Partly solid pulmonary nodules: waiting for change or surgery outright?

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INTRODUCTION

The frequency of early detection of focal ground-glass opacity nodules (GGOs) has increased due to computed tomography (CT) screening programmes and advances in the quality of high-resolution computed tomography (HRCT) [1]. Persistent GGOs present as one of several different types, from benign lesions, such as atypical adenomatous hyperplasia (AAH) or fibrosis, to malignant lesions [2]. Persistent partly solid tumours have particularly strong malignant potential [3]. Existing studies on the natural history of partly solid tumours have shown that some never change in size or growth in their solid component when the overall size of ground-glass opacity (GGO) is less than 3 cm and the proportion of GGO is greater than 50%. However, it remains unclear when the size of the whole or the invasive component of partly solid tumours changes.

Based on our previous experience, partly solid tumours that contain less than 50% GGOs and are less than 3 cm are regarded as invasive lung cancer and require surgical resection immediately, whereas when lesions contain 50% or more GGOs, we tend to keep them under observation rather than performing immediate resection. After a period of follow-up, patients can either undergo surgery following an observed increase on follow-up CT images, or due to their own concerns that it is cancerous even though there are no changes in the size of the tumour. We conjectured that, if there was a difference in the rate of lymph node metastasis or the prognosis of the patients with or without an increase in the size of the solid component of partly solid tumours, this could be used to help to decide the timing of surgery of partly solid tumours. Therefore, this study compared differences in the pathological results and prognosis after surgical resection between those with no change and those with change in partly solid tumours during the preoperative period.

METHODS

Surgery was performed in patients who had an increased size of the solid component during the follow-up observation of partly solid tumours, as well as patients who had no change in the size of the solid component during a certain period of time. The ‘No change group’ in this study comprised those who had no change in at least two chest computed tomography scans during a minimum period of 6 months, but who underwent surgery.

RESULTS

Twenty-four patients were enrolled in this study. Among these patients, 14 were included in the No change group, and ten were included in the ‘Change group’. There was no difference in the ratio of other postoperative pathological results, adenocarcinoma in situ, minimally invasive adenocarcinoma or invasive adenocarcinoma between the two groups. There was no difference in the pathological size of the tumour, including the in situ component between the two groups, but the size of the invasive component in the Change group was 2.5-fold that of the No change group, a statistically significant difference. During the median follow-up period of 59 months, neither recurrence nor cancer-related deaths occurred.

CONCLUSIONS

The pathological results and prognosis of lung cancer patients with persistent partly solid tumours who develop changes in their lesions after a certain period of follow-up time were not different from those of patients who did not develop any changes in the lesions. Therefore, surgery can be deferred until those lesions demonstrate changes in size or growth in their solid component when the overall size of ground-glass opacity (GGO) is less than 3 cm and the proportion of GGO is greater than 50%.

Keywords: Ground-glass opacity • Solid component • Adenocarcinoma • Prognosis

OBJECTIVES: It has been assumed that if the prognosis and rate of lymph node metastases differ between two groups of patients being followed up for partly solid tumours, those with an increased solid component and those without change, these differences can help to decide on the time of surgery for patients with partly solid tumours. Therefore, this study compared the differences in pathological results and prognosis after surgical resection between patients with no change and and those with change in partly solid tumours during the preoperative period.

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MATERIALS AND METHODS

Patients

The data used in this study were collected from the records of patients who received surgical resection for partly solid tumours...
between January 2004 and August 2009. The inclusion criteria were as follows: (i) a tumour size of less than 30 mm; (ii) those with a GGO component of more than 50%; (iii) preoperative observation duration for 6 months or longer unless the solid component was not changed; and (iv) those who had follow-up CTs for at least 2 years after the operation. In the enrolled patients, all partly solid tumours had been detected with 1-mm thickness HRCT images at our hospital and followed up until the time of operation. After surgery, all of the patients who were diagnosed with any type of lung cancer were observed at 6-month intervals with follow-up chest CT for at least 2 years. This study was approved by the institutional review board of Seoul National University Bundang Hospital. Informed consent was waived due to the retrospective study design.

Calculation of the ground-glass opacity nodule component

The proportion of GGO in a nodule was measured by the same method reported elsewhere [8]. In brief, the images were photographed with a window level of –600 HU and a window width of 2000 HU, as the lung window. GGO was defined as a hazy increase in lung attenuation without obscuring the underlying bronchial or vascular structures. Solid attenuation was defined as an increase in lung attenuation obscuring the underlying structures. The quantitatively estimated GGO area was defined as $1 - \left( \frac{\text{ratio of solid attenuation to the maximum tumour dimension}}{\text{ratio of GGO attenuation to the maximum tumour dimension}} \right)$. For evaluation of the size change, the changes in size of the solid component were recorded on all available preoperative CT scans. An increased size of the solid component of GGO was defined as an increase of at least 2 mm from the size on initial CT scans.

Surgical indications and grouping

Partly solid tumours sized 30 mm or larger were excluded from this study because they were surgically resected after work-up. However, those that were sized 30 mm or less, with a GGO component of more than 50%, were followed up with CT scans at 3-month intervals without immediately undergoing surgery. Those who were found to have an increased size of GGOs during the follow-up time underwent surgical resection, along with those in whom the GGOs did not increase in size but the patient had anxiety associated with the GGOs. Therefore, the ‘No change group’ in this study comprised patients who underwent surgery without a change in at least two CT scans during the follow-up of 6 months, while the ‘Change group’ comprised those who underwent surgery due to an increase in the size of only the solid component (not total size) as shown in the CT scans during the follow-up period.

Surgery

If partly solid tumours were located in the peripheral regions, the tissue was sent to the pathology laboratory for frozen section after wedge resection. If the tissue was invasive adenocarcinoma, anatomical resection and mediastinal node dissection were generally performed; however, wedge resection was sufficient if adenocarcinomas in situ (AIS) or minimally invasive adenocarcinomas (MIA) were confirmed on frozen section. Those that were located too deep for wedge resection underwent anatomical resection. All patients who were diagnosed with lung cancer underwent mediastinal node dissection.

Histopathological evaluation

The histopathological classification of the specimens was sorted by the regulations set forth by the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma [9]. Regarding the mixed subtype of adenocarcinoma, the histological pattern of >5% in the tumour was recorded. The tumours were AIS, MIA and invasive adenocarcinomas. Tumour size was measured in two ways: (i) the total tumour size; and (ii) the invasive tumour size based on only the invasive component, not including the lepidic growth.

Statistical analysis

The $\chi^2$ test and Fisher’s exact test were applied to assess differences in categorical variables. The unpaired Student’s t-test and Mann–Whitney U-test were used for discrete and continuous variables. A P-value of less than 0.05 was considered to be statistically significant. All analyses were performed using IBM SPSS 20.0 software (IBM Co., Chicago, IL, USA).

RESULTS

Patients

There was a total of 86 patients who underwent surgery for partly solid tumours during the study period. Of these patients, 27 who had tumours sized 30 mm or larger, and 35 patients who were not followed up for at least 6 months preoperatively were excluded, resulting in a total of 24 patients who were enrolled in this study. Thirteen (54%) of these 24 patients were male, and the median age was 62.6 years (range, 31–85). In 16 (67%) patients, GGOs were incidentally found on the CT scan during their regular health check-ups. In terms of smoking history, 13 (54%) patients had never smoked, 6 (25%) were ex-smokers and five (21%) were current smokers. The pathological results showed that 20 (83%) patients had malignancies and four (17%) had benign disease. The benign disease comprised two cases of AAH, one case of fibrosis and one case of inflammation.

No change group

There were 14 patients included in this group. Among them, three patients underwent surgical resection due to anxiety associated with the persistent presence of GGO. The median preoperative follow-up period was 413 (185–1092) days, and the mean number of the follow-up HRCT scans was 2.8. The mean size of the whole nodules on HRCT was 17.5 ± 7.9 mm, and the median proportion of the GGO component was 66 (56–95%). There were five patients who underwent percutaneous needle biopsy, and three of the five were diagnosed as having cancer and the rest were not. The types of surgery performed in this study included lobectomy, segmentectomy and wedge resection in nine (64%), one (7%) and four (29%) patients, respectively. Video-assisted thoracic surgery (VATS) was performed in nine patients, while open thoracotomy was carried out in five patients.
Ten patients were included in this group. The median preoperative follow-up period until a change in the size of the tumour was observed was 743 (40–1967) days; there were six patients who were observed over 6 months, and the mean number of follow-up HRCT scans was 2.5. The mean size of the whole nodule on HRCT was 17.4 ± 10.3 mm, and the median GGO component was 70 (53–93)%.

Comparison of clinicoradiological and pathological findings between the two groups

There was no significant difference in the preoperative observation interval, sex, age, smoking history, total size in HRCT, GGO component or surgical extent between the two groups (Table 1). The number of patients with benign disease in the No change group and the Change group was three (21%) patients and one (10%) patient, respectively, and there was no statistically significant difference between the two groups.

Postoperative pathological results showed no differences in the ratio of AIS, MIA and invasive adenocarcinoma between the two groups. There was no significant difference in the size of the pathological lesions including the in situ component, but when comparing the size of the invasive component, the size in the Change group was found to be 2.5-fold of that of the No change group, which was a statistically significant difference. No lymph node metastases were found in either group, and there was no significant difference in lymphovascular invasion, which can affect lymph node metastasis, in either group (Table 2).

Comparison of prognosis between the two groups

The median follow-up duration was 59.1 (47.1–110.5) months and all patients were followed up with chest CT after 24 months. Since neither recurrence nor cancer-related deaths occurred during the follow-up period, it was not possible to compare these outcomes between the two groups.

**DISCUSSION**

With the advancement in CT resolution and the introduction of CT screening programmes, more GGOs are being identified, many of which are diagnosed as lung cancer [10, 11]. Of the GGO form of tumours, partly solid tumours have a higher malignancy potential compared with non-solid tumours and, thus, the majority are surgically resected [12, 13]. They have a better post-surgical prognosis compared with non-solid tumours, suggesting that the early identification, early diagnosis and early treatment pattern applies to this type of tumour as for other solid cancers. Therefore, many thoracic surgeons believe that if partly solid tumours found on CT have radiological characteristics of cancer, they should be actively resected. Many studies so far have focused on the clinical and radiological findings of partly solid tumours that make them highly likely to be cancerous, and on finding more definite factors for the purpose of surgical treatment [10]. The post-surgical pathology of partly solid tumours from such a treatment process is generally diagnosed as either invasive adenocarcinoma, or AIS or

**Table 1: Comparison of pathological findings after surgery between the groups with no change and changes during the preoperative follow-up period**

<table>
<thead>
<tr>
<th>Pathological diagnosis</th>
<th>No change (n = 14)</th>
<th>Change (n = 10)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>3 (21.4)</td>
<td>1 (10.0)</td>
<td>0.301</td>
</tr>
<tr>
<td>Malignant</td>
<td>11 (78.6)</td>
<td>9 (90.0)</td>
<td></td>
</tr>
<tr>
<td>AIS/MIA</td>
<td>2 (18.2)</td>
<td>0 (0.0)</td>
<td>0.934</td>
</tr>
<tr>
<td>Invasive adenocarcinoma</td>
<td>9 (69.2)</td>
<td>9 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Pathological tumour size, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total size including in situ</td>
<td>16.2 ± 7.1</td>
<td>16.2 ± 7.7</td>
<td>0.996</td>
</tr>
<tr>
<td>Invasive size</td>
<td>4.0 ± 5.8</td>
<td>11.1 ± 7.1</td>
<td>0.035</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (100.0)</td>
<td>8 (88.9)</td>
<td>0.257</td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td>EGFR mutation, n (%)</td>
<td></td>
<td></td>
<td>0.719</td>
</tr>
<tr>
<td>No</td>
<td>4 (36.4)</td>
<td>1 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (63.6)</td>
<td>8 (88.9)</td>
<td></td>
</tr>
</tbody>
</table>

between the two groups, but there was no case of lymph node metastasis in either group. Therefore, there were no cancer-related deaths or recurrences in the two groups during the post-surgical follow-up period, with a median length of 5 years.

Our results would potentially be useful in older patients or medically debilitated patients who show no changes in the size of the tumour in CT scans, because they will have no need for surgery. Our study showed that even in those who had invasive adenocarcinoma, most did not have lymph node metastasis or had a lepidic-predominant type of tumour, which has a very good post-surgical survival rate. The CT surveillance group of the National Lung Screening Trial showed that a survival gain of 20% and the widespread use of VATS lobectomy will lead to more frequent detection of partly solid tumours, most of which will be candidates for surgical resection. Hence, there will be concern about unnecessary resection of these lesions. Kobayashi et al. [19] also evaluated the pathological differences between a lung lesion with GGO that persisted without changing in size and those that gradually but obviously grew within the first 3 years and concluded that these lesions should be followed for at least 3 years. In addition to CT finding, the maximum Standardized Uptake Value in positron emission tomography might have a role in deciding whether the tumours that have showed no change in size of their solid component should be resected [20].

The limitations of this study include the fact that it is a retrospective study and not all of the patients were treated according to the same protocol, due to a lack of specific treatment guidelines for partly solid tumours. Second, this study included only a small number of patients, and third, the follow-up period was relatively short. Although the patients were followed up for 60 months, we believe that there is a need or a longer follow-up period in patients with a GGO form of lung cancer.

In conclusion, the prognosis of lung cancer patients with persistently partly solid tumours that changed in size after follow-up was not different from that of patients who had partly solid tumours that did not change in size. Therefore, surgery can be deferred until those lesions demonstrate changes in size in their solid component when the overall size of GGO was less than 3 cm and proportion of GGO was greater than 50%. In addition, before change in the solid component is seen, the interval of follow-up might not be a factor that has impact on outcome in less invasive lung cancer.

Conflict of interest: none declared.

REFERENCES


