Intraoperative Lavage Cytologic Analysis of Surgical Margins as a Predictor of Local Recurrence in Pulmonary Metastasectomy

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Hypothesis: Cytologic analysis of intraoperative lavage at the surgical margin during wedge or segmental resection for pulmonary metastatic lesions predicts postoperative local failure at the surgical margin of the pulmonary parenchyma.

Design: Prospective nonrandomized trial.

Settings: Institution-based study.

Patients: Fifty-one consecutive patients undergoing wedge or segmental resection for 87 pulmonary metastatic lesions of various primary tumor types from November 1, 1997, through January 31, 2001, were prospectively enrolled.

Interventions: An intraoperative lavage cytologic technique at the surgical margin for each pulmonary metastasis was performed as described previously.

Main Outcome Measures: Incidence of positive cytologic findings and postoperative local recurrence at the surgical margin.

Results: Of the examined lesions, 10 (11%) showed positive cytologic results at the surgical margin, despite a macroscopically safe margin in the attempted resection. Of these, metastasectomy was converted to segmentectomy in 3. An additional wedge resection and evaporation using an Nd:YAG laser in the surgical margin were performed in 1 and 4 lesions, respectively. Complications precluded further treatment in 2 lesions. By July 2001, although no local recurrence at the surgical margin area was found among the lesions with negative cytologic results, recurrence at the surgical margin occurred in 2 with positive cytologic results, including 1 receiving no treatment and 1 receiving Nd:YAG laser evaporation, indicating that a significant difference in the recurrence rate according to lavage cytologic status (P<.001).

Conclusions: This intraoperative lavage cytologic technique in wedge or segmental resection of pulmonary metastases of various primary tumors may be a useful predictor of local recurrence at the surgical margin. With these test results, local recurrence at the surgical margin may be controllable in patients undergoing pulmonary metastasectomy.

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The recent increasing incidence of aggressive surgery for pulmonary metastases of a variety of primary tumor sites has resulted in prolonged survival in some patients with such diseases. At our institution, metastasectomy for pulmonary metastases in more than 250 cases has been performed with modifications and advances in surgical techniques, and a portion of this population may be cured.

Although consideration of the operation for metastasectomy should include lesion size, number, and anatomical location, pulmonary metastases have principally come to require less invasive surgery, such as wedge resection or segmentectomy, with open thoracotomy or video-assisted thoracic surgery (VATS). For example, in cases of multiple metastatic lesions in different pulmonary lobes, such less invasive operations may be a practical selection.

One of the unfavorable recurrent patterns after a wedge or segmental resection for pulmonary metastases is local failure, found at the surgical margin of the pulmonary parenchyma. Because pulmonary metastasis in itself may be a manifestation of systemic disease, this failure is not always a major problem. Few reports describe this failure, and even its clinical rate remains unknown. Nevertheless, this type of local failure should be avoided technically during metastasectomy.

Wedge or segmental resections usually are performed while technically maintaining a safe surgical margin. A tumor-free surgical margin is checked macroscopically and, if necessary, by means of frozen-section
PATIENTS AND METHODS

CHARACTERISTICS

From November 1, 1997, through January 31, 2001, metastasectomy by means of limited operations, including wedge and segmental resections, was attempted prospectively in 51 consecutive patients. We performed 56 operations for 87 metastatic lesions in the Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan. Lesions for which lobectomy or pneumonectomy were first performed were excluded in this analysis. The patients, aged 16 to 80 years (mean age, 56.6 years), included 29 men and 22 women. Thirty-seven metastatic lesions in 18 patients were due to colorectal cancer; 18 in 13 patients, bone or soft tissue sarcoma; 10 in 5 patients, renal cell carcinoma; 7 in 4 patients, testicular tumor; 4 in 4 patients, breast cancer; 3 in 2 patients, urinary bladder cancer; 2 in 2 patients, hepatocellular cancer; 3 in 1 patient, thyroid cancer; 2 in 1 patient meningioma; and 1 in 1 patient, salivary gland cancer. Tumor size varied from 2 to 60 mm (median size, 12 mm). Thirty-four lesions were 10 mm or smaller; 33, 11 to 20 mm; 14, 21 to 30 mm; and 6, larger than 30 mm.

ATTEMPTED OPERATION AND CUTTING METHOD

For the 87 metastatic lesions, wedge resection surgery (n=69) or segmentectomy (n=18) was initially attempted by means of open thoracotomy (n=69), minithoracotomy with a skin incision of less than 10 cm (n=13), or VATS (n=5). These operative techniques have been described previously.8,12,16-18 We used staplers, an Nd:YAG laser, and/or electric scissors to cut into the pulmonary parenchyma with a macroscopically safe margin of more than 10 mm, if possible, or at least more than 5 mm from the lesion. We resected 30 lesions using staplers; 5, staplers with VATS; 11, electric scissors; 11, the Nd:YAG laser; and 10, a combination of staplers and an Nd:YAG laser or electric scissors. In all lesions except 1, we performed pleural lavage cytologic analysis immediately after thoracotomy to avoid tumor cell contamination of the surgical margin.19 The exceptional case showed severe adhesion in the pleural cavity.

LAVAGE CYTOLOGIC TECHNIQUE

AT THE SURGICAL MARGIN

The lavage cytologic technique at the surgical margin for each lesion was performed as described previously.15 Briefly, when surgery was performed using staplers alone, all fired staples were washed in 200 mL of isotonic sodium chloride solution. When tumor excision was performed using the Nd:YAG laser or the electric scissors alone or in combination with staplers, the resected specimens were similarly washed in 200 mL of isotonic sodium chloride solution without flooding of the pleural surface. When tumors were resected using combined methods, the fired cartridges and the resected samples were washed. These lavage techniques were carefully performed before obtaining cross sections of the specimens.

After centrifugation, the sediment was immediately fixed with Saccamanno solution,20 and then smeared on a glass slide with Cytospin (Shandon Cytospin; JEOL Trading Co, Ltd, Tokyo, Japan). Next, after final fixation with ethanol and diethyl ether, the sediment was stained using the Papanicolaou method. The cytologic results were judged to be positive or negative by a cytologist (J.A., Y.N., or S.N.), and were immediately reported in the operating room at approximately 20 to 25 minutes after the beginning of the procedure.

POSTOPERATIVE HISTOLOGICAL ANALYSIS OF THE SURGICAL MARGIN

For lesions with positive cytologic results obtained by means of the lavage cytologic technique, we reviewed the histological findings of the surgical margin. We used the formalin-fixed specimens obtained during the initial operation.

POSTOPERATIVE FOLLOW-UP INVESTIGATIONS AND DIAGNOSIS OF LOCAL RECURRENCE

Postoperative follow-up investigations in the chest were principally performed by means of chest radiography every 2 to 4 months and computed tomography every 6 months for at least 2 years. Local recurrence at the surgical margin of the pulmonary parenchyma was usually carefully checked by means of computed tomography and was finally diagnosed by means of radiological findings, clinical course, or, if possible, surgical resection. The final follow-up date was July 30, 2001. The median follow-up for surviving patients was 22 months (range, 5-44 months).

STATISTICAL ANALYSIS

We used the Fisher exact probability test to determine the statistical significance of any differences.

RESULTS

Of the 87 examined lesions, 10 (11%) (in 10 patients) showed positive cytologic results at the surgical margin, despite a macroscopically safe margin in the attempted operation. Five lesions were due to colorectal cancer; 3,
bone or soft tissue sarcoma; and 1 each, a testicular tumor and a hepatocellular carcinoma (Table 1). Lesions larger than 10 mm showed significantly more frequent positive findings than those 10 mm or smaller ($P = .045$; Table 1). The incidence of positive findings was significantly higher in surgery that used the Nd:YAG laser or staplers combined with the Nd:YAG laser or electric scissors, compared with the other methods ($P = .005$; Table 1).

Table 2 summarizes the surgical results of these 10 lesions. Wedge resection was converted to segmentectomy (completion segmentectomy) in 3 lesions (lesions 1, 4, and 9); additional wedge resection was performed in 1 (lesion 5), and as much evaporation as possible using the Nd:YAG laser at the surgical margin $^{16,18}$ was added in 4 (lesions 2, 3, 6, and 8). New surgical margins in the 3 patients undergoing completion segmentectomy and the 1 patient undergoing additional wedge resection were checked using the lavage cytologic technique, and negative cytologic results were finally achieved. Surgical margin status in the 4 lesions for which Nd:YAG laser evaporation was added was estimated due to technical problems. In the remaining 2 lesions, no additional resection was performed because of noncurative resection due to pleural dissemination (lesion 7) or positive cytologic findings of pleural lavage at the time of thoracotomy $^{19}$ (lesion 10).

Postoperative histological findings of the surgical margin in the specimens obtained from the initial operations were analyzed in lesions with positive cytologic lavage results. In the histological review, the nearest distance between the tumor front and cutting line was less than 5 mm for all 10 lesions, but focal tumor exposure on the line of the surgical margin was demonstrated in results of histological examination only in 4 lesions (lesions 2, 4, 7, and 8), despite macroscopically tumor-free appearance.

By July 2001, recurrence was found at the surgical margin in 2 lesions (Table 2). Of these, 1 patient (lesion 7) was given no additional treatment. The other patient with pulmonary metastases due to colorectal cancer (lesion 3) showed local recurrence at the surgical margin 10 months after surgery, although evaporation using the Nd:YAG laser was performed toward the surgical margin with positive cytologic findings (Figure 1). Subsequently, this patient underwent a completion lower lobectomy 3 months after recurrence. On the other hand, no local recurrence was found at the surgical margin among the 81 lesions with final negative cytologic results, whereas 2 (33%) of the other 6 lesions had surgical margin recurrence. A significant difference was found in the rate of postoperative surgical margin recurrence (Fisher exact probability, 0.004; $P < .001$).

### Table 1. Positive Finding of Lavage Cytologic Analysis at the Surgical Margin

<table>
<thead>
<tr>
<th>Origin of tumor</th>
<th>No. of Lesions (N = 87)</th>
<th>No. (%) With Positive Finding (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectum</td>
<td>37</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Bone/soft tissue</td>
<td>18</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
<td>2 (6)*</td>
</tr>
<tr>
<td>Lesion size, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10†</td>
<td>34</td>
<td>1 (3)</td>
</tr>
<tr>
<td>11-20</td>
<td>33</td>
<td>5 (15)</td>
</tr>
<tr>
<td>21-30</td>
<td>14</td>
<td>3 (21)</td>
</tr>
<tr>
<td>≥31</td>
<td>6</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Cutting method‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stapler</td>
<td>50</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Stapler with VATS§</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Electric scissors</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Nd:YAG laser</td>
<td>11</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Combination of stapler and Nd:YAG laser or electric scissors</td>
<td>10</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

*Includes testicular tumor in 1 patient and hepatocellular carcinoma in the other.
†$P = .045$ (Fisher exact probability, 0.043) compared with all lesions >10 mm.
‡$P = .005$ (Fisher exact probability, 0.011) for Nd:YAG laser or staplers combined with the Nd:YAG laser or electric scissors compared with the other methods.
§VATS indicates video-assisted thoracic surgery.

### Table 2. Surgical Results of Lesions With Positive Findings of Lavage Cytologic Analysis*

<table>
<thead>
<tr>
<th>Primary Lesion, Lesion No.</th>
<th>Tumor Size, mm</th>
<th>Attempted Surgery</th>
<th>Cutting Method</th>
<th>Conversion</th>
<th>Recurrence at the Surgical Margin (Follow-up, mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>Left S1+2 wedge resection</td>
<td>S and Y</td>
<td>No (23)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>Right S9 wedge resection</td>
<td>Y</td>
<td>No (20)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Right S10 wedge resection</td>
<td>Y</td>
<td>Yes (15)†</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>Right S3 wedge resection</td>
<td>S</td>
<td>No (9)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Right S3 wedge resection</td>
<td>S</td>
<td>Additional wedge resection</td>
<td>No (8)</td>
</tr>
<tr>
<td>Bone/soft tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>Left S3 wedge resection</td>
<td>Y</td>
<td>Evaporation using Y</td>
<td>No (12)</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Right S1 wedge resection</td>
<td>S</td>
<td>Follow-up of pleural dissemination</td>
<td>Yes (8)</td>
</tr>
<tr>
<td>8</td>
<td>11</td>
<td>Right S8 wedge resection</td>
<td>S and Y</td>
<td>Evaporation using Y</td>
<td>No (8)</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>Right S9 wedge resection</td>
<td>Y</td>
<td>Right basal segmentectomy</td>
<td>No (12)</td>
</tr>
<tr>
<td>Testis</td>
<td>10</td>
<td>Right S9 wedge resection</td>
<td>S</td>
<td>Follow-up of positive pleural lavage findings</td>
<td>No (11)</td>
</tr>
</tbody>
</table>

*Includes staple; Y, Nd:YAG laser; and S and Y, combination of staple and Nd:YAG laser.
†Completion lower lobectomy was performed.
At present, surgeons who routinely perform metastasectomy should be confident in the interpretation of preoperative radiographic evaluation mainly by means of computed tomography, so that they can plan a complete resection with consideration of location, number, and size of lesions. The operation mode should be decided on the basis of these conditions and the pulmonary function status of the patients, but in principle, less invasive surgery may be performed. Therefore, wedge or segmental resection of the lung is the most commonly applied technique for metastasectomy. Most operations for metastasectomy with such limited resection were also performed at our institution.

However, wedge or segmental resection potentially carries the risk for local recurrence at the surgical margin. We previously experienced this trouble in 2% of patients with lung cancer undergoing limited surgery on an intentional indication. Thus, the incidence of this frustrating recurrence was found by several investigators to be surprisingly high after limited surgery for primary lung cancer.

To overcome this problem, we developed a novel technique to check the residual tumor cells at the surgical margin during wedge or segmental resection. This technique offers some advantages compared with conventional techniques. During the operation, the whole area of the resected margin can be examined, and, if necessary, each margin can be separately checked in a relatively short time. In addition, any aspects of the surgical margin, regardless of cutting method, can be easily examined. We proposed that this novel system for checking surgical margins could provide useful information during limited surgery for lung cancer.

The cytologic and clinical summary of the enrolled lesions is schematically illustrated in Figure 2.
In this study, we applied this checking technique clinically in metastasectomy for pulmonary metastases of various origins. We found a rate of positive findings of 11% when using this lavage cytologic method. This incidence was almost the same as that experienced in primary lung cancer, suggesting that even if the surgical margin appears macroscopically safe, about 10% of the resections may be microscopically incomplete, regardless of tumor type. In fact, among pulmonary metastases of various origins, no significant difference in positive results was found, but the size and locations of the resected lesions were more notable. Lesions larger than 10 mm showed more frequent positive results than those that were 10 mm or smaller (P = .045). In our institution, metastatic lesions larger than 30 mm are considered to be an appropriate indication for lobectomy. The present data suggest that even smaller lesions should be carefully resected when performing limited resection.

The incidence of positive cytologic findings in surgery using the Nd:YAG laser alone or combined with staplers was significantly higher than that in other types of surgery. Previous studies have reported the usefulness of metastasectomy using the Nd:YAG laser, especially for deep-seated lesions located in the pulmonary pleura. Therefore, this finding may be strongly associated with technical handicaps because of tumor location.

When positive cytologic results in such limited surgery with macroscopically tumor-free margins are proven by means of this technique, the surgeon should note whether a tumor truly exposes on the cutting surface. In the present series, only 4 lesions were histologically diagnosed as tumor exposure by means of postoperative formalin-fixed specimens. However, considering that the distance of the surgical margin in all these specimens was histologically insufficient (<5 mm) to maintain tumor-free status, minute tumor exposure that cannot be observed by means of macroscopic or postoperative histological analysis may occur elsewhere in the surgical margin surface. In this respect, we believe that the present intraoperative lavage cytologic technique is superior to the other examination techniques.

The problem of whether a tumor recurs in the surgical margin with positive cytologic findings is clinically interesting. In the present series to date, no local recurrence has been observed in cases with negative cytologic findings, whereas surgical margin relapse occurred in 2 lesions, one with a positive cytologic result (lesion 7) and another with a finally unknown result (lesion 3), suggesting that negative cytologic results obtained by means of this novel lavage technique may be a useful predictor of local completeness of resection at the surgical margin area. In addition, in a retrospective study using 57 surgically resected pulmonary metastases of primary colorectal cancer before introduction of this lavage cytologic technique at our institution, local recurrence at the surgical margin area occurred at a 9% incidence rate in the total number of examined resected lesions (data not shown). This rate almost coincided with the present rate (14% in metastasectomy for primary colorectal cancer) of positive lavage cytologic data. Thus, the lavage cytologic status determined by means of this novel checking system may prevent local recurrence at the surgical margin by conversion of the operation when positive cytologic results are found.

In practice, we ultimately performed a converted operation in 4 lesions (segmentectomy in 3 and additional wedge resection in 1) and evaporation using the Nd:YAG laser in 4 lesions because of positive cytologic results. In primary lung cancer, the conversion from limited surgery on an intentional indication to standard resection, ie, lobectomy, was aggressively completed without any difficulties. In metastasectomy, however, such conversion should be carefully and systematically decided after consideration of lesion number and location, pulmonary function, general condition, and prognosis. In practice, segmentectomy can be maximally performed to achieve potentially complete resection. A lavage cytologic check should be conducted for the new safe margin in the case of a converted operation.

In contrast, 1 case (lesion 3) showed recurrence at the surgical margin, although evaporation using the Nd:YAG laser was performed. Evaporation using the Nd:YAG laser in the surgical margin may be a promising therapeutic modality for compromised cases. However, since tumor residue cannot be accurately evaluated, this therapeutic mode leaves further room for technical improvement to complete local control.

Recently, pulmonary metastasectomy has been aggressively performed with VATS. However, the completeness of local curability remains controversial, as with limited surgery with VATS for lung cancer. Lin et al reported local recurrence that was attributed to technical failure of VATS for metastasectomy. In this study, only 5 lesions were successfully resected with VATS when negative cytologic results occurred at the surgical margin. If is fortunate that all of these lesions were smaller and located almost beneath the pulmonary surface. We think that metastasectomy with VATS may be indicated for smaller pulmonary metastases located almost beneath the pulmonary surface, and, for confirmation, this novel checking system for local curability in the surgical margin should be routinely used.

According to many analyses of the prognostic factors regarding metastasectomy for pulmonary metastases of various organ origins, the following prognostic factors were proposed: number of metastases, disease-free interval from the resection of the primary tumor to the detection of pulmonary metastases, tumor type, tumor doubling time, intrathoracic node status, prethoracotomy serum carcinoembryonic antigen level, extrathoracic metastases, and complete resectability. Although repeated metastasectomy for new pulmonary metastases has been conducted in selected patients with a promising favorable prognosis, our knowledge, no large-scale study has reported repeated resection for local failure at the surgical margin. In patients with local failure at the surgical margin, more invasive surgery, such as a completion lobectomy or a more aggressive operation, is often necessary. Therefore, postoperative local failure at the surgical margin of the lung may be avoided. This novel intraoperative lavage cytologic technique is a promising test to predict local recurrence at the surgical margin in patients with pulmonary metastases as well as primary lung cancer. Further analy-
sis is required to evaluate its clinical usefulness in long-term follow-up.

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REFERENCES


Surgical Anatomy

The anterior compartment of the leg contains the anterior tibialis, extensor hallucis longus, extensor digitorum longus, and peroneus tertius muscles; the deep peroneal nerve; and the anterior tibial artery.