Cytologically malignant margin without continuous pulmonary tumor lesion: cases of wedge resection, segmentectomy and lobectomy

Noriyoshi Sawabata*, Youko Karube, Hideo Umezua, Motohiko Tamura, Norio Seki, Hiromi Ishihama, Koichi Honma, Shinichiro Miyoshi

1. Introduction

Surgical margin recurrence can be predicted from results of a cyto-pathological examination of the margin. The parenchyma margin can be diagnosed for the presence of a continuous lesion from the original tumor. However, there are some cases in which the parenchyma margin is revealed to be pathologically malignant negative and cytologically malignant positive, and recurrence is possible in the cyto-pathological positive region [1, 2]. Therefore, analysis of such malignancy is crucial before making a treatment strategy. We conducted a retrospective observation of patients with pulmonary malignant tumors who underwent wedge resection, segmentectomy and lobectomy procedures.

2. Materials and methods

We analyzed cases of malignant tumors that were resected surgically at Dokkyo Medical University Hospital between April 2006 and February 2007. In our institution, a surgical margin cytology examination is mandatory in cases of wedge resection and segmentectomy, and it is optional in lobectomy cases. During the study period, there were 21 cases treated by wedge resection (3 primary lung cancer, 18 metastasis; 8 males; median age 60 years, range 28–75 years), 17 cases treated by segmentectomy (13 primary lung cancer, 4 metastasis; 9 males; median age 67 years, range 55–75 years), and 4 lobectomy (all primarily lung cancer) cases. Six cases showed malignant cells in the surgical margin, of which one had a microscopic skip lesion pattern and five an ‘occult’ pattern (positive cytology, negative pathology). Cytological malignancy occurred even in cases of wedge resection of a tiny (4 mm in diameter) lesion metastasized from colon cancer, as well as segmentectomy with a sufficient gross margin containing microscopic skip lesions and right middle lobectomy with an additional right upper lobectomy due to two previous cytological malignancies in a residual lobe. Surgical margin cytology revealed remaining malignancy in the residual lobe, which provided important information for deciding additional procedures during surgery.

Received 21 May 2008; received in revised form 14 August 2008; accepted 15 August 2008

Abstract

The surgical margin is usually investigated during the operation using a pathological method, though cytological methods are also used to identify remaining malignant cells. We reviewed cases of pulmonary resection for a malignant tumor. At our institution, an on-site surgical margin examination using a cytological method is mandated for cases of wedge resection and segmentectomy, and an option in lobectomy cases. We examined 21 wedge resection (3 primary lung cancer, 18 metastasis), 17 segmentectomy (13 primary lung cancer, 4 metastasis), and 4 lobectomy (all primarily lung cancer) cases. Six cases showed malignant cells in the surgical margin, of which one had a microscopic skip lesion pattern and five an ‘occult’ pattern (positive cytology, negative pathology). Cytological malignancy occurred even in cases of wedge resection of a tiny (4 mm in diameter) lesion metastasized from colon cancer, as well as segmentectomy with a sufficient gross margin containing microscopic skip lesions and right middle lobectomy with an additional right upper lobectomy due to two previous cytological malignancies in a residual lobe. Surgical margin cytology revealed remaining malignancy in the residual lobe, which provided important information for deciding additional procedures during surgery.
Fig. 1. Location classification of tumors in excision cases. The tumor locations can be classified into 2 regions according to the difficulty of resection followed by the concept of Lewis et al. The apex (AP), edge (ED), and lingual (LI) belong to the difficult to resect group of regions (dotted circles), while the deep in the fissure (DIF), large ovoid surface (LOS), and base of the lung (BA) regions are considered to be easily resectable (closed circles).

totally stapled (type A), partially stapled (type B-1: central stapling, or type B-2: side stapling), and totally unstapled (type C).

Two types of cell extraction from the margin were employed. In one of the techniques, a glass slide was run across the surgical margin to extract cells, with the cells on the side of the slide spread over onto another glass slide, after which the samples were stained and examined (run-across method) [4, 5]. In the other method, which has recently become available, the tissue at the surgical margin was extracted by use of a spatula (Micro-Spatula 300, AS-ONE co. Osaka, Japan), then collected in heparinized normal saline in a spit tube and spread onto a glass-slide by an automatic smear machine. Thereafter, the following steps were the same as those of the run-across method. As a rule, the cytological examinations were carried out as quickly as possible. It takes approximately 10 min using the slide technique and 30 min using the saline spit tube technique.

3. Results

The backgrounds of the tumors and results of cyto-pathological diagnoses by the stapling method are summarized in Table 1. A tumor excision was carried out using video-assisted thoracic surgery (VATS), as such 13 patients with a lesion located difficult to resect underwent wedge resection. In addition, VATS was not an option for segmentectomy or lobectomy, thus the number of VATS cases was only 21.

There were six cases with cytologically malignant positive surgical margins. Of those, five cases were so-called ‘occult’, that is, no pathological malignancy was revealed in the margin. In the other case, the margin was sufficient grossly, however, there were some microscopic skip lesions around the tumor as well as in the resected residual lobe.

Results of additional analyses of the cytological positive malignant margin cases are shown in Table 2. In the lung
## Table 2
Cases with malignant positive surgical margin cytology findings

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Disease</th>
<th>P-stage</th>
<th>Comorbidity</th>
<th>Location</th>
<th>Resection type</th>
<th>Stapling type</th>
<th>Tumor size (cm)</th>
<th>Margin distance (cm)</th>
<th>Margin pathology</th>
<th>Margin cytology</th>
<th>Additional treatment</th>
<th>Follow-up period (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>LC (ad)</td>
<td>IV</td>
<td>Pleural carcinomatosis</td>
<td>O</td>
<td>Wedge</td>
<td>A</td>
<td>2.5</td>
<td>1.0</td>
<td>N</td>
<td>P</td>
<td>CTx</td>
<td>13</td>
<td>No relapse</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>F</td>
<td>Meta (colon)</td>
<td>No</td>
<td>O</td>
<td>Wedge</td>
<td>C</td>
<td>0.4</td>
<td>0.5</td>
<td>N</td>
<td>P</td>
<td>Lung PR</td>
<td>1</td>
<td>No relapse</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>LC (ad)</td>
<td>IB</td>
<td>HF (MR, NYHA3)</td>
<td>LUL apex</td>
<td>Seg</td>
<td>B</td>
<td>3.5</td>
<td>1.0</td>
<td>N</td>
<td>P</td>
<td>No*</td>
<td>13</td>
<td>No relapse</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>LC (sq)</td>
<td>IA</td>
<td>LLL apex</td>
<td>LUL apex</td>
<td>Seg</td>
<td>C</td>
<td>1.0</td>
<td>1.5</td>
<td>P*</td>
<td>P</td>
<td>Lung PR</td>
<td>12</td>
<td>No relapse</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>LC (ad)</td>
<td>IA</td>
<td>No</td>
<td>RML</td>
<td>Lo</td>
<td>A</td>
<td>7.0</td>
<td>1.0</td>
<td>N</td>
<td>P</td>
<td>Lung PR + Lo.</td>
<td>20</td>
<td>No relapse</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>M</td>
<td>LC (ad)</td>
<td>IA</td>
<td>RLL apex</td>
<td>LUL apex</td>
<td>Seg</td>
<td>C</td>
<td>2.5</td>
<td>1.5</td>
<td>N</td>
<td>P</td>
<td>No**</td>
<td>3</td>
<td>No relapse</td>
</tr>
</tbody>
</table>

LC, lung cancer; Meta, metastasis; ad, adenocarcinoma; sq, squamous cell carcinoma; HF, heart failure; MR, mitral regurgitation; NYHA, New York Heart Association classification; O, ovoid surface; LUL, left upper lobe; LLL, left lower lobe; RML, right middle lobe; RLL, right lower lobe; Seg, segmentectomy; Lo, lobectomy; N, negative malignancy; P, positive malignancy; CTx, chemotherapy; PR, partial resection.

*Microscopic skip lesion in margin of residual lobe, **compromised candidate, §off-site cytology.

---

**Fig. 4.** Case 4. Segmentectomy with sufficient gross margin distance. (a) An undiagnosed lesion in the apex region of the left lower lobe. (b) First, a segmentectomy was carried out after needle aspiration. Cytology of the resected remaining left lower lobe revealed clustered malignant cells. (c) The residual left lower lobe had a microscopic skip lesion metastasized from the original tumor.

**Fig. 3.** Case 2. Wedge resection of tiny lesion. (a) Tiny (0.4 cm) lesion in the right upper lobe was suspected to be metastasis from colon cancer. (b) The lesion was excised using an electric cautery technique (type C) with a margin distance of 0.5 cm. (c) The cut surface revealed clustered malignant cells. (d) Cytology findings revealed clustered malignant cells.

In cancer cases, the distance from the tumor to the margin was smaller than the size of the tumor. None had a continuous lesion pattern, while one had a skip lesion pattern and five had occult lesion patterns (4 stapled sites and 1 unstapled site). For example, case 2 was an occult lesion pattern of a tiny lesion (Fig. 3a), case 4, a segmentectomy case had a sufficient gross margin containing microscopic skip lesions (Fig. 4a), and case 5, which underwent right middle lobectomy with an additional right upper lobectomy conducted twice due to cytological malignancy in the residual lobe, had an ‘occult’ lesion pattern (Fig. 5a).
4. Discussion

Loco-regional recurrences following resection of pulmonary malignant tumors vary in regard to their location, such as the surgical margin, residual lobe, mediastinal lymph node, and pleural space, as well as other regions. However, more than the others, surgical margin recurrence is thought to depend considerably on the technical capability of the surgeon, because residual lesions could be removed by resection of additional tissues if presented. Goldstein et al. reported microscopic malignant lesions in the stapled margin of cases that underwent excision of pulmonary adenocarcinomas [6]. In those cases, all staples were removed from the pulmonary tissue in order to make an accurate diagnosis of the margin. However, cytological diagnostic findings occasionally differ from pathological results if such a detailed method is not employed [1, 2, 4, 5, 7].

A cytological malignant margin can be classified into three types; continuous lesion, skip lesion, and ‘occult’ lesion, the latter of which is associated with pathological examination findings that reveal no evidence of malignancy in the margin. The present case 4 is a representative skip lesion case. In that case, frozen section pathological diagnosis might have detected malignancy if performed. However, it is sometimes difficult to obtain stable tissue from low and soft areas of the lung. On the other hand, with a cytological method, extraction of tissue samples from the margin can be performed with ease. In the present case 2, tissue samples were easily collected from the cut surface of the residual lobe with a spatula. In addition, case 5 may be an example of ‘occult’ malignancy, which may occur when malignant cells spread through the lymphatics.

In cases with a malignant positive margin, additional resection of the residual lung should be mandated, because the ratio of surgical margin recurrence is 50% if margin cytological or morphological results are positive and no additional resection is performed (Table 3) [1, 2, 8]. Although those results were obtained from limited resection cases, a cytological malignant positive surgical margin may be a predictive factor for surgical margin recurrence in cases that undergo a segmentectomy or lobectomy.

The distance from the surgical margin to the tumor is crucial to obtain a malignant free surgical margin. Previously, we found that the distance from the tumor to the margin to obtain a malignant negative margin was greater than the diameter of the tumor in a study of excised tumors [7], which was recently confirmed in a study of segmentectomy cases by Schuchert et al. [9]. Thus, a tiny lesion may provide a sufficient distance at the surgical margin. However, margin cytology is useful to detect remaining malignant cells in cases of tiny lesions, such as the present case 2.

The clinical significance of a cytological malignant margin for a lung tumor must be proven in a prospective study. Presently, a prospective phase III clinical trial is being conducted by the American College of Surgeons Oncology Group (ACSOG Z4032), who are investigating the clinical significance of brachytherapy at the surgical margin in cases of limited resection of non-small cell lung cancer in compromised patients [10]. Stump cytology of the surgical margin is mandatory in that trial. Thus, it is anticipated that the clinical significance of margin cytology will be revealed in the near future.

To remove a malignant tumor, complete resection is crucial to avoid recurrence and surgical margin recurrence may be avoided when the operator is skillful. As shown in the present study, margin cytology can reveal remaining malignancy, thus providing important information for surgeons to consider additional options, even in cases of tiny lesions, as well as in those that undergo a segmentectomy with a grossly sufficient margin distance or a lobectomy with division between the lobes.

References


Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method</th>
<th>Malignant margin (%)</th>
<th>Margin relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sawabata et al. [1]</td>
<td>2002</td>
<td>Cytology</td>
<td>7/15 (45)</td>
<td>4/7 (56)</td>
</tr>
<tr>
<td>Higashiyama et al. [2]</td>
<td>2003</td>
<td>Cytology</td>
<td>11/112 (9.8)</td>
<td>4/7 (56)</td>
</tr>
<tr>
<td>Masayasu et al. [8]</td>
<td>2004</td>
<td>RT-PCR</td>
<td>9/13 (70)</td>
<td>6/9 (66)</td>
</tr>
</tbody>
</table>

*An additional resection was performed in 3 cases with finally malignant negative margin.


