo main carina biopsy. Based on classical staging alone, 31 patients were deemed at a suitable stage for surgery; however, 7 of these individuals were eliminated as surgical candidates based on clinical and cardiac status, and pulmonary function testing. Thus, in total, 24 of the overall 66 radiologically operable primary bronchogenic carcinoma patients (36.4%) were classically operable. Results of the blind biopsies from the main carina changed the stage of five patients from stage I ($n = 2$) and stage IIIA ($n = 3$) to stage IIIB. Blind biopsy specimens were obtained from the upper-lobe carina in six stage I, three stage II, four stage IIIA, two stage IIIB, and two stage IV patients. Histology revealed main/upper-lobe carinal metastases in 2/1 stage I patients, 0/1 stage II patient, 3/1 stage IIIA patients, 1/1 stage IIIB patients, and 1/0 stage IV patient, respectively. As with the other parameters, we found no correlation between metastasis to either carina and tumor stage, T or N status ($p > 0.05$).

The status of five patients who had main carinal involvement and one patient with upper-lobe carinal involvement was changed from operable to inoperable based solely on the blind biopsy results. This reduced the rate of operability to 27.3%. Biopsy findings of upper-lobe carina involvement also led to a change in surgical approach for 2 of 18 patients (11.1%) who ultimately went to surgery. These individuals underwent sleeve resection instead of upper lobectomy.

### Discussion

Our is the first assessment of how blind biopsy of the main carina and upper-lobe carina ipsilateral to the primary tumor contributes to evaluation of radiologically operable patients with NSCLC at initial FOB. In our study group, these biopsies changed the status of 25% of the classically operable patients to inoperable, and led to a change in the surgical approach in 11.1% of those who finally did undergo surgery.

The potential routes for spread of bronchogenic carcinoma have been debated for > 50 years. Several

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**Table 1—Types of Cancer in the Study Group and Microscopic Metastases to the Main Carina and Upper-Lobe Carina**

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<tbody>
<tr>
<td>Epidermoid carcinoma</td>
<td>35</td>
<td>5</td>
<td>3</td>
<td></td>
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<tr>
<td>Adenocarcinoma</td>
<td>12</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Large cell carcinoma</td>
<td>5</td>
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**Table 2—Location of the Primary Tumor and Metastases to the Main Carina and Upper-Lobe Carina**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Blind Main Carinal Biopsies, No.</th>
<th>Blind UL Carinal Biopsies, No.</th>
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<tr>
<td></td>
<td>UL Location</td>
<td>Non-UL Location</td>
</tr>
<tr>
<td>Tumor positive by blind biopsies</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Tumor negative by blind biopsies</td>
<td>27</td>
<td>17</td>
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*UL = upper lobe.
investigators\textsuperscript{9–11} have shown that dissemination occurs mainly in the mucosal layer, submucosal lymphatics, and outer fibrous layer of the bronchus. Approximately 10 to 20\% of successfully operated patients encounter local recurrence postoperatively, even when care is taken to ensure pathologically clear wide excisional margins.\textsuperscript{12,13}

Very few studies in the literature have focused on histologically detecting bronchogenic carcinoma spread at key anatomic sites.\textsuperscript{4–7} Microscopic evidence of malignancy at the main carina almost always eliminates surgery as a treatment option,\textsuperscript{14,15} and this was first studied by Rabin et al.\textsuperscript{4} These authors performed blind biopsy of the main carina in 124 patients using a rigid bronchoscope, and found that 12.9\% of the patients had histologic signs of tumor spread. More recent series\textsuperscript{5–7} have yielded tumor-positive main carinal biopsies in 13\%, 6\%, and 4.7\% of the patients studied, respectively. In the latter two studies, biopsy was carried out via FOB. Although these investigators concluded that the procedure was low risk, simple, inexpensive, and, most importantly, that it identified a subgroup of inoperable patients in which further staging was unnecessary, it could not become a common practice. Like the main carina, the upper-lobe carina ipsilateral to the tumor site is another important region where tumor involvement can influence patient management. But interestingly, blind biopsy of this structure has not been investigated until now.

In our study, we found microscopic evidence of metastasis in seven of the main carina biopsy specimens (13.7\%) and four of the ipsilateral upper-lobe carina biopsy specimens (23.5\%). When the biopsy results were not considered, 24 of 66 patients with primary bronchogenic carcinoma were found classically operable. As detailed above, the finding of main carinal involvement alone eliminated five patients as surgical candidates. In addition, involvement of the upper-lobe carina ruled out surgery in another patient and changed the surgical approach in 2 of 18 patients (11.1\%) who ultimately went to the operating room. These changes confirm that blind carinal biopsy significantly influences decisions regarding operability and surgical approach in NSCLC patients.

We do not discuss the biopsy results of the suspicious main carina (n = 1) and upper-lobe carina (n = 13). Standard procedure in any bronchoscopic examination involves performing biopsy of suspicious sites. Results of these biopsies and gross evidence of upper-lobe carina invasion (n = 22) unavoidably influenced our patients’ classical staging and classical operability status. Postoperatively, it turned out that 1 of the 18 patients who underwent thoracotomy was actually inoperable because of multiple mediastinal N2 involvement that had not been detected preoperatively. Postoperative histopathologic examination of surgical specimens also confirmed metastasis in the resected upper-lobe carinae of two patients whose surgical approach had been changed by tumor-positive blind biopsy findings at these sites. Three other patients whose blind upper-lobe carina biopsy findings were negative were also operated on, but their surgery did not involve resection of this carina.

Results from earlier studies\textsuperscript{1,5} that considered only the microscopic metastasis to the main carina performed through a rigid bronchoscope were similar to ours (12.9\% and 13\%, respectively, vs 13.7\% in our investigation); however, the most recent two studies\textsuperscript{6,7} on this subject in which biopsy was performed via FOB yielded significantly lower rates (6\% and 4.7\%, respectively). Two factors might be responsible for this, as they had described in their methods: a suboptimal number of forceps biopsies\textsuperscript{16,17} or the different optical or biopsy capabilities of the instruments they had used. To date, all studies that have discussed the optimal number of forceps biopsies for diagnosing bronchogenic carcinoma have considered only directly observed tumors,\textsuperscript{16} and no controlled study has yet been published on microscopic metastasis. It is reasonable that higher numbers of biopsies than the standards should be taken from such regions, as in our study. Our investigation is the first study of blind main carina biopsy by FOB that has yielded results comparable to those from rigid bronchoscope studies.\textsuperscript{4,5}

Previous reports have suggested that tumors that are not visualized on bronchoscopic examination are not associated with microscopic metastasis to the main carina. Our findings dispute this claim. Fourteen of the patients had such tumors. Thirteen of these individuals were evaluated for main carina involvement, and 8 for upper-lobe carina involvement. Two of the main carina investigations (15.4\%) showed malignancy, and three of the upper-lobe carina investigations (37.5\%) indicated tumor spread as well. The relatively higher rate of metastasis at the upper-lobe carina in the tumors that were not directly observed may be related to the location of the primary tumor, though not statistically significant. The primary was located in the upper lobe in three of nine directly observed tumors (33.3\%), one of which metastasized to the upper-lobe carina, and in five of eight tumors that were not seen through the bronchoscope (62.5\%), two of which metastasized to the upper-lobe carina. To summarize, overall we found no significant statistical relationships between metastasis to either carina and tumor type, tumor location, tumor stage, direct observation of tumor via FOB, T status, or N status (p > 0.05).

The limitation of our study is that we did not have
a conventionally investigated and treated control group. This would have allowed comparison of tumor recurrence and survival, and further controlled studies are needed in this area.

Also noteworthy is that, although the histology of the positive blind biopsy result matched that of the primary tumor in all patients, there is a slim possibility that some carinal findings actually represent second primary tumor. The only way to distinguish metastasis from the second primary in these cases is chromosomal analysis. Since the likelihood of such synchronous cases is very low, and the majority of them reveal different histology, contrary to our results, we traditionally considered all positive blind biopsy results to represent metastases.

Finally, it must be mentioned that there is always a small risk of contamination in bronchoscopic studies. To date, only one report has addressed this possibility. As detailed earlier, we minimized this risk by using separate forceps to obtain blind biopsy material from each carina. Besides, biopsies were considered positive only if there was clear evidence of tissue invasion by tumor cells.

Blind forceps biopsy of the main carina and upper-lobe carina should be considered separate from, but complementary to, other methods of investigating lung cancer. Clearly, histologic analysis of these sites can save many patients from inappropriate or unnecessary thoracotomy and further staging procedures with their associated morbidity and risk. Carinal biopsy is low risk, inexpensive, and easy to perform. In our opinion, blind biopsy of the main carina and upper-lobe carina ipsilateral to the lesion site should be routinely done as part of the initial bronchoscopy protocol for all radiologically operable patients with suspected bronchogenic carcinoma.

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