Limited resection trial for pulmonary ground-glass opacity nodules: case selection based on high-resolution computed tomography—interim results

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Abstract

Objective: Our previous trial for small ground-glass opacity nodule on high-resolution computed tomography suggested all these cancers might have been radically managed with limited resection. Good correlation between radiologic and pathologic findings in early lung adenocarcinomas has been reported. We aimed to confirm limited resection efficacy as radical surgery in patients with high-resolution computed tomography-indicated minimally invasive lung cancer. The purpose of this interim analysis is to report the details of the patient and nodule characteristics, intraoperative cytology capability as a negative margin indicator, and patient outcome with the median follow-up period of 7 years and 4 months.

Methods: Enrollment required patients with a tumor \( \leq 2 \) cm, diagnosed or suspected as a cT1N0M0 carcinoma in the lung periphery and depicted on high-resolution computed tomography as a subsolid nodule with tumor disappearance ratio \( \geq 0.5 \). We performed a wedge or segmental resection as appropriate. The primary endpoint is 10 year local recurrence-free survival rate.

Results: This study started in November 2003, and 101 patients were enrolled as of November 2009. Of them, 95 were eligible for analysis. There were 38 men and 57 women, aged 30–75, averaging 62 years. Tumor sizes ranged from 7 to 20 mm on computed tomography, averaging 15 mm. There were 11 Noguchi type A tumors, 54 type B tumors, 24 type C tumors, one malignant lymphoma and 5 non-cancerous lesions. All cancers showed no vessel invasion. With a median follow-up period of 88 months, there have been no recurrences.

Conclusion: So far, high-resolution computed tomography appears to predict non- or minimally invasive ground-glass opacity lung cancers with high reliability, warranting limited resection as curative surgery in this cohort.

Key words: ground-glass opacity, lung cancer, Noguchi classification, limited resection, high-resolution computed tomography
Introduction

At our institution in 1998, we started a prospective clinical trial of limited resection for probable in situ adenocarcinoma in the lung periphery, depicted as a small (≤20 mm) ground-glass opacity (GGO) nodule on high-resolution computed tomography (HRCT) (1). We aimed to confirm limited resection efficacy in patients with Noguchi type A and B tumors (2), with Noguchi’s classification determined intraoperatively by frozen section examination. With a median follow-up period of 50 months, there were no recurrences. We were convinced that limited resection is sufficient for Noguchi type A and B <20 mm tumors. Post-operative pathologic study of the Noguchi type C tumors in this trial found no nodal involvement, pulmonary metastases, lymphatic permeation or vascular invasion. This suggests all eligible GGO lung cancers in the study, including the type C tumors, might have been radically managed with only limited resection (1,3).

This trial required a highly experienced pathologist and very patient surgeons and operating room staff who had to wait for about an hour until the intraoperative pathologic examination was completed. Since all the GGO lung cancers in our previous trial might have been radically managed with only limited resection, we started looking for better ways to select suitable patients and to establish a non-cancerous resected margin.

Several articles by Japanese researchers showed good correlation between radiologic and pathologic findings in early lung adenocarcinomas (4–8). This, along with an earlier investigation by us (9,10) suggested how to find suitable candidates. For negative margin confirmation, we found a technique using lavage and cytological examination first reported by Higashiyama et al (11) in 2000.

Based on these existing information and techniques, we decided to start the present trial, aiming to confirm limited resection efficacy in patients with HRCT indicated minimally invasive lung cancer, and to confirm intraoperative cytology as a negative margin indicator and reliable margin non-recurrence predictor (3). In this interim analysis, we report the details of the patient and nodule characteristics, intraoperative cytology capability as a negative margin indicator, and patient outcome with the median follow-up period of 7 years and 4 months.

Patients and methods

Patients with a tumor 2 cm or smaller in maximum dimension, diagnosed or suspected as a clinical T1N0M0 carcinoma in the lung periphery based on a computed tomography (CT) scan were enrolled. They had to have a HRCT scan indicating a pure or mixed GGO nodule with a tumor disappearance ratio; tumor disappearance ratio (TDR) 0.5 or greater. We used multi-detector row scanners (Toshiba Medical Systems, Tochigi, Japan, General Electric Healthcare, Japan, Tokyo, Japan, or Siemens Japan, Tokyo, Japan) with slice thickness of 0.5–2 mm. The image reconstruction algorithm was bone algorithm, with 1- or 2-mm slice intervals within 1 month before surgical resection. The window widths/levels for lung and mediastinal settings were 1000–2000/−500 to −700 and 350–600/30–60, respectively.

Patients with a malignancy history within 5 years, and those unfit for lobectomy and systematic lymph node dissection were excluded. Patients were also excluded if the nodule was deep and close to the intersegmental plane thereby requiring extended segmentectomy for margin-free resection.

TDR was defined as follows (Fig. 1A): On a HRCT slice, the maximum tumor diameter is measured on lung setting; DL. Then on mediastinal setting, the ground-glass area disappears leaving only the consolidation area. The remaining consolidation area maximum diameter is measured; DM. TDR is calculated as $1 - \frac{DM}{DL}$.

Figure 1B shows an example of TDR measurement and calculation. A ground-glass diameter of 17 mm and consolidation diameter of 6 mm yields a 0.65 TDR. The tumor proved to be a Noguchi type B. TDR ≤ 0.5 corresponded that the solid consolidation size was a maximum 50% of the entire GGO tumor size, and a maximum 25% of the total slice displayed GGO tumor area.

Figure 2 shows the treatment flow chart. We performed a wedge or segmental resection, depending on the tumor location. Three-port
procedures were performed when the tumor was close to the lung surface or hard enough to palpate directly with one or two fingers through the ports (Endo-finger). When it was impossible to determine the tumor location or its margin through the ports, we converted to a small 5 cm thoracotomy. When a tumor was deep in the middle of a segment, we chose segmentectomy. Also, when a tumor could not be localized during surgery, a segmentectomy was performed to avoid missing the tumor. A resection margin greater than 1 cm was required in all cases. No lymph node resection was required. Using the method described below, the cytologist examined the specimen margin immediately. If the cytology result was cancer positive, additional margin was resected and cytologic examination repeated. If the second cytologic exam was also positive, a routine lobectomy and systematic lymph node dissection were to be performed.

To establish a clean margin faster and easier, we employed the method described by Higashiyama et al. (11). The used stapling cartridges were washed repeatedly with 30 ml of saline. We usually used Endo GIA Universal Rotacular cartridges (Covidien Japan, Tokyo, Japan), and both the knife in the shaft and anvil faces were flushed using a washing syringe from the shaft end. The washing saline was centrifuged. The sediment was Papanicolaou-stained and examined for cancer cells (3).

The resected specimens were managed in the fashion similar to what we described in the previous trial (1). In brief, with the specimen in a closed, phosphate-buffered saline-filled syringe, the piston was pulled back quickly and repeatedly, re-inflating the alveolar structure by replacing alveolar air with phosphate-buffered saline. The inflated specimens were sliced into 2 mm thick slices and were fixed in 10% formalin and embedded in paraffin. In addition to routine hematoxylin–eosin staining, Victoria blue van Gieson staining was used to facilitate accurate evaluation of the alveolar wall elastic fibers. The pathology slides were evaluated by the pathologists (G.I. and T.Y.), who were blinded to patient identity. Evaluation result discrepancy between the pathologists was resolved by consensus. Pathological stage and nodal stage were determined based on the TNM classification 7th edition of the Union for International Cancer Control (12). Histological typing of the primary tumors was performed based on the World Health Organization classification (13), with special attention paid to Noguchi’s lung adenocarcinoma subtype (2).

Patients are followed up on an outpatient basis every 6 months by chest CT for the first 3 years, and annually thereafter. Local recurrence was diagnosed when a consolidation area was radiologically detected close to the resection staple line and the same histology as the initially resected nodule was confirmed cyto/pathologically. Cyto/pathological proof was not essential if the consolidation area showed evident growth overt time. The primary endpoint was initially the 5-year local recurrence-free survival, but it was later replaced with 10-year local recurrence-free survival. This was because of the possible delayed (≥5 years after surgery) cut-end recurrences we experienced among patients undergoing limited resection during the previous trial (14,15). Intraoperative cytology as a negative margin indicator and reliable margin non-recurrence predictor was also evaluated as the secondary endpoint.

Noguchi reported there were no cancer recurrences after 5 years following lobectomy and lymph node dissection in the type A and B patients (2). Statistically, it is impossible to compare the limited resection outcome for these tumors with the event-free standard surgery outcome. We previously reported an 85% 5-year survival rate in patients with tumors 2 cm or less and T1N0M0 pathologically, who underwent lobectomy and systematic lymph node dissection at our institution (16). Allowing one local recurrence cases in 30 patients, a 95% confidence interval of 84–100% results, and the lower limit would be similar to our earlier study. In 60 patients, allowing two local recurrence cases, a 95% confidence interval of 90–100% results. Therefore, we decided to recruit 100 patients, with a trial- quitting rule of two or more local recurrence cases among the initial 30 or 3 or more among the initial 60.

This study protocol was reviewed by the National Cancer Center Hospital East Institutional Review Board and was approved in October 2003. The Department of Thoracic Oncology, Kanagawa Cancer Center Hospital (Kanagawa, Japan) joined the trial in November 2006, after their institutional review board approved the protocol.

**Results**

This prospective study started in November 2003, and we finished recruiting the intended 100 patients in 6 years. There were 101 patients in total, and surgeons decided to perform standard lobectomy and node dissection in 5 of them based on intraoperative diagnosis that the lesions were invasive adenocarcinomas. One patient received right middle lobectomy because surgeons diagnosed the remnant lobe was highly deformed and small after wedge resection. As the main purpose of this study is to confirm if sublobar resection is curative for the study cohort, we excluded these six lobectomy patients, and the remaining 95 patients were evaluated in detail. This was 4.3% of all lung cancer patients treated over this period, with a mean age of 62 years (range: 30–75). Fifty-seven were women. Tumor sizes ranged from 7 to 20 mm on HRCT. Eighty-six had wedge resection, and nine segmentectomy. In all these cases, we started thoracoscopically. If we could not confidently locate the tumor even with an Endo-finger through a 2 cm VATS port incision, we did not hesitate to enlarge the best located 2 cm incision to 5 cm. If we were not sure about lesion location even with a 5 cm incision, we opted for a 10 cm incision, which allowed segmentectomy if necessary.

Pathologically, there were 11 Noguchi type A tumors, 54 type B tumors, 24 type C tumors, 1 mucosa associated lymphoid tissue (MALT) lymphoma, 2 hyperplastic lesions, and 3 inflammatory fibroses (Table 1). None of the cancers, including the type C, had vessel invasion.

No patients were found to have positive margin intraoperatively. Pathologically positive margin was identified post-operatively in one type C patient. The patient agreed to undergo completion lobectomy and systematic node dissection after detailed discussion, but no cancer cells were observed in the resected tissue.

There seemed to be a trend towards lower TDR in type C tumors compared with type A’s, and the differences were significant between type A vs. C and type B vs. C. However, there were no clear cut-offs to differentiate these subtypes (Fig. 3).

**Table 1. Pathological types of resected tumors (n = 95)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Number of patients</th>
<th>Pathological nodule size: Median, range (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>11</td>
<td>10, 7–15</td>
</tr>
<tr>
<td>Type B</td>
<td>54</td>
<td>12, 6–30</td>
</tr>
<tr>
<td>Type C</td>
<td>24</td>
<td>13, 6–22</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>1</td>
<td>Not available</td>
</tr>
<tr>
<td>Atypical adenomatous</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar hyperplasia</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Inflammatory fibrosis</td>
<td>3</td>
<td>7, 2–8</td>
</tr>
</tbody>
</table>

Types A–C are Noguchi’s classification subtypes (2).
Although significant differences in TDR were observed between NO:

No mortality occurred, but one patient developed post-operative pneumothorax and pneumonia, and another hemorrhagic gastric ulcer. There have been no recurrences as this is being written (January 2015), with a median follow-up period of 88 months (range: 61–133 months). No patients were lost to follow up during this period.

Discussion

The first prospective limited resection trial for GGO lung cancer patients was reported by Yamato et al. (17) in 2001. Since then, several reports from Japan have concluded (18,19) limited resection resulted in excellent recurrence-free survival, although all of these were single-arm, limited resection-only studies. The numbers of patients were small, and follow-up periods were short in a situation where patients may be at risk for recurrence for up to 10 years or maybe even longer.

In this trial, the number of patients is relatively large at ~100. With the median follow-up period of 7 years and 4 months, the survival has been excellent without any recurrences. However, as we have repeatedly warned, delayed (≥5 years after surgery, up to 10.5 years) cut-end recurrences are possible following limited resection for GGO lung adenocarcinomas (14,15). We also reported that late recurrence of almost 10 years after surgery is possible even among patients undergoing complete tumor resection and systematic lymph node dissection (20). The current follow-up period is still too short to conclude limited resection is curative in this setting, and therefore the survival outcome is provisional. Ten-year follow-up period is necessary to understand the results of this trial.

There were 5 over-treated or over-examined patients with hyperplastic lesions or inflammatory changes. We suspected three of the five patients had inflammatory changes and recommended a watchful waiting strategy. However, they wanted immediate resection for emotional reasons. It was of note that of the 92 patients, excluding these five patients had inflammatory changes and recommended a watchful waiting strategy. However, they wanted immediate resection for emotional reasons. It was of note that of the 92 patients, excluding these 5 patients, 90 (98%) patients actually had malignant lesions, indicating the high specificity of our differential diagnosis based on HRCT. Although significant differences in TDR were observed between Noguchi’s type A vs. C and type B vs. C, there were no clear cut-offs to differentiate these subtypes. It remains unclear whether it is helpful in clinical practice to differentiate Noguchi’s subtypes based on radiological findings, but TDR is not helpful in differential diagnosis of these pathological subtypes.

It is also noteworthy only one type C patient out of 90 patients with malignancy had pathologically positive margin identified post-operatively. It remains unclear whether cytologic lavage or pathological cut-end evaluation is the better margin non-recurrence predictor. However, our result showed they were in high concordance at 99%.

In this study, pathological types of the tumors have not been cross consensus reviewed between the participating two institutions. It is necessary to cross-review the pathological specimens based on the proposal by Travis et al. (21) HRCT findings in indicating limited resection have not been cross consensus reviewed either. During this trial, the ratio of consolidation to the maximum tumor diameter was reported to best predict non-invasive peripheral lung adenocarcinoma radiologically (22). Computerized evaluation for the percentages of ground-glass/consolidation component has been studied (23). We need to review HRCT scans using these novel methods to establish more reliable and reproducible evaluation criteria and correlate them with pathological findings and outcome. These are our future directions of research along with the long-term 10-year follow-up outcome.

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Conflict of interest statement

Junji Yoshida, Masahiro Tsuboi, Hiroyuki Ito, Haruhiko Nakayama and Kanji Nagai have received consulting and/or speaking fees from Covidien Japan and Johnson & Johnson.

References


